SciMedCentral

JSM Arthritis

Review Article

Melatonin an Emerging Management against Fibromyalgia

Trapletti V[1], Favero G[1], Bonomini F[1,2], Rodella L.F[1,2] and Rezzani R[1,2]*

[1]Department of Clinical and Experimental Sciences, University of Brescia, Italy
[2]Interdipartimental University Center of Research "Adaption and Regeneration of Tissues and Organs- (ARTO)", University of Brescia, Italy

*Corresponding author
Rita Rezzani, Anatomy and Physiopathology Division, Department of Clinical and Experimental Sciences, University of Brescia, Italy, Phone: +390303717483; Fax: +390303717486; Email: rita.rezzani@unibs.it

Submitted: 16 August 2017

Accepted: 18 September 2017

Published: 20 September 2017

ISSN: 2475-9155

Keywords

- Fibromyalgia
- Melatonin
- Oxidative stress

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 up 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

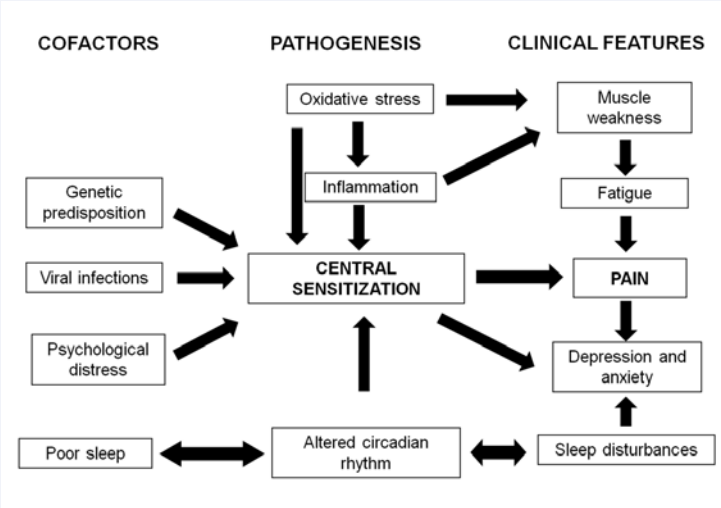

Figure 1 Schematic representation of fibromyalgic etiopathogenetic. Fibromyalgia is a chronic pain condition correlated mainly with central sensitization.

Table 1: The most common rheumatic and autoimmune diseases that coexist with fibromyalgia syndrome.

DISEASE	COMMON SYMPTOMS	DIFFERENTIAL DIAGNOSIS	FREQUENCE OF OVERLAP
Rheumatoid Arthritis	Widespread pain, myalgia, fatigue	Joint erosion and destruction	25%
Systemic Lupus Erythematosus	Musculoskeletal pain, fatigue, stiffness, vasospasm, cognitive dysfunction, depression	Organ system involvement, malar rush, neurological signs	30%
Sjogren Syndrome	Pain, fatigue, depression, sicca symptoms	Schirmer and Saxon's test, salivary gland biopsies	45-55%
Autoimmune Thyroiditis	Profound fatigue, muscle weakness and general achiness, cold intolerance, depression	Thyroid antibodies	37%

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 managements 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 Q_{10} [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*.

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 Minacipram	• 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

Abbreviations: FDA: Food and Drug Administration; QoL: Quality of Life; FM: Fibromyalgia

Table 3: Different anti-fibromyalgic approaches: pharmacological vs "alternative" treatments.

Pharmacological Treatments	Non-pharmacological treatments
• tricyclic antidepressants • serotoninergic-norepinephrine reuptake inhibitors • anticonvulsive drugs • opioids	• aerobic exercise and resistence or flexibility training • mind and body therapy (ex. tai chi) • massage therapy • acupuncture

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. [46-47,50-51,59].

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/retinoid 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,

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]. It is also able to prevent the onset of inflammation by limiting the production of pro-inflammatory cytokines [51,94]. In addition, 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 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 during the 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-blinded 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 focalized their attention on improving the FM clinical picture using agomelatine. Agomelatine is a

