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What is the progress of experimental drug development for fibromyalgia?

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1. Introduction

Fibromyalgia is a complex condition defined by chronic widespread pain but also characterized by fatigue, sleep disorder, cognitive dysfunction, and mood problems [1]. The diverse symptoms and comorbidities identified by patients with fibromyalgia are heterogeneous in occurrence suggesting the existence of subgroups of patients. The perception of pain, which can be spontaneous or provoked at variable anatomical locations, affects the entire body.

The pain experienced by patients with fibromyalgia is often associated with increased sensory processing in the central nervous system (CNS) independent of an obvious pathologic abnormality in the affected body region [1]. Thus, the altered nociception in fibromyalgia, referred to as “nociplastic pain”, does not involve tissue damage or somatosensory system lesion leading to the activation of peripheral nociceptors. The pathophysiology has been reported to involve a diversity of mechanisms within many systems, including peripheral and central sensitization, and neurogenic inflammation. The presence of central sensitization is consistent with increased excitatory neurotransmitters and reduced levels of inhibitory neurotransmitters [1]. Contribution of inflammation with changes in inflammatory mediators, particularly presenting as neuroinflammation, has been associated with the development and perpetuation of, at least, chronic pain in fibromyalgia [1].

2. Therapeutic options for fibromyalgia

The current treatment approach often involves the integration of pharmacologic and non-pharmacologic interventions focused on symptom management [1,2]. Centrally acting analgesics targeting inhibitory and excitatory neurotransmitters, such as gabapentinoids, and serotonin and norepinephrine reuptake inhibitors, are often the first-line drug therapies [2]. Available therapeutics for fibromyalgia however fail to provide adequate relief of the characteristic symptoms, especially the nociplastic pain, leading to the use of combinations of drugs with various mechanisms of action [2]. Non-pharmacological interventions, which are often core treatment approaches to fibromyalgia, include exercise, pacing through education and coping techniques (e.g. cognitive behavioural therapy) and sleep hygiene [1,2]. To address the limitations of current treatments there has been a focus on the identification of alternative pharmacologic targets. This editorial will consider selected novel agents and mechanisms of action gaining attention.

3. Selected novel drugs for fibromyalgia

Palmitoylethanolamide (PEA), an endogenous endocannabinoid mediator synthesized by, and downmodulates activation of, mast cells and microglia, exhibits analgesic and anti-inflammatory properties [3]. Cannabis-based medications exhibit therapeutic properties for insomnia, depression and anxiety that would be relevant in the treatment of fibromyalgia. These pharmacologic properties involve activation of nuclear peroxisome proliferator-activated receptor- α (PPAR- α) and the orphan receptor G-protein coupling (GPR55). In conditions of neuropathic pain, levels of PEA in brain regions involved in nociception have been reported to be altered [3]. The lipid structure and large heterogeneous particles limit the solubility and bioavailability of PEA, which can be resolved by micronization or ultram micronization. In a study evaluating the efficacy of duloxetine plus pregabalin in patients with fibromyalgia co-administration of PEA providing additional benefits was investigated [4]. Duloxetine (mean dose 39.3 mg/day (30 – 60 mg/day)) and pregabalin (mean dose 47.2 mg/day (25 – 75 mg/day)) only decreased Tender Point scores and Visual Analog Scale (VAS) pain intensity (Table 1). In the prospective observational arm of the study, patients who received duloxetine (mean dose 36 mg/day (30 – 60 mg/day)) and pregabalin (mean dose 49.2 mg/day (25 – 75 mg/day)) for 3 months were administered ultram micronized PEA (600 mg twice daily) for one month then micronized

PEA (300 mg twice daily) for a further 2 months [4]. For this group of patients, the decrease in Tender Point scores and VAS pain intensity following the introduction of PEA provided a greater clinical improvement in pain symptoms relative to the duloxetine/pregabalin combination only (Table 1). All patients completed the treatment period with no report of adverse effects. In a retrospective observational study, data were obtained from 359 patients with fibromyalgia prescribed oral ultramicrosized PEA as an add-on treatment regardless of concomitant pharmacologic therapy [5]. Over a period of 15 months, the VAS pain score and the quality-of-life Fibromyalgia Impact Questionnaire score (mean \pm SEM) significantly decreased (Table 1).. Adverse effects, predominantly gastrointestinal, were reported by 36 patients. Although observational studies may reflect the outcomes of patients in the community such data should be considered with caution considering a potential high placebo effect often observed in pain studies.

