Safety and efficacy of lithium in combination with riluzole for treatment of amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial

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Summary

Background **In a pilot study, lithium treatment slowed progression of amyotrophic lateral sclerosis (ALS). We aimed to confirm or disprove these findings by assessing the safety and efficacy of lithium in combination with riluzole in patients with ALS.**

Methods **We did a double-blind, placebo-controlled trial with a time-to-event design. Between January and June, 2009, patients with ALS who were taking a stable dose of riluzole for at least 30 days were randomly assigned (1:1) by a centralised computer to receive either lithium or placebo. Patients, caregivers, investigators, and all site study staff with the exception of site pharmacists were masked to treatment assignment. The primary endpoint was the time to an event, defined as a decrease of at least six points on the revised ALS functional rating scale score or death. Interim analyses were planned for when 84 patients had been allocated treatment, 6 months later or after 55 events, and after 100 events. Analysis was by intention to treat. The stopping boundary for futility at the first interim analysis was a p value of at least 0·68. We used a log-rank test to compare the distributions of the time to an event between the lithium and placebo groups. This trial is registered with ClinicalTrials.gov, NCT00818389.**

Findings **At the first interim analysis, 22 of 40 patients in the lithium group had an event compared with 20 of 44 patients in the placebo group (log rank p=0·51). The hazard ratio of reaching the primary endpoint was 1·13 (95% CI 0·61–2·07). The study was stopped at the first interim analysis because criterion for futility was met (p=0·78). The difference in mean decline in the ALS functional rating scale score between the lithium group and the placebo group was 0·15 (95% CI –0·43 to 0·73, p=0·61). There were no major safety concerns. Falls (p=0·04) and back pain (p=0·05) were more common in the lithium group than in the placebo group.**

Interpretation **We found no evidence that lithium in combination with riluzole slows progression of ALS more than riluzole alone. The time-to-event endpoint and use of prespecified interim analyses enabled a clear result to be obtained rapidly. This design should be considered for future trials testing the therapeutic efficacy of drugs that are easily accessible to people with ALS.**

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Introduction

Amyotrophic lateral sclerosis (ALS) is a rare, progressive neurological disease that has high socioeconomic impact because of the young age at onset (40–60 years), the extent and duration of disability, and the cost of long-term care for patients. A pilot study in Italy reported slowing of neurological decline in patients with ALS treated with lithium carbonate and riluzole, as measured with the ALS functional rating scale revised (ALSFRS-R), decline in forced vital capacity, and increased survival.[1] In this pilot study, lithium was tested as a drug to induce autophagy at a serum concentration range of 0·4–0·8 mEq/L.[1,2]

Both autophagy and the proteasome are important for the clearance of aggregate-prone proteins, such as mutant superoxide dismutase 1, mutant huntingtin, and α synucleins.[3,4] Lithium was tested in animal models and people with ALS because of its ability to induce autophagy.[1,2] Lithium pretreatment protected cultured neurons from glutamate-induced, NMDA receptor-mediated apoptosis.[5] G93A mice treated with lithium survived longer than G93A mice treated with saline.[1,6,7] The number of autophagic vacuoles in spinal cord sections was increased in the G93A mice treated with lithium compared with those treated with saline; there was also increased clearance of α synuclein, ubiquitin, and superoxide dismutase 1, which is consistent with the theory that lithium induces autophagy.[1,2] In rats with thoracic spinal cord transection or contusion injuries, inactivation of glycogen synthase kinase-3 with lithium improved sprouting of descending corticospinal and serotoninergic axons in caudal spinal cord and promoted locomotor functional recovery.[8] Lithium enhanced neuronal differentiation of neural progenitor cells in vitro and after transplantation into the avulsed ventral horn of adult rats by inducing the secretion of brain-derived neurotrophic factor.[9] Filimonenko and colleagues[10] found that clearance of TAR DNA binding protein, the major cytoplasmic inclusion in patients with sporadic ALS and

in a subset of patients with familial ALS, is dependent on activation of autophagy, which is disrupted by mutation of endosomal sorting complexes required for transport.

