

Current Literature

In Clinical Science



AED Trials in Newly Diagnosed Patients: Out With the Old Versus New, in With the New Versus New

Efficacy and Safety of Pregabalin Versus Lamotrigine in Patients With Newly Diagnosed Partial Seizures: A Phase 3, Double-Blind, Randomised, Parallel-Group Trial.

Kwan P, Brodie MJ, Kälviäinen R, Yurkewicz L, Weaver J, Knapp LE. *Lancet Neurol* 2011;10:881–890.

BACKGROUND: Efficacious and safe monotherapy options are needed for adult patients with newly diagnosed epilepsy. As an adjunctive treatment for partial seizures, pregabalin compares favourably with lamotrigine and is an effective, approved treatment. We studied the efficacy and safety of pregabalin as monotherapy, using a design that complied with European regulatory requirements and International League Against Epilepsy guidelines. **METHODS:** This phase 3, double-blind, randomised, non-inferiority study compared the efficacy and tolerability of pregabalin and lamotrigine monotherapy in patients with newly diagnosed partial seizures at 105 centres, mostly in Europe and Asia. Randomisation to treatment groups (1:1 ratio) was by a computer-generated pseudorandom code (random permuted blocks), with patients sequentially assigned numbers by telephone. Investigators, site staff, and patients were masked to the assigned treatment. After randomisation, patients were titrated to either 75 mg oral pregabalin or 50 mg oral lamotrigine twice daily during a 4-week dose-escalation phase, followed by a 52-week efficacy assessment phase during which the daily dose could be increased as needed to a maximum of 600 mg and 500 mg, respectively. The primary efficacy endpoint was the proportion of patients who remained seizure-free for 6 or more continuous months during the efficacy assessment phase; analysis included all patients who were randomly assigned to treatment groups and received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT00280059. **FINDINGS:** 660 patients were randomly assigned to treatment groups (330 pregabalin, 330 lamotrigine), of whom 622 entered the efficacy assessment phase (314 pregabalin, 308 lamotrigine). Fewer patients in the pregabalin group than in the lamotrigine group became seizure-free for 6 or more continuous months (162 [52%] vs 209 [68%]; difference in proportion, -0.16 , 95% CI -0.24 to -0.09). The overall incidence of adverse events was similar between the groups and consistent with that in previous studies; dizziness (55 [17%] vs 45 [14%] patients), somnolence (29 [9%] vs 14 [4%]), fatigue (27 [8%] vs 19 [6%]), and weight increase (21 [6%] vs 7 [2%]) were numerically more common in the pregabalin group than in the lamotrigine group. **INTERPRETATION:** Pregabalin has similar tolerability but seems to have inferior efficacy to lamotrigine for the treatment of newly diagnosed partial seizures in adults. Inferior efficacy of pregabalin might have been attributable to limitations in the study design, as treatment doses might have not been optimised adequately or early enough.

Commentary

New antiepileptic drugs (AEDs) are almost universally approved initially as adjunctive therapy. The trials that are performed to gain this approval are randomized, placebo-controlled adjunctive trials in patients with frequent, treatment-resistant seizures. Clinicians are often unsatisfied with these studies, since they find them poorly generalizable to the more commonly seen epilepsy patient, with less severe epilepsy. Also, while these trials support that the new drugs are better

than placebo, they do not give the clinician a sense of relative efficacy or tolerability in comparison with other antiepileptic drugs that are already available. Moreover, these studies do not determine whether the newly approved medications are effective when used alone, rather than as add-on therapy. Since the evidence for use of the new agents in a less-resistant population is wanting, newly approved AEDs tend to be used initially in the more treatment-resistant patients, who have failed other available therapies.

The new study by Kwan and colleagues was performed to address many of these concerns, in relation to the new antiepileptic drug pregabalin (PGB). The study compared pregabalin in a randomized, well-controlled design, not against placebo but against another popular new AED (lamotrigine [LTG]). The

Epilepsy Currents, Vol. 12, No. 4 (July/August) 2012 pp. 126–127
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study was performed in all comers with partial epilepsy, not just treatment-resistant patients, and was performed as head-to-head monotherapy. The design was consistent with the recent recommendations of the European Medicines agency (EMA, the European equivalent of the FDA) (1) and the International League Against Epilepsy (ILAE) (2).

This study is notable for several reasons. The first is that it compared two second-generation AEDs, whereas the vast majority of controlled, comparative, head-to-head studies in epilepsy have compared a new AED to a standard AED (2, 3). Comparing with a new AED, and lamotrigine in particular, seems a reasonable choice, since the new AEDs have gained popularity as first-line agents, and a recent head-to-head study of several new and old AEDs crowned lamotrigine the drug of first choice for initial monotherapy (based on equal efficacy and better tolerability than other AEDs) in patients with partial-onset seizures (4). The second very notable aspect of this study is that the drug under study, pregabalin, was found to be inferior to the active comparator (lamotrigine) in terms of the ability of the drug to render patients seizure free. This is unusual, as it is notoriously difficult to uncover differences in efficacy between two active AEDs when they are assessed head to head in the newly diagnosed population. It has been speculated that the reason for this difficulty relates to the rather simplistic outcome measure of “seizure free” or “not seizure free” for 6 months. This may be too low a bar in this population. Many of these patients have a low intrinsic seizure frequency (minimum criterion was two seizures in 12 months and one within the last 6 months). Even a small reduction in seizures as a result of drug initiation could drop the seizure frequency enough to produce a 6-month seizure-free interval, which is the primary outcome variable for most of these studies. In fact, the new ILAE criteria suggest that the appropriate assessment duration to determine treatment success should be individualized, and should be at least three times the previous inter-seizure interval. In this case, not only was there a lower percentage of patients seizure free for 6 months, but all the secondary efficacy measures (e.g., time to first seizure, time to exit owing to lack of efficacy) also demonstrated superiority of lamotrigine over pregabalin. However, one issue that could make the study less than completely definitive was the question of comparability of the doses. About half the patients in the study remained at the initial target dose of PGB (150 mg/d), which might not be comparable to the initial target dose of LTG (100 mg/d).

If lamotrigine was indeed superior to pregabalin in the newly diagnosed population, as it appeared to be, the finding is also interesting because it would not have been expected based on the results in the adjunctive trials of the two agents. In a recent meta-analysis, when approved doses were assessed, relative risk for being a responder (last observation carried forward based analysis) among patients enrolled in placebo-controlled adjunctive therapy trials in refractory partial epilepsy was higher (3.29, 95% confidence interval [CI] 2.35–4.63) for PGB as compared with LTG (2.04, 95% CI 1.31–3.17) (5). Of course, dosing was higher in the adjunctive trial; but in the monotherapy trial, dosing was flexible and increases up to 600 mg of PGB and 500 mg of LTG (the maximum doses in the add-on trial) were possible.

In conclusion, this study is a good reminder that efficacy and tolerability in newly diagnosed patients is not always equivalent to what is seen in treatment-resistant patients. Well-designed and adequately controlled studies are needed in both populations.

by *Jaqueline A. French, MD*

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