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Review

Is there a role for melatonin in fibromyalgia?

Kim Lawson*

Department of Biosciences and Chemistry, Biomolecular Sciences Research Centre, Sheffield Hallam University, Faculty of Health and Wellbeing, Sheffield S1 1WB, United Kingdom

* Correspondence: Email: k.lawson@shu.ac.uk; Tel: +44(0)1142253057.

Abstract: Fibromyalgia, characterised by persistent pain, fatigue, sleep disturbance and cognitive dysfunction, is a central sensitivity syndrome that also involves abnormality in peripheral generators and in the hypothalamic pituitary adrenal axis. Heterogeneity of clinical expression of fibromyalgia with a multifactorial aetiology has made the development of effective therapeutic strategies challenging. Physiological properties of the neurohormone melatonin appear related to the symptom profile exhibited by patients with fibromyalgia and thus disturbance of it's production would be compatible with the pathophysiology. Altered levels of melatonin have been observed in patients with fibromyalgia which are associated with lower secretion during dark hours and higher secretion during daytime. However, inconsistencies of available clinical evidence limit conclusion of a relationship between levels of melatonin and symptom profiles in patients with fibromyalgia. Administration of melatonin to patients with fibromyalgia has demonstrated suppression of many symptoms and an improved quality of life consistent with benefit as a therapy for the management of this condition. Further studies with larger samples, however, are required to explore the potential role of melatonin in the pathophysiology of fibromyalgia and determine the optimal dosing regimen of melatonin for the management of fibromyalgia.

Keywords: melatonin; fibromyalgia; sleep; persistent pain; fatigue; anxiety

Abbreviations: ACR: American College of Rheumatology; BDNF: Brain-derived neurotrophic factor; cAMP: Cyclic adenosine monophosphate; CNS: Central nervous system; CS: Central sensitization; CSF: Cerebrospinal fluid; DNIC: Diffuse noxious inhibitory control; FIQ: Fibromyalgia Impact Questionnaire; GABA: Gamma-aminobutyric acid; HPA: Hypothalamic pituitary adrenal axis; HRQOL: Health-related quality of life; MT: Melatonergic; NO: Nitric oxide; NMDA: N-methyl-D-aspartate; RCT: Randomized controlled trial; 6-SMT: 6-sulfatoxymelatonin

1.   Introduction

Fibromyalgia, characterised by persistent pain, fatigue, sleep disturbance and cognitive dysfunction (i.e. attentional capacity and memory), is a central sensitivity syndrome [1,2]. Central sensitization (CS) with neuronal excitability linked to amplified responses of the central nervous system (CNS) to peripheral input has been proposed to underlie the pathophysiology of fibromyalgia [2]. Peripheral sensory generators, such as nerve pathologies, neuroinflammation, skeletal muscle abnormalities and ischaemia, have been reported to contribute to this heightened activity of the CNS [3,4]. Consequently, fibromyalgia is dominated by disorder of central pain processing producing heightened responses to painful stimuli (hyperalgesia) and painful responses to non-painful stimuli (allodynia). Heterogeneity of clinical expression with a multifactorial aetiology has made the development of effective therapeutic strategies challenging. The aim of this review is to consider the relationship of fibromyalgia and melatonin, with respect to involvement in the pathophysiology or as a treatment approach of the condition. MEDLINE database, Web of Science and Google Scholar were used to identify relevant studies and publications up to August 2019 using the terms 'melatonin' and 'fibromyalgia'.

2.   Fibromyalgia

Classification of fibromyalgia has been based on the American College of Rheumatology (ACR) 1990 criteria of widespread pain (for at least 3 months) in all four quadrants of the body and pain in 11 of 18 tender point sites [5]. The assessment of the range of symptoms by determination of somatic symptom severity (sleep disturbance, cognitive disturbance and fatigue) and widespread pain, avoiding reliance on tender points was introduced as a revision of the criteria in 2010, with further revision in 2016 to limit potential misclassification and introduce the use of a fibromyalgia symptom scale [6,7]. A worldwide prevalence, based on application of ACR 1990 criteria, of 0.4–8% of the population has been reported for fibromyalgia, being seven times more common in females than males [8]. The occurrence of comorbidities (e.g. chronic fatigue syndrome) exhibiting similar symptoms however often complicates the recognition of fibromyalgia [2].

