Review Article

Melatonin an Emerging Management against Fibromyalgia

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Abstract

Fibromyalgia is a complex and common musculoskeletal syndrome characterized by chronic and widespread pain and other associated somatic and psychological symptoms that significantly compromise quality of life. In last years, various pathogenetic hypotheses have been described, including the role of inflammation and oxidative stress in the development of this syndrome. To date, there are many, but not resolutely pharmacological approaches, like antidepressants, which are not fully effective against the wide spectrum of fibromyalgic symptoms and, unfortunately, they are associated to many side effects. Among emerging strategies evaluated to counteract fibromyalgia, melatonin has been shown to be suitable and useful in its management because of its numerous and multiple properties.

In this review, we present a brief overview of the emerging potentiality of melatonin in the management of fibromyalgia, reporting the few clinical trials in which melatonin was tested and presenting a possible melatonin mechanism of action against fibromyalgia musculoskeletal alterations in vivo.

ABBREVIATIONS

FM: Fibromyalgia; ROS: Reactive Oxygen Species; RIM: Reserpine-Induced Myalgia; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; ROR/RZR: Retinoid Orphan Receptors/Retinoid Z Receptors; FIQ: Fibromyalgia Impact Questionnaire

INTRODUCTION

Fibromyalgia (FM) is a complex musculoskeletal syndrome characterized by chronic and widespread pain [1,2], fatigue, tenderness (generalized allodynia/hyperalgesia) and functional symptoms, like sleep disorders, depression, cognitive impairment and psychological distress [3-6]. This disease is one of the most common pathological state seen in the primary health care [3,7] and, in particular, FM is the second most common condition among the rheumatic disorders, after osteoarthritis [3]. FM mainly affects young women; in fact the ratio of female to male is 9:1 [8]. In addition, there is a difference in prevalence between urban (0.69 and 14.4%) and rural areas (0.1 and 5.2%) [9,10]. These findings underlined that socio-economic and cultural factors influence the development of this syndrome [11] (Figure 1). It is important to point out that FM patients consistently score very low in quality of life compared to other chronic conditions, such as rheumatoid arthritis, osteoarthritis and chronic obstructive pulmonary disease [3]. In fact, they report also difficulties with several daily life activities, such as climbing stairs and walking two blocks [3,12]. FM often coexists with and has a tendency to mimic other illness, like rheumatic and autoimmune diseases [13-15] (Table 1), and so it is still an underdiagnosed and disabling condition [16,17].

Despite significant evolvements in the understanding of its pathophysiology and its epidemiological relevance, the etiology of FM is still unknown [18-20]. To date, FM represents a significant medical and socio-economic burden, particularly because the pathognomonic chronic pain is connected to FM often leads to early retirement and important psychological disorders [21,22].

TREATMENT OF FIBROMYALGIA

Since FM’s etiology and pathogenesis are still unknown, actually there are many, but not resolutely, pharmacological approaches [23] and various, but contradictory, guidelines employed in the FM management [24]. Chronic pain and depression characterize FM, so antidepressant drugs, like tricyclic, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, or anticonvulsants, as pregabalin, have traditionally been used to treat this syndrome [25-27]. Even if clinical trials reported that antidepressants significantly improved pain, fatigue, depressed mood, sleep disturbance and health-related quality of life [28-30], there is...
no evidence that these treatments maintain the benefits for long term (Table 2). In addition, among the most widely used drugs against FM, there are also opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle-relaxing medications [22,31], but actually there are no conclusive demonstrations that these drugs are significantly beneficial for pain reduction or any other outcome in FM [32].

