

Comparison of Efficacy of Duloxetine versus Amitriptyline in Fibromyalgia Patients

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ABSTRACT

Objective: To compare the outcomes of Duloxetine and Amitriptyline therapy in fibromyalgia patients regarding change in Symptom Severity Scale (SSS) score and Widespread Pain Index (WPI) from baseline after three months of treatment.

Methodology: This quasi-experimental study was done in the Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad, from November 2022 to April 2023. One hundred fifty-six fibromyalgia patients of either gender between the ages of 25-70 years were included in the study. They were erratically assigned into two groups. Group A patients were given Duloxetine, while group B patients were given Amitriptyline for 12 weeks with main outcome of change in WPI and SSS scores three months after the therapy.

Results: There were 2.6% (n=2/78) males and 97.4% (n=76/78) females in group A and 1.3% (n=1/78) males and 98.7% (n=77/78) females in group B (P 0.560). At baseline, the mean WPI score in group A was 15.8 ± 1.3 SD, and it was 16.1 ± 1.4 SD in group B (P 0.286), and the mean SSS score was 6.6 ± 1.6 SD in group A, and it was 6.8 ± 1.5 SD in group B (P 0.467). At 12 weeks, the mean WPI score in group A was 11.2 ± 2.2 SD, and it was 8.9 ± 3.1 SD in group B (P 0.001), and the mean SSS score was 4.5 ± 1.7 SD in group A, and it was 3.6 ± 1.3 SD in group B (P 0.001).

Conclusions: Outcomes were better with Amitriptyline compared to those patients taking Duloxetine in diagnosed cases of fibromyalgia.

KEYWORDS: Amitriptyline, Duloxetine, Fibromyalgia, Symptom Severity Scale, Widespread Pain Index.

INTRODUCTION

Fibromyalgia (FM) is a chronic disorder characterized by musculoskeletal discomfort,

tenderness, and fatigue. The exact etiology and pathophysiology of fibromyalgia are not fully understood; however, researchers believe it involves a multifaceted interaction of genetic, environmental, neurobiological, and psychosocial factors.^{1,2} Fibromyalgia is more frequent in women than in men. It is commonly reported in individuals aged 20 – 55 years; however, it can present at other ages too. Around 2 – 3% of the general population is affected by fibromyalgia with different prevalence across the globe. Even children can present with fibromyalgia.^{1,3}

In the 20th century, FM was recognized as an isolated phenomena by many rheumatologists, and they proposed diagnostic criteria for it. These criteria were further evaluated and then authorized.⁴ A study conducted in United Kingdom based on population found occurrence of FM of 5% and chronic widespread pain (CWP) of 14%.⁵ A rise was observed in cases of FM from 2001 to 2003 by

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The National Health Service record in the United Kingdom.⁶ FM patients experience cognitive disturbances due to the ongoing musculoskeletal pain and discomfort. There is lack of attention and failure to demonstrate higher cognitive functions like fine motor skills. Neuropsychological testing helps differentiate FM from other psychiatric disorders.⁷ Brain radiographs and / or validated instruments have demonstrated that subjective cognitive deficits are much more common than changes in objective measures in FM patients.¹ A meta-analysis, incorporating 23 case-control studies provides detailed outline of the existing evidence on cognitive function in fibromyalgia patients compared to healthy controls. Such analyses are valuable in synthesizing data from multiple studies to draw more robust conclusions.⁸ General physical examination of FM patients is unremarkable except for extensive soft tissue tenderness. Serological and radiographic investigations are done to rule out other differential diagnoses. It seems that patients with FM do not suffer from any concomitant comorbidity, and that FM occurs as a sole entity with psychogenic and or psychosomatic presentation. Research has demonstrated that FM is a pain disorder which is categorized among central sensitization.⁹ Standardized treatment is not available for FM at the moment, and treatment is targeted more towards the symptomatic relief of individual patients.¹ Anti-depressants e.g. serotonin and noradrenaline reuptake inhibitors, selective serotonin reuptake inhibitors and tricyclic antidepressants (TCAs) have shown improvement in pain, depression, and physical asthenia in FM patients.¹ Tricyclic antidepressants are used to treat FM through their effect on amine reuptake, specifically serotonin and epinephrine. They enhance production of endogenous opioids and adjust central motor activities, thereby lessening symptoms of depression. The TCA, amitriptyline has demonstrated efficacy as an anti-FM drug apart from its anti-depressant properties. It supersedes selective serotonin reuptake inhibitors in the management of FM.

