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The cognitive effects of oxcarbazepine versus carbamazepine or valproate in newly diagnosed children with partial seizures

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Summary

Objective: To investigate the effect of oxcarbazepine against standard antiepileptic drug therapy (carbamazepine and valproate) on cognitive function in children and adolescents (aged 6 to <17 years) with newly diagnosed partial seizures.
Methods: A multicentre, open-label, randomised, active-control, three-arm, parallel-group, 6-month study. The primary cognitive variable, the Computerized Visual Searching Task (CVST), assessed mental information processing speed and attention. Secondary variables included additional tests assessing psychomotor speed, alertness, memory and learning, and non-verbal intelligence.
Results: Of 112 patients randomised, 99 completed the study. The dropout rate was 11.6%; 13 patients discontinued due to adverse events ($n = 5$) or unsatisfactory therapeutic effect ($n = 8$). Mean CVST time decreased in all groups, indicating an

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improvement of mental processing speed and no cognitive impairment in any treatment group. No statistically significant difference was observed between oxcarbazepine and combined carbamazepine/valproate. Analysis of secondary variables did not show statistically significant differences between oxcarbazepine, carbamazepine and valproate. Analysis of intelligence test results showed that the number of correct answers increased at end point in all groups. The percentage of patients remaining seizure free throughout treatment was comparable across all groups (oxcarbazepine 58%; carbamazepine 46%; valproate 54%; carbamazepine/valproate 50%). The most common adverse events were fatigue and headache for oxcarbazepine, fatigue and rash for carbamazepine, and headache, increased appetite and alopecia for valproate.

Conclusion: Oxcarbazepine treatment over 6 months does not display any differential effects on cognitive function and intelligence in children and adolescents with newly diagnosed partial seizures relative to standard antiepileptic drug therapy. No impairment in cognitive function was observed in any treatment group over a 6-month period.

Introduction

Children with epilepsy have an increased risk of developing cognitive impairment. Several factors contribute to this, including the effect of the seizures themselves, EEG abnormalities and psychosocial issues.[1–3] In addition, antiepileptic drugs (AEDs) may adversely affect cognitive functioning in these patients.[2,4–6] A recent survey assessing the impact of AEDs on cognitive functioning reported that 56% of patients blamed their medication, either solely (14%) or in combination with their epilepsy (42%), for their cognitive impairment.[7]

The major cognitive effects associated with AEDs in patients with epilepsy are impaired attention, vigilance, and mental and psychomotor speed.[6,8] Although these effects are usually offset by the therapeutic benefit of AEDs in seizure reduction, they are of special concern in children, as they can impact negatively on learning, school performance and psychosocial interactions.[4,9] However, there are few adequately designed clinical studies to date aimed at examining the differential effect of AEDs on cognitive function in children with epilepsy, particularly among the newer agents.[2]

Oxcarbazepine is a newer AED, structurally related to carbamazepine with a more favourable pharmacokinetic profile and an improved tolerability profile.[10,11] Clinical experience indicates that oxcarbazepine is a well tolerated and effective AED for the treatment of adults and children with partial seizures with or without secondarily generalised seizures.[12–17]

The effects of oxcarbazepine on cognitive function have previously been evaluated in two studies in healthy volunteers and in three studies in adult patients with epilepsy.[18–21] In a double-blind, placebo-controlled, crossover study in healthy volunteers,[19] the effects of two doses of oxcarbazepine (300 mg/day and 600 mg/day) on cognitive function and psychomotor performance were assessed. Oxcarbazepine improved performance on a focused attention task and increased manual writing speed, and had no effect on long-term memory processes. In a comparative study in healthy volunteers, oxcarbazepine treatment was shown to induce less cognitive slowing than carbamazepine.[22] Three comparative monotherapy studies have also evaluated the effects of oxcarbazepine on cognitive function (intelligence, learning and memory, attention, psychomotor speed, verbal span, visuospatial construction) in newly diagnosed adult patients with epilepsy compared with carbamazepine, valproate, or phenytoin.[18,20,21] In the first, an active-control study, no deterioration in cognitive function was observed in the carbamazepine, valproate, or oxcarbazepine treatment groups.[21] In the study by Aikia et al., which evaluated the effects of phenytoin and oxcarbazepine on memory, attention and psychomotor speed, no significant differential cognitive effects were found between treatments.[18] McKee et al. reported no important changes in cognitive function among patients treated with oxcarbazepine who had previously been receiving carbamazepine, valproate or phenytoin.[20] The results of these studies indicate that oxcarbazepine has no or at least minimal effects on cognitive function in adult patients with epilepsy.

