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Pharmacological Treatment of Fibromyalgia Syndrome
New Developments

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Abstract

Fibromyalgia is a chronic pain disorder characterized by widespread pain, stiffness, insomnia, fatigue and distress. Several randomized controlled trials (RCTs) have shown moderate effectiveness of pharmacological therapies for fibromyalgia pain. Evidence from these trials suggests that pharmacological therapy can not only improve pain but also fatigue, function and well-being in patients with fibromyalgia. Duloxetine and milnacipran, two highly selective serotonin-norepinephrine (noradrenaline) reuptake inhibitors, and the $\alpha_2\delta$ agonist pregabalin have been approved by the US FDA for the treatment of fibromyalgia symptoms. In general, about half of all treated patients seem to experience a 30% reduction of symptoms, suggesting that many patients with fibromyalgia will require additional therapies. Thus, other forms of treatment, including exercise, cognitive behavioural therapies and self-management strategies, may be necessary to achieve satisfactory treatment outcomes.

Despite promising results of pilot trials, RCTs with dopamine receptor agonists and sodium channel antagonists have so far been disappointing for patients with fibromyalgia. However, new pharmacological approaches for the treatment of fibromyalgia pain and insomnia using sodium oxybate appear to be promising.

Fibromyalgia is a prevalent, chronic pain disorder with high numbers of symptoms and limited treatment success.[1,2] It is characterized by widespread pain for more than 3 months in all four body quadrants and the presence of ≥11 of 18 tender points.[3] In addition, fibromyalgia is associated with stiffness, fatigue, nonrefreshing sleep, depression, anxiety and cognitive deficits.[4] Although the prevalence of fibromyalgia is much greater in women than men (9 : 1), this difference is tied to the lower number of tender points found in men. In the similar but more broadly defined 'chronic widespread pain syndrome', the difference in prevalence of females to males is much lower (3 : 1). Furthermore, fibromyalgia is common in patients with rheumatic conditions, including rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome.[5] In North America the prevalence of fibromyalgia is estimated to be 2–5%.[6,7] This prevalence is similar to most other countries studied, including countries in Europe and Asia.[8-11] Like many other chronic pain syndromes, the pathophysiology of fibromyalgia comprises abnormal sensory processing in the

peripheral and central nervous system (CNS) as well as dysfunction of the stress response systems including the autonomic nervous system and the hypothalamic-pituitary-adrenal axis.[12-14]

Currently used fibromyalgia treatments include pharmacological and physical therapy, self-management and alternative interventions. Treatment options have significantly improved over the last 10 years, and are able to improve persistent symptoms and functional limitations as well as quality of life in most patients. Many of the currently recommended fibromyalgia therapies have been summarized by the American Pain Society consensus report[1] and the very similar European League Against Rheumatism recommendations.[15] These recommendations not only summarize evidence-based treatment choices for patients with fibromyalgia but also provide clinical practice guidelines. There are three agents approved by the US FDA for the treatment of fibromyalgia symptoms and several new drug therapies are currently under investigation.

1. Randomized Controlled Trials in Fibromyalgia: Study Designs and Outcome Measures

Several outcome measures are frequently used in clinical fibromyalgia trials, including change in pain intensity and functional status. More recently the FDA has required study designs to provide so-called 'responder analyses', which take into account individual variability in treatment responses. Response rates of 30% and 50% from therapeutic interventions are used to report the percentage of individuals who experience clinically significant improvements of their symptoms.[16,17] Composite endpoints are often used for this type of analysis, which may include pain, physical function and patient-reported levels of symptom improvements.

Fibromyalgia pain can be highly variable, fluctuate during the day,[18] and is most commonly assessed with visual analogue scales (VAS)[19] or numerical pain scales.[20] In contrast to numerical pain scales, VAS are ratio scales with excellent measurement properties, including exquisite sensitivity and very good reliability.[19] Individuals from 5 years old to advanced age can successfully rate sensations using this scale, which is available in mechanical[21] and electronic versions.[19] Similar to most rating scales, VAS are anchored by 'no sensation at all' at one end and 'the most intense sensation imaginable' at the other end. VAS have been used to assess fibromyalgia symptoms such as general fatigue, tiredness upon awakening, sleep and mood.[22] Other validated methods of assessing fibromyalgia-associated symptoms include the McGill Pain Questionnaire,[23] Beck Depression Inventory[24] and Spielberger State-Trait Anxiety Inventory.[25] Paper or electronic diaries can be used for long-term data collection.[26]

