Comparative Effectiveness of 10 Antiepileptic Drugs in Older Adults With Epilepsy

Hiba Arif, MD; Richard Buchsbaum; Joanna Pierro, BA; Michael Whalen, BA; Jessica Sims, MD; Stanley R. Resor Jr, MD; Carl W. Bazil, MD, PhD; Lawrence J. Hirsch, MD

Objective: To compare the effectiveness of antiepileptic drugs (AEDs) for use in older adults with epilepsy.

Design: Retrospective review.

Setting: Columbia Comprehensive Epilepsy Center, New York, New York.

Patients: Four hundred seventeen outpatients 55 years and older newly taking any of the 10 most commonly prescribed AEDs between 2000 and 2005.

Main Outcome Measure: The percentage of patients who remained taking the AED for 12 or more months (12-month “retention”). We also measured efficacy (12-month seizure freedom) and adverse effects leading to dose change. Retention and seizure-freedom rates were analyzed by pairwise comparisons using \( \chi^2 \) for the overall group and patients with refractory and nonrefractory disease as well as patients newly taking their first AED.

Results: The 10 AEDs newly taken by 10 or more patients were analyzed. There were no significant non-AED predictors of retention. Without controlling for severity, lamotrigine had the highest 12-month retention rate (79%), significantly higher than carbamazepine (48%), gabapentin (59%), oxcarbazepine (24%), phenytoin (59%), and topiramate (56%). The retention rate for levetiracetam (73%) was second highest and significantly higher than carbamazepine and oxcarbazepine. Oxcarbazepine had the lowest retention rate, significantly lower than all other AEDs. Lamotrigine had the highest 12-month seizure-freedom rate (54%), followed by levetiracetam (43%). When stratified into patients with non-refractory and refractory disease, relative rates of seizure freedom and retention remained comparable with the overall group. Imbalance, drowsiness, and gastrointestinal symptoms were the most common intolerable adverse effects.

Conclusion: In this study of older adults with epilepsy, lamotrigine was the most effective AED as measured by 12-month retention and seizure freedom, with levetiracetam a close second. Oxcarbazepine was consistently less effective than most other AEDs.

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Seizures occur in an age-dependent, bimodal pattern, with an initial peak in incidence during the first year of life and then a sustained rise in incidence beginning around the age of 60 years that surpasses incidence at all other ages. The management of epilepsy in the older age group can be complicated by many factors, including concurrent medical illnesses, drug interactions, changes in pharmacokinetics, and altered central nervous system pharmacodynamics. Any or all of these factors may result in an increased likelihood of adverse events.

Some newer antiepileptic drugs (AEDs) claim more favorable adverse effect profiles and minimal pharmacokinetic interactions, which may offer improved AED “effectiveness” in the older age group. Effectiveness of a drug combines both efficacy (seizure control) and tolerability and can be measured by retention (time remaining on the drug). Retention can be quantified as the percentage of patients who started taking a drug who remain taking it after a given period and is considered to be a composite measure of efficacy and tolerability.

To our knowledge, the only previous randomized controlled trials comparing effectiveness of AEDs in older adults have included 2 or 3 AEDs: lamotrigine, gabapentin, and carbamazepine. Brodie et al randomized 150 adults older than 65 years to lamotrigine or carbamazepine treatment for 24 weeks. They reported significantly better retention with lamotrigine (71% of patients at a median dose of 100 mg/d) compared with carbamazepine (42%...
at a median dose of 400 mg/d) treatment, and fewer patients dropped out because of adverse events with lamotrigine (18%) than carbamazepine (42%). Rowan et al 17 randomized 593 adults older than 60 years to lamotrigine (150 mg/d), gabapentin (1500 mg/d), or carbamazepine (600 mg/d) monotherapy, allowing dose adjustments. Carbamazepine therapy had more early terminators (prior to 52 weeks) than either gabapentin (P = .008) or lamotrigine (P < .001) therapy. Fewer patients taking lamotrigine terminated treatment for adverse reactions than patients taking either carbamazepine (P < .001) or gabapentin (P = .02). In another recent trial assessing the comparative efficacy and tolerability of lamotrigine and sustained-release carbamazepine treatment in elderly subjects with epilepsy, 657% of patients taking carbamazepine completed the study without seizures in the last 20 weeks compared with 52% of patients taking lamotrigine (not significant).

