# Cognitive effects of Lamotrigine as first line add-on in patients with localized related (partial) epilepsy

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# Cognitive Effects of Lamotrigine as First-line Add-on in Patients with Localization-related (Partial) Epilepsy

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The objective of this study is to explore clinically relevant central cognitive side effects of lamotrigine (LMT) in patients with localization-related (partial) epilepsy. Attentional processes, short-term memory, and speed factors (motor and mental speed) were investigated in an open-label first-line add-on clinical nonrandomized study with carbamazepine (Tegretol-CR) as baseline medication. Twenty-five patients were assessed at baseline (monotherapy carbamazepine) and after 5 months of add-on treatment with lamotrigine. During this 5 month period, the baseline medication was unchanged. Evidence supported the hypothesis that the cognitive profile of lamotrigine is similar to that of carbamazepine. None of the test scores showed a statistically significant decrease after adding lamotrigine, and most of the changes were in the positive direction. The most marked change was that patients showed fewer complaints after 5 months of add-on treatment with lamotrigine. **Key Words:** Cognitive function—Lamotrigine—Side effects of AEDs. 

Cognitive side effects of antiepileptic drugs (AEDs) are the adverse effects of drugs on cognitive functions such as attention, reaction speed, or memory. At first glance this type of side effect seems less dramatic than some of the idiosyncratic reactions to drugs or the acute dose-related effects. Nonetheless, a number of studies have claimed that drug-induced cognitive impairment may have a much greater impact on critical daily life functions, such as on learning behavior in children or on memory in elderly, than had hitherto been suspected (1,2). The cognitive side effects represent the long-term outcome of the chronic toxicity of the AEDs. This may contribute to the impact on daily life functioning, as the effects may increase with prolonged therapy (3).

Lamotrigine (LMT), a phenyltriazine derivative, is a relatively novel and broad-spectrum antiepileptic drug that is considered to have satisfactory seizure control efficacy in both generalized and localization-related epilepsies (4). It is absorbed rapidly and completely following oral administration (5). Its bioavailability is 95–100%, with peak concentrations occurring around 3 hours after dosing. It is subject to first-order kinetics (6) and has an elimination half-life of 22–36 hours. The metabolism of LMT is induced by enzyme-inducing anticonvulsants, such as carbamazepine (CBZ) and phenytoin, dropping the elimination half-life to around 15

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| CBZ | pretest | CBZ + LMT | posttest |
|---|---|---|---|
| steady-state treatment of >1 year with Tegretol-CR | prospective baseline | 5 months treatment with Tegretol-Controlled Release and lamotrigine | |

**Figure 1.** *First-line add-on design with CBZ as the baseline medication.*

hours. Valproate, however, inhibits its conjugation, leading to a half-life of around 60 hours (7).

Thus far, empirical information about the psychometric effects of LMT on cognitive function is almost completely lacking (8,9), although other central side effects, such as ataxia, diplopia, and blurred vision have been documented (10), and some reports have explored cognitive complaints.

The main objective of this study is, therefore, to explore possible cognitive side effects of LMT in a clinical study. Within the cognitive domain, functions that are typically sensitive to pharmacological effects of a broad range of agents were measured, i.e., attention, short-term memory, and motor and mental speed (11).

## Methods

### *Design*

Several designs are proposed for analyzing cognitive side effects of AEDs (11). Some designs may be regarded as generally uninterpretable, such as the posttest-only design, but in fact all designs appeared to have some disadvantages. Even the randomized controlled comparative monotherapy study in the newly diagnosed, often suggested to be the gold-standard design, has serious complications due to the uncontrollable effect of epileptic activity on the baseline test (which is measured when the patients are not yet on antiepileptic medication).

A satisfactory model is the first-line add-on design in which a new drug is given as an add-on to a baseline drug. The design requires that the baseline drug be a drug that generally does not affect cognitive function. The hypothesis that is tested in such a design is that adding the new drug to the baseline drug does not induce new impairments of cognitive function. Previous information on cognitive side effects of lamotrigine is lacking, so a controlled study was not considered appropriate as it would not allow us to explore all effects of the drugs in clinical practice. We therefore decided for an open-label first-line add-on design with carbamazepine as the baseline treatment. Patients with a localization-related (partial) epilepsy and on steady-state treatment with carbamazepine (Tegretol-CR) for over one year were included in the study. After a baseline assessment of cognitive functions on monotherapy of carbamazepine (pretest), the patients were given add-on treatment with 150–400 mg of lamotrigine and reassessed after a period of 5 months of treatment (posttest). The doses of the baseline medication were kept constant during the total study period of 5 months. Figure 1 gives an illustration of the design.