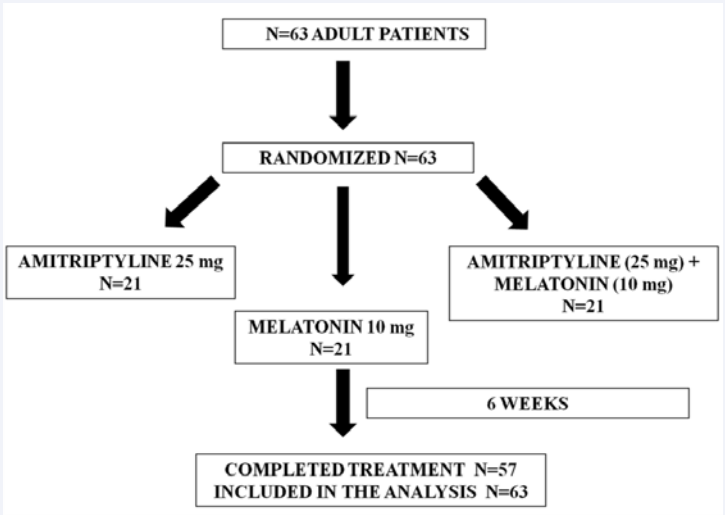

Figure 2 Schematic representation of the clinical trial performed by de Zanette and colleagues [46].

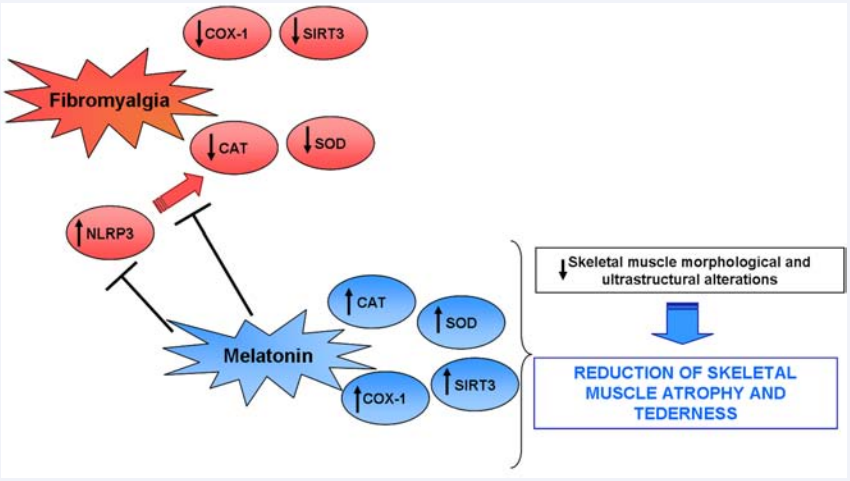

Figure 3 Schematic representation of a potential mechanism by which melatonin counteract the muscoloskeltal fibromyalgic-related alterations through the block of NLRP3 activation. CAT: catalase; COX-1: cyclooxygenase-1; SIRT3: sirtuin3 and SOD: superoxide dismutase.

