Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial

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Summary

Background  Partial blockade of voltage-gated sodium channels is neuroprotective in experimental models of inflammatory demyelinating disease. In this phase 2 trial, we aimed to assess whether the sodium-channel blocker lamotrigine is also neuroprotective in patients with secondary progressive multiple sclerosis.

Methods  Patients with secondary progressive multiple sclerosis who attended the National Hospital for Neurology and Neurosurgery or the Royal Free Hospital, London, UK, were eligible for inclusion in this double-blind, parallel-group trial. Patients were randomly assigned via a website by minimisation to receive lamotrigine (target dose 400 mg/day) or placebo for 2 years. Treating physicians, evaluating physicians, and patients were masked to treatment allocation. The primary outcome was the rate of change of partial (central) cerebral volume over 24 months. All patients who were randomly assigned were included in the primary analysis. This trial is registered with ClinicalTrials.gov, NCT00257855.

Findings  120 patients were randomly assigned to treatment (87 women and 33 men): 61 to lamotrigine and 59 to placebo. 108 patients were analysed for the primary endpoint: 52 in the lamotrigine group and 56 in the placebo group. The mean change in partial (central) cerebral volume per year was –3·18 mL (SD –1·25) in the lamotrigine group and 0·06 mL (SD 1·10) in the placebo group (difference –3·24 mL, 95% CI –5·00 to –1·48; p=0·0002). The effect of lamotrigine on cerebral volume of patients with secondary progressive multiple sclerosis did not differ from that of placebo over 24 months, but lamotrigine seemed to cause early volume loss that reversed partially on discontinuation of treatment. Future trials of neuroprotection in multiple sclerosis should include investigation of complex early volume changes in different compartments of the CNS, effects unrelated to neurodegeneration, and targeting of earlier and more inflammatory disease.

Interpretation  The effect of lamotrigine on cerebral volume of patients with secondary progressive multiple sclerosis preserves electrophysiological function in the dorsal column in experimental autoimmune encephalomyelitis. These findings raise the possibility that partial blockade of voltage-gated sodium channels could result in neuroprotection in multiple sclerosis. We aimed to assess whether the sodium-channel blocker lamotrigine has a neuroprotective, disease-modifying effect on tissue loss and disability in patients with secondary progressive multiple sclerosis.

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either from clinical documentation or from an increase of at least 1 point in EDSS measurements. Patients were excluded if they were eligible for disease-modifying treatments under the 2001 recommendations of the Association of British Neurologists, if drugs that block sodium or calcium channels had been used in the past 2 weeks, if corticosteroids had been used in the past 2 months, or if immunomodulatory drugs had been used in the previous 6 months (1 year for mitoxantrone). Exclusion criteria were pregnancy, major systemic disease, or disabling temperature-dependent multiple sclerosis symptoms (lamotrigine treatment might make these patients vulnerable to increased disability because of axonal conduction block caused by inhibition of sodium channels).

The study was approved by the Joint University College London and University College London Hospitals Committee on the Ethics of Human Research and was monitored by an independent data monitoring and ethics committee. All participants gave written informed consent before entry into the study.

Randomisation and masking

Patients were randomly assigned (1:1) to lamotrigine or placebo via a website by minimisation, with age (≤45 years and >45 years), sex, centre (National Hospital for Neurology and Neurosurgery, London, UK, or Royal Free Hospital, London, UK), evaluating physician (JF or TH), and EDSS (≤5.5 or ≥6.0) as binary minimisation variables. Patients were given a randomisation number, which was matched to a confidential treatment number by the study pharmacist to assign patients either to lamotrigine (in a sustained-release formulation, Lamictal XR, GlaxoSmithKline) or to placebo (of identical appearance) for 24 months. Only the pharmacist was aware of treatment allocation throughout the study; treating physicians, evaluating physicians, and patients remained masked to treatment allocation.