The treatment of FM is complex, involving both pharmacological and non-pharmacological approaches, including regular physical exercise and cognitive behaviour therapy [33,34] (Table 3). Nevertheless, the available options display limited effects being related to adverse reactions, which compromise further the life quality of patients [15,35]. The 40% - 60% of patients do not respond well to drug therapy, so the efficacy of currently used pharmacological interventions for the management of FM remains disappointingly low [31,36]. FM patients tend to be extremely sensitive to medication side effects and all interventions must be initiated gradually and at low doses [15]. Furthermore, it is important to discuss the pros and cons of pharmacological treatment(s) with FM patients before starting, in order to adjust expectation and, in many cases, the possibility of adhering to a non-pharmacological treatment plan may be the best course [21,37].

In summary, none of the currently available drugs are fully effective against the whole and complex spectrum of symptoms of this syndrome and so FM continues to pose a significant and challenging problem with far reaching consequences regarding quality of life as well as significant socio-economic cost. There is an urgent need of "alternative" therapies; in fact, a current approach is to develop new biological compounds that counteract FM symptoms with enhanced efficacy and minimal side effects [31,38].

Due to recent evidences suggest the involvement also of oxidative stress in the pathogenesis of FM, antioxidants supplementation may be evaluated in its management [39-41]. In fact, it is known that antioxidants preserve organism from oxidative stress-related damage (that includes lipid and protein peroxidation and DNA fragmentation) by detoxifying from reactive oxygen species (ROS) [42]. To confirm the role of oxidative stress in this syndrome, previous studies have demonstrated the effectiveness in the FM management of antioxidants supplementation, like coenzyme Q10 [42], vitamins (like vitamin B12 and D) [43,44], polyphenols [39] and melatonin [45-47]. Among the emerging strategies, melatonin has been shown to be suitable and useful in the management of FM because of its numerous and multiple properties [47-51]. In this review, we present a brief overview of the emerging potentiality of melatonin in the management of FM, reporting the few clinical trials and experimental studies in which this molecule was tested and presenting its possible mechanisms of action against FM musculoskeletal alterations in vivo.
MELATONIN: A MULTITASKING MOLECULE

Melatonin is a small indoleamine synthesized from tryptophan and secreted in the blood stream by the pineal gland [52]. Furthermore, many extrapineal organs have been identified in vertebrates as sites of melatonin production, such as skeletal muscle, gastrointestinal tract, immune system cells, retina, spleen, liver, kidney and heart [47,53-55].

One of the most unique features of melatonin is its circadian rhythm in vertebrates, with its secretory peak at night and low levels during the day [56,57]. The primary function of melatonin was act as the free radical scavenger, this function is consistent with the existence of melatonin in primitive photosynthetic bacteria. During evolution, the genes for melatonin synthesis of these bacteria were horizontally transferred to other species [58]. However, in vertebrates melatonin is involved in a variety of mechanisms that modulate the physiology and molecular biology of cells, tissues and organs. Melatonin in fact has been linked to a wide range of functions including anti-inflammation, antioxidant, analgesic, oncostatic, circadian rhythm regulation, etc. [46-47,50-58].

As an antioxidant, melatonin has several unique features differing from those of classic antioxidants. These include the cascade pathway for scavenging numerous free radicals and its inducible capacity under stressful conditions. Melatonin, due to its secondary and tertiary metabolites, is able to neutralize numerous toxic oxygen derivatives, in detail, one melatonin molecule has the capacity to scavenge up to ten ROS respect to the classic antioxidants that scavenge one or less ROS [58].

