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REVIEW

Pregabalin and Fibromyalgia Syndrome: A Treatment Option

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Abstract: Fibromyalgia (FM) is a chronic complex pain disorder that is multidimensional and exhibits heterogeneity requiring a long-term multidisciplinary approach to management. Many of the drugs used in the treatment of FM have been focused to the management of single symptoms; often such drugs fail to demonstrate acceptable efficacy in the majority of the patient population. Pregabalin is an α_2-δ ligand that regulates the release and postsynaptic actions of neurotransmitters related to analgesic, anticonvulsant and anxiolytic properties. In randomized, double-blind, placebo-controlled studies, pregabalin has demonstrated an improvement in pain, sleep and fatigue symptoms associated with FM, as well as offering an improvement in parameters related to quality of life. Although the positive outcomes obtained with pregabalin support its use as an option for the management of FM, the efficacy was restricted to a selected patient population outside of the usual care setting. Current data do not allow an explanation where there are any limitations of pregabalin as a treatment of patients with FM, as to whether this is a deficiency of the drug or the process of assessment (e.g. assessment tools of FM, clinical trial design).

Keywords: fibromyalgia, pregabalin, treatment, pain, fatigue, sleep

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Introduction

Pregabalin

Pregabalin (S-[+]-3-isobutylgaba, (S)-3-(aminomethyl)-5-methylhexanoic acid) is structurally related to the neurotransmitter GABA (γ-aminobutyric acid) and exhibits analgesic, anxiolytic and anticonvulsant properties.[1] To facilitate diffusion across the blood–brain barrier this lipophilic analog was produced by substitution at the 3' position of GABA.[2,3] The pharmacological properties of pregabalin, like gabapentin, are consistent with the blockade of voltage-dependent calcium channels (VDCC) that are located presynaptically and are involved in the regulation of calcium entry leading to selective neurotransmitter release from nerve terminals. In addition, postsynaptically located channels are involved in specific gene expression and activation of calcium-dependent ion channels with subsequent changes in cell excitability.[1,4] VDCCs are divided into six classes (P, Q, N, L, R and T) based on their voltage dependence, kinetics and sensitivity to a range of drugs of which the N-type calcium channel plays a role in pain sensitization processes and increased central excitability.[5–7] The pore and voltage sensor of VDCCs is formed of an α_1 protein with associated auxiliary α_2-δ, β and γ subunits. The α_2-δ subunit of presynaptic VDCCs, that are widely distributed throughout the peripheral and central nervous system (CNS), is the primary site of action of pregabalin and gabapentin.[8] This subunit is expressed in the dorsal root ganglia neurons, in several regions of the brain including CA1 (field 1 of the hippocampus), the subiculum and in regions involved in processing nociceptive information, including the thalamus, periaqueductal gray matter (PAG) and amygdala, and the superficial laminas of the dorsal spinal cord.[9,10] In models of neuropathic pain, the α_2-δ subunit is upregulated in the dorsal root ganglia and spinal cord, and may play an important role in hypersensitization processes.[11–13] As a consequence, pregabalin produces an inhibitory modulation of neuronal excitability with an apparent reduction of the release of neurotransmitters, such as glutamate and substance P, particularly in areas of the CNS dense in synaptic connections such as the neocortex, amygdala and hippocampus.[1,4,14–16] Importantly, the α_2-δ subunit ligands have been purported to exert a minimal modulation of normal synaptic transmission in the dorsal horn (i.e. have negligible antinociceptive effect), but are able to modulate the development of and synaptic transmission during central sensitization (i.e. have an antihyperalgesic effect).[17,18] Pregabalin has no effect on arterial blood pressure or cardiac function supporting a lack of action on the calcium channels, such as L-type, in these cells.

There are four genes for α_2-δ, designated CACNA2D(1–4) of which only α_2-δ_1 and α_2-δ_2 bind pregabalin and gabapentin, while α_2-δ_3 and α_2-δ_4 lack drug binding.[19–21] The binding of pregabalin is dependent on the presence of arginine at position 217 in the α_2-δ subunit. In mutant mice that have a single amino acid substitution (alanine for arginine) at position 217 in the α_2-δ subunit, a loss of pregabalin binding and reduction in analgesic efficacy was reported.[22] Therefore pregabalin, and gabapentin, are α_2-δ subunit-specific ligands, a property that is associated with the pharmacological profile of these drugs that includes analgesia.

The α_2-δ subunit has a heterogeneous distribution in the brain and thereby is not expressed equally at all glutamatergic synapses, suggesting differential sensitivity of glutamate pathways to the α_2-δ subunit ligands.[8] Pregabalin, and gabapentin, have been reported to selectively reduce glutamate synaptic activity in different brain regions.[23–25] Such selective actions may also be expressed by pregabalin due to the α_2-δ subunit distribution between neuronal systems whereby glutamatergic pathways seem to express largely α_2-δ_1, while GABAergic neurons express mostly α_2-δ_2 subunits.[8] This, in combination with the subunit selective properties of pregabalin and gabapentin, could afford discrete modulation of neuronal activity that may be relevant to the pathophysiology of fibromyalgia (FM).

