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MINIREVIEWS

Emerging pharmacological strategies for the treatment of fibromyalgia

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Abstract

Fibromyalgia (FM) has been described as a chronic clinical condition related to multisensory hypersensitivity presenting with a complex of symptoms dominated by chronic widespread pain associated with the existence of a range of co-morbidities, such as fatigue, sleep disturbance, cognitive impairment, anxiety and depression. Current treatments include drugs that target serotonin and noradrenaline levels within the central nervous system, *e.g.*, tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors, and voltage-gated calcium channel subunit ligands, *e.g.*, gabapentin and pregabalin. Investigation of a range of novel targets, such as melatoninergic, cannabinoid, dopamine, NMDA, angiotensin, orexin and opioid receptors, and ion channels, in addition revisiting bioamine modulation and subunits has provided efficacy outcomes that improve the health status of patients with FM. Nevertheless, modest and limited efficacy is often observed reflecting the heterogeneity of FM with existence of subpopulations of patients, the contribution of peripheral and central components to the pathophysiology, and the extensive range of accompanying co-morbidities. The complexity and multidimensional nature of FM is emphasized by the diversity of pharmacological targets gaining interest. Clues to underlying mechanisms which offer themselves as novel and potential targets for new medications are being provided by advances in the understanding of the pathophysiology of FM.

Key words: Fibromyalgia; Chronic pain; Fatigue; Central sensitization; NMDA receptors; Melatonin receptors; Gabapentanoids

Core tip: Fibromyalgia (FM) is a multidimensional chronic pain condition that current therapies provide modest and limited efficacy due to the heterogeneity of the condition, contribution of peripheral and central components to the pathophysiology, and a range of co-morbidities. Drugs acting on novel and existing targets, such as melatoninergic, cannabinoid, dopamine, NMDA, angiotensin, orexin and opioid receptors, ion channels, bioamine processes and

subunits have provided efficacy outcomes that improve the health status of patients with FM. An understanding of the pathophysiology of FM is providing potential targets for new medications.

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INTRODUCTION

Fibromyalgia (FM) has been described as a chronic clinical condition related to multisensory hypersensitivity[1,2]. Thus, FM presents with a complex of symptoms dominated by chronic widespread pain, characterized by hyperalgesia and allodynia, as a consequence of amplified responses of the central nervous system (CNS) to peripheral sensory input leading to enhanced neuronal excitability. It is further complicated by the existence of a range of co-morbidities, such as fatigue, sleep disturbance, cognitive impairment, anxiety and depression, which present with variable intensity[1,2].

Epidemiology

The classification of FM has often been based on fulfilment by the patient of the American College of Rheumatology (ACR) 1990 criteria which require a history (at least 3 mo) of widespread pain in all 4 quadrants of the body and pain in 11 of 18 tender point sites at 9 symmetrical locations[3]. Application of the ACR 1990 criteria has resulted in the reporting of the prevalence of FM to be 0.4%-8% of the population with the condition being more common in females than males[4,5]. As a consequence, FM presents a major financial and social burden to patients and healthcare systems. Although the ACR 1990 criteria are often used for diagnosis they were developed for research classification of FM and are focused to the pain and subjective tender point score with no consideration of the other symptoms characteristic of FM. The subjectivity of the current diagnostic approach and the lack of biochemical tests for FM have led to many patients that would fulfil the ACR 1990 FM criteria remaining undiagnosed[6,7]. Thus, to accommodate the spectrum of symptoms and remove reliance on tender points 2010 ACR criteria were developed to assess somatic symptom (sleep disturbance, cognitive disturbance and fatigue) severity and widespread pain[8]. A 2016 update was published based on the assessment of validation studies comparing the 2010 criteria with the ACR 1990 classification and clinical criteria[9]. The 2016 revision puts emphasis on generalised pain criterion to limit misclassification of regional pain disorders, recommends use of the FM symptom scale (FS scale), eliminates recommendation regarding diagnostic exclusion by the return to original 1990 proposal that "FM remains a valid construct irrespective of other diagnoses", and combines "physician" and "patient self-report" criteria into a single set.