The Fibromyalgia Impact Questionnaire (FIQ)[27,28] is commonly used for assessments of physical and emotional function of patients with fibromyalgia. The FIQ is a ten-item instrument to assess physical function, fibromyalgia symptoms and general well-being over the previous week. A change in the total score of 20% or greater has been suggested to be clinically significant.[28] Similarly, subscales of the self-administered Short-Form 36 Health Survey (SF-36) can be used as reliable measures of physical and emotional function and quality of life in fibromyalgia.[29]

2. Nonpharmacological Therapies

Except for exercise, there is no conclusive evidence at this time that other nonpharmacological remedies are effective for fibromyalgia, including dry needling of muscles, massage and prolotherapy ('proliferative injection therapy'). Similarly, acupuncture has not consistently demonstrated significant treatment benefits compared with placebo in patients with fibromyalgia.[30-32] Several treatment modalities, including massage, ultrasound and mineral baths, have demonstrated short-term benefits for fibromyalgia pain compared with placebo.[33-35] Cognitive behavioural therapy has become a promising therapeutic approach for fibromyalgia,[36] but many patients lack access to skilled therapists.

2.1 Self Management

Self management implies that patients have an active role in performing activities that promote health and well-being, while improving fibromyalgia-specific symptom and functional status.[37] The area of patient self management is a rapidly growing aspect of care for people with fibromyalgia and has been an integral part of treatment for other chronic conditions.[38]

2.2 Exercise

Most clinicians encourage exercise in patients with fibromyalgia to improve their abnormal functional status. Strong benefits of exercise for fibromyalgia symptoms have been well known for more than 25 years.[39] Specifically, water-based exercises have been shown to be beneficial in patients with fibromyalgia,[40-42] and strength training appears to provide additional health and function-related benefits.[43,44] Strength training can result in considerable increases in muscle strength (33–36%), the quadriceps cross-sectional area (5%) and voluntary activation of muscles (47–57%).[43] Notably, no adverse events have been reported from such intense training in patients with fibromyalgia. In addition to strength training, aerobic exercise,[45] muscle strengthening and spa therapy[46] have been found to be helpful. Patients with fibromyalgia can attain symptom relief, particularly decreased pain and fatigue as well as improved sleep and mood, with low- to moderate-intensity exercise of any type.[47] Even very low movement therapies such as Qigong have shown significant benefits for symptom improvement in fibromyalgia. Low-intensity exercise studies also seem to have lower attrition and better symptom improvement than those with higher intensity. However, higher-intensity training seems to result in greater fitness gains in patients with fibromyalgia than lower-intensity exercises.[39]

3. Pharmacological Management of Fibromyalgia

To date, three drugs have been approved by the FDA for the treatment of fibromyalgia symptoms. They include the antiepileptic drug pregabalin and two serotonin-norepinephrine (noradrenaline) reuptake inhibitors (SNRIs), duloxetine and milnacipran, (for more information see sections 4.2 and 4.3). Several new drugs are currently in clinical trials[48] as investigators continue to search for ways to apply currently available medications and other medical interventions to improve the clinical outcomes of patients with fibromyalgia.

3.1 Antidepressants

Some of the most effective pharmacological therapies for fibromyalgia pain include low doses of tricyclic antidepressants (TCAs).[49] These agents exert their effects at the serotonin and norepinephrine transporters of the presynaptic terminals of neurons. TCAs increase the extracellular levels of neurotransmitters by inhibiting their reuptake into the presynaptic terminals. TCAs, particularly amitriptyline and the chemically similar muscle relaxant cyclobenzaprine, can improve the symptoms of pain, poor sleep and fatigue associated with fibromyalgia.[50,51] Because of better adverse effect profiles, newer antidepressants including selective serotonin reuptake inhibitors (SSRIs) and SNRIs are frequently used in patients with fibromyalgia. These SSRIs include fluoxetine, sertraline, citalopram and paroxetine, which have been evaluated in several randomized, placebo-controlled trials.[52,53] In general, the ineffectiveness of SSRIs on fibromyalgia symptoms reflect the disappointing experience in other chronic pain conditions such as neuropathic pain, i.e. the newer highly selective serotonin reuptake inhibitors (e.g. fluoxetine) seem less effective for fibromyalgia pain than the older SSRIs, which have mixed serotonergic-noradrenergic activity at higher doses.[54]

