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Pharmacological treatments of fibromyalgia: Do complex conditions need complex therapies?

Kim Lawson

Biomedical Research Centre, Sheffield Hallam University, Faculty of Health and Wellbeing, City Campus, Sheffield S1 1WB, UK

Fibromyalgia (FM) is a chronic pain condition, with auxiliary symptoms, such as sleep disturbances and fatigue. Although many of the mechanisms of action targeted by the drugs used to treat FM have been focused to the management of single symptoms, drugs (e.g. pregabalin, duloxetine) have now been identified that demonstrate a multidimensional effect. However, such drugs often fail to demonstrate acceptable efficacy in the majority of the patient population. Thus, the mechanisms of action of the drugs studied as treatments for FM are either identifying subgroups within the pathophysiology of the condition or suggesting that a mechanism of action that will offer universal efficacy has, as yet, to be identified.

Introduction

Fibromyalgia (FM) is a common chronic diffuse pain condition [1]. Patients with FM typically present with allodynia and hyperalgesia, in addition to experiencing many auxiliary symptoms, such as sleep disturbances, chronic fatigue and cognitive difficulties [1–3]. Localized or regional pain in most patients with FM precedes the widespread pain, which could suggest the latter develops from the former. Although pain is a predominant feature of FM, pathophysiology related to the alteration in pain processing does not, however, clearly explain other commonly experienced symptoms, such as fatigue and sleep disturbances. Classification of FM is often further complicated by the presence of co-morbid conditions (Figure 1). It is estimated to affect 2–4% of the general population, increasing to greater than 7% of those over 70 years of age [4]. The management of FM is complicated by the lack of understanding of whether the pathophysiological mechanisms proposed are causal or consequential and overlap with symptoms of other health conditions (e.g. chronic fatigue syndrome, myofascial pain, systemic lupus erythematosus). It is generally assumed to be a complex and difficult to treat disorder, which usually requires a multidisciplinary approach, using both pharmacological and non-pharmacological interventions [5,6].

Several hypotheses have been proposed regarding the pathophysiology of FM, which include a dysfunction of pain modulatory systems within the central nervous system (CNS), neuroendocrine dysfunction and dysautonomia [7–10]. This article will consider the value of potential drug targets for treatment of FM and how this information can offer insight into the pathophysiology of the condition. The predominant mechanisms of action, which this review will focus on, by which drugs have demonstrated efficacy in patients with fibromyalgia or are currently in clinical trials are summarized in Table 1.

Central sensitization

FM is often described as a condition of heightened generalized sensitization to pain, which is associated with spatially distributed allodynia and hyperalgesia. A lack of underlying peripheral structural damage and inflammatory signs suggests that little peripheral stimulation is required [7,56]. This is supported by the failure of anti-inflammatory medications, such as the non-steroidal anti-inflammatory drugs, naproxen and ibuprofen, and prednisone to be effective treatments of FM [57–59]. Indirect evidence suggests a sensory abnormality, with alterations in substance P levels, *N*-methyl-D-aspartate acid (NMDA) receptors and mono-aminergic activity in patients with FM that would be consistent with central sensitization of nociceptive afferent pathways [60].

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Corresponding author: Lawson, K. (K.Lawson@shu.ac.uk)