Altered neurotransmitter functioning and possible neuroplasticity consistent with an enhanced excitation and reduced inhibition within the CNS leading to augmented sensory processing has been suggested to contribute to the CS in patients with fibromyalgia [3]. Raised levels of glutamine (2-fold), nerve growth factor (4-fold), brain-derived neurotrophic factor (BDNF, 2 to 4-fold), substance P (2 to 3-fold) and endogenous opioids (3 to 4-fold) compared to healthy subjects are observed in the cerebrospinal fluid (CSF) of people with fibromyalgia, consistent with involvement of wind-up phenomenon (a progressive increase in response reflective of slow temporal summation) leading to self-maintaining CS [2,9]. Further, in pain-related brain regions, including the posterior insula, in addition to the CSF elevated glutamate, glutamine and glycine levels which correlate to the levels in pain in fibromyalgia have been reported [10,11]. In contrast, lower CSF levels of the main metabolites of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), and noradrenaline, 3-methoxy-4-hydroxyphenylglycol (MHPG), and blood levels of serotonin and L-tryptophan in people with fibromyalgia relative to healthy subjects have been reported [2,9]. In addition, in response to painful stimuli in patients with fibromyalgia dopamine release into the basal ganglia is attenuated [12].

Alterations in the hypothalamic pituitary adrenal axis (HPA), autonomic nervous system and cardiovascular system enhancing or underlying the symptoms of fibromyalgia have been linked to systemic stress-related events [2,3]. The symptoms of fibromyalgia being linked to HPA and autonomic systems dysregulation has raised interest in the involvement of melatonin and the melatonergic system in the pathophysiology of fibromyalgia.

The characteristic spectrum of symptoms of fibromyalgia cannot be accounted for by any of the factors in isolation, such as central or peripheral sensitization, neuroendocrine dysfunction, oxidative stress, immunological factors and genetics, linked with the pathophysiology. Treatments of the challenges associated with fibromyalgia, as with many chronic pain conditions, require the combination of pharmacological and non-pharmacological therapeutic approaches [1,6]. An empiric approach to drug therapies is often involved with a focus towards individual symptoms, primarily pain, rather than the condition [1]. A primary aim of many of the pharmacological treatments is lowering levels of pronociceptive excitatory neurotransmission and/or increasing antinociceptive neurotransmission in the CNS. Decreased activity of the descending serotonergic-noradrenergic efferent pathways responsible for an aberrant diffuse noxious inhibitory control (DNIC) has been observed in people with fibromyalgia [2,3]. Thus, current therapeutic options for fibromyalgia are drugs that raise serotonin and noradrenaline levels in the CNS (e.g. tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors) or target voltage-gated calcium channel subunits (e.g. gabapentin and pregabalin) [1,6].

3. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine), a neurohormone synthesized from tryptophan and serotonin (Figure 1), is produced mainly by the pineal gland then crosses the blood-brain barrier diffusing into the CSF [13,14]. With a well-defined secretory rhythm linked to the circadian rhythm resulting in high circulating concentrations of at night and lower during the day melatonin plays in a role in the regulation of the 24-hour pattern of bodily functions. Three G-protein coupled melatonergic receptors subtypes have been identified at which melatonin acts as a full agonist [14]. Stimulation of MT1 and MT2 receptors by melatonin leads to activation of inward rectifying potassium channels (Kir) and block of Ca^{2+} channels resulting in a blunting of cell stimulation due to reduced formation of cyclic adenosine monophosphate (cAMP) and a lowered intracellular level of Ca^{2+} ions [14,15]. The MT3 receptor has been identified to be quinone reductase protein type 2, an antioxidant enzyme which is inhibited by melatonin [14]. Various physiological functions are affected by melatonin because of the widespread distribution of the melatonergic receptors (for example, in the CNS, immune system, gastrointestinal tract, blood vessels) [14]. Additional effects of melatonin may also be evoked due to affinity for other receptor types including opioid, gamma-aminobutyric acid (GABA), adrenergic, serotonergic, cholinergic and N-methyl-D-aspartate (NMDA) [14]. Melatonin is metabolised in the liver to produce 6-hydroxymelatonin which is conjugated with sulphate to generate the major melatonin metabolite, 6-sulfatoxymelatonin (6-SMT; Figure 1) [16,17]. 6-SMT is excreted in urine and is used as an indirect measurement of melatonin production by the pineal gland [16,17].
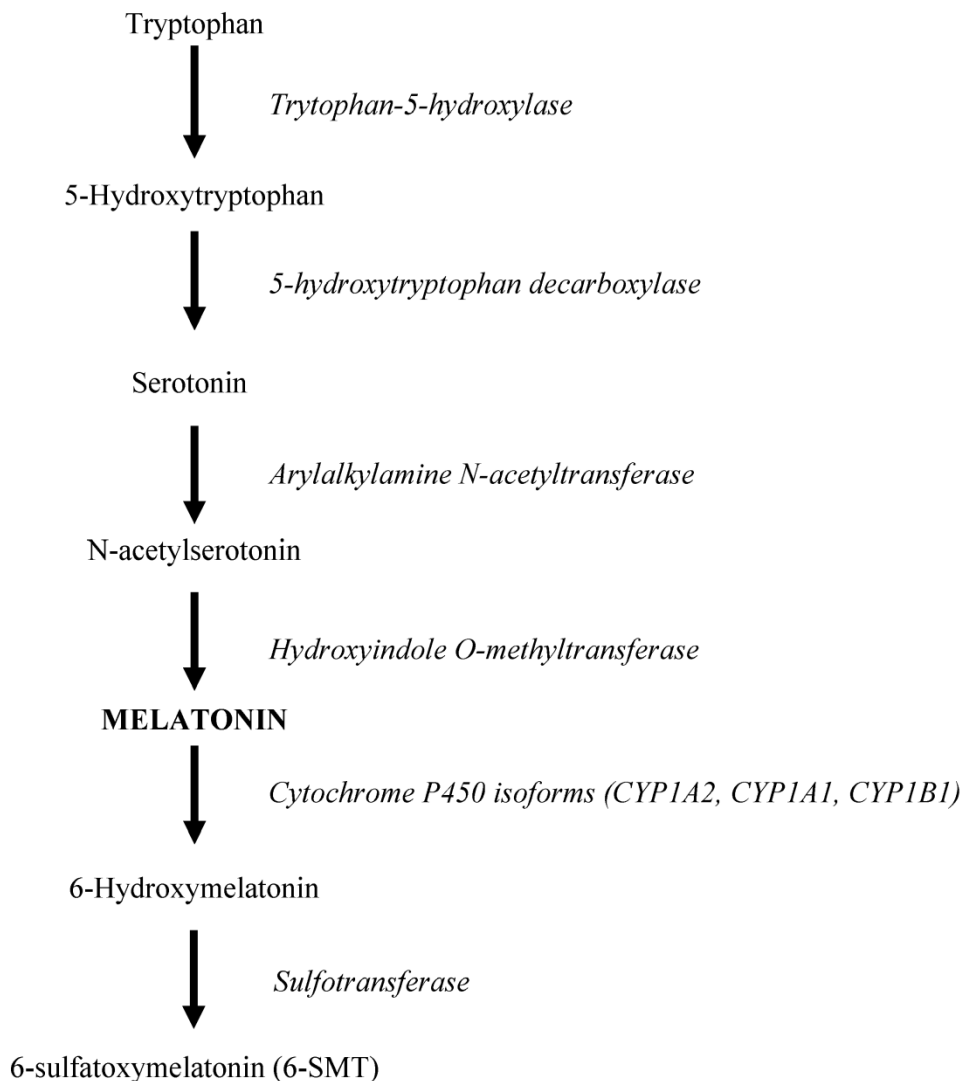
Tryptophan

↓ *Trytophan-5-hydroxylase*

5-Hydroxytryptophan

↓ *5-hydroxytryptophan decarboxylase*

Serotonin

↓ *Arylalkylamine N-acetyltransferase*

N-acetylserotonin

↓ *Hydroxyindole O-methyltransferase*

MELATONIN

↓ *Cytochrome P450 isoforms (CYP1A2, CYP1A1, CYP1B1)*

6-Hydroxymelatonin

↓ *Sulfotransferase*

6-sulfatoxymelatonin (6-SMT)

Figure 1. Biosynthesis of melatonin. Melatonin synthesis begins with the conversion of tryptophan to serotonin which is acetylated to form N-acetylserotonin. Methylation of N-acetylserotonin leads to the production of N-acetyl-methoxytryptamine or melatonin. In the liver, melatonin is metabolised to 6-hydroxymelatonin which is conjugated with sulphate to 6-sulfatoxymelatonin which is used as an indirect measurement of melatonin production.