Most TCAs provide balanced reuptake inhibition of serotonin and norepinephrine, and represent some of the most effective analgesics amongst antidepressants. Similarly, newer dual uptake inhibitors (SNRIs) are considered to be more effective than pure serotonergic or noradrenergic agents. These drugs are similar to

TCAs in their ability to inhibit the reuptake of both serotonin and norepinephrine, but unlike TCAs do not possess significant affinity to other receptor systems. This selectivity results in diminished adverse effects and enhanced tolerability. Available trial data for venlafaxine, the first SNRI on the market, support its use in the management of neuropathic pain and fibromyalgia.[55] Several additional SNRIs, including duloxetine and milnacipran, have been studied in randomized controlled trials (RCTs) of patients with fibromyalgia (see sections 4.2 and 4.3). Although many chronic pain syndromes, including fibromyalgia, show high co-morbidity with depression, several trials showed that the analgesic efficacy of antidepressants was independent of their effects on mood.[56,57]

Overall, a recent meta-analysis of 18 RCTs confirmed that antidepressants can improve fibromyalgia pain, depression, fatigue, sleep disturbances and health-related quality of life.[58]

3.2 Muscle Relaxants

After TCAs, the second most frequently studied drugs for the treatment of fibromyalgia are muscle relaxants, in particular cyclobenzaprine. A meta-analysis of cyclobenzaprine studies for fibromyalgia pain demonstrated robust benefits similar to amitriptyline.[59] Even doses as low as 1–4 mg at bedtime have demonstrated some analgesic efficacy in fibromyalgia.[60] Carisoprodol given at a dosage of 1200 mg/day decreased fibromyalgia pain compared with placebo in one study,[61] but this result could not been confirmed in a subsequent study.[62] Similarly, many other muscle relaxants are routinely used by clinicians without supporting evidence from rigorous trials. Another frequently used medication for fibromyalgia pain is tizanidine. Although approved by the FDA as a muscle relaxant for spasticity in multiple sclerosis and stroke, this medication is an α_2-adrenergic receptor agonist, similar to clonidine. Treatment with tizanidine (4–24 mg/day) resulted in lowering of increased levels of cerebrospinal fluid neuroamines and substance P in a study of patients with fibromyalgia.[63]

3.3 Tramadol

Tramadol is a centrally acting analgesic that binds to μ-opioid receptors and inhibits reuptake of norepinephrine and serotonin.[64] Paracetamol (acetaminophen)/tramadol combinations, in a ratio of 8 : 1, have been found to be synergistic in animal models of pain.[65] In a 13-week, multicentre RCT, tramadol/paracetamol 37.5 mg/325 mg relieved fibromyalgia pain more effectively than placebo.[66] The adverse events reported in this study were consistent with the well known, transient and non-serious adverse events profile typically expected with tramadol, including dizziness/vertigo, nausea, vomiting, constipation, somnolence, headache and weakness.

3.4 Benzodiazepines

The efficacy of benzodiazepines for fibromyalgia symptoms has not been well studied and many trials have provided conflicting results. For example, benzodiazepines, including alprazolam (0.5–3.0 mg at bedtime), were not found to be superior to placebo for fibromyalgia pain,[67] but clonazepam, an antiepileptic drug approved for petit mal seizures, was effective for pain from temporomandibular disorder,[68] which is similar to fibromyalgia. It also effectively reduced restless legs syndrome (RLS) symptoms, a common cause of arousal and fragmented sleep in patients with fibromyalgia.[69]

3.5 Local Anaesthetics

Local anaesthetics are frequently used for treatment of myofascial pain, particularly for trigger point injections. In addition, attenuation of the pain pathway can be achieved by systemic administration of local anaesthetics through inhibition of voltage-gated sodium channels. Use of intravenous lidocaine has shown moderate improvement in several neuropathic pain conditions such as diabetic[70] and postherpetic neuralgia.[71] Patients with these conditions sometimes reported prolonged relief from such treatments.[72] Similarly, systemic lidocaine has been used in patients with fibromyalgia, and single and repetitive infusions of lidocaine 5–7 mg/kg

Table I. Promising new therapies for fibromyalgia symptoms

Drug (US trade name)	Manufacturer	Mechanism of action
Nabilone (Cesamet®)	Valeant Pharmaceutics	CB1 activation
Naltrexone (Nalorex®)	DuPont Pharmaceuticals	Opioid receptor blockade
Modafinil (Provigil®), armodafinil (Nuvigil®)	Cephalon	Unknown
Dextromethorphan, ketamine	Various	NMDA receptor blockade
Sodium oxybate (Xyrem®)	Jazz Pharmaceuticals	GABA precursor

