



Potential drug therapies for the treatment of fibromyalgia

LAWSON, Kim <<http://orcid.org/0000-0002-5458-1897>>

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Kim Lawson

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Article highlights

- Effectiveness of current pharmacological treatments is limited with many patients discontinuing use.
- Several drugs with diverse mechanisms of action are being investigated as potential treatment approaches.
- The current and potential drugs primarily focus on suppression of central neuronal hyper-excitability.
- Modest efficacy has been reported for a few drugs against selective symptoms such as pain, anxiety and depression.
- Although primary focus has been towards modulation of bioamines and of the $\alpha 2\delta$ subunits of neuronal calcium channels, drugs acting on novel targets such as cannabinoid receptors, melatonin receptors and potassium channels are being investigated.

Review

Potential drug therapies for the treatment of fibromyalgia

Kim Lawson

Department of Biosciences and Chemistry,

Biomolecular Sciences Research Centre,

Sheffield Hallam University,
Faculty of Health and Wellbeing,
City Campus, Sheffield S1 1WB

Tel: +44 (0)114 225 3057

Fax: +44 (0)114 225 3066

Email: k.lawson@shu.ac.uk

Abstract

Introduction: Fibromyalgia (FM) is a common, complex chronic widespread pain condition is characterized by fatigue, sleep disturbance and cognitive dysfunction. Treatment of FM is difficult, requiring both pharmacological and non-pharmacological approaches, with an empiric approach to drug therapy focused toward individual symptoms, particularly pain. The effectiveness of current medications is limited with many patients discontinuing use.

Areas Covered: A systemic database search has identified 26 molecular entities as potential emerging drug therapies. Advances in the understanding of the pathophysiology of FM provides clues to targets for new medications. Investigation of bioamine modulation and $\alpha 2\delta$ ligands and novel targets such as dopamine receptors, NMDA receptors, cannabinoid receptors, melatonin receptors and potassium channels has identified potential drug therapies.

Expert opinion: Modest improvement of health status in patients with FM has been observed with drugs targeting a diverse range of molecular mechanisms. No single drug, however, offered substantial efficacy against all the symptoms characteristic of FM. Identification of new and improved therapies for FM needs to address the heterogeneity of the condition, which suggests existence of patient subgroups, the relationship of central and peripheral aspects of the pathophysiology and a

requirement of combination therapy with drugs targeting multiple molecular mechanisms.

Keywords: fibromyalgia, clinical trials, central sensitization, pain, fatigue, cognitive dysfunction.

ACCEPTED MANUSCRIPT

1. Introduction

Fibromyalgia (FM) is characterised by the core symptoms of generalized chronic pain, fatigue, stiffness, and sleep disturbance of variable intensity and thus considered to be a phenotype of a large spectrum of disorders that have substantial overlap [1-5]. In addition, the cognitive performance (working memory, verbal fluency, episodic memory) of FM patients is poor with the distraction of chronic pain and fatigue contributes to increased impairment of cognition [6,7]. The condition affects 2-4% of populations worldwide, is 7 times more prevalent in females than males and is complicated by the occurrence of co-morbidities which often belong to the family of CSS exhibiting similar symptoms [1-5].

Although aspects of the pathophysiology of FM are still unclear, evidence of involvement of genetics, neurotransmitter and neuroendocrine dysfunctions, autonomic nervous system (ANS) dysfunction, and psychophysiological and cerebral abnormalities has been demonstrated [1-6]. Biological amplification of sensory stimuli (eg mechanical and electrical stimulation, heat, auditory tones) as a result of decreased thresholds are consistent with the pathophysiology of FM [9]. The most common symptom is chronic widespread pain with hyperalgesia (an increased response to a stimulus expected to cause pain) and allodynia (pain caused by a non-noxious stimulus). The presence of central sensitization (CS), an amplified response of the central nervous system to peripheral input, is a characteristic of central sensitivity syndromes where neuronal excitability and hypersensitivity leads, at least, to persistent pain [1-4]. The pain in FM being associated with CS is consistent with an aberrant mechanism of the central nervous system (CNS) processing that causes hypersensitivity to peripheral input. In addition to the central aspects of the condition, the role of peripheral nociceptive generators enhancing the level of CS and the extent of symptoms characteristic of the FM has increasingly received attention. An interrelationship of the various components that could contribute to the pathophysiology of FM acting as amplifiers of each other has been suggested as a cyclic model [5]. Peripheral nerve pathologies, neuroinflammation and skeletal muscle abnormalities and ischaemia have been reported to contribute to the pathophysiology of FM [4,10]. Peripheral small nerve fibre function impairment and epidermal nerve fibre density reduction that may be associated with small fibre neuropathy has been observed in patients with FM [11]. Evidence from a number of

studies support the role of small fibre neuropathy in a subset of FM patients [4,12]. Structural, functional and metabolic alterations in skeletal muscle reported in FM patients include decreased respiratory enzyme activity, distribution of mitochondria, oxidative stress, production of pro-inflammatory cytokines [3,4]. The results have been inconsistent. In addition, a cause of muscle pain in FM patients being associated with aspects of ischaemia such as oxygen uptake and metabolism, lactate accumulation and blood flow have been the subject of investigation [3,4]. Although data are inconclusive, enlarged arteriole-venule shunts due to an increase peptidergic and sympathetic innervation have been reported in FM patients which may contribute to muscle ischaemia and the pain and fatigue characteristic of FM [13]. Peripheral mechanisms involvement in the pathophysiology of FM needs to be taken into consideration in the management of the condition, because of the potential role of input generators to the predominant central mechanisms. Further work is awaited that will clarify the contribution (e.g. a cause or consequence of the condition, identify patient subsets) of the peripheral generators to the pathology of FM and thereby the potential as a treatment target.