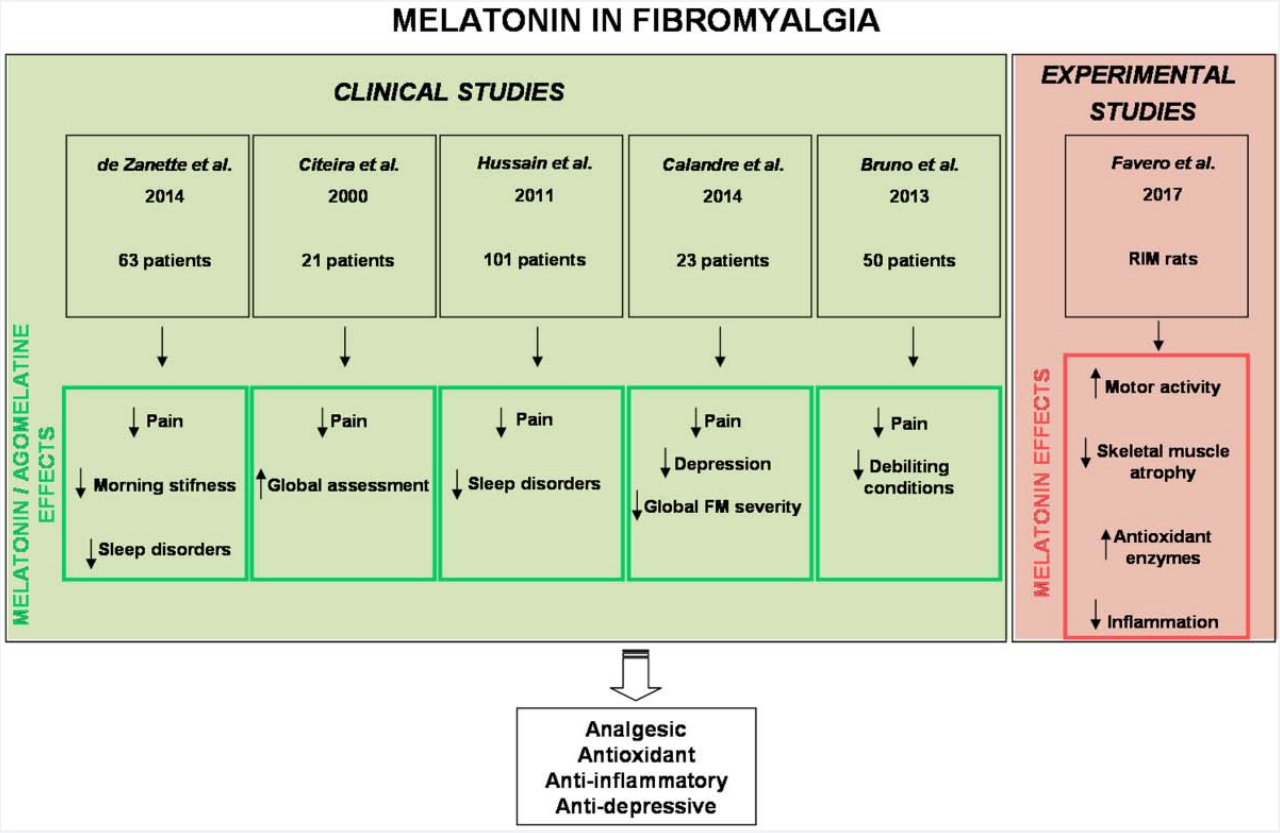

Figure 4 Schematic representation of the reported clinical and experimental studies, confirming the beneficial roles of melatonin/agomelatine in the management of FM.

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 studied 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 (cyclooxigenase-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, ant-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 these reasons, 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.

