Levetiracetam improves verbal memory in high-grade glioma patients

Marjolein de Groot†, Linda Douw†, Eefje M. Sizoo, Ingeborg Bosma, Femke E. Froklage, Jan J. Heimans, Tjeerd J. Postma, Martin Klein, and Jaap C. Reijneveld

Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands (M.d.G., L.D., E.M.S., I.B., F.E.F., J.J.H. T.J.P. J.C.R.); Stichting Epilepsie Instellingen Nederland, Heemstede, The Netherlands (F.E.F.); Department of Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands (M.K.); Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands (J.C.R.)

Background. Treatment of high-grade glioma (HGG) patients with anti-epileptic drugs (AEDs) has met with various side effects, such as cognitive deterioration. The cognitive effects of both older and newer AEDs in HGG patients are largely unknown. The aim of this study was to determine the effect of older and newer AEDs on cognitive performance in postoperative HGG patients.

Methods. We selected HGG patients from 3 separate cohorts for use of older, newer, or no AEDs, as they represented distinct treatment eras and provided the opportunity to compare older and newer AEDs. In all 3 cohorts, patients were included within 6 weeks following neurosurgery before the start of postoperative treatment. Cognitive functioning was evaluated by an extensive neuropsychological assessment, executed in 6 cognitive domains (attention, executive functioning, verbal memory, working memory, psychomotor functioning, and information processing speed).

Results. One hundred seventeen patients met the inclusion criteria; 44 patients used no AED, 35 were on monotherapy with a newer AED (all levetiracetam), and 38 were on monotherapy with an older AED (valproic acid or phenytoin). Patients on older and newer AEDs performed equally well as patients not on an AED, and patients on levetiracetam performed even better on verbal memory tests than patients not on an AED. Post-hoc analyses revealed that within the group using older AEDs, patients on valproic acid performed better than patients on phenytoin.

Conclusions. Neither levetiracetam nor valproic acid was associated with additional cognitive deficits in HGG patients. Both AEDs even appeared to have a beneficial effect on verbal memory in these patients.

Keywords: high-grade glioma, cognitive functioning, anti-epileptic drugs, epilepsy, primary brain tumor.
Levetiracetam (a newer AED) has been reported not to lead to significant cognitive side effects in epilepsy patients, potentially even enhancing performance in some cognitive domains.\textsuperscript{12–15} It remains to be determined, however, to what extent AEDs affect cognitive functioning in HGG patients. Since HGG patients already have impaired cognitive functioning due to their tumor, one might hypothesize that the impact of cognitive side effects of AEDs is likely to be more prominent in glioma patients. Owing to the vast array of AEDs with comparable efficacy, the cognitive side effect profile of these drugs may become increasingly crucial when choosing an AED.

Based on previous literature, we hypothesize that (i) HGG patients using a newer AED (levetiracetam) have similar performance on cognitive tests as patients not using AEDs, (ii) HGG patients on levetiracetam show better cognitive performance than patients using an older AED (valproic acid, phenytoin), and (iii) HGG patients using valproic acid or phenytoin are more cognitively impaired than patients not using AEDs. In order to investigate these hypotheses, we assessed the effect of levetiracetam, valproic acid, and phenytoin monotherapy on cognitive functioning in HGG patients.

Materials and methods

Patients

We selected patients with HGG from 3 prospective cohort studies (see Fig. 1) that were performed at several tertiary referral centers for brain tumor patients in the Netherlands. We included these cohorts representing 2 distinct treatment eras in order to compare older AEDs with the newer AED levetiracetam. In all 3 cohorts, patients were included at the time of initial diagnosis following neurosurgical intervention. Cohort 1 comprised HGG patients who were recruited between June 2007 and October 2010, all using levetiracetam. Cohort 2 consisted of newly diagnosed HGG patients who were recruited between February 1997 and June 1999, all of whom used older AEDs or no AED. Quality of life and cognition in this cohort have been reported previously.\textsuperscript{8} Cohort 3 comprised newly diagnosed glioblastoma multiforme (GBM) patients who were recruited between March 2005 and October 2010 and used levetiracetam, older AEDs, or no AED. Cognitive performance of 13 patients in this cohort has been described in a study investigating cognition during the currently standard therapy of radiation with concomitant and adjuvant temozolomide.\textsuperscript{16}

Fig. 1. Flowchart of patient inclusion. Abbreviations: NPA, neuropsychological assessment; VPA, valproic acid; LEV, levetiracetam; PHT, phenytoin; CBZ, carbamazepine; poly, polytherapy.
In all cohorts, the following inclusion criteria were applied: (i) histopathologically confirmed HGG (ie, WHO grade III astrocytoma, oligodendroglioma, or oligoastrocytoma and WHO grade IV GBM), (ii) no previous irradiation or chemotherapy, (iii) age > 18 years, and (iv) ability to communicate in the Dutch language. In cohort 3, only patients with a GBM diagnosis were included. In cohort 1, an extra inclusion criterion was levetiracetam monotherapy.