Although the effect of lithium in the pilot study was substantial,[1] only 16 patients received lithium, patients were not masked to treatment assignment, and at study entry the cohort enrolled in the study seemed to have more slowly progressive disease than the general ALS population. Despite these limitations, the promising results in this pilot study combined with the preclinical data supporting the use of lithium as a potential treatment for ALS warranted further investigation. Furthermore, an increase in off-label use of lithium in patients with ALS has been noted in many ALS clinical centres, presumably because lithium is readily available by prescription and the results of the pilot study generated intense interest in lithium treatment.

We aimed to assess the safety and efficacy of lithium in combination with riluzole in patients with ALS.

Methods

For the **trial protocol** see http://www.nealsconsortium.org/nealsclinicalresearch_lithium_riluzole_ALS.html

Patients

We did a randomised, double-blind, placebo-controlled trial of lithium in patients with ALS. From January to June, 2009, patients were enrolled at 21 clinical sites (11 in the USA and ten in Canada) from the Northeast ALS (NEALS) and Canadian ALS (CALS) consortia.

Patients were eligible if they were aged 18 years or more, had familial or sporadic ALS diagnosed as clinically possible, laboratory-supported probable, probable, or definite according to the World Federation of Neurology El Escorial criteria,[11] and had been on a stable dose of riluzole for at least 30 days before screening. Inclusion criteria were the ability to provide informed consent and comply with study procedures; disease duration of less than 36 months from symptom onset; slow vital capacity greater than 60% predicted value for sex, height, and age; serum creatinine less than 1·5 mg/dL (133 μmol/L); normal thyroid function for at least 3 months; absence of or inactive psoriasis for at least 30 days before screening; ability to travel to the study site; and fluency in English, Spanish, or French (Canadian). Women of childbearing potential could be included if they were using adequate birth control and a screening pregnancy test was negative. Exclusion criteria were known sensitivity or intolerability to lithium; exposure to lithium within the past 90 days; exposure to any investigational drug within the past 30 days; use of digoxin or iodide salts; malnourishment, dehydration, or a sodium-free diet; substance misuse within the past year; an active significant medical disorder (cardiac, pulmonary, renal, hepatic, endocrine, haematological, active malignancy, or infectious disease) or psychiatric disease (psychosis or untreated major depression within 90 days of screening visit); AIDS or AIDS-related complex; being pregnant or breastfeeding; thyroid stimulating hormone more than 20% above the upper limit of 5·50 μIU/mL); or significant cardiac conduction abnormality identified on screening electrocardiogram.

See **Online** for webappendix

All enrolling sites had institutional regulatory board or research ethics board approval, and all patients provided written informed consent before the start of treatment.

Randomisation and masking

Patients were assessed for eligibility at the screening visit. Eligibility was confirmed by site principal investigators via an electronic signature in an electronic data-capture system, and the patients were randomly assigned to a three-digit randomisation code number in the electronic data-capture system. The biostatistics centre at Massachusetts General Hospital used the statistical software package R to generate the randomisation sequence, which was used to allocate treatment to each patient according to their treatment number.

Patients were randomly assigned (1:1) to receive lithium or placebo. Randomisation was stratified by site to ensure a balanced number of patients receiving lithium and placebo at each site. A list of three-digit numbers was generated for each site and was listed alongside the list of randomly allocated pairs of lithium and placebo codes. This algorithm generated a randomisation sheet unique for each site that was then sent to each site pharmacist (unmasked). The three-digit randomisation code numbers assigned to each patient were also available in the electronic data-capture system. The three-digit site number followed by the three-digit randomisation number made up the patients' six-digit ID numbers. The unmasked site pharmacist assigned the treatment by matching the randomisation number to a corresponding treatment from the randomisation code sheet. The site pharmacist then dispensed either lithium carbonate or placebo according to the site-specific randomisation sheet.

Patients, caregivers, all site study staff with the exception of site pharmacists, and investigators were masked to treatment assignment.