We sought to evaluate effectiveness by comparing 12-month retention, efficacy (seizure freedom), and tolerability of all commonly used AEDs (newer and older) in older adults (≥55 years) with epilepsy.

**RESULTS**

We then analyzed 12-month retention and 12-month seizure freedom for each newly started AED treatment in the 436 drug exposures (for AEDs prescribed to ≥10 patients) for which data regarding the length of treatment and treatment discontinuation were available. For statistical comparison of the 12-month retention and seizure-freedom rates between AEDs, we performed a series of χ² analyses. Each drug was compared with each of the other AEDs in a 2 × 2 comparison. When χ² analyses included expected values less than 5, P values were calculated using Fisher exact test.

Those who were seizure-free but stopped taking an AED in less than 1 year because of adverse effects were excluded from the seizure-freedom analysis. For both 12-month retention and seizure freedom, results were calculated for the overall group and after stratifying for degree of refractoriness, estimated by the number of prior AED treatments tried: 0 to 2, nonrefractory; 3 or more, refractory; and 5 or more, very refractory. One patient may have started taking more than 1 AED and hence may have been included in more than 1 group when comparing retention and seizure-freedom rates for all the AEDs.

For each AED, the most common adverse effects leading to dose change or discontinuation (“intolerability”) were determined.

Three hundred twenty-four of 417 patients (77.6%) had localization-related epilepsy. The mean age was 66 years and half the patients were men (see **Table 1** for more demographics). None of the patient-related variables tested as potential predictors of retention was significant in the univariate analysis, thus eliminating the need to control for any significant predictors in the analysis for retention.

**COMPARATIVE RATES OF 12-MONTH RETENTION**

Overall, 329 of 417 patients (78.8%) remained taking at least 1 AED for at least 1 year. Of the 247 patients newly started on any AED that 10 or more people took, the average 12-month retention rate for any AED was 65% (285 of 436 patient-drug combinations). Results of the χ² × 2 × 2 comparison analysis of 12-month retention for all AED combinations (number of patients newly started on an AED = 247; patient-drug combinations = 436) are shown in the **Figure, Table 2** and **Table 3**, and supplementary Table 1 and supplementary Table 2 (http://docs.google.com/View?id=dgrw7kb_37c29t2zcc).

Without controlling for severity of epilepsy (Table 2), lamotrigine had the highest 12-month retention rate (78.6%), which was higher (P < .05) than the 12-month retention rates seen with carbamazepine (48.4%; n = 31), gabapentin (39%; n = 39), oxcarbazepine (23.5%; n = 34), phenytoin (39.3%; n = 27), and topiramate (55.6%; n = 18). The second highest retention rate was seen with levetiracetam (72.5%; n = 102), which was statistically higher than with carbamazepine (48.4%) and oxcarbazepine (23.5%). Oxcarbazepine had the worst retention rate (23.9%; n = 34), which was significantly lower than all other AEDs. See **Table 2** for further details.

In a subgroup analysis of patients with refractory disease (n = 250 patient-drug combinations) (Table 3), relative rates of 12-month retention were similar to the over-
all group, but significant differences were seen only between oxcarbazepine, which had the lowest 12-month retention rate (12.5%; n = 24), and all other AEDs. Valproate had the best retention rate in the refractory subgroup (90%), but only 10 patients were newly started on it; this was followed by lamotrigine (77.8%), with levetiracetam, zonisamide, and topiramate all around 70% retention.

Relative rates of 12-month retention for most AEDs were comparable in patients with nonrefractory disease (supplementary Table 1). In patients newly taking their first AED (supplementary Table 2), retention rates were slightly higher for most AEDs, although smaller numbers precluded any conclusions regarding significant differences.

### COMPARATIVE RATES OF 12-MONTH SEIZURE FREEDOM

The drug-drug comparisons of 12-month seizure freedom for all AEDs are shown in Table 4 and Table 5 and supplementary Table 3 and supplementary Table 4 (number of patients = 195; patient-drug combinations = 314).

Without controlling for severity (Table 4), lamotrigine had the highest 12-month seizure-freedom rate (54.1%; n = 85), which was higher (P < .05) than the 12-month seizure-freedom rates seen with all other AEDs except levetiracetam, which was second best (42.6%; n = 68); levetiracetam was statistically superior to gabapentin (18.3%; n = 27) and oxcarbazepine (9.4%; n = 32).
Other than lamotrigine and levetiracetam, all other AEDs had 12-month seizure-freedom rates less than 40%.