Duloxetine acts as a selective inhibitor of 5-hydroxytryptamine and noradrenaline reuptake within the central nervous system (CNS). Through this mechanism, descending pain inhibitory pathways in the central nervous system are enhanced.¹ Research conducted on FM patients in other parts of the world have demonstrated efficacy of duloxetine over placebo.¹⁰

Japanese patients with FM were studied in a phase III trial which was aimed to determine the clinical safety and effectiveness of duloxetine in FM's management. The study reported that duloxetine proved beneficial in almost all secondary and post hoc analyses. The baseline pain score (VAS) was 6.05 ± 1.29 , which after three months of therapy reduced to 4.15 ± 1.02 SD at 0–10-degree pain scale; the difference was substantial related to the placebo group ($P < 0.001$).¹¹ Some studies reported significant improvement in patients treated with Amitriptyline after 12 weeks. The pain was reduced from 7.77 ± 1.65 at baseline to 3.37 ± 1.76 SD at 12 weeks ($p < 0.05$).¹²

The current study was aimed to compare the effectiveness of Duloxetine and Amitriptyline in treating fibromyalgia patients. Both medications are sometimes used in the management of fibromyalgia, and such studies are important for providing evidence-based insights into their efficacy. Comparing Duloxetine and Amitriptyline in a clinical trial is valuable for understanding how these two medications perform in treating fibromyalgia symptoms. Both drugs belong to different classes of medications and may have different mechanisms of action. Data comparing Duloxetine and Amitriptyline for fibromyalgia treatment are scarce in the local population.¹³ This emphasizes the importance of conducting research that is specific to the characteristics and needs of the local community, as responses to medications can vary among different populations. The study results, once available, can aid physicians in making informed decisions about treatment options for fibromyalgia patients in the local population. This is fundamental for shaping treatment plans to

individual patient needs and refining outcomes.

METHODOLOGY

It was a quasi-experimental study conducted for six months in the Department of Rheumatology, Pakistan Institute of Medical Sciences, Islamabad. The sample size was calculated by using the WHO sample size calculator, leading to $n=156$. Consecutive non-probability sampling was the sampling technique. Inclusion criteria comprised of diagnosed cases of fibromyalgia as per criteria recommended by the American College of Rheumatology. Both genders were included, with ages between 25 and 70. Patients with a past history of surgical procedures performed for herniated lumbar discs, recent history (within 2 months) of physiotherapy for pain relief, recent history of anti-depressant therapy, recent use (within 2 months) of duloxetine before being enrolled in the trial, active inflammation or malignancy, pregnancy or lactation, psychiatric issues or systemic disorders, or allergy / contraindications to amitriptyline or duloxetine were excluded from the study.

Hospital's ethical review board provided the ethical approval before initiation of this study vide F.No. 20-4/ASRB-M/SZABMU/2022. The aim and expectations from the study were clarified to all study participants and they were guaranteed about confidentiality. Informed consent was taken from all study participants. Patients fulfilling the inclusion criteria were involved in the study. Patients were randomly allocated into two groups, A & B. Group A patients were given Duloxetine in a dose of 20 mg daily for one week followed by 30 mg daily for one week and then 60 mg daily for 12 weeks while in group B patients, Amitriptyline was given in a daily dose of 12.5 mg to 25 mg for 12 weeks. To avoid any bias in the study results, a double-blinded approach was followed. The primary outcome was the change in WPI and SS score three months after the therapy. Standard care and treatment were provided to all patients involved in the study.

