Substitution Monotherapy With Levetiracetam vs Older Antiepileptic Drugs

**A Randomized Comparative Trial**

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**Objective:** To determine whether patients who fail their first antiepileptic drug (AED) have better neuropsychiatric and quality-of-life (QOL) outcomes if substituted to levetiracetam monotherapy compared with a second older AED.

**Design:** Randomized comparative trial. Participants with partial epilepsy who had failed monotherapy with phenytoin sodium, carbamazepine, or valproate sodium were randomized to substitution monotherapy with levetiracetam or a different older AED. Assessments were performed at baseline, 3 months, and 12 months using questionnaires measuring neuropsychiatric, QOL, seizure control, AED adverse effects, and neurocognitive outcomes.

**Setting:** Epilepsy service of a teaching hospital.

**Patients:** Fifty-one patients were randomized to levetiracetam and 48 were randomized to a second older AED (25 to valproate and 23 to carbamazepine).

**Main Outcome Measures:** Proportions showing improvements in depression (on the Hospital Anxiety and Depression Scale) and QOL scores (on the 89-item Quality of Life in Epilepsy Inventory) at 3 months.

**Results:** There were no differences between the groups in depression scores at 3 months (improvement in 17 of 43 patients [39.5%] in the levetiracetam group and 15 of 44 patients [34.1%] in the older AED group; *P*=.60), but a greater proportion of the older AED group improved on the 89-item Quality of Life in Epilepsy Inventory compared with the levetiracetam group (27 of 38 patients [71.1%] vs 21 of 43 patients [48.8%], respectively; *P*=.04). The QOL, anxiety, and AED adverse effects scores were improved in both groups at 3 and 12 months after randomization.

**Conclusions:** Substitution monotherapy in a patient experiencing ongoing seizures or tolerability issues is associated with sustained improvements in measures of QOL, psychiatric, and adverse events outcomes. Patients switched to levetiracetam do not have better outcomes than those switched to a second older AED.

**Trial Registration:** anzctr.org.au Identifier: ACTRN12606000102572

psychiatric adverse events and even noted that levetiracetam could have a positive effect on cognition and quality of life (QOL). Herein, we report the KONQUEST (Keppra vs Older AEDs evaluating Neuropsychiatric, Neurocognitive and Quality of life outcomes in treatment of Epilepsy as Substitution monoTherapy) randomized comparative trial, which tested the hypothesis that substitution monotherapy with levetiracetam in patients who have failed AED monotherapy with an older AED would be associated with better patient outcomes on a range of neuropsychiatric, QOL, and epilepsy measures compared with those substituted with another older AED (carbamazepine or valproate sodium).

**METHODS**

**PATIENTS**

The KONQUEST trial was a pragmatic, single-center, prospective, randomized, open-label study with blinded end-point ascertainment. Eligible patients had failed initial monotherapy for partial epilepsy with an older AED (carbamazepine, valproate, or phenytoin sodium). Failure was defined as a need to substitute the first AED owing to lack of efficacy in controlling seizures and/or intolerable adverse effects. Exclusion criteria were an intellectual handicap, a history of psychiatric morbidity, a history of substance abuse, a treatment history of antidepressant, anxiolytic, or other medications that could alter mood or cognition within 3 months prior to recruitment, pregnancy, breastfeeding, or planned pregnancy in the next year.

**RANDOMIZATION**

Enrolled patients were randomized to substitution monotherapy treatment with levetiracetam or another older AED, ie, controlled-release carbamazepine (Tegretol CR) or enteric-coated valproate (Epilim). If the initial AED treatment had been carbamazepine or phenytoin, the patient was randomized to levetiracetam or valproate; if the initial AED treatment was valproate, the patient was randomized to levetiracetam or carbamazepine (Figure 1A). A balanced randomization schedule, based on the baseline Hospital Anxiety and Depression Scale (HADS) depression score permuted blocks, was used to ensure that the 2 treatment groups were equivalent with regard to the numbers of patients reporting depressive symptoms (HADS depression score >7) at baseline. Permuted blocks ensured a balance after every fourth treatment allocation within each level of baseline scores. Randomization was conducted by a research scientist who had no contact with study patients. Physicians screening and enrolling patients were blinded to the patients' treatment allocation.