1.1 Neurotransmitters and central sensitization

Altered neurotransmitter functionality (eg changed levels, sensitivity of receptors) are associated with the neurophysiological aspects of CS leading to enhanced excitability and increased spontaneous activity. The neurotransmitter abnormalities are associated with a progressive increase in response reflective of slow temporal summation (wind-up phenomena) leading to neuroplasticity perpetuating self-sustaining CS without the need for further stimuli [1-4]. In the cerebrospinal fluid (CSF) of FM patients increased concentrations of substance P (2-3 fold), endogenous opioids (3-4 fold) and glutamate (2 fold) relative to healthy subjects have been observed [9]. In contrast, the CFS of FM patients have lower levels of 5-HIAA, the main metabolite of serotonin, and 3-methoxy-4-hydroxyphenethylene (MPHG), the main metabolite of noradrenaline and blood levels of L-tryptophan and serotonin are lower compared to healthy controls [9]. Further, raised CSF levels of nerve growth factor and brain-derived neurotrophic factor have also been found in FM patients, which may be mediated through glutamatergic transmission [14,15].

Harris et al [16] demonstrated that glutamate levels are higher in the posterior insula in FM patients than controls and these levels change in response to improvements in clinical pain and tenderness. The raised glutamate may be responsible for stimulation of N-methyl-D-aspartic acid (NMDA) glutamate receptors in the dorsal horn of the spinal cord responsible for the wind-up phenomenon [17]. In addition, the diffuse noxious inhibitory control (DNIC), which involves descending opioidergic and serotonergic-noradrenergic efferent pathways from the brain to the spinal cord that downregulate the pain signal, is aberrant in FM patients [18].

Dopamine deficiency in the CNS has also been implicated in the pathophysiology of FM [19]. Dopamine is involved in regulation of CNS pain processing and chronic stress, which is implicated in FM, disrupts dopaminergic activity [20]. In patients with FM dopamine release into the basal ganglia in response to painful stimuli is attenuated or absent [19].

The cerebral mechanisms and abnormalities involved in CS identified in FM patients are reflected by increased activity in the pain processing regions of the brain during painful stimulation [1-4]. Functional imaging of the CNS has demonstrated an altered functioning within the somatosensory cortex, anterior and posterior cingulate, amygdala, medial frontal and parahippocampal gyrus and cerebellum in FM patients [21]. Interestingly, treatment with the tricyclic antidepressant amitriptyline, and thereby modulation of serotonin and noradrenaline levels, correlated clinical response with normalization of function within the bilateral thalamus and basal ganglia [22].

Familial predisposition and genetic polymorphisms have been identified with candidate genes associated with FM including the serotonin 5-HT_{2A} receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 receptor and COMT (catechol O-methyltransferase) polymorphisms [23]. These polymorphisms affect metabolism or transport of monoamines and as identified play a role in sensory pain processing and human stress response. Insight into characterization of FM and possible classification of subgroups leading to more focused treatment with fewer adverse effects could be provided by improved understanding of the genetics of FM.

1.2 Stress processes

FM patients have abnormal responses to stress and an inadequate reaction to stressful events which appear related to functional alterations of the ANS (dysautonomia) and neuroendocrine abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis [24]. The HPA axis in FM shows a decreased cortisol response, and increased adrenocorticosteroid hormone (ACTH) activity to a corticotrophin-releasing factor challenge [17]. A decreased expression of corticosteroid receptors has been associated with the deviation of the HPA system in FM [25]. In addition, disrupted sleep architecture and a decrease in stage 4 sleep in FM patients may be related to decreased levels of growth hormone [26].

Abnormalities of the ANS also seen in patients may be responsible for many of the additional symptoms reported in FM such as alterations in the cardiovascular system efficiency (through increased hypotension, variations in heart rate, pseudoRaynauds and microcirculatory vasoconstriction), sleep disturbance, dry eyes, and gastrointestinal and bladder disorders [27].

1.3 Inflammation

FM is not characterised by demonstrable tissue damage or inflammation, however the impact of the symptoms related to the pathophysiology, particularly CS, will lead to inactivity, exercise intolerance, skeletal muscle deconditioning and raised BMI. As a consequence, inflammatory mediators have been observed to be altered in patients with FM [28]. Various neurochemicals, such as substance P, that are raised in FM due to CS, stimulate a number of immune cells and increase the release and expression of inflammatory mediators (eg cytokines) at nerve endings, increasing nociceptive and sensory sensitivity [29]. Neurotransmitters, cytokines or chemokines can also activate glial cells and mast cells which can thus contribute to enhancement of the CNS activity and CS [1-4].