CB = cannabinoid.

demonstrated significant pain relief in patients with fibromyalgia.[73,74] In a recent RCT of patients with fibromyalgia, lidocaine 50 mg was injected into a single painful trapezius muscle tender point.[12] This injection not only reduced local pain at the injection site but also widespread hyperalgesia, which represents a hallmark of fibromyalgia. This proof-of-concept study not only provided evidence for the important role of peripheral tissues for fibromyalgia hyperalgesia, but also suggests clinical use of local anaesthetic injections for fibromyalgia pain.

3.6 Other Medications

Tropisetron, a serotonin 5-HT_3-receptor antagonist, and oxitriptan, an intermediate metabolite of L-tryptophan, were found to be more effective than placebo in several RCTs of fibromyalgia pain.[75,76]

Several different classes of medication used to treat fibromyalgia pain have not demonstrated superior efficacy compared with placebo, including the NSAIDs ibuprofen (2400 mg/day for 3 weeks)[77] and naproxen (1000 mg/day for 6 weeks),[78] prednisone (15 mg/day for 2 weeks)[79] and hypnotics.[80] Some hypnotics, such as zopiclone and zolpidem, have been shown to improve sleep and fatigue of patients with fibromyalgia;[80,81] however, in contrast to TCAs, hypnotics seem to lack beneficial effects on fibromyalgia pain.[67]

4. New Pharmacological Therapies for Fibromyalgia Pain

Research on the pathogenesis and therapy of fibromyalgia has grown rapidly over the last 15 years, and more effective treatment options are now available. However, there are many obstacles that interfere with successful treatment of patients with fibromyalgia, including drug adverse effects. Many pharmaceutical companies are currently investing in drug development for fibromyalgia symptoms (table I).

4.1 Pregabalin and Gabapentin

Antiepileptic drugs are widely used in the treatment of neuropathic pain conditions, including postherpetic neuralgia and painful diabetic neuropathy.[82] Amongst these, gabapentin and pregabalin play an important role in the treatment of neuropathic pain. Pregabalin, the precursor of which is gabapentin, has analgesic, anxiolytic and antiepileptic effects in animals. Like gabapentin, pregabalin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels in the CNS without affecting GABA receptors. Its activity is limited to neurons and it does not affect vascular calcium channels. However, the exact mechanism of action of pregabalin is unknown. Reduction of calcium influx into neurons may reduce the release of substance P, glutamate and norepinephrine, which is thought to mediate its analgesic and anxiolytic actions.

In a large RCT of 528 patients with fibromyalgia, pregabalin demonstrated significant improvement in pain scores, sleep quality, fatigue and global measures of change.[83] Subjects were assigned to placebo or one of three pregabalin doses (150, 300 or 450 mg/day) for 8 weeks. The study population mostly consisted of women with long-standing fibromyalgia and a mean pain score of 7 (range: 0–10). All patients with

fibromyalgia were required to discontinue prior medications and the majority (75%) completed the trial. All patients assigned to active treatments improved within 2 weeks and demonstrated sustained improvement until the end of the trial. Treatment with pregabalin was associated with modest but statistically significant dose-dependent improvements of fibromyalgia pain, sleep disturbances and fatigue. Adverse events were common but mild and transient, including dose-dependent dizziness (49%), somnolence (28%), dry mouth (13%), peripheral oedema (11%) and weight gain (7%). During a subsequent 6-month placebo-controlled trial of pregabalin responders, the durability of therapeutic efficacy was evaluated in 566 patients with fibromyalgia.[84] The primary outcome was time to loss of therapeutic response (LTR), defined as <30% reduction in pain from baseline or worsening of fibromyalgia. Time to LTR was longer for pregabalin than placebo ($p < 0.0001$). At the end of the trial, 61% of placebo patients showed LTR versus 32% of pregabalin-treated patients. Pregabalin was well tolerated, although more pregabalin than placebo patients discontinued treatment because of adverse events.

Finally, the efficacy of pregabalin in the treatment of fibromyalgia was assessed in a meta-analysis of six RCTs studying more than 2000 patients with fibromyalgia.[85] This analysis provided strong evidence for a moderate reduction of fibromyalgia pain by pregabalin (Cohen's d: –0.28), improved sleep (Cohen's d: –0.39) and improved health-related quality of life (Cohen's d: –0.30), but not for depressed mood. In addition, small improvements of fatigue (Cohen's d: –0.16) and anxiety (Cohen's d: –0.18) were observed in patients with fibromyalgia treated with pregabalin.