**TREATMENTS**

During the initial 4-week titration period following randomization, the initial AED was weaned and the study drug was increased in 2 weekly step-ups to a target dosage of 1000 mg/d for levetiracetam, 1000 mg/d for valproate sodium, and 400 mg/d for carbamazepine. After this time, dosage adjustments by the treating neurologist were allowed if the patient had further seizures or if there were issues with tolerability. If seizures were unable to be controlled with monotherapy with the study drug, another AED could be added. If intolerable adverse effects persisted, the patient could be withdrawn from the study medication and treated with a different AED. Patients continued to be followed up and received all scheduled assessments for the 12-month postrandomization period irrespective of treatment changes.

**OUTCOME ASSESSMENTS**

The primary outcomes were the proportions of patients who showed improvement in depression symptoms and QOL at 3 months following randomization. Improvement was defined as the 3-month score being lower than the baseline score. Secondary outcomes were the following: depression and QOL at 12 months; changes in anxiety symptoms; Liverpool Adverse Events Profile (LAEP) scores; symptoms; cognitive function testing using IntegNeuro; seizures (excluding those occurring dur-
Table. Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Levetiracetam (n = 51)</th>
<th>Older AEDs (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>38.2 (24.5-57.5)</td>
<td>42.5 (29.7-53.4)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (54.9)</td>
<td>33 (68.8)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (45.1)</td>
<td>15 (31.2)</td>
</tr>
<tr>
<td>Prrerandomization AED, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>21 (41.2)</td>
<td>21 (43.8)</td>
</tr>
<tr>
<td>Phenytoin sodium</td>
<td>19 (37.3)</td>
<td>18 (37.5)</td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>11 (21.5)</td>
<td>9 (18.7)</td>
</tr>
<tr>
<td>Cause of failure of prerandomization AED, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse drug effect</td>
<td>28 (54.9)</td>
<td>30 (62.5)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>14 (27.5)</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td>Both</td>
<td>9 (17.6)</td>
<td>11 (22.9)</td>
</tr>
<tr>
<td>Duration of treatment before randomization, median (IQR), y</td>
<td>0.58 (0.25-4.67)</td>
<td>1.75 (0.33-5.00)</td>
</tr>
<tr>
<td>Seizure frequency before randomization, median (IQR), No./y</td>
<td>2.0 (0-10.0)</td>
<td>2.5 (0-10.0)</td>
</tr>
<tr>
<td>Baseline HADS depression score, mean (SD)</td>
<td>4.92 (4.11)</td>
<td>4.69 (3.66)</td>
</tr>
<tr>
<td>Baseline QOLIE-89 overall score, mean (SD)</td>
<td>116.56 (32.61)</td>
<td>112.35 (28.19)</td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drug; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; QOLIE-89, 89-item Quality of Life in Epilepsy Inventory.

All analyses were performed using the SAS Enterprise Guide version 4.2 statistical package (SAS Institute, Inc).

ETHICS APPROVAL AND REGISTRATION

The study protocol was approved by the Melbourne Health Human Research Ethics Committee. All participants provided written informed consent. The study was registered as an International Standard Randomized Controlled Trial with the Australian New Zealand Clinical Trial Registry.

RESULTS

PATIENT RECRUITMENT AND FOLLOW-UP

During a 23-month period (February 15, 2006, to December 23, 2008), 99 patients were enrolled (61 [61.6%] male; median [interquartile range] age, 39.2 [27.7-55.6] years). As a result of slower than anticipated recruitment, the original target of 150 patients was not reached. Nonetheless, the sample size achieved provided 66.2% power to detect a relative risk of improvement in depressive symptoms of 1.5.

Fifty-one patients (51.5%) were randomized to the levetiracetam treatment group and 48 (48.5%) were randomized to the older AED treatment group (23 to valproate and 23 to carbamazepine). The groups were similar in terms of demographic and clinical factors (Table). Figure 2 shows the flowchart for enrolled patients. In total, 10 of 99 patients (10.1%) withdrew or died during the study, and this did not significantly influence the drug titration period; adherence to treatment; and treatment failure.