However, the effects of oxcarbazepine on cognitive function have not been systematically studied in children. Carbamazepine and valproate, which are standard AEDs indicated and widely prescribed for the treatment of children and adolescents with newly diagnosed epilepsy, are considered to have a similar impact on cognitive functioning in these patients.[6] Consequently, these standard AEDs were chosen as comparators. This study aimed to investigate the

effect of oxcarbazepine against the standard AED therapy on cognitive function in children aged 6 to <17 years with partial seizures. Cognitive function was tested primarily using a test for mental processing speed and attention, and six additional tests assessing psychomotor speed, alertness, memory and learning, and non-verbal intelligence.[23–25]

Methods

Study design

This was a multicentre, open-label, randomised, active-control, three-arm, parallel-group study conducted at 21 neuropaediatric and epilepsy sites in seven European countries between December 2001 and December 2003. The study consisted of two phases: a screening phase and a 6-month open-label treatment phase. Patients were assigned to oxcarbazepine, carbamazepine or valproate in a 2:1:1 ratio. An interactive voice response system was used to automate the randomisation of patients to treatment groups and within age strata. Study medication was administered as monotherapy according to the prescribing information for the respective AED. The age limits for the study participants were selected to include paediatric and adolescent patients in accordance with the European oxcarbazepine prescribing information and the Committee for Proprietary Medicinal Products guidelines. The study was conducted in accordance with the Declaration of Helsinki.

Discussion of design

An active-control design was chosen to compare the effects of oxcarbazepine with standard AED therapy. Parallel groups were used to avoid carry-over effects. To control for the confounding effects of seizures on cognitive function during baseline, patients were only included if they experienced no more than two secondarily generalised partial seizures within the 3 months prior to study commencement. The patient population was a homogenous group of newly diagnosed patients with a localisation-related epilepsy. Randomisation was used to avoid bias in the assignment of patients to treatment, increase the likelihood that patient attributes were proportionately allocated across treatment groups, and enhance the validity of statistical comparisons. The use of an open-label study design seemed to be acceptable as the primary and secondary cognitive outcome assessments were based on an objective measurement (computerised cognitive testing).

A treatment duration of 6 months was deemed sufficient to evaluate the effects of treatment on seizures, tolerability, and cognition in previously untreated children and adolescents with partial seizures. Moreover, tests cannot be repeated before at least 6 months have passed, to avoid any learning of the tests.

Patients

Previously untreated male or female patients aged 6 to <17 years with a history of at least two unprovoked partial seizures (including all seizure subtypes of simple and complex partial seizures and partial seizures evolving to secondarily generalised seizures) were included in the study. Patients with more than two secondarily generalised tonic-clonic seizures within the 3 months prior to randomisation were excluded. In addition, patients were excluded if they had a history of clinically relevant psychiatric disorders (Diagnostic and Statistical Manual of Mental Disorders, 4th ed.), attention deficit disorder (minimal brain dysfunction in children), comorbid neurological disease (other than epilepsy), or other diseases adversely affecting cognitive abilities.

Cognitive function testing

Cognitive function (psychomotor speed and alertness, mental information processing speed and attention, memory and learning) and non-verbal intelligence were assessed by neuropsychological testing at Visits 1 (baseline) and 3 (after 6 months of treatment), or at the time of premature discontinuation, using the 'FePsy' computerised neuropsychological test battery, the Rey Auditory Verbal Learning Test (AVLT) and Raven's Standard Progressive Matrices for children. Neuropsychological testing was delayed for at least 48 h after the occurrence of a secondarily generalised seizure, and 24 h after the occurrence of a complex partial seizure. If benzodiazepines were prescribed for acute seizure treatment, testing was delayed by 5 times the half-life of the respective benzodiazepine (minimum 48 h).