The treatment of a number of neuropathic pain conditions with pregabalin has been associated with significant often immediate (by day 2 of treatment) decreases in pain scores.[4,26] Pregabalin has also demonstrated sleep-modulating properties related to increasing the duration of nonrapid eye movement and decreasing rapid eye movement sleep.[27] For example, pregabalin has been shown to increase slow-wave sleep, which has been correlated with the restorative aspect of sleep and decrease night-time awakenings in healthy volunteers and in patients with chronic pain syndromes.[28,29]

Pharmacokinetics

After oral administration, pregabalin is rapidly absorbed, primarily in the proximal colon, with peak plasma concentrations within 1.5 h.[30] The absorption exhibits linear pharmacokinetics and is not affected by food consumption with the average bioavailability, which is independent of dose, exceeding 90%. Pregabalin does not bind to plasma proteins and thereby is available to cross the blood–brain barrier, which may involve the system L transporter for transport of large amino acids. The drug is not metabolized in the liver. The elimination half-life of pregabalin, which is also independent of dose and repeated dose administration, is 6.3 h with a range from 5.5 to 6.7 h. Pregabalin is excreted renally and up to 99% of the absorbed dose is excreted unchanged in the urine. Elimination is nearly proportional to creatinine clearance (Cl_{Cr}) thus in subjects with impaired renal function dose reduction is necessary with the need for Cl_{Cr} to be monitored.[31] No interactions with other drugs are known.[32]

Fibromyalgia

FM is a complex chronic widespread pain condition in which patients present with allodynia, hyperalgesia and experience many auxiliary symptoms (Box 1).[33–35] The classification of FM as established in 1990 by The American College of Rheumatology (ACR) criteria requires a history of at least 3 months of widespread pain and tenderness, determined by a force of 4 kg, in at least 11 of 18 defined tender points.[33] The presence of FM cannot be determined by objective clinical findings, radiographic abnormalities or routinely used laboratory tests and thereby is reliant on the patient's self-reported presence and severity of symptoms.[36,37] The widespread pain is preceded by localized or regional pain in most patients with FM, which could suggest the latter is a trigger for the former.[38] FM is a difficult to treat chronic condition of which pain is often considered the predominant feature, usually requiring a multidisciplinary approach using both pharmacological and nonpharmacological management. Fatigue in FM is considered by patients to be the second most important domain after pain and may play a role of relative importance in the deterioration of the active state particularly with respect to the long duration of the symptom.[39] Further, a typical waxing and waning course of the symptoms and the presence of comorbid conditions (Box 2) often further complicate the classification and treatment of FM. As a consequence this condition can have an immense impact on daily life, limiting the patient's functioning and emotional wellbeing.

In clinical practice many of the symptoms (fatigue, sleep dysfunction, stiffness, depression, anxiety, cognitive disturbance) reported in addition to the pain and tenderness, however, present a complexity that is probably beyond the ACR 1990 classification.[40] Nevertheless epidemiological studies using the ACR 1990 criteria report a prevalence of 2%–4% within the general population, which increases to greater than 7% of those over 70 years of age.[41] A female to male ratio of 9:1 is observed in the patient population, where the most common age group is 45–60 years. Over the past 20 years, FM has emerged as a leading cause of visits to rheumatologists, either alone or as

Box 1. Symptoms of fibromyalgia.

Widespread pain
Hyperalgesia and allodynia
Chronic fatigue
Sleep disturbance
Stiffness
Anxiety and depressed mood
Bowel dysfunction (e.g. irritable bowel syndrome)
Paresthesias
Cognitive disruption
Exercise intolerance
Headaches

Box 2. Examples of conditions frequently comorbid with fibromyalgia.

Chronic low back pain
Irritable bowel syndrome
Depression/anxiety
Temporomandibular joint disorder
Chronic fatigue syndrome
Multiple chemical sensitivities
Interstitial cystitis
Rheumatoid arthritis
Hypothyroidism

an accompaniment of other rheumatic disorders.[42] Although an epidemiological study can provide insight into the incidence, distribution, and control of a particular disease in a population, the outcomes understandably are dependent on the definition of the condition. The complexity of FM has the potential of limiting the reliability of epidemiological data and a likely underestimation of the impact on the general population where subjects presenting with FM symptoms remain undiagnosed.

Symptom expression, both physical and psychological, in FM tends to vary on an individual basis, indicative of heterogeneity within the condition.[43] Differences in biological variables (e.g. positive antinuclear antibodies, cytokine abnormalities, growth hormone, thyroid hormones) indicative of the heterogeneity in the presentation of FM are supportive of subgroups within the patient population.[44–48] Patient subgroups based on responses to pharmacological interventions and psychosocial responses have also been proposed.[49–53]

In 2003, the effectiveness of therapy for patients with FM was related to general satisfaction with quality of life improvement and health status, with limited or no improvement in pain.[54] The positive outcomes and satisfaction was suggested to be the result of patient instruction and education of the disease. Frustration with current treatment modalities in combination with the consequence of high prevalence and frequent comorbidities identifies FM as a significant challenge requiring a novel therapeutic approach offering clinical efficacy.[55]

The management of FM has been complicated by the lack of a single, universally accepted pathophysiological mechanism and overlap with symptoms of other health conditions (e.g. chronic fatigue syndrome, myofascial pain, systemic lupus). The development of focused and mechanistically based therapeutic options targeting the array of symptoms of FM has been limited. Current management approaches of improving health status in FM use a rehabilitation model integrating exercise, education (stress management programs, cognitive behavior therapy (CBT)) and pharmacological treatments.[56,57]

Dysfunction of pain modulatory systems within the CNS, neuroendocrine dysfunction, and dysautonomia are among the hypotheses that have been proposed regarding the pathophysiology of FM.[58–61] FM is often described as a condition of heightened generalized sensitization to sensory input presenting as a complex of symptoms including pain, although lacking signs of underlying peripheral structural damage and inflammation. Evidence suggests patients with FM exhibit greater sensitivity to a range of sensory stimuli including auditory, tactile, heat, and pressure.[62–65] The heightened responsiveness to sensory stimulation may be related to a lack of inhibitory control over repetitive or irrelevant somatosensory stimulation. These findings are consistent with FM being in part due to a global disturbance in sensory processing rather than an isolated abnormality in pain processing.