REFERENCES

1. Bazzichi L, Sernissi F, Consensi A, Giacomelli C, Sarzi-Puttini P. Fibromyalgia: a critical digest of the recent literature. Clin Exp Rheumatol. 2011; 29: 1-11.
2. Lee KH, Kim CH, Shin HC, Sung EJ. Clinical characteristics of patients with medically unexplained chronic widespread pain: a primary care center study. Korean J Fam Med. 2011; 32: 277-284.
3. Christidis N, Ghafouri B, Larsson A, Palstam A, Mannerkorpi K, Bileviciute-Ljungar I, et al. Comparison of the levels of pro-inflammatory cytokines released in the vastus lateralis muscle of patients with fibromyalgia and healthy controls during contractions of the quadriceps muscle--A microdialysis study. PLoS One. 2015; 10: 143856.
4. Flodin P, Martinsen S, Löfgren M, Bileviciute-Ljungar I, Kosek E, Fransson P. Fibromyalgia is associated with decreased connectivity between pain- and sensorimotor brain areas. Brain Connect. 2014; 4: 587-594.
5. Pérez de Heredia-Torres M, Huertas-Hoyas E, Máximo-Bocanegra N, Palacios-Ceña D, Fernández-De-Las-Peñas C. Cognitive performance in women with fibromyalgia: A case-control study. Aust Occup Ther J. 2016; 63: 329-337.
6. Steiner J, Bigatti S, Slaven J, Ang D. (506) The complex relationship between pain intensity and physical functioning in fibromyalgia: the mediating role of depression. J Pain. 2016; 17: 101.
7. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014; 311: 1547-1555.
8. Schweiger V, Del Balzo G, Raniero D, De Leo D, Martini A, Sarzi-Puttini P, et al. Current trends in disability claims due to fibromyalgia syndrome. Clin Exp Rheumatol. 2017; 35: 119-126.
9. Marques AP, Santo AS, Berssaneti AA, Matsutani LA, Yuan SL. Prevalence of fibromyalgia: literature review update. Rev Bras Reumatol. 2016; 57: 356-363.
10. Turhanoglu AD, Yilmaz S, Kaya S, Dursun M, Kararmaz A, Saka G. The epidemiological aspects of fibromyalgia syndrome in adults living in turkey: A population based study. J Musculoskelet Pain 2008; 16: 141-147.
11. Macfarlane GJ, Barnish MS, Pathan E, Martin KR, Haywood KL, Siebert S, et al. The co-occurrence and characteristics of patients with axial spondyloarthritis who meet criteria for fibromyalgia: Results from a UK national register (BSRBR-AS). Arthritis Rheumatol. 2017.
12. Macfarlane GJ, Barnish MS, Pathan E, Martin KR, Haywood KL, Siebert S, et al. The co-occurrence and characteristics of patients with axial spondyloarthritis who meet criteria for fibromyalgia: Results from a UK national register (BSRBR-AS). Arthritis Rheumatol. 2017.
13. Cabo-Meseguer A, Cerdá-Olmedo G, Trillo-Mata JL. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. Med Clin (Barc). 2017.
14. Atzeni F, Cazzola M, Benucci M, Di Franco M, Salaffi F, Sarzi-Puttini P. Chronic widespread pain in the spectrum of rheumatological diseases. Best Pract Res Clin Rheumatol. 2011; 25: 165-171.
15. Di Franco M, Guzzo MP, Spinelli FR, Atzeni F, Sarzi-Puttini P, Conti F, et al. Pain and systemic lupus erythematosus. Reumatismo. 2014; 66: 33-38.
16. Klein CP, Sperotto ND, Maciel IS, Leite CE, Souza AH, Campos MM. Effects of D-series resolvins on behavioral and neurochemical changes in a fibromyalgia-like model in mice. Neuropharmacology. 2014; 86: 57-66.
17. Eichenberger C, Dudler J, Marion-Veyron R, Gonthier A, Cornuz J, Favrat B. Doctor: I hurt everywhere. Rev Med Suisse. 2016; 12: 1852-1856.
18. Anaïs Lacasse, Patricia Bourgault, Manon Choinière. Fibromyalgia-related costs and loss of productivity: a substantial societal burden. BMC Musculoskelet Disord. 2016; 17: 168.
19. Blasco-Serra A, Escrihuela-Vidal F, González-Soler EM, Martínez-Expósito F, Blasco-Ausina MC, Martínez-Bellver S, et al. Depressive-like symptoms in a reserpine-induced model of fibromyalgia in rats. Physiol Behav. 2015; 151: 456-462.
20. Talotta R, Bazzichi L, Di Franco M, Casale R, Batticciotto A, Gerardi MC, et al. One year in review 2017: fibromyalgia. Clin Exp Rheumatol. 2017; 35: 6-12.
21. Üçeyler N, Burgmer M, Friedel E, Greiner W, Petzke F, Sarholz M, et al. Etiology and pathophysiology of fibromyalgia syndrome: Updated guidelines 2017, overview of systematic review articles and overview of studies on small fiber neuropathy in FMS subgroups. Schmerz. 2017; 31: 239-245.
22. Ablin JN, Häuser W. Fibromyalgia syndrome: novel therapeutic targets. Pain Manag. 2016; 6: 371-381.
23. Oezel L, Then H, Jung AL, Jabari S, Bonaterra GA, Wissniowski TT, et al. Fibromyalgia syndrome: metabolic and autophagic processes in intermittent cold stress mice. Pharmacol Res Perspect. 2016; 4: 00248.
24. Romeyke T, Noehammer E, Scheuer HC, Stummer H. Severe forms of fibromyalgia with acute exacerbation of pain: costs, comorbidities, and length of stay in inpatient care. Clinicoecon Outcomes Res. 2017; 9: 317-325.
25. Kia S, Choy E. Update on Treatment Guideline in Fibromyalgia Syndrome with Focus on Pharmacology. Biomedicines. 2017; 5: 5020020.
26. Chinn S, Caldwell W, Gritsenko K. Fibromyalgia Pathogenesis and Treatment Options Update. Curr Pain Headache Rep. 2016: 25.
27. Halpern R, Shah SN, Cappelleri JC, Masters ET, Clair A. Evaluating

guideline-recommended pain medication use among patients with newly diagnosed fibromyalgia. Pain Pract. 2015; 16: 1027-1039.

28. Lee H, Im J, Won H, Nam W, Kim YO, Lee SW, et al. Effects of tianeptine on symptoms of fibromyalgia via BDNF signaling in a fibromyalgia animal model. Korean J Physiol Pharmacol. 2017; 21: 361-370.

29. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005; 119: 5-15.

30. Häuser W, Bernardy K, Uçeyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. JAMA. 2009; 301: 198-209.

31. Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain. 2008; 136: 432-444.

32. Simone de Souza Nascimento, Josimari Melo DeSantana, Fernando Kenji Nampo, Êurica Adélia Nogueira Ribeiro, Daniel Lira da Silva, João Xavier Araújo-Júnior, et al. Efficacy and safety of medicinal plants or related natural products for fibromyalgia: a systematic review. Evid Based Complement Alternat Med. 2013; 2013: 149468.

33. Derry S, Wiffen PJ, Häuser W, Mücke M, Tölle T, Bell RF, et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. Cochrane Database Syst Rev. 2016; 3: 012332.