PATHOPHYSIOLOGY

Neuronal excitability associated with amplified responses to peripheral input of the CNS leading to central sensitization (CS) is believed to be an underlying pathophysiology of FM[1,2]. The enhanced excitability of the neurophysiology reflects altered neurotransmitter function and possible neuroplasticity leading to augmented sensory processing[10]. Peripheral nociceptive generators, such as nerve pathologies, neuro-inflammation, skeletal muscle abnormalities and ischaemia, have been reported to play a role in the enhanced activity of the central components and thereby the symptoms[11,12]. Thus, the chronic pain experience of patients with FM is consistent with balance shifts to an enhanced excitation and reduced inhibition within the CNS.

Altered biochemistry in FM, where increased concentrations of substance P (2 to 3-fold), endogenous opioids (3 to 4-fold), glutamine (2-fold), nerve growth factor (4-fold) and brain-derived neurotrophic factor (2 to 4-fold) in the cerebrospinal fluid (CFS) have been observed, is consistent with the wind-up phenomenon (a progressive increase in response reflective of slow temporal summation) leading to self-sustaining CS[1,13].

In healthy subjects, application of intense painful stimuli activates the diffuse noxious inhibitory control (DNIC), leading to a whole-body analgesia, which involves descending opioidergic and serotonergic-noradrenergic efferent pathways from the brain to the spinal cord that downregulate the pain signal. DNIC has consistently been reported to be reduced or absent in FM, compared to healthy controls[14]. An altered biochemistry of serotonin and noradrenaline in the cerebrospinal fluid (CSF) and serum is consistent with a decreased endogenous serotonergic and noradrenergic activity associated with reduced DNIC in FM patients. The CFS levels of 5-hydroxy indoleacetic acid (5-HIAA), the main metabolite of serotonin, and 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of noradrenaline, and blood levels of L-tryptophan and serotonin are lower in patients with FM compared to healthy controls[1,13]. In contrast, data from FM patients indicates high baseline occupancy of opioid receptors rather than a deficiency of endogenous opioid release, as a consequence of normal or increased (3 to 4-fold) endogenous opioid activity[13].

Alterations in the hypothalamic pituitary adrenal axis (HPA), and autonomic and cardiovascular system associated with systemic stress-related effects have also been proposed to enhance or underlie the symptoms, particularly the pain, of FM[2,13]. However, studies in patients with FM regarding alterations of these stress systems, are often inconsistent with abnormal HPA or autonomic function in only a small proportion of patients with marked patient and healthy subject overlap. In contrast, HPA and autonomic abnormalities have been suggested to be a consequence of the pain in FM patients[15].

Although the pathophysiology of FM has been suggested to involve an inflammatory component, studies of cytokines have provided variable findings and have several limitations which could influence the outcomes[1,2,13]. Thus, the role of cytokines in FM have been questioned because of the inconsistency of measurements and lack of correlation with parameters of the disease[16]. The generation and enhancement of chronic pain characteristic of FM may be associated with raised pro-inflammatory cytokines, however it is not possible to conclude whether the inflammatory response is the cause of the symptoms or due to the changed physiology initiating the pain. Clinical trials have indicated no or very limited efficacy of anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDS) and steroids, in the treatment of FM consistent with a lack of a role of inflammation[2,13].

TREATMENT STRATEGIES

Pharmacological and non-pharmacological therapeutic approaches are often required as treatments of the challenges associated with FM with drug therapy often focused towards the individual symptoms primarily the pain[1,2,9]. The complexity of FM has identified that psychological and social factors along with biological variables are associated with a biopsychosocial model[17]. Thus biological, psychological, and social factors require to be simultaneously addressed. As a consequence, non-pharmacological treatments such as acupuncture, biofeedback, cognitive behavioural therapies, exercise, hydrotherapy, hyperbaric oxygen therapy, mindfulness/mind-body therapy, massage, transcranial magnetic stimulation, have been evaluated for the management of the symptoms of FM.