In a subgroup analysis of the refractory group (n=250 patient-drug combinations) (Table 5), the highest rates of seizure freedom were again seen with lamotrigine (47.4%; n=38) and levetiracetam (38.9; n=54); both these rates were significantly higher than with oxcarbazepine (4.3%; n=23), the AED with the lowest seizure-freedom rate. No other significant differences were seen in this analysis.

Table 2. Pairwise Comparisons of 12-Month Retention Rates in Older Adults With Epilepsy Newly Started on an AED Regimen

<table>
<thead>
<tr>
<th>AED</th>
<th>No. of Patients</th>
<th>Retention Rate, %</th>
<th>P Value</th>
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<tbody>
<tr>
<td>CBZ</td>
<td>31</td>
<td>48.4</td>
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<td>CBZ</td>
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<td>LEV</td>
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<td>23.5</td>
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<tr>
<td>LEV</td>
<td>22</td>
<td>68.2</td>
<td>.04</td>
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Table 3. Pairwise Comparisons of 12-Month Retention Rates in Older Adults With Refractory Epilepsy Newly Started on an AED

<table>
<thead>
<tr>
<th>AED</th>
<th>No. of Patients</th>
<th>Retention Rate, %</th>
<th>P Value</th>
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<tr>
<td>CLB</td>
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<td>58.3</td>
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<tr>
<td>CLB</td>
<td>21</td>
<td>57.1</td>
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<td>CLB</td>
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<td>71.8</td>
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<tr>
<td>CLB</td>
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<td>77.8</td>
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</tr>
<tr>
<td>CLB</td>
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<td>12.5</td>
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<td>CLB</td>
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<tr>
<td>CLB</td>
<td>10</td>
<td>90</td>
<td>.95</td>
</tr>
<tr>
<td>CLB</td>
<td>20</td>
<td>70</td>
<td>.95</td>
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</tbody>
</table>

Table 4. Pairwise Comparisons of 12-Month Seizure-Freedom Rates in Older Adults With Epilepsy Newly Started on an AED

<table>
<thead>
<tr>
<th>AED</th>
<th>No. of Patients</th>
<th>Seizure-Freedom Rate, %</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>CBZ</td>
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<td>CBZ</td>
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<tr>
<td>CBZ</td>
<td>18</td>
<td>22.2</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PHT, phenytoin; TPM, topiramate; VPA, valproate sodium; ZNS, zonisamide.

*Includes all AEDs newly started in at least 10 patients. Overall, n=247 patients; 436 patient-drug combinations.

*Significant (<=.05).

*Includes all AEDs newly started in at least 10 patients. Two hundred fifty patient-drug combinations.

*Significant (<=.05).
In patients with nonrefractory disease (supplementary Table 3), and in patients newly started on their first AED (supplementary Table 4), relative seizure-freedom rates were slightly higher for most AEDs.

### MOST COMMON ADVERSE EFFECTS LEADING TO INTOLERABILITY

Overall, 29.1% of patients experienced an intolerable adverse effect due to any AED; the rates of intolerability for each AED are reported in Table 6. The most common treatment-emergent adverse effects leading to dose change and/or discontinuation of an AED treatment (intolerability) in more than 2.0% of patients are reported in Table 6. Imbalance was the most common intolerable adverse effect overall (14.1% experienced significant imbalance attributed to at least 1 AED) and for lamotrigine (13.8%) and occurred at rates higher than 5% with gabapentin, levetiracetam, oxcarbazepine, phenytoin, and valproate. Drowsiness (8.8%), gastrointestinal disturbances (8.8%), dizziness (6.8%), cognitive adverse effects (5.4%), allergies (4.9%), and psychiatric adverse effects (4.3%) were other common intolerable adverse effects overall. Drowsiness was most likely to oc-
cur with carbamazepine, clobazam, gabapentin, levetiracetam, oxcarbazepine, and toprimate (>10% of patients required lowering of dose because of this on at least 1 occasion). Dizziness was another common intolerable adverse effect attributed to clobazam, gabapentin, lamotrigine, oxcarbazepine, phenytoin, and zonisamide at rates higher than 5%. The most common adverse effects for levetiracetam were drowsiness (23.3%) and psychiatric adverse effects (14.2%). Phenytoin intolerability was most often due to allergies (9.1%); toprimate, due to cognitive adverse effects (24%) and drowsiness (20%); valproate, due to tremor (10.8%); and zonisamide, due to cognitive adverse effects and gastrointestinal disturbances (13.6% each).

