

## IN THE END, NEW ANTIEPILEPTICS MAY BE LESS EXPENSIVE THAN OLDER ANTIEPILEPTICS FOR GERIATRIC PATIENTS

### New Onset Geriatric Epilepsy: A Randomized Study of Gabapentine, Lamotrigine, and Carbamazepine

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*Neurology* 2005;64:1868–1873

**OBJECTIVE:** To determine the relative tolerability and efficacy of two newer antiepileptic drugs, lamotrigine (LTG) and gabapentin (GBP), as compared with carbamazepine (CBZ) in older patients with epilepsy.

**METHODS:** This was an 18-center, randomized, double-blind, double dummy, parallel study of 593 elderly subjects with newly diagnosed seizures. Patients were randomly assigned to one of three treatment groups: GBP 1,500 mg/day, LTG 150 mg/day, CBZ 600 mg/day. The primary outcome measure was retention in trial for 12 months.

**RESULTS:** Mean age was 72 years. The most common etiology was cerebral infarction. Patients had multiple medical conditions and took an average of seven comedications. Mean plasma levels at 6 weeks were as follows: GBP  $8.67 \pm 4.83 \mu\text{g/mL}$ , LTG  $2.87 \pm 1.60 \mu\text{g/mL}$ , CBZ  $6.79$

$\pm 2.92 \mu\text{g/mL}$ . They remained stable throughout the trial. Early terminations: LTG 44.2%, GBP 51%, CBZ 64.5% ( $p = 0.0002$ ). Significant paired comparisons: LTG vs CBZ:  $p < 0.0001$ ; GBP vs CBZ:  $p = 0.008$ . Terminations for adverse events: LTG 12.1%, GBP 21.6%, CBZ 31% ( $p = 0.001$ ). Significant paired comparisons: LTG vs CBZ:  $p < 0.0001$ ; LTG vs GBP:  $p = 0.015$ . There were no significant differences in seizure-free rate at 12 months.

**CONCLUSIONS:** The main limiting factor in patient retention was adverse drug reactions. Patients taking LTG or GBP did better than those taking CBZ. Seizure control was similar among groups. LTG and GBP should be considered as initial therapy for older patients with newly diagnosed seizures.

### COMMENTARY

Neurologists and epileptologists appear to have reached a consensus (albeit not totally supported by evidence-based data) that the 13 antiepileptic drugs (AEDs) available for the treatment of partial epilepsy fail to differ with respect to efficacy. Although 8 of 13 are new AEDs, approved by the FDA in the last decade, efficacy has not significantly improved, which is disappointing news for patients and clinicians alike. However, the silver lining may be that *some* of these newer AEDs do appear to be better tolerated. In fact, this point is nicely exemplified in the article by Rowan et al., in which the safety and efficacy of two of the new AEDs, gabapentin (GBP) and lamotrigine, (LTG) are compared to the old AED carbamazepine, (CBZ) in geriatric patients with new-onset epilepsy. Head-to-head studies involving geriatric patients and AEDs (or drugs in general) are particularly relevant, given the pharmacokinetic and pharmacodynamic changes that typically occur with aging, including a slower metabolism, increased susceptibility to adverse events, and a narrower therapeutic range (1).

The data presented in this study, however, are not completely new. Brodie et al. previously compared the efficacy and tolerability of LTG and CBZ in a head-to-head study carried out among a similar group of geriatric patients and demonstrated equivalent antiepileptic efficacy but better tolerability of LTG (2). In contrast, no such data are available for GBP use with geriatric patients. Clearly, tolerability should play an important role in the decision-making process of selecting an initial AED for geriatric patients—most of whom are likely to require lifetime pharmacotherapy.

However, there are additional considerations that clinicians have to factor-in when favoring LTG or GBP over CBZ. CBZ is an enzyme-inducing AED, which accelerates the clearance of concomitant medications metabolized by the liver, lowering their serum concentration and potentially limiting their efficacy (lest their dosage is adjusted, which rarely happens). CBZ's enzyme-inducing property is highly relevant to the treatment of geriatric patients, since this patient population characteristically suffers from comorbid medical and psychiatric disorders that require the use of pharmacotherapy. For example, Lackner et al. found that elderly home residents being administered an AED take an average of five other medications (3), with psychotropic drugs being the most frequently prescribed, followed by cardiac medications and anticoagulants.