Studies utilizing neuroimaging techniques such as functional magnetic resonance imaging (fMRI), and single photon emission computed tomography (SPECT) have demonstrated that patients with FM exhibit neural activity in regions involved in processing the sensory pain sensation, in response to the administration of a noxious pressure or heat stimulus, that differs from that observed in healthy controls.[66,67] A full range of perceived pain stimuli are detected and experienced in both patients with FM and healthy controls, however the stimulus intensity threshold of the former group is significantly lower. Mood states, such as depression, did not appear to influence the outcome supporting the status of neural activity in the patients with FM being related to physiologic, not psychologic stimuli. Neuroimaging techniques infer activity from localized changes in regional cerebral blood flow occurring in response to neural metabolic demand and do not measure neural activity directly. Therefore, further work is required to determine whether these observations are related to neural demand influencing vascular status or whether a compromised vasculature, due to dysautonomia, is impacting on neural activity, or a combination of both.

Central to the manifestation of the condition is the suggestion of altered processing within the central nociceptive system. Pain, as a consequence, has been described as both a symptom and a contributor of other symptoms such as fatigue, impairment of concentration, negative mood, degraded sleep, and diminished overall activity.[68] The nociceptive system is probably one component of a complex network of physiological aspects that express a level of interdependence creating the clinical profile of FM.

Physical insult, leading to traumatized tissue and localized pain, or a psychological insult, such as stress, has been related to initiation of altered functioning and sensitization of the central nociceptive system.[69–73] In patients with FM, temporal summation of nociceptive stimuli (where the intensity of rapidly repeated noxious stimuli is perceived to increase) is enhanced and diffuse noxious inhibitory control is reduced.[74–76] Central sensitization implies spontaneous nerve activity, expanded receptive fields, and abnormal temporal summation (or 'wind-up') within the spinal cord. N-methyl-D-aspartic acid (NMDA) receptors, found at the postsynaptic membrane in the dorsal horn of the spinal cord, are proposed to play a role in these phenomena. Once central (sensitization) hyperexcitability has been established, subsequent responses to normal stimuli are exaggerated and the threshold for the activation of new inputs is reduced. Central to a variety of neuronal processes including synaptic plasticity and neurotoxicity, is the activation of NMDA receptors by glutamate leading 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).[77–79] In addition, nitric oxide production by neuronal nitric oxide synthase is induced by the calcium influx, which is believed to evoke a retrograde signaling action enhancing presynaptic glutamate release.[80] Studies on levels of nitric oxide in FM, however, have not been conclusive.[81] Similarly substance P, a peptide neurotransmitter associated with pain transmission, in addition to many other actions, enhances the responsiveness of NMDA receptors to glutamate.[80] Thus, modulators of glutamatergic processes, such as α_2-δ ligands could offer an approach to the management of the symptoms of FM.

The sensory inputs also appear to lead to activation of circuits of the limbic system such as the autonomic nervous system and the neuroendocrine hypothalamic pituitary adrenal (HPA) axis in patients with FM. The HPA axis dysfunction is characterized by elevated cortisol levels lacking diurnal fluctuation with blunted secretion in response to stress.[59,61] This is consistent with the HPA axis being underactivated to stimuli and some patients with FM exhibiting a subnormal adrenocortical function. Current data do not allow an explanation of the location of the defect of the HPA dysfunction with no structural abnormalities of the associated endocrine glands. Dysautonomia has also been suggested to be responsible for the generation and maintenance of the symptoms of FM.[82,83] A persistently hyperactive sympathetic nervous system (SNS) that is hyporeactive in response to stress with concomitant decreased parasympathetic activity has been reported in patients with FM.[84–86] The chronic hyperstimulation of the α-adrenergic receptors of the SNS could lead to receptor desensitization and downregulation. The augmented sympathetic activity appears to be greater in women than men, suggesting that women with FM may have more severe autonomic dysfunction. The modulation of bioamine levels (e.g. inhibition of norepinephrine and/or serotonin reuptake), may achieve benefit in the treatment of FM by an effect on descending pain pathways and accommodating for the receptor desensitization within the SNS.

An increased sensitivity to stressors, perhaps due to the altered functioning of the limbic circuits, HPA axis and autonomic nervous system preventing a normal physiological regulation of such an event, could be related to mood arousal, resulting in altered sleep architecture and enhanced anxiety leading to depression. Such outcomes within the limbic system may also be related to the memory and cognitive function, and mental fatigue (fibrofog) in patients with FM.[57] The prevalence of symptoms such as syncope, morning stiffness, pseudo-Raynaud's phenomenon, and intestinal irritability observed in this patient population may also be associated with blunted sympathetic activity to stress and impaired parasympathetic modulation of the dysautonomia.[58,82,83]

In addition to a central action, an altered SNS activity related to the dysautonomia will, for example, lead to generalized widespread peripheral vasoconstriction (in addition to other autonomic responses). The resulting reduced blood flow could lead to a relatively mild challenge (e.g. stretching, light exercise) to the skeletal muscle evoking a state of ischemia and changed muscle energy metabolism. Low levels of phosphocreatine and ATP at rest, low phosphorylation potential, and total oxidative capacity, and a reduced number and size of mitochondria in skeletal muscle of patients with FM have been identified.[87–90] The altered functioning of the skeletal muscle following

such a vascular event could cause the sensitization of ergoreceptors, with the potential outcome of muscle fatigue, and the sensitization or activation of nociceptors leading to multifocal muscular pain and hyperalgesia well beyond the area of the initial insult. The generalized sensitization to pain within skeletal muscle will be associated with spatially distributed allodynia and hyperalgesia (tender points). Therefore, changes in intramuscular microcirculation and in muscle energy metabolism, could act as further excitatory triggers of the nociceptive system in the CNS and for multifocal pain in the muscles.[38,59]