Melatonin exerts its multiple effects binding with high affinity G-protein coupled seven transmembrane receptors, known as MT1 and MT2 [60,61]. These receptors are localized in different areas of the brain, such as hypothalamus, particularly in suprachiasmatic nucleus [62], thalamus [63] and retina [64]. MT1 and MT2 have also been found in bone marrow [65] and skeletal muscle [53], suggesting that melatonin has ubiquitous and fundamental functions. Recently, it has been found that melatonin also binds to MT3 receptor that is a quinone reductase II enzyme and it is actually not found in human [51,66]. In fact, its highest levels are found in liver and kidney and a moderate amount in heart, adipose tissue and brain of hamster [67] and it is also expressed in retina of rabbit [68]. Finally, melatonin carries out some of its activities binding nuclear receptors, defined retinoid orphan receptors/retnoid Z receptors (ROR/RZR) [67,69]. The subfamilies that bind melatonin include: RZRα, RORα, RORα2 and RZRβ [67,70-71]. The structure of the nuclear receptors consists of an N-terminal domain, a DNA binding domain that contains a zinc double finger, a hinge region and a ligand-binding domain included in the C-terminal [67,69,72]. The nuclear receptors may be differentially distributed among tissues (like adipose tissue, skin, testes, cartilage, liver and muscle) [51], but they are best functionally described in the immune system [51,73], where they regulate the generation of Th17 and Treg cells, key elements in the control of the adaptive immunity [73,74]. The potential role of pineal gland dysfunction in FM has been speculated in the past [75,76] and reports on the levels of circulating melatonin in FM patients have yielded highly variable results [49,77], ranging from decreased [76] to increased [78]. However, the “normal” rhythm of melatonin secretion seems disturbed in patients with FM. Therefore, many of the symptoms associated to FM are similar to those observed in individuals whose circadian peacemaker is altered and the increase of cyclic alternating pattern rate indicates a worst quality of sleep in patients with FM that, in turn, strongly correlated to severity of FM symptoms [77]. It is known that melatonin has used as analgesic [79,80], anxiolytic [81,82], neuroprotector in neurodegenerative conditions, like Alzheimer and multiple sclerosis [83], anti-inflammatory [84,85] and antioxidant [51,58,86-87]. It has also been demonstrated that this indoleamine has an important role in metabolic diseases: it reduces obesity [88-90] and it is a potential therapy in type II diabetes mellitus [91,92]. In particular, due to its analgesic,

| Table 2: Schematic view of pros and cons of traditional drugs used to counteract fibromyalgia. |
|-----------------|-----------------|-----------------|-----------------|
| **DRUG**        | **PROS**         | **CONS**        |
| Amitriptyline   | - evaluated in 17 trials, many of them placebo-controlled  
                 | - improves pain, sleep disorders  
                 | - at this low dose (25 mg), it has no substantial adverse effects  | - no evidence to support the efficacy of amitriptyline at higher doses or for periods >8 weeks |
| Duloxetine and Minapram | - FDA-approved drugs for FM  
                     | - multiple placebo trials showed an improvement in pain, depressive symptoms and QoL | - adverse effects: nausea, headache, constipation, dry mouth  
                     |                                | - effective only in about 40% of FM patients (no effect in fatigue and sleep disturbances) |
| Fluoxetine, Paroxetine and Sertraline | - improvements in pain, fatigue, depression, and overall symptomatology, but only for larger than standard dosing (80 mg) | - few clinical trial  
                             |                                | - no superior to placebo in treating FM symptoms |

**Table 3: Different anti-fibromyalgia approaches: pharmacological vs “alternative” treatments.**

<table>
<thead>
<tr>
<th>Pharmacological Treatments</th>
<th>Non-pharmacological treatments</th>
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| - tricyclic antidepressants  
- serotoninerg-norepinephrine reuptake inhibitors  
- anticonvulsive drugs  
- opioids | - aerobic exercise and resistance or flexibility training  
- mind and body therapy (ex. tai chi)  
- massage therapy  
- acupuncture |

*Abbreviations: FDA: Food and Drug Administration; QoL: Quality of Life; FM: Fibromyalgia.*
Taking into account the anti-inflammatory and antioxidant effects, melatonin has been proposed in FM management [45-46,48-49]. In fact, it increases the inhibitory endogenous pain-modulating system that is altered in FM patients [93]. Melatonin is also able to prevent the onset of inflammation by limiting the production of pro-inflammatory cytokines [51,94]. Moreover, melatonin neutralizes free radicals and indirectly stimulates the expression of endogenous antioxidants [47,86-87], counteracting the oxidative stress.

