

PREGABALIN: INSIGHTS FROM RANDOMIZED TRIALS

Pregabalin Add-on Treatment: A Randomized, Double-blind, Placebo-controlled, Dose-response Study in Adults with Partial Seizures

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PURPOSE: To evaluate pregabalin (PGB), 150 mg/day, and PGB, 600 mg/day, as an add-on treatment for patients with refractory partial seizures concurrently treated with one to three anticonvulsants (AEDs).

METHODS: An international (13 countries), multicenter (45 centers), 12-week, double-blind, randomized study in which patients with partial seizures received placebo ($n = 96$); PGB, 150 mg/day ($n = 99$); or PGB, 600 mg/day ($n = 92$); given 3 times a day (t.i.d.). The primary efficacy criterion was reduction in seizure frequency during treatment as compared with baseline, as measured by RRatio, the symmetrical percentage change in seizure rates determined from daily seizure diaries. The RRatio between the 8-week baseline (pretreatment phase) and the 12-week treatment period was compared between each of the PGB groups and the placebo group by using an analysis of variance analysis of the intent-to-treat population.

RESULTS: PGB, 150 mg/day and 600 mg/day, was significantly more effective than placebo in reducing the RRatio [-11.5 ($P = 0.0007$) and -31.4 ($P \leq 0.0001$), respectively, vs. 0.9]. These RRatio values correspond to seizure-frequency reductions from baseline of -1.8 , 20.6 , and 47.8% for placebo, 150 mg/day, and 600 mg/day, respectively. PGB efficacy was significantly dose related ($P \leq 0.0001$). Secondary efficacy variables corroborated the findings of the primary analysis. Significantly more patients were responders ($\geq 50\%$ reduction in seizure frequency) in the PGB, 600 mg/day (43.5%), group than in the placebo group (6.2%) ($P \leq 0.001$). PGB was well tolerated. Dose-related, treatment-emergent adverse events ($\geq 10\%$), mostly mild or moderate in intensity, were somnolence, dizziness, ataxia, diplopia,

and weight gain. The withdrawal rate due to adverse events was 10% of patients at 150 mg/day and 18.5% of patients at 600 mg/day, compared with 6.2% of patients receiving placebo.

CONCLUSIONS: PGB, 150 mg/day and 600 mg/day, is highly effective and well-tolerated add-on therapy in patients with partial seizures.

COMMENTARY

Pregabalin (PGB) is likely the next antiepileptic drug (AED) to be marketed in the United States. In the randomized, double-blind, placebo-controlled trial reported by Arroyo et al., PGB was found to be effective at both tested doses of 150 mg per day and 600 mg per day. The primary efficacy variable in this trial was the RRatio, which is defined as: $100 \times (\text{Treatment seizure frequency} - \text{Baseline seizure frequency}) / (\text{Treatment seizure frequency} + \text{Baseline seizure frequency})$. This measure is not intuitive for the clinician but has some statistical advantages, particularly for evaluating seizure subtypes that may have occurred during treatment but not during baseline. At the 600-mg/day dose, the RRatio corresponds to a 47.8% seizure reduction, consistent with the previously published value of 54% (1). The responder rate for that dose was 43.5%, also close to the value of 51% previously reported. Because this trial followed a standard add-on design, it can be compared with other pivotal add-on trials of new AEDs. The high responder rate makes PGB comparable in efficacy to topiramate and levetiracetam.

PGB development for epilepsy has heeded the lessons learned from gabapentin (GBP) trials, which underestimated the therapeutic range. Even though a therapeutic plateau was not reached in this trial, the PGB dose of 600 mg/day is well within the therapeutic range and likely close to its upper end: the discontinuation rate as a result of adverse events at this dose was 18.5%. In addition, adverse effects, such as somnolence and ataxia, were no different between placebo and the 150-mg/day dose but occurred significantly more often at 600-mg/day dose. Another lesson learned from the development of GBP relates to its application in the treatment of pain and psychiatric disorders. Positive randomized, double-blind trials evaluating PGB

for anxiety disorders and neuropathic pain already have been published and will likely lead to indications in these areas (2,3).

PGB shares with GBP several pharmacokinetic advantages, including the fact that it is not metabolized and does not bind to protein. However, it is superior in its linear and predictable absorption, which leads to the differential efficacy and adverse-effect profile for the two doses tested. Not only was the efficacy of 600 mg clearly greater than that of 150 mg, but all adverse events listed occurred more often at 600 mg than at 150 mg. Such a relation between different GBP doses was not found in the U.S. GBP trial (4). With PGB, somnolence, dizziness, ataxia, and weight gain were clearly dose related. Among these adverse effects, weight gain (reported in 14.1% of the patients) was not listed in the GBP study (4).

Weight gain is an adverse event that may not be easily recognized in a short-term study. This could explain why it was not noted in the GBP pivotal trials, even though it is now recognized as a potential GBP adverse effect (5). Weight gain is described as mild in the current PGB study. However, the time course and enduring magnitude or severity of weight gain with

PGB will have to be evaluated in long-term studies. Weight gain notwithstanding, PGB will be a welcome addition to our AED armamentarium.

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References

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