Acupuncture has been shown to reduce pain in various pain conditions, including FM[18]. It has been proposed that acupuncture reduces inflammation, causes the release of endorphins and creates a calmer mind. The analgesic effects of acupuncture may be associated with the adenosine metabolised from released adenosine triphosphate (ATP) activating adenosine A1 receptors[19]. In patients with FM, acupuncture demonstrated a small improvement in pain and fatigue[18]. Psychological and mind-body therapies, which include biofeedback, mindfulness, relaxation, incorporate strategies to improve psychological and physical well-being. In patients with FM mind-body therapies have been suggested to improve physical functioning, pain and mood, however due to the inconsistency in the design of studies the quality of the evidence is low[20]. Cognitive behavioural therapies provided sustained (up to 6 mo) reduction of pain, negative mood and disability in patients with FM[21].

Many patients with FM are deconditioned and thereby will gain from activity programs that involve the activation of endogenous analgesic conditions and increase well-being[22]. In trials of aerobic exercise and resistance training improvement in pain, physical function and well-being has been observed[23]. Although land and aquatic exercise were reported to be equally effective, for severely deconditioned individuals hydrotherapy or exercising in water may be particularly valuable[23,24].

Increasing oxygen concentration by hyperbaric oxygen therapy (HBOT) can induce neuroplasticity leading to repair of chronically impaired brain functions which may change the brain metabolism and glial function to rectify FM-associated brain abnormal activity[25,26]. In a study of patients with FM HBOT led to improvement of all FM symptoms, with significant changes in pain, physical function and quality of life assessments[27]. Although these outcomes are encouraging HBOT requires further study as a treatment for FM.

There is evidence of transcranial magnetic stimulation (rTMS) being effective in reducing the severity of the pain in patients with FM which has led to the use of this treatment approach for at least a decade[28]. Other studies of rTMS as a treatment of FM however remain inconclusive questioning the routine recommendation of this method[29-31].

The pharmacological treatments of FM are primarily aimed at lowering levels of pronociceptive excitatory neurotransmission or/and increasing antinociceptive neurotransmission in the CNS. Current treatments (Table 1) include drugs that target serotonin and noradrenaline levels, *e.g.,* tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors (SNRIs), or voltage-gated calcium channel subunit ligands, *e.g.,* gabapentin and pregabalin[2,9]. The modulation of serotonin and noradrenaline levels has led to a reduction of pain, depression and fatigue, and an improvement of quality of life in patients with FM supporting the involvement of the low levels of these neurotransmitters in the pathogenesis of FM[2,9]. Voltage-gated calcium channel subunit ligands decrease calcium influx with a reduction of the release of neurotransmitters that transmit, at least nociceptive signals reducing pain, anxiety and fatigue and improving sleep in patients with FM. Although the bioamine modulators and the ligands demonstrate efficacy in the management of FM symptoms, the outcomes are limited with only a proportion of patients experiencing a partial reduction of symptom severity. The limitation of the effectiveness of current medications is exacerbated by the incidence of adverse effects leading many patients to discontinue use[32,33].

Suppression of neuronal excitability and neurotransmitter release appears to be a key pharmacological property to the management of FM as observed with the ligands and the bioamine modulators. Clues to underlying mechanisms as potential targets for new and novel medications are becoming available through advances in the understanding of the pathogenesis of FM. The complexity of FM is emphasized by the diversity of pharmacological targets gaining interest (Table 2). The alteration at both central and peripheral levels of multiple biological mechanisms and systems has however presented a complex pathophysiology with a lack of clarity which processes are a cause or consequence of FM. Inconsistent success of current treatments has led to the investigation of a range of novel targets, such as melatoninergic,

Table 1 Currently recommended drugs for the management of fibromyalgia[9,30,31]