Gabapentin, which has a pharmacological profile similar to that of pregabalin, has been investigated in a 12-week RCT of 150 patients with fibromyalgia sponsored by the US National Institutes of Health.[86] Gabapentin-treated patients showed significantly greater improvement of average pain than placebo. In addition, gabapentin significantly improved FIQ total scores, Patient Global Impression of Change (PGIC) scores and the Medical Outcomes Study Sleep Problems Index. Compared with placebo, gabapentin treatment was associated with a significantly higher incidence of sedation, lightheadedness and dizziness. Overall, results from this study indicate that gabapentin has similar effectiveness for fibromyalgia symptoms as pregabalin.

4.2 Duloxetine

Duloxetine is an FDA-approved SNRI for the treatment of major depressive disorder, and pain associated with diabetic neuropathy and fibromyalgia. Its major mechanism of action includes inhibition of serotonin and norepinephrine reuptake without interacting with opioid, muscarinic, histamine H_1, α-adrenergic, dopamine or serotonin receptors. Preliminary studies in animal models have shown that duloxetine reduced pain behaviour more effectively than venlafaxine, amitriptyline or desipramine.[87]

An RCT of 207 patients with fibromyalgia assigned participants to either duloxetine 60 mg twice daily for 12 weeks or placebo.[56] Although there was no difference in study patients between treatment arms, a large number of patients (38%) were diagnosed with major depression. Compared with placebo, duloxetine-treated patients with fibromyalgia showed greater improvements of total FIQ scores and Brief Pain Inventory (BPI) scores, but did not differ in their FIQ pain scores. The presence of co-morbid depression had no impact on the observed treatment response of patients with fibromyalgia. Interestingly, men with fibromyalgia did not experience a significantly greater response to duloxetine than to placebo. Reported adverse events with duloxetine therapy included insomnia, dry mouth and constipation. A total of 354 women with fibromyalgia were enrolled in a subsequent 12-week RCT of duloxetine.[88] Primary and secondary outcome measures included the BPI and FIQ, respectively. BPI scores decreased significantly more in patients with fibromyalgia treated with duloxetine than with placebo and a 30% pain reduction was achieved in 54% of patients with fibromyalgia taking duloxetine compared with 33% in those on placebo. In a subsequent analysis

of 538 female patients with fibromyalgia pooled from these studies,[89] duloxetine was found to be superior on all efficacy measures. Specifically, a direct treatment effect of duloxetine on fibromyalgia pain could be demonstrated that was independent of mood improvements.

Safety data for duloxetine in patients with fibromyalgia combined from four randomized, double-blind, placebo-controlled studies and a 1-year, open-label safety study showed that this treatment was well tolerated over an extended period of time. The most common adverse events were nausea (29.3%), headache (20.0%), dry mouth (18.2%), insomnia (14.5%), fatigue (13.5%), constipation (14.5%), diarrhoea (11.6%) and dizziness (11.0%).[90]

4.3 Milnacipran

SNRIs have received widespread attention as a promising treatment for patients with chronic pain, including fibromyalgia. Two open-label studies of the SNRI venlafaxine showed effectiveness for fibromyalgia pain,[55,91] particularly at 150 mg/day, but an RCT reported no significant effects of venlafaxine on fibromyalgia pain.[92]

Milnacipran, which is widely used as an antidepressant in Europe and Japan, is a novel SNRI that favours reuptake inhibition of norepinephrine over serotonin (and is therefore sometimes referred to as a norepinephrine-serotonin reuptake inhibitor [NSRI]). Reduction of pain was shown in a variety of animal models using milnacipran, which may be related to norepinephrine and serotonin signalling via descending inhibitory pathways in the spinal cord.[93] TCAs attenuate pain through serotonin and norepinephrine neurotransmission, and SNRIs share this ability to modulate pain but have far fewer adverse effects.[94]

This ability to attenuate chronic pain has generated considerable interest for the use of norepinephrine-selective SNRIs in fibromyalgia. In a 12-week, phase II RCT, 125 patients with fibromyalgia were randomized to receive milnacipran once or twice daily (up to 200 mg/day) or placebo.[95] Thirty seven percent of patients with fibromyalgia achieved 50% pain reduction with twice daily dosing, 22% on once-daily dosing and 14% on placebo. However, only milnacipran taken twice daily was statistically superior to placebo. The PGIC, FIQ and Short-Form McGill Pain Questionnaire scores were superior for all active drug combinations compared with placebo. Only minor adverse drug events were reported. A 27-week, phase III, milnacipran trial of 888 patients with fibromyalgia identified 56% as treatment responders (pain, PGIC and physical function) and 40% as responding to placebo.[96] This difference was highly statistically significant. Importantly, effectiveness was sustained during this trial. Adverse effects were generally mild and included nausea and headache.