The selective orexin receptor (OX1R and OX2R) antagonist suvorexant, in a double-blind placebo-controlled trial, improved sleep time with an associated reduction of pain sensitivity in patients with fibromyalgia [6]. Stimulation of orexin neurons in the hypothalamus is involved in arousal and sleep-to-wake transition, while non-rapid eye movement (NREM) sleep is induced by neuronal activity suppression [7]. The clinical trial involving patients with fibromyalgia used a within-subject crossover design of 9 nights each of suvorexant (20 mg) and placebo treatment separated by a 7-day washout period [6]. Following suvorexant treatment, total sleep time (TST) was increased and wake after sleep onset (WASO) was reduced compared to placebo (TST: 7.2 hours with suvorexant versus 6.7 hours with placebo; WASO: 37 minutes with suvorexant versus 67 minutes with placebo). Next-day pain sensitivity to a radiant heat stimulus following suvorexant treatment was modestly reduced relative to placebo treatment.

Noninflammatory serum immunoglobulin G (IgG) autoantibodies that specifically bind to structures within dorsal root ganglia have been suggested to contribute to the pathogenesis of fibromyalgia [8]. Investigations into antibody therapeutics have gained consideration as treatment approaches to fibromyalgia. Rozanolixizumab, an antineonatal Fc receptor humanized monoclonal antibody, is the subject of a double-blind, placebo-controlled clinical trial to determine if this treatment will reduce the levels of IgG antibodies in patients with severe fibromyalgia and improve their symptoms [9].

The N-methyl-d-aspartate receptor (NMDAR)-positive allosteric modulator, NYX-2925 (20 mg/day for 2 weeks followed by 200 mg/day for 2 weeks), reduced the glutamate and glutamine to total creatine ratio levels in the dorsal anterior cingulate cortex and posterior insular cortex of patients with fibromyalgia following an evoked-pain stimulus [10]. Although these findings support the role of NMDAR-hypofunction and restoration to the perception of pain in fibromyalgia, NYX-2925 (50 mg/day or 100 mg/day for 12 weeks) did not significantly reduce fibromyalgia pain in a 300 patient Phase 2b clinical trial [11].

Psilocybin exhibits serotonin receptor agonist properties with a high affinity for 5-HT_{2A} receptors that regulate nociceptive pathways leading to analgesia [12]. The potential benefit of a formulation of psilocybin (TRP-8802, two oral doses of 15 mg then after 2 weeks 25 mg) as a treatment of pain symptoms in participants with fibromyalgia is being investigated in an open-label study [13].

4. Expert opinion

Current pharmacological treatments for fibromyalgia, which presents with a complex of symptoms dominated by chronic pain, do not meet the benefit expectations of patients. Although efficacy has been demonstrated by some drugs, such as bioamine modulators and gabapentinoids, often only a proportion of patients observe a partial reduction of symptom severity. These observations are consistent with the suggestion of the existence of subgroups of fibromyalgia and leading to the use of combinations of drugs with various mechanisms of action [1,2]. Reporting of a high incidence of adverse effects, however, impacts on the experience of current medications leading patients to discontinue use.

The novel therapeutic approaches highlighted in this editorial (Table 2) are examples that recognize the requirement of co-administrations, management of the non-pain symptoms and alternative drug targets. Advances in the understanding of the multifactorial pathophysiology of fibromyalgia are providing clues of potential novel targets and treatments, the outcomes of which will provide further insight into the biology of patients with fibromyalgia. For example, reduced pain and improved quality of life experienced following PEA treatment is consistent with the role of microglia and mast cells in fibromyalgia and association with the presence of pain [5]. The real-life study demonstrated long-term symptom improvement applicable for this patient group. In addition, an interrelationship between insomnia and pain in patients with fibromyalgia was demonstrated with the improvements in sleep by suvorexant [7].