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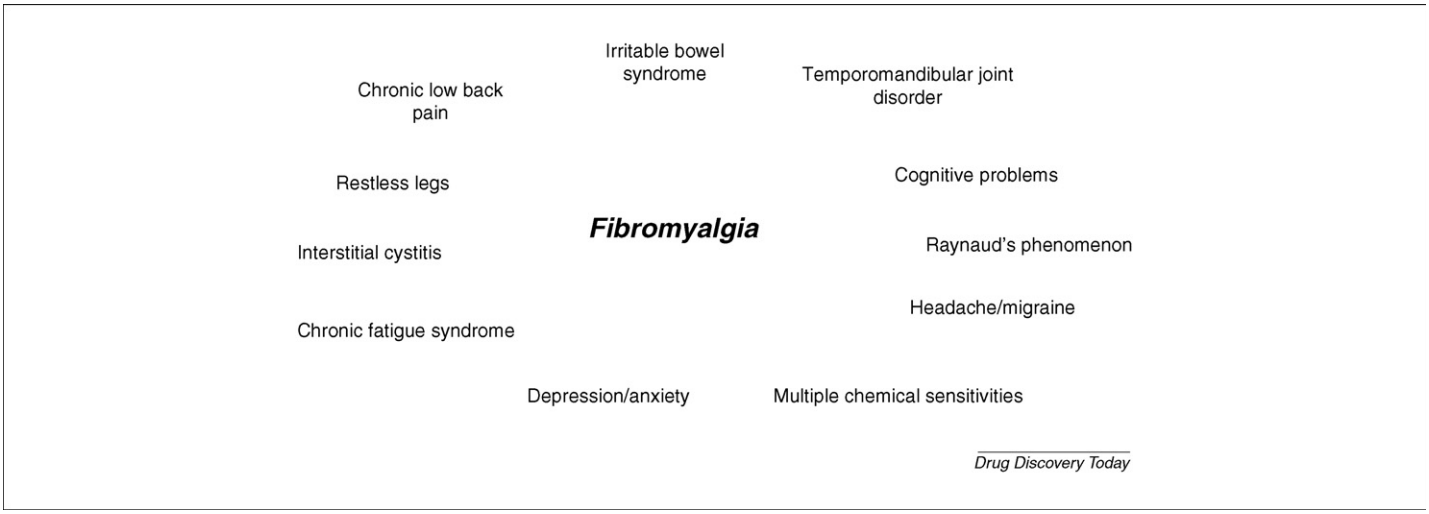

FIGURE 1

Conditions frequently co-morbid with fibromyalgia.

TABLE 1

Summary of pharmacological treatments of fibromyalgia

Mechanism of action	Drug	Benefit outcome	Refs
Serotonin/noradrenaline reuptake inhibition	Amitriptyline	Pain, sleep quality	[11,12,78,79,80,81]
	Duloxetine	Pain, PGI score, CGI score, FIQ score	[13,14]
	Milnacipran	Pain, PGI score, FIQ score	[15,16]
	Venlafaxine	Pain, FIQ score, depression	[17]
Selective serotonin reuptake inhibition	Fluoxetine	Pain, FIQ score, depression	[18–20]
	Paroxetine	CGI score, FIQ score	[21]
	Citalopram	Inconsistent	[22]
Noradrenaline reuptake inhibition	Reboxetine	Awaiting RCT completion	[23]
	Lofepramine	Awaiting RCT completion	[24]
Serotonin/noradrenaline/dopamine reuptake inhibitor	Sibutramine	Pain, fatigue, sleep quality	[25]
Dopamine receptor agonism	Pramipexole	Pain, fatigue, FIQ score	[26]
	Ropinirole	Awaiting RCT completion	[27]
	Rotigotine	Awaiting RCT completion	[28]
5HT receptor antagonism	Tropisetron	Pain, cardiac dysfunction	[29]
NMDA antagonism	Ketamine	Pain	[30]
	Dextromethorphan	Pain	[31,32]
	EVT101	Awaiting RCT completion	[33]
$\alpha 2\delta$ subunit ligand	Gabapentin	Pain, FIQ scores, CGI scores, PGI scores, sleep quality	[34]
	Pregabalin	Pain, FIQ scores, CGI scores, PGI scores, sleep quality, fatigue	[35–38]
GABA receptor agonism	Sodium oxybate	Pain, sleep quality, fatigue	[39,40]
	Levetiracetam	Awaiting RCT completion	[41]
	Gaboxadol	Awaiting RCT completion	[42]
Benzodiazepine receptor agonism	Temazepam	Sleep quality	[43]
	Alprazolam	Sleep quality	[44]
	Bromazepam	Inconclusive	[45]
	Zolpidem	Sleep quality	[46]
	Zopiclone	Sleep quality	[47,48]
	Eszopiclone	Awaiting RCT completion	[49]
Cannabinoid	Nabilone	Pain, FIQ score	[50]
	Dronabinol	Awaiting RCT completion	[51]
Na^+ channel blocker	Lacosamide	Awaiting RCT completion	[52]
	Zonisamide	Awaiting RCT completion	[53]
Growth hormone	Ibutamoren	FIQ score, tender point score	[54]
Glucocorticoid	Hydrocortisone	Awaiting RCT completion	[55]

5HT: 5-hydroxytryptamine, NMDA: *N*-methyl-D-aspartate acid, GABA: γ-aminobutyric acid, PGI: patient global impression, CGI: clinical global impression, FIQ: fibromyalgia impact questionnaire, RCT: randomized controlled trial.

