

A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Pregabalin in the Treatment of Patients with Fibromyalgia

by Michelle Carrillo, 2009 Pharm. D. Candidate and Rosalin Preechakul, 2010 Pharm. D. Candidate, and Craig Stern, Pharm. D., MBA, FASHP With Guest Editors, Sheri A. Strite and Michael E. Stuart, MD

Introduction

This phase III trial assessed the efficacy and safety of pregabalin for the symptomatic relief of pain in patients with fibromyalgia (FM) and for management of FM. FM is a chronic disorder that afflicts approximately 2% of the US population. It is characterized by widespread muscle pain, fatigue, and several tender points, in which pain is felt in response to slight pressure. Pharmacological treatment of FM can include antidepressants, benzodiazepines, and analgesics. Currently, only pregabalin and duloxetine have FDA-approved indications for FM.

This randomized, double-blind, placebo-controlled trial assigned 748 patients to one of four treatment groups: placebo, pregabalin 300, 450, or 600 mg/day, dosed twice daily. The primary outcome for objective 1 was symptomatic relief of pain, which was measured by comparing the endpoint mean pain scores between treatment groups. The outcome variable for objective 2 was management of FM and included endpoint mean pain scores, Patient Global Impression of Change (PGIC), and Fibromyalgia Impact Questionnaire (FIQ)-Total Score. Secondary outcomes were evaluations of sleep, fatigue, and mood disturbance.

The authors concluded that all pregabalin doses in the study were efficacious and safe for treatment of pain due to FM and offer meaningful benefit to patients when used as a monotherapy. The purpose of this evidence-based review is to evaluate the validity and utility of this phase III trial of pregabalin.

Author's Results and Conclusions

The authors found that the monotherapy with all three pregabalin dosages showed statistically significant improvement in

endpoint mean pain score and in PGIC response compared with placebo. For the secondary outcome variables, all pregabalin treatment groups demonstrated statistically significant improvement in sleep quality at endpoint, consistently on a weekly basis. Of the 748 patients who were randomized, 263 withdrew from the study: 21% due to adverse effects, 5% due to lack of efficacy, and 9% other reasons. A direct correlation between adverse events and pregabalin dose was observed; among the 157 patients who withdrew due to an adverse effect, 33% were in the 600 mg/day pregabalin group, 22% were in the 450 mg/day group, 19% were in the 300 mg/day group, and 10% were in the placebo group. Dizziness (9%) and somnolence (6%) were the most common adverse events that led to withdrawal among the pregabalin-treated patients.

The authors of this trial support pregabalin monotherapy for symptomatic relief of pain and for improvement of sleep in FM patients.

Reviewer's Conclusions

Although the authors reported many statistically significant findings in the randomized controlled trial, we question its application in clinical practice due to major threats to internal and external validity. It is unclear if group assignments were truly random and if allocation of treatment was concealed. These can contribute to selection bias and threaten the internal validity. Performance bias (confounding factors) may have been introduced if usage of aspirin and acetaminophen as rescue medication differed between groups. Moreover, the trial lacked data on the number of patients who used them, dose, and frequency of use. Another potential bias is that pregabalin's manufacturer, Pfizer, is one of the sponsors of this phase III pregabalin trial, which may

potentially limit the utility and quality of this study.

There were many threats as well to external validity, limiting the trial's application to the general population. The first limitation was that patients had to discontinue fibromyalgia medications at baseline, excluding the most severe patients from trial participation. Thus, the results may not extend to those with secondary fibromyalgia because patients with other rheumatologic disorders were excluded. Furthermore, the study results were only based on 13 weeks of treatment. However, since fibromyalgia is a chronic condition, a longer duration of treatment is required to determine its efficacy and safety. Lastly, in addition to placebo, the results would have been more meaningful if an active comparator was compared to pregabalin. In general, the phase III pregabalin trial does not provide sufficient evidence in making clinical decisions, and the many threats to internal and external validity render some uncertainty in its usefulness.

