

Adjuvant use of melatonin for treatment of fibromyalgia

Abstract: Fibromyalgia syndrome (FMS) is a chronic musculoskeletal disorder characterized by generalized muscular pain accompanied by fatigue and tenderness at specific anatomic sites called tender points. Although preliminary evidence indicates that melatonin may be effective in treating the pain associated with FMS, no definitive evidence supports this claim. This study was designed to evaluate the significance of using different doses of melatonin, alone or in combination with fluoxetine for the management of FMS. A double-blind, placebo-controlled clinical study was performed on 101 patients (95 women and 6 men) who fulfilled the criteria of the American College of Rheumatology (ACR) of FMS. The patients were randomized into four groups: group A (24 patients) treated with 20 mg/day fluoxetine alone; group B (27 patients) treated with melatonin 5 mg alone; group C (27 patients) treated with 20 mg fluoxetine plus 3 mg melatonin; group D (23 patients) treated with 20 mg fluoxetine plus 5 mg melatonin. Both drugs were given once daily in the morning and night time, respectively, for 8 wk. Each patient was clinically evaluated through direct interview with the patients using the Fibromyalgia Impact Questionnaire (FIQ) at zero time and after 8 wk. Using melatonin (3 mg or 5 mg/day) in combination with 20 mg/day fluoxetine resulted in significant reduction in both total and different components of FIQ score compared to the pretreatment values. In conclusion, administration of melatonin, alone or in a combination with fluoxetine, was effective in the treatment of patients with FMS.

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Introduction

Fibromyalgia syndrome (FMS) is characterized by chronic widespread debilitating musculoskeletal pain, increased pain sensitivity including allodynia and hyperalgesia and stiffness throughout the body [1]. In addition, patients with FMS complain of fatigue, sleep disturbances, anxiety, depression and lack of concentration, cognitive and memory dysfunction, often referred to as 'fibro fog' [2, 3]. The pathophysiology of FMS is related not to peripheral musculoskeletal changes, but to abnormalities of the central pain processing mechanisms [4] that result in central pain sensitization [5]. It has been reported that patients with FMS have a lower melatonin secretion during the hours of darkness than do healthy subjects; this may contribute to impaired sleep at night, fatigue during the day, and changed pain perception [6]. Melatonin, the pineal hormone with pleiotropic activity [7–10], has not been studied in a blinded fashion in reference to fibromyalgia; but a previous study did reveal that treatment of FMS patients with 3 mg melatonin daily for 30 days significantly improved the tender point count, severity of pain, global physical assessments, and sleep [11]. Moreover, in a limited number of cases, administration of 6 mg/day melatonin to patients with FMS resulted in normal sleep/wake cycles, normal diurnal activity, lack of pain, and fatigue and claims significant improvement of the behavioral symptoms including lack of depression [12]. This study was designed

to evaluate the clinical significance of using different doses of melatonin, alone or in combination with fluoxetine for the management of FMS.

Patient selection and methods

This randomized, double-blinded and placebo-controlled study was performed on 101 patients (6 men and 95 women) with age range of 18–65 (38.8 ± 11.2), early diagnosed as having primary fibromyalgia (FM) according to the American College of Rheumatology (ACR) criteria of FM symptoms [13], at the Rheumatology Consulting Clinic, Baghdad Teaching Hospital, Baghdad; the study protocol was approved by the scientific and ethic committee for clinical research there. All of the selected patients had no other marked pathologic disorders that may interfere with the outcome of the study protocol as revealed by the clinical investigation. Patients who were pregnant or breast-feeding were excluded. They were not on analgesic, anti-inflammatory drugs, or antioxidant therapy including aspirin. The patients were randomly allocated into four groups and treated as follows. Group A included 24 patients treated with 20 mg/day fluoxetine capsule (Cipla, Mumbai, India) and placebo formula containing lactose only. Group B included 27 patients treated with 5 mg/day melatonin capsules (Rupal Chemicals Ltd, Tarapur, India; specially formulated for this purpose) and placebo formula. Group C included 27 patients treated with 20 mg/day

fluoxetine capsules with 3 mg/day melatonin capsules. Group D included 23 patients treated with 20 mg/day fluoxetine with 5 mg/day melatonin. Fluoxetine capsules were administered as single daily dose in the morning, while melatonin capsules were administered as single daily dose at night time for 60 days. The four patients groups were matched for age, sex, and duration of complain; no significant differences among groups were reported concerning the baseline values of the studied parameters. Clinical evaluation of treatment outcome was performed using Fibromyalgia Impact Questionnaire (FIQ) score at baseline (before starting treatment) and after 60 days [14]. All results were expressed as mean ± SE. Analysis of variance (ANOVA) was used for comparison. Post hoc testing was carried by Student's *t*-test with log transformation. *P* < 0.05 was considered statistically significant.