The cause of the interference in pain processing remains unclear, although involvement of chronic psychological stressors, peripheral pain generators and inflammatory mediators has been proposed [7,61]. For example, changes in peripheral factors, especially in intramuscular microcirculation and in muscle energy metabolism, could act as excitatory triggers for the alterations in the nociceptive system in the CNS and for multifocal pain in the muscles [7,62].

Central sensitization implies spontaneous nerve activity, expanded receptive fields and abnormal temporal summation (or 'wind-up') within the spinal cord. NMDA receptors, found at the postsynaptic membrane in the dorsal horn neurons of the spinal cord, are proposed to play a role in these phenomena. The activation of NMDA receptors by glutamate, central to a variety of neuronal processes including synaptic plasticity and neurotoxicity, leads to a rise in intracellular calcium and the initiation of second messenger pathways that mediate long-term potentiation (enduring enhancement of synaptic transmission after the initiating stimulus has ceased) [63–65]. In addition, the calcium influx induces nitric oxide production by neuronal nitric oxide synthase which is believed to evoke a retrograde signalling action, enhancing presynaptic glutamate release [66]. Studies on levels of nitric oxide in FM, however, have not been conclusive [67].

Substance P, a peptide neurotransmitter associated with pain transmission, in addition to many other actions, enhances the response of NMDA receptors to glutamate [66]. Elevated levels of substance P are found in the cerebrospinal fluid of patients with FM [68,69]. Thus, NMDA-receptor-mediated mechanisms seem to be potential candidates for the pain in FM.

NMDA antagonism

NMDA receptor antagonists are not widely accepted as treatments of chronic pain, because of a lack of specificity and thereby associated adverse effects. Nevertheless, ketamine and dextromethorphan have demonstrated efficacy (pain score) as antihyperalgesics in the treatment of FM [30–32]. Selective antagonists of the NR2B subunit-containing NMDA receptor, for example ifenprodil, are antinociceptive in preclinical pain models, with much lower side effect profiles compared with other NMDA receptor antagonists [70]. Further controlled trials in FM would be beneficial to determine the role of NMDA receptors in this condition, especially since the lack of selectivity of ketamine has questioned the role of this mechanism in the antinociceptive properties observed with the suggestion of, at least, dopamine receptor agonism being involved [71,72].

A recent study demonstrated that the reduction of temporal summation of pain from repeated thermal and mechanical pressure stimulation of the skin by dextromethorphan did not significantly differ between patients with FM and normal controls [73]. These findings suggest that NMDA-receptor-related mechanisms are not altered in patients with FM and are consistent with the FM pain involving dysfunction of another mechanism, such as enhanced descending facilitation [5].

Descending pain-modulating pathways

The endogenous descending pain-modulating system links the periaqueductal grey and the rostal ventromedial medulla with the spinal cord. Evidence suggests that in FM there is a failure to modulate pain, that is a consequence of noxious stimuli, because of dysfunction in the descending inhibitory pathways [74–76]. Serotonergic and noradrenergic neurons are involved in the inhibitory mechanisms of the descending pain-modulating pathways in the brain and spinal cord [7]. Thus, enhancement of the activity of serotonin and noradrenaline within these structures would be expected to reduce pain.