Procedures

Patients returned for the baseline visit (week 0) within 21 days of the screening visit. Vital signs, weight, ALSFRS-R (the summed score of 12 functional and respiratory items rated on a scale of 0–4),[12] ALS-specific quality of life (ALSSQOL), quick inventory of depressive symptomatology self-report (QIDS-SR_{16}), and slow vital capacity were assessed at the baseline visit. Each site investigator, clinical evaluator, and research coordinator was trained on study procedures. Site evaluators were NEALS certified to use the ALSFRS-R and assess the slow vital capacity and met reliability criteria established by NEALS (webappendix). Outcome measure training, compliance, and study monitoring for the trial were done by the NEALS outcome measures and monitoring centre at the State University of New York Upstate Medical University (NY, USA). The Massachusetts General Hospital Biostatistics Department did the randomisation, statistical plans, and analyses for

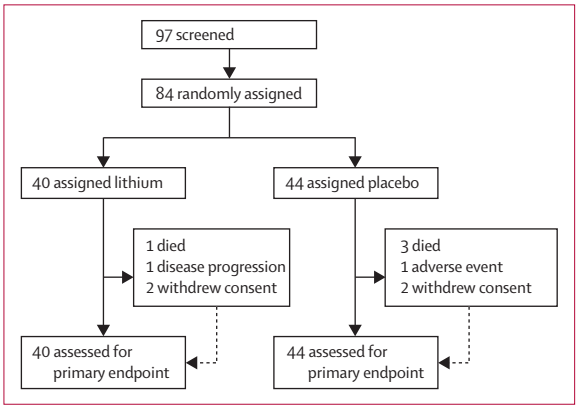

Figure 1: **Trial profile**

	Lithium (n=40)	Placebo (n=44)
Age (years)	58·3 (10·2)	55·5 (11·9)
Men	30 (75%)	24 (55%)
White	39 (98%)	42 (95%)
Family history of amyotrophic lateral sclerosis	3 (8%)	1 (2%)
Time from symptom onset to diagnosis (years)	1·1 (0·6)	1·0 (0·5)
Time from symptom onset to baseline (years)	1·6 (0·6)	1·7 (0·7)
Limb onset	34 (85%)	33 (75%)
Body mass index	26·6 (3·7)	26·2 (4·6)
Maximum slow vital capacity (predicted percentage)	94·0 (18·1)	86·9 (16·9)
ALSFRS-R score	38·4 (4·6)	36·5 (5·7)
ALSSQOL score	417·8 (70·7)	425·2 (81·4)
QIDS-SR_{16} score	6·6 (2·7)	6·3 (4·2)

Data are mean (SD) or number (%). ALSFRS-R=amyotrophic lateral sclerosis functional rating scale revised. ALSSQOL=amyotrophic lateral sclerosis-specific quality of life. QIDS-SR_{16}=quick inventory of depressive symptomatology self-report.

Table 1: **Demographics and baseline characteristics**

the study. The steering committee and an independent data and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke monitored the safety, data integrity, and conduct of the trial.

Lithium carbonate was purchased from Apotex (Toronto, Canada) and dispensed as 150 mg capsules. Apotex provided matching placebo capsules in the same shell. Patients were initially given three capsules of the study drug per day: one in the morning and two in the evening. Drug concentrations were measured at each inpatient visit and the drug was titrated to achieve a serum lithium concentration of 0·4–0·8 mEq/L, which matches the range used in the Italian pilot study.[1] Lithium concentrations were recorded for all patients at each visit 7–13 h after the last dose. Patients were instructed to take the evening dose of the study drug the day before the study visit at a time that would ensure that the last dose was taken 7–13 h before the draw; this information was provided in writing on the consent form. Any concentrations recorded outside the time window were remeasured. Lithium doses were adjusted centrally by an unmasked drug monitor (JS) and were not available to site personnel. If concentrations were less than 0·4 mEq/L, dose was increased by one capsule per day. For patients taking an odd number of capsules, the additional capsule was taken in the morning; for those taking an even number of capsules, the extra capsule was taken in the evening. If concentrations were between 0·8 mEq/L and 1·2 mEq/L, the dose was decreased by one capsule in the evening for patients taking an odd number of capsules and in the morning for those taking an even number of capsules. For patients with concentrations greater than 1·2 mEq/L, treatment was suspended and lithium concentrations were tested 3–5 days later, at which time treatment was either restarted at half the previous dose, if lithium concentrations were below 0·4 mEq/L, or was permanently discontinued, if concentrations were 0·4 mEq/L or more. To maintain masking of patients and investigators throughout the study, sham dose modifications were done for patients assigned to placebo.