### *Instruments*

All patients included in this study were examined with the **FePsy** computerized neuropsychological test battery. Test presentation and response registration was controlled by a microcomputer, but the test procedure was always fully managed by a trained test technician who could adjust instructions to the individual performance level of the patient. The test program is amply discussed elsewhere (12,13). From this system, the tests used in earlier drug studies (14,15) were selected. All tests used in this study have minimal test-retesting effects that were further controlled statistically (for norms and psychometric data such as the test-retest effects of all tests; see (13–15). All tests have been proven to show sensitivity for cognitive drug effects, despite other factors such as focal lesion that may affect cognitive function (11–15).

#### Speed measures

The following tasks were used to enable differentiation between motor and mental speed:

Tasks measuring primarily motor speed:

A. The finger tapping task, measuring motor speed and motor fluency in 5 consecutive trials for the index finger of the dominant and the nondominant hand separately.
B. Simple reaction-time measurement on either auditory (800 Hz tones) or visual (a white square on the screen) stimuli that are presented at random intervals by the computer. These tests mea-

**Table 1.** *Demographic and clinical characteristics of the studied group*

| | |
|---|---|
| Gender | 18 male/7 female |
| Age | 39.4 yrs (range 22–63 yrs; sd: 10.1) |
| Average final dose of LMT | 262.0 mg/day (60.0); range: 150–400 mg/day |
| Average dose of CBZ | 992.0 mg/day (295); range 400–1600 mg/day |
| Intelligence | 105.7 (12.5); range: 82–129 |
| Type of epilepsy | localization-related (partial) epilepsy in all patients |
| Seizure types | |
| Complex partial seizures | 13 patients |
| Complex partial seizures with secondary generalization | 9 patients |
| Simple partial seizures | 3 patients |

sure activation/alertness and a strong motor speed component is involved.

Tasks measuring primarily mental speed:

A. The binary choice reaction test in which a decision component is introduced into the reaction-time measurements. The patient has to react differentially to a red square, presented on the left side of the screen, and to a green square, presented on the right side. Reaction time here reflects not only motor speed but also the (mental) decision-making process.
B. The computerized visual searching task (CVST), an adaptation of Goldstein's Visual Searching Task. A centered 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.

Tasks measuring short-term memory:

A. Recognition of words and figures in which test stimuli are presented simultaneously or serially during a learning phase. In the simultaneous form, 6 words and 4 figures are presented with a presentation time of 1 sec per item. After a delay of 2 secs the screen shows one of these words/figures between distracters. The target item has to be recognized. In the serial presentation, recall of the order of the stimuli is required.
B. The A–B Neurotoxicity Scale was used (16). This 24-item scale has proven sufficient reliability and validity in establishing patient-based cognitive complaints in relation to drug treatment.

### *Number of Patients*

Patients were eligible for this study when they were between 21 and 65 years old; when they had a diagnosis of localization-related epilepsy with well-documented epileptic seizures (complex partial or simple partial seizures, with or without secondary generalization); and when they had confirmation of the diagnosis by a recent EEG. Patients with progressive neurological disorder or psychiatric disorders were excluded. In total, 34 patients were included. Nine patients dropped out prematurely (before the second cognitive assessment). None of the patients dropped out because of side effects. The most common reasons for discontinuation were lack of effect of the drug (4 patients) and withdrawal of consent, mostly because their traveling expenses could not be reimbursed (5 patients). The group available for pretest-posttest comparisons is therefore 25 patients.

### *Statistical Analysis*

Differences between the groups were tested with the student paired T-test, using the Bonferroni procedure to correct for multiple testing. The significance level (one-tailed testing) was set at 5%. This group would yield sufficient power (17) to show effects sizes of ±0.5 sd that are generally found for phenytoin, phenobarbitone, or polytherapy (see 18).

## Results

### *Demographic and Clinical Characteristics of the Studied Group*

Most patients (18/25) were male, their average age was 39.4 years (sd = 10.1), and they had an average intelligence (105.7; sd = 12.5). All patients had a localization-related (partial) epilepsy, mostly with complex partial seizures (n = 22). Nine patients also had secondary generalized seizures. Three patients had simple partial seizures. The av-