The outcomes of the highlighted clinical trials and the development of future trials should provide further clues to the pathophysiology of fibromyalgia and the methodologic requirements of intended investigations into this condition.

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ACCEPTED MANUSCRIPT

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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Legends

Table 1. Palmitoylethanolamide (PEA) treatment of fibromyalgia patients in observational studies.

The treatment regimen were duloxetine (mean dose 39.3 mg/day) and pregabalin (mean dose 47.2 mg/day) for 6 months, duloxetine (mean dose 36 mg/day) and pregabalin (mean dose 49.2 mg/day) for 3 months plus ultramicronized PEA (600 mg twice daily) for one month then micronized PEA (300 mg twice daily) for a further 2 months or ultramicronized PEA add-on of 600 mg three times per day for 10 days, followed by 600 mg twice daily for 20 days and finally followed by 600 mg per day in the maintenance therapy (15 months). Visual analogue scales (VAS, 0 –10) of pain, positive Tender Point scores (TPs, 0 –18) and Fibromyalgia Impact Questionnaire scores (FIQ, 0 – 100) were determined. Data are presented as mean \pm standard error of the mean for n observations. Statistical difference is indicated by * $p < 0.01$, ** $p < 0.001$, vs previous evaluation.

Reference	Treatment	Study Type	Outcomes	Baseline	3 months	6 months	15 months
Del Giorno et al 2015 [4]	Duloxetine and Pregabalin	Retrospective observational arm n = 45	VAS	6.9 \pm 0.09	4.0 \pm 0.11*	3.0 \pm 0.12*	
	Duloxetine and Pregabalin plus ultramicronized PEA then micronized PEA	Prospective observational arm n = 45		6.6 \pm 0.15	3.7 \pm 0.17*	1.9 \pm 0.17*	
	Duloxetine and Pregabalin	Retrospective observational arm n = 45	TPs	13.5 \pm 0.33	8.0 \pm 0.17*	4.2 \pm 0.18*	
	Duloxetine and Pregabalin plus ultramicronized PEA then micronized PEA	Prospective observational arm n = 35		13.8 \pm 0.28	7.6 \pm 0.19*	1.0 \pm 0.14	
Schweiger et al 2019 [5]	Ultramicronized PEA add-on treatment to concomitant pharmacologic therapy	Retrospective observational n = 359	VAS	7.6 \pm 1.5			5.25 \pm 1.7**
			FIQ	68.4 \pm 14			49.1 \pm 19.6**

Table 2. Summary of novel drugs as treatments in fibromyalgia.

Table 2. Summary of novel drugs as treatments in fibromyalgia.

Treatment	Molecular target/class	Outcomes	Ref
Palmitoylethanolamide (PEA)	Nuclear peroxisome proliferator-activated receptor- α (PPAR- α) and orphan receptor G-protein coupling (GPR55)	Reduced pain and improved quality of life in participants with fibromyalgia of observational studies.	4,5
Suvorexant	Orexin receptors (OX1R and OX2R)	Improved sleep architecture in patients with fibromyalgia, although pain sensitivity was only modestly reduced.	6
Rozanolixizumab	Antineonatal Fc receptor humanized monoclonal antibody	Double-blind, placebo-controlled clinical trial currently recruiting participants with expected completion 2024.	9
NYX-2925	N-methyl-d-aspartate receptor	Reduced hyperactivity in pain-regulating brain regions, e.g. insular and anterior cingulate cortex in a 22 participant Phase 2 study with improvement of fibromyalgia symptoms. In a 300 patient Phase 2b trial a statistically significant reduction in pain was not observed.	10,11
Psilocybin	Serotonin 5-HT _{2A} receptors	An open-label clinical trial currently recruiting participants with expected completion 2024.	13