During the study, site personnel were instructed to fill in case-report forms in the electronic data-capture system within 48 h of each visit. An edit checking and data clarification process ensured accuracy and completeness of the database. The system automatically created electronic queries on behalf of the data manager if saved forms contained data that were out of range, out of time window, missing, or not calculated correctly. The data manager identified the errors in the electronic data-capture system by use of electronic logic checks, and the study monitors identified errors by direct visualisation and comparison of data entered into the system with the source documents. A medical reviewer was responsible for reviewing all adverse events and associated study data remotely via the electronic data-capture system for accuracy and consistency. Any inconsistent or questionable data points were queried with the site personnel and followed up by the study monitors, data managers, and project manager as needed.

The primary outcome was time to an event, defined as a decrease of at least six points from baseline on the overall ALSFRS-R score or death. After a decrease of at least six points on the ALSFRS-R was reported, patients assigned to placebo were switched to lithium, and those assigned to lithium continued receiving lithium. All patients remained masked to treatment unless circumstances meant it was necessary to inform a patient of their treatment allocation.

The amount of decline on ALSFRS-R that defines the time to event was not known to the patients. The ALSFRS-R questionnaire was administered by the clinical investigators, but the total score was not tallied and the scores from previous visits were not available in the electronic data-capture system. The local study-site staff and all personnel at the coordination centre and site management centres were masked to total ALSFRS-R scores from all patients and date of transition to active study drug for those initially assigned to placebo.

Secondary endpoints were changes in the ALSFRS-R,[12–14] slow vital capacity, ALSSQOL,[15] and QIDS-SR_{16},[16,17] and

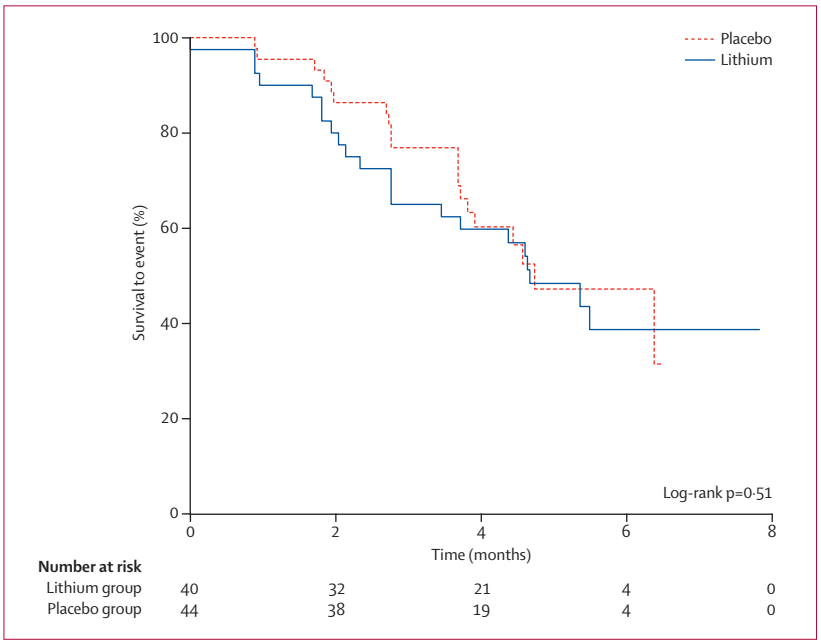

Figure 2: **Kaplan-Meier curve for primary endpoint**

tracheostomy-free survival. Lithium concentrations in the blood and safety and tolerability of lithium were also assessed.