34. Bateman L, Palmer RH, Trugman JM, Lin Y. Results of switching to milnacipran in fibromyalgia patients with an inadequate response to duloxetine: a phase IV pilot study. J Pain Res. 2013; 6: 311-318.

35. Carta M, Ruggiero V, Sancassiani F, Cutrano F, Manca A, Peri M, et al. The Use of Antidepressants in the Long-Term Treatment Should not Improve the Impact of Fibromyalgia on Quality of Life. Clin Pract Epidemiol Ment Health. 2013; 9: 120-124.

36. Marcus DA, Bernstein CD, Haq A, Breuer P. Including a range of outcome targets offers a broader view of fibromyalgia treatment outcome: results from a retrospective review of multidisciplin. Musculoskeletal Care. 2014; 12: 74-81.

37. Clauw DJ, Arnold LM, Mc Carberg BH. Fibro Collaborative. The science of fibromyalgia. Mayo Clin Proc. 2011; 86: 907-11.

38. Ablin JN, Buskila D. Fibromyalgia syndrome--novel therapeutic targets. Maturitas. 2013; 75: 335-340.

39. Di Tommaso Morrison MC, Carinci F, Lessiani G, Spinas E, Kritas SK, Ronconi G, et al. Fibromyalgia and bipolar disorder: extent of comorbidity and therapeutic implications. J Biol Regul Homeost Agents. 2017; 31: 17-20.

40. Costa de Miranda R, Paiva ES, Suter Correia Cadena SM, Brandt AP, Vilela RM. Polyphenol-Rich Foods Alleviate Pain and Ameliorate Quality of Life in Fibromyalgic Women. Int J Vitam Nutr Res. 2016; 21:1-10.

41. Di Pierro F, Rossi A, Consensi A, Giacomelli C, Bazzichi L. Role for a water-soluble form of CoQ10 in female subjects affected by fibromyalgia. A preliminary study. Clin Exp Rheumatol. 2017; 35: 20-27.

42. Yildirim T, Alp R. The role of oxidative stress in the relation between fibromyalgia and obstructive sleep apnea syndrome. Eur Rev Med Pharmacol Sci. 2017; 21: 20-29.

43. Mario D Cordero, Francisco Javier Cano-García, Elísabet Alcocer-Gómez, Manuel De Miguel, José Antonio Sánchez-Alcázar. Oxidative stress correlates with headache symptoms in fibromyalgia: coenzyme Q10 effect on clinical improvement. PLoS One. 2012; 7: 35677.

44. Regland B, Forsmark S, Halaouate L, Matousek M, Peilot B, Zachrisson O, et al. Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia. PLoS One. 2015; 10: 0124648.

45. Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, et al. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. Pain. 2014; 155: 261-268.

46. Citera G, Arias MA, Maldonado-Cocco JA, Lázaro MA, Rosemffet MG, Brusco LI, et al. The effect of melatonin in patients with fibromyalgia: a pilot study. Clin Rheumatol. 2000; 19: 9-13.

47. de Zanette SA, Vercelino R, Laste G, Rozisky JR, Schwertner A, Machado CB, et al. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. BMC Pharmacol Toxicol. 2014; 15: 40.

48. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res. 2016; 61: 253-278.

49. Favero G, Trapletti V, Bonomini F, Stacchiotti A, Lavazza A, Rodella LF, et al. Oral supplementation of melatonin protects against fibromyalgia-related skeletal muscle alterations in reserpine-induced myalgia rats. Int J Mol Sci. 2017; 18.

50. Reiter RJ, Acuna-Castroviejo D, Tan DX. Melatonin therapy in fibromyalgia. Curr Pain Headache Rep. 2007; 11: 339-342.

51. Reiter RJ, Tan DX, Fuentes-Broto L. Melatonin: a multitasking molecule. Prog Brain Res. 2010; 181:127-51. 079-6123: 127-151.

52. Reiter RJ, Tan DX1, Galano A2. Melatonin reduces lipid peroxidation and membrane viscosity. Front Physiol. 2014;5:377.

53. Reiter RJ. Aging and oxygen toxicity: Relation to changes in melatonin. Age (Omaha). 1997; 20: 201-213.

54. Dauchy RT, Blask DE, Dauchy EM, Davidson LK, Tirrell PC, Greene MW, et al. Antineoplastic effects of melatonin on a rare malignancy of mesenchymal origin: melatonin receptor-mediated inhibition of signal transduction, linoleic acid metabolism and growth in tissue-isolated human leiomyosarcoma xenografts. J Pineal Res. 2009; 47: 32-42.