All the data collected was entered into SPSS

version 23, and the results were analyzed accordingly. The results were presented in tables. Descriptive statistics were calculated, and the mean standard deviation was measured for continuous variables like age, gender, BMI, duration of disease, WPI, and SS score at baseline and after three months in both groups of patients. Frequency and percentage were calculated for categorical variables like gender. Both groups' outcomes (WPI and SS score) were compared by applying a t-test for independent samples, and a P value ≤ 0.05 was considered significant. Effect modifiers like age, gender, BMI, and disease duration were controlled by stratification. A post-stratification t-test for independent samples was applied, and a P value ≤ 0.05 was considered significant.

RESULTS

A total of one hundred and fifty-six ($n=156$) adult patients of either gender between age 25-70 years were included in the trial.

Table 1: Mean WPI and SS score at baseline and at 12 weeks in both groups

Time	Groups		Mean	Std. Dev	P-Value t-test
Baseline	WPI	Duloxetine	15.8	1.3	0.266
		Amitriptyline	16.1	1.4	
	SS Score	Duloxetine	6.6	1.6	0.467
		Amitriptyline	6.8	1.5	
12 Weeks	WPI	Duloxetine	11.2	2.2	0.001
		Amitriptyline	8.9	3.1	
	SS Score	Duloxetine	4.5	1.7	0.001
		Amitriptyline	3.6	1.3	
Mean percentage change from baseline in WPI and SS score in both groups					
Groups			Mean	Std. Dev	P-Value t-test
WPI (% change from baseline)	Duloxetine		28.6	14.4	0.001
	Amitriptyline		44.3	19.3	
SS Score (% change from baseline)	Duloxetine		32.4	14.2	0.001
	Amitriptyline		46.6	17.8	

P value ≤ 0.05 taking significant

All the patients were diagnosed with fibromyalgia as per the operational definition. The primary outcome was the change in WPI and SS scores three

months after the therapy. There were 2.6% (n=2/78) males and 97.4% (n=76/78) females in group A and 1.3% (n=1/78) males and 98.7% (n=77/78) females in group B (P 0.560). The mean age of group A patients was 39.2 years $\pm$ 13.2 SD, and 37.6 years $\pm$ 10.6 SD in group B (P 0.402; Table 2). In group A, there were 76.9% (n=60/78) patients belonging to age group 25-50 years and 23.1% (n=18/78) belonging to age group 51-70 years.

Table 2: Mean percentage change from baseline in WPI in both groups (stratification for effect modifiers)

Variables	Groups	Mean	Std. Dev	P-VALUE t-test
Age 25-50 years	Duloxetine	28.8	12.9	0.001
	Amitriptyline	44.1	18.1	
Age 51-70 years	Duloxetine	27.9	18.9	0.001
	Amitriptyline	45.1	24.8	
Males	Duloxetine	25.0	5.1	0.001
	Amitriptyline	56.3	0.0	
Females	Duloxetine	28.7	14.5	0.001
	Amitriptyline	44.1	19.4	
BMI <30 kg/m ²	Duloxetine	27.0	14.2	0.001
	Amitriptyline	45.2	19.4	
BMI $\geq$ 30 kg/m ²	Duloxetine	32.6	14.3	0.001
	Amitriptyline	42.1	19.3	
Duration $\leq$ 12 months	Duloxetine	29.1	14.5	0.001
	Amitriptyline	45.8	18.7	
Duration >12 months	Duloxetine	26.9	14.3	0.001
	Amitriptyline	39.1	20.9	

P value $\leq$ 0.05 taking significant

The proportions in group B were 80.8% (n=63/78) and 19.2% (n=15/78), respectively (P 0.556; Table 2). The mean BMI of group A patients was 26.5 kg/m² $\pm$ 4.0 SD and 27.1 kg/m² $\pm$ 4.1 SD in group B (P 0.406). In group A, there were 71.8% (n=56/78) patients belonging to BMI group $\leq$ 30 kg/m² and 28.2% (n=22/78) belonging to BMI group >30 kg/m². The proportions in group B were 69.2% (n=54/78) and 30.8% (n=24/78), respectively (P 0.725). The mean duration of disease in group A patients was 10.6 months $\pm$ 10.7 SD, and 13.8 months $\pm$ 18.6 SD in group B (P 0.191). In group A, there were 78.2% (n=61/78) of

patients belonging to the duration group $\leq$ 12 months and 21.8% (n=17/78) belonging to the duration group >12 months. The proportions in group B were 76.9% (n=60/78) and 23.1% (n=18/78), respectively (P 0.848).