Bioamine reuptake modulators

First-line pharmacological therapies for FM are often antidepressants, particularly tricyclic antidepressants (TCAs), such as amitriptyline and dothiepin [5,77]. The analgesic effects of TCAs could be explained by inhibition of the reuptake of serotonin and noradrenaline into the neuronal terminal modulating the descending tracts, influencing the dorsal horn neurons. In addition, low-dose TCAs have been significantly effective in the management of sleep and fatigue in patients with FM [6,11,12,78–81]. Although clinically applicable improvement in pain ($\geq$30% reduction) with TCAs was observed in randomized controlled trials (RCTs), this was often limited to 25–45% of FM patients given these drugs. The limited utility of TCAs as treatments of FM has been related to unpredictable responses, the adverse effects and the lack of long-term efficacy evidence. The pharmacological properties profile of TCAs (e.g. noradrenaline vs. serotonin) has been suggested as being responsible for the unpredictable responses [5,82].

The evaluation of selective serotonin reuptake inhibitors (SSRIs) in clinical trials with FM patients have shown mixed results [18,19,21,22]. SSRIs with higher specificity for serotonin reuptake inhibition (e.g. citalopram) have been less successful than those with mixed serotonin and noradrenaline activity (e.g. fluoxetine and paroxetine). These findings suggest that agents with selective serotonin activity are less consistent as treatments of FM than those with effects on both serotonin and noradrenaline levels. This conclusion is supported by the finding that the combination of fluoxetine and amitriptyline was more effective (reduced pain score, fibromyalgia impact questionnaire (FIQ) score and improved sleep) than either drug alone in FM [20]. Although moclobemide, an inhibitor of monoamine oxidase that elevates concentrations of serotonin, noradrenaline, dopamine and adrenaline, improved pain symptoms, it failed to provide benefit related to the sleep dysfunction which plays a central role in FM [83].

This has led to a focus on new selective serotonin and noradrenaline reuptake inhibitors (SNRIs; e.g. duloxetine, milnacipran) [5,77]. Milnacipran, similarly to amitriptyline, preferentially inhibits noradrenaline reuptake and also exhibits weak NMDA receptor inhibition [84,85]. Duloxetine has a balanced inhibitory profile of serotonin and noradrenaline reuptake [84].

In an RCT, milnacipran relieved pain symptoms and improved measures of quality of life (e.g. patient global impression of change (PGI) score, FIQ) associated with FM [15,16]. A reduction of pain by $\geq$50% was only observed in up to 37% of the patient population receiving milnacipran. Patients with and without depression were included in the study and a greater improvement in pain reduction was recorded in non-depressed subjects treated with milnacipran. These findings are consistent with the analgesic effects of milnacipran not being as a consequence of improvement of mood. The

effectiveness of milnacipran as a treatment of FM has been further confirmed in a 3-month Phase III RCT involving 1196 patients, and publication of the data is awaited [86].

In two RCTs involving patients with FM, with and without depression, duloxetine significantly improved measures of pain and several measures of quality of life (e.g. FIQ, clinical global impressions (CGI), PGI) [13,14]. The reduction of pain and improved quality of life by duloxetine were independent of the presence of depression, suggesting the symptoms of FM are not related to this mood state. Although the RCTs provided evidence that duloxetine is an effective treatment of FM this was limited to female patients and a ≥50% decrease in any pain score was only achieved in up to 41% (dependent on the treatment regime) of subjects.

SNRIs lack many of the adverse effects of TCAs because their pharmacological profiles do not involve interaction with adrenergic, cholinergic or histaminergic receptors, or sodium channels. This was reflected by duloxetine and milnacipran being well tolerated; however, it is of note that insomnia was a frequently reported adverse effect for duloxetine in a condition that presented sleep dysfunction as a major symptom [13,14].

SNRIs are effective treatments of some, but not all, patients with FM. Although they are well-tolerated, which is an issue that has limited the use of TCAs, a significant number of patients do not gain benefit from SNRI treatment, which questions the relationship between the mechanism(s) of action and the pathophysiology of FM. The balance of the noradrenaline versus serotonin reuptake inhibition may be a critical issue that could be addressed by other SNRIs being evaluated in clinical studies. However, initial indications could suggest that this mechanism alone is not sufficient to control the pathophysiology of FM. Recently, the SNRIs, desvenlafaxine and AD-337, failed to achieve the primary endpoint in Phase II trials in patients with FM [87,88]. Although modulation of bioamine levels is the primary mechanism of TCAs, SSRIs and SNRIs described above, these agents act on multiple nociceptive targets at central and peripheral locations, which could contribute to the clinical effects obtained [77,82,89]. These molecules have often been developed to act optimally at sites related to the bioamine systems and not at the additional targets, which could account for the lack of universal effectiveness in this patient population. Although the glutamate–NMDA receptor complex plays an important role in pain transmission and milnacipran and amitriptyline evoke NMDA receptor antagonism [82,89], the clinical relevance of this property is unclear.

