Pregabalin Versus Amitriptyline in the Treatment of Fibromyalgia Patients (A Double Blind Comparative Study)

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ABSTRACT:

BACK GROUND:

Fibromyalgia is a disorder characterized by widespread musculoskeletal pain, fatigue, sleep and mood disturbances. Its etiology and treatment remain challenging. Oxidative stress may play a role in its pathogenesis.

OBJECTIVE:

The efficacy of pregabalin to that of amitriptyline on FM and the effect of treatment on oxidative status were examined.

METHODS:

123 patients fulfilling the Wolfe 2010 criteria for fibromyalgia diagnosis and assessment were randomized to receive amitriptyline (25 mg) or pregabalin (75 mg) once daily for 12 weeks. The revised fibromyalgia impact questionnaire criteria were also used. Malondialdehide and glutathaion levels were checked at the beginning and at the end of the study.

RESULTS:

Improvement in the pain was better with pregabalin than with amitriptyline (P=0.0001) at 4 weeks of treatment, but achieved comparable improvement at 8 and 12 weeks. The reduction in the somatic symptoms scale was significant for both drugs in favour of pregabalin. Sleep was improved significantly but pregabalin over amitriptyline (P=0.0001). Oxidative status was significantly improved.

CONCLUSION:

Both drugs improved the symptoms. Pregabalin was better than amitriptyline concerning SSS and sleep, but with a comparable effect on pain. Oxidative status was improved. Amitriptyline was better than pregabalin concerning patient compliance and tolerability.

KEY WORDS: fibromyalgia, pregabalin, amitriptyline.

INTRODUCTION:

1.1. Definition:

Fibromyalgia (FM) is a common and complex clinical syndrome characterized by chronic and widespread musculoskeletal pain, fatigue, sleep disturbance, and physical and psychological impairment [1].

1.2. **Prevalence and epidemiology**.

It affects all age groups, including children, all racial/ethnic groups, and all socioeconomic strata (2).

Epidemiological studies report a FM prevalence of between 2 and 7% in most nations, with a female to male ratio of approximately 9:1[3].

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1.3. The role of neurotransmitters.

a-Serotonin: [4].

b-Adrenaline and noradrenaline: [5].

c-**Substance P**: [6].

d- Nerve growth factor: [7].

e-Dopamine: [8].

1.4. Role of glutathione (GSH):

GSH can prevent or retard the pain response from fibromyalgia, and has also been identified as centrally acting anti-inflammatory agent [9].

1.5. Role of malondialdehyde (MDA) in fibromyalgia:

There is a correlation between symptoms and lipid peroxidation and oxidative stress in FM. Significant correlation has been observed between antioxidants levels in plasma and serum on visual analogue scale (VAS) of pain, and morning stiffness [10].

1.6. Diagnosis and assessment of FMS.

The ACR 1990 criteria which was the most dependent method for diagnosis in the past10 years included widespread pain (axial plus upper and lower segment plus left- and right-sided pain). The combination of widespread pain and mild or greater tenderness in greater than or equal to 11 of 18 tender point sites yielded a sensitivity of 88.4% and a specificity of 81.1 % [11]. There is still another important problem with fibromyalgia diagnosis. Patients who improved or whose symptoms and tender points decreased could fail to satisfy the ACR 1990 classification definition. It was not clear how to categorize or assess these patients. In addition, the ACR classification criteria set such a high bar for diagnosis that there was little variation in symptoms among fibromyalgia patients. These two considerations suggested the need for a broad-based severity scale that could differentiate among patients according to the level of fibromyalgia symptoms [12].

The Fibromyalgia Impact Questionnaire (FIQ) was developed in the late 1980s and was first published in 1991[13]. With minor revisions in 1997 and 2002 [14]. The FIQR attempts to address the limitations of the FIQ while retaining the essential properties of the original instrument.

