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Comparative neuropsychological effects of carbamazepine and eslicarbazepine acetate

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ABSTRACT

People with epilepsy are at increased risk for neuropsychological dysfunction due to multiple factors, of which the most amendable are antiseizure medications (ASMs). Antiseizure medication effectiveness is frequently determined by tolerability. In this study, we compared the neuropsychological effects of eslicarbazepine acetate (ESL) and carbamazepine immediate-release (CBZ) using a randomized, double-blind, crossover design in healthy volunteers with a 2-week titration and 4-week maintenance phase in each treatment arm (CBZ = 400 mg BID and ESL = 800 mg qAM). Neuropsychological testing was performed at the initial visit, repeated at 1st baseline nondrug condition, end treatment #1, 2nd nondrug condition one month after treatment #1, end treatment #2, and 3rd nondrug condition one month after treatment #2. Neuropsychological testing was conducted 2 h after morning dose and included computer (i.e., dual task test, selective attention test, symbol digit, verbal memory, visuospatial memory, and 1- & 2-back continuous performance) and noncomputer tasks (i.e., Medical College of Georgia (MCG) paragraph memory, Stroop, Symbol Digit Modalities Test, Profile of Mood States). z-Scores calculated from nondrug conditions were used to compare ESL and CBZ for the 23 completers. Follow-up analyses included individual test scores and distribution of individual raw means. Mean blood levels on test day were CBZ = 8.9 μg/ml and ESL = 15.3 μg/ml. Omnibus z-score was significantly better for ESL ($p = .0001$). For individual measures, executive function and selective attention tests were statistically significantly better for ESL. Individual test raw means favored ESL over CBZ on 22 of 30 measures ($p = .016$, 2-tailed sign test). Eslicarbazepine acetate demonstrated less adverse neuropsychological effects than CBZ.

1. Introduction

Antiseizure medications (ASMs) have similar efficacy for those seizure types in which they are effective. Therefore, ASM tolerability frequently determines differential effectiveness. Neuropsychological side effects are very common for ASMs and can reduce a patient's perceived quality of life [1] and even lead to ASM withdrawal. Thus, cognitive and behavioral side effects of ASMs play an important role in therapeutic decisions [2]. Eslicarbazepine acetate (ESL) is a new generation ASM that is chemically related to carbamazepine and oxcarbazepine (OXC), but with structural and metabolic differences. Eslicarbazepine acetate is rapidly hydrolyzed to eslicarbazepine; its main mechanism is blockade of voltage-gated sodium channels, but it is also a selective, low-affinity-N-Methyl-D-Aspartic acid (NMDA) antagonist [3]. Eslicarbazepine acetate has demonstrated good efficacy in adjunctive and monotherapy therapy for focal seizures with and without evolution to bilateral tonic–clonic seizures [4–8]. Eslicarbazepine acetate's cognitive effects in relation to the established ASMs are unknown.

Only one report has formally assessed the cognitive effects of ESL [9]. This investigation consisted of two single-blind parallel-group studies in a total of 56 healthy subjects. In the first study, a single dosage of 900 mg of either ESL or OXC was given. This was followed by one week of placebo, then one week of ESL 800 mg daily or OXC 300 mg BID, then one week of ESL 1200 mg daily or OXC 600 mg BID. Cognitive testing was conducted pre and 3 h post in the single dose and 1 h post dose at the end of each week. The overall treatment-emergent adverse effects (TEAEs), especially central nervous system (CNS)-related, were greater

Abbreviations: ASMs, antiseizure medications; ESL, eslicarbazepine acetate; CBZ, carbamazepine immediate-release; CNS, central nervous system; C-SSRS, Columbia-Suicide Severity Rating Scale; MCG paragraph memory, Medical College of Georgia; SDMT, Symbol Digit Modalities Test; POMS, Profile of Mood States; TEAEs, Treatment-emergent adverse events.

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for OXC with 83% of subjects reporting adverse events compared to 30% for ESL. In contrast, differences between ESL and OXC on the cognitive measures were not significant. This disparity may be related to weaknesses in the study design, which include small sample size for a parallel group design, short duration of therapy, and lack of control for repeated testing (placebo tested only after the first week). In addition, primary comparisons were for each ASM to the predose in the first single dose phase "or" to the placebo phase. Direct comparisons between ASMs were done as secondary analyses. Thus, this investigation did not adequately assess the cognitive effects of ESL.