55. Gonzalez-Arto M, Hamilton TR, Gallego M, Gaspar-Torrubia E, Aguilar D, Serrano-Blesa E, et al. Evidence of melatonin synthesis in the ram reproductive tract. Andrology. 2016; 4: 163-171.

56. Maldonado MD, Mora-Santos M, Naji L, Carrascosa-Salmoral MP, Naranjo MC, Calvo JR. Evidence of melatonin synthesis and release by mast cells. Possible modulatory role on inflammation. Pharmacol Res. 2010; 62: 282-287.

57. Kalsbeek A, Perreau-Lenz S, Buijs RM. A network of (autonomic) clock outputs. Chronobiol Int. 2006; 23: 521-535.

58. Pfeffer M, Korf HW, Wicht H. Synchronizing effects of melatonin on diurnal and circadian rhythms. Gen Comp Endocrinol. 2017. 17:30172-30177.

59. Tan DX, Manchester LC, Esteban-Zubero E, Zhou Z, Reiter RJ. Melatonin as a potent and inducible endogenous antioxidant: synthesis and metabolism. Molecules. 2015; 20.

60. Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gögenur I. Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. J Pineal Res. 2011; 51: 270-277.

61. Cecon E, Oishi A, Jockers R. Melatonin receptors: molecular pharmacology and signaling in the context of system bias. Br J

Pharmacol. 2017.

62. Dubocovich ML, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine. 2005; 27: 101-110.

63. Srinivasan V, Lauterbach EC, Ho KY, Acuña-Castroviejo D, Zakaria R, Brzezinski A. Melatonin in antinociception: its therapeutic applications. Curr Neuropharmacol. 2012; 10: 167-178.

64. Lacoste B, Angeloni D, Dominguez-Lopez S, Calderoni S, Mauro A, Fraschini F , et al. Anatomical and cellular localization of melatonin MT1 and MT2 receptors in the adult rat brain. J Pineal Res. 2015; 58: 397-417.

65. Scher J, Wankiewicz E, Brown GM, Fujieda H. MT1 melatonin receptor in the human retina: expression and localization. IOVS. 2002; 43; 889-897.

66. Tan DX, Manchester LC, Reiter RJ, Qi WB, Zhang M, Weintraub ST, et al. Identification of highly elevated levels of melatonin in bone marrow: its origin and significance. Biochim Biophys Acta. 1999; 1472: 206-214.

67. Nosjean O, Nicolas JP, Klupsch F, Delagrange P, Canet E, Boutin JA. Comparative pharmacological studies of melatonin receptors: MT1, MT2 and MT3/QR2.Tissue distribution of MT3/QR2. Biochem Pharmacol. 2001; 61: 1369-1379.

68. Slominski RM, Reiter RJ, Schlabritz-Loutsevitch N, Ostrom RS, Slominski AT. Melatonin membrane receptors in peripheral tissues: distribution and functions. Mol Cell Endocrinol. 2012; 351: 152-166.

69. Pintor J, Martin L, Pelaez T, Hoyle CH, Peral A. Involvement of melatonin MT(3) receptors in the regulation of intraocular pressure in rabbits. Eur J Pharmacol. 2001; 416: 251-254.

70. Smirnov AN. Nuclear melatonin receptors. Biochemistry (Mosc). 200; 66: 19-26.

71. Becker-André M, Wiesenberg I, Schaeren-Wiemers N, André E, Missbach M, Saurat JH, et al. Pineal gland hormone melatonin binds and activates an orphan of the nuclear receptor superfamily. J Biol Chem. 1994; 269 (46): 28531-28534. Erratum in: J Biol Chem 1997; 272: 16707.

72. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. Endocrine. 2005; 27: 189-200.

73. Jetten AM. Retinoid-related orphan receptors (RORs): critical roles in development, immunity, circadian rhythm, and cellular metabolism. Nucl Recept Signal. 2009; 7: 003.

74. Korn T, Oukka M, Kuchroo V, Bettelli E. Th17 cells: effector T cells with inflammatory properties. Semin Immunol. 2007; 19: 362-371.

75. García-Mauriño S, Pozo D, Calvo JR, Guerrero JM. Correlation between nuclear melatonin receptor expression and enhanced cytokine production in human lymphocytic and monocytic cell lines. J Pineal Res. 2000; 29: 129-137.

76. Webb SM. Fibromyalgia and melatonin: are they related? Clin Endocrinol (Oxf). 1998; 49: 161-162.

77. Wikner J, Hirsch U, Wetterberg L, Röjdmark S. Fibromyalgia--a syndrome associated with decreased nocturnal melatonin secretion. Clin Endocrinol (Oxf). 1998; 49: 179-183.