The pathophysiologic mechanisms of FM have been proposed previously as a cyclic process enabling a trigger (e.g. tender points, tissue trauma, exercise, stress) at any point within the loop to initiate and express (to varying degrees) the array of symptoms typical of FM.[73] The intensity and duration of the physical or psychological insult, and thereby resulting symptoms, required to achieve the level of sensitization related to FM is not understood. A familial predisposition, however, in subjects vulnerable to the development of FM has been proposed from data from genetic studies.[91] Although the frequency of polymorphisms of the serotonin transporter promoter gene, 5-HT2A receptor gene, catechol-O-methyltransferase gene, and dopamine D4 receptor gene is altered in patients with FM, the relevance to the etiology and pathophysiology is unknown.[92–96]

Pregabalin and Fibromyalgia: Clinical Data

The goals of treatment of FM are to alleviate pain, increase restorative sleep and improve physical function.[53,97] Pregabalin has been proposed as part of a multimodal approach to pain management and is proving useful for the treatment of a wide range of chronic pain syndromes, acute postoperative pain, and inflammatory pain.[4] This has supported the clinical evaluation of pregabalin as a treatment of FM.

Clinical Trial Design

The published literature on the use of pregabalin monotherapy for the treatment of FM is limited to four randomized controlled trials. Three studies (an 8-week, a 13-week, and a 14-week) were designed to assess the efficacy and safety of pregabalin (150, 300, 450, or 600 mg/d BID or TID) monotherapy for treatment of FM.[98–100] In addition to determining whether the treatment would reduce the severity of pain, the effect of pregabalin on other domains of FM, sleep, fatigue, and health-related quality of life were examined. The fourth study, the FREEDOM (Fibromyalgia Relapse Evaluation and Efficacy for Durability Of Meaningful relief) trial, involved the assessment of the durability of the beneficial effects of pregabalin (300, 450, or 600 mg/d BID) using an enriched enrolment with randomized withdrawal (EERW) design.[101]

All studies involved male and female patients aged 18 years or over who met the 1990 ACR classification criteria for FM (widespread pain for ≥3 months and pain in 11 of 18 tender points). Subjects were required to have a pain score of 40 mm or greater on the 100 mm visual analog scale (VAS) at screening and randomization. Variability within the patient population was limited by the application of exclusion criteria. Subjects were excluded from any of the studies if they had evidence of inflammatory rheumatic disease or other severe painful disorders (that might confound assessment of FM pain), and/or had clinically significant or unstable medical or psychological conditions that would compromise participation in the study. Further, because the excretion of pregabalin is dependent upon a viable renal system subjects with a Cl_{Cr} rate of 60 ml/minute or less were specifically excluded.[31] Three studies indicated that subjects with pending or settled worker's compensation, civil litigation or disability claims pertinent to the patient's FM were excluded.[98–100] Patients who failed to respond to previous treatment with gabapentin (dosages ≥1,200 mg/d) for pain associated with FM were excluded from the 8-week study.[98] The design of the trials to evaluate the response of patients with FM to pregabalin monotherapy prohibited the subjects from concomitant medications usually taken for treatment of their condition. Thus, patients were required to discontinue, where applicable, antidepressants, antiepileptic agents, or other medications to treat pain and insomnia. However, acetaminophen (≤4 g/d) as rescue medication for pain and aspirin (≤325 mg/d) for cardiac prophylaxis were permitted during the trials. All patients were instructed to maintain normal daily routines and not

to alter their nonpharmacological therapy regimens such as physical therapy (e.g. exercise), massage or chiropractic care. Thus the patient populations within the trials exhibited a high level of commonality, albeit associated with a degree of selectivity due to the strict criteria of exclusion and inclusion.

The dosage program in the 8-week study involved patients randomly assigned to receive either pregabalin (150, 300, or 450 mg/d) or placebo three times daily in equal doses for the duration of the trial.[98] While the patients of the 13- and 14-week efficacy and safety studies were randomized to receive either pregabalin (300, 450, or 600 mg/d) or placebo twice daily.[99,100] Finally, the FREEDOM trial included a 6-week open label (OL) pregabalin treatment period to determine each patient's optimal dosage (300, 450, or 600 mg/d, twice daily). Pregabalin responders during the OL phase were then included in 26-week double-blind treatment (twice daily) phase with placebo or pregabalin (with patients receiving their fixed optimal dosage of 300, 450, or 600 mg/d).[101]

The assessment tools used to determine outcome measures are summarized in Table 1. The proportion of responders with respect to the primary efficacy measurement within the 8-week study was defined as patients with 50% or greater reduction in mean pain score from baseline to endpoint.[98] Mease et al (2008) defined responders with respect to the primary efficacy measurement in the 13-week study as patients with a 30% or greater decrease in mean pain score from baseline to endpoint.[100] While Arnold et al (2008) determined the proportion of responders during the 14-week study with 30% or greater and 50% or greater reduction of weekly mean pain scores from baseline to endpoint.[99] In the 8-week study and the 14-week study, endpoint analyses were based on the last observation carried forward (LOCF). A reduction in pain on an 11-point pain intensity numerical rating scale of at least 30% represents a clinically important improvement to patients.[102] Responders with respect to primary efficacy measurement within the OL phase of the FREEDOM trial were identified by 50% or greater reduction in pain VAS score from baseline and a self-rating overall improvement on the patient global impression of change (PGIC) scale of "much improved" or "very much improved". During the double-blind phase of the FREEDOM trial, the primary efficacy parameter was time to "loss of therapeutic response" (LTR) defined as having either less than 30% reduction in pain VAS score relative to OL baseline or worsening of FMS symptoms necessitating alternative treatment.[101]

Clinical Efficacy in Pregabalin Monotherapy Trials

These clinical trials have demonstrated that in patients with FM pregabalin can reduce the severity of pain and fatigue, and improve sleep and health-related quality of life (Tables 2 and 3).