Procedures

Patients received lamotrigine or placebo up to 400 mg daily, depending on the maximum tolerated dose achieved during an initial 8-week dose-escalation period. The primary outcome was rate of reduction in partial (central) cerebral volume over 2 years. Secondary imaging outcome measurements were whole brain volume, grey matter volume, white matter volume, mean cross-sectional cervical spinal cord area, and T1 and T2 lesion volumes. Secondary clinical outcome measurements were the EDSS; the multiple sclerosis functional independence measure; 9-hole peg test, and paced auditory serial addition test; and the multiple sclerosis impact scale.

Partial (central) cerebral volume and secondary clinical outcomes were measured at months 0, 6, 12, 18, and 24, and secondary imaging outcomes were measured at months 0, 12, and 24. Imaging was delayed for at least 6 weeks after corticosteroid treatment. Patients who discontinued the trial drug were still classified as having received either lamotrigine or placebo for the intention-to-treat analysis and followed up in the usual way.

During the trial, concern was raised from studies of experimental autoimmune encephalomyelitis that withdrawal of sodium-channel blockade could lead to clinical deterioration from a rebound of inflammation. For this reason, and also to assess the reversibility of any change of volume during treatment, we measured partial (central) cerebral volume, whole brain volume, and clinical outcomes at month 27 (3 months after stopping treatment).

Imaging was done on a Signa 1.5 T machine (GE Healthcare, Milwaukee, WI, USA) at the Institute of Neurology, London, UK. The following images were obtained: 3 mm contiguous slices from axial 2D T1-weighted spin echo (echo time 15 ms, repetition time 550 ms); 3 mm contiguous slices from axial T2-weighted dual fast spin echo (echo time 20 ms and 80 ms, repetition time 2500 ms); 124 contiguous 1·5 mm thick coronal slices from 3D T1-weighted gradient echo ( repetition time 15 ms, inversion time 450 ms, echo time 5 ms); and 64 partitions in the sagittal plane of 1 mm thick equivalents from 3D inversion recovery prepared T1-gradient echo (repetition time 15 ms, inversion time 450 ms, echo time 5 ms) of the cervical spine.

Partial (central) cerebral volume was measured on 2D T1-weighted images of six contiguous 3 mm axial slices with the most caudal at the level of the velum interpositum. A semi-automated thresholding program, the medical image display and analysis system (MIDAS) was used to segment the brain. Whole brain volume was measured using a fully automated SIENA program (FSL software, Oxford, UK) applied to axially reorientated 3D T1-weighted images. SIENA is an automated registration-based method that measures the percentage of brain volume change over time. SIENA identifies the edges of the brain and measures their change over time and does not adjust measurements to exclude brain lesions. Grey matter volume and white matter volume were measured using 3D T1-weighted sequences reformatted into a pseudoaxial plane and then registered to the 2D proton density images by use of a normalised mutual information algorithm; grey and white matter were segmented with an automated program, SPM5 (Statistical Parametric Mapping, University College London, London, UK). A lesion mask was applied to the grey matter segment to remove any misclassified voxels, and all grey matter segments were visually checked to ensure adequate segmentation and exclusion of white matter lesions. Lesion voxels were reclassified as white matter. Cross-sectional cervical spinal cord area was measured by use of an in-house algorithm based on five contiguous 3 mm pseudoaxial slices perpendicular to the spinal cord rostral to the centre of the C2/C3 intervertebral disc. T2 lesion volume and T1 lesion volume were estimated using a semiautomated local thresholding technique on in-house software (DispImage, University College London, UK).
London, London, UK). T2 lesions were contoured on the corresponding proton density image and T1 lesions were contoured on the 2D T1-weighted images.

Statistical analysis
The target sample size of 48 patients per group was based on a power of 80% to detect a treatment effect of 60% reduction in the rate of loss of partial (central) cerebral volume at the 5% significance level, on the basis of data from the placebo group of the European trial of interferon beta 1b in secondary progressive multiple sclerosis, allowing for a combined rate of loss to follow-up and non-adherence of 20%.

The primary analysis included all patients who were randomly assigned to treatment. Two per-protocol comparisons were also done: a comparison of tablet-compliant patients, defined as those who consumed at least 80% of prescribed tablets and were still being prescribed tablets at 24 months; and a serum-compliant comparison, which compared participants in the lamotrigine group who had detectable serum lamotrigine at 24 months with the entire placebo group. Adherence was assessed by counting tablet returns and by measuring serum lamotrigine concentrations at months 6, 12, 18, and 24.