2. Pharmacological Management

Treatment of FM is challenging requiring both pharmacological and non-pharmacological approaches often with an empiric approach to drug therapy focused toward individual symptoms with an emphasis to pain [3,5]. The efficacy of antidepressants (tricyclic, serotonin and noradrenaline reuptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI)) in the reduction of pain, depression and fatigue, and improvement of quality of life has led to regular use in the treatment of FM patients [30]. The $\alpha 2\delta$ ligands, gabapentin and pregabalin, are also used regularly to manage the pain, sleep and fatigue, and improve quality of life of FM patients [30]. Although pregabalin, duloxetine and milnacipran are FDA approved for the treatment of FM, currently prescribed drugs appear to have little effect on reducing healthcare utilization [31]. The effectiveness of current medications is limited and many patients discontinue use due to the incidence of adverse effects [32,33].

Advances in the understanding of the pathophysiology of FM has started to provide clues to the underlying mechanisms offering potential targets for new medications (Figure 1). Pharmacological treatment focused to the modulation of the central neurotransmitters, serotonin, noradrenaline, dopamine, glutamate and substance P would be compatible with the central component in the pathophysiology of FM [8,30]. Interestingly, greater efficacy has been observed with drugs that inhibit the re-uptake of both serotonin and noradrenaline, modulating at least the DNIC descending inhibitory pathways, relative to selective inhibition of each neurotransmitter [30]. In addition, the $\alpha 2\delta$ ligand pregabalin probably achieves benefit by targeting glutamate and substance P disturbances. The inconsistent success for FM patients of current treatments has led to investigation of bioamine modulation and $\alpha 2\delta$ ligands in addition to novel targets such as dopamine receptors, NMDA receptors, cannabinoid receptors, angiotensin receptors, melatonin receptors and potassium channels for the development of potential drug therapies. Table 1 lists potential drug therapies with specified mechanisms of action exhibiting potential efficacy for the treatment of FM.

3. Search strategy

New and emerging drugs being actively developed in FM clinical trials were reviewed following a comprehensive search of Pubmed, Google, Google Scholar, ClinicalTrials.gov, adisinsight.springer.com and Controlled-trials.com without date restrictions up to 31 January 2016. ClinicalTrials.gov was initially searched using broad terms for fibromyalgia, medications and treatments. The results of this search provided the terms, names of drugs, sponsors, and mechanisms of action that were used in a systematic search the other databases. Studies identified for drugs already marketed for FM were excluded. Google enabled the identification of sources not formally published, such as company and academic institution websites, scientific meeting abstracts. Potential agents that formed the subject of studies whether non-successful or discontinued were considered to provide an understanding of the therapeutic targets investigated.

4 Potential therapies

4.1 Bioamine neurotransmitters

Abnormalities in bioaminergic neurotransmitters (noradrenaline, serotonin and dopamine) have been associated with the core clinical symptoms of FM and modulators of these systems have gained interest are potential treatments [8].

Cyclobenzaprine (flexeril, Amrix) is a tricyclic antidepressant with muscle relaxant properties that exhibits noradrenaline and serotonin reuptake inhibition. A meta-analysis of randomized controlled trials conducted in the 1990s demonstrated that cyclobenzaprine, after 4 to 24 weeks, treatment evoked overall improvement in FM patients with moderate reductions in the individual symptoms of pain and sleep dysfunction [34]. A recent double-blind randomized placebo-controlled trial has provided further evidence in FM patients that very low-dose cyclobenzaprine (1-4mg at bedtime) improved sleep, decreased fatigue, pain and tenderness and improved mood after 8 weeks [35]. In a 12-week, randomized, double-blind, placebo-controlled trial TNX-102 SL (Tonmya) sublingual very low dose (VLD) cyclobenzaprine (2.8mg at bedtime) evoked a significant improvement on sleep quality associated with improvements in multiple other symptoms, such as pain in patients with FM

compared to placebo [36]. Significant improvements with Tonmya were also observed on several fibromyalgia impact questionnaire (FIQ) items (pain, sleep quality, anxiety, stiffness, and sensitivity).

TD-9855 is a noradrenaline and serotonin reuptake inhibitor developed to treat chronic pain and ADHD [37]. In a double-blind placebo-controlled 6-week study TD-9855 (20mg) significantly reduced pain, fatigue and the FIQ score and improved quality of life [37].