**Table 2.** *Outcome of the trial; cognitive effects*

| | Monotherapy CBZ | CBZ + LMT | Diff[a] | *p*-value |
|---|---|---|---|---|
| Speed measures | | | | |
| Motor speed | | | | |
| Auditory reaction time; dominant hand (msec) | 244.6 (49.7) | 233.5 (43.0) | +11.1 | NS[b] |
| Auditory reaction time; nondominant hand (msec) | 245.2 (67.6) | 236.5 (58.2) | +8.7 | NS |
| Visual reaction time; dominant hand (msec) | 279.1 (52.2) | 271.2 (39.8) | +7.9 | NS |
| Visual reaction time; nondominant hand (msec) | 272.0 (54.6) | 264.3 (34.0) | +7.7 | NS |
| Finger tapping; dominant hand | 54.8 (9.1) | 53.9 (10.2) | −0.9 | NS |
| Finger tapping; nondominant hand | 52.7 (7.6) | 51.4 (8.7) | −1.3 | NS |
| Speed measures | | | | |
| Mental speed | | | | |
| Binary choice reaction time | 427.7 (110.1) | 430.3 (124.8) | −2.5 | NS |
| Binary choice errors | 4.2 (6.8) | 3.8 (6.1) | +0.4 | NS |
| Computerized visual search task | 13.1 (5.3) | 12.5 (4.9) | +0.6 | NS |
| Short-term memory | | | | |
| Recognition word simultaneously | 17.4 (4.6) | 18.0 (4.2) | +0.6 | NS |
| Recognition figures simultaneously | 12.8 (2.7) | 12.7 (3.0) | −0.1 | NS |
| Recognition words serial | 14.7 (4.9) | 15.2 (5.2) | +0.5 | NS |
| Recognition figures serial | 13.2 (3.3) | 14.8 (3.4) | +1.6 | NS |
| Neurotoxicity scale | | | | |
| Overall score | 21.8 (14.1) | 16.7 (13.8) | +5.1 | NS |

[a]Average difference between baseline (pretest) and posttest. Positive signs indicate improvement.
[b]NS, nonsignificant.

erage dose of the baseline medication, carbamazepine, was 992.0 mg/day (sd = 295 mg). LMT was given twice daily, with an average dose of 262.0 mg/day (sd = 60.0). In none of these 25 patients did idiosyncratic or acute dose-related side effects occur.

### *Cognitive Test Results*

*Speed measures:* No significant differences between baseline measures and reassessment were found after 5 months of add-on treatment with LMT. Small changes could be seen toward faster reaction times for tests measuring motor speed, except for finger tapping, which showed small nonsignificantly lower scores for motor fluency and speed.

The tests measuring mental speed reveal the same pattern: small changes in the direction of improvement, except for a small decline in reaction time for the binary choice reaction which, however, showed a more accurate performance (fewer errors) at second assessment.

*Memory tests:* The recognition tests showed small improvements in the capacity of the short-term working memory at second assessment. Three of the four tests showed improvement in performance after add-on of LMT.

*Neurotoxicity scale (subjective complaints):* The overall score showed a tendency, although not on a statistically significant level, toward fewer complaints when LMT was added to the existing medication. An additional measure that indicated the subjective evaluation of the treatment was the number of patients who requested continuation of LMT

treatment after the 5-month trial period (either as add-on therapy with carbamazepine or as monotherapy); 19 out of 25 patients met this criterion.

Adding LMT to the baseline treatment may result in improved seizure control that itself may positively influence cognitive test results. At posttest, 8 out of 25 patients were seizure-free for >3 months. This group was not responsible for the cognitive test scores, as there was no statistically significant difference between this group and the remaining patients on any of the cognitive test scores.

## Discussion

Carbamazepine is reported to be a drug without apparent cognitive side effects (11), with the exception of temporary reactions to high-peak serum levels (19). In all 25 patients, Tegretol-CR was used, a carbamazepine formulation that minimizes peak levels without altering other pharmacological and pharmacokinetic properties such as bioavailability (4). We may therefore assume that all patients were treated with a drug without cognitive side effects. No idiosyncratic, acute dose-related, or "early" side effects could have affected the baseline measurement, as all patients were on steady-state treatment for over 1 year.

Our main hypothesis was that adding LMT to the existing medication would not alter the favorable cognitive profile, suggesting that lamotrigine has a cognitive profile similar to that of carbamazepine. None of the outcome measures showed a change on a statistically significant level and 10 out of 14 changes were in the positive direction. Also, the patients reported fewer complaints on a standardized cognitive complaints scale, and almost all patients insisted on continuing with the drug after the 5-month trial period. This result could not be explained by other factors such as improved seizure control. Of course, the absence of a control group and a double-blind procedure may have introduced placebo effects, but it is most unlikely that these effects would still be active after 5 months of treatment (20).

Our study results may provide a direction for testing in future controlled studies.

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