Overall Grade: U = Uncertain validity and clinical usefulness

Guest Editor Comments

Although this study was a double-blinded RCT, it suffers from a combination of problems in design, reporting and conduct. Details of randomization and concealment of allocation of the randomization sequence are not provided and such omissions are frequently indicators of a low quality study. Loss of 35% of subjects is a lethal threat especially without subjecting the data to reasonable sensitivity analyses. Because bias tends to favor interventions and because of the all-important issues of patient harms and costs, such analytic testing should be designed in a

way that raises the bar against the intervention. The student reviewers wisely did not focus on efficacy results. Reported results from studies with fatal flaws in their design or conduct are likely to bias readers.

We are frequently asked if study results should automatically be considered suspect if they are favorable to a product and the manufacturer was involved in the support or conduct of the research. Our response is that users of medical information should be mindful that potentially anyone involved in the conduct of research is biased, not just those with financial interests. Further, industry has conducted or supported some very important valid and clinically-useful work. Those working in purely academic settings are motivated to publish and often

feel the pressure of obtaining positive outcomes. Therefore, it is important to be aware of potential conflicts of interest; however, high quality can come from any source and bias can come from any source. Critical appraisal should be performed for all sources that utilize medical science. The conduct of multiple studies on topics, especially by varying groups, can be helpful to diminish concerns about such conflicts of interest. ☹

About the Authors

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About the Guest Editors:

Michael E. Stuart MD and Sheri A. Strite of Delfini Group LLP combine decades of academic and practical experience in health care, clinical quality health systems improvements, research, training and leadership. To learn more, visit www.delfini.org.

References:

1. Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP Jr, Martin SA, Sharma U. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *The Journal of Rheumatology*. 2008 Mar;35(3):502-14. 2008 Feb 15.
2. Chart adapted from Delfini Group, LLC. Short Critical Appraisal Checklist

Element	Criteria	Comments/Threat
Study Design Assessment	Is the design appropriate to the research question? Is the research question useful?	This phase III trial of pregabalin was a multicenter, double-blinded, randomized, placebo-controlled trial.
Internal Validity Assessment	Can bias or chance explain the study results?	THREAT: The randomization and concealment of allocation (selection bias) details were not explained.
Performance Bias	Is there any bias or difference, except for what is under study, between groups during course of study?	The frequency of use of aspirin (≤ 325 mg/day) and acetaminophen (≤ 4 g/day) as rescue medication for pain was missing.
	Are reasonable interventions and reasonable comparators used?	THREAT: Although a placebo was used, the study did not include an active medication comparator to pregabalin.
Attrition Bias	Are there any missing data points?	THREAT: Of the 748 patients who were randomized to receive study medication, 263 (35%) withdrew from the trial during the double blind treatment phase. Of these, the percentage who withdrew due to an adverse event is as follows: 32.6% of pregabalin 600mg/day, 22.4% of pregabalin 450mg/day, 18.9% of pregabalin 300mg/day, and 10% of placebo. The large number of withdrawals threatens the internal validity of the trial. THREAT: The last observation carried forward (LOCF) is not an appropriate method for imputing missing data points and sensitivity analyses, which might more effectively have tested the strength of the data, including challenging the agent, were not performed.
Assessment Bias	What is the likelihood of findings due to chance? Is there statistical significance?	THREAT: There were no confidence intervals provided in conjunction with p values for efficacy measurements.
Usefulness Assessment	Is there a clinically significant area and sufficient benefit size?	THREAT: Although the study focused on a clinically significant area, there were high dropouts and significant threats to internal and external validity, which limited the clinical application in clinical practice.
External Validity	How likely are research results to be realized in the real world considering population and circumstances for care?	THREAT: The requirement to discontinue all medications used to treat FM prior to enrollment may have excluded the most severely affected patients and those with substantial psychiatric comorbidity.
		THREAT: The population study consisted of 90% Caucasians.
		THREAT: The results were based on an acute trial of 13 weeks.