In the NEALS database of placebo groups of previous clinical trials, the ALSFRS-R declined by an average of one point per month. Therefore, the time-to-event endpoint in this study was expected to occur after about 6 months in the placebo-treated patients. Thus, a 6-month period of active treatment was thought to be the minimum duration after which we could reasonably expect to see a therapeutic response. Inpatient assessments were therefore done at weeks 4, 8, 12, 20, 28, 36, 44, and 52; at these visits vital signs, weight, ALSFRS-R, slow vital capacity, adverse events and concomitant medications, drug accountability, and trough lithium concentration assessments were done. At weeks 16, 24, 32, 40, and 48, the ALSFRS-R and adverse events were assessed by telephone. The ALSSQOL was assessed at baseline, week 28, and week 50, and the QID-SR_{16} was assessed at baseline and weeks 12, 36, and 52.

Statistical analysis

The trial was designed to have greater than 80% power to detect a 40% decrease in the rate of decline in ALSFRS-R in the treatment group if 250 patients were enrolled.

We used a group sequential design to calculate the time points for the interim analyses according to a mathematical function that is proportional to the number of events predicted to have occurred.[18] 167 events were expected if 250 patients were enrolled. We developed stopping rules to investigate at each interim analysis whether the study should be stopped for either efficacy or futility (webappendix). The first interim analysis was planned for when 84 patients had been randomly allocated treatment. At that time, the trial could stop for efficacy or for futility, continue enrolment, or stop enrolment and continue to follow up the 84 patients and reanalyse the data after 6 months. The second interim analysis was planned for 6 months after the first interim analysis or after there were 55 events, based on the decision taken at the first interim analysis. The third interim analysis was planned for when there had been 100 events. At each interim analysis, the stopping boundaries for futility and efficacy were prespecified on the basis of a monitoring method.[18,19] The log-rank statistic was calculated on the basis of the number of events that had occurred. The futility stopping boundary was defined for a one-sided p value testing the superiority of lithium. A p value less than 0·50 would favour lithium, whereas a p value greater than 0·50 would favour placebo. For the first interim analysis, the stopping boundary for futility was calculated as a p value of 0·68; the p value for stopping for efficacy was 0·001.

Analysis was by intention to treat. All patients who were randomised and received at least one dose of study drug were eligible for inclusion in the primary efficacy analysis. If a participant was lost to follow-up, they were censored in the primary analysis. The primary efficacy analysis used a log-rank test to compare the distributions of the time to an event between the lithium group and the placebo group.[20] This measure accounts for the variable length of time that each patient remained in the study while using all available data for each patient.

Distributions of baseline characteristics, adverse events, and laboratory abnormalities were compared using Fisher's exact tests and *t* tests. We used random-effects models to examine the changes over time for the secondary endpoints. Each patient was included in these analyses from baseline until the time that they experienced an event, dropped out, or until their final visit. Tolerability was defined as the ability to complete 52 weeks of treatment on study drug.

This trial is registered at ClinicalTrials.gov, NCT00818389.

Role of the funding source

The funding sources approved the design and protocol, but had no involvement in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. SPA, LZ, ES, DS, JS, and MC had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between January and June, 2009, 97 patients with ALS were screened (figure 1) and 84 were randomly assigned to receive lithium and riluzole (n=40) or placebo and riluzole (n=44). Demographic features, clinical variables, and values of primary and secondary outcome variables were much the same in the two treatment groups at baseline (table 1). Patients were assessed for a mean of

5·4 months (SD 1·5, range 0·8–8·3) until the study was stopped for futility in September, 2009.

In September, 2009, at the first interim analysis, a log-rank statistical analysis testing the superiority of lithium favoured placebo (p=0·78, which exceeded the one-sided p value of 0·68 to stop for futility). The results were reviewed by the data and safety monitoring board who recommended, with National Institute of Neurological Disorders and Stroke agreement, that the trial be stopped for futility. All participants were asked to stop taking the study drug and to schedule a final safety visit with the site study staff.