The consequences of the pharmacokinetic interactions between CBZ and some of the concomitant medications frequently prescribed to geriatric patients are well documented. For example, CBZ has been reported to cause a decrease in the plasma concentrations of tricyclic antidepressants and neuroleptic drugs (4). Ucar et al. found that for patients taking the cholesterol-lowering agent simvastatin, the addition of CBZ resulted in a reduction of its serum concentration by more than 50% (5). Furthermore, Gidal estimated a 75% increase in the cost of simvastatin to avert a drop in serum concentration after the addition of an enzyme-inducing AED (6). The enzyme-inducing properties of CBZ also can impact negatively on life-saving therapies, such as a variety of chemotherapies. Indeed, Villikka et al. found that the addition of CBZ or phenytoin increased the clearance of the chemotherapeutic agent vincristine by 63% in nine patients being treated for a brain tumor, while its half-life was shortened by 35% (7). Clearly, failure to adjust the dose of concomitant medications can limit their efficacy with dire consequences and are certain to increase their cost.

The AEDs, LTG, and GBP do not have an impact on the metabolism of concomitant medications. Yet, LTG is metabolized in the liver, primarily by glucuronidation, and its clearance can be accelerated or reduced in the presence of concomitant enzyme inducers or inhibitors; in these instances, dose adjustments may be necessary. GBP, in contrast, is metabolized in the kidneys and hence has no pharmacokinetic interaction with most drugs that are metabolized in the liver. Dose adjustments, therefore, may only be necessary in case of renal failure.

In addition, enzyme-inducing antiepileptic drugs have been associated with other types of comorbidities that can be particularly problematic in geriatric patients. Comorbidities include an increased risk of worsening or developing osteopenia, osteoporosis, or both, which in turn can result in a greater risk of pathological fractures. Enzyme-inducing AEDs also have been associated with an elevation of serum concentrations of homocysteine, which has been identified as a risk factor for small-vessel disease in the central nervous system as well as for coronary artery and peripheral vascular disease (8). Furthermore, there is speculation that high homocysteine serum concentrations play a pathogenic role in the development or worsening of the dementing processes (9,10). It is worth noting that in Rowan's study, a significant percentage of patients suffered from comorbid dyslipidemia, hypertension, cardiac disease, stroke, or mild cognitive impairment (a precursor to Alzheimer's disease). Such data are not unique to this study. The impact of enzyme-inducing AEDs on the course of a vascular or dementing disorder, however, remains to be studied in a systematic manner in geriatric patients with epilepsy. Nonetheless, the theoretical arguments against the use of enzyme-inducing AEDs in geriatric patients are quite compelling, as they may potentially worsen a serious

comorbid disorder. Their use should be minimized until this issue is resolved.

About one-third to one-half of geriatric patients with epilepsy have suffered from a stroke. Among these, 20–50% are expected to develop a poststroke depression, which can have dire consequences for cognitive and physical recovery, including a direct negative impact on quality of life and mortality (11). In such cases, the use of AEDs with positive psychotropic properties is favored to minimize risks. All three AEDs used in Rowan's study fall into this category but have different psychotropic properties. For example, GBP has anxiolytic properties that have been shown to be efficacious in treating social anxiety in young adults but was not superior to placebo as a mood-stabilizing agent. While LTG and CBZ are both mood-stabilizing agents, only LTG has been shown to have antidepressant properties in younger adults with bipolar depression. Whether LTG has antidepressant properties that can prevent or minimize the impact of a poststroke depression in geriatric patients with epilepsy is yet to be established.

Despite these theoretical principles, the vast majority of geriatric patients with epilepsy continue to be treated with enzyme-inducing AEDs, particularly phenytoin and to a lesser degree, phenobarbital and CBZ. The preferential choice of enzyme-inducing AEDs is multifactorial and includes the clinicians' familiarity with or level of discomfort for this class of AEDs. In addition, economic factors are becoming a frequent reason—cited by private and governmental health maintenance organizations as well as by patients without insurance coverage for medications—to choose older, equally effective AEDs. Yet, as shown above, in the case of geriatric patients with epilepsy, the choice of an old enzyme-inducing AED may, in the end, cost more than a new AED!

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