Stimulation by melatonin of the MT1 and MT2 receptors of the suprachiasmatic nucleus of the hypothalamus improves sleep quality due to a reduction of sleep onset latency, increase in sleep duration, sleep efficiency improvement and regulation of sleep-wake cycle [18]. The role of melatonin in the suppression of neuronal stimulation leading to sleep onset could be relevant in the development and management of aberration of awake-sleep transition evident in fibromyalgia [2,5]. The suppressed neuronal stimulation following activation of melatonergic receptors by melatonin has also been associated with antinociceptive properties [19]. The wide distribution of MT1 and MT2 receptors in CNS, including regions crucial for pain control such as the thalamus, hypothalamus, trigeminal tract and nucleus, and dorsal horn of the spinal cord, supports the involvement in nociceptive modulation [19–22]. In addition to melatonergic receptors the analgesic actions of melatonin also involve GABA

receptors, β-endorphins, opioid μ-receptors and the NO-arginine pathway, which also lead to a reduction of the intracellular concentration of cAMP [23]. Melatonin could through action on the NO-arginine pathway reduce and eliminate wind-up, a perceived progressive increase in pain intensity over time when a given painful stimulus is delivered repeatedly that is associated with CS in fibromyalgia [2,24].

A delayed secretion of melatonin with change in the circadian rhythm has also been associated with features of fatigue [15]. In healthy individuals and people with pain conditions a strong negative correlation between melatonin level and fatigue has been demonstrated [9,25]. Interestingly, the melatonergic receptor agonist agomelatine, but not melatonin, reduced the perception of fatigue in subjects with chronic fatigue syndrome [26]. In addition to acting as an agonist at MT1 and MT2 receptors, agomelatine exhibits antagonistic properties at serotonin 5-HT2C receptors [27]. The action on 5-HT2C receptors by agomelatine leads to an increase in the prefrontal cortex of dopaminergic and noradrenergic tone resulting in the reduction of fatigue perception [26,27]. Thus, melatonin and related drugs may have a role in the fatigue characteristic of fibromyalgia. Melatonin, however, may have limited effect of the perception of fatigue in patients with fibromyalgia since relative to agomelatine the affinity for 5-HT2C receptors is low [19].

Alteration of melatonin levels have also been suggested to contribute to the development of cognitive-behavioural problems such as anxiety and depression [28,29]. Activation of the melatonergic system, through MT2 receptors, and the GABAergic system, through GABA receptors, are believed to be the targets of melatonin for the effects on anxiety [30,31]. People with major depression exhibit lowered levels of melatonin, however when used as a treatment melatonin does not reduce the depressive symptoms [32–34].

4.   Fibromyalgia and melatonin

The chronotropic, analgesic and anxiolytic properties of melatonin have stimulated interest from both pathophysiological and potential therapeutic perspectives of it's role in fibromyalgia where there is a limited understanding of the pathophysiology and limitations of current management strategies. Low levels of tryptophan and serotonin observed in patients with fibromyalgia could be associated with a decrease in melatonin synthesis which may result in the characteristic symptoms of fibromyalgia of pain and abnormal sleeping patterns [2,5]. The abnormal sleeping patterns in patients with fibromyalgia are characterised by less sleep efficiency, higher proportion of non-rapid eye movement sleep and more arousals per hour of sleep which could be consistent with an abnormal availability of melatonin [18,35].

4.1. Melatonin and pathophysiology of fibromyalgia

Investigation of the levels of melatonin in patients with fibromyalgia have observed conflicting outcomes with both abnormal levels of melatonin and levels not different relative to health controls being reported (Table 1) [36–42]. The inconsistency of outcomes may be associated with all studies having low participant numbers, the heterogeneity of the clinical characteristics of fibromyalgia and/or methodological variability between the studies, such as sample type (urine, serum, blood), marker used (melatonin or 6-SMT) and lack of accommodation for circadian rhythm related melatonin dysregulation. In addition, the

diversity of participant profiles, e.g. sex, pre- or post-menopausal females, may affect the outcomes of such studies.

Lower melatonin secretion during dark hours in patients with fibromyalgia compared to healthy subjects, which may contribute to worse sleep at night, daytime fatigue and higher pain perception, has been reported in 2 studies [36,41]. Wikner and colleagues (1998) observed that the secretion of melatonin during hours of darkness (23:00–07:00 hours) was 31% lower in patients with fibromyalgia relative to matched healthy controls with a 36% lower peak serum value [36]. In the patients with fibromyalgia a tendency towards decreased urinary excretion of melatonin was reported, however statistical significance was not achieved. Pernambuco and colleagues (2015) however reported excretion of the major melatonin metabolite 6-SMT from 20:00 to 08:00 hours were substantially lower (36%) in the urine of patients with fibromyalgia compared to healthy controls [41]. The urinary levels of 6-SMT did not correlate with the presence or severity of symptoms assessed by quality of life and sleep questionnaires [41]. Altered functioning of the pineal gland and neuroendocrine changes related to stress responses could be associated with a reduced production of melatonin in people with fibromyalgia [43]. In contrast, Korszun and colleagues (1999) reported a higher nocturnal (23:00–06:50 hours) melatonin level in plasma from females with fibromyalgia compared with healthy controls [38].