Assessments were performed at baseline and at 3, 6, and 12 months following randomization (Figure 1B). The assessments included the following: (1) seizure diary; (2) LAEP scores; (3) score on the 89-item Quality of Life in Epilepsy Inventory; (4) HADS score (psychiatric status assessment); measured at baseline, 3 months, and 12 months; and (5) IntegNeuro score (comprehensive neuropsychological assessment; measured at baseline and 3 months).

STATISTICAL ANALYSIS

The sample size calculation was based on the depression primary end point. Pilot data from first-seizure clinics at the Royal Melbourne Hospital in 2004 (n = 117) found that 56 patients (47.9%) who remained on older AEDs experienced improvement in depressive symptoms from baseline to 3 months. Based on this assumption, 66 patients in each treatment arm would provide 80% power to detect a relative risk of improvement of at least 1.5 associated with levetiracetam, assuming a 2-sided \( \alpha \) value of 0.05. To allow for patient withdrawals and noncompliance, it was planned to recruit an additional 10% in each arm, giving a target sample of 73 patients per treatment arm.

Analyses were undertaken on an intent-to-treat basis. The primary analysis comprised an unadjusted comparison between the treatment groups of the proportions of patients whose depressive symptoms improved at 3 months. An assessment of interaction between baseline depression score and treatment effect was performed as a secondary analysis, as were the outcomes at 12 months. Freedom from seizures, treatment adherence, and treatment failure were analyzed in survival analyses.
differ between the treatment groups (4 randomized to levetiracetam, 5 to carbamazepine, and 1 to valproate). Withdrawals from the study were due to the following: (1) noncompliance with the study procedures (6 patients, including 1 receiving levetiracetam, 4 receiving carbamazepine, and 1 receiving valproate); (2) medication adverse effects (1 patient receiving levetiracetam who had a balance problem and poor seizure control); (3) conversion to high-grade brain tumor (1 patient receiving levetiracetam); and (5) death (2 patients, including 1 receiving carbamazepine with sudden unexplained death in epilepsy and 1 receiving levetiracetam who died of carcinoma of the stomach).

**PRIMARY OUTCOMES**

There was no difference between the treatment groups in the proportion of patients in whom there was an improvement in the HADS depression score from baseline to 3 months (17 of 43 patients [39.5%] in the levetiracetam group; 15 of 44 patients [34.1%] in the older AED group; \( P = .60 \), \( \chi^2 \) test).

From baseline to 3 months, a significantly greater proportion of the older AED group showed improvement in the 89-item Quality of Life in Epilepsy Inventory score compared with the levetiracetam group (27 of 38 patients [71.1%] vs 21 of 43 patients [48.8%], respectively; \( P = .04 \), \( \chi^2 \) test).

**SECONDARY OUTCOMES**

The HADS depression scores are summarized in Figure 3A. The proportion of patients with borderline or possible clinical depression did not differ between the time points or the treatment groups. There were also no differences between the treatment groups in the proportion of patients who had an improvement in depression scores at 12 months (18 of 42 patients [42.9%] in the levetiracetam group; 19 of 41 patients [46.3%] in the older AED group; \( P = .33 \)).

The HADS anxiety scores are summarized in Figure 3B. The proportion of patients with a borderline or possible clinical disorder of anxiety decreased in both treatment groups at 3 and 12 months compared with baseline but did not differ between the groups. The anxiety scores improved in 21 of 43 patients (48.8%) in the levetiracetam group and 24 of 44 patients (54.6%) in the older AED group from baseline to 3 months (\( P = .75 \)) and in 22 of 42 patients (52.4%) in the levetiracetam group and 25 of 41 patients (61.0%) in the older AED group from baseline to 12 months (\( P = .71 \)).
The 89-item Quality of Life in Epilepsy Inventory scores are summarized in Figure 4. Reductions of both the overall mean score and many of the subscores were observed at 3 and 12 months compared with baseline for both groups, but there were no significant differences between the groups. At 12 months, 27 of 43 patients (62.8%) in the levetiracetam group and 25 of 38 patients (65.8%) in the older AED group recorded an improvement in the 89-item Quality of Life in Epilepsy Inventory score compared with baseline, but this was not different between the groups ($P = .78$).

The LEAP scores are summarized in Figure 5. Reductions of both the global LEAP scores and many of the individual symptoms were observed at 3 and 12 months compared with baseline for both groups, but there were no significant differences between the groups.