Selective serotonin enhancement has been studied with paroxetine (12.5-62.5 mg/day), a selective serotonin reuptake inhibitor, in patients with FM. Pain, depression and anxiety, sleep improvement and functionality increase was assessed in FM patients and paroxetine improved the overall symptomatology [38]. However, paroxetine failed to significantly reduce the pain associated with FM. Trazodone is a second-generation antidepressant of the serotonin antagonist and reuptake inhibitor (SARI) class with strong sedative activity. In a 12-week open-label study trazodone (50-300mg/day) markedly improved sleep quality, sleep duration and sleep efficiency with more moderate effects on FIQ scores, anxiety, depression and pain [39]. In a second open-label study, patients who experienced benefit to trazodone (50-300 mg/day) after 12-weeks treatment received pregabalin (75-450 mg/day), added to the trazodone treatment for an additional 12-week period [40]. Again trazodone significantly improved global fibromyalgia severity, sleep quality, and depression, as well as pain interference with daily activities. After pregabalin combination additional and significant improvements were seen on fibromyalgia severity, depression and pain interference with daily activities, and a decrease in bodily pain was also apparent [34]. 5-hydroxytryptamine (5-HT) 3 receptors are located on neurons in the central and peripheral nervous system, and activation has been shown to cause release of neuropeptides, such as substance P, involved in pain processing [41,42]. Thus, the stimulation of 5-HT3 receptors may be responsible for widespread pain mediated by substance P. The 5-HT3 receptor antagonist, dolasetron, (12.5mg/d iv intermittent) in a randomised, double-blind, placebo-controlled trial of patients with FM reduced pain greater than observed in the placebo group [43]. The secondary outcomes (e.g. fatigue, quality of life) failed to achieve a significant change. Thus, dolasetron was limited to controlling only pain in FM and required to be administered intravenously. Mirtazapine is a selective antagonist at 5-HT2 and 5-HT3 receptors

which also blocks α_2 adrenergic auto-receptors in the CNS. In a randomized placebo-controlled pilot study, mirtazapine (30mg per day) exhibited significant within group improvement of pain and FIQ [44]. Thus in contrast, to combined modulation of serotonin and noradrenaline levels, treatments selective for the serotonergic system produced inconsistent outcomes in FM patients.

Enhancement of the noradrenaline response only has also been studied as a treatment approach to FM. The selective noradrenaline reuptake inhibitor esreboxetine (4, 8 or 10 mg/day), the active enantiomer of reboxetine, has been studied in a double-blind, randomized, placebo-controlled study [45]. Although esreboxetine improved pain, fatigue, FIQ and quality of life scores in patients with FM, the efficacy lacked a dose-response relationship. Droxidopa, a prodrug of noradrenaline, increases CNS levels of noradrenaline [46]. In a double-blind placebo-controlled proof-of-concept study droxidopa monotherapy (200, 400 or 600mg three times daily) or in combination with carbidopa (25 or 50mg three times a daily) reduced pain and FIQ scores in patients with FM, however significance compared with placebo treatment was not observed [47]. The enhancement of noradrenaline levels alone does suggest utility in FM, however current evidence from drugs studied is not consistent as a treatment approach.

Patients with FM have been reported to have an abnormal dopamine response and dopamine D2/D3 receptor availability to pain [48,49]. Consequently, dopamine D3/D2 receptor agonists have been tested in patients with FM in an attempt to rectify this dysfunction. Pramipexole (4.5mg once daily) demonstrated therapeutic benefit in a double-blind, placebo-controlled FM trial with improvements in pain, fatigue and overall function determined by a reduction in the FIQ total score [50]. Pain was decreased by 50% or greater in 42% of patients (but only 14% receiving placebo), with the most common adverse effects, anxiety and weight loss, were transient. Concomitant medications were being taken by most patients in this trial, but it was not clarified whether the improvements due to pramipexole were a summative effect or those FM symptoms not contained by current therapies. The benefits of modulation of the dopaminergic system by dopamine agonists however is not clear because the dopamine agonists ropinirole and terguride failed to evoke a significant therapeutic response in patients with FM [51,52].

The inconsistency of clinical data for drugs that individually target the serotonin, noradrenaline or dopamine pathways in patients with FM again supports the requirement of therapies that modulate more than one of the dysfunctional neurotransmitters, as observed with SNRIs and tricyclic antidepressants. A multi-target approach was further supported with the serotonin/noradrenaline/dopamine reuptake inhibitor, sibutramine, which improved the pain, sleep and fatigue in patients with FM; the symptoms returned within 3-7 days when treatment was terminated [53].

Focus on drugs that target the activities of both dopamine and noradrenaline have received attention as a treatment approach to FM. Modafinil and armodafinil are non-amphetamine stimulants that release dopamine and noradrenaline in the CNS and histamine in the hypothalamus. In the regions of the brain where fatigue is believed to be interpreted modafinil and armodafinil are proposed to elevate histamine, noradrenaline, serotonin, glutamine and dopamine activity [54], thus treatment may allow the brain to interpret a lower fatigue state in patients with FM. In retrospective studies, fatigue associated with FM was reported to be reduced by modafinil [55]. However, armodafinil (50-250mg/d), in a proof-of-concept blinded, randomized placebo-controlled study, however failed to treat the fatigue associated with FM; however, a large placebo effect (up to 46%) was observed in the patient population making interpretation of the outcomes unreliable [55]. Methylphenidate (Ritalin; 10-60mg/day), a neuronal stimulant that inhibits dopamine and noradrenaline reuptake, has been observed to enhance mood and concentration in patients with FM after 30-day treatment, although other symptoms such as pain intensity failed to improve [56].