Results

Before starting treatment (zero time), all patients with FMS demonstrated poor symptoms, which included pain, fatigue, altered sleep, stiffness, anxiety, depression, and reduced health-related quality of life (HRQOL), which consisted of physical impairment, feeling badly, missed work, and difficulty performing work; there was a high FIQ score in all groups which indicates severe or extreme symptoms of FMS (Table 1). Treatment with 20 mg fluoxetine alone (group A) resulted in significant reduction in the total FIQ score (21.5%) after 8 wk of treatment compared to pretreatment value, while significant improvement in total FIQ score was reported in patients treated with 5 mg melatonin alone (group B); this treatment caused 18.9% score reduction compared to pretreatment values. Also, treatment with different doses of melatonin (3 mg and 5 mg/day) in combination with 20 mg/day fluoxetine (groups C and D) resulted in comparable and highly significant reduction in total FIQ score (28.8% and 28.9%, respectively) compared to pretreatment values. All treatment approaches significantly improved the HRQOL after 8 wk (Table 2). The combination of 20 mg/day fluoxetine with both 3 and 5 mg of melatonin showed better improvement in the components of this score, revealed as 23.7% and 37% reduction in the score of physical impairment, 24.6% and 25% reduction in the score for feeling good, 29% and 23.8% reduction for work missed

Table 1. Effects of treatment with melatonin, fluoxetine, or their combination on total FIQ score in patients with fibromyalgia syndrome

Treatments	n	FIQ score Pretreatment	FIQ score Post-treatment
Fluoxetine (20 mg/day)	24	61.18 ± 3.15	48.0 ± 3.88*
Melatonin (5 mg/day)	27	60.42 ± 2.91	49.0 ± 3.38*
Fluoxetine (20 mg/day)	27	59.42 ± 1.20	42.33 ± 1.87**
Melatonin (3 mg/day)			
Fluoxetine (20 mg/day)	23	61.90 ± 1.67	44.0 ± 2.88**
Melatonin (5 mg/day)			

Each value represents Mean ± SEM; *significantly different (*P* < 0.05) compared to pretreatment value within the same group; **highly significant difference (*P* < 0.001) compared to pretreatment value within the same group.

Table 2. Effects of treatment with melatonin, fluoxetine, or their combination on health-related quality of life (HRQOL) parameters of FIQ score in patients with fibromyalgia syndrome

Treatment groups	Fluoxetine (20 mg/day) n = 24		Melatonin (5 mg/day) n = 27		Fluoxetine (20 mg/day) Melatonin (3 mg/day) n = 27		Fluoxetine (20 mg/day) Melatonin (5 mg/day) n = 23	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Physical improvement	6.6 ± 0.22	5.5 ± 0.27**	6.66 ± 0.31	6.25 ± 0.35	6.66 ± 0.26	5.08 ± 0.28**	4.9 ± 0.28	3.10 ± 0.23**
Feel good	6.0 ± 0.58	4.36 ± 0.54*	6.17 ± 0.67	5.58 ± 0.74**	6.5 ± 0.29	4.92 ± 0.34**	6.8 ± 0.25	5.1 ± 0.35**
Work missed	6.36 ± 0.39	4.27 ± 0.54**	6.25 ± 0.37	5.58 ± 0.51*	5.75 ± 0.43	4.08 ± 0.43**	6.7 ± 0.30	5.1 ± 0.46*
Doing work	6.73 ± 0.51	5.36 ± 0.53*	6.0 ± 0.62	5.08 ± 0.60*	7.08 ± 0.36	5.58 ± 0.45**	7.4 ± 0.27	5.7 ± 0.45**

Each value represents Mean ± SEM; n = number of patients; *significantly different (*P* < 0.05) compared to pretreatment value within the same group; **highly significant difference (*P* < 0.001) compared to pretreatment value within the same group.

Table 3. Effects of treatment with melatonin, fluoxetine, or their combination on symptoms parameters of FIQ score in patients with fibromyalgia syndrome