Tramadol exhibits a mixture of pharmacological properties with the (+)-enantiomer evoking serotonin reuptake inhibition and weak μ-opioid receptor agonism, while the (−)-enantiomer has a higher affinity for the noradrenaline reuptake mechanism. Tramadol alone, or in combination with paracetamol, has demonstrated a reduction in pain and an improvement in health-related quality of life in patients with FM [90]. The contribution of the opioid receptor agonist activity to these outcomes is unknown. Clinical trials of opioid agonists as treatments of FM have been limited and have not provided clear scientific evidence supporting or against such an approach. The usefulness of opioids in controlling FM pain may be hindered by the suggestion that the opioid systems may be maximally activated or a decreased availability of central μ-opioid receptors results in a reduced efficacy in this patient group [91,92].

Dopamine

In addition to noradrenaline and serotonin being involved in the spinal descending inhibitory pathways, dopamine plays a role at the supraspinal level of the thalamus, basal ganglia and limbic cortex [93–96]. A reduction of presynaptic dopamine metabolism in FM, as demonstrated by positron emission tomography, supports a disruption of dopaminergic neurotransmission being involved in the pathophysiology of FM [97]. In addition, it has been reported that patients with FM have an abnormal dopamine response to pain [98]. In an attempt to rectify this dysfunction, the dopamine D3/D2 receptor agonists pramipexole and ropinirole have been tested in patients with FM [26,27]. Pramipexole reduced pain and improved fatigue and overall function as indicated by the FIQ score in patients with FM with no withdrawals from the study because of adverse effects [26]. As observed with SNRIs, pramipexole failed to evoke ≥50% decrease in pain in the majority of patients with this efficacy level only being achieved in 42% of subjects. The patients in this trial, however, were taking their current medication, which included opioid analgesics, making the study outcomes difficult to interpret. By contrast, ropinirole failed to achieve a significant therapeutic response in patients with FM [27].

Interestingly, sibutramine, a serotonin/noradrenaline/dopamine reuptake inhibitor, has been reported to improve pain, sleep and fatigue in patients with FM in a pilot retrospective study; when sibutramine was stopped, FM symptoms returned within 3–7 days [25]. Further studies with sibutramine are required to determine the value of such a combined pharmacological profile in the treatment of FM.

$\alpha_2\delta$ ligands

The $\alpha_2\delta$-subunit of voltage-gated calcium channels is responsible for calcium influx into nerve terminals and the subsequent release of neurotransmitters, such as glutamate and substance P, that play a role in pain processing [99,100]. Thus, ligands of the $\alpha_2\delta$-subunit that block presynaptic calcium channels will decrease the release of multiple neurotransmitters and attenuate abnormal hyperexcitability of neuronal networks as that associated with chronic pain. The $\alpha_2\delta$-subunit ligand, gabapentin, improved pain, FIQ, CGI and PGI scores and sleep quality in patients with FM, although it demonstrated a high incidence of adverse effects (e.g. sedation, dizziness) [34]. A ≥30% reduction in pain score was only achieved in 51% of gabapentin-treated patients. Pregabalin, like gabapentin, is an $\alpha_2\delta$-subunit ligand that exhibits anti-hyperalgesic, anxiolytic and anticonvulsant properties and has recently been approved by the FDA for the treatment of FM [100,101]. In two RCTs (of 8 weeks and 14 weeks) involving patients with FM, pregabalin significantly reduced the pain score and improved sleep and fatigue demonstrating efficacy against the three major symptoms of the condition [35,36]. Although significantly more patients had ≥50% improvement in pain in the pregabalin than in the placebo group, this level of benefit was in a limited (up to 30%) number of subjects. When ≥30% decrease in pain scores was determined, the number of responders only increased up to 50%.

