



## Efficacy of New Antiepileptic Drugs

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Regarding efficacy of new antiepileptic drugs (AEDs) for seizure control, there are three important clinical questions. How effective are new AEDs when corrected for the efficacy of placebo? And even more important: How do new AEDs fare in terms of seizure remission compared with established agents? And finally: Have patients seizure-free on new AEDs a better chance for lasting remission after withdrawal versus those withdrawing from older agents? The answers raise concerns. Although add-on therapy with marketed new AEDs is more effective than placebo, as expected, the treatment difference for becoming seizure-free is disappointingly small (6%; 95% CI: 4–8%;  $z = 6.47$ ;  $p < 0.001$ ). Although many, but not all, new AEDs have comparable efficacy to old standard drugs in well-controlled trials, none of the new AEDs is superior to old drugs in terms of seizure remission. So far, we have no antiepileptogenic treatments that prevent the development of epilepsy or modify its detrimental course. The sobering results suggest the need for novel experimental and clinical strategies for the development of more effective new AEDs that interrupt ictogenesis more effectively and prevent or abort epileptogenesis. Ideally, we need new drugs that block both ictogenesis and epileptogenesis, resulting in complete cure of epilepsy.

Although a large number of new antiepileptic drugs (AEDs) that suppress or prevent seizures are now available, about 30 to 40 percent of the patients, children as well as adults, remain resistant to drug treatment (1). The situation is even worse for a range of severe epilepsy syndromes of infancy and adolescence. So far, we have no antiepileptogenic treatments that prevent the development of epilepsy or modify its detrimental course (2). The introduction of each new AED into the market raises valid expectations in patients and physicians for more effective treatment of epilepsy. Although safety, tolerability, and lack of interactions are important, better efficacy is a crucial feature for a new AED. This brief review is limited to a discussion of the efficacy of new versus old AEDs. In that respect, three questions are of particular clinical interest: How effective are new AEDs when corrected for the efficacy of placebo? And even more relevant: Are new AEDs more often leading to seizure remission compared with established agents? And finally: Can more patients maintain seizure remission after withdrawal of new AEDs compared with withdrawal of older agents? The following brief overview, which is not a comprehensive literature review, outlines the available evidence on the efficacy of modern AEDs based on randomized controlled trials of marketed modern AEDs.

### Question 1: How effective are new AEDs when corrected for efficacy of placebo: Add-on?

Although adjunctive treatment with new AEDs is standard care in treatment resistant epilepsy, it is less well known how much of the effect can be directly attributed to the AEDs and how much of the beneficial changes are due to placebo. A recent meta-analysis determined the placebo-corrected net efficacy of adjunctive treatment with modern AEDs on the market for treatment resistant epilepsy in more than 11,000 adults and children (3). The overall weighted pooled risk difference in favor of AEDs over placebo was 6% (95% CI: 4–8%;  $z = 6.47$ ;  $p < 0.001$ ) for seizure freedom and 21% (95% CI: 19–24%;  $z = 17.13$ ;  $p < 0.001$ ) for 50% seizure reduction (3). Although the presence of moderate heterogeneity between studies was a limitation of the analysis, the study indicated that the placebo-corrected efficacy of adjunctive treatment with modern AEDs is disappointingly small and suggested that better strategies for finding drugs are needed for treatment resistant epilepsy (3).

### How effective are new AEDs when corrected for efficacy of placebo: Monotherapy?

Monotherapy trials have raised some ethical concerns, as the designs require patients with known epilepsy to either be undertreated or treated with placebo. A few studies have been performed, but there is a paucity of data in this area. There were no data for lamotrigine (LTG), levetiracetam (LEV), or topiramate (TPM) monotherapy versus placebo, and only two trials compared oxcarbazepine (OXC) with placebo (4). Data were only available for proportion of seizure-free participants and the time to event outcomes (first seizure and exit/withdrawal). Both OXC trials were short term and included only patients



with partial seizures (treatment resistant in one trial and newly diagnosed patient in the other (4)). The trial of patients with refractory partial seizures only included treatment over 10 days and was carried out in patients undergoing evaluation for possible surgery. Therefore the findings of this trial have limited applicability to the general population of patients with partial seizures (4). The evidence to support OXC in favor of placebo was also very limited. The data come from small trials conducted over short treatment durations and one trial relates specifically to patients undergoing evaluation for surgery, limiting its applicability. Considering all of these factors, the statistically significant differences observed in the proportion of seizure-free participants in favor of OXC versus placebo should be regarded with caution (4). There is no evidence on which to base an assessment of LEV, LTG, and TPM (4).

### **Question 2: How do AEDs fare in terms of seizure remission compared to established AEDs?**

#### ***Treatment of Idiopathic Generalized Epilepsy***

The efficacy of new versus old AEDs for the treatment of idiopathic generalized epilepsy was studied in Arm A of the SANAD trial, which compared valproate (VPA), LTG, and TPM for treatment of mostly untreated epilepsy in an unmasked randomized design (5). SANAD was designed to assess whether any of the new AEDs available at the time (LTG, TPM) should become first-line treatment and thereby replace VPA as the existing first-line agent (5). The result was that VPA was more efficacious than LTG and similar in efficacy to TPM for the subgroup of patients with idiopathic generalized epilepsy (5). A multicenter double-blind randomized trial compared treatment with ethosuximide (ESM), LTG, or VPA in 453 children with new-onset absence epilepsy of childhood (6). After 16 weeks of therapy, the freedom-from-failure rates for ESM and VPA were similar (53% and 58%), but for both the rates were higher than for LTG (29%;  $p < 0.001$  for both comparisons).