The present study investigates the cognitive and behavioral effects of ESL compared to carbamazepine immediate-release (CBZ) in healthy subjects employing a double-blind, two-period, crossover design. The design provides robust statistical strength and controls for selection bias created by individual variability in cognitive performance. The use of healthy subjects controls for the effect of changes in seizure frequency on cognitive function. In addition, examining ASM cognitive effects in healthy subjects allows potential extrapolation of the results to other patient populations.

2. Methods

2.1. Study design

This was a randomized, double-blind, double-dummy, 2-period crossover study in healthy paid volunteers to compare differences in neuropsychological parameters after administration of ESL = 800 mg qAM or CBZ = 400 mg BID (see Table 1 for study timeline). Target dosages were chosen to be typical therapeutic dosages used in clinical practice. Carbamazepine immediate-release was employed as the comparator drug to allow results to be compared to multiple prior studies in which it was employed [10–16]. Subjects and study personnel in contact with subjects were blinded to drug randomization. An investigator who was not in contact with subjects assessed blood tests for safety purposes during the study. The subjects received ASMs with a 2-week titration and 4-week maintenance phase in each treatment arm.

2.2. Standard protocol approvals, registrations, and patient consents

The study protocol, amendments, and subject informed consent were approved by the Stanford University institutional review board (IRB). Informed consent was obtained and documented in accordance with local regulations and the principles of the Declaration of Helsinki. The clinical study was registered on www.clinicaltrials.gov (NCT02912364).

2.3. Subjects

Healthy men and women between the ages of 18 and 55 were enrolled. Exclusion criteria included: 1) the presence of clinically significant cardiovascular, endocrine, hematopoietic, hepatic, neurologic, psychiatric, or renal disease; 2) the presence or history of drug or alcohol abuse; 3) use of concomitant medications which are known to affect ESL or CBZ or the use of any concomitant medications that might affect study medications or cognitive and behavioral functions; 4) prior adverse reaction to or prior hypersensitivity to either study medication or to related compounds; 5) prior participation in studies involving ASMs; or 6) received any investigational drug within the previous thirty days. After enrollment, subjects were excluded if they had: 1) an intelligence quotient (IQ) < 70 as determined by the Peabody Picture Vocabulary Test [17]; 2) abnormal complete blood count or chemistries; 3) a positive urine drug screen; 4) the presence of HLA B*1502 in subjects of Asian descent; or 5) positive pregnancy test (obtained before initiation of each ASM). Women were required to use approved birth control methods during the study.

Following initial screening, subjects were seen for the initial visit, received informed consent, were randomized (1:1) to 1 of 2 treatment sequences: ESL/CBZ or CBZ/ESL, underwent additional screening tests, and underwent the cognitive battery to familiarize them with the tests. Then, they received each ASM for 6 weeks, which included a 2-week titration period and a one-month maintenance period. Each ASM treatment period was followed by a 3-day taper and a washout period off ASM for the remainder of the 4 weeks. During the study, subjects were not to consume alcohol or take over-the-counter medications in the 72 h preceding cognitive and behavioral testing. They were to consume a standard breakfast on the morning of cognitive testing.

2.4. Study medications

Study medications were over-encapsulated in identical capsules and administered 2 times daily in a double-dummy fashion. The accompanying packaging was identical in appearance so that neither the investigator nor the subject was able to tell whether the subject was receiving ESL or CBZ. The dosages of ESL 800 mg qAM (placebo dose given qHS) and CBZ 400 mg/day BID were chosen because they represent effective therapeutic doses [18,19]. During each titration period, matched number of capsules was given, and ASMs were titrated to a maintenance dosage as follows: 1) ESL 400 mg qAM weeks 1–2 and then 800 mg qAM; 2) CBZ 200 mg BID week 1, 200 mg q AM & 400 mg qHS week 2, then 400 mg BID. During the taper/washout period, both treatments were tapered over 3 days, followed by a 28-day washout without ASM. Study medication compliance was assessed during each treatment period. Compliance was computed at each visit by determining the

Table 1
Study timetable.