8-week study

In a multicenter, double-blind, placebo-controlled 8-week randomized study, of the 825 patients screened 529 (64%) subjects were eligible for inclusion and 410 patients (77.5%) completed the trial.[98] Inability of subjects to discontinue concurrent medication was reported as a factor particular to screening failure. For patients who completed the 8-week study, only the 450-mg/d pregabalin group presented a significantly ($P = 0.0009$) lower endpoint mean pain score, than that observed for the placebo group (a difference of –0.93). Subjects in this pregabalin group exhibited a significant ($P < 0.05$) improvement, relative to the placebo group (ranging from –0.8 to –1.2), in the weekly mean pain scores at week 1 which was maintained through to week 7, but not week 8. Although the endpoint mean pain scores for the 150 and 300 mg/d pregabalin groups were not significantly different from placebo, improvements relative to placebo were observed at weeks 1 and 2 in the 150 mg/d pregabalin group (–0.4; $P < 0.05$) and week 1 through week 5 in the 300 mg/d pregabalin group (–0.6 to –0.9; $P < 0.05$).

At endpoint, the proportion of patients that were classified as responders (a ≥50% improvement in endpoint pain score from baseline) again was only significantly greater than placebo (13.2%) in the 450 mg/d pregabalin group (28.9%; $P = 0.003$). Using the clinically meaningful criteria of 30% improvement,[102] the proportion of patients classified as responders was greater than that achieving 50% or greater improvement but still only achieved significance in the 450 mg/d pregabalin group compared with the placebo group (Table 2). In contrast, a significant improvement of the mean FM intensity scores from the manual tender point survey (MTPS),

Table 1. Assessment tools used in the evaluation of pregabalin monotherapy as a treatment of patients with FM. Text in italics indicates primary efficacy measurements.

Study	Crofford et al 2005[98]/ Arnold et al 2007[103]	Mease et al 2008[100]	Arnold et al 2008[99]	Crofford et al 2008[101]
Duration (weeks)	8	13	14	32 (6 open-label and 26 double-blind)
Assessment				
Pain ~ 11-point numerical rating scale	*Daily*	*Daily*	*Daily*	*Baseline, weeks 1, 2, 3, 4, 5, 6, 8, and every 4 weeks thereafter*
Sleep ~ rated sleep quality	Daily	Daily	Daily	
SF-MPQ	Screening, baseline, weeks 1, 3, 5, and 8	Baseline, weeks 5 and 9, and endpoint		
Medical outcomes (MOS)-Sleep measure	Baseline and endpoint	Baseline, weeks 5 and 9, and endpoint	Baseline and endpoint	Baseline, weeks 1, 2, 3, 4, 5, 6, 8, and every 4 weeks thereafter
MAF	Baseline and endpoint	Baseline, weeks 5 and 9, and endpoint	Baseline and endpoint	Baseline, weeks 1, 2, 3, 4, 5, 6, 8, and every 4 weeks thereafter
HADS	Baseline and endpoint	Baseline, weeks 5 and 9, and endpoint	Baseline and endpoint	
SF-36	Baseline and endpoint	Baseline, weeks 5 and 9, and endpoint	Baseline and endpoint	Baseline, weeks 1, 2, 3, 4, 5, 6, 8, and every 4 weeks thereafter
SDS		Baseline, weeks 5 and 9, and endpoint		
F-HAQ		Baseline, weeks 5 and 9, and endpoint		
PGIC	Endpoint	*Endpoint*	*Endpoint*	Baseline, weeks 1, 2, 3, 4, 5, 6, 8, and every 4 weeks thereafter
CGIC	Endpoint			
FIQ		*Baseline and endpoint*	*Baseline and endpoint*	Baseline, weeks 1, 2, 3, 4, 5, 6, 8, and every 4 weeks thereafter
MTPS	Baseline and endpoint			

Abbreviations: SF-MPQ, Short-form McGill Pain Questionnaire; MAF, Multidimensional Assessment of Fatigue; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form 36 Health Survey; SDS, Sheehan Disability Scale; F-HAQ, Fibromyalgia Health Assessment Questionnaire; PGIC, Patient Global Impression of Change; CGIC, Clinical Global Impression of Change; FIQ, Fibromyalgia Impact Questionnaire; MTPS, Manual Tender Point Survey.

relative to the placebo group, was not achieved in the pregabalin groups.

Although statistically significant improvement in pain in the 8-week study[98] was only observed following administration of the higher dose of pregabalin studied, at endpoint an improvement in the mean sleep quality scores (–0.6 (P = 0.035) and –1.3 (P = 0.0003), respectively) and Multidimensional Assessment of Fatigue (MAF) global fatigue index scores (–3.5 and –3.4, respectively; P = 0.019) were obtained in the 300 and 450 mg/d pregabalin groups relative to the placebo group (Table 3). Further all three pregabalin groups demonstrated significant improvement (–8.5, –8.9, and, –13.7 for 150, 300, and 450 mg/d, respectively; P < 0.001) compared with placebo in several scales of the Medical Outcomes Study (MOS)-Sleep measure. In addition, assessment of health-related quality of life, by scores in general health perception, domains of the short form (SF)-36, PGIC, and Clinical Global Impression of Change (CGIC), exhibited an apparent dose-related improvement due to pregabalin (150, 300, and 450 mg/d) treatment relative to placebo (Table 3).