Treatment groups	Fluoxetine (20 mg/day) n = 24		Melatonin (5 mg/day) n = 27		Fluoxetine (20 mg/day) Melatonin (3 mg/day) n = 27		Fluoxetine (20 mg/day) Melatonin (5 mg/day) n = 23	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Pain	7.64 ± 0.36	6.55 ± 0.34**	8.33 ± 0.22	6.08 ± 0.36**	7.33 ± 0.4	5.33 ± 0.47**	7.7 ± 0.30	5.4 ± 0.37**
Fatigue	6.45 ± 0.61	5.81 ± 0.58	6.33 ± 0.4	4.83 ± 0.5*	5.75 ± 0.82	4.58 ± 0.87*	4.9 ± 0.99	3.2 ± 0.78*
Rest/sleep	7.09 ± 0.41	6.36 ± 0.45	8.25 ± 0.28	5.67 ± 0.36**	6.92 ± 0.36	4.42 ± 0.43**	7.5 ± 0.30	4.4 ± 0.30**
Stiffness	4.64 ± 0.98	3.55 ± 0.89*	4.33 ± 0.77	3.33 ± 0.73*	4.25 ± 0.64	2.67 ± 0.69**	3.6 ± 0.88	2.7 ± 0.84*
Anxiety	4.09 ± 1.02	3.36 ± 0.88	5.0 ± 0.86	4.42 ± 0.65	4.42 ± 0.72	3.0 ± 0.58**	5.1 ± 0.75	4.0 ± 0.67**
Depression	4.82 ± 1.05	3.64 ± 0.87*	2.83 ± 0.78	2.17 ± 0.72*	5.25 ± 0.6	3.17 ± 0.63**	5.2 ± 0.83	3.0 ± 0.65**

Each value represents Mean ± SEM; n = number of patients; *significantly different ($P < 0.05$) compared to pretreatment value within the same group; **highly significant difference ($P < 0.001$) compared to pretreatment value within the same group.

score, and 21% and 23% reduction in the score for doing work of the FIQ parameters (for groups C and D, respectively) compared to pretreatment values. Treatment with fluoxetine alone (group A) shows also a significant reduction in the previously mentioned HRQOL parameters (Table 2), where 16.7%, 23.7%, 32.9%, and 20.4% decrease reported in the scores of physical impairment, feel good, worked missed, and doing work, respectively. The effect of treatment with melatonin (group B) on the HRQOL parameters was lower compared to group A or when combination therapy was used (groups C and D), as revealed by 16.6%, 9.6%, 10.7%, and 15.3% decrease in the scores of physical impairment, feel good, work missed, and doing work, respectively, compared to pretreatment values. At zero time, all patients with FMS showed signs of poor management of their symptoms, revealed by high score according to FIQ rule, which includes parameters for pain, fatigue, sleep, morning stiffness, anxiety, and depression (Table 3). All treatment approaches significantly reduced the pain score, demonstrated by 14.3%, 27%, 27.3%, and 30% decrease in this score for all groups (A, B, C, and D, respectively) compared to pretreatment values. The fatigue score was significantly reduced as a result of treatment in groups B, C, and D (23.7%, 20.3%, and 34.7%, respectively). Group A treated with fluoxetine alone demonstrated only 9.9% decrease in fatigue score. Rest/sleep parameter was significantly improved in FMS patients treated with either melatonin alone or its combination with fluoxetine (groups B, C, and D), where 31.3%, 36%, and 41.3% decrease in this score was reported for these groups, respectively. Treatment with fluoxetine alone (group A) did not change the rest/sleep score (Table 3). Concerning the stiffness score, all treatments significantly improved the stiffness symptom and this effect was found to be comparable in all groups, revealed as 23.5%, 23.0%, 37.2%, and 25% decrease in that score for groups A, B, C, and D, respectively, compared to pretreatment values. For the anxiety parameter, Table 3 shows that using a combination of melatonin with fluoxetine (groups C and D) resulted in significant reduction in anxiety score compared to both fluoxetine alone and melatonin alone, as revealed by 47.3%, 21.6%, 17.8%, and 11.6% decrease in anxiety score for groups C, D, A, and B, respectively, compared to pretreatment values. Finally, patients treated with combination of melatonin and fluoxetine (groups C and D) showed highly significant improvement in depression symptoms (39.6% and 42.3% decrease in score, respectively) compared to those who are treated with either fluoxetine alone or melatonin alone (groups A and B), who demonstrated 24.5% and 23.3% decrease in depression score, respectively. Values for this score in all groups were significantly different from that reported for baseline values.

Discussion

Although various pharmacological approaches have been evaluated treating FMS, no single drug or group of drugs has proven to be useful in this respect [15].