Procedure	Screening		First drug period	Taper/washout	Second drug period	Taper/washout	Final visit
Week	−1	0	1 to 6	7 to 10	11 to 16	17 to 20	20
Visit	1	2	3	4	5		6
Informed consents	X						
Complete physical & neuro exam	X						X
Brief physical exam			X	X		X	
CBC & chemistries	X		X		X		X
Pregnancy test	X[a]			X[a]			X[a]
HLA B*1502	X[b]						
ASM levels			X		X		
Cognitive & behavioral testing	X[c]	X	X	X	X		X
Study drug dispensed		X	X[d]	X	X[d]		

ASM = antiseizure medication.
[a] Done only in women of child bearing potential.
[b] HLA B*1502 testing in subjects of Asian descent.
[c] Screening tests include Peabody IQ at first visit only, then remainder of neuropsychological battery (which is repeated each testing session).
[d] Taper schedule over 3 days.

number of tablets and capsules taken relative to the number of tablets and capsules that should have been taken according to the protocol.

2.5. Neuropsychological outcome variables

The battery was selected to be sensitive to neurocognitive effects of ASMs [2,16,20,21], and included both computerized cognitive battery assessments and noncomputerized cognitive and behavioral assessments. The computerized testing battery (CNS Vitals Signs) [22] was administered first in the following order: verbal memory immediate assessment, visual memory immediate assessment, symbol digit coding assessment, shifting attention test, dual task test, one- and two-back continuous performance test, verbal memory delay assessment, and visual memory delay assessment. Domain scores for executive function and processing speed were calculated from the computerized tests to calculate z-scores for the primary outcome. The noncomputerized cognitive/behavioral tests included the following in this order: Medical College of Georgia (MCG) paragraph memory - immediate recall [23], Symbol Digit Modalities Test (SDMT; a timed graphomotor task) [24], Stroop test (a measure of concentration effectiveness and response inhibition) [25], Profile of Mood States (POMS; a checklist of adjectives describing mood states) [26], Columbia-Suicide Severity Rating Scale (C-SSRS), included as a safety measure [27], and MCG paragraph memory-delay recall assessment [23]. Testing was conducted in a fixed order, at the same time of day, and approximately 120 min after final dosing of each treatment period. Neuropsychological testing was performed at the screening visit, then prior to the initiation of the first ASM for treatment period 1, at the end of each treatment period, and at the end of each washout period after each ASM treatment (see Table 1 for a complete study timetable).

2.6. Other variables

Safety was assessed by TEAEs, vital signs, pregnancy tests, and the C-SSRS at every visit. Physical examinations and laboratory tests (hematology, chemistry) were performed at baseline, and at the end of each treatment period, and at the end of each washout period. Pregnancy tests were conducted at screening, before the 2nd ASM treatment, and end of study. For pharmacokinetic assessment, blood samples for the determination of plasma concentrations of ESL or CBZ were collected at the end of each treatment approximately 90 min after morning ASM dose. Carbamazepine immediate-release levels were conducted at the Stanford clinical lab, and blood samples were sent to an outside contract lab to obtain levels of ESL.