**FIBROMYALGIA AND MELATONIN: CLINICAL AND EXPERIMENTAL STUDIES**

To date, there are few clinical trials evaluating and confirming the role of melatonin in the management of FM. de Zanette and colleagues [46] demonstrated in a randomized, double dummy, placebo-controlled study that melatonin alone (10 mg) or in combination with amitriptyline (25 mg) for six weeks is more efficient than amitriptyline alone in reducing pain, morning stiffness, and sleep disorders in 63 FM patients (Figure 2). Furthermore, the authors reported also minor (nausea, mild dizziness, weight gain, dry mouth, and mild headache) and major (severe dizziness, vivid nightmares, crippling drowsiness, severe headache, behavioral changes, and pain worsening) side effects observed during the different treatments. In the amitriptyline group, 38.09% of patients presented minor side effects and 23.8% of patients presented major side effects. In the melatonin group, 23.8% of patients presented minor side effects and 23.8% of patients reported major side effects. The association of melatonin with amitriptyline resulted in 14% of patients experiencing minor side effects and 28.57% of patients presented major side effects. The association of melatonin with amitriptyline resulted in 14% of patients experiencing minor side effects and 28.57% of patients presented major side effects. The comparisons in the incidence of minor side effects between the amitriptyline and the melatonin plus amitriptyline groups was statistically significant. However, neither the incidence of minor side effects nor the incidence of major side effects was significant when the groups were compared [46]. Citera et al. [45], recruited, in an open pilot study of 4 weeks’ duration, 21 female FM patients with a mean age of 51 years and mean duration of disease of 24 months. After a one week of washout, 3 mg of melatonin were administered daily to each patient 30 minutes before the expected sleeping time. Remarkably, at the end of the melatonin treatment, the tender point count and severity of pain as well as patient and physician global assessments were significantly improved. Even if one patient withdrew because of the mild adverse effect (migraine) and another was lost to follow-up. In the patient with migraine, the symptom was of moderate intensity and it was presumed to be related to the study drug because of a positive dechallenge and rechallenge test. Furthermore, during the study period four patients reported adverse events, but they were all transient and mild (heartburn, tremor, anxiety, and somnolence). These preliminary results suggest that melatonin can be an alternative and safe treatment for patients with FM.

Hussain et al. [95], performed a randomized, double-blind and placebo-controlled study involving 101 FM patients (6 men and 95 women) with age range of 18-65 years. The patients were randomly divided into four groups: 1) 24 patients treated with 20 mg/day fluoxetine capsule and placebo formula containing lactose only; 2) 27 patients treated with 5 mg/day melatonin capsules and placebo formula; 3) 27 patients treated with 20 mg/day fluoxetine capsules with 3 mg/day melatonin capsules and 4) 23 patients treated with 20 mg/day fluoxetine with 5 mg/day melatonin. In particular, during this clinical trial fluoxetine capsules were administered as single daily dose in the morning, while melatonin capsules were administered as single daily dose at night time for 8 weeks. Each FM patient was clinically evaluated through direct interview using the Fibromyalgia Impact Questionnaire (FIQ) baseline and after 8 weeks of treatments. Melatonin (3 mg or 5 mg/day) in combination with 20 mg/day fluoxetine induced a significant reduction in both total and different parameters of FIQ score compared to the pre-treatment values. So, Hussain and colleagues [95] concluded that administration of melatonin was effective in the treatment of patients with FM. The use of melatonin as adjuvant therapy with the currently approved medication may be the right approach for the management of FM patients.