All patients were included directly after neurosurgical intervention (either biopsy or tumor resection). They underwent neuropsychological testing within 6 weeks after neurosurgery and before starting other antitumor treatment (ie, chemotherapy and/or radiotherapy). Various clinical parameters were recorded, such as Karnofsky performance status, type of neurosurgery (biopsy or resection), and histopathological diagnosis. Furthermore, AED use, AED type, and corticosteroid use were registered.

All 3 studies received approval from the ethics committees of the participating hospitals and all patients gave written informed consent prior to the day of testing.

Neuropsychological Assessment

Identical neuropsychological assessments were administered in all cohorts by a trained psychometrician under the supervision of a board-certified clinical neuropsychologist (M.K.) and included the letter-digit substitution test, concept shifting test, Stroop color and word test, visual verbal learning test, memory comparison test, and categoric word fluency (see Table 1). The total time required to complete the assessments was ~60 min.

Patients’ scores on each subtest were compared with those of a group of healthy controls who have been described previously, matched for age, sex, and educational level. Individual patients’ test scores were converted to z-scores using the mean and standard deviation of the matched control group. In order to explore different aspects of cognition, the z-scores were summarized into 6 cognitive domains: (i) attention, (ii) executive functioning, (iii) verbal memory, (iv) working memory, (v) psychomotor functioning, and (vi) information processing speed. Construction of these domains has been reported previously and was based on a principal component analysis using varimax rotation with Kaiser normalization performed on the z-scores of a large group of healthy controls. These domains are commonly used in clinical practice and research.

Statistical Analyses

All statistical analyses were performed using SPSS 15.0 for Windows. Differences in patient characteristics of the different groups (no AEDs, older AEDs, levetiracetam) were tested by means of Fisher exact tests (sex, histopathological diagnosis, tumor lateralization, type of surgery) or Student's t-tests (age, performance status). In order to test our first hypothesis that patients on levetiracetam would not perform more poorly than patients not using AEDs, backward linear regression analyses were performed, with the different cognitive domains as dependent variables and levetiracetam use versus no AED use as the predicting categorical variable. The second hypothesis, that levetiracetam is related to better cognitive performance compared with valproic acid and phenytoin, was tested in similar regression analyses, using levetiracetam versus the other AEDs as the predictor. Finally, the third hypothesis, which concerns poorer cognition in patients using valproic acid or phenytoin compared with patients not on AED treatment, was investigated using older AED use versus no AED use as the predicting variable. In addition, clinical variables that significantly differed among patient cohorts (in this case only Karnofsky Performance Score [KPS]) were entered in the regression model. The significance level for all of these regression analyses was set at $P < .05$, but because multiple tests were performed (per cognitive domain), the significance level of the regression model was set to $P < .008$ (according to Bonferroni’s correction).

Results

Patient Characteristics

Figure 1 shows the flowchart of patients per cohort. Initially, 133 patients were included in these cohorts.

<table>
<thead>
<tr>
<th>Name of Test</th>
<th>Cognitive Correlates</th>
<th>Cognitive Domain(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter digit substitution</td>
<td>Psychomotor speed relatively unaffected by intellectual ability</td>
<td>Information processing speed, psychomotor functioning</td>
</tr>
<tr>
<td>Concept shifting</td>
<td>Executive (frontal) function, attention, visual scanning, and</td>
<td>Executive functioning, psychomotor functioning</td>
</tr>
<tr>
<td>Stroop color and word</td>
<td>mental processing speed</td>
<td>Attention</td>
</tr>
<tr>
<td>Visual verbal learning</td>
<td>Executive (frontal) function, attention, mental speed, and</td>
<td>Verbal memory</td>
</tr>
<tr>
<td>Memory comparison</td>
<td>mental control</td>
<td>Working memory</td>
</tr>
<tr>
<td>Categoric word fluency</td>
<td>Various aspects of verbal learning, organization, and memory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Selective attention, mental concentration, memory, and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>information processing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frontal dysfunction and flexibility of verbal thought</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Neuropsychological tests administered and the cognitive domain scores
However, 15/133 had to be excluded due to inability to finish the neuropsychological assessment, inadequate documentation of AED use, or use of AED polytherapy. Furthermore, 1 patient used carbamazepine, which prompted us to remove this patient from the analyses. Therefore, 117 patients were included in the analyses (see Table 2 for patient characteristics). The 3 cohorts did not differ with respect to sex, age, type of surgery, dexamethasone use, and tumor lateralization. However, cohort 3 had significantly lower KPS scores (median [range] = 80 [30–100]) than cohort 1 (90 [70–100]) and cohort 2 (90 [30–100]).