4.4 Dopamine Receptor Agonists

New approaches for the treatment of fibromyalgia included the evaluation of the dopamine receptor agonists ropinirole, pramipexole and rotigotine. Their mechanism of action involves binding to dopamine autoreceptors and postsynaptic receptors D_2 and D_3, which reduce dopamine release and subsequent dopamine turnover.[97,98] There is some evidence to suggest that pramipexole induces secretion of trophic factors that protect dopamine neurons. Adverse effects may include orthostatic hypotension, hallucinations, dyskinesias, somnolence and dry mouth.

4.4.1 Ropinirole

Ropinirole is a dopamine receptor agonist with high affinity for the D_2 autoreceptor and D_3 postsynaptic receptor, and moderate *in vitro* affinity for opioid receptors. This medication is FDA approved for the treatment of Parkinson's disease and RLS. It is metabolized in the liver by the cytochrome P450 1A2 isoenzymes and has only minimal affinity for muscarinic, acetylcholine, adrenergic or serotonin receptors. Although ropinirole had been used for the treatment of fibromyalgia symptoms in an open-label trial of 17 patients resulting in a 64% reduction of

tender-point scores over 4 months on a mean dose of 6 mg/day,[99] it failed to reach its primary endpoints in a recent phase IIa clinical fibromyalgia study of 112 participants (GlaxoSmithKline Clinical Study Register, 21 February 2006).[100] Thus, it is unclear at this time whether further clinical trials will be performed with this drug.

The most common adverse events were typical for dopamine receptor agonists, including mild to moderate nausea. Interestingly, characteristic adverse effects of dopamine receptor agonists, such as sleep attacks (sudden uncontrolled daytime sleepiness) as well as orthostatic hypotension, were not reported in these fibromyalgia trials. The proposed mechanisms of action for ropinirole in fibromyalgia included normalization of these patients' abnormal stress responses. Such abnormalities have been well documented in chronic pain syndromes such as fibromyalgia, and are comprised of heightened sympathetic arousal and blunted autonomic responses.[101,102]

D_3 receptors are primarily found in the limbic system, including the hippocampus, a region that receives dopaminergic input from the ventral tegmental area of the midbrain and is known to be associated with cognitive, emotional and endocrine functions.[103] The hippocampus is involved in the control of sympathetic activity[104] and inadequate dopaminergic control of the autonomic drive has been suggested as a relevant mechanism for fibromyalgia symptoms.[105] However, despite such promising characteristics, ropinirole was not more effective than placebo for patients with fibromyalgia.

4.4.2 Pramipexole

Similar to ropinirole, pramipexole is approved for the treatment of Parkinson's disease as well as moderate to severe RLS.[106] Its pharmacokinetic and pharmacodynamic profiles are similar to ropinirole, except that it is eliminated by urinary excretion and has mild affinity for central α_2-adrenergic receptors in addition to D_2 and D_3 receptors. Although pramipexole was analgesic for 60 patients with fibromyalgia (57 women, 3 men) in an RCT conducted over 14 weeks,[107] a subsequent phase II study of extended-release pramipexole did not achieve its target endpoints.

4.4.3 Rotigotine

The dopamine agonist rotigotine is approved by the FDA for the treatment of Parkinson symptoms and is marketed as a skin patch. In a phase IIa RCT, several doses of rotigotine were evaluated for the treatment of fibromyalgia symptoms. However, similar to pramipexol and ropinirole, rotigotine was unable to achieve its primary endpoints in a study of 240 patients with fibromyalgia.[108] Thus, the failure of three recent well designed RCTs of dopamine receptor agonists for fibromyalgia pain casts doubt on the future of these agents for the treatment of fibromyalgia.