Cognitive end points

Information processing speed ('mental speed') has been identified as the most susceptible cognitive function affected by AED treatment in general[6,23,26] and the resulting mental slowing is considered to be the most clinically relevant of potential affected functions in children (affecting for example school performance). Therefore, a test for assessing information processing speed was selected as the primary cognitive variable. We used the Computerized Visual Searching Task (CVST), which has been shown

to assess mental information processing speed accurately in a number of other cognitive drug studies.[26]

CVST

The CVST is an adaptation of Goldstein's Visual Searching Task, in which a centred grid pattern has to be compared with 24 surrounding patterns, one of which is identical to the target pattern. The test consists of 24 trials and gives an indication of the speed of information processing and perceptual mental strategies. The test score is the total average searching time of correct answers in seconds (variable 1).

Secondary variables included six additional cognitive tests assessing psychomotor speed and alertness (measured with a finger-tapping task and visual reaction time), mental information processing speed and attention (evaluated by binary choice reaction time) and memory and learning (assessed by recognition of word and figures and the AVLT). Intelligence was also assessed using a non-verbal test for intelligence: Raven's Standard Progressive Matrices.[25]

Psychomotor speed and alertness

The finger-tapping task measures motor speed and motor fluency for the index finger of the dominant (variable 2) and non-dominant hand (variable 3) separately, in average number of taps for five consecutive trials.

Simple reaction-time measurement was measured using visual stimuli (white square on the screen) presented at random intervals by the computer. These tests measure activation/alertness; a strong motor speed component is involved. The test score is the reaction time in milliseconds for the dominant (variable 4) and the non-dominant (variable 5) hand.

Mental information processing speed and attention

The binary choice reaction test introduces a decision component. The patient has to react differentially to a red square presented on the left side of the screen than to a green square presented on the right side. Reaction time reflects motor speed and the decision-making process. The test score is the reaction time in milliseconds (variable 6).

Memory and learning

Recognition of words and figures involved test stimuli presented simultaneously during a learning phase. Six words and four figures are presented, with a presentation time of 1 s per item. After a delay of 2 s, the screen shows one of these words/figures between distracters. The target item has to be recognised. The test score is the number correct out of 24 (variable 7 and variable 8).

The Rey AVLT measures memory span and learning strategies. Fifteen words are presented on tape (this test is not presented by computer and not part of the 'FePsy' test system) and have to be recalled on five consecutive trials. After 20 min, long-term recall is requested. The test score is the number correct out of 75 (immediate recall; variable 9) or out of 15 (delayed recall; variable 10).

Intelligence test

Intelligence is assessed using Raven's Standard Progressive Matrices.[25] The Raven's test is a short test for intelligence based on visual spatial tasks.

Neuropsychological testing of five of the seven cognitive tests was conducted with the 'FePsy' computerised neuropsychological test battery for children. The tests, test procedures, and validation of the tests (i.e. the evaluation of correlations with standard neuropsychological tests) have been described elsewhere.[24,26–28] In addition, the AVLT non-computerised neuropsychological test was used, as well as the Raven.[25] All tests control for retesting effects either by presenting parallel items at retesting or by presenting items randomly, to avoid any 'learning' of the test. Retesting effects have been reported as minimal.[24,26–28]

Efficacy and overall treatment satisfaction

Even though evaluating the efficacy of the study medication was not the primary aim of this study, the occurrence of seizures was recorded at baseline, during the open-label treatment phase, and at study completion, and classified according to the International Classification of Epileptic Seizures.[29,30] In addition, an overall assessment of treatment satisfaction among investigators, patients, and parents/carers was recorded using a 4-point scale ranging from 'poor' to 'very good'.

Safety evaluation

The safety assessment was based on the frequency of adverse events and the number of laboratory values that fell outside predetermined notable ranges. AED serum levels were not measured during this study.

Statistical analyses

The per-protocol patient population, comprising all randomised patients who received at least one dose of study medication and who performed a CVST assessment at baseline and at the completion of the 6-month open-label treatment phase, was used for the primary analysis. The intent-to-treat patient

population included all randomised patients who received at least one dose of study medication and from whom a neuropsychological measurement (any of the seven tests) was obtained before and after randomisation. Seizure frequency evaluations and overall treatment satisfaction were analysed using the intent-to-treat population. All randomised patients who received study medication were used for the safety analysis.