Drug	Mechanism of action	Symptom improved
Amitriptyline	Tricyclic antidepressant	Pain, sleep, fatigue
Cyclobenzaprine	Tricyclic antidepressant	Sleep
Duloxetine	Serotonin-noradrenaline reuptake inhibitor	Pain, sleep
Milnacipran	Serotonin-noradrenaline reuptake inhibitor	Pain, fatigue
Pregabalin	α2δ ligand	Pain, sleep, fatigue
Tramadol	Weak opioid and serotonin-noradrenaline reuptake inhibitor	Pain

cannabinoid, dopamine, NMDA, angiotensin, orexin and opioid receptors, and ion channels, in addition revisiting bioamine modulation and α2δ ligands (Tables 2 and 3). This article will focus on emerging pharmacological strategies involving many of these targets.

EMERGING THERAPIES

Bioamine modulation

The clinical symptoms of FM have been associated with altered bioaminergic neurotransmitters (noradrenaline, serotonin and dopamine) and involvement of serotonin and noradrenaline in several aspects of the pathophysiology of FM has, for example, been supported by the tricyclic antidepressant amitriptyline correlated the clinical response with normalization of neuronal function of areas such as the bilateral thalamus and basal ganglia[59]. Further, dopamine deficiency in the regulation of pain processes and chronic stress has been implicated in the pathophysiology of FM[60]. Drugs (droxidopa, esreboxetine, mirtazapine, pramipexole, TD-9855, cyclobenzaprine, trazodone) that modulate the bioamine system by targeting receptors, reuptake processes and neurotransmitter availability either individual or in various combination have demonstrated efficacy in the treatment of FM with a reduction in pain and fibromyalgia impact questionnaire scores (FIQ) (Table 2). Although dopamine release into the basal ganglia in response to painful stimuli is attenuated or absent, outcomes with dopamine receptor agonists have been inconsistent with pramipexole, but not ropinirole and terguride, improving symptoms in studies with FM patients[48,61,62]. The design of the clinical trials being single dose monotherapy has limited comparison of the outcomes of the different treatments and thereby mechanisms. Whilst enhancement of the activity of the serotonergic, noradrenergic and dopaminergic pathways demonstrate benefit in the management of FM symptoms, further studies are required to identify the preferable profile of drug activity and patient profile that will profit.

Gabapentanoids

The gabapentanoid ligands, gabapentin and pregabalin, are used regularly in FM patients to improve quality of life through the reduction of pain, sleep dysfunction and fatigue[63]. The gabapentanoids have been suggested to down regulate brain glutamate release and inhibit astrocyte induction of glutamatergic synapse formation[64]. Thus, the analgesia observed with pregabalin and gabapentin in clinical settings has been suggested to be linked to the modulation of glutamatergic activity and functional brain connectivity. Interestingly, FM patients with the highest levels of glutamate were the most likely to respond to pregabalin decreasing glutamatergic activity in the insula[65]. Further, short-term pregabalin treatment of FM patients reduced brain gray matter volume assessed by voxel-based morphometry within the posterior insula bilaterally and in the medial frontal gyrus[64]. The gray matter volume reductions were associated with reductions in evoked pain-pressure assessed functional brain connectivity and reduced clinical pain.

The analgesic effects and CNS side effects of the gabapentanoids have been associated with subtypes of the subunits[66]. The α2δ-1 subunit has been shown to be primarily responsible for the analgesic effects and the CNS side effects involve binding of the drugs to the α2δ-2 subunit[66]. Preferentially selective α2δ-1 subunit ligands could provide a more successful therapeutic option with a clinically preferable efficacy/safety profile. Mirogabalin, a novel selective-1 subunit ligand (5-30 mg/d) reduced pain with an acceptable safety profile in diabetic peripheral neuropathic pain during a double-blind, randomized, placebo controlled study[67]. The potential of mirogabalin as a treatment of FM is being investigated in a double-blind, randomized, placebo controlled trial and results are awaited[54].