For MRI measures and the multiple sclerosis impact scale, multiple sclerosis functional composite, 25-foot timed walk, 9-hole peg test, and paced auditory serial addition tests, primary comparisons were of annual rates of change over 0–24 months in a linear mixed model; the outcome measure (including baseline) was the response variable, with prespecified baseline covariate adjustment comprising all binary minimisation variables apart from treating centre. Secondary comparisons included time as a categorical variable in the model, to give cross-sectional comparisons at 6, 12, 18, and 24 months.

A time of 180 s was given for unsuccessfully completed 25-foot timed walk attempts and the inverse of the within-patient mean time for the two attempts was used as the timed walk measure. The inverse time was prespecified to improve statistical validity, because this is generally more normally distributed than the walk time and Z score, which are usually skewed; the inverse time can be interpreted as the fraction of the walk completed in one second. Finally, when modelling the rate of change of inverse time, as for the other measures above, to adjust for use of walking aids, additional terms for the number of sticks used were added to the model: this adjustment increases the precision of the between-group comparison while simultaneously reducing any bias that might result from the randomisation failing to balance level of aid use. The EDSS treatment effect was assessed by an exact test for trend for 24-month EDSS stratified by baseline EDSS.

Two post-hoc approaches were used to assess any non-linearity in partial (central) cerebral volume atrophy. First, the linear mixed model was adapted to estimate gradients separately before and after a given threshold time (eg, 12 months); a significant difference in before threshold versus after threshold gradients is evidence of non-linearity over the whole period. Second, a quadratic term in time was added into the estimating model, with significance (at 5%) of the quadratic term coefficient being evidence of a curved, non-linear trajectory. Analyses were done in Stata 10.1 and SAS 9.1.

This study is registered with ClinicalTrials.gov, NCT00257855.

Role of the funding source
The study was funded by the Multiple Sclerosis Society of Great Britain and Northern Ireland and sponsored by University College London. Neither the funding body nor the sponsor had any involvement in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication. RK had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Results

Patients were recruited between January and December 2006, and final assessments were done in January 2009. 120 participants were randomly assigned to receive lamotrigine (n=61) or placebo (n=59; figure 1). The lamotrigine and placebo groups were similar for all baseline variables (table 1). 12 patients (nine in the lamotrigine group and three in the placebo group) were lost to imaging follow-up, leaving 108 who had imaging for the primary outcome at 24 months (52 on lamotrigine and 56 on placebo). 16 patients (11 on lamotrigine and five on placebo) withdrew from treatment but continued to be followed up. The combined rate of loss to follow-up and withdrawal from treatment was 23%.

The mean change in partial (central) cerebral volume per year was –3·18 mL (SD –1·25) in the lamotrigine group and –2·48 mL (–0·97) in the placebo group (difference –0·71 mL, 95% CI –2·56 to 1·15; p=0·40; table 2). Partial (central) cerebral volume seemed to decline more steeply in the lamotrigine group during the first 12 months (figure 2) and the cross-sectional difference in volume between the groups at 18 months was –2·17 mL (95% CI –4·71 to 0·40; p=0·09).

There was no difference between groups in the rate of loss per year of whole brain volume, grey matter volume, or cross-sectional cervical spinal cord area, or in the increase of T1 lesion volume or T2 lesion volume (table 2). The lamotrigine and placebo groups did not differ in the numbers of new and enlarging T1 lesions (ratio 1·13; p=0·74) or T2 lesions (0·94; p=0·87) over 24 months. However, both whole brain volume and white matter volume were lower in the lamotrigine group than the placebo group at 12 months (difference: whole brain volume –0·28%, 95% CI –0·54 to –0·02; p=0·03; white matter volume –3·55 mL, –6·23 to –0·88; p=0·01). There were no significant differences at 24 months (data not shown).