WPI AND SS SCORES IN BOTH GROUPS
At baseline, the mean WPI score in group A was 15.8 $\pm$ 1.3 SD, and it was 16.1 $\pm$ 1.4 SD in group B (P 0.286, table 1), and the mean SS score was 6.6 $\pm$ 1.6 SD in group A, and it was 6.8 $\pm$ 1.5 SD in group B (P 0.467, table 1).

At 12 weeks, the mean WPI score in group A was 11.2 $\pm$ 2.2 SD, and it was 8.9 $\pm$ 3.1 SD in group B (P 0.001, table 1), and the mean SS score was 4.5 $\pm$ 1.7 SD in group A, and it was 3.6 $\pm$ 1.3 SD in group B (P 0.001, table 1).

Table 3: Mean percentage change from baseline in SS score in both groups (stratification for effect modifiers)

Variables	Groups	Mean	Std. Dev	P-value T-test
Age 25-50 years	Duloxetine	33.7	15.7	0.001
	Amitriptyline	45.5	16.7	
Age 51-70 years	Duloxetine	28.2	6.4	0.001
	Amitriptyline	51.2	21.9	
Males	Duloxetine	20.0	0.1	0.001
	Amitriptyline	37.5	0.0	
Females	Duloxetine	32.8	14.3	0.001
	Amitriptyline	46.7	17.9	
BMI <30 kg/m ²	Duloxetine	34.5	13.8	0.001
	Amitriptyline	46.6	17.5	
BMI $\geq$ 30 kg/m ²	Duloxetine	27.3	14.3	0.001
	Amitriptyline	46.5	19.1	
Duration $\leq$ 12 months	Duloxetine	32.5	15.3	0.001
	Amitriptyline	47.2	18.4	
Duration >12 months	Duloxetine	32.3	9.8	0.001
	Amitriptyline	44.6	16.2	

P value $\leq$ 0.05 taking significant

At 12 weeks, the mean percentage change from baseline in WPI score in group A was 28.6% $\pm$ 14.4 SD, and it was 44.3 $\pm$ 19.3 SD in group B (P 0.001,

table 1), and the mean percentage change from baseline in SS score in group A was $32.4\% \pm 14.2$ SD, and it was $46.6\% \pm 17.8$ SD in group B ($P < 0.001$, table 1).

Mean WPI and SS scores were significantly lower, and the mean percentage reduction in WPI and SS scores at 12 weeks was significantly higher in patients taking Amitriptyline than in those taking Duloxetine as evident in table 3.

Stratification For Effect Modifiers

WPI and SS score data at 12 weeks were further stratified for age, gender, BMI, and disease duration (Tables 1 and 2). Similar trends appeared, and mean percentage reduction in WPI and SS scores were considerably higher in patients taking Amitriptyline compared to those taking Duloxetine across all strata ($P < 0.05$ in all cases).

DISCUSSION

Management of FM aims at relief of the symptoms of FM, either through non-pharmacologic or pharmacologic modalities. These therapies are often provided in combination and a stepwise fashion.¹⁴ A multidisciplinary approach with individualized treatment is needed for FM patients.¹ This particular study was designed to prospectively compare the outcomes of Duloxetine and Amitriptyline therapy (two frequently used pharmacological agents) in fibromyalgia patients in terms of change in WPI and SS from baseline after 3 months of treatment.