2.7. Statistical analyses

Statistical analyses were performed using SPSS® Version 24. Descriptive statistics of categorical and continuous variables were used to provide an overview of the study results. Individual z-scores were calculated based upon the average of the nondrug treatment conditions. They included the 1st baseline nondrug condition, 2nd nondrug condition one month after treatment #1, and 3rd nondrug condition one month after treatment #2 (i.e., visits 2, 4, and 6). Because the testing at the initial visit was used to familiarize subjects with the tests, the initial visit results were not used for the z-score calculation. Our a priori primary outcome variable was the comparison of the two ASMs on the overall neuropsychological composite z-score, calculated by averaging individual z-scores of the selected performance measures from the computerized cognitive test battery (i.e., z-scores for the domain scores for executive function and processing speed) and the noncomputerized cognitive (i.e., average of z-scores for MCG immediate, MCG delayed, SDMT, Stroop-average score) and behavioral (i.e., z-score for POMS total score) assessment scores for each ASM at the end of each 6-week treatment period. Thus, the overall z-score neuropsychological composite included: 1) computer executive function domain score, 2) computer processing speed domain score, 3) average noncomputerized cognitive scores, and 4) POMS total score. This method with a similar overall score has been employed in prior investigations [15,16,28] to allow a single direct comparison of ASMs. This approach avoids potential Type I errors from multiple statistical comparisons and Type II errors resulting from reduced statistical sensitivity as a result of correcting for multiple comparisons. Analyses of individual components of the computer and neuropsychological assessment are secondary endpoints meant to evaluate sensitivity of the primary endpoint and examine the pattern of neuropsychological effects. All other endpoints are supportive and are safety assessments. Hence, no adjustment for multiplicity was planned. P-values for these safety variables are not meant to show superiority, and thus, testing each of these variables at the $p = .05$ level without multiplicity adjustment is a more conservative approach, which is appropriate for safety assessments and for secondary analyses of the pattern of impairments. The importance of the results should be evaluated in terms of actual differences and the risk/benefits offered by the drug to the patients.

The composite z-scores for the two ASMs were compared via *t*-tests. Descriptive statistics for each of individual scores and components of the overall composite scores were presented for the nondrug condition, ESL, and CBZ. Additional secondary analyses included comparisons of the treatments across individual variables, and comparisons between the ASMs and nondrug average across individual variables were conducted using paired *t*-tests. In addition, comparisons of number of raw means favoring each ASM across individual measures were made using two-tailed sign tests. Descriptive statistics (mean, SD) were performed for the study medication plasma concentrations, and correlations of plasma levels to neuropsychological measures were conducted.

TEAEs were those events which started on or after the date of first ESL or CBZ administration, or whose severity worsens on or after the date of first administration. TEAEs were summarized descriptively by MedDRA System Organ Class and preferred term for each study medication. Comparisons of the occurrences of total and CNS-related TEAEs for the two ASMs were made using two-tailed sign tests.

2.8. Determination of sample size

Estimations based on an overall composite score from prior studies [15,16] predicted that a sample size of 30 subjects in a 2-period crossover study would provide a probability of 90% that the study detected a treatment difference at a 2-sided $p = .01$ significance level, if the true difference between the treatments was 0.370 units, assuming that the standard deviation of the difference in the response variables was 0.490. Given an estimated dropout of 30% to 40%, the planned sample size needed to enroll was 46 subjects to complete 30.

3. Results

3.1. Subjects

Patient disposition is displayed in Fig. 1. Demographics are depicted in Table 2. Dropouts were similar across both randomized groups although there were more dropouts due to TEAEs while subjects were taking CBZ (5 subjects) compared with ESL (1 subject). The five discontinuations due to TEAE for CBZ were one for dizziness & nausea; one for headache, hot flashes, & grogginess; one for fatigue, disorientation, vomiting, dry mouth, & agitation; one for upset stomach, and one for nausea, fatigue, & coordination/balance problems. The one discontinuation due to TEAE for ESL was for fatigue. See Section 3.6 below for more information on TEAEs. In Period 1, the two CBZ withdrawals for Other were due to: one lost to follow up and one demonstrated lack of effort on the tasks; the 4 ESL withdrawals for Other were due to: 3 lost to follow up and one opened the blinded capsules and became unblinded.