#### ***Treatment of Focal Epilepsy***

Arm B of the SANAD trial was designed as a pragmatic trial to assess whether any of the new AEDs (LTG, gabapentin [GBP], TPM, or OXC) should become first-line treatment and thereby replace the existing first-line agent carbamazepine (CBZ) (5). Based on efficacy criteria alone, and only those are discussed here, none of the new AEDs were superior in efficacy to CBZ although LTG and OXC were considered to be noninferior in efficacy, while CBZ was reported to be more efficacious compared with GBP and TPM (5). Levetiracetam (LEV), which entered the market later, could not be studied in SANAD. However, a well-controlled noninferiority trial has shown that, at per-protocol analysis, 73.0% of patients randomized to LEV and 72.8% receiving controlled-release CBZ were seizure free at the last evaluated dose (adjusted absolute difference 0.2%; 95% CI:  $-7.8$ – $8.2$ %) for at least 6 months indicating equivalent seizure remission for LEV versus slow-release CBZ (7). Although the incidence of epilepsy in those 65 years and older is increasing over the last decades (8), there are only a few studies comparing new versus old AEDs for treatment of epilepsy in the elderly. In a 24-week double-blind trial, LTG and CBZ were compared in 150 patients 65 years and

older with newly diagnosed epilepsy (9). Here we primarily address the efficacy results. Forty patients on LTG (39%) remained seizure-free during the final 16 weeks and did not discontinue drug treatment compared with 10 (21%) patients taking CBZ ( $p = 0.027$ ). In addition, the authors determined the proportion of patients who remained seizure-free as a proportion of those patients remaining in the study. No differences were detected between treatments on this outcome measure. The hazard ratio was 0.86 (95% CI: 0.42–1.77;  $p = 0.68$ ). The wide confidence intervals indicate that the study had a low power to detect a difference between treatments in terms of this outcome measure (9). In this study, retention on treatment at the end of the trial was significantly higher in patients treated with LTG than in those treated with CBZ (71% vs 42%, respectively), the difference being ascribed primarily to lower rates of withdrawal because of adverse events in the LTG group. More recently, 593 elderly subjects with previously untreated or under-treated seizures were randomized in a study to LTG, CBZ, or GBP (10). Retention in the trial at 12 months was significantly greater in the groups allocated to LTG and GBP (56% and 49%, respectively) than in the group allocated to CBZ (36%). However, there were no significant differences in seizure-free rate at 12 months (10).

Although these studies suggest that new AEDs may offer tolerability advantages over CBZ for the treatment of epilepsy in old age, both studies used immediate-release rather than sustained-release CBZ, and at least in the U.S. trial the initial target dosages for LTG and CBZ were relatively high compared with those reported to be optimal in most patients (9). The comparative effectiveness, efficacy, and tolerability of LTG and sustained-release CBZ in the treatment of newly diagnosed focal epilepsy in the elderly was assessed in a 40-week, multicenter double-blind, parallel group design (11). In the LTG group, 68 patients (73%) completed the 40-week study period compared with 61 (67%) in the CBZ group, a nonsignificant difference. The number of subjects who completed the 40-week period and were seizure-free in the last 20 weeks was 48 (52%) in the LTG group and 52 (57%) in the CBZ group. A total of 110 subjects did not have any seizure during the study, and of these 50 (54% of the intention-to-treat [ITT] cohort) had been randomized to LTG and 60 (66%) had been randomized to CBZ. No significant differences between treatments were identified by the time to first seizure analysis in the intention-to-treat population. In the per-protocol population, however, time to first seizure was significantly longer in the CBZ group than in the LTG group (11). In summary, LTG and CBZ showed comparable effectiveness as measured by retention, with a trend for higher seizure-free rates for CBZ and better tolerability for LTG. Differences in outcome compared with previous trials may be related to different dosing rates and use of a sustained-release formulation for CBZ (11).

### **Question 3: Do patients on new AEDs have a better chance of maintaining remission after withdrawal of AEDs than patients on older AEDs?**

Approximately two-thirds of patients with new-onset epilepsy will become seizure-free when treated with new AEDs, as discussed previously. In a proportion of these patients



who maintain prolonged remission over several years, complete withdrawal of AED treatment is a worthwhile consideration. Unfortunately, we currently have no information from randomized withdrawal trials to determine the risk–benefit balance of stopping new AEDs in seizure-free patients. A lower rate of relapse after withdrawal of new versus old AEDs would be a clinically important efficacy benefit in favor of new drugs.

### Conclusions

Although the introduction of new AEDs brought substantial advantages over old AEDs, in particular through the absence of severe hypersensitivity reactions and of detrimental drug interactions mediated by enzyme-induction in some new AEDs, we found no evidence that any new AED was superior to old AEDs such as CBZ and VPA in efficacy in well-controlled trials of recent-onset epilepsy. This is cause for major concern, given the unimproved proportion of patients with drug-resistant epilepsy. However, several new AEDs such as LEV, LTG, and OXC have been shown to be noninferior in efficacy to CBZ. Moreover, GBP was shown to be less efficacious versus CBZ and LTG in mostly untreated partial epilepsy and LTG was

shown to be less efficacious versus VPA and ESM for previously untreated childhood absence epilepsy.

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### Highlights

There is a need for the following:

- More efficacious new AEDs for suppression or prevention of seizures to lower the incidence of drug-resistant epilepsy
- More direct comparisons of newer versus newer and newer versus older AEDs within clinical trials, both for monotherapy and adjunctive therapy
- Good-quality trials with appropriate designs, ideally adopting the International League Against Epilepsy guidelines on the design of trials, particularly with regard to length of follow-up
- Randomized withdrawal trials to determine the risk–benefit balance of stopping new versus old AEDs in seizure-free patients
- Development of antiepileptogenic agents to prevent epilepsy in people at risk and to attenuate the detrimental course of epilepsy



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