Amitriptyline is not widely prescribed for pain relief, and it finds usage as an anti-depressant drug; however, it has been found more efficacious in management of FM as compared to selective serotonin reuptake inhibitors in the relief of pain associated with FM. Duloxetine exerts analgesic effects by enhancing 5-hydroxytryptamine and noradrenaline actions within the CNS, either by increasing the descending pain inhibitory pathways in the brain and spinal cord or via other unidentified CNS mechanisms.¹⁵ The results of our study favor amitriptyline as compared to duloxetine in the relief

of pain as measured by improvement in WPI and SS scores at 12 weeks. Literature has demonstrated a 25 to 45% improvement in pain with the use of amitriptyline as compared with 0 to 20% of those taking placebo.¹⁶ Despite this percentage of pain relief, the widespread use of amitriptyline is limited by its side effect profile. Also, its efficacy may decrease over time, hence prolonged use may not guarantee improvement in pain.¹⁷ Most of the trials investigating the use of tricyclic antidepressants in fibromyalgia have incorporated their use for less than three months period.

Our results are comparable with a systematic review and meta-analysis from 2017 that delivered an indirect comparison that suggested superior efficacy of Amitriptyline compared with Duloxetine and Milnacipran in dropping symptoms like pain, sleep disturbance, and fatigue, without alterations in acceptability.¹⁸ Research from 2017 compared antidepressants for fibromyalgia's treatment. It included 18 randomized trials of a diversity of agents, finding evidence for the efficacy of antidepressants for pain relief, physical asthenia, mood swings, altered sleep pattern, and development in health-related quality of life.¹⁹ It did not include two additional placebo-controlled randomized trials, also signifying benefits with the use of the SNRI Milnacipran, published subsequently.²⁰ A recent systematic qualitative review on Amitriptyline in fibromyalgia patients also concluded that Amitriptyline demonstrated a better therapeutic response compared with placebo and Duloxetine in the areas of pain, sleep, and fatigue.²¹ In another very recent systematic review, Farias AD et al. compared evidence of the efficacy and safety of Duloxetine with Amitriptyline in treating patients, mostly adults, with fibromyalgia. They included eight systematic reviews in their analysis and demonstrated that both antidepressants are efficient in the treatment of fibromyalgia, with their efficacy varying according to the patient's symptoms and profile. Amitriptyline showed low evidence for pain, moderate proof for sleep and fatigue, and strong evidence for improving quality

of life. Duloxetine promises high quality proof in patients with mood disorders.^{22,23}

Moore RA et al., in their systematic review of nine studies comprising 649 participants, compared the efficacy of Amitriptyline with placebo treatment. Amitriptyline's daily dose was 25 mg to 50 mg. Using the risk ratio (RR) for at least 50% pain relief, or equal, with Amitriptyline compared with placebo, there were no constant differences between Amitriptyline and placebo for relief of symptoms. More participants felt at least one adverse event with Amitriptyline (78%) than with placebo (47%). Authors concluded that Amitriptyline has been considered a first-line treatment for fibromyalgia for decades and is still considered one of the options in the treatment of fibromyalgia while recognizing that only a tiny proportion of patients will gain satisfactory pain relief.²¹ Welsch P et al. in their research concluded that both Duloxetine and milnacipran are effective in improving patient's perception of pain. However, there was no clinical advantage over placebo for betterment in pain relief of 50% or more.²³

The current study favors use of amitriptyline over duloxetine for pain in FM patients. The concomitant use of both the drugs has not been tried in any trial; however, it might prove to be a beneficial trial which will aim to demonstrate the synergistic effects of both the drugs. In future, concomitant therapy might be reflected upon for reducing the patient's general symptom burden by targeting specific symptoms like sleep and aiming at common co-morbid conditions like irritable bowel syndrome or diseases.

The major strength of this study is that it is a randomized controlled trial which has better research implications. However; it has some limitations too; primarily, it needs a larger sample size to be recommended for implementation. Secondly, the duration of follow up can be increased further to see any late effects of duloxetine. Thirdly, the use of adjunct medications might change the study results. More thorough RCTs with more extended follow-up periods are

essential to establish the long-term efficacy and safety of monotherapy and combination therapy in patients with fibromyalgia.

CONCLUSION

The trial concluded that amitriptyline superseded duloxetine for pain of FM patients. Mean WPI and SS scores were significantly lower, and the mean percentage reduction in WPI and SS scores at 12 weeks was considerably higher in patients treated with Amitriptyline compared to those treated with Duloxetine.

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