Opiates

An increased endogenous opioid activity observed in the CNS of FM patients may be related to a form of opioid hyperalgesia[13]. The use of the opioid receptor antagonist naltrexone to block endogenous opioid release has been proposed as an effective treatment strategy in FM patients[47]. In a double-blind, randomized, placebo-controlled study in FM patients low-dose naltrexone (LDN, 4.5 mg/d) reduced pain and improved mood, but failed to alter fatigue and sleep disorder[47]. The beneficial effects observed with LDN in patients with FM have been suggested to involve microglia antagonism in addition to blocking endogenous opioid release. Pro-inflammatory factors released into the CNS from microglia, which may be abnormally sensitized in FM, could lead to central facilitation of the pain processing[68]. These outcomes are encouraging of LDN as a promising treatment of FM, however further studies are required to identify the value of these mechanisms of action particularly glial cell

Table 2 Emerging drug therapies with potential efficacy for the treatment of fibromyalgia

Drug	Mechanism of action	Regime	Effect on pain	Secondary domains accessed		Trial sponsor	Ref.
			VAS-P	Significantly improved	No observed effect		
Agomelatine	Melatoninergic receptor agonist and 5-HT2 receptor antagonist	25 mg/d during 12 wk 25-50 mg/d during 12 wk	-1.06 (5.13 - 4.07)	FIQ, anxiety, depression,	Sleep disorder, cognitive/executive function, quality of life index	University of Messina	[34] [35]
Capsaicin	Transient receptor potential vanilloid 1 subunits	Topical 0.075% TID during 6 wk	No significant effect	FIQ (-9.81), fatigue severity, depression, myalgic score, pressure pain threshold	Anxiety, physical functioning	Rheumatology Service at the Specialist Clinic of Cantabria	[36]
Dronabinol (delta-9-tetrahydrocannabinol)	Cannabinol	Daily dose 2.5 -15 mg during 7 mo	-3.5 (7.9-4.4)	Anxiety, depression, quality of life		Heidelberg University	[37]
Droxidopa	Noradrenaline prodrug	600 mg TID during 9 wk	-1.64 (cf pl -0.74)	FIQ (-9.72)		Chelsea Therapeutics/ Lundbeck	[38]
Esreboxetine	Noradrenaline reuptake inhibitor	4/8/10 mg/d during 14 wk	-1.55 - 1.85 (cf pl -0.42 - -0.76)	FIQ (-3.88 to -7.12), PGIC score, GFI score (-0.30 to -0.64)	SF-36 physical function score	Pfizer	[39]
IMC-1 Celecoxib + famciclovir	Viral suppression of herpes virus	Fixed dose combination during 16 wk	-1.9	FIQ (-17.5), PGIC, fatigue		Innovative Med Concepts	[40]
Melatonin	Endogenous melatonin receptor ligand	10 mg/d during 6 wk	-1.74 (6.49-4.75)	FIQ (-17.7), sleep, tender points		Brazilian Committee for Development of Higher Education Personnel and National Council for Scientific and Technological Development	[41]
		10 mg/d plus 25 mg/d amitriptyline during 6 wk	-2.1 (6.96-4.86)	FIQ (-24.7), sleep, tender points			
Memantine	NMDA antagonist	20 mg/d during 5 mo	-1.9 (cf pl -3.1) (6.9-5.0)	FIQ (-13.2), CGI, Quality of life score,	Cognitive state, depression	Aragon Institute of Health Sciences	[42]
Mirtazapine (Org 3770)	a2 adrenergic and 5-HT2 and 5-HT3 receptor antagonist	15 mg/d during 1 wk then 30 mg/d during 12 wk	-1.6 (cf pl -0.4)	FIQ (-12.9), anxiety, depression, PGIC, quality of life		Meiji Seika Pharma Co., Ltd.	[43,44]
Nabilone	Cannabinoid receptor agonist	0.5-1.0 mg during 4 wk	-2.04 (cf pl -1.43)	FIQ (-12.07), anxiety		University of Manitoba	[45]
		0.5-1.0 mg during 2 wk	No effect	Sleep	Pain, mood, quality of life	Winnipeg Regional Health Authority	[46]
Naltrexone	Opioid receptor antagonist	4.5 mg/d during 12 wk	-1.55 (cf pl -0.43)	Mood	Sleep, fatigue	Stanford University	[47]
Pramipexole	Dopamine agonist	4.5 mg/d during 14 wk	-2.48 (cf pl -1.77)	FIQ (-9.57), physical function, fatigue	Mood, depression, anxiety, tender point score		[48]
TD-9855	Noradrenaline serotonin reuptake inhibitor	20 mg/d during 6 wk	-1.4 (cf pl -0.5)	FIQ (-16.2), PGIC, global and cognitive fatigue		Theravance Biopharm	[49]
TNX102SL cyclobenzaprine	Noradrenaline, serotonin reuptake inhibition, adrenergic and serotonin receptor antagonist	1-4 mg/d during 8 wk	-0.6 (cf pl -0.6)	Fatigue, tenderness, sleep, depression		Tonix Pharmaceuticals	[50,51]
Trazodone	5-HT receptor antagonist and serotonin reuptake inhibitor	50-300 mg/d during 12 wk then trazodone/ pregabalin (max 450 mg/d) during 12 wk	-0.45 -1.29	FIQ (-10), fatigue, stiffness, anxiety, depression, PGI FIQ (-13.4)		Universidad de Granada	[52]