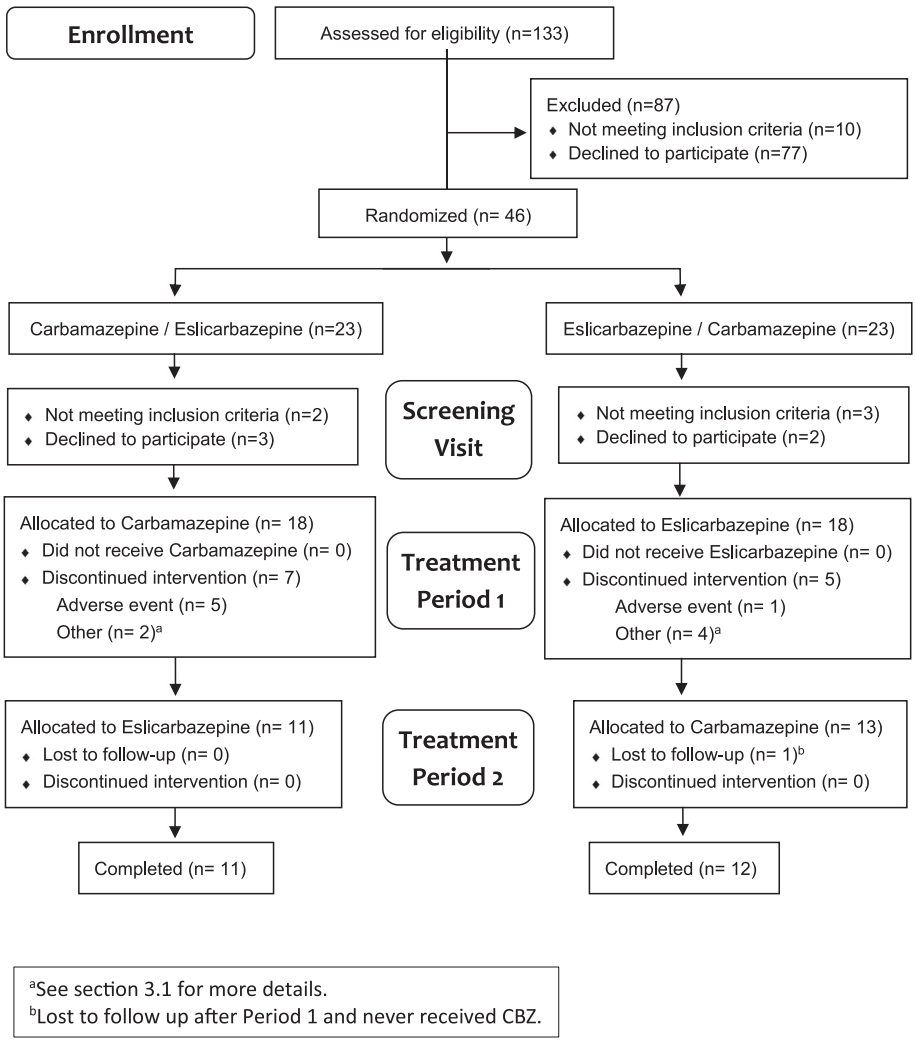

Fig. 1. Patient disposition.

3.2. Primary outcome

The primary outcome of the overall neuropsychological composite z-scores demonstrated better performance for ESL over CBZ (see Table 3).

3.3. Other neuropsychological outcomes

The summary z-score for computerized tests and the subcomponent z-score for executive function domain from the computerized test were significantly better for ESL (see Table 3). Means for individual measures are listed in Tables 4 and 5. The Selective Attention Test showed a statistically better performance for ESL over CBZ ($t(22) = 4.35$; $p = .0003$). None of the other individual variables differed statistically between CBZ and ESL or between each ASM and the nondrug state. Examining the distribution of raw means, 22 of the 30 individual computerized and noncomputerized measures favored ESL over CBZ ($p = .016$, two-tailed sign test).

Table 2
Demographics.

	Completers	All subjects
n	23	46
Gender	16 men, 7 women	28 men, 18 women
Race	5 Asian, 4 Hispanic/Latino, 14 White/Caucasian	3 African American, 13 Asian, 6 Hispanic/Latino, 24 White/Caucasian
Age: mean, (SD)	38.5 (12.7)	38.0 (12.0)
Years education: mean, (SD)	14.8 (1.8)	15.0 (1.9)
IQ estimate: mean, (SD)	97.8 (8.6)	98.6 (12.2)

na = not applicable, ns = nonsignificant, SD = standard deviation.

3.4. Plasma levels

Mean ASM plasma concentrations (SD) assessed 90- to 120-min postmorning dosage at the end of week 6 of each treatment period (combined for each drug) were 8.9 (2.7) μg/ml for CBZ (range = 4–12 μg/ml) and 15.3 (8.7) μg/ml for ESL (no established therapeutic range; trough levels at 400–2400 mg/day average 2–28 μg/ml and peak levels at 2400 mg/day average 55 μg/ml). Plasma levels for CBZ and ESL were not significantly correlated with neuropsychological outcomes. The primary outcome was not alter when covaried for ASM levels.