1.7. Pharmacological treatments:

1- Antidepressants: [15]

2- Non-steroidal anti-inflammatory drugs (NSAIDs): (16).

3- Antiepileptic Drugs:

The analgesic effect of the antiepileptic (gabapentin and pregabalin) appears to be due to their ability to block sodium and/or calcium channels or by increasing inhibitory neuro-transmission (17).

Pregabalin which is now approved by FDA demonstrated efficacy on pain, sleep disturbances, and fatigue in FMS patients [17].

4- Sedative-hypnotics: [16].

5- Muscle relaxants: [16].

6- Opiates: [18].

1.9.7. HT3 antagonists: [18].

1.9.8. NMDA antagonists: [19]

1.9.9. Growth Hormone: [20]

The use of amitriptyline in fibromyalgia:

Several studies addressed the effectiveness of amitriptyline when compared with placebo in the treatment of FM [21].

Amitriptyline was recommended as first-line pharmacological therapy of FMS by the association of the Scientific Medical Societies in Germany guideline. In contrast, another systematic review could not make a definitive clinical recommendation regarding the efficacy of amitriptyline in Europe for FMS [22].

Pregabalin use in fibromyalgia:

The efficacy and safety of pregabalin up to 450 mg/day (150) mg thrice daily) were evaluated for reducing pain and associated symptoms in patients with fibromyalgia [23].

Chapter two

PATIENTS AND METHODS:

This double blind controlled trial was conducted on 123 patients with FM fulfilling the Wolfe 2010criteria. These patients were randomized to receive either amitriptyline in a dose of 25 mg once daily (61patients) or pregabalin in a dose of 75 mg once daily (62patients) for a period of 12 weeks. The revised fibromyalgia impact questionnaire (FIQR) criteria were also used for the assessment of 54 patients entering the study (27 patients for each treatment group). The patients were followed up at 4 weeks intervals; clinical improvement was assessed by calculating the patients' scores at each follow up visit according to Wolfe 2010 and FIQR criteria. In order to study the drug effects on the oxidative status, blood samples were taken at the beginning of the study and at the end of the 12 weeks for the estimation of MDA and GSH levels. Patients with rheumatic inflammatory diseases, pregnancies and who had cardiovascular problems were excluded from the study.

Wolfe 2010 criteria is the most reliable and simplest method to perform and its questionnaire could be answered by the patient himself, that is helpful for the rheumatologist. It consist from two parts, part one or wide pain index which measure the pain and part two (a&b) or also called somatic symptoms scale (SSS) that measure the other features of FMS.

RESULTS:

a- According to Wolfe criteria.

3.1- Table (3-4): comparison between the effect of amitriptyline and pregabaline on the wide pain index.

3.2-

Table 3-7: The difference in the effect of the two drugs on somatic symptoms scale part a.

WPI	Treatment group	N	Mean	SD	P
(4 weeks)	Amitriptyline	51	15.04	2.735	0.0001*
	Pregabalin	46	11.65	3.814	
(8 weeks)	Amitriptyline	49	9.16	3.837	0.15 (N.S)
	Pregabalin	34	7.74	4.712	
(12 weeks)	Amitriptyline	45	8.71	3.727	0.11 (N.S)
	Pregabalin	33	7.12	4.601	

WPI= Wide pain index.

3.3-

Table (3-10): The comparison between amitriptyline group and pregabalin group on somatic symptoms scale part b.

Somatic symptoms scale Part a	Treatment group	N	Mean	SD	P
(4 weeks)	Amitriptyline	51	7.71	1.026	0.0001*
	Pregabalin	46	4.65	2.415	
(8 weeks)	Amitriptyline	49	5.43	1.173	0.0001*
	Pregabalin	34	3.06	2.546	
(12 weeks)	Amitriptyline	45	5.02	1.177	0.0001*
	Pregabalin	33	2.82	2.506	

3.4-

Table 3-16: Compare the effect of amitriptyline versus pregabalin on sleep.