78. Mahdi AA, Fatima G, Das SK, Verma NS. Abnormality of circadian rhythm of serum melatonin and other biochemical parameters in fibromyalgia syndrome. Indian J Biochem Biophys. 2011; 48: 82-87.

79. Korszun A, Sackett-Lundeen L, Papadopoulos E, Brucksch C, Masterson L, Engelberg NC, et al. Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. J Rheumatol. 1999; 26: 2675-2680.

80. Chen WW, Zhang X, Huang WJ. Pain control by melatonin: Physiological and pharmacological effects. Exp Ther Med. 2016; 12: 1963-1968.

81. Danilov A, Kurganova J. Melatonin in Chronic Pain Syndromes. Pain Ther. 2016; 5: 1-17.

82. Hansen MV, Halladin NL, Rosenberg J, Gögenur I, Møller AM. Melatonin for pre- and postoperative anxiety in adults. Cochrane Database Syst Rev. 2015; 4:009861.

83. Madsen MT, Hansen MV, Andersen LT, Hageman I, Rasmussen LS, Bokmand S, et al. Effect of melatonin on sleep in the perioperative period after breast cancer surgery: A randomized, double-blind, placebo-controlled trial. J Clin Sleep Med. 2016; 12: 225-233.

84. Hardeland R, Cardinali DP, Brown GM, Pandi-Perumal SR. Melatonin and brain inflammaging. Prog Neurobiol. 2015; 127-128: 46-63.

85. Dong Y, Fan C, Hu W, Jiang S, Ma Z, Yan X, et al. Melatonin attenuated early brain injury induced by subarachnoid hemorrhage via regulating NLRP3 inflammasome and apoptosis signaling. J Pineal Res. 2016; 60: 253-262.

86. Najafi M, Shirazi A, Motevaseli E, Rezaeyan AH, Salajegheh A, Rezapoor S. Melatonin as an anti-inflammatory agent in radiotherapy. Inflammopharmacology. 2017; 25: 403-413.

87. Favero G, Rodella LF, Nardo L, Giugno L, Cocchi MA, Borsani E, et al. A comparison of melatonin and a-lipoic acid in the induction of antioxidant defences in L6 rat skeletal muscle cells. Age (Dordr). 2015; 37: 9824.

88. Galano A, Castañeda-Arriaga R2, Pérez-González A, Tan DX, Reiter RJ. Phenolic melatonin-related compounds: Their role as chemical protectors against oxidative stress. Molecules. 2016; 21: 1442.

89. Favero G, Stacchiotti A, Castrezzati S, Bonomini F, Albanese M, Rezzani R4, et al. Melatonin reduces obesity and restores adipokine patterns and metabolism in obese (ob/ob) mice. Nutr Res. 2015; 35: 891-900.

90. Wongchitrat P, Klosen P, Pannengpetch S, Kitidee K, Govitrapong P, Isarankura-Na-Ayudhya C. High-fat diet-induced plasma protein and liver changes in obese rats can be attenuated by melatonin supplementation. Nutr Res. 2017; 42: 51-63.

91. Xu P, Wang J, Hong F, Wang S, Jin X, Jia L, et al. Melatonin prevents obesity through modulation of gut microbiota in mice. J Pineal Res. 2017; 62: 12399.

92. Sharma S, Singh H, Ahmad N, Mishra P, Tiwari A. The role of melatonin in diabetes: therapeutic implications. Arch Endocrinol Metab. 2015; 59: 391-399.

93. She M, Laudon M, Yin W. Melatonin receptors in diabetes: a potential new therapeutical target? Eur J Pharmacol. 2014; 744: 220-223.

94. Albrecht PJ, Rice FL. Fibromyalgia syndrome pathology and environmental influences on afflictions with medically unexplained symptoms. Rev Environ Health. 2016; 31: 281-294.

95. Cuzzocrea S, Reiter RJ. Pharmacological actions of melatonin in acute and chronic inflammation. Curr Top Med Chem. 2002; 2: 153-165.

96. Hussain SA, Al-Khalifa II, Jasim NA, Gorial FI. Adjuvant use of melatonin for treatment of fibromyalgia. J Pineal Res. 2011; 50: 267-271.

97. Tang F, Zhou R, Cheng Z, Yang G, Chen A, Liu Z, et al. Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products of agomelatine in Chinese subjects. Acta Pharm Sin B. 2016; 6: 71-78.