Other clinical trials focused their attention on improving the FM clinical picture using agomelatine. Agomelatine is a...
novel antidepressant with a unique pharmacology among licensed antidepressant drugs that act through a combination of antagonist activity at serotonin 5-HT$_{2C}$ receptors and agonist activity at melatonergic MT1/MT2 receptors [96]. Calandre et al., [97], conducted a pilot study of 12 weeks involving 23 patients with FM and depressive symptomatology that received daily agomelatine. The Authors interestingly observed that agomelatine significantly improved depression, global FM severity and pain intensity; however, no improvement was seen in sleep quality. Remarkably, agomelatine therapy was well tolerated and only 5% of patients reported mild and transient side effects. In detail, the most frequently side effects reported were dizziness (39%), fatigue (17%), nausea and/or vomiting (13%) and insomnia (13%).
Furthermore, another open-label, preliminary study, evaluated the efficacy and safety of agomelatine for the treatment of FM. It was conducted by Bruno and colleagues [98] who recruited 50 female FM patients (aged 20 to 65 years). Agomelatine was administered at a single daily dose of 25 mg/day for 12 weeks. In detail, 20 patients out of whole sample completed the study and, interestingly, was observed a significant improvement in pain symptoms. However, regarding cognitive/executive functions was not detected a significant improvement, but should be noted a general tendency to a better performance of the patients, in particular in the maintenance of attention during interfering stimuli. Furthermore, the administration of agomelatine was generally well tolerated; only 1 patient (6.6%) presented adverse effects due to the treatment (headache), which regressed after agomelatine suspension. In fact, due to its peculiar pharmacological profile, agomelatine does not induce common adverse events as other classes of antidepressants (like gastrointestinal disorders, weight gain, insomnia, and withdrawal syndrome treatment). As Bruno et al., [98], declared, this study offered evidence of a potential new treatment strategy in FM patients, but showed also several limitations: the sample size is small, even for an open-label trial, the observational period is short and the lack of control group impairs the results obtained. All the reported clinical trials demonstrated important potentiality of melatonin efficacy in the management of this painful and debilitating condition, but are required multicentre, crossover trials involving a larger number of FM patients diagnosed by rigorous criteria and with a careful objective evaluation of the symptoms. As reported previously, FM causes multiple symptoms, including depression, anxiety and cognitive dysfunction [5,6] and these concomitant psychological disorders have a negative impact on the clinical outcome of FM. Furthermore, antidepressants are frequently used drugs to treat FM patients [25,26]. In detail, some of the reported clinical studies evaluated also the correlation between melatonin treatment and depression, sometimes in combination with anti-depressive treatment. de Zanette et al., [46], evaluated also the FM patient’s perceptions of mood, anxiety and depression and observed that the antidepressant amitriptyline treatment associated with melatonin improved FM symptoms. Citera and colleagues [45], besides sleep disturbances and fatigue, evaluated also depression symptoms observing, after one week melatonin treatment, that depression and anxiety perceptions were reduced in FM patients. Finally, Hussain et al., [95], evaluated baseline anxiety and depression and observed that all FM patients involved in the study showed signs of poor management of also these symptoms. Patients treated with combination of melatonin and fluoxetine showed highly significant improvement in depression symptoms compared to those who are treated with either fluoxetine alone or melatonin alone, who demonstrated 24.5% and 23.3% decrease in depression score, respectively. Patients treated with fluoxetine showed a better response in terms of stiffness, anxiety and depression parameters with comparable effect on other parameters like sleep alteration and fatigue; this finding is in agreement with previous data that reported a positive effect for fluoxetine compared to either placebo or amitriptyline in treating sleep, pain, fatigue and depression [99]. Although, actually, there are many conflicting data in the clinical trials concerning fluoxetine treatment in FM management. In conclusion, melatonin may have important functions also in combination with anti-depressive drugs in the management of FM correlated symptoms due to its anti-inflammatory, antioxidant, antinociceptive and anxiolytic properties [100]. However, the use of melatonin in combination with currently used anti-depressive drugs requires additional investigations. Actually, there are few studies in literature that used in vivo model to understand the etiopathogenesis of FM and to confirm the potential beneficial effects of melatonin. Nagakura and colleagues [101] established a FM animal model by using reserpine, a monoamine depleting agent, which irreversibly and non-selectively blocks the vesicular monoamine transporters [102,103] and reproduces the symptoms of FM. In fact, subcutaneous injection of reserpine causes widespread pain, long-lasting muscular mechanical hyperalgesia and tactile allodynia in rats. Animal treated with reserpine presented also an increase in immobility time during forced swim test and an aversion to eating, which are indicative of depression [18,104]. In addition, Klein and co-workers [105] demonstrated that repeated injections of reserpine produced an increase of ROS in central nervous system, confirming the role of oxidative stress in FM. Furthermore, Nade et al., [106], reported that reserpine increased lipid peroxidation and reduced the levels of endogenous antioxidant enzymes, like catalase, superoxide dismutase and glutathione, as documented in FM patients also by Bagis and co-workers [107]. Recently, our research group used this reserpine-induced myalgia (RIM) model to obtain data about the FM-related musculoskeletal damages and the effectiveness of melatonin against FM syndrome [48]. According with Nagakura and colleagues [101,108], we observed that RIM exhibited a significant reduction in spontaneous motor activity, measured using running wheel, that is a motor test in which the locomotion is not forced and potentially reflects whether the activity is painful [109]. The RIM model presented also, at skeletal muscle level, a significant rise of inflammasome NLRP3, a prominent marker of ROS generation and inflammation processes [110], and a reduction of expression of endogenous antioxidant enzymes and of constitutive molecules involved in inflammation, oxidative stress and myogeneses (cyclooxygenase-1 and sirtuin3) [48]. Furthermore, our research group demonstrated that melatonin administration has important beneficial effects against the alterations induced by FM pathogenesis in vivo. In particular, melatonin improved the voluntary motor activity, reduced skeletal muscle atrophy, increased expression of superoxide dismutase, catalase, cyclooxygenase-1 and sirtuin3 through the inhibition of the NLRP3 dependent mechanisms, as summarized in (Figure 3). In summary, we suggested that melatonin via its important inhibiting effect against inflammasome NLRP3 activation, together with its known antioxidant, anti-inflammatory and analgesic properties, counteracts FM pathological processes. Experimental researches that characterize the molecular and biological contributors of FM symptoms may offer new therapeutic targets and new classes of medications. At this aim, further studies on this topic are mandatory to better assess the potential melatonin mechanism(s) of action.