Caumo and colleagues (2019) reported a higher melatonin secretion during daytime (06:00–18:00 hours) in patients with fibromyalgia which was associated with larger number of tender points, lower pain pressure threshold, depressive symptoms and decreased sleep quality [42]. The 24 hours load of 6-SMT as a marker of melatonin secretion however did not differ between patients with fibromyalgia or healthy controls. The higher daytime hours load of melatonin secretion makes patients prone to higher intensity of symptoms characteristic of fibromyalgia thus disruption of melatonin secretion rhythm could play a role in the pathophysiology of this condition. Alteration of the rhythmic secretion of melatonin will affect regulation of the limbic-HPA and sympathetic-adrenergic-noradrenergic systems, processes considered to contribute to the pathophysiology of fibromyalgia, due to the density and location of the melatonergic receptors [14,44].

Similar levels of melatonin in patients with fibromyalgia and healthy controls have been observed in three studies [37,39,40]. Press and colleagues (1998) reported nocturnal (22:00–07:00 hours) urine levels of 6-SMT to not be different between the two groups of subjects [37]. No difference in the circadian rhythm of the blood melatonin levels over 24 hours in patients with fibromyalgia and healthy controls was reported by Klerman and colleagues (2001) [39]. A study by Senel and colleagues (2013) again reported similar melatonin levels in plasma of patients with fibromyalgia and healthy controls, however measurement was made at only one time point (08:00 hours) [40]. In the latter two studies the melatonin levels did not correlate with time of onset of symptoms and sleep disorder, nor with the scores of pain and fatigue [39,40].

4.2. Melatonin as a therapy

A therapeutic role of melatonin in the management of fibromyalgia has been investigated in several studies which included open-pilot, double-blind randomized controlled trial (RCT) and longitudinal placebo-controlled design (Table 2) [45–50]. In all studies administration of melatonin (3–15 mg daily) alone or as an adjuvant to patients with

fibromyalgia evoked an improvement in the parameters of pain, sleep quality, fatigue, mood and quality of life.

In an open 4-week pilot study, 19 patients with fibromyalgia who received melatonin 3 mg daily reported at day 30 significant reduction in tender point count and severity of pain, and improvement in patient and physician global assessment, and sleep quality [45]. Although assessments of fatigue, depression and anxiety appeared to indicate an improvement, statistical significance was not achieved. In a second open pilot study, after 15 days of melatonin 6 mg daily supplementary to their current treatments patients with fibromyalgia exhibited an improved sleep/wake cycle with a significant reduction in pain, fatigue and depressive symptoms [46]. Thirty days after the initiation of melatonin all other medications were withdrawn with no deterioration in control of symptoms. Patients were monitored for up to 15 months receiving melatonin 6 mg daily alone and outcomes were supportive of chronic melatonin therapy being beneficial in controlling the symptoms of fibromyalgia [46].

In longitudinal placebo-controlled studies, melatonin 6–15 mg daily alone improved the symptoms related to pain, fatigue and sleep quality in patients with fibromyalgia leading to a beneficial outcome on quality of life [49,50]. Melatonin treatment (10 consecutive days) improved objective sleep quality (12 and 15 mg daily), as assessed by actigraphy, and subjective sleep quality (6–15 mg daily), assessed by the Pittsburgh tool, of patients with fibromyalgia [49]. Administration of melatonin decreased sleep latency (9–15 mg daily) and total nocturnal activity (15 mg daily), and increased sleep efficiency, actual sleep time and assumed sleep. In addition to an improved sleep quality, an increase in antioxidant capacity levels in the urine of patients with fibromyalgia was observed following treatment with melatonin (9–15 mg daily), with the higher dose increasing serum total antioxidant [49]. Oxidative stress, particularly in the mitochondria in the peripheral nerves and reduced oxidative capacity have been suggested to participate in the pathophysiology of fibromyalgia [51,52]. Thus, the elevated antioxidant capacity observed following melatonin treatment may play a role in countering oxidative stress and thereby stabilization of the physiology of these patients. Further, Castaño and colleagues (2019) observed a significant decrease in pain levels with melatonin at 9, 12 and 15 mg daily and a decrease in anxiety state at 12 and 15 mg daily [50]. A decrease in urinary cortisol levels was also observed in patients with fibromyalgia administered melatonin at 9, 12 and 15 mg daily, consistent with a potential inhibitory effect of melatonin on the secretion of cortisol [50,53]. In patients with fibromyalgia elevated evening serum cortisol level and blunted morning serum cortisol level contrary to that observed in health controls have been reported [54,55]. Thus, the intake of melatonin probably decreased circulating cortisol during the night which would provide benefit for the patients with fibromyalgia.