CGI: Clinical Global Impressions; FIQ: Fibromyalgia impact questionnaire; GFI: Global fatigue index; PGI: Patient global improvement; PGIC: Patient's global impression of change; SF-36: 36-item short form health survey; cf pl: Compared with placebo; TID: 3 times daily; VAS-P: Visual Analog Scale of Pain based on a 0-10 scale.

modulation.

NMDA receptors

The glutamate NMDA receptors, particularly those within the dorsal horn of the spinal cord, are fundamental in nociceptive transmission and synaptic plasticity and thereby are considered a target for the treatment of neuropathic pain[69]. Elevated levels of glutamate in key pain-processing areas of the brain, which change in response to treatment that attenuates the pain, have been observed in FM patients[70,71]. NMDA receptor antagonists, ketamine, dextromethorphan and memantine, have shown efficacy in FM patients which is consistent with an attenuation of an increased glutaminergic activity[2,13]. Memantine in a double-blind, randomized placebo-controlled trial evoked a significant reduction in pain and improved quality of life assessment, but did not provide benefit against the cognitive state and depression in FM patients[42]. Further, an increase in cerebral metabolism with a correlation between the FIQ score and the choline levels in the posterior insula was reported in FM patients receiving memantine[42]. Use of memantine, like other NMDA antagonists, in the clinic is limited due to the adverse effects profile and the treatments not being well tolerated, in addition to the benefits in FM appear to be within a subset of patients. Several adverse effects of NMDA receptor antagonists are believed to be interference with physiological NMDA receptor function in the CNS[69]. Thus, development of NMDA receptor subtype specific antagonists (*e.g.,* NR2A, NR2C, NR2D) that maintained the physiological function whilst suppressing the increased activity of glutamatergic pathways could offer a preferable treatment approach to FM. To target mechanisms that regulate NMDA receptor activity, such as phosphorylation sites and interacting kinases (*e.g.,* casein kinase 2, Src-NADH dehydrogenase), rather than the channels may offer an alternative approach to improve the therapeutic window[69]. Expression levels of regulating signal mechanisms of NMDA receptor function were increased in the spinal cord neurons in a mouse model of FM, where hyperalgesia was induced by intramuscular acid saline injection[72]. Improved pain effects in this animal model implicated a reduced NMDA-pCAMKIIa-pCREB signalling which may represent a novel therapeutic target for FM[72].

The contribution of NMDA receptor activity in the symptoms of FM has also been related to the efficacy of the gabapentanoid drugs. Pregabalin treatment decreased glutamatergic activity in the insula of FM patients[65], further supporting the contribution of glutamatergic activity to the pathophysiology of the symptoms of FM and highlighting modulation as a therapeutic approach of interest.