**DISCUSSION & CONCLUSION**

FM is a disabling and common condition characterized by a wide spectrum of symptoms [1]. The underlying pathophysiology of FM is still poorly understood [111]. Many studies point out the
role of central sensitization that leads to the dysregulation of the nociceptive system, and so to widespread pain, that is the most representative symptom of FM [2]. The etiology of FM is unclear and the treatment is often unsatisfactory [109]. Traditionally, antidepressant and anticonvulsant drugs have been used to treat FM patients [25], but many clinical trials showed that 40%-60% of patients do not respond well to these therapies [31]. For these reasons, there is a need of a new approach: the possible link between FM and oxidative stress [112,113] presents a logical proposal that antioxidants supplementation may be evaluated in the FM management [114]. It is known that melatonin has antioxidant and also anti-inflammatory properties [47]. For this, it has been proposed in FM management, in fact, recent clinical trials showed that melatonin is more efficient than traditional drugs in reducing FM symptoms [46]. Despite this, clinical trials performed up today are no sufficient and they involved a small sample size [98]; in addition there are few studies that used in vivo model to confirm the potential beneficial effects of melatonin in FM syndrome [48,101] (Figure 4). Schematically summarized the reported clinical and experimental studies. Confirming the beneficial roles of melatonin/agomelatine in the management of FM. Further clinical and experimental studies are needed to better understand the melatonin efficiency and mechanism(s) of action in this syndrome.

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