Patients not using AEDs, patients using levetiracetam, and patients using phenytoin or valproic acid did not differ significantly with respect to age, sex, type of surgery, tumor grade, tumor lateralization, and
dexamethasone use. However, patients using levetiracetam had significantly better performance status (median [range] = 90 [70–100]) than patients not using AEDs (80 [40–100]) and patients on older AEDs (80 [30–100]). Because of the difference in performance status between groups, KPS was used as a covariate in subsequent analyses.

### Cognitive Effects of Newer and Older AEDs

Our first hypothesis, that levetiracetam use was not associated with poorer cognitive functioning than no AED use, was confirmed. Notably, patients on levetiracetam even performed significantly better (mean [SD] = −0.07 [1.04]) than patients not using AEDs (mean [SD] = −0.73 [1.05]) with respect to verbal memory (see Table 3), regardless of KPS (which was also a significant predictor). Although there were no significant differences between groups in terms of tumor location (ie, frontal, temporal, occipital, or parietal) or lateralization (left, right, or bilateral), we subsequently entered these variables in the same backward regression analysis (verbal memory as dependent, levetiracetam vs no AED use, and tumor location/lateralization as predictors) to ensure that our results were not due to tumor location or lateralization. Results show that although tumor lateralization in the left hemisphere is related to poorer verbal memory (beta = −0.306, P = .005), the use of levetiracetam is still significantly related to better verbal memory performance (beta = 0.320, P = .003) in the same model. Tumor location was not significantly related to verbal memory in this analysis.

We performed post-hoc analyses to further explore which aspects of verbal memory were positively influenced by levetiracetam use compared with no AED use, as the test used for verbal memory assesses different aspects of memory and may further elucidate the report-ed differences in memory functioning. Cognitive z-scores per subtest were compared by means of Student’s t-tests, showing significantly higher scores in the levetiracetam group on the first trial of the visual verbal learning test, t(76) = −2.93, P = .004. Maximum number of words remembered during the 5 trials, t(76) = −3.63, P = .001, and total number of words remembered

### Table 2. Patient characteristics

<table>
<thead>
<tr>
<th>Domain Predictor/Covariate</th>
<th>All Patients</th>
<th>No AEDs</th>
<th>AEDs</th>
<th>B</th>
<th>SE B</th>
<th>Beta</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO grade III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade III</td>
<td>48 (41)</td>
<td>23 (52)</td>
<td>25 (34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>34 (29)</td>
<td>19 (43)</td>
<td>15 (21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>11 (10)</td>
<td>4 (9)</td>
<td>7 (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>3 (2)</td>
<td>–</td>
<td>3 (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade IV (GBM)</td>
<td>69 (59)</td>
<td>21 (48)</td>
<td>48 (66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>68 (58)</td>
<td>26 (59)</td>
<td>42 (58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>48 (41)</td>
<td>17 (39)</td>
<td>31 (42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor localization, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>34 (29)</td>
<td>14 (32)</td>
<td>20 (27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>22 (19)</td>
<td>6 (14)</td>
<td>16 (22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>22 (19)</td>
<td>5 (11)</td>
<td>17 (23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Othera</td>
<td>39 (33)</td>
<td>19 (43)</td>
<td>20 (27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27 (23)</td>
<td>14 (32)</td>
<td>13 (18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>59 (50)</td>
<td>20 (46)</td>
<td>39 (53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>31 (27)</td>
<td>10 (23)</td>
<td>21 (29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of neurosurgery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stereotactic biopsy</td>
<td>26 (21)</td>
<td>9 (21)</td>
<td>17 (23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>91 (78)</td>
<td>35 (80)</td>
<td>56 (77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** LEV, levetiracetam; VPA, valproic acid; PHT, phenytoin.