In double-blind RCT studies, melatonin (5 and 10 mg daily for 8 and 6 weeks, respectively) alone and as an adjuvant to fluoxetine (20 mg daily) or amitriptyline (25 mg daily) further demonstrated an improvement of the spectrum of symptoms in patients with fibromyalgia [47,48]. Hussain and colleagues (2011) assessed the effects of melatonin alone or melatonin plus fluoxetine in patients with fibromyalgia using the Fibromyalgia Impact Questionnaire (FIQ), which includes parameters for pain, fatigue, sleep, morning stiffness, anxiety, depression, and health-related quality of life (HRQOL) [47]. Administration of melatonin 5 mg daily alone for 60 days significantly reduced FIQ scores relative to pre-treatment scores for pain (27%), fatigue (23.7%) sleep disturbance (31.3%), morning

stiffness (23%), anxiety (11.6%), depression (23.3%), and HRQOL (10–16.6%) in patients with fibromyalgia [47]. When melatonin 5 mg daily was administered in combination with fluoxetine 20 mg daily for 60 days to patients with fibromyalgia FIQ scores relative to pre-treatment scores were significantly reduced for pain (30%), fatigue (34.7%) sleep disturbance (41.3%), morning stiffness (25%), anxiety (21.6%), depression (42.3%), and HRQOL (23–37%). Although with combined therapy a greater outcome for HRQOL, pain score, fatigue and rest/sleep score was observed with the higher melatonin dose (5 mg daily) plus fluoxetine, a better improvement to morning stiffness and anxiety was obtained with melatonin (3 mg daily) plus fluoxetine. Interestingly, the administration of melatonin (5 mg daily) alone improved fatigue and sleep quality which was not observed with fluoxetine alone. Thus, administration of melatonin, alone or in combination with fluoxetine, was effective in the treatment of patients with fibromyalgia. De Zanette and colleagues (2014) investigated the effects of melatonin 10 mg daily alone or in combination with amitriptyline 25 mg on the DNIC, the descending pain-modulating system, on pain parameters, sleep quality and FIQ scores, and tender point number in patients with fibromyalgia [48]. Melatonin alone or in combination with amitriptyline significantly reduced pain score, FIQ score and tender point number, improved pain threshold scores and sleep quality; and increased the function of the inhibitory DNIC. The combination of melatonin and amitriptyline provided additional improvement of the FIQ and pain threshold than melatonin alone, thus the concomitant stimulation of melatonergic receptors could possibly enhance the aberrant serotonergic-noradrenergic components of the descending endogenous pain-modulating system observed in patients with fibromyalgia [48]. Interestingly, serum BDNF levels, which are raised in patients with fibromyalgia and may be involved in CS and the reduced descending inhibitory system activity, were lowered following administration of melatonin alone or in combination with amitriptyline [48].

The benefits of melatonin in patients with fibromyalgia varied with respect to dose (3–15 mg per day), delay of onset (10 days–8 weeks) and symptom between different studies which may be the result of the heterogeneity of subjects (clinical profile), the low participant numbers, length of treatment and design of the study. Further work is required to establish the optimal dosing regimen (dose, time and method of administration, duration of treatment, symptoms targeted) of melatonin for the management of fibromyalgia.

4.3. Agomelatine, a melatonergic receptor agonist

The melatonin analogue agomelatine exhibits both high-affinity human melatonergic MT1 and MT2 receptors agonist and a serotonin 5-HT2C receptor antagonist properties [27]. In two 12 week open-label uncontrolled studies agomelatine (25–50 mg per day) also significantly improved pain, depression and anxiety symptoms in patients with fibromyalgia [56,57]. But in contrast to melatonin, an improvement in sleep quality was not seen with agomelatine [57]. The stimulation of melatonergic receptors is consistent with effectiveness in analgesia and mood treatment of patients with fibromyalgia. The outcomes with agomelatine, albeit from uncontrolled studies, suggest the control of the sleep disorder by melatonin involves mechanisms additional to melatonergic receptors.