The mean time to experiencing an intolerable adverse effect ranged from 3.1 months (median, 3.3 months) for oxcarbazepine to 11.6 months (median, 9.1 months) for gabapentin. The mean time to discontinuation (due to an intolerable adverse effect) ranged from 2.6 months (median, 3.8 months) for oxcarbazepine to 7.7 months (median, 6.2 months) for levetiracetam. Of 121 patients, 7.9% with intolerable adverse effects experienced the onset of these adverse effects within the first month of treatment; 9.1% of treatment discontinuations occurred in the first 2 months.

### COMMENT

In this retrospective, uncontrolled study of older patients with epilepsy, lamotrigine was the most effective newer AED as measured by 12-month retention and seizure freedom, followed closely by levetiracetam; all other AEDs had lower but comparable retention and seizure-freedom rates with the exception of oxcarbazepine, which was consistently worse than most other AEDs for both retention and seizure freedom.

Despite the well-known differences in pharmacokinetics and pharmacodynamics between older and younger people, there are few studies comparing AED effectiveness in older adult patients with epilepsy. Lamotrigine is the only newer AED that has been extensively studied in older patients with epilepsy in uncontrolled studies, and most notably by 3 double-blind comparative studies, it appears that the major difference between carbamazepine and these 2 newer AEDs (gabapentin and lamotrigine) is their tolerability.

Another recently published multicenter, randomized, double-blind trial assessed the comparative effectiveness, efficacy, and tolerability of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in elderly subjects (≥65 years). The trial duration was 40 weeks, which included a 4-week dose escalation followed by a maintenance phase during which dosages could be adjusted according to response. Initial, maintenance, and maximum dosages were 25 mg, 100 mg, and 500 mg per day for lamotrigine and 100 mg, 400 mg, and 2000 mg per day for carbamazepine, respectively. The primary end point was retention in the trial. In the lamotrigine group, 68 patients (73%) completed the 40-week study period compared with 61 (67%) in the carbamazepine group (not significant). Time to withdrawal from any cause did not differ between groups (P = .34). Adverse events leading to withdrawal occurred in 13 subjects (14%) in the lamotrigine group and 23 subjects (25%) in the carbamazepine group (P = .08). Overall, more patients completed the study without seizures in the last 20 weeks with carbamazepine than with lamotrigine (57% vs 52%), although the difference did not reach significance. This study used target dosages and titration rates similar to the UK trial by Brodie et al. One possible explanation for the better outcome of carbamazepine-treated patients in this study is the use of a sustained-release formulation, which may reduce the occurrence of adverse effects associated with high peak drug levels.
Our study confirms the findings reported in the head-to-head studies by Brodie et al and Rowan et al of better retention with newer AEDs such as lamotrigine. Our data also add to the available literature regarding the use of most other AEDs in older adults, as, to our knowledge, no prior comparison studies in this age group have included more than 3 AEDs. The strength of our study is that we were able to compare rates of retention and seizure freedom for 10 commonly used AEDs, some new and some old, in the setting of routine clinical practice, while attempting to control for potential non-AED predictors of retention and seizure freedom and while stratifying our findings by severity of epilepsy.

Some points must be kept in mind while interpreting our results. Higher retention rates do not necessarily mean better efficacy. Not everyone in our data set was seizure-free but many of them continued to take their AEDs even when they were not completely efficacious (data not shown). Therefore, retention rates may reflect tolerability more than efficacy. It is also quite likely that physician bias/preference played a role in AED selection and decisions to discontinue certain AED treatments, and no statistical method can remove this effect or fully account for it in a retrospective study (or even a prospective, nonblinded study). We attempted to account for potential patient-related factors that may have affected retention, but a logistic regression analysis was unable to identify any significant non-AED predictors. Prior studies investigating clinical predictors of AED response have been inconclusive.