Somatic Symptoms Scale part b	Treatment group	N	Mean	SD	P
(4 weeks)	Amitriptyline	51	2.63	0.56	0.0001*
	Pregabalin	46	1.96	0.63	
(8 weeks)	Amitriptyline	49	1.96	0.76	0.01*
	Pregabalin	34	1.53	0.70	
(12 weeks)	Amitriptyline	45	1.67	0.64	0.008*
	Pregabalin	33	1.27	0.62	

3.5- Effect of amitriptyline and pregabalin on oxidative state.

Sleep	Treatment group	N	Mean	SD	P value
(4 weeks)	Amitriptyline	51	2.78	0.415	0.0001*
	Pregabalin	46	1.20	0.980	
(8 weeks)	Amitriptyline	49	1.82	0.601	0.0001*
	Pregabalin	34	0.97	1.029	
(12 weeks)	Amitriptyline	45	1.62	0.716	0.0001*
	Pregabalin	33	0.79	0.740	

1. Effect of amitriptyline:

a-On GSH.

Table 3-17: The effect of amitriptyline on GSH.

GSH	Mean(µM) ± SD	N	P
(0 week)	0.826 ± 0.807	45	0.0001*
(12weeks)	1.160 ± 0.912	45	

a-On MDA:

Table 3-18: The effect of amitriptyline on MDA levels.

MDA	Mean(µmol/l) ± SD	N	P
(0 week)	1.803 ± 1.188	45	0.0001*
(12 weeks)	1.266 ± 0.9	45	

2. Effect of pregabalin.
a- On GSH

Table 3-19: The effect of pregabalin on GSH levels.

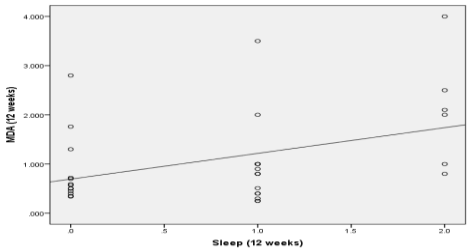
GSH	Mean(µM) ± SD	N	P
(0 week)	0.993 ± 0.873	33	0.0001*
(12 weeks)	1.7 ± 1.04	33	

a- On MDA.

Table 3-20: The effect of pregabalin on MDA levels.

MDA	Mean(µmol/l) ± SD	N	P
(0 week)	1.74 ± 1.065	33	**0.0001***
(12 weeks)	1.105 ± 0.96	33	

3. 6- Correlations between the improvement in clinical Parameters and reduction in oxidative stress at 12 Weeks of treatment with amitriptyline and pregabalin.



r = 0.381 p = 0.029*

Figure 3-16: Correlation between MDA and sleep in pregabalin group.

b- According to FIQR:

Table 3-23: The comparison between the effects of the two drugs according to FIQR criteria.

FIQR	Treatment group	N	Mean	SD	P
(4 weeks)	Amitriptyline	25	75.53	12.48	0.0001*
	Pregabalin	21	50.37	20.79	
(8 weeks)	Amitriptyline	22	66.78	16.21	0.001*
	Pregabalin	15	39.89	25.16	
(12 weeks)	Amitriptyline	20	60.98	19.01	0.018*
	Pregabalin	14	40.06	26.10	

3.7- Tolerability and frequency of side effects.

Table 3-24: Side effects appeared spontaneously in amitriptyline group and pregabalin group.

side effects	amitriptyline n=51		Pregabalin n=46	
Drowsiness and sleepiness	n=39	76.4%	n=23	50%
dry mouth	n=30	66.66%		
Palpitation	n=8	19.6%		
Weakness	n=4	7.8%	n=22	47.82%

DISCUSSION:

When the effect on the WPI score between the two drugs was compared at 4 weeks, 8 weeks and 12 weeks of the treatment respectively, their was a significant difference in favor for pregabalin at 4 weeks indicating that pregabalin achieve a better improvement and earlier than amitriptyline . This difference was not shown after week 8 and also at week 12 probably because of the small sample size at 8 weeks and 12 weeks. The mechanism by which amitriptyline and pregabalin improve fatigue is unknown but may related to the improved energy supplied and muscle metabolism, several studies approved that fibromyalgia patients has a defect in energy and abnormal tissue metabolism [24].