3.5. TEAEs

There were 63 total TEAEs of which 60 were probably drug related. Drug-related TEAEs were assessed to be related to CNS or Other (i.e., nonCNS). For CBZ, there were 41 total TEAEs of which 26 were CNS (9 fatigue, 5 lightheaded/dizziness, 4 sedation, 1 agitation, 1 disoriented, 1 incoordination, 1 memory problems, 1 naming difficulties, 1 change in pitch perception, 1 taste changes, 1 visual problems), and 15 were Other (4 headache, 4 nausea/vomiting, 2 dry mouth, 2

Table 3
Neuropsychological z-scores.

	Mean (SD) z-scores (n = 23)	Mean (CIs) z-score ESL – CBZ difference	t (df) value, p value
Omnibus[a]			
CBZ	−0.23 (0.61)	0.23 (0.13 to 0.34)	t (22) = 4.61; p = .000
ESL	0.001 (0.50)		
Average computerized			
CBZ	−0.26 (74)	0.37 (0.20 to 0.54)	t (22) = 4.56; p = .000
ESL	0.11 (0.58)		
Average non-computerized			
CBZ	−0.20 (0.69)	0.10 (−0.05 to 0.25)	t (22) = 1.39; p = .178
ESL	−0.10 (0.65)		
Computerized subcomponent z-scores			
Executive function			
CBZ	−0.32 (0.76)	0.54 (0.30 to 0.79)	t (22) = 4.60; p = .000
ESL	0.22 (0.53)		
Processing speed			
CBZ	−0.20 (0.51)	0.20 (−0.03 to 0.42)	t (22) = 1.786; p = .088
ESL	0.00 (0.40)		
Non-computerized subcomponent z-scores			
Cognitive			
CBZ	−0.15 (0.63)	0.06 (−0.05 to 0.18)	t (22) = 1.15; p = .260
ESL	−0.08 (0.58)		
POMS			
CBZ	−0.25 (−0.12)	0.13 (−0.10 to 0.36)	t (22) = 1.15; p = .264
ESL	−0.12 (−0.25)		

CBZ = carbamazepine, ESL = eslicarbazepine, SD = standard deviation, CIs = 95% confidence intervals; df = degrees of freedom.
[a] The composite z-score is calculated by averaging the individual z-scores of selected performance measures from a computerized cognitive test battery with a set of noncomputerized cognitive and behavioral assessment scores for each drug (i.e., ESL 800 mg/day and CBZ 800 mg/day) at the end of each 6-week treatment period. See Methods for details.

muscle twitches, 1 constipation, 1 hot flashes, 1 rash). For ESL, there were 19 total TEAEs of which 12 were CNS (10 fatigue, 1 memory problems, 1 visual problems), and 7 were Other (4 headache, 1 nausea/vomiting, 1 constipation, 1 hunger). Statistical differences in TEAEs (two-tailed sign test) were present for total TEAEs (41 CBZ vs 19 ESL; p = .017) and for CNS TEAEs (26 CBZ vs 12 ESL; p = .034).

3.6. Columbia-Suicide Severity Rating Scale

In responding to the C-SSRS, no subjects reported suicidal ideation.

4. Discussion

4.1. Main findings

The results demonstrate that ESL exhibits a favorable cognitive profile compared to CBZ. Treatment with ESL 800 mg/day showed statistically significantly fewer adverse neuropsychological effects than treatment with CBZ 800 mg/day (400 mg BID) in healthy subjects. The primary outcome, the omnibus z-score, was significantly better for ESL. For individual measures, executive function and selective attention

Table 4
Means (SD) of raw scores for computerized battery assessments.