This may be attributed to the complexity of this syndrome or to the difficulty in the measurements of

treatment outcome [16]. However, the FIQ has been used with acceptable level of success to assess the severity of chronic pain to determine the impact of FMS on every day life activities and disability, as well as the therapeutic outcome of drugs used for the management of pain in patients with FMS [17]. In the present study, the use of fluoxetine alone produced significant improvement in the FIQ score, which is consistent with data previously reported by others. Arnold et al. [18] showed that fluoxetine was effective on most outcomes of FIQ scores and generally well tolerated when used for 12 wk. Moreover, Wolfe et al. [19] reported that treating FMS patients with 20 mg/day fluoxetine for 6 wk did not produce significant improvement in the primary outcome measures compared to placebo and stated that higher doses and/or longer duration might result in different outcomes. Treatment of FMS patients with fluoxetine alone significantly improved HRQOL parameters of FIQ compared to other groups, while the effect on the pain score was lower than that reported in other groups. This is in accordance with the findings reported by Goldenberg et al. [20], where the serotonergic activity alone was found not sufficient to affect analgesia in the chronic pain compared to the effects of other antidepressants. This may be attributed to the fact that SSRIs are generally less effective on these parameters, because of their delayed clinical response [21]. Patients treated with fluoxetine showed better response in terms of their stiffness, anxiety, and depression parameters with comparable effect on other parameters like sleep and fatigue; this finding is like that reported by others, where a positive effect was reported for fluoxetine compared to either placebo or amitriptyline in treating sleep, pain, fatigue, and depression [21]. Overall, there was strong evidence for reduction of pain, fatigue and depressed mood, improved sleep and HRQOL with the use of antidepressants; however, SSRIs found to have the lowest effect for reducing pain and sleep disturbances compared to other classes of antidepressants [22]. Although there are many conflicting data in the clinical trails that deal with assessment of the analgesic activity of fluoxetine in FMS, it may be useful owing to its ability to elevate serotonin levels in the neuronal synapses; this is associated with improvement in mood control, regulation of sleep and cognitive function in patients with FMS [23]. Many clinical studies showed that most patients with FMS complain of sleep disturbance, fatigue, and pain; these symptoms might be a consequence of defects in melatonin secretion [6]. Moreover, serum levels of melatonin precursors (tryptophan and serotonin) were reported to be low in patients with FMS affecting both sleep and pain perception [24]. In the present study, the use of melatonin as single treatment for patients with FMS significantly improved the total FIQ scores. This result was found comparable to that reported by Citera et al. [11] who reported that treatment with 3 mg of melatonin at bed time produced significant improvement in the pain score, measured by Visual Analog Scale, and sleep parameters were the mostly affected parameters compared to other variables, but without reaching significant level. Also, the results of another clinical trail indicated that using 6 mg/day melatonin at night for 30 days showed that all included patients with FMS developed a relatively normal sleep/wake cycle,

which accompanied by significant reduction in pain and improvement of behavioral symptoms [25]. This finding highlights the importance of long-term use of effective doses of melatonin for the management of patients with FMS. Although the alteration in the neurotransmitters level in the CNS and/or melatonin rhythm in FMS is not completely known, the successful use of melatonin in this respect may be related to normalization of neurotransmitters and influence the hypothalamo-pituitary-adrenal axis [26]. According to the current evaluation of the literature, there are no other studies (in addition to the current one) that focus on using combination of melatonin with fluoxetine; therefore, these findings draw attention to the expected synergism or enhancement of the activity of SSRIs in FMS, where the results clearly showed such pattern of activity for melatonin.

The amount of data obtained from randomized controlled trials in FMS treatment has increased steadily over past decade; yet treatment remains inadequate to resolve the syndrome in most patients. Such outcomes may be attributed to the complex interplay between pain, sleep disturbances, and depression, the most characteristic symptoms of FMS [24]. Results obtained from clinical trails regarding the analgesic activity of SSRIs are disappointing and conflicting and indicate that they are not superior in this respect [27]. Thus, adjunct use of melatonin with SSRIs for the management of FMS seems to be reasonable based on the pharmacological properties of the former. Sleep disturbances have been reported in 60–90% of patients with FMS, and whether this is a primary or secondary problem related to pain is not clearly defined [28]. Some sleep problems of FMS may be linked to the levels of signaling chemicals that regulate sleep and awaking cycle such as serotonin and melatonin, which are found to be low in previous clinical studies [25, 29]. Accordingly, based on the previously mentioned evidence, the use of melatonin in FMS may be considered a valuable means for targeting the pathophysiologic mechanism behind the disorder. Recently, melatonin was suggested to play a regulatory role in pain sensitivity owing to presence of opioid fibers in the pineal gland [30]. Although melatonin is approved as a sleep aid, it has a variety of other beneficial effects that may account for its potential role in the treatment of fibromyalgia. Improving sleep and rest and decreasing anxiety derived from sleeplessness may be related to normalization of the neurotransmitters rhythms in patients with FMS. Thus, the use of melatonin as adjuvant therapy with the currently approved medication (e.g., SSRIs) may be the right pharmacological approach for the management of patients with FMS [25]. Moreover, considering the oxidative damage associated with this syndrome by using powerful antioxidant like melatonin [31–33] may improve the outcome in the practice of treating FMS [34]. In conclusion, adjuvant use of melatonin with fluoxetine improves the clinical picture of patients with FMS.

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