Another major limitation of this study is the lack of reliable titration data for all AEDs. We recognize that titration rate can have an important relationship with tolerability; in our database, titration rates were not consistently well documented and therefore were not analyzed. It is also likely that many patients were not examined by the treating physician at the time of the occurrence of an adverse effect, particularly when patients called in to report the occurrence of an adverse effect. Despite the retrospective nature of this review, it is unlikely that important adverse effects would be underreported, since any adverse effect that is clinically significant or bothersome is likely to be reported by the patient on our intake questionnaires or noted by the physician. These limitations reflect the situation in real-world clinical care, where imperfect reporting and recall bias is common. Furthermore, only 7.9% of 121 patients with intolerable adverse effects experienced the onset of these adverse effects within the first month of treatment, while only 9.1% of treatment discontinuations occurred in the first 2 months. These results, and the fact that the mean times to intolerability were in the range of 3.1 months (for oxcarbazepine, the least-tolerated AED) to 11.6 months (for gabapentin, the best-tolerated AED), may support the notion that only a small proportion of intolerable adverse effects could have been due to rapid titration.

There is evidence that older patients respond well to low or moderate doses of the first prescribed AED. Therefore, an AED used after 2 to 3 prior AED trials may be more likely to be discontinued because of inefficacy as compared with one that was tried at an earlier point. There may be a potential bias in our retrospective sample if 1 or more of the AEDs tested were systematically used first. Our reporting of retention and seizure freedom in patients on the first newly started AED treatment (supplementary Table 2 and supplementary Table 4) and the stratification of our analyses by refractoriness should compensate for this bias to some extent; in the analysis of patients newly started on their first AED, relative rates of retention and seizure freedom were similar to those of the overall group, though notably lamotrigine, levetiracetam, and carbamazepine were comparable in terms of retention and efficacy. Another recent study reported outcomes in 117 older patients (median age, 73 years) with newly diagnosed localization-related epilepsy whose AED treatment was begun at a single center over a 20-year period. Seventy-three patients (62%) became seizure-free for at least 12 months while taking the first AED. No individual AED was statistically more likely to confer seizure freedom than any other, and rates of seizure freedom were comparable for lamotrigine (63%), carbamazepine (67%), and valproate (65%) treatment. In our analysis of patients with refractory disease (Table 3), valproate treatment showed relatively high retention rates, particularly in the refractory group (90%), though only 10 patients were in this group. We attempted to control for this potential bias by looking at 12-month retention and seizure-freedom rates in patients with “very refractory” epilepsy (those who had tried 5 or more prior AED treatments that failed; data not shown) and found the relative rates of both retention and seizure freedom to be comparable with those reported in Tables 2, 3, and 4 and supplementary Tables 1, 2, 3, and 4.

In summary, our retrospective, uncontrolled study suggests that lamotrigine and levetiracetam are more effective than most other AEDs in older patients with epilepsy. Carbamazepine and gabapentin may have comparable effectiveness to lamotrigine and levetiracetam in newly diagnosed patients starting their first AED treatment. Valproate treatment appears to be effective in refractory cases. Oxcarbazepine was considerably less effective than other AEDs in our experience. Overall, imbalance, drowsiness, and gastrointestinal adverse effects were the most troublesome for the older patients, though there were AED-specific adverse effect profiles (Table 6), mostly consistent with prior literature. This study underscores the need for further prospective trials for evaluating safety and effectiveness of multiple AEDs in older adults, a cohort that has been consistently underrepresented in prior studies, and suggests that lamotrigine and levetiracetam should be included in any future trials of treatment of epilepsy in older adults.
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Correspondence: Lawrence J. Hirsch, MD, Comprehensive Epilepsy Center, Columbia University, Neurological Institute, Box NI-135, 710 W 168th St, New York, NY 10032 (ljh3@columbia.edu).

Author Contributions: Study concept and design: Arif, Buchsbaum, Resor, and Hirsch. Acquisition of data: Buchsbaum, Pierro, Whalen, and Sims. Analysis and interpretation of data: Arif, Sims, Bazil, and Hirsch. Drafting of the manuscript: Arif and Pierro. Critical revision of the manuscript for important intellectual content: Arif, Buchsbaum, Whalen, Sims, Resor, Bazil, and Hirsch. Statistical analysis: Arif. Obtained funding: Hirsch. Administrative, technical, and material support: Arif, Buchsbaum, Pierro, Whalen, and Sims. Study supervision: Resor and Hirsch.

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REFERENCES