Due to the limited efficacy observed with antidepressants modulating bioamines and the $\alpha_2\delta$ ligands, pregabalin and gabapentin, in the management of FM symptoms the potential of greater benefit or more preferable outcomes from combined pharmacological therapies has been considered. In a single-blind randomized trial, the combined use of pregabalin (75 mg/day) plus paroxetine (25 mg/day), amitriptyline (25 mg/day) or venlafaxine (75 mg/day) resulted in significantly lower somatic symptom and depression scale scores, better life satisfaction, mood, and sleep quality, higher medication tolerability, and less frequent adverse effects in patients with FM [57].

4.2 Antipsychotic drugs

Second generation antipsychotic drugs have attracted interest in the treatment of chronic pain which is consistent with the receptor affinities exhibited [58]. This has led to the testing of antipsychotic drugs in FM. In a pilot double-blind, randomized, placebo-controlled study the antipsychotic drug quetiapine (up to 300 mg daily), that has affinity for D₂, 5-HT_{2A}, H₁, α ₁ and 5-HT_{1A} receptors demonstrated significant benefits on sleep but not against the other symptoms of FM [59]. However, in patients with a dual diagnosis of major depressive disorder and FM quetiapine (50 to 300 mg daily) significantly improved depression, pain and quality of life scores [60-62]. No significant differences were found between quetiapine XR and amitriptyline treatments for any of the secondary outcomes measured in patients with major depressive disorder and FM [61]. Use of quetiapine in fibromyalgia should therefore be limited to patients with comorbid major depression or have unresolved and disabling depressive and/or anxiety symptoms.

The antipsychotic amisulpride has preferential affinity for pre-synaptic dopamine D₂ and D₃ autoreceptor subtypes but also acts as a potent antagonist at the 5-HT₇ receptor [63]. In contrast to quetiapine, amisulpride in an open-label study did not provide any benefits as a treatment of FM [64]. Interestingly, ziprasidone which has affinity for the dopamine D₂ and D₃, the serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1D}, α ₁-adrenergic receptors and histamine H₁ receptor and inhibits serotonin and noradrenaline reuptake of synaptic reuptake exhibits similarities to the pharmacology of quetiapine [63]. Ziprasidone also failed to provide an appropriate improvement in symptoms of patients with FM [65].

4.3 Anticonvulsants

Mirogabalin (DS 5565), like pregabalin and gabapentin which have demonstrated efficacy in the treatment of FM, is an α _{2 δ} ligand [66]. Identification of α _{2 δ} -1 and α _{2 δ} -2 subunits have shown that a ligand binding to the former contributes to analgesic effects, whereas binding to α _{2 δ} -2 appears to contribute to CNS side effects [67]. Mirogabalin is a novel, preferentially selective α _{2 δ} -1 ligand with a unique binding

profile that may translate to clinically meaningful differences in both efficacy and safety [60]. In a double-blind, randomized, placebo-controlled study of diabetic peripheral neuropathic pain mirogabalin (5-30mg/day) reduced pain [66], results from a randomized, double-blind, placebo-controlled study of microgabalin for treatment of FM are awaited [68].

The efficacy of anticonvulsants is based on the ability to suppress neuronal hyperexcitability, thus drugs exhibiting mechanism of action other than $\alpha 2\delta$ ligand have gained interest as treatments of FM. Levetiracetam binds to a synaptic vesicle glycoprotein, SV2A, and inhibits presynaptic calcium channels reducing neurotransmitter release [69]. Several cellular targets have been proposed to be relevant to the therapeutic activity of topiramate involves several cellular targets which includes inhibition of voltage-activated calcium channels, although the relevance to clinical activity is uncertain [70]. The mechanism of action of lacosamide is not fully defined but is believed to act through voltage-gated sodium channels [71]. Although pregabalin and gabapentin, have exhibited beneficial effects in the treatment of FM reducing pain, fatigue and sleep disturbance [66], evidence was insufficient to draw conclusions on the efficacy of levetriactem, topiramate and lacosamide in the treatment of FM [72,73].

4.3 Glutamate

Memantine is an NMDA glutamate receptor antagonist that has been studied in a double-blind, randomized placebo-controlled trial to assess pain threshold, pain perception, cognitive state, anxiety and depression in FM patients [74,75]. Preliminary evidence of memantine as a treatment of FM demonstrated a significant decrease in pain with an improvement in all other secondary outcomes except anxiety. Memantine treatment resulted in an increase in cerebral metabolism in FM patients with a correlation between choline levels and the FIQ score in the posterior insula [76].

Yokukansan (TJ-54), a traditional Japanese medicine, is used in clinical situations for treating psychiatric disorders by acting mainly on the glutamatergic and serotonergic nervous system [77]. Yokukansan has demonstrated clinical efficacy in

neuropathic pain conditions with suggested greater effectiveness than traditional medicines, such as tricyclic antidepressants, carbamazepine, gabapentin, and opioids [78]. Although the mechanism of Yokukansan on neuropathic pain has not been established, the potential of alleviating pain in FM have been suggested and the outcomes of clinical trials are awaited [79,80].