The proportion of patients included in the 8-week study with any anxiety symptoms was 71% and with any depressive symptoms was 56% with baseline mean Hospital Anxiety and Depression (HAD) scores in the mild range for both anxiety symptoms (10.1) and depression (8.6).[98,103] Interestingly pregabalin failed to demonstrate an improvement in the HAD scores consistent with the improvement in FM pain symptoms being independent of the patients' status of anxiety or depression.[103]

13-week study

In the 13-week multicenter, double-blind, placebo-controlled randomized trial, of the 1328 patients screened, 748 (56%) received study medication (300, 450, or 600 mg/d pregabalin or placebo) of which 485 (65%) patients completed.[100] Reasons for screening failure, and thereby noninclusion, were not detailed. In contrast to the outcomes of the 8-week study,[98] patients in all three pregabalin treatment (300, 450, or 600 mg/d) groups showed statistically significant improvement in endpoint mean pain score (Table 2) compared to the placebo group.[100]

Table 2. Summary of pain outcomes in the evaluation of pregabalin monotherapy as a treatment of patients with FM.

Study	Treatment	≥30% reduction of mean pain score		≥50% reduction of mean pain score		Endpoint mean pain score
		Proportion of responders (%)	Δ	Proportion of responders (%)	Δ	Δ VAS
8-week	Placebo	27.1	–	13.2	–	–
	PGB 150	31.3	4.2	13.0	–0.2	na
	PGB 300	37.9	10.8	18.9	5.7	na
	PGB 450	48.4	21.3*	28.9	15.7*	–0.93*
13-week	Placebo	35	–			–
	PGB 300	43	7			–0.43*
	PGB 450	43	7			–0.47*
	PGB 600	44	8			–0.66*
14-week	Placebo	30	–	13.2	–	–
	PGB 300	42	12*	24	9*	–0.71*
	PGB 450	50	20*	27	12*	–0.98*
	PGB 600	48	18*	30	15*	–1.00*

Notes: *Significantly different relative to placebo, P ≤ 0.05; 8-week, Crofford et al 2005;[98] 13-week, Mease et al 2008;[100] 14-week, Arnold et al 2008.[99]
Abbreviations: PGB, pregabalin with indication of dose as mg/d; Δ, change relative to placebo; VAS, visual analog scale; na, data not available.

Table 3. Summary of nonpain efficacy outcomes in the evaluation of pregabalin monotherapy as a treatment of patients with FM.

		Δ MOS-sleep measure	Δ Sleep quality scores	Δ MAF scores	PGIC (proportion of patients much or very much improved)¥	CGIC (proportion of patients improved)	FIQ Total score change
8-week	Placebo	–	–	–	26	25	
	PGB 150	–8.5*	na	na	32	33	
	PGB 300	–8.9*	–0.6*	–3.5	45	41	
	PGB 450	–13.7*	–1.3*	–3.4	52	52	
13-week	Placebo	–	–	–	35		–13.66
	PGB 300	–4.81*	–0.87*	na	43		–16.15
	PGB 450	–6.10*	–0.97*	na	41		–15.71
	PGB 600	–5.20*	–1.21*	na	46		–14.88
14-week	Placebo	–	–	–	24		–7.74
	PGB 300	–4.74*	–0.74	–0.92	32		–10.70
	PGB 450	–6.20*	–1.12	–1.41	47		–12.98*
	PGB 600	–8.44*	–1.35	–1.50	44		–13.08*

Notes: *Significantly different relative to placebo, $P \leq 0.05$; ¥Outcome from statistical analysis not clearly indicated; 8-week, Crofford et al 2005;[98] 13-week, Mease et al 2008;[100] 14-week, Arnold et al 2008.[99]
Abbreviations: PGB, pregabalin with indication of dose as mg/d; Δ, change relative to placebo; MOS, Medical Outcomes Study; MAF, Multidimensional Assessment of Fatigue; PGIC, Patient Global Impression of Change; CGIC, Clinical Global Impression of Change; FIQ, Fibromyalgia Impact Questionnaire; na, data not available.

Although efficacy was observed at week 1 within all three pregabalin treatment groups, it only remained consistently improved for the duration of the study in the 600 mg/d group with improvement versus placebo observed at every weekly time point. Although the proportion of patients that were responders (defined as ≥30% decrease in mean pain score) were higher in the pregabalin treatment groups than in the placebo group (Table 2), the differences did not reach statistical significance.

Consistent with the outcomes of the 8-week study,[98] a significant improvement, at the endpoint of the study, in aspects of sleep (Table 3) was obtained with all three pregabalin doses relative to placebo. It is of note however that although the MOS-Sleep Somnolence measure was improved in all three pregabalin groups, the changes observed in the placebo group were the larger. In contrast to the outcomes of the 8-week study,[98] there was no statistical difference between the pregabalin treatment groups and the placebo group in the global fatigue index scores obtained during the 13-week study, although data was not shown.[100]

During the 13-week study, minimal improvement at endpoint in PGIC responses was reported by 71%, 72%, 69%, and 56% of patients in the 300 mg/d, 450 mg/d, 600 mg/d pregabalin, and placebo treatment groups, respectively.[100] Although an improvement in the Fibromyalgia Impact Questionnaire (FIQ)-Total score was obtained for all patient groups, the changes in the pregabalin treatment groups were not significantly different from those obtained in the placebo group.