The primary comparison was made between the CVST results for the oxcarbazepine group and the combined carbamazepine and valproate treatment group in the per-protocol patient population. Differences between treatment groups on the CVST and cognitive end points were tested using an analysis of covariance (ANCOVA), with end point test score as the dependent variable, country and age group as factors, and baseline score as covariate. Changes in intelligence test scores (from baseline to end point) and comparisons between treatment groups were analysed using a Van Elteren test (Cochran-Mantel-Haenszel test with modified Ridit Scores) stratified by age group.

Sample size and power considerations

The sample size calculation was based on the primary cognitive variable (CVST). To have a power of at least 90% to detect a meaningful difference between treatment groups (oxcarbazepine versus standard AED) of approximately three-quarter standard deviation (as seen in previous studies with this test, assessing for example the effect of phenytoin)[4] 78 evaluable patients were necessary. Taking into account an expected 40% dropout rate, approximately 130 patients were planned for randomisation.

Results

Patient demographics and disposition

Patient demographics are presented in Table 1. Of the 112 patients randomised, 99 completed the study and 97 (per-protocol population) were eligible for the primary analysis. Due to the low dropout rate of 11.6%, recruitment was stopped after 112 patients had been randomised. Thirteen patients discontinued due to adverse events ($n = 5$) or unsatisfactory therapeutic effect ($n = 8$). Treatment groups were well balanced with respect to their baseline demographic characteristics. Age, weight, and sex distribution were comparable between treatment groups. Moreover, the distribution of seizure types was similar for the oxcarbazepine group and the combined carbamazepine/valproate treatment group (Table 1), indicating that the patient population was homogenous. Similarly, there was no difference in epilepsy type between the oxcarbazepine and combined carbamazepine/valproate treatment groups (Table 1). Mean daily doses (S.D.) during the 4 weeks prior to assessments

Table 1 Patient demographics including baseline seizure and epilepsy classification (safety population)

Characteristic	OXC ($n = 55$)	CBZ ($n = 28$)	VPA ($n = 29$)	CBZ/VPA ($n = 57$)
Male, *n* (%)	21 (38.2)	16 (57.1)	14 (48.3)	30 (52.6)
Age (years)				
Median (range)	10 (6—16)	10 (6—16)	9 (6—15)	9 (6—16)
Age group, *n* (%)				
6 to <12 years	40 (72.7)	17 (60.7)	23 (79.3)	40 (70.2)
12 to <17 years	15 (27.3)	11 (39.3)	6 (20.7)	17 (29.8)
Weight (kg)[a]				
Median (range)	37.3 (18.5—82.0)	40.2 (20.9—65.5)	33.3 (22.0—61.0)	35.5 (20.9—65.5)
ILAE seizure classification, *n* (%)				
Simple partial	23 (41.8)	9 (32.1)	12 (41.4)	21 (36.8)
Complex partial	23 (41.8)	17 (60.7)	15 (51.7)	32 (56.1)
Partial evolving into secondarily GTC	31 (56.4)	16 (57.1)	11 (37.9)	27 (47.4)
ILAE epilepsy classification, *n* (%)[b]				
Idiopathic	31 (56.4)	16 (57.1)	17 (58.6)	33 (57.9)
Symptomatic	9 (16.4)	2 (7.1)	4 (13.8)	6 (10.5)
Cryptogenic	14 (25.5)	10 (35.7)	8 (27.6)	18 (31.6)

CBZ = carbamazepine; GTC = generalised tonic-clonic; ILAE = International League Against Epilepsy; OXC = oxcarbazepine; VPA = valproate.

[a] OXC, $n = 54$; VPA, $n = 28$; CBZ/VPA, $n = 56$.

[b] Information on one patient in the oxcarbazepine group relating to epilepsy classification was not provided by the investigator.

at 6 months were 19.6 (6.4) mg/kg for oxcarbazepine, 14.4 (3.6) mg/kg for carbamazepine, and 20.7 (7.5) mg/kg for valproate.

Cognitive end points

Mean CVST time decreased in all three treatment groups (indicating an improvement in mental information processing speed) and similar CVST outcomes were found in the two age groups, indicating that there was no cognitive impairment in any treatment group. The primary end point comparison of the CVST results did not show a significant difference between oxcarbazepine and combined carbamazepine/valproate (Tables 2 and 3; $p = 0.195$). The quite large baseline imbalance in the CVST (mean values: oxcarbazepine 19.9, carbamazepine 16.7, valproate 14.7, carbamazepine/valproate 15.7) was adjusted for in the model for the end point analysis (mean values at end point: oxcarbazepine 16.0, carbamazepine 14.9, valproate 14.5, carbamazepine/valproate 14.7). A numerical benefit for the combined treatment group of 1.3 using the raw mean values is reversed to a numerical benefit of 1.1 for oxcarbazepine by applying the ANCOVA model. Due to the baseline imbalance, results have to be interpreted cautiously, but the overall conclusion remains that there were no meaningful differences between the treatment groups.