Computerized battery tests[a]	Nondrug condition Average[b]	CBZ	ESL
Executive function domain[c]	52 (16)	47 (12)	56 (8)
Processing speed domain[c]	64 (15)	61 (15)	64 (12)
Verbal memory immediate – correct minus incorrect[c]	10 (5)	11 (4)	10 (5)
Verbal memory immediate – reaction time for correct[d]	790 (125)	780 (106)	800 (161)
Verbal memory delayed – correct minus incorrect[c]	9 (5)	9 (5)	9 (6)
Verbal memory delayed – reaction time for correct[d]	819 (113)	833 (137)	796 (96)
Visual memory immediate – correct minus incorrect[c]	9 (5)	8 (4)	7 (6)
Visual memory immediate – reaction time for correct[d]	879 (134)	877 (141)	867 (145)
Visual memory delayed – correct minus incorrect[c]	8 (5)	7 (6)	8 (6)
Visual memory delayed – reaction time for correct[d]	861 (145)	880 (137)	836 (135)
Symbol digit coding – correct minus incorrect[c]	63 (17)	61 (15)	64 (12)
Shifting attention test – correct minus incorrect[c]	51 (17)	47 (12)	56 (8)*
Shifting attention test – reaction time for correct[d]	943 (216)	994 (229)	944 (180)
Dual task test – correct minus incorrect[c]	30 (11)	26 (13)	27 (17)
Dual task test percent in box[c]	62 (33)	60 (34)	62 (33)
Dual task test – reaction time for correct[d]	696 (153)	709 (164)	680 (123)
Continuous performance test – 1 correct minus incorrect[c]	12 (5)	11 (5)	9 (6)
Continuous performance test – 1 reaction time for correct[d]	526 (253)	573 (373)	452 (292)
Continuous performance test – 2 correct minus incorrect[c]	8 (6)	7 (5)	8 (5)
Continuous performance test – 2 reaction time for correct[d]	573 (296)	607 (320)	639 (327)

[a] Means based on completers (n = 23).
[b] The nondrug condition average was calculated from the 1st baseline nondrug condition, 2nd nondrug condition one month after treatment #1, and 3rd nondrug condition one month after treatment #2 (i.e., visits 2, 4, and 6).
[c] Higher score is better.
[d] Lower score is better.
* SAT results: t (df 22) = 4.35, p = .000, mean difference ESL-CBZ = 0.46 (95% confidence intervals = 0.24 to 0.69).

Table 5
Means (SD) of raw scores for noncomputerized neuropsychological assessments.

Neuropsychological assessments[a]	Non-drug condition Average[b]	CBZ	ESL
MCG paragraph immediate recall[c]	34 (17)	31 (15)	33 (12)
MCG paragraph delay recall[c]	33 (18)	30 (16)	31 (13)
SDMT[c]	53 (11)	51 (10)	53 (10)
Stroop (word score)[c]	103 (20)	103 (18)	102 (20)
Stroop (color score)[c]	76 (16)	72 (13)	74 (14)
Stroop (word/color)[c]	50 (15)	47 (14)	48 (13)
POMS (total score)[d]	8 (25)	15 (32)	11 (29)
POMS (tension-anxiety)[d]	6 (5)	8 (6)	6 (6)
POMS (depression-dejection)[d]	4 (5)	5 (7)	4 (7)
POMS (anger-hostility)[d]	3 (5)	5 (5)	4 (5)
POMS (vigor-activity)[c]	17 (7)	17 (8)	15 (7)
POMS (fatigue-inertia)[d]	5 (5)	8 (7)	7 (7)
POMS (confusion-bewilderment)[d]	5 (4)	6 (5)	5 (4)

[a] Means based on completers (n = 23).
[b] The nondrug condition average was calculated from the 1st baseline nondrug condition, 2nd nondrug condition one month after treatment #1, and 3rd nondrug condition one month after treatment #2 (i.e., visits 2, 4, and 6).
[c] Higher score is better.
[d] Lower score is better.

tests were statistically significantly better for ESL. Individual raw test means favored ESL over CBZ on 20 of 28 measures, which was statistically significant. The occurrence of total TEAEs and CNS-related TEAEs were statistically greater for CBZ. Thus, ESL demonstrated less adverse neuropsychological effects than CBZ. The findings are clinically significant because greater adverse neuropsychological side effects negatively impact patients' quality of life [1].