4.5 NMDA Receptor Antagonists

The neurotransmitters involved in central sensitization include excitatory amino acids, tachykinins, substance P and neurokinin A. These signalling molecules are important for the activation of NMDA receptors of dorsal horn neurons, which results in temporal summation of neuronal responses by repetitive or continuous nociceptive input. Slow temporal summation represents an early stage of central sensitization in which NMDA receptors allow increased calcium influx and initiate cascades of intracellular biochemical events.[109-112] These intracellular biochemical events are associated with long-term neuroplastic changes that lead to increased excitability of central pain-related neurons. Thus, pharmacological therapies that target NMDA receptor activity hold great promise for the treatment of central sensitization, one of the major mechanisms for fibromyalgia pain.

Several NMDA receptor antagonists have been used for the treatment of fibromyalgia pain, including ketamine and dextromethorphan. In an RCT of 11 patients with fibromyalgia, ketamine (0.3 mg/kg bodyweight) or placebo (isotonic saline) was given as a single intravenous dose over a 10-minute period.[73] A ketamine responder was defined as a person whose pain was reduced by at least 50%. At the end of this trial, there was a significant pain reduction with ketamine compared with placebo. Eight of the 11 patients were ketamine responders and the analgesic effects

lasted 2–7 days. Pressure pain thresholds and pressure pain tolerance increased at many tender-point sites. However, almost all patients with fibromyalgia reported adverse effects, such as a feeling of unreality, dizziness and changes in hearing, which disappeared within 15 minutes after the injection. In a double-blind, placebo-controlled, crossover study of patients with fibromyalgia, single oral doses of dextromethorphan 60 mg and 90 mg reduced central sensitization significantly more than placebo, with dextromethorphan 90 mg being most effective.[113] However, no effects of dextromethorphan on clinical fibromyalgia pain were detected in this trial.

4.6 Sodium Oxybate

Pervasive sleep abnormalities, including diminished slow-wave sleep (stage IV) have been identified as important clinical features of fibromyalgia and thus may represent relevant therapeutic targets for future therapies.[114] Sodium oxybate has been found to increase stage IV sleep but is FDA-approved only for the treatment of cataplexy. A 1-month RCT of sodium oxybate (6.0 mg at bedtime) was conducted in 24 patients with fibromyalgia.[115] All patients with fibromyalgia were evaluated by polysomnography and tender-point score. Significantly greater improvements of polysomnography measures, pain and fatigue scores as well as tender-point scores were reported with sodium oxybate therapy than with placebo. This study provided preliminary evidence for the effectiveness of sodium oxybate in improving fibromyalgia pain and fatigue by normalizing slow-wave sleep and α-wave intrusions. Frequently reported adverse reactions of sodium oxybate therapy included dizziness, headache, nausea, pain, somnolence and pharyngitis. Less common adverse effects were vomiting, sleepwalking, urinary incontinence, depression and confusion. The results of a large, phase III, multicentre, RCT of sodium oxybate treatment for fibromyalgia symptoms over 8 weeks showed significant improvements of composite outcome measures (pain, FIQ score and PGIC) with sodium oxybate but not with placebo.[48] Altogether, these findings emphasize the important role of restoring deep sleep in patients with fibromyalgia and provide new directions for future fibromyalgia therapies.

4.7 Nabilone

Over the past 2 decades several cannabinoid receptors and their endogenous ligands, so-called endocannabinoids, have been identified. Endocannabinoids are involved in complex physiological functions such as pain modulation, control of appetite, motor coordination, memory procession and neuroprotection. Endocannabinoid receptors are widely distributed in the CNS as well as most peripheral tissues. Endocannabinoid- and cannabinoid-related analgesia seems to depend on activation of endocannabinoid receptors at peripheral nerve endings and not on those within the CNS.[116] Specific loss of peripheral endocannabinoid receptors located on nociceptors appears to lead to major reductions in the analgesia produced by cannabinoids. These important findings indicate that peripheral endocannabinoid receptors constitute a prime target for producing cannabinoid analgesia.[116] These results may have particular relevance for fibromyalgia symptoms, because increased peripheral nociceptive input represents an important pain mechanism in this syndrome.[12]

Currently only two cannabinoids, nabilone and dronabinol, are approved by the FDA for clinical use. Whereas dronabinol contains tetrahydrocannabinol (THC), the major psychoactive compound found in marijuana plants (cannabis), nabilone is a synthetic analogue of THC. Their indications include chemotherapy-induced nausea as well as anorexia and weight loss in AIDS. Although nabilone has been found to benefit neuropathic pain and central pain hypersensitivity, cannabinoids as a group do not seem to be more effective than codeine. Depressant effects on the CNS as well as addictive potential have limited their widespread use.