Analysis of the secondary neuropsychological variables (psychomotor speed and alertness, memory and learning, and attention) did not show any significant differences between oxcarbazepine and combined carbamazepine/valproate, or between carbamazepine and valproate (Tables 2 and 3). Analysis of the intelligence test results (Raven's Standard Progressive Matrices) showed that the number of correct answers increased at end point in all treatment groups, indicating improvement of intelligence scores. However, there were no statistically significant differences between treatment groups (Table 4).

Efficacy and overall treatment satisfaction

Although efficacy was not formally analysed in this study, the percentage of patients in the intent-to-treat population who were seizure free throughout the 6-month treatment phase was comparable across all treatment groups (oxcarbazepine 58%; carbamazepine 46%; valproate 54%; carbamazepine/valproate 50%). Assessment of overall treatment satisfaction showed that 84% of investigators, 82% of patients, and 86% of parents/carers in the oxcarbazepine group rated their treatment as

Table 2 Analysis of cognitive variables for comparison of oxcarbazepine with combined carbamazepine/valproate treatment (per-protocol population)

OXC-CBZ/VPA	Psychomotor speed and alertness					
	Finger-tapping task			Visual reaction time (ms)		
	Dominant hand	Non-dominant hand		Dominant hand	Non-dominant hand	
LS mean (95% CI)	0.8↑ (−0.5, 2.2)	0.1↑ (−1.2, 1.4)		0.6 (−27.1, 25.9)	−15.3↑ (−46.2, 15.6)	
p value	0.231	0.895		0.966	0.328	
Mental information processing speed and attention		Memory and learning				
BCRT	CVST	Recognition		Rey AVLT		
Mean BCRT (ms)	CVST (s)	Word	Figure	Immediate recall	Delayed recall	
14.1 (−24.1, 52.3)	−1.1↑ (−2.9, 0.6)	−1.2 (−2.4, 0.1)	−0.7 (−2.0, 0.6)	1.1↑ (−2.0, 4.1)	0.4↑ (−0.5, 1.4)	
0.464	0.195	0.067	0.298	0.483	0.389	

OXC = oxcarbazepine; VPA = valproate; CBZ = carbamazepine; AVLT = auditory verbal learning test; BCRT = binary choice reaction time; CVST = computerised visual searching task; LS = least square. LS mean and *p* values based upon analysis of covariance (ANCOVA).
↑ indicates that the results of oxcarbazepine group were numerically better than the combined carbamazepine/valproate treatment group.

Table 3 Analysis of cognitive variables for each treatment group (per-protocol population, $n = 97$)

	Oxcarbazepine ($n = 47$)		Carbamazepine ($n = 26$)		Valproate ($n = 24$)	
	Mean baseline value (S.D.)	Mean change from baseline (S.D.)	Mean baseline value (S.D.)	Mean change from baseline (S.D.)	Mean baseline value (S.D.)	Mean change from baseline (S.D.)
Psychomotor speed and alertness						
Finger-tapping task						
Dominant hand	48.91 (8.2)	0.15 (3.4)↑	49.13 (8.7)	−1.03 (5.0)↓	48.53 (7.3)	−0.45 (2.9)↓
Non-dominant hand	41.43 (8.1)	−0.48 (3.3)↓	42.98 (7.9)	−0.47 (3.9)↓	41.66 (6.8)	−1.05 (2.5↓)
Visual reaction time (ms)						
Dominant hand	394.6 (126.7)	−20.5 (85.5)↑	379.2 (108.0)	−7.0 (67.3)↑	362.0 (76.4)	−13.4 (48.2)↑
Non-dominant hand	431.2 (184.5)	−16.4 (96.6)↑	391.3 (104.0)	5.6 (66.3)↓	366.4 (86.8)	23.2 (81.1)↓
Mental information, processing speed and attention						
Mean binary choice reaction time (ms)	406.3 (186.5)	−21.4 (113.3)↑	416.0 (215.3)	−30.6 (181.5)↑	402.1 (138.2)	−41.4 (105.5)↑
Computerised visual searching task (s)	19.9 (12.5)	−3.9 (7.1)↑	16.7 (8.8)	−1.8 (3.8)↑	14.7 (3.4)	−0.1 (3.0)↑
Memory and learning						
Word recognition[a]	17.0 (4.0)	−0.7 (3.7)↓	17.5 (3.8)	−0.6 (3.0)↓	18.4 (3.8)	0.4 (4.0)↑
Figure recognition[b]	11.9 (3.6)	−1.4 (3.6)↓	13.0 (3.4)	−1.7 (3.3)↓	12.9 (4.3)	−1.0 (4.7)↓
Rey AVLT immediate recall[b]	45.6 (12.4)	1.2 (7.3)↑	45.5 (12.5)	0.7 (9.5)↑	43.5 (10.6)	1.3 (9.8)↑
Rey AVLT delayed recall[b]	10.6 (3.2)	−0.3 (2.8)↓	10.5 (2.9)	−0.2 (1.6)↓	10.0 (3.2)	−0.8 (3.1)↓