In the final dataset, 22 of 40 patients in the lithium group had an event compared with 20 of 44 patients in the placebo group (p=0·51; figure 2). Of the patients who had an event, four died (one in the lithium group and three in the placebo group) and 38 had a decrease of at least six points on the ALSFRS-R (21 in the lithium group and 17 in the placebo group). The point estimate for the hazard ratio of reaching the primary endpoint was 1·13 (95% CI 0·61–2·07). The difference in mean decline between the lithium group and the placebo group was 0·15 for the ALSFRS-R (95% CI –0·43 to 0·73, p=0·61; figure 3), –1·22 for slow vital capacity (–2·58 to 0·13, p=0·08; figure 3), and –0·04 for QIDS-SR_{16} (–0·37 to 0·30, p=0·83).

The lithium doses in the study ranged from 150 mg/day to 1050 mg/day (1–7 capsules). At the week 4 visit, 14 of 38 patients in the lithium group had serum lithium concentrations in the target range of 0·4–0·8 mEq/L (mean 0·31 mEq/L; figure 4). At week 8, concentrations of lithium in 18 of 38 patients were in the target range (mean 0·36 mEq/L), and at week 12, 25 of 34 had therapeutic serum lithium concentrations (mean 0·40 mEq/L). Of the 40 patients initially randomly assigned lithium, six did not reach a drug concentration in the therapeutic range; two of these patients discontinued study drug early: one after receiving one dose and one 2 weeks after drug initiation. Two of 36 patients assigned to the placebo group had therapeutic lithium concentrations at their week 12 visit. A patient in the placebo group who had detectable lithium at week 12 had previously discontinued study drug and had started lithium treatment outside the study.

27 of 40 patients in the lithium group and 38 of 44 in the placebo group completed the study up to the final analysis without any dose reductions, suspensions, or permanent discontinuations because of adverse events (p=0·07). 12 patients permanently discontinued treatment (excluding those who died) before the first interim analysis: seven in the placebo group and five in the lithium group. Time to study drug discontinuation did not differ significantly between the treatment groups (log-rank p=0·55). The reasons for permanent study drug discontinuation in the placebo group included disease progression, raised thyroid stimulating hormone, and constitutional symptoms such as fatigue, anorexia, and nausea. In the lithium group, the study drug was discontinued after an episode of delirium (deemed unrelated to study drug), tremor and dizziness, depression, consent withdrawal, and disease progression. One participant in the lithium group stopped taking the study drug because of perceived lack of efficacy, and the study drug was discontinued in another patient on the recommendation of the drug monitor because of lithium concentrations above 1·2 mEq/L.