98. Calandre EP, Slim M, Garcia-Leiva JM, Rodriguez-Lopez CM, Torres P, Rico-Villademoros F. Agomelatine for the treatment of patients with fibromyalgia and depressive symptomatology: an uncontrolled, 12-week, pilot study. Pharmacopsychiatry. 2014; 47: 67-72.

99. Bruno A, Micò U, Lorusso S, Cogliandro N, Pandolfo G, Caminiti M , et al. Agomelatine in the treatment of fibromyalgia: a 12-week, open-label, uncontrolled preliminary study. J Clin Psychopharmacol. 2013; 33: 507-511.

100. Montgomery SA. Efficacy in long-term treatment of depression. J Clin Psychiatry. 1996; 57: 24-30.

101. Maldonado MD, Reiter RJ, Pérez-San-Gregorio MA. Melatonin as a potential therapeutic agent in psychiatric illness. Hum Psychopharmacol. 2009; 24: 391-400.

102. Nagakura Y, Oe T, Aoki T, Matsuoka N. Biogenic amine depletion causes chronic muscular pain and tactile allodynia accompanied by depression: A putative animal model of fibromyalgia. Pain. 2009; 146: 26-33.

103. De Freitas CM, Busanello A, Schaffer LF, Peroza LR, Krum BN, Leal CQ, et al. Behavioral and neurochemical effects induced by reserpine in mice. Psychopharmacology (Berl). 2016; 233: 457-467.

104. Schuldiner S, Steiner-Mordoch S, Yelin R. Molecular and biochemical studies of rat vesicular monoamine transporter. Adv Pharmacol. 1998; 42: 223-227.

105. Can A, Dao DT, Arad M, Terrillion CE, Piantadosi SC, Gould TD. The mouse forced swim test. J Vis Exp. 2012; 59: 3638.

106. Peres Klein C, Rodrigues Cintra M, Binda N, Montijo Diniz D, Gomez MV, Souto AA, et al. Coadministration of resveratrol and rice oil mitigates nociception and oxidative state in a mouse fibromyalgia-like model. Pain Res Treat. 2016; 2016: 3191638.

107. Nade VS, Shendye NV, Kawale LA, Patil NR, Khatri ML. Protective effect of nebivolol on reserpine-induced neurobehavioral and biochemical alterations in rats. Neurochem Int. 2013; 63: 316-321.

108. Bagis S, Tamer L, Sahin G, Bilgin R, Guler H, Ercan B, et al. Free radicals and antioxidants in primary fibromyalgia: an oxidative stress disorder? Rheumatol Int. 2005; 25: 188-190.

109. Nagakura Y, Takahashi M, Noto T, Sekizawa T, Oe T, Yoshimi E, et al. Different pathophysiology underlying animal models of fibromyalgia and neuropathic pain: comparison of reserpine-induced myalgia and chronic constriction injury rats. Behav Brain Res. 2012; 226: 242-249.

110. Cobos EJ, Ghasemlou N, Araldi D, Segal D, Duong K, Woolf CJ. Inflammation-induced decrease in voluntary wheel running in mice: a nonreflexive test for evaluating inflammatory pain and analgesia. Pain. 2012; 153: 876-884.

111. Harijith A, Ebenezer DL, Natarajan V. Reactive oxygen species at the crossroads of inflammasome and inflammation. Front Physiol. 2014; 5:352.

112. Schmidt-Wilcke T, Diers M. New insights into the pathophysiology and treatment of fibromyalgia. Biomedicines. 2017; 5: 22.

113. Bozkurt M, Caglayan M, Oktayoglu P, Em S, Batmaz I, Sariyildiz MA, et al. Serum prolidase enzyme activity and oxidative status in patients with fibromyalgia. Redox Rep. 2014; 19: 148-153.

114. Sánchez-Domínguez B, Bullón P, Román-Malo L, Marín-Aguilar F, Alcocer-Gómez E, Carrión AM, et al. Oxidative stress, mitochondrial dysfunction and, inflammation common events in skin of patients with Fibromyalgia. Mitochondrion. 2015; 21: 69-75.

115. Ozgocmen S, Ozyurt H, Sogut S, Akyol O. Current concepts in the pathophysiology of fibromyalgia: the potential role of oxidative stress and nitric oxide. Rheumatol Int. 2006; 26: 585-597.

Cite this article

Trapletti V, Favero G, Bonomini F, Rodella LF, Rezzani R (2017) Melatonin an Emerging Management against Fibromyalgia. JSM Arthritis 2(2): 1025.