Melatonin receptors

Melatonin (N-acetyl-5-methoxytryptamine) and novel melatonin analogues have exhibited analgesic properties in addition to regulating sleep consistent with potential use as a therapeutic approach of chronic pain conditions such as FM[73]. Severity of pain, tender point score, sleep quality, depression and anxiety were significantly improved by melatonin (3 or 5 mg at bedtime) in studies in patients with FM[41,74]. Studies involving combined therapy of melatonin and the tricyclic antidepressant amitriptyline demonstrated superior improvement in symptoms relative to amitriptyline alone, but not over melatonin treatment alone[41]. Thus, the serotonergic-noradrenergic components of the descending endogenous pain-modulating system appeared to be improved by the concomitant stimulation of melatoninergic receptors and thereby abnormality of the melatoninergic system may also play a role in the pathogenesis of FM. Consistent with this proposal agomelatine, a melatonin analogue with melatoninergic receptor antagonist and serotonin 5-HT2C receptor antagonistic properties, improved pain, depression and anxiety symptoms, but failed to improve sleep quality in patients with FM[34,35].

Cannabinoids

The proposal of cannabinoids as a treatment of FM is consistent with the implication that endocannabinoids, which are involved in regulation of pain processing and chronic stress, are deficient in the CNS of patients with FM[75]. The cannabinoids nabilone (0.5-1.0 mg/d) and dronabinol (a synthetic form of delta-9-tetrahydrocannabinol, THC; 7.5 mg/d) significantly reduced pain, depression and anxiety levels in patients with FM leading to an improvement of quality of life[37,45,46]. The incidence of adverse effects and drop-out rates up to 25% during the clinical trials would suggest the clinical use of nabilone and dronabinol may be limited[37,45,46]. The hepatic metabolites from first-pass metabolism of cannabinoids are believed to be responsible for the psychotropic effects. The transdermal delivery of D-(-)-glyceric acid ester of THC, ZYN001, avoids first-pass hepatic metabolism and leads to rapid hydrolyzation by esterases in the skin to THC[58,76]. Evaluation of the transdermal application of ZYN001 in FM patients should provide an improved tolerability profile for a cannabinoid[58].

Substance P

In patients with FM the cerebrospinal fluid levels of substance P are raised which would lead to the activation of neurokinin (NK) receptors with the possibility of inducing pain[13]. NK receptor antagonists in clinical trials in FM and other chronic pain states either failed to demonstrate efficacy or provided inconsistent outcomes[2]. Nociceptive processes, however, are desensitized, due to the depletion of substance P, by the action of capsaicin on transient receptor potential vanilloid 1 subunits (TRPV1) located in peripheral nociceptors[77]. In patients with FM refractory to other treatments, significant improvement in myalgic scores, pain threshold, mood and fatigue were reported following topically applied capsaisin (0.075% 3 times daily during 6 wk)[36]. Although the visual analogue scale (VAS) of pain was not significantly changed in this study, the impact of FM on the patients as determined by the fibromyalgia impact questionnaire was reduced leading to short-term improvement. These findings are consistent with substance P-induced modulation of peripheral nociceptors leading to activation of central neuronal mechanisms responsible for the symptoms of FM.

Table 3 Novel drugs in clinical trials for potential treatment of fibromyalgia

Drug	Mechanisms of action	Domains	Trial Sponsor	Ref.
EMA401	Angiotensin 2 receptor antagonist	Pain	Novartis/Spiniflex	[53]
Flupirtine	Potassium channel activation	Pain	Not available	[54]
Mirogabalin (DS-5565)	α2δ ligand	Pain	Daiichi Sankyo	[55]
Suvorexant	Orexin receptor antagonist	Sleep, insomnia, pain	Henry Ford Health System	[56]
Yokukansan	Herbal medication; glutamatergic and serotonergic systems	Insomnia, sleep	St Marianna University, school of Medicine	[57]
ZYN001	Cannabinoid	Pain, quality of life	Zynerba	[58]

Sources of information, MEDLINE (PubMed), ClinicalTrials.gov, adisinsight.springer.com and Controlled-trials.com.