### Table 3. Regression analyses performed to investigate cognitive functioning in the 3 groups

<table>
<thead>
<tr>
<th>Domain Predictor/Covariate</th>
<th>B</th>
<th>SE B</th>
<th>Beta</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.511</td>
<td>0.246</td>
<td>0.234</td>
<td>0.041</td>
</tr>
<tr>
<td>Performance status</td>
<td>0.023</td>
<td>0.011</td>
<td>0.235</td>
<td>0.041</td>
</tr>
<tr>
<td>older AEDs vs no AEDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older AEDs vs no AEDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* R² = 0.142 (P = .003). B. coefficient.
during the encoding phase, \(t(76) = -2.85, P = .007\). All 3 of these subscores indicate better encoding, storage, and active retrieval in patients using levetiracetam. This effect can be seen in Fig. 2, in which the number of words remembered over all 5 trials and during delayed recall and recognition per group are plotted. We found a trend toward better performance by patients using levetiracetam compared with non-AED users regarding active retrieval of information 20 min following encoding, \(t(75) = -1.71, P = .091\). There were no significant differences in recognition of the words, indicating that passive retrieval was not positively influenced by levetiracetam use.

Our second hypothesis was not confirmed: there were no significant cognitive differences between patients using levetiracetam and patients using older AEDs (phenytoin and valproic acid). Furthermore, patients on older AEDs did not perform more poorly than patients not using AEDs, thereby invalidating the third hypothesis. These results were unchanged when tumor location and lateralization were taken into account.

**Post-hoc Analyses: Valproic Acid and Phenytoin**

Because there were no significant differences in cognitive functioning between patients taking older AEDs and the 2 other groups, post-hoc analyses were performed in order to explore whether this could be due to differences between the 2 older AEDs (valproic acid and phenytoin) compared with the other groups separately (Fig. 3). Backward regression analyses were performed (with performance status as a covariate), investigating cognitive differences among all individual AED groups (no AEDs, levetiracetam, valproic acid, phenytoin). Interestingly, these analyses revealed that patients on valproic acid performed more strongly (mean [SD] = -0.20 [0.93]) in verbal memory than patients not using an AED (-0.73 [1.05]; Table 4). This difference was again due mainly to differences in the encoding phase of the visual verbal learning test, as patients on valproic acid performed more strongly with respect to verbal recall after the first trial, \(t(62) = -2.28, P = .026\), and the third trial, \(t(62) = -2.20, P = .31\).

In their working memory capacity, patients using levetiracetam were superior (mean [SD] = -0.93 [1.09]) to patients using phenytoin (-1.97 [2.32]) (see Table 4). There were no significant differences between other AED groups.

---

**Fig. 2.** Mean results of the visual verbal learning test in patients on levetiracetam and those not using AEDs. Abbreviation: LEV, levetiracetam. Error bars are SDs. **\(P < .01\).**

**Fig. 3.** Mean cognitive domain z-scores of patients per AED used. Abbreviations: EF, executive functioning; VM, verbal memory; WM, working memory; IPS, information processing speed; A, attention; PS, psychomotor speed; Total, total cognitive functioning of 117 glioma patients using no AEDs (n = 44); LEV, levetiracetam (n = 35); VPA, valproic acid (n = 22) or PHT, phenytoin (n = 16).
Discussion

We evaluated the effects of phenytoin, valproic acid, and levetiracetam on cognitive functioning in HGG patients. We confirmed our first hypothesis that the use of levetiracetam is not associated with additional cognitive deficits; patients on levetiracetam performed equally well as patients not using AEDs and even performed better regarding encoding and memorization of verbal information. Although patients with left-sided tumors as a group performed more poorly in the domain of verbal memory, these results with respect to levetiracetam remained significant when controlling for tumor location and lateralization. We could not confirm our second and third hypotheses; patients on levetiracetam did not perform more strongly than to patients on older AEDs (phenytoin, valproic acid), and patients on older AEDs did not perform less strongly than non-AED users. We performed post-hoc analyses in order to explore whether this could be due to differences between the 2 older AEDs (valproic acid and phenytoin). Results indicate that the positive effect of valproic acid on verbal memory probably outbalanced the negative impact of phenytoin on cognition.