A 6-month double-blind, placebo-controlled trial demonstrated durability of the effects of pregabalin on pain, fatigue and sleep disturbance with an onset of effects within 1 week of treatment [37,38]. Pregabalin significantly delayed the time to loss of therapeutic response, with 68% of patients maintaining therapeutic response at the end of the trial.

The trials involved selection of 'responders' to pregabalin before randomizing patients to the double-blind phase of the studies [37,38]. The criteria for responders in the acute studies was a $\geq$30% decrease in pain scores and in the 6-month study a more demanding $\geq$50% decrease in pain scores was required. Of the 1051 patients enrolled on the 6-month study, only 566 (54%) were included in the double-blind phase.

Functionally, $\alpha_2\delta$-subunit ligands exhibit use-dependent properties [100]. The property of use-dependence gives these drugs a significant clinical advantage in that they will be expected only minimally to alter physiological synaptic function, but significantly modulate pathological function related to maintained depolarization or hyperexcitability. Although this pharmacological profile is consistent with the anti-hyperalgesic benefits observed during the RCTs of pregabalin in patients with FM, the high number of non-responder subjects has yet to be explained pharmacologically. The highest dose (600 mg/day) of pregabalin studied in fact conferred little additional benefit relative to that gained with the lower doses (300 and 450 mg/day), suggesting that in pregabalin-responders an efficacy ceiling was met, but this dose did demonstrate an increase in the incidence of adverse effects [35-37].

Gamma-aminobutyric acid (GABA)

Gamma-hydroxybutyrate (GHB) is a precursor to GABA and exhibits agonist activity at both the GHB-specific receptor and $GABA_B$ receptor [102]. Sodium oxybate, the sodium salt of GHB, provided significant improvements in the major symptoms of FM (i.e. pain, tenderness, sleep quality and fatigue) during an 8-week study [39,40]. The benefits of sodium oxybate in FM have been largely attributed to its capacity to consolidate and improve deep sleep. A significant correlation ($r = 0.55$, $p < 0.001$) was achieved between changes in the pain scale and improvements in sleep quality with the suggestion that the improvement in pain was related to improved sleep. The specific mechanism responsible for the sleep disruption in FM is unclear and, therefore, the related trigger of the pain cannot be explained. Whether the pathophysiology for one symptom is responsible for the initiation of another symptom, or a single mechanism is concomitantly responsible for more than one symptom still requires determination.

Benzodiazepine (BZD) and non-BZD modulators of the BZD receptors (BZD1 and BZD2) located on the $GABA_A$ receptor complex have been evaluated in patients with FM as sedative hypnotics [4,5,77]. In clinical trials with the BZDs, temazepam, alprazolam and bromazepam, which act non-selectively at the two BZD receptors, outcomes were inconsistent [4,5,77]. Although temazepam improved sleep quality in patients with FM, there was no concomitant improvement in pain or fatigue symptoms [43]. Thus modulation of BZD receptors evokes a general sedative effect in the patient rather than management of the condition. The short-acting non-BZDs, zolpidem and zopiclone, which interact preferentially with the BZD1 receptor, improved sleep in patients with FM, but again, in contrast to sodium oxybate, also failed to improve pain [46–48]. These findings question modulation of the GABA receptor (alone) as a primary mechanism responsible for the beneficial outcomes with sodium oxybate and could suggest that other mechanisms of action, such as the GHB receptor, could be responsible for the effectiveness of this drug [103].

Hypothalamic–pituitary–adrenal (HPA) axis

Research suggests that the pain-processing pathways may not be the only part of the CNS involved in the pathophysiology of FM, but may also include the HPA axis and the autonomic nervous system.

In some patients with FM the HPA axis is disturbed with elevated cortisol levels lacking diurnal fluctuation and blunted cortisol secretion in response to stress [7,10]. This is consistent with the HPA axis being underactivated and some patients with FM exhibiting a subnormal adrenocortical function. There is no evidence of structural abnormalities in the endocrine organs of the HPA axis; therefore, the altered cortisol levels found in patients reflect HPA dysfunction. The current data do not allow an explanation of the pathophysiological implications or location of the defect of the HPA dysfunction. As a consequence whether the changes in the HPA axis are causal or consequential of FM remains a point of controversy. Further there is not sufficient evidence to recommend corticosteroid replacement as a general therapy in FM.