IMC-1

IMC-1 is a a proprietary fixed-dose combination of celecoxib, a COX-2 inhibitor, and famciclovir, an anti-viral nucleoside analog, that has demonstrated efficacy in the treatment of FM in a 16-wk, double-blind, placebo-controlled trial[40]. In patients with FM, IMC-1 reduced the pain and fatigue, and improved the overall wellbeing as assessed by the fibromyalgia impact questionnaire and patient global impression of change. In January 2016, IMC-1 as a potential treatment for FM was granted "Fast Track" designation by the FDA[78].

Novel drugs

A number of drugs that have demonstrated efficacy in neuropathic pain conditions have gained interest as potential treatments of FM and thereby been proposed as candidates for clinical trials (Table 3).

EMA401 is a small molecule angiotensin II type 2 receptor antagonist that has exhibited analgesic properties in postherpatic neuralgia[79]. FM has been identified as a pain condition that may gain benefit from such a treatment approach[53]. Flupirtine is an analgesic that exhibits Kv7 channel activator properties resulting in the stabilization of neuronal activity[54,80]. A preliminary open-label study demonstrated that flupirtine had the potential to improve the pain, fatigue and sleep disturbance associated with FM[81]. Controlled clinical trials in FM with flupirtine have been proposed[54]. Orexin peptides and the two orexin receptors (A and B) play a fundamental role in the arousal and sleep/wake cycle[82]. Abnormality in the orexin system can lead to sleep disorders such as catalepsy and narcolepsy. Thus, antagonists of orexin receptors blocking the binding of wakefulness-promoting neuropeptides orexin A and orexin B to their respective receptor sites represent a new class of medications for the treatment of insomnia and other sleep disturbance disorders. Suvorexant is a dual orexin receptor antagonist approved by the FDA which has demonstrated efficacy in decreasing time to sleep onset and increasing total sleep time[82]. The investigation of suvorexant in insomnia co-morbid with FM has been proposed with the assessment of effects on sleep, pain and fatigue[56]. Yokukansan, a Japanese herbal medicine, acts on the glutamatergic and serotonergic nervous systems and is used in the treatment of psychiatric disorders[83]. Efficacy as an analgesic has been demonstrated by yokukansan in neuropathic pain conditions with suggested greater effectiveness than tricyclic antidepressants, carbamazepine, gabapentin, and opioids[84]. Thus, the potential of alleviating pain in FM by yokukansan has been suggested, and the outcomes of clinical trials are awaited[58].

CONCLUSION

FM is a complex chronic pain condition where current and emerging pharmacological therapies suppress the central hyper-excitability associated with the pathophysiology. A diversity of pharmacological targets and mechanisms such as bioamine modulation, subunits, NMDA receptors, melatonin receptors and cannabinoid receptors, has been identified at which drugs act to demonstrate effectiveness in the management of the symptoms of FM. Although efficacy has been demonstrated by many of the drug treatments discussed leading to improved health status in patients with FM, outcomes related to individual mechanisms of action were not always consistent and not all symptoms were controlled by a single drug. The modest and limited efficacy often observed may reflect the heterogeneity of FM with existence of subpopulations of patients, the contribution of peripheral and central components to the pathophysiology, and the extensive range of accompanying co-morbidities. Although the optimal treatment approach would be drug monotherapy, the complexity and multidimensional nature of FM emphasizes the need for a pharmacology targeting multiple molecular mechanisms. In addition to biological variables psychological and social factors have been identified to contribute to the complexity of FM supporting consideration of a biopsychosocial model. Nevertheless, clues to underlying mechanisms as novel and potential targets for new medications are being provided by advances in the understanding of the pathophysiology of FM.

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