Klein et al.\textsuperscript{11} found that low-grade glioma patients on AEDs performed poorer on cognitive tasks pertaining to information processing, psychomotor function, attention, working memory, and executive function than those not using AEDs. The differences between the present study and these earlier findings might be explained by the type of drugs used: all epileptic patients in the study by Klein et al.\textsuperscript{11} used older AEDs (carbamazepine, valproic acid, phenytoin, and phenobarbital), and no separate analyses regarding different types of AEDs were performed. In line with this, studies comparing effects of different AEDs on cognition in non-tumor-related epilepsy patients also report higher risk for cognitive impairment with use of older AEDs (see review\textsuperscript{5}). Adverse effects with respect to attention, motor speed, and memory are similar among older AEDs (phenytoin, carbamazepine, and valproic acid).\textsuperscript{5}

Our results indicate better verbal memory in patients using levetiracetam monotherapy compared with patients not using AEDs. A previous longitudinal study evaluating 29 brain tumor patients on levetiracetam monotherapy reported significant decreases in Mini-Mental State Examination (MMSE) score, suggesting that cognitive functioning deteriorated.\textsuperscript{19} However, it is well known that the MMSE is limited in assessing multiple aspects of cognitive function, as opposed to the more extensive cognitive battery applied in our study.\textsuperscript{20} Furthermore, the patient population in the former study was heterogeneous (eg, meningioma, glioma, hemangiopericytoma). Corroborating our results, one study\textsuperscript{11} evaluated 293 non-tumor-related epilepsy patients on levetiracetam treatment, demonstrating significant improvements in cognitive functioning over time (median follow-up of 51 months). Another study\textsuperscript{12} reported improvements in attention and verbal fluency in 35 patients with partial epilepsy 7 weeks after start of levetiracetam treatment compared with 35 epilepsy patients who were treated with various other AEDs. Several other studies in the nontumor population have reported improvement of cognitive functioning\textsuperscript{14,15} or few or no negative cognitive effects of levetiracetam,\textsuperscript{21,22} particularly when compared with other AEDs.\textsuperscript{23–27} In addition to levetiracetam, other newer AEDs, such as oxcarbazepine and lamotrigine, have been reported to have relatively few cognitive effects on the epilepsy population.\textsuperscript{5,6,28,29}

We also report beneficial effects of valproic acid on verbal memory, although these results were obtained in post-hoc analyses and must thus be interpreted with caution. Previous reports on the effect of valproic acid on cognition are highly ambiguous. A number of studies in rats and humans have shown valproic acid to be associated with cognitive improvement in alertness, attention, and immediate recall,\textsuperscript{6} but the majority of studies report modest deterioration.\textsuperscript{5}

The mechanisms by which AEDs influence cognitive function are still the subject of research. One may expect that AEDs improve cognitive function by decreasing seizure burden. However, amply described cognitive deficits due to AED treatment, both in patients who are seizure free as well as in patients who are not, contradict this explanation.\textsuperscript{6} The effects that AEDs exert on cognition are probably explained by their influence on receptors, inhibitory and excitatory neurotransmitters, and ion channels.\textsuperscript{5} Negative effects on cognitive functioning are attributed mainly to sodium blockade, increased activity of gamma-aminobutyric acid, and decreased glutamate activity. Several studies suggest that functioning of various receptors and ion channels is altered in glioma tissue, which could contribute to cognitive deficits.\textsuperscript{30} Newer AEDs, such as levetiracetam, may affect the altered receptor and ion channels in glioma tissue and thereby improve cognitive function. Based on our findings regarding verbal memory in patients using levetiracetam, we may speculate that levetiracetam specifically promotes processes that enhance efficient storage of information. Positive effects on cognition of AEDs are attributed to inhibition of calcium-mediated cellular function (eg, phosphorylation, neurotransmitter release), reduction of glutamate release from presynaptic terminals, and psychotropic effects.\textsuperscript{6} L"{e}vetiracetam has

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Domain Predictor/Covariate} & \textbf{B} & \textbf{SE} & \textbf{Beta} & \textbf{P} \\
\hline
Valproic acid vs no AEDs & & & & \\
Verbal memory* & & & & \\
\hspace{1em} Group & 0.278 & 0.130 & 0.254 & .037 \\
\hspace{1em} Performance status & 0.023 & 0.010 & 0.275 & .025 \\
\hline
Levetiracetam vs phenytoin & & & & \\
Working memory\textsuperscript{5} & -0.519 & 0.257 & -0.278 & .049 \\
\hline
\end{tabular}
\caption{Significant post-hoc regression analyses comparing 4 groups (no AEDs, levetiracetam, valproic acid, phenytoin)}
\end{table}

\textsuperscript{*}R\textsuperscript{2} = 0.135 (P\textsuperscript{.} = .012).
\textsuperscript{5}R\textsuperscript{2} = 0.077 (P\textsuperscript{.} = .049).
a distinct mechanism of action that possibly contributes to these positive effects. It binds to the synaptic vesicle protein (SV2A) and is believed to restore the function of SV2A. Dysfunction of SV2A leads to calcium accumulation during repeated action-potential generation. Therefore, restoring the function of SV2A results in inhibition of calcium-mediated cellular function. Furthermore, levetiracetam reduces neuronal necrosis and is suggested to have a protective effect on astrocytes, which could contribute to a positive effect on cognition, as a recent study demonstrated that astrocytes play an important role in the formation and maintenance of long-term memories. In addition, it has been suggested that levetiracetam might influence the metabolism of attention and the language area.