4.2. Design issues

Multiple factors can affect cognition in epilepsy including the underlying etiology, seizures, interictal discharges, and treatments such as drugs and surgery [2]. Antiseizure medications can reduce seizures and interictal discharges, which may improve cognition and obscure adverse cognitive effects of the drug. A study with healthy volunteers avoids this potential confounding effect. Furthermore, it allows a crossover design, which is difficult in patients with epilepsy (because of risk for breakthrough seizures). In addition, prior studies of ASM cognitive effects in healthy volunteers have exhibited relative ASM effects similar to studies in epilepsy patients. The neuropsychological variables in this study are sensitive to ASMs [16]. The design in the present study is similar to multiple prior studies of ASM cognitive effects employing healthy volunteers [10–16,28], which have proven to be predictive of cognitive differences between ASMs. The cognitive testing was conducted 2 h after the morning dosage of the two ASMs (i.e., ESL 800 mg and CBZ 400 mg given BID). Since ESL would be more likely to be given qHS in the real world, there might be less daytime cognitive effects for ESL than demonstrated in our study.

4.3. Strengths

Study strengths include the double-blind, randomized, crossover design with neuropsychological measures that are sensitive to ASM effects. The design allows comparison to prior studies which have demonstrated differential ASM effects. The dosages of the two ASMs are both known clinically effective dosages, and the mean blood level concentrations on test day were in the therapeutic range for both ASMs.

4.4. Limitations

Our study has several limitations. The sample size is small, but the crossover design markedly increases the power and reduces the required sample size. The overall composite z-score was significant, and the findings of significantly more individual tests with higher means for ESL and the higher occurrence of CNS-related TEAEs for CBZ suggest that the significantly better overall composite z-score for ESL is valid.

The overall dropout rate of our study was 50%, but dropouts due to TEAEs were differentially more common for CBZ, which would bias against ESL because it might lead to less of a difference in neuropsychological tests between the completers. However, by analyzing completers, the results are similar to the real-world situation where subjects who can tolerate the ASM and would still be receiving treatment. In an intent-to-treat analysis for ASM efficacy trial for seizures, a dichotomous outcome can be employed with noncompleters conservatively counted as failures. However, cognitive effects are not dichotomous, and if the subject drops out of the study, there is no cognitive testing and thus no outcome data. Testing usually cannot be conducted when a subject drops out because the drug is frequently discontinued before testing can be conducted, or if the testing is conducted before ASM withdrawal, there will be unequal times for habituation or for test–retest intervals, which could bias results.

The present study also did not include multiple doses to allow demonstration of dose response curves. Plasma levels for CBZ and ESL were not significantly correlated with neuropsychological outcomes, which is likely due to the limited range of plasma levels since it is difficult to demonstrate plasma level effects when the levels are within the standard therapeutic ranges.

Immediate-release CBZ was employed to allow comparison to prior studies, which used this formulation as the comparator drug. It is possible that extended-release CBZ would have less cognitive effects, but there is no study directly comparing the cognitive effects of immediate- and extended-release CBZ formulations using objective neuropsychological measures. Further, a Cochran review could not confirm or refute an advantage for extended-release over immediate-release CBZ for seizure control or adverse events [29]. Thus, future studies are needed to determine the cognitive effects of extended-release vs. immediate-release CBZ.

4.5. Conclusions

This study provides evidence that subjects treated with ESL perform better on neuropsychological testing than subjects on CBZ. This information should be useful to clinicians in assessing relative risk of cognitive side effects.

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Author contributions

Dr. Meador contributed to the design of the study, analyses, and data interpretation, drafted the manuscript, approved the final manuscript for submission, accepts accountability for all aspects of the work, and controlled the decision to publish. Dr. Loring contributed to the design of the study, statistical analyses, and data interpretation, and edited the manuscript. Mr. Boyd and his company designed, programmed, and validated the computerized neurocognitive application, CNS Vital Signs, extracted and delivered the data for analysis, assisted in the analyses, and edited the manuscript. Mr. Seliger, and Drs. Razavi, Falco-Walter, and Le contributed to the conduct of the study, data interpretation, and edited and approved the manuscript.

Disclosures of conflicts of interest

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