4.4 Substance P

Patients with FM have raised levels of substance P within the CNS which could lead to the induction of pain through the activation of neurokinin1 (NK1) receptors [9]. Thus, NK1 receptor antagonists could provide a novel therapeutic approach to counteract central pain transmission. Casopitant, an NK1 receptor antagonist, has been evaluated in a double-blind randomized, placebo controlled trial in FM patients with comorbid depression, and outcomes are awaited [81]. Capsaicin desensitizes nociceptive processes possibly due to depletion of substance P, thus preventing sensory factors activating central neuronal mechanisms responsible for the symptoms of FM. Capsaicin binds to the transient receptor potential vanilloid 1 subunits (TRPV1) which are located in peripheral nociceptors [82]. Topical capsaicin therapy (0.075% 3 times daily for 6 weeks) significantly improved myalgic scores, pain threshold and fatigue, in addition to mood variables in patients with FM that was unresponsive to other treatments [83]. Thus, suppression of the actions of substance P appear to offer benefit in the treatment of FM and further investigations are required.

4.5 Naltrexone

Although naltrexone is an opioid receptor antagonist used in the treatment of alcohol and opioid dependence, low-dose naltrexone (LDN) has exhibited benefit in the treatment of diseases not related to chemical dependency or intoxication. LDN (4.5 mg/day) in a double-blind, randomized, placebo-controlled study in FM patients reduced the pain and depressed mood, but not fatigue and sleep disorder [84]. Microglia antagonism has been suggested as the novel mechanism by which LDN reduces the FM severity [84]. Microglia, which may be abnormally sensitized in FM, can release pro-inflammatory factors in the CNS which interact with neurons, leading to the central facilitation of pain processing [85].

4.6 Cannabinoids

FM has been proposed to be a form of endocannabinoid deficiency which has led to the evaluation of cannabinoids as a treatment approach [80]. Evidence in uncontrolled trials of efficacy of cannabinoids for FM symptoms, although inconsistent, has suggested benefits [87]. In double-blinded, placebo-controlled studies nabilone (0.5-1.0 mg before bedtime) after 4 weeks evoked a significant reduction in pain and anxiety and improvement in quality of life in FM patients [88, 89]. The role of cannabinoids in the treatment of FM is being further investigated with dronabinol (a synthetic form of delta-9-tetrahydrocannabinol, THC) and ZYN001, a pro-drug of delta-9-tetrahydrocannabinol. Dronabinol (mean daily dose of 7.5mg) produced a significant reduction in pain intensity and depression in patients with FM leading to an improvement of quality of life in those patients able to tolerate (approximate 25% drop out rate) the treatment [90]. ZYN001 is the D-(-)-glyceric acid ester of THC which is rapidly hydrolysed by esterases in the skin to THC [91]. Transdermal delivery should provide stable plasma levels and avoid first-pass hepatic metabolism associated with THC metabolite psychotropic effects thereby improving the tolerability profile in FM patients [92].

4.8 Potassium channel

Flupirtine is a centrally acting, non-opiate analgesic that activates Kv/M-channel activity and indirectly suppresses NMDA receptor activity resulting in the inhibition of sustained neuronal activity associated with pain [93]. Effective analgesia has been observed in acute pain conditions, such as traumatic injury, headache and migraine, and in chronic musculoskeletal pain [94]. Initial evidence supports the use of flupirtine as a treatment approach in FM patients where a reduction of pain, sleep disturbance, fatigue and depressive symptoms was observed [95]. Controlled clinical studies are required for the confirmation of the utility of flupirtine in FM.

4.9 Melatonin

Melatonin, *N*-acetyl-5-methoxy tryptamine, is involved in the regulation of sleep. In addition to sleep-inducing properties melatonin and novel melatonin analogues, such as ramelteon, have exhibited analgesic properties suggesting potential use in the management of pain and insomnia of chronic pain conditions such as FM [96]. In an open 4-week pilot study melatonin (3 mg at bedtime) significantly improved severity of pain, tender point count and sleep quality, but not fatigue, depression and anxiety in patients with FM [97]. Improvement of the FM symptoms of pain, sleep disorder and depression were further demonstrated in double-blinded randomized trials with melatonin alone and in combination with fluoxetine or amitriptyline [98,99]. Hussain et al [98] observed that melatonin (3 or 5 mg per day) reduced the pain, sleep disorder, depression and anxiety in patients with FM in contrast to fluoxetine (20 mg per day) which only decreased anxiety, depression and fatigue. The combination of melatonin and fluoxetine was effective in the treatment of most of the symptoms of FM. In a 6 week randomized controlled trial, melatonin (10 mg per day), amitriptyline (25 mg per day) and melatonin (10 mg per day) plus amitriptyline (25 mg per day) significantly improved the pain and sleep quality in patients with FM [99]. Compared with amitriptyline alone, melatonin alone or in combination with amitriptyline gave superior improvement in symptoms, with the combination producing only marginal additional clinical effects. The melatonin analogue agomelatine exhibits both high-affinity human melatonergic MT1 and MT2 receptors agonist and a serotonin 5-HT_{2C} receptor antagonist properties. In two 12 week open-label studies agomelatine (25-50 mg per day) also significantly improved pain, depression and anxiety symptoms in patients with FM [100,101]. But in contrast to melatonin, an improvement in sleep quality was not seen with agomelatine [101]. The stimulation of melatonergic receptors is associated with effectiveness in analgesia and mood treatment of patients with FM, but control of the sleep disorder is inconsistent.