Dysautonomia, involving exaggerated neural sympathetic activation, has also been suggested to be responsible for the generation and maintenance of the symptoms of FM [11]. A reduction in pain and number of tender points in patients with FM follows selective sympathetic blockade with guanethidine with restoration of the symptoms by noradrenaline injections [104,105]. Studies (e.g. analysis of heart rate variability) indicate that there is increased sympathetic and decreased parasympathetic activity in patients with FM, resulting in a persistently hyperactive sympathetic nervous system that is hyporeactive in response to stress [106–108]. In such circumstances chronic hyperstimulation of the β-adrenergic receptors of the sympathetic nervous system could lead to receptor desensitization and downregulation. In addition to a relationship between the major symptoms (pain, sleep disorders and fatigue) of FM and dysautonomia, the blunted sympathetic activity to stress and impaired parasympathetic modulation would explain the prevalence of syncope, morning stiffness, pseudo-Raynaud's phenomenon and intestinal irritability observed in this patient population [9,11]. As with changes in the HPA axis whether the dysautonomia is causal or consequential still requires clarification. Although TCAs and SNRIs, through modulation bioamine levels, may achieve benefit in the treatment of FM by an effect on descending pain pathways, the lack of tolerance or efficacy of these drugs may be associated with an augmentation of the sympathetic component of the dysautonomia.

Future directions

Although drugs as treatments of FM are being identified that demonstrate efficacy against multiple domains (e.g. pain and function) of the condition, such agents are identifying refractory subgroups of patients. In addition, because the pharmacological properties (bioamine modulation, calcium channel blockade) of these treatments are similar to those of currently available medications, the potential of long-term (years rather than months)

adverse effects to which patients with this chronic condition are highly sensitive are awaited to determine true efficacy value.

Current clinical studies (Table 1) will provide essential information in two directions of future pharmacological approaches, optimal bioamine modulation and novel therapeutic targets, to FM. Although drugs that modulate bioamine levels (noradrenaline, serotonin and dopamine) and associated structures (dopamine receptors) have demonstrated efficacy, present data do not indicate the optimal pharmacological profile required. Therefore, the outcomes of studies with the selective noradrenaline reuptake inhibitors, reboxetine [23] and lofepramine [24], and the dopamine agonists, ropinirole [27] and rotigotine [28], will provide further clues to the role(s) played by the bioamine neurotransmitters and could indicate whether all three need concurrent modulation to achieve the desired benefits profile. Novel therapeutic approaches to the management of FM include cannabinoids and sodium channel blockade. The synthetic cannabinoids, nabilone, has recently been shown to significantly reduce pain and improve function in patients with FM [50]. It was suggested that cannabinoids, such as nabilone, which was well-tolerated by the patients, may be useful adjuncts for pain management in FM. Isoforms of the voltage-gated sodium channel have been implicated in neuropathic and inflammatory pain states and thus isoform-specific blocking drugs may evoke analgesia without the limitations of the current broad-spectrum sodium channel blockers [109]. The assessment of lacosamide and zonisamide in patients with FM will provide insight into the potential of sodium channels as therapeutic targets in this condition [52,53].

Conclusion

FM is a complex and difficult to treat disorder, which usually requires a multidisciplinary approach using both pharmacological and non-pharmacological interventions. Many of the mechanisms of action targeted by the drugs used to treat FM have been focused to the management of single symptoms rather than the condition. Drugs (e.g. pregabalin, duloxetine and sodium oxybate) have now been identified that demonstrate a multidimensional effect in this condition. However the relationship of their primary mechanism of action to the pathophysiology of FM is difficult to determine, especially in light of the large percentage of patients who are refractory to these treatments. Whether the refractory state of these patients is a multidrug property or is drug specific cannot be concluded from the available data. While the former would indicate that the optimal drug target(s) for FM has not, as yet, been identified, the latter situation would support the existence of subgroups of patients with potentially differing pathophysiology.

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