IntegNeuro neurocognitive results are summarized in Figure 6. There was no significant change in overall performance between the assessments in either group and no differences between them.

Thirty-eight of 51 patients (74.5%) randomized to levetiracetam and 34 of 48 patients (70.8%) randomized to an older AED remained on the allocated treatment at 12 months (Figure 7A). Reasons for study drug discontinuation were the following: (1) adverse drug effects, notably fatigue, hand tremor, and memory impairment in 10 patients randomized to levetiracetam, 6 randomized to valproate, and 5 randomized to carbamazepine; (2) lack of efficacy in 1...
patient randomized to levetiracetam and 3 randomized to valproate; and (3) treatment nonadherence in 2 patients randomized to levetiracetam.

There were no significant differences between treatment groups with regard to the proportion of patients who remained seizure free at 12 months (Figure 7B) or the proportion of patients with treatment failure (defined as cessation of the allocated drug, seizure recurrence, or commencement of a new medication) (Figure 7C).

The KONQUEST trial assessed outcomes in a clinically important but understudied group of patients in whom initial treatment with an older AED had failed owing to either inadequate seizure control or intolerable adverse effects. The results showed that patients randomized to substitution monotherapy with levetiracetam did not experience better outcomes than those randomized to treat-
ment with a second older AED, valproate or carbamazepine, in terms of depression or QOL. Similar outcomes were also seen between the treatments for a range of secondary outcome measures, including seizure control, retention rate, treatment failure, anxiety symptoms, AED adverse effects, and neurocognitive performance.

Overall, both groups of patients showed improvements in QOL measures, anxiety symptoms, and AED adverse effects at 3 months, and these improvements were sustained at the 12-month follow-up. This indicates that changing to monotherapy with another AED in a patient who is having unsatisfactory treatment outcomes with their first drug is associated with improvements in a range of psychosocial measures. It should be noted that for most patients, the reason for failure of the first AED treatment was intolerable adverse effects rather than lack of efficacy (Table).

To our knowledge, only 1 previously published randomized study has compared outcomes of substitution monotherapy with a newer AED vs another older AED, in this case, lamotrigine vs carbamazepine, phenytoin, or valproate. This multicenter open-labeled study had a shorter evaluation period (24 weeks) and did not assess neuropsychiatric measures. No statistically significant differences were found for the primary outcome measure (retention rate) between the treatments, although the authors noted that “lamotrigine monotherapy was perceived by both physicians and patients to have benefits over monotherapy with older antiepileptic drugs.” Consistent with the results of our study, improvements in measures of QOL were seen in both treatment groups, although this was greater in the lamotrigine group.

Psychiatric symptoms and disorders are common in patients with epilepsy, and AEDs may be an important contributor. Anecdotal clinical experience and nonrandomized studies have implicated levetiracetam as having a particular propensity to induce or aggravate psychiatric symptoms, in particular irritability, agitation, aggressive behavior, and mood disorders. However, in this study we found that the proportion of patients with HADS scores indicating either possible or borderline clinical depressive or anxiety disorders decreased at 3 and 12 months following randomization of treatment to levetiracetam. The LAEP also assessed several symptoms relevant to the “moody irritability” that many clinicians commonly attribute to levetiracetam treatment, including nervousness, aggression, and depression, with none of these differing between the treatment groups (Figure 3B and C). Furthermore, there was no difference in the number of patients who withdrew from the study drug because of psychiatric adverse effects. Our results are consistent with the conclusions of a Cochrane systematic review of 4 randomized controlled trials of levetiracetam therapy involving 1023 patients, which did not
identify significant excess psychiatric adverse events with therapy. Of note, these previous trials had a relatively short follow-up period of 16 to 24 weeks, while our study had follow-up for 12 months. It should be acknowledged that patients with a history of major depression or having been treated with antidepressant medications in the previous 3 months were excluded from this study. Therefore, we cannot determine whether such patients may have been more vulnerable to mood-altering effects of the treatments.

