COMMENTARY

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Invited Commentary: Understanding the Fibromyalgia Syndrome

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In this edition, Rao et al. have updated their previous review of the psychopharmacology of fibromyalgia. Indeed, much has happened since the publication by Kranzler et al.[1], including the approval, by the US Food and Drug Administration, of pregabalin for the management of fibromyalgia, and the subsequent submission of two additional compounds for regulatory review. Rao et al. provide an excellent review of the topic; this commentary intends to supplement their review with additional, contemporary data.

The review by Rao et al. provides a comprehensive overview of descending pain pathways at the molecular level. Though the focus of the review is on monoaminergic pathways, they allude to other modulatory systems that may play key roles in pain pathways, including those that attenuate presynaptic calcium influx. Given the reports of altered levels of spinal fluid excitatory amino acids[2], substance P[3], and nerve growth factor[4] in fibromyalgia patients, modulation of these excitatory systems by means other than descending inhibition should be similarly efficacious.

Gabapentin and pregabalin are structurally related to the amino acid gamma aminobutyric acid but are inactive at GABA receptor complexes. Gee et al.[5] showed that gabapentin binds to an auxiliary protein on the voltage-gated calcium channel. Ligands binding to these $\alpha_2\delta$ subunits have been shown to decrease influx of neuronal calcium in rat[6] and human[7] neocortical tissue and subsequently to reduce release of glutamate[8], calcitonin gene-related peptide (CGRP), and substance P in a state-dependent fashion[9,10]. Binding studies show high levels of $\alpha_2\delta$-1 radiolabeling in the dorsal horn of the spinal cord[11] and expression of $\alpha_2\delta$-1

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is upregulated following peripheral nerve injury[12]. The $\alpha_2\delta$-1 subtype seems to be responsible for analgesic properties of $\alpha_2\delta$ ligands as knockout mice, in which a single substitution at position 217 of the $\alpha_2\delta$ subunit occurs, lack an analgesic response to pregabalin[13].

As noted by Rao et al., sleep disruption is a common clinical manifestation of fibromyalgia.[14,15] Sleep disruption is commonly associated with chronic pain states[16]. Unlike other anticonvulsants studied by Legros and Bazil[17], gabapentin was shown to improve sleep architecture. In animal models[18] and in other polysomnographic studies of normal volunteers[19] or patients with epilepsy[20], pregabalin was demonstrated to increase slow wave sleep, decrease nocturnal awakenings, and/or improve sleep efficiency. Regardless of sleep effects in other disease states, demonstration of sleep benefits in the fibromyalgia population will be critical for overall patient management.

Pregabalin has been studied extensively in peripheral neuropathic pain related to diabetic peripheral neuropathy,[21,22,23,24,25] post-herpetic neuralgia[26,27,28] and central neuropathic pain following spinal cord injury.[29] It has also been shown to be efficacious in the adjunctive treatment of partial onset epilepsy in adults.[30,31,32,33]

The efficacy of pregabalin in the management of fibromyalgia was demonstrated in 3 fixed dose trials[34,35,36] and one six-month, relapse-prevention study[37]. While the data from two of the pivotal, fixed-dose trials and the six-month trial have yet to appear in peer reviewed journals, the data has been presented publicly for all of the studies. One study has recently been accepted for publication[36]; the other two studies, identified as F1 and F2 in the Lyrica® C-V US Package Insert (USPI), are currently under review for publication.

Results for the primary endpoint in two of the three studies are summarized in Table 1. In the third fixed dose trial[36], statistically significantly greater improvement in the primary endpoint, weekly mean pain score, was also noted. Key secondary endpoints for the fixed dose trials induded the Short Patient Global Assessment of Change (PGIC), Fibromyalgia Impact Questionnaire (FIQ – not assessed in Crofford et al., 2005), Medical Outcomes Study Sleep Scale (MOS-SS), Hospital Anxiety and Depression Scale, Short From 36 Health Survey, and Multidimensional Assessment of Fatigue. Across studies, statistically significant differences were noted in sleep benefit and PGIC. FIQ total scores were significantly better in two of the three studies that included this instrument.[35,37] No significant differences were noted in the HADS subscale or MAF scores. SF-36 results were inconsistent. A full description of secondary endpoints will be published in a manuscript under review.

TABLE 1

ENDPOINT[a] MEAN PAIN SCORES FOR FIBROMYALGIA PATIENTS BEING TREATED WITH BLINDED PREGABALIN DOSAGES OR PLACEBO: RESULTS OF ANCOVA[b]: FAS POPULATION

STUDY/TREATMENT GROUP	n	LEAST SQUARES MEAN CHANGE	LEAST SQUARES DIFFERENCE	TREATMENT COMPARISON (PREGABALIN – PLACEBO) 95% CI	TREATMENT COMPARISON (PREGABALIN – PLACEBO) ADJUSTED P-VALUE
Study 1[c]					
Placebo	184	−1.04			
PGB 300 mg	183	−1.75	−0.71	[−1.13, −0.29]	0.0009*
PGB 450 mg	190	−2.03	−0.98	[−1.34, −0.57]	<.0001*
PGB 600 mg	188	−2.03	−1.00	[−1.41, −0.59]	<.0001*
Study 2[d]					
Placebo	129	−1.15			
PGB 150 mg	131	−1.28	−0.13	[−0.62, 0.36]	0.6044
PGB 300 mg	132	−1.56	−0.40	[−0.90, 0.09]	0.2228
PGB 450 mg	128	−2.08	−0.93	[−1.43, −0.43]	0.0009*

Range 0–10; decrease in score represents improvement

*Statistically significant at 0.05 based on adjusted p-values according to Hochberg's procedure.

[a]Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

[b]Based on LS Means using ANCOVA model (including effects for treatment, center, and the baseline score value as covariate).

[c]Arnold et al. (2007)[35]

[d]Crofford et al. (2005)[34]

ANCOVA = Analysis of covariance; CI = Confidence interval; FAS = Full analysis set; LS = Least squares; PGB = Pregabalin; SE = Standard error.

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In the six month study[37], the time to loss of therapeutic response, defined as an increase of pain to less than 30% improvement over baseline or PGIC score >2, patients treated with placebo had worsening of symptoms in a significantly shorter time compared to those patients treated with pregabalin. Time to loss of therapeutic response in secondary endpoints was also longer in patients treated with pregabalin. Results of secondary endpoints will be detailed in a manuscript currently under review.

The adverse event profile in the fibromyalgia studies[35,36,37] overall was qualitatively similar to that observed with other indications for which pregabalin is currently approved. The most common adverse events reported were dizziness and somnolence. Blurred vision, headache, weight gain, dry mouth, and peripheral edema also were reported. By contrast, the incidence of serious adverse events in the fixed dose trials was similar between pregabalin and placebo.

Consensus is growing that the pathophysiology of fibromyalgia involves central sensitization or some similar dysfunction of central pain processing. Pain, sleep disruption, and associated changes in mood occur commonly in patients with fibromyalgia[38]. Though the patient's pain response appears to be independent of baseline depression[39], a holistic approach to these patients is nevertheless critical to achieving optimal care. It appears that multidisciplinary interventions, will be required, to include concomitant, nonpharmacologic and strategic polypharmacologic approaches.[38] With the recent approval by the FDA of pregabalin for the management of fibromyalgia, the Agency has helped to validate the condition, and offers hope of relief for those suffering from the condition.

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