4.10 IMC-1

IMC-1 is a fixed-dose-combination of the anti-herpes virus nucleoside analog famciclovir and celecoxib developed as a treatment for FM, irritable bowel syndrome, chronic fatigue syndrome/ME, and other conditions that may share a similar underlying pathophysiology [102,103]. In a double-blinded, randomized, placebo-

controlled Phase II study IMC-1, evoked significant reductions in pain, fatigue and FIQ scores with improvements in functionality and quality of life at 16 weeks in patients with FM [103]. The outcomes of the study with IMC-1 suggest that tissue-resident herpes virus may be causally related to FM symptoms or recurrence.

5. Conclusion

The effectiveness of current medications for FM is limited and many patients discontinue use due to the incidence of adverse effects. Consequently, the number of drugs being investigated emphasizes the continued interest and need to improve the management of FM. The majority of drugs under investigation are focused towards controlling the hyper-excitability of the central neuronal system. Although benefits have been demonstrated involving a diversity of pharmacological targets, the complexity of FM has resulted in limitations and barriers in drug development. Of the drugs investigated none have provided substantial improvement across the spectrum of symptoms of FM leading to clues of the preferential pharmacology targets for the optimal treatment of the condition.

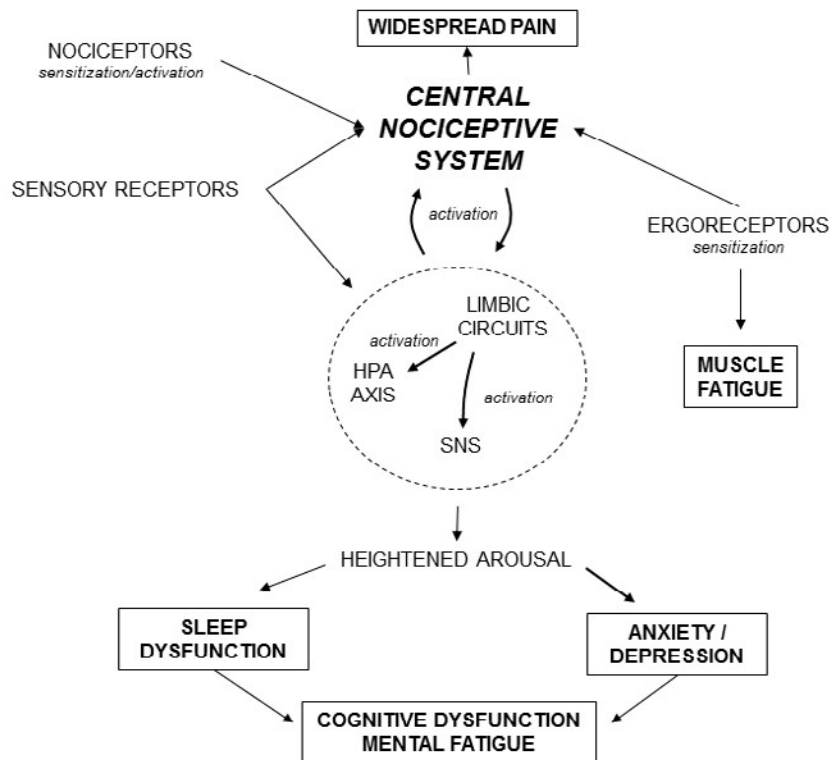
6 Expert opinion

Treatment of FM has been identified as requiring both pharmacological and non-pharmacological approaches often with an empiric approach to drug therapy focused toward individual symptoms with an emphasis to pain. The pharmacological approach of current and potential therapies has been primarily directed towards suppression of the central hyper-excitability associated with the pathophysiology of FM. This has resulted in the evaluation of a range of molecular targets and mechanisms such as bioamine modulation, $\alpha 2\delta$ ligands, dopamine receptors, NMDA receptors, cannabinoid receptors, melatonin receptors and potassium channels that have the potential of suppressing neuronal activity. Although some of the drug treatments discussed are capable of improving health status in patients with FM, not all symptoms were resolved by a single drug and often the consistency of efficacy associated to an individual mechanism of action was not always observed. The range of efficacies, from partial to none, demonstrated by the various therapeutic

approaches in recent clinical trials have provided, albeit limited, insight into potential drug treatment profiles and important clues for condition-focused therapies and improved diagnosis. But barriers in drug development continue to be encountered for the identification of new and improved therapies for FM. The existence of subgroups of FM has been proposed by many studies [104]. The heterogeneity of the condition may be responsible for the modest and limited efficacy often observed. Most of the clinical trials and studies of the pathophysiology of FM and treatments have not taken into account subgrouping and have been directed by the comparison of average outcomes of patient populations. In addition, consideration of targeting peripheral mechanisms that contribute to the pathophysiology and possibly act as sensory input generators has received limited and inconsistent attention. Although drug monotherapy would be the optimum treatment approach, the multidimensional aspects of FM and its high comorbidity with other disorders is consistent with the requirement of combination therapy using drugs targeting different molecular mechanisms and thereby symptoms.