The lamotrigine group and the placebo group did not differ in the mean change in EDSS between baseline and 24 months (p=0·73; table 2) or in decline of the multiple sclerosis functional composite (p=0·88), paced auditory serial addition test (p=0·52), 9-hole peg test (p=0·90), or multiple sclerosis impact scale (p=0·50). The mean annual change in the inverse of the 25-foot timed walk was –0·0035 s⁻¹ in the lamotrigine group and –0·0098 s⁻¹ in the placebo group (p=0·022). This translates to an annual rate of reduction of walking speed that was 0·0063×25=0·16 feet/s less in the lamotrigine group than in the placebo group. The beneficial effect in the lamotrigine group remained significant after a post-hoc sensitivity analysis of the possible influence of missing data points. (data not shown). The adjusted 24-month difference in the inverse of the 25-foot timed walk was 0·013 s⁻¹ between the lamotrigine and placebo groups (95% CI 0·0022–0·0243; p=0·02).

At 24 months, 31 of 52 patients receiving lamotrigine (mean dose 78 mg) and 45 of 56 receiving placebo (mean dose 240 mg) were tablet compliant (χ² p=0·018). 25 of 52 patients in the lamotrigine group were serum compliant (mean serum concentration 14·1 mg/L [SD 8·6]). In a post-hoc exploratory analysis, patients with a lower baseline EDSS tolerated a higher mean serum lamotrigine concentration (p=0·03).

Partial (central) cerebral volume was lower in the lamotrigine group than in the placebo group in the serum-compliant per-protocol comparison at 18 months (difference –3·60 mL; p=0·04) and at 24 months (–2·87 mL; p=0·05). In the tablet-compliant per-protocol comparison, the difference between groups was –3·26 mL (p=0·15) at 18 months and –1·36 mL at 24 months (p=0·55).

The difference in annual rate of decline in partial (central) cerebral volume between the lamotrigine group and the placebo group was –0·76 mL (p=0·47) in the per-protocol tablet-compliant comparison and –1·38 mL (p=0·07) in the serum-compliant per-protocol analysis. For whole brain volume, the annual difference between groups was –0·15% (p=0·10) in the tablet-compliant per-protocol analysis and –0·05% (p=0·61) in the serum-compliant per-protocol analysis. For white matter volume, the annual difference was 0·13 mL (p=0·89) in the tablet-compliant analysis and –0·57 mL (p=0·62) in the serum-compliant analysis. Finally, the difference in the inverse of the 25-foot timed walk annual rate between the lamotrigine group and the placebo group was 0·0081 s⁻¹ year⁻¹ (p=0·01) in the tablet-compliant analysis and 0·0049 s⁻¹ year⁻¹ (p=0·17) in the serum-compliant analysis.

Two exploratory longitudinal models to assess non-linearity of partial (central) cerebral volume gave similar...
intention-to-treat comparison, the gradient of volume loss was greater in the lamotrigine group before (–283 mm³/month) than in the placebo group (–6·05 mm³/month) (p=0·03). Similar results were found in the lamotrigine group by tablet-compliant and serum-compliant per-protocol comparisons (data not shown). By intention-to-treat comparison, the gradient of volume loss was greater in the lamotrigine group before (–283 mm³/month) than after (–66 mm³/month) a 12-month so-called pivot (p=0·04). The gradient remained constant at –140 mm³/month throughout in the placebo group. Similar gradient changes were found in the active group for a 12-month pivot in the serum-compliant per-protocol comparison and for a 6-month pivot in the tablet-compliant per-protocol comparison. 69 patients (37 in the lamotrigine group and 32 in the placebo group) were available for follow-up at month 27. In the longitudinal model, by intention-to-treat comparison, there was a change of gradient in the lamotrigine group of 620 mm³/month (p=0·04) after compared with before a 24-month pivot, indicating a change from volume loss to volume gain in the group. Similar gains of volume were found in the tablet-compliant and serum-compliant per-protocol comparisons. Volume continued to decline slowly and linearly in the placebo group after treatment was withdrawn (data not shown).

Treatment with lamotrigine was associated with more rashes (p=0·03), gastrointestinal disturbances (p=0·10), and transient, dose-related deterioration of mobility (p=0·001) than placebo (table 3). These adverse events occurred as the dose of drug was escalated during the first 2 months in 35 of 40 (88%) of those affected, and reversed promptly when the daily dose was reduced by 25–50 mg (data not shown).