The improvement of sleep in patients on pregabalin was significantly better than those on amitriptyline.

There is a relationship between disturbed sleep and pain because neurohormones and other molecules are synthesized during sleep and poor sleep may lead to poor synthesization of these neurohormons [7].

By comparing between the effects of the two drugs on somatic symptoms part b, the difference was significant and the preference was for pregabalin

In this study FIQR was also used to evaluate the improvement in the same patients who were previously evaluated by Wlofe 2010 criteria and had insignificant improvement in spite that the improvement is exist. As it was mentioned previously FMS has unclear etiology however it is hypothesized that the oxidative stress may have a role. A limited number of in vivo or in vitro studies regarding the effects of antioxidant redox systems and lipid peroxidation levels on the etiology of fibromyalgia have been reported [25], Amitriptyline may exhibit tissue antioxidant capacity by inhibiting induced peroxidation in an inflammatory animal model [26].

Oxidative status in amitriptyline group and in pregabalin group was improved at the end of the study by an unknown mechanism because amitriptyline and pregabalin are not antioxidants by themselves.

However the effect may be throught modulating of substance P [27] and NGF [7] which may indirectly affect oxidative statuse. While the result with pregabalin agrees with [28] who found that pregabalin may prevent oxidative stress in the rat liver tissues. Correlation between clinical parameters and oxidative state of the patients was also examined. The only significant correlation was found only with sleep. This may be due to the prominent effect of pregabalin on sleep in comparison with its effect on the other clinical parameters.

Patients with fibromyalgia syndrome have a lower melatonin secretion during the hours of darkness than healthy subjects. This may contribute to impaired sleep at night, fatigue during the day, and changed pain perception [29], melatonin is an antioxidant and it functions against oxidative stress in red blood cells and when its level is low, this will lead to an increase in MDA and decrease GSH [30]. So in this study when the patients get improved sleep, this gives an indication that melatonin level improved. Since melatonin has an antioxidant action, it may have decreases the MDA levels.

The CNS side effects like drowsiness and sleepiness, were the most frequent side effects appeared in the patients and they were more in amitriptyline group than in pregabalin group, that most of the patients in the amitriptyline group complained from drowsiness during all the day time and this was the main cause that made the patients in this group to drop out. For the pregabalin group, weakness was the most important side effect that the patients suffered from and was the main cause for the drop outs. Anticholinergic side effects which includes dry mouth and palpitation was shown only in amitriptyline group and no patients complained from these side effects in pregabalin group. Iraqi rheumatologist studied FM which is coexisting with other diseases like Al-Izzi. 2004 [31] have that FMS and widespread pain are more prevalent in patients with bowel disease than in the general population and While Al-Bidri, *et al*. 2009 [32], found a significant relationship between ischemic heart disease and FM in a prevalence of 18% and others.

CONCLUSION:

Amitriptyline was better than pregabalin concerning patient compliance and tolerability and this is clear from dropout rate, that it was 46.77% for pregabalin group, while for amitriptyline group 26.22%.

RECOMMENDATIONS:

1- Implementing the Wolfe criteria for diagnosis and assessment in rheumatology consultation clinics.

2- More investigation to be done to know the etiology of FMS.
3- Use the antioxidants in the future studies to see the effect of the oxidative state on the syndrome.
4- Using pregabalin in higher doses than that used in this trial like 300 or 450 mg to increase the patient response to treatment.
5- further investigations about the role of melatonin in FM pathophysiology.

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