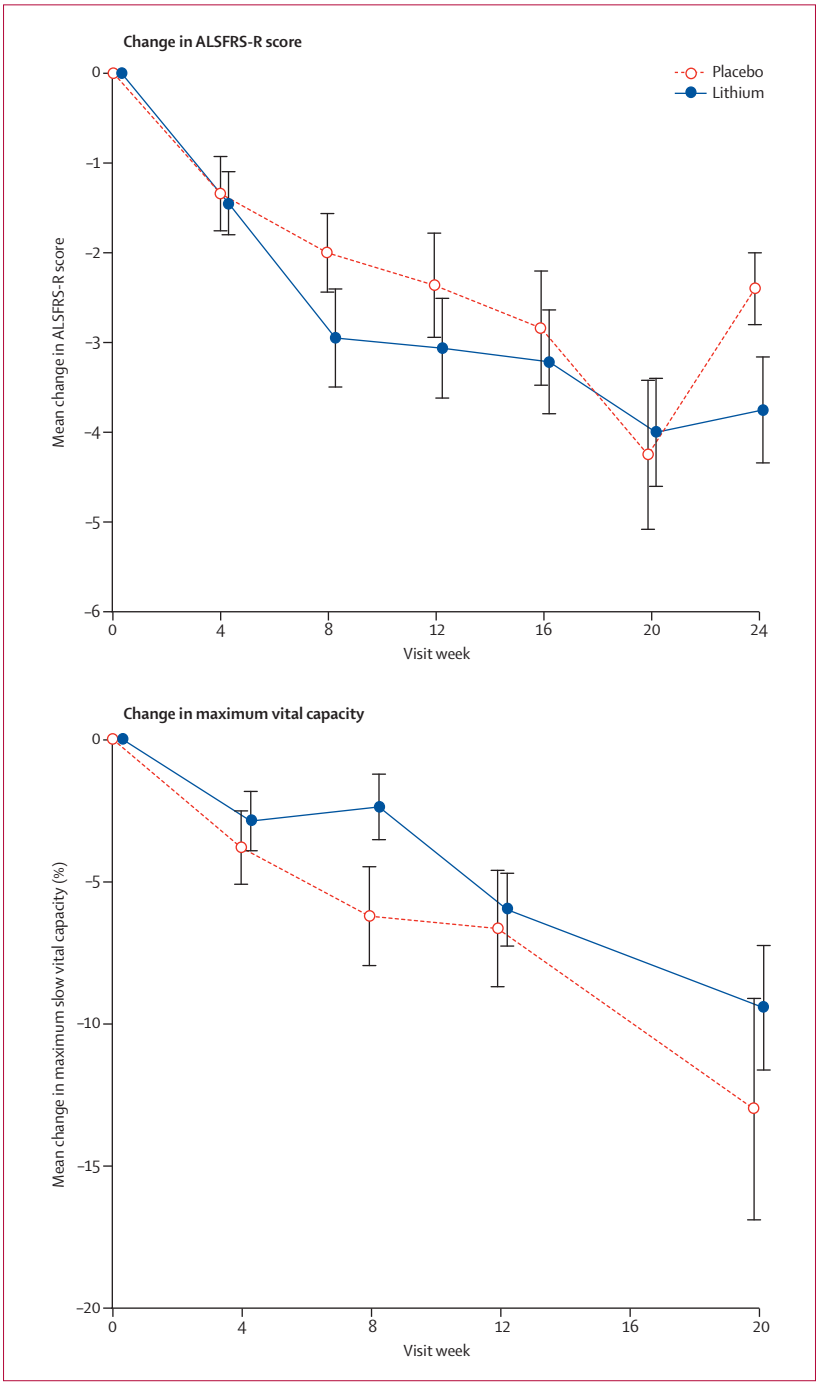

Figure 3: **Total changes in amyotrophic lateral sclerosis functional rating scale revised and slow vital capacity**
Bars are SE. ALSFRS-R=amyotrophic lateral sclerosis functional rating scale revised.

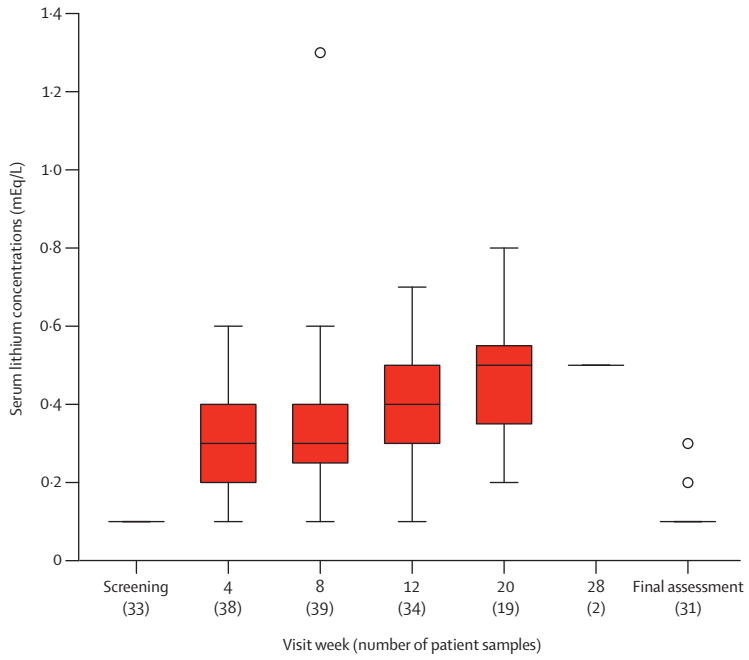

Figure 4: **Serum lithium concentrations**
Bands are median lithium concentrations. Boxes are the 25th to 75th percentiles. Whiskers are 1·5×interquartile range. Circles=outliers.