AVLT = auditory verbal learning test. Evaluable patients were those with observations at both baseline and end point. ↑ and ↓ indicates a trend towards improvement or deterioration respectively, based on the mean change from baseline for each cognitive variable—differences were not statistically significant.

[a] Carbamazepine, $n = 23$; valproate, $n = 23$.

[b] Carbamazepine, $n = 25$.

Table 4 Analysis of intelligence test (per-protocol population)

	Oxcarbazepine (n = 45)	Carbamazepine/ valproate (n = 45)	Carbamazepine (n = 24)	Valproate (n = 21)
Number of correct answers: change from baseline				
Mean (S.D.)	2.2 (5.20)	3.3 (4.10)	3.0 (4.02)	3.7 (4.27)
Median	2	2	2	3
Range	−9—14	−5—11	−4—11	−5—11

Changes from baseline were not statistically significant. For seven patients in the per-protocol population, either baseline and/or end of study assessments were not performed, thus the change from baseline values are missing.

'good' or 'very good', as did 77% of investigators, 73% of patients, and 80% of parents/carers in the combined carbamazepine/valproate group. This high rate of treatment satisfaction was also reflected by the low dropout rate of 12%, which was lower than the assumed 40%.

Safety and tolerability

The most frequently reported treatment-emergent adverse events (>10%) were fatigue and headache for oxcarbazepine, fatigue and rash for carbamazepine, and headache, increased appetite and alopecia for valproate (Table 5). Adverse events suspected to be drug related occurred in 30.9% of patients in the oxcarbazepine, 28.6% in the carbamazepine group, and 44.8% in the valproate group. One serious adverse event was reported for each treatment group: oxcarbazepine, activation of focus in EEG; carbamazepine, skin rash; and valproate, prolonged sedative effect. All serious adverse events were mild in severity and considered by the investigators to be unrelated to the study drugs. One patient each in the oxcarbazepine and carbamazepine treatment groups experienced an adverse event that led to treatment discontinuation, in both cases due to skin rash. In addition, one patient in the oxcarbazepine group discontinued treatment after a serious adverse event (activation of focus in EEG), which was classed as being due to unsatisfactory therapeutic effect.

Discussion

Although individual sensitivity may lead to severe cognitive effects in individual cases, most studies have not found clinically relevant effects of standard AED therapy (such as carbamazepine and valproate) in study populations.[2,6] Therefore, it is important to compare the cognitive effects of any new AED against standard agents in an equivalence design. This study was formally not an equivalence study, since the sample size for such a study would

Table 5 Most frequent adverse events (≥5% in any treatment group, sorted by frequency in oxcarbazepine) during the open-label treatment phase