Recently, a 4-week RCT of patients with fibromyalgia provided evidence for nabilone as an effective and well tolerated treatment option for fibromyalgia pain and anxiety.[117] The effects of nabilone on pain were comparable with that

of other currently used fibromyalgia medications.[83] However, a responder analysis of 30% or 50% symptom relief was not reported. Although nabilone-treated patients had more adverse effects than controls, they were generally mild. No drug-related euphoria was observed in this trial, indicating low abuse potential. However, future studies will be necessary to determine possible risks for drug addiction as well as the long-term efficacy of this drug.

4.8 Modafinil and Armodafinil

Fatigue is one of the most prominent symptoms of fibromyalgia, second only to pain. A retrospective study of modafinil showed promising effects on fibromyalgia-related fatigue.[118] This study evaluated 98 patients with fibromyalgia who took either modafinil 200 or 400 mg/day. On average, two-thirds of patients with fibromyalgia experienced a 50% reduction in fatigue levels. One-third reported no benefit from the modafinil treatment.

Similar to modafinil, armodafinil is FDA approved for excessive daytime sleepiness during waking hours caused by narcolepsy, sleep apnoea and shift-work sleep disorder. Most of what is known about armodafinil is based on studies of modafinil. The main benefit of armodafinil over modafinil is its longer half-life in the body. The most common adverse effects of both stimulants are mild nausea and/or tachycardia. Whether the longer half-life of armodafinil will translate into superior efficacy on daytime fatigue remains to be seen in patients with fibromyalgia. Studies to show superior efficacy of armodafinil are currently lacking.

4.9 Naltrexone

In addition to antagonizing opioid receptors on neurons, naltrexone also inhibits microglia activity in the CNS. Modulation of microglia function can attenuate the production of excitatory and neurotoxic agents. The effectiveness of low-dose naltrexone (4.5 mg/day) on fibromyalgia symptoms was tested in a small pilot trial.[119] In this single-blind, placebo-controlled, crossover trial, patients with fibromyalgia showed that low-dose naltrexone reduced fibromyalgia symptoms with a >30% reduction of symptoms over placebo. In addition, mechanical and heat pain thresholds were improved by the drug. Adverse effects (including insomnia and vivid dreams) were described as minor and transient.

5. Conclusion

Fibromyalgia is a chronic pain syndrome that is characterized by widespread pain in peripheral tissues, psychological distress, nonrefreshing sleep and central sensitization. Whereas the important role of chronic stress and psychological factors for patients with fibromyalgia pain has been well established, little is known about the origin of the sensory abnormalities for pain. Deep tissue pain receptor input is most likely relevant for the initiation and/or maintenance of abnormal central pain processing and represents an important opportunity for new treatments and prevention of this chronic pain syndrome. Abnormalities of stress response systems lead to increased sympathetic tone and may result in abnormalities of peripheral tissues, particularly muscles. Fragmented and nonrefreshing sleep is correlated with increased pain sensitivity and pain in fibromyalgia.

Four important strategies for fibromyalgia therapy (see table II) appear useful at this time: (i) reduction of peripheral pains, particularly from muscles; (ii) improvement or prevention of central sensitization; (iii) normalization of sleep abnormalities; and (iv) treatment of negative affect, particularly depression. The first strategy is most likely to be relevant for acute fibromyalgia pain exacerbations and includes physical therapy,

Table II. Pharmacological treatment recommendations for fibromyalgia

Strategy	Treatment
Reduction of peripheral deep tissue pain	Local anaesthetics
Improvement or prevention of central sensitization	Anti-epileptics, antidepressants
Normalization of sleep abnormalities	GABA agonists
Treatment of negative affect, particularly depression	Antidepressants

muscle relaxants, muscle injections and analgesics. Central sensitization can be successfully ameliorated by cognitive behavioural therapy, sleep improvement, antidepressants, NMDA receptor antagonists and anti-epileptics. Sleep dysfunction can be normalized by stress reduction, aerobic exercise and GABA agonists. The pharmacological and behavioural treatment of secondary pain affect (anxiety, anger, depression and fear) is equally important and may currently be one of the most powerful interventions for fibromyalgia pain. Although future therapies with any combination of these interventions will probably be beneficial for patients with fibromyalgia, only head-to-head comparison trials will provide evidence for the superiority of one treatment over another. However, as with many other chronic syndromes, risk stratification and prevention will be of great importance and benefit for fibromyalgia.

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