Table 1. Studies determining the melatonin secretion and 6-sulfatoxymelatonin excretion levels in patients with fibromyalgia.

Reference	Subjects	Biomarker	Sample	Outcome
Wikner J et al. 1998 [36]	8 females with FM; 8 female HC	Melatonin	Serum collected 18:00–08:00. Urine collected 22:00–07:00	Hours of darkness (23:00–07:00) (1.70±0.17 *vs* 2.48±0.38 nmol/l; *P* < 0.05) and peak (0.28±0.03 *vs* 0.44±0.06 nmol/l, *P* < 0.05) serum melatonin levels significantly lower (> 30%) in FM compared to HC. Total serum melatonin secretion (18:00–08:00) and urinary excretion of melatonin not different between FM and HC.
Press J et al. 1998 [37]	39 females with FM; 39 female HC	6-SMT	Urine collected 22:00–07:00	6-SMT levels not statistically different between FM and HC (16.7±9.2 *vs* 16.0±11.3 g). No association between 6-SMT levels in patients with fibromyalgia and disease duration and symptoms
Korszun A et al. 1999 [38]	9 females with FM; 17 female HC	Melatonin	Plasma collected hourly over 24 h	Nocturnal melatonin (23:00–06:50) higher in FM compared to HC (75.2±7.5 *vs* 58.5±4.8 pg/ml, respectively, *P* < 0.05). No difference in timing of offset, onset or peak of melatonin secretion between FM and HC.
Klerman EB et al. 2001 [39]	10 females with FM; 12 female HC	Melatonin	Blood collected hourly over 24 h	No significant difference in circadian rhythm (phase and amplitude) of melatonin levels in FM and HC.
Senel K et al. 2013 [40]	25 premenopausal females with FM; 20 premenopausal female HC	Melatonin	Plasma collected at 08:00	Melatonin levels of patients with fibromyalgia not different from healthy controls (10.9±7.3 *vs* 11.6±7.0 pg/ml, respectively). No correlation between melatonin levels and pain scores, fatigue, sleep disorders and duration of the disease.
Pernambuco et al. 2014 [41]	58 females with FM; 39 female HC	6-SMT	Urine collected 20:00–08:00	Night (20:00–08:00 hours) load lower in FM compared with HC (8.5 (0.3–24.4) *vs* 13.3 (0.5–39.8) ng/ml, respectively, *P* < 0.05). Differences in levels did not correlate with FM symptoms.
Caumo et al. 2019 [42]	18 females with FM; 17 female HC	6-SMT	Urine collected 06:00–12:00, 12:00–18:00, 18:00–24:00, 24:00–06:00.	No difference in daily load of 6-SMT between FM and HC. Daytime (06:00–18:00 hours) load higher in FM (0.27 ng/ml; 41.5% of total 24 hr load) compared with HC (0.17 ng/ml; 20.7% of total 24 hr load). Daytime load in FM correlated with larger number of tender points, lower pain pressure threshold, depressive symptoms and decreased sleep quality.

Note: FM: fibromyalgia; HC: healthy controls; 6-SMT: 6-sulfatoxymelatonin.

Table 2. Clinical studies of melatonin as a treatment of fibromyalgia.