Adverse event	No. of patients (%)		
	Oxcarbazepine (n = 55)	Carbamazepine (n = 28)	Valproate (n = 29)
Any adverse events	31 (56.4)	17 (60.7)	17 (58.6)
Fatigue	7 (12.7)	4 (14.3)	2 (6.9)
Headache	6 (10.9)	2 (7.1)	7 (24.1)
Rash NOS	4 (7.3)	3 (10.7)	0 (0)
Dizziness	4 (7.3)	0 (0)	0 (0)
Appetite increased NOS	2 (3.6)	1 (3.6)	3 (10.3)
Pyrexia	2 (3.6)	0 (0)	2 (6.9)
Rhinitis NOS	1 (1.8)	1 (3.6)	2 (6.9)
Abdominal pain NOS	1 (1.8)	2 (7.1)	2 (6.9)
Respiratory tract infection NOS	1 (1.8)	2 (7.1)	1 (3.4)
Pharyngitis	1 (1.8)	0 (0)	2 (6.9)
Alopecia	0 (0)	1 (3.6)	3 (10.3)
Psychomotor activity	0 (0)	1 (3.6)	2 (6.9)
Sedation	0 (0)	1 (3.6)	2 (6.9)
Influenza	0 (0)	0 (0)	2 (6.9)
Weight increased	0 (0)	0 (0)	2 (6.9)

NOS = not otherwise specified.

have been unreasonably high, but was powered in order to detect an eventually clinically meaningful difference between the treatment groups. The study presented here was conducted to evaluate systematically the effects of oxcarbazepine on cognitive functions in children aged 6 to <17 years with partial seizures. The results indicate that oxcarbazepine monotherapy over 6 months does not adversely affect cognitive function and intelligence in children or adolescents with newly diagnosed partial seizures relative to standard AED therapy; no differential effects were observed between treatment groups and none of the tests showed a deterioration of cognitive function after the 6-month treatment period relative to the untreated baseline measurements in this patient population. These results confirm previous findings from smaller studies in adult patients with epilepsy and healthy volunteers, which indicated that oxcarbazepine was not associated with cognitive impairment or intelligence, learning and memory, attention, psychomotor speed, verbal span, and visuospatial construction.[18–21]

This is the first well-controlled and adequately powered study to investigate cognitive function in children receiving oxcarbazepine using a fully validated cognitive function test battery. The study was powered to detect not only a statistically significant difference, but also a clinically meaningful difference in the primary cognitive variable of mental processing speed (CVST). As standard AEDs are available for treatment initiation in children with partial epilepsy, an active-control design was chosen to evaluate the effects of oxcarbazepine relative to standard antiepileptic monotherapy. Although the open-label design of this study may be criticised, this was acceptable in our opinion because the primary and secondary cognitive outcome assessments were based on an objective measurement (computerised testing). In addition, we believe that this approach has contributed significantly to the extremely low dropout rate (11.6%) observed in the study. Furthermore, the treatment duration of 6 months in previously untreated children and adolescents with partial seizures was considered of appropriate length to discover any possible cognitive deterioration associated with AED therapy over time. Indeed, the relatively long duration of this study (6 months' treatment), the use of an untreated baseline in newly diagnosed patients, and the use of AEDs as monotherapy are powerful factors in the design of this study.

To control the confounding effects of seizures on cognitive function during baseline, only those patients with two or fewer secondarily generalised partial seizures occurring within the 3 months preceding the study were included. Nonetheless seizure effects during the study may be a confounding factor. Seizures were well controlled throughout the study, with >50% of patients being seizure free during the 6-month treatment period, which is in line with other comparative studies of oxcarbazepine in newly diagnosed patients.[10,15,31,32] None of the comparisons between the study groups yielded statistically significant differences in the efficacy parameters. Thus, seizure frequency was not a potential interfering factor that may have confounded our results. Indeed, the valproate group had fewer patients with secondarily generalised seizures, the seizure type with most cognitive impact. Potentially, the results could therefore be biased positively for valproate.

All AEDs employed in the study were well tolerated by patients and the safety profile of oxcarbazepine was similar to that reported previously.[10,11] Only one patient (in the oxcarbazepine group) discontinued therapy because of activation of focus in their EEG. Although, carbamazepine is known to be associated with EEG changes,[33–36] only three cases have been reported following treatment with oxcarbazepine.[37]

In conclusion, the results of this study confirmed previous findings in adult patients and healthy volunteers that oxcarbazepine monotherapy has no impact on cognitive function in newly diagnosed children and adolescents with partial seizures. Oxcarbazepine did not differ from standard therapy (i.e. carbamazepine and valproate) as monotherapy over 6 months on cognitive function and intelligence in children or adolescents with newly disgnosed partial seizures. No impairment in cognitive function was observed in any treatment group over a 6-month period.

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