Although a significant proportion of pain patients adequately respond to current analgesics, many patients, such as those with FM do not achieve an adequate experience and often present with major adverse effects. A greater understanding of the pathophysiology of FM, particularly the role of aberrant CNS functioning leading to heightened generalized sensitization to sensory input and peripheral input generators, and efficacy clues gained from current drug investigations has directed interest to a range of potential targets for the identification of new medications. Several existing drugs have demonstrated efficacy in chronic pain conditions and these novel analgesics could offer potential in the treatment of the symptoms of FM [105]. Repurposing of drugs, identifying new uses for existing drugs, bypasses most of the time and cost consuming components of drug development. Thus, these approaches could not only expand the options for the identification of the direction required for condition-focused drugs, but also readily make products available in the usual-care setting. Although the primary endpoints of recent clinical trials with FM patients have changed with more recent attention to global health status rather than over emphasis on any single particular symptom, the ability to transfer the observed outcomes to management requires confirmation.

Figure 1. Pathophysiological processes associated with fibromyalgia that have been identified as potential drug targets. Core symptoms of the condition are indicated in boxes. HPA – hypothalamic pituitary adrenal axis; SNS – sympathetic nervous system.



Declaration of interest

K Lawson has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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106. Table 1. Emerging drug therapies with potential efficacy for the treatment of fibromyalgia.

Drug	Mechanism of Action	Domains accessed	Trial Sponsor	Status
AGN203818	$\alpha 2$ adrenergic agonist	pain	Allergan	Terminated 2015, outcome not published
Agomelatine	Melatonergic receptor agonist and 5-HT ₂ receptor antagonist	pain, mood, cognitive function	University of Messina	Phase II, improved pain and mood
Capsaicin	transient receptor potential vanilloid 1 subunits (TRPV1)	myalgic, pain, fatigue scores	Rheumatology Service at the Specialist Clinic of Cantabria	Phase II, improved symptoms
Casopitant (GW679769)	Neurokinin1 receptor agonist	FIQ	GlaxoSmithKline	Phase II completed
Dolasetron	5-HT ₃ receptor antagonist	pain, fatigue, quality of life	University Hospital of Limoges, France	Phase II, reduced pain only
Dronabinol	Cannabinol	pain, depression, quality of life	Heidelberg University	Phase II, reduced pain and depression
Droxidopa	Noradrenaline prodrug	pain, FIQ	Chelsea Therapeutics	Phase II, improved symptoms
DS-5565	$\alpha 2\delta$ ligand	pain	Daiichi Sankyo	Phase II planned
EMA401	Angiotensin II receptor antagonist	pain	Spiniflex	Phase II planned
Esreboxetine	Noradrenaline reuptake inhibitor	pain, FIQ, fatigue, quality of life	Pfizer	Phase II, improved symptoms
Flupirtine	Potassium channel activation	pain, FIQ	Lupin	Phase II planned
IMC-1	Viral suppression of herpes virus	pain, fatigue, FIQ	Innovative Med Concepts	Phase II, improved symptoms
Levetiracetam	Synaptic vesicle glycoprotein ligand	pain	UCB Pharma & Uni of California	Phase II, inconclusive outcomes
Memantine	NMDA antagonist	pain, cognitive state, depression	Aragon Institute of Health Sciences	Phase II, improved symptoms
Mirtazapine (Org 3770)	Adrenergic and serotonin receptor antagonist	pain, FIQ	Meiji Seika Pharma Co., Ltd.	Pilot, reduced pain and FIQ scores
Nabilone	Cannabinoid receptor agonist	pain, sleep, quality of life	Winnipeg Regional Health Authority	Phase II, improved symptoms
Naltrexone	Opioid receptor antagonist	pain, fatigue, mood, sleep	Stanford University	Phase II, improved pain and mood
Neurotrophin	Neuromodulator	pain	<i>Yukioka Hospital, Osaka</i>	Phase II, reduced pain
Paroxetine	Serotonin reuptake inhibitor	pain, mood, sleep, functionality	Duke University Medical Center, USA & GlaxoSmithKline	Phase II, improved symptoms
Pramipexole	Dopamine agonist	FIQ	Boehringer Ingelheim	Phase II, improved symptoms
Quetiapine	Antipsychotic	FIQ	East Tennessee State Uni & Astra Zeneca	Phase II benefits limited to patient subgroup
TD-9855	Noradrenaline serotonin reuptake inhibitor	pain, fatigue, FIQ	<i>Theravance Biopharm</i>	Phase II, improved symptoms

TNX102SL cyclobenzaprine	Noradrenaline, serotonin reuptake inhibition	pain, sleep	Tonix Pharmaceuticals	Phase II improved symptoms.
Trazodone	5-HT receptor antagonist and serotonin reuptake inhibitor	FIQ	Universidad de Granada EP Calandre	Phase II, improved symptoms
Yokukansan	Herbal medication	insomnia	St. Marianna University School of Medicine	Phase II planned
ZYN001	Cannabinoid	pain, quality of life	Zynerba	Phase II planned

107.

108. Sources of information, Medline(Pubmed), ClinicalTrials.gov, adisinsight.springer.com and
Controlled-trials.com.

109. FIQ – fibromyalgia impact questionnaire;

110.

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