Multiple factors, including seizure type and frequency, AED adverse effects, and comorbid medical and psychiatric disorders, play a role in the QOL for patients with epilepsy. A number of studies have reported that a change to levetiracetam treatment was associated with improvements in QOL. In this study, we found that substitution monotherapy with levetiracetam was associated with sustained improvement in QOL measures, and an even greater proportion of patients randomized to a second older AED showed an improvement in QOL at 3 months, with no difference between the groups at 12 months. The difference in the improvement in the 3-month QOL scores between the treatment groups was not explained by differences in seizure control. However, the magnitude of these differences was relatively small (Figure 4A), and the clinical significance of this is uncertain particularly as there were no differences seen at 12 months.

Neurocognitive symptoms such as impaired memory, attention, and concentration are commonly reported by patients with chronic epilepsy. Objective neurocognitive deficits are commonly found on neuropsychometric testing, with the domains most affected being memory and psychomotor speed. Patients and their physicians commonly attribute these problems to their AED treatment. A potential advantage of the newer AEDs such as levetiracetam is that they may be associated with fewer neurocognitive effects. Using a computer-based cognitive testing battery that has been specifically designed and validated for use in clinical trials evaluating the effects of drug treatment on neurocognition, we found no significant change in overall cognitive performance at 3 months and no difference between patients randomized to treatment with levetiracetam vs another older AED. However, it should be noted that the patients enrolled in this study had already failed treatment with 1 AED and therefore may be overall a more drug-resistant group who may be expected to have a higher baseline level of neurocognitive dysfunction than a newly treated cohort.

One of the potential advantages advocated for the newer-generation AEDs is an improved tolerability profile. In this study, we found that reported adverse effects using the LAEP scale decreased in all patients at 3 and 12 months compared with baseline, but there was no difference between levetiracetam and the older AEDs. At 12 months, all of the symptom subscores had improved in both groups except for weight gain (increased in both the levetiracetam and older AED groups) and hair loss (increased in only the older AED group). Headache had the highest proportion of improvement in the levetiracetam group, followed by aggression. The latter finding is noteworthy given the belief that patients receiving levetiracetam more often become irritable and aggressive.

Rendering a patient seizure free for a sustained period is the fundamental measure of treatment efficacy for epilepsy and is associated with improvements in QOL. In this study, similar proportions of patients randomized to levetiracetam (27 of 51 patients [52.9%]) and older AEDs (24 of 48 patients [50.0%]) remained seizure free for 12 months. This is in line with a previous study in patients with newly treated epilepsy in which equivalent 6-month seizure-free rates were found between patients randomized to levetiracetam and those randomized to carbamazepine (173 of 237 patients [73.0%] and 171 of 235 patients [72.8%], respectively). Other studies that have directly compared new and older AEDs in newly treated epilepsy populations have also found equivalent rates of being seizure free. The long-term retention rate on an AED is a popular pragmatic measure of the effectiveness of epilepsy treatment as it is dependent on both efficacy and tolerability. In this study, similar 12-month retention rates were seen for the levetiracetam group (38 of 51 patients [74.5%]) and the older AED group (34 of 48 patients [70.8%]).

One potential limitation of this study is that the treatments were open labeled, which means that there was greater potential for information bias arising from patient, physician, and investigator preconceptions. However, these biases would be expected to be in favor of levetiracetam, and our study found a benefit associated with the older AED group. Hence, the open-labeled nature of our study led to a conservative estimate of the benefit of older AEDs vs levetiracetam (biased to the null). It also should be noted that, wherever possible, outcome ascertainment was undertaken in a blinded manner.

In conclusion, this is the first randomized comparative trial, to our knowledge, of levetiracetam vs older AEDs as substitution monotherapy in partial epilepsy. We found that switching treatment to a different older AED, carbamazepine or valproate, led to positive clinical outcomes similar to those of switching to levetiracetam, with the older AEDs associated with a better QOL outcome at 3 months. The study findings should inform treatment decisions for the important group of patients who have failed treatment with their initial AED because of inadequate seizure control or intolerable adverse effects.

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Author Contributions: Drs Hakami and Todaro contributed equally to the literature review. Study concept and design: MacGregor, Yerra, and O’Brien. Acquisition of data: Hakami, Todaro, Petrovski, Tan, Matkovic, Yerra, and O’Brien. Analysis and interpretation of data: Hakami, Todaro, Petrovski, MacGregor, Velakoulis, Gorelik, Liew, Yerra, and O’Brien. Drafting of the manuscript: Hakami, MacGregor, Yerra, and O’Brien.

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REFERENCES