The assessing physician guessed correctly whether participants were in the placebo or lamotrigine group for 68 of 120 patients (p for the null hypothesis that the assessing physician guessed the allocation to placebo versus lamotrigine correctly in 50% of patients=0·17).

Discussion
In this phase 2 clinical trial, we have tested for the first time whether partial blockade of voltage-gated sodium channels is neuroprotective in secondary progressive multiple sclerosis. We did not observe a neuroprotective effect of treatment with lamotrigine. However, further analysis of secondary imaging outcomes and exploratory analyses of the primary outcome suggested that use of lamotrigine was associated with complex brain volume changes: treatment did not affect grey matter volume loss, but there seemed to be a greater loss of white matter volume than in the placebo group; treatment led to greater loss of partial (central) cerebral volume, white matter volume, and whole brain volume than in the placebo group during the first 12 months; and partial (central) cerebral volume and whole brain volume began to increase again when treatment was stopped. These findings suggest that lamotrigine has a selective effect on white matter but not on grey matter, which is consistent with suggestions that the mechanisms of tissue injury might be different in these two compartments.20,21

The overall rate of loss to follow-up and withdrawal from treatment was 23%, but non-adherence in the lamotrigine group rose to 40–50% when tested using tablet returns and serum lamotrigine concentrations, although interindividual differences in drug metabolism could have contributed to the variations in lamotrigine concentrations. This high rate of non-adherence reduces
the statistical power of the study, but the interpretation of our results is supported by the consistency among the intention-to-treat, serum-compliant per-protocol, and tablet-compliant per-protocol comparisons.

Increased loss of brain volume—termed pseudo-atrophy—has been described in the first few months of treatment with some immunomodulatory drugs\textsuperscript{22–25} and is associated with reversible fluid shifts or a reduction of inflammation,\textsuperscript{26} as indicated by lower rates of relapse and of T1 and T2 lesion activity. The loss of volume we describe developed more slowly than that in other studies;\textsuperscript{22–26} our exploratory analyses suggested that lamotrigine caused greater loss of partial (central) cerebral volume over at least 6–12 months compared with placebo, and there was no effect of treatment on relapse rates or lesion activity. Therefore, the greater volume loss associated with lamotrigine might be caused by a deleterious effect on cerebral tissue—that is, increased axonal loss. However, the volume loss in the lamotrigine group reversed partly when treatment was withdrawn, and treatment did not worsen the deterioration of any of the clinical outcomes. Thus, although treatment was associated with dose-related deterioration of ambulation, this effect reversed promptly when the dose of lamotrigine was reduced, and was therefore most likely to be related to reversible axonal conduction block. A higher EDSS at entry was associated with a lower mean concentration of lamotrigine, suggesting that people with secondary progressive multiple sclerosis who have significant pre-existing disability might be particularly sensitive to such conduction block, and this is consistent with the reduced expression of sodium channels in chronically demyelinated axons.\textsuperscript{27} Conduction block might also help to explain why lamotrigine was tolerated poorly in this trial compared with previous reports of its use in trigeminal neuralgia in multiple sclerosis.\textsuperscript{28} By contrast with this initial and reversible treatment effect, deterioration of the 25-foot timed walk was less in the lamotrigine group than in the placebo group. This positive outcome must be treated with caution and not over-interpreted, although comparisons of different outcome measurements in primary progressive multiple sclerosis suggest that the 25-foot timed walk might be the most responsive of the clinical endpoints we used.\textsuperscript{29}