14-week study

Of 1195 patients screened, 750 (63%) were included in a 14-week multicentered, double-blind, placebo-controlled randomized study of which 486 (65%) subjects completed.[99] Primary reasons for failure of inclusion were inability to withdraw from prohibited medication and estimated Cl_{Cr} of 60 ml/minute or less (because of the excretion of pregabalin being dependent on the renal system). Although pregabalin again improved the weekly mean pain score relative to the placebo group, unlike the outcome of the 13-week

study, the significant difference that was observed at week 1 was maintained until the endpoint (week 14) in all three treatment (300, 450, and 600 mg/d) groups. At endpoint, the proportion of patients that were classified as responders (by either criteria of ≥30% or 50% improvement in pain from baseline) was significantly greater than placebo in all pregabalin treatment groups (Table 2). For the 30% or greater pain reduction responder rate, the numbers needed to treat (NNTs) were calculated as 9.01, 5.25, and 5.73 for 300, 450, and 600 mg/d pregabalin, respectively. While for the 50% or greater pain reduction responder rate the NNTs were calculated as 11.33, 8.23, and 6.62 for 300, 450, and 600 mg/d pregabalin, respectively. Regarding secondary efficacy measures, patients in pregabalin treatment groups demonstrated a consistent improvement in quality of sleep, but not anxiety, depressive symptoms, functioning, or fatigue.

As previously observed in the 8-week[98] and 13-week studies,[100] a greater improvement for PGIC was obtained in the pregabalin (300, 450, and 600 mg/d) treatment groups relative to placebo.[99] Further, a greater improvement in the FIQ-Total score than that obtained with the placebo group was observed with the two higher doses of pregabalin (450 and 600 mg/d) only.

FREEDOM trial

In this long-term EERW trial, of the 1777 patients screened, 1051 (59%) entered an OL treatment phase and 663 (63%) completed.[101] Reasons for failing screening included inability to withdraw from prior pain medication, inability to comply with visit schedule, and laboratory results outside of protocol limits. From the OL treatment phase, 566 patients met the responder criteria (≥50% reduction in pain VAS score from baseline) and were randomized to 26-week double-blind treatment with placebo or pregabalin (with patients receiving their fixed optimal dosage of 300, 450, or 600 mg/d). The patient population had had FM for a median duration of 7.8 years, baseline VAS score was 78 mm and at least 50% of the subjects presented with pain in all 18 tender points. Of those subjects assigned to the placebo arm, 19% (55/287) completed the trial, while from the pregabalin treatment arm 38% (107/279) of the patients completed the trial. Reasons for lack of completion of the study included LTR, adverse effects (AEs), and withdrawn consent or lost to follow-up.

It is of note that, from the available patients with FM, only 32% were applicable for inclusion in the double-blind phase of the trial and only 9% were capable of completing the 26-week treatment phase of a clinical trial designed to assess durability of the beneficial effects of pregabalin. Whether such outcomes were related to the design of the trial being a deviation from the usual care setting of this patient group or as a consequence of limited efficacy of pregabalin in this patient population is not clear.

Time to LTR, during the 26-week double-blind treatment phase was significantly longer for patients treated with pregabalin than for patients receiving placebo.[101] LTR was experienced by 90 patients (32%) receiving pregabalin and 174 patients (61%) in the placebo arm by the end of the 26-week period. Although each fixed-dosage pregabalin (300, 450, and 600 mg/d) treatment group was associated with a significantly longer time to LTR than that observed in the placebo group, the greatest difference between pregabalin- and placebo-treated patients in time to LTR was obtained in the 300 mg/d pregabalin group.

Secondary efficacy endpoints of PGIC, FIQ-Total score, Overall Sleep Problems Index of the MOS-Sleep Scale, MAF and SF-36 Health Survey's Physical and Mental component scores demonstrated significantly greater time to LTR in the pregabalin group compared with the outcomes of the placebo group.[101] These findings support pregabalin being of benefit to several components of FM in addition to a reduction in pain. It is of interest to note that when the FIQ was used as an assessment of the patient, the benefits obtained with pregabalin treatment were not as marked as with other assessment tools.[101] Further studies are required to determine whether the FIQ, in its present form, is the most appropriate form of assessment of this patient group.

Tolerability and Safety

During the pregabalin efficacy and safety studies, most patients with FM (72%–92%) in each group reported treatment-emergent AEs.[98–100] An apparent dose-relationship was often suggested for the occurrence of AEs, although statistically significant differences were not always achieved. A similar incidence of one or more AEs (82%), of which most

were mild to moderate in intensity, were reported by the patients with FM who entered the OL treatment phase of the FREEDOM durability trial.[101] During the double-blind treatment phase of the FREEDOM trial, AEs were reported by 45%–63% of the patients. A range of adverse events, which are consistent with known side effects of pregabalin, were reported, of which dizziness (23%–49%), somnolence (13%–28%), and weight gain (8%–14%) exhibited the greatest frequency and were dependent on the dose of pregabalin. Both dizziness and somnolence had a median time of onset of 1–2 days, irrespective of dose of pregabalin, and time-limited properties with durations of 6–15 days and 18–31 days, respectively. Although headache was reported as being a commonly experienced AE (by 14% of subjects) during the OL phase of the FREEDOM trial, the frequency in patients in the pregabalin treatment groups was often less than that in patients in the placebo groups during the other studies. Interestingly, dizziness and somnolence were not reported as common AEs during the double-blind treatment phase of the FREEDOM trial, although weight gain was still observed in patients (4%). During the efficacy and safety studies discussed, there were no clinically significant differences in laboratory evaluations, vital signs, physical and neurological examinations, or electrocardiogram findings. During the OL treatment phase of the FREEDOM trial although three patients withdrew for clinical laboratory-related AEs (hemoglobin deceased, hepatic enzyme increased, Cl_{Cr} decreased) it was not specified which treatment group the subjects belonged to. In contrast, no patients withdrew from the double-blind treatment phase of the FREEDOM trial for clinical laboratory-related AEs.