In addition, it would be interesting to elaborate these results to other conditions of impaired memory, such as Alzheimer disease (AD) and mild cognitive impairment (MCI). As the neural substrates differ between brain tumor patients and AD/MCI patients, results in HGG patients cannot be extrapolated to other patient groups with cognitive deficits. There is some evidence, however, that effects are similar in AD patients. Cumbo and Ligori investigated the effect of levetiracetam, lamotrigine, and phenobarbital in 95 patients with epilepsy and AD. Corroborating our results, they found that levetiracetam was associated with improved cognitive performance, specifically regarding attention level and oral fluency items. Dolder and Nealy recently reviewed literature regarding anticonvulsants as a possible treatment in demented patients with behavioral disturbances, taking cognitive treatment also into consideration. They concluded that levetiracetam might play a role in the treatment of behavioral symptoms in dementia and that it appears to have less deleterious effects on cognition than other anticonvulsants, but study limitations substantially hampered the strength of such a recommendation.

Although these studies also suggest that levetiracetam may add value in patients with impaired memory, such as those with MCI or AD, more extensive efforts in this research area are required to address this issue and provide more definitive answers.

Our study consisted of a homogeneous population of HGG patients who all underwent a complete neuropsychological assessment after neurosurgery and before adjuvant treatment. This standardized procedure permitted a reliable evaluation of the effect of AED on cognitive functioning in HGG patients. However, this study has some limitations. First, because the patients were not randomized in treatment groups, bias regarding choice of medical anti-epileptic treatment could exist. Physicians choose AEDs by determining seizure type and burden, patient characteristics (eg, ability to comply with complex treatment schemes), and evidently financial aspects. However, apart from performance status, we found no statistically significant differences among relevant clinical characteristics. Performance status was therefore entered as a covariate in all analyses. Furthermore, different cohorts were used, which may have induced some form of bias. However, the study protocols in the 3 cohorts were identical, and there were no significant differences in clinical characteristics (except performance status, for which we corrected our analyses).

Third, we did not register seizure burden, dosage range, and AED serum levels. Although different dosages may be related to cognitive performance within a patient group using a particular AED, our group-level analyses are likely to minimize the effect of dosage on cognition: all groups will likely have a comparable dosage range of that particular AED. In addition, the dispersal in dosage range and serum levels by which individual patients are confronted with side effects such as poor cognition is large and variable. This makes it impossible to determine whether dosage range or serum levels affect cognition. Furthermore, comparing dosage among different AEDs poses a problem in itself.

In conclusion, our results indicate that levetiracetam does not induce additional cognitive deficits in HGG patients and even improves verbal memory function. Valproic acid also seems to improve verbal memory, while phenytoin in particular is harmful to cognition in these patients. Our findings provide arguments to consider prescribing either levetiracetam or valproic acid to epileptic HGG patients, especially those who have memory complaints. Well-designed controlled studies in brain tumor patients and non–brain tumor patients are needed to further address the potential positive influence on cognition of AEDs.

### Acknowledgments

None.

**Conflict of interest:** The sponsors were not involved in the writing of this manuscript. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. I. B. and T. J. P. report no conflicts of interest.

### Funding

M. d. G. was sponsored by an unrestricted grant from UCB Pharma. L. D. was sponsored by a grant from the Dutch Epilepsy Foundation (NEF no. 08-08). F. E. F. was supported by a research grant from the European Community’s Seventh Framework Programme under grant agreement no. 201380 (EURIPIDES). J. J. H., J. C. R., and M. K. received research support from the Dutch Epilepsy Foundation (NEF), Dutch Cancer Society (KWF Kankerbestrijding), Foundation NutsOhra and/or Foundation STOPHersentumoren.nl, and Tug McGraw Foundation and/or unrestricted grants from UCB Pharma and Sanofi Aventis. E. M. S. is sponsored by the Jacobus Stichting The Hague.
References