Taken together, our findings suggest that several additional potential mechanisms might have contributed to the greater early volume loss associated with lamotrigine treatment compared with placebo. First, the high rate of non-adherence in the lamotrigine group and the consequent effects on volumes measured after an initial lag period might have contributed to volume loss apparently plateauing in the second year. However, this effect is likely to be small because there were similar volume changes in the serum-compliant and tablet-compliant comparisons. Second, sodium-channel blockade could decrease cell volume by reducing the entry of sodium ions and water. This effect would be expected to have a rapid onset, and
Inflammation and axonal degeneration are potential mechanisms of this unanticipated treatment. Sodium-channel blockade might have reduced the extent of axonal injury, and volume loss in the lamotrigine group might have plateaued later in the trial because the phagocytic and inflammatory processes that occur secondary to axonal degeneration subsided. The presence of white matter lesions can affect tissue volume measures, particularly the measurement of grey and white matter volumes, when automated image analysis algorithms such as SIENA and SPM are used. We therefore reclassified lesions as white matter when using SPM5 for grey and white matter segmentation. Even with this adjustment, slight lesion effects have been observed, with larger lesion loads associated with higher grey matter volumes and lower white matter volumes. This might have led to a slight underestimation of grey matter atrophy and an overestimation of white matter atrophy but is unlikely to have had much effect on our results, in which grey matter atrophy was predominant. The difference in white matter volume changes between the study groups should also not have been affected because the lesion volume changes in each group were similar and small.

Several other implications of our findings should be considered in the design of future trials of neuroprotection. First, the limited tolerability of lamotrigine and the targeting of secondary progressive multiple sclerosis might both have contributed to the negative outcome. Trials of sodium-channel blockade might therefore focus on earlier disease, because sodium-channel blockade seems to be tolerated better in less disabled participants; the mechanisms of axonal damage in relapsing disease might also be more similar to those in the inflammatory experimental models from which this strategy arose. Also, in trials of neuroprotection in which brain volume is an outcome measure, the potential effects on mechanisms other than neuroprotection per se should always be kept in mind. These effects could be overcome by including a run-in period before comparing structural changes in the lamotrigine and placebo groups, and adjusting the sample size and trial duration accordingly. A better understanding of the mechanisms of the associated volume changes would be useful when choosing the run-in period. Our analyses suggest that lamotrigine produces greater loss of partial (central) cerebral volume than placebo during about the first 12 months. Notwithstanding these caveats, data and expert consensus support the use of brain volume measurement in investigation of potential new neuroprotective treatments. Finally, the possibility that different drugs might have selective effects on different compartments within the CNS suggests that, despite the additional workload, volumetric imaging measurements should continue to be done on not only the whole brain, but also the white matter, grey matter, and spinal cord.

In conclusion, the results of this clinical trial suggest that sodium-channel blockade does not prevent loss of cerebral or spinal cord volume over 24 months, but has complex effects on cerebral volume, and might affect the progression of the 25-foot timed walk. Our results could be useful in the selection of drugs for and the design of future clinical trials and to encourage further work on ion channel modulation as a potential neuroprotective strategy in multiple sclerosis.

Contributors
RK was the principal investigator and DHM was the imaging investigator. DRA did the statistical plan and the data analysis. JF and TH recruited patients, did the investigations, follow-up, and data acquisition, and assisted with data analysis. KJS, DRA, RB, JC, RACH, RK, and DHM contributed to the concept and design of the study. RK wrote the first draft and all the authors contributed to and approved the final version.

Conflicts of interest
RK has received honoraria from Biogen Idec, Merck Serono and MS Therapeutics for participation in scientific advisory boards, and travel or accommodation expenses have been covered by Biogen Idec, Merck Serono, and Teva. KJS has received consultancy fees from Merck Serono, and has received support from the Brain Research Trust for preclinical work on sodium-channel blockade in inflammatory neuropathy. RB has received honoraria from Merck Serono for participation in advisory boards, and travel or accommodation expenses have been covered by Biogen Idec and Merck Serono. JC has received consultancy fees from Biogen Idec. RACH has received consultancy fees from Octapharma, Baxter, LFB, Talecris, and Biogen Idec, and travel or accommodation expenses have been covered by Talecris and Baxter. For DHM, University College London Institute of Neurology has received payments for membership of multiple sclerosis trial advisory boards of Biogen Idec, Bayer Schering, GlaxoSmithKline, and Novartis; payments for consultancies with Biogen Idec, GlaxoSmithKline, and Novartis; honoraria from Biogen Idec, GlaxoSmithKline, Novartis, the National Institutes of Health, and the University of Texas Health Science Center;
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