Withdrawal from the efficacy and safety studies due to AEs were 8%, 7%–19%, 13%–22%, 26%–33%, and 8%–12% for the 150, 300, 450, and 600 mg/d pregabalin and placebo groups, respectively. The most common AEs that led to discontinuation in pregabalin-treated patients were dizziness and somnolence. During the OL phase of the FREEDOM trial, AEs were responsible for the withdrawal of 196 (19%) patients, although data for the individual treatment groups was not available. The AEs were severe in 70 patients who withdrew within the OL phase of the FREEDOM trial. During the double-blind treatment phase of the FREEDOM trial 7%, 19%, 18%, and 15% of patients withdrew from the placebo, 300, 450, and 600 mg/d pregabalin groups, respectively. Although weight gain was clinically significant in approximately 10% of patients in each pregabalin treatment group, this AE accounting for discontinuation was only reported for a single subject in one of the studies.[100]

Pregabalin and Quetiapine Combination Trial

An open-label prospective 12-week trial assessed the combination of pregabalin and quetiapine as treatment of patients with FM.[104] Nineteen patients, who had been receiving and reported improvement on a patient global impression from the antipsychotic quetiapine (25–100 mg/d) for at least the previous 6 months, were administered an add-on treatment of pregabalin (initial dosage 75 mg/d adjusted for efficacy and tolerability). Outcomes were assessed by the FIQ, the Pittsburgh Sleep Quality Index (PSQI), the Beck Depression Inventory (BDI), the State and Trait Anxiety Inventory (STAI), and the SF-12 Health Survey (SF-12). Seven patients withdrew before the study endpoint due to: AEs (2 patients), lack of efficacy (1 patient), adverse reaction plus lack of efficacy (1 patient), or lost to follow-up (3 patients).

Although the change in mean FIQ-Total score did not achieve significant improvement, the FIQ pain subscore demonstrated a significant decrease.[104] This outcome was not obtained with the other subscores of the FIQ assessment. The physical, but not the mental, component of the SF-12, exhibited a statistically significant change and significant decreases in depression and in state-anxiety scores were also reported related to treatment with pregabalin. Ten of the 12 patients who completed the study reported an improved outcome of which eight subjects requested to continue on the combination therapy. The most frequent AEs reported were dizziness, light-headedness, dry-mouth, weight increase, and somnolence. However, due to the transient nature of most of the AEs, 77% of patients who completed the 12-week study were free of AEs. Although the combination of pregabalin and quetiapine therapy was reported in an open-label prospective study to significantly improve pain and quality of life, whether such a combination approach in the usual-care-setting

of patients with FM would be preferable to either drug alone remains to be determined.

Conclusion

Pregabalin has been shown to improve pain, sleep, and fatigue symptoms associated with FM as well as offering an improvement in parameters related to quality of life. FM is a chronic complex pain disorder that is multidimensional and exhibits traits of heterogeneity that often require a long-term multidisciplinary approach to management in clinical practice. Consequently randomized controlled trials involving patients with FM are generally difficult due to many of these aspects but also due to limitations in the understanding of the pathophysiology of this condition. Although the positive outcomes obtained with pregabalin in clinical trials supports consideration of this agent as an option for the management of FM, the efficacy was restricted to a selected, mostly middle-aged, female patient population (as possibly determined by the exclusion criteria of trials) outside of the usual care setting. Current data do not allow the opportunity of a conclusion to the reasons for any limitations of pregabalin as a treatment of patients with FM, whether due to a deficiency of the drug or the process of assessment (e.g. assessment tools, clinical trial design).

There has been a rise in the development of new interventions for the treatment of FM and a variety of outcome measures have been used during clinical trials to assess improvement in patients with FM. Partly due to issues related to the classification of FM there often has not been uniform agreement as to which domains or which assessment tools should be utilized where often measurement of pain can be a primary domain of the instrument.[39,53] Thus, the complexity of this condition may limit in clinical practice the potential of a single instrument covering the diversity of symptoms of FM raising difficulties such as insensitivity or efficacy misinterpretation associated with the multidimensionality.[105]

Clinical trials of FM have varied in the assessment of pain and other domains. Meta-analyses of FM clinical trials have demonstrated some of the problems associated with the lack of consistency in study design and outcomes. Symptoms, such as depression, anxiety, and cognition, were not explored in all studies. Furthermore, although pain is the primary outcome in clinical trials, focus is on the effect of treatment on pain intensity, and often does not explore other dimensions of pain such as the duration or course (characteristics reported to be important by patients). Fatigue has been inconsistently evaluated in clinical trials,[37] but from patients' perspectives, is an important multidimensional domain to address in treatment.[39] The heterogenous nature of FM, as demonstrated by the diverse symptom profile, reflects the individuality of each patient and the requirement of individualized management approach (rather than a "one-size-fits-all" attitude). To appreciate the full potential of pregabalin as a treatment of FM many of these aspects, which have not been included in clinical studies to date, require evaluation.

Finally it is pertinent to mention that pharmacologic fMRI is a robust and reliable technique to detect central effects of pain-relieving drugs,[106,107] and the combination of drug administration with fMRI has been recommended in European guidelines for neuropathic pain assessment.[108] Evaluation of brain signaling images using fMRI following drug treatment of patients with FM will provide important information in the understanding of the physiological changes associated with the efficacious effects of pharmacological management. Current clinical trials propose studying the effects of pregabalin on pain processing in patients with FM by fMRI to measure brain glutamine and glutamate levels and to define brain regions responding to pain stimuli in patients receiving pregabalin. Such studies should provide clues regarding the management of the neurophysiology of patients with FM to attain reduction of symptom severity and possibly guide to the optimal therapeutic requirements of this patient group.

Disclosure

The author reports no conflicts of interest.

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