Reference	Dose	Study design	N	Duration	Domains assessed	Outcomes
Citera et al. 2000 [45]	Melatonin 3 mg	Pilot	19	4 weeks	Tender points Pain intensity Sleep quality	All domains improved
Acuna-Castroviejo et al. 2006 [46]	Melatonin 6 mg daily	Pilot	4	Up to 60 weeks	Pain intensity Fatigue Sleep-wake cycle	Improved pain and fatigue, Sleep-wake cycle normalized
Hussain SA et al. 2011 [47]	Melatonin 5 mg daily alone; Melatonin 3 mg daily plus fluoxetine 20 mg daily; Melatonin 5 mg daily plus fluoxetine 20 mg daily	Double-blind RCT	101	8 weeks	FIQ score (quality of life, pain, fatigue, sleep quality, anxiety, depression)	FIQ score improved with melatonin alone or in combination with fluoxetine. Combination achieved a greater effectiveness.
De Zanette et al. 2014 [48]	Melatonin 10 mg daily alone, Amitriptyline 25 mg daily alone, Melatonin 10 mg daily plus amitriptyline 25 mg daily	Double-blind RCT	63	6 weeks	Pain, pain threshold, tender points, sleep quality	Melatonin alone or in combination was more effective than amitriptyline alone on pain symptoms and threshold. All 3 treatments were equally effective on tender points and sleep quality.
Castaño et al. 2018 [49]	Melatonin 3, 6, 9, 12, 15 mg daily	Longitudinal placebo-controlled design	33	10 days	Objective sleep assessment (actigraphy), subjective sleep assessment (Pittsburgh test), Total antioxidant capacity	Objective and subjective sleep quality was improved by 12 and 15 mg, and 6–15 mg melatonin respectively. Total antioxidant capacity was increased by 9–15 mg melatonin.
Castaño et al. 2019 [50]	Melatonin 3, 6, 9, 12, 15 mg daily	Longitudinal placebo-controlled design	36	10 days	FIQ score, Pain Score, SF-36. State-Trait Anxiety Inventory, Mood Scale,	Pain levels, mood, quality of life, anxiety levels and FIQ scores improved.

Note: FIQ: Fibromyalgia impact questionnaire; N: number of participants; RCT: randomized controlled trial; SF-36: Short Form-36 Health Survey.

5. Conclusion

Melatonin is involved in circadian rhythm synchronisation and thereby regulation of the sleep-awake cycle and fatigue, and in addition enhances endogenous pain inhibition processes and mood. Thus, the physiological processes maintained by the availability of melatonin are relevant to the clinical features of fibromyalgia where persistent pain, fatigue, sleep disorder and cognitive impairment are characteristic. Lowered levels of serotonin and tryptophan, precursors of melatonin, in patients with fibromyalgia have been correlated with many of the symptoms and consequently have led to melatonin playing a role in the pathophysiology of this condition being investigated [2,5]. An increased nociception may be associated with the reduced production of melatonin observed in patients with fibromyalgia which could present clinically as hyperalgesia and/or allodynia [19,36,41]. Thus, if a disturbance in melatonin production is associated with the pathophysiology of fibromyalgia, the use of melatonin could offer a novel treatment approach.

Altered levels of melatonin have been observed in patients with fibromyalgia which are associated with lower secretion during dark hours and higher secretion during daytime. The changes in melatonin levels during dark hours would contribute to sleep disturbance with raised pain perception and fatigue during the day. The changes in melatonin levels during daytime would exacerbate the symptoms of pain and fatigue, lead to depressive symptoms and enhance disturbance of sleep quality. A bidirectional relationship exists between pain and sleep, such that poor sleep is linked with next-day pain and daytime pain is associated with reduced night-time sleep [58]. The altered circadian rhythm and sleep architecture due to changes in melatonin secretion may amplify pain and mask the ability to inhibit pain. Thus, melatonin could be involved in the pathophysiology of fibromyalgia with the aberrant secretion consistent with expression of the main symptoms of fibromyalgia. Conflicting studies, however, have reported melatonin levels in patients with fibromyalgia not different from those observed in healthy subjects. Although the properties of melatonin appear consistent with an involvement in the expression of the main symptoms presented by patients with fibromyalgia, there does not appear to be a relationship between melatonin levels and the profile of symptoms. Studies have used low participant numbers to investigate a condition that exhibits heterogeneity of clinical characteristics and methodological inconsistencies that would introduce variability of outcomes.

The chronotropic, analgesic and anxiolytic properties have led to melatonin being investigated as a potential therapeutic agent to treat fibromyalgia. Although the number of studies is limited with a diversity of trial design, all investigations have demonstrated beneficial outcomes of melatonin as a therapy for the management of fibromyalgia with a suppression of many of symptoms and an improved quality of life. The outcomes of melatonin administration to patients with fibromyalgia are consistent with improvement of the symptoms due to regulation of circadian rhythm synchronisation and a direct effect on pain pathways, and/or on the levels of signalling chemicals that regulate pain [48-50]. Combination therapy studies with melatonin plus fluoxetine or amitriptyline have provided further evidence of efficacy as a treatment of fibromyalgia and support investigation of other concomitant medications. The available combination therapy evidence is not sufficient to identify preferable treatment options. Further studies with larger samples are required to explore the optimal dosing regimen of melatonin for the management of fibromyalgia.

Conflict of interest

The author declares no conflict of interest for the contributions in this manuscript.

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