	Lithium	Placebo	p
Leg muscle weakness	16/33 (48%)	17/33 (52%)	1·00
Arm muscle weakness	20/37 (54%)	17/37 (46%)	0·38
Fatigue	14/23 (61%)	9/23 (39%)	0·15
Nausea	10/19 (53%)	9/19 (47%)	0·79
Falls	8/10 (80%)	2/10 (20%)	0·04
Dyspnoea	8/14 (57%)	6/14 (43%)	0·56
Limb oedema	6/13 (46%)	7/13 (54%)	1·00
Fasciculations	7/11 (64%)	4/11 (36%)	0·34
Dysphagia	6/15 (40%)	9/15 (60%)	0·58
Headache	7/15 (47%)	8/15 (53%)	1·00
Whole body or generalised muscle weakness	4/11 (36%)	7/11 (64%)	0·53
Back pain	6/7 (86%)	1/7 (14%)	0·05

Data are number of patients with the event/total number of patients (%). Events listed by common terminology criteria for adverse events.

Table 2: **Adverse events**

The most common adverse events were muscle weakness in the arms or legs, fatigue, nausea, falls, dyspnoea, limb oedema, fasciculations, dysphagia, headache, whole body or generalised muscle weakness, and back pain (table 2). Falls (p=0·04) and back pain (p=0·05) were more common in the lithium group. Six patients died during the study: one before randomisation, two in the lithium group (one more than 30 days after stopping study drug), and three in the placebo group. All deaths were deemed unlikely to be or not associated with the study drug. 19 patients had a total of 30 serious adverse events: one patient had a serious adverse event before randomisation, ten patients in the lithium group had 14 events, and eight patients in the placebo group had 15 events. There was no significant difference in the occurrence of serious adverse events between the two groups. All serious adverse events were unexpected with respect to the study drug with the exception of five: two in the placebo group (nausea and somnolence or depressed level of consciousness caused by oversedation from another drug) and three in the lithium group (syncope, encephalopathy, or delirium caused by an anticholinergic reaction, and dysphagia secondary to a traumatic seizure after a motor vehicle accident). One unexpected serious adverse event (depression with suicide attempt) in a patient given lithium was deemed possibly related to the study drug by the site investigator.

Discussion

Lithium in combination with riluzole does not substantially slow disease progression in patients with ALS. The trial was stopped for futility because of sufficient evidence that a large effect of lithium would not be seen by enrolling more patients, or by assessing patients already enrolled in the trial for longer to increase the proportion of patients with lithium concentrations in the target range. However, we cannot rule out the possibility that lithium has a small positive effect or that other serum concentration ranges might be beneficial. In the final analysis, the lower limit of the 95% CI around the difference in rates of decline of the ALSFRS-R total score was –0·43, suggesting that although a modest benefit of lithium was not ruled out by this study, an effect of 43% or more could be eliminated.

Our goal was to test the validity of the results of the Italian pilot study;[1] therefore, we targeted the same range of serum concentrations of lithium. Also, preclinical data suggest a potential limited range of efficacy for lithium and a concentration above which there might be activation of different pathways and potential for toxicity: lithium-induced neural progenitor cell differentiation towards a neuronal fate reached a plateau at 1 mM in the dose-response curve.[9,21] About half of the patients receiving lithium were in the therapeutic range at week 8 and about 75% of patients were in this range at week 12. Target serum concentrations of lithium took several months to achieve; however, we checked lithium only at monthly intervals for the first 3 months to avoid inconvenience to the patients. Nonetheless, stable lithium concentrations are reached within 1 week of dose adjustment,[22] which suggests that patients who had concentrations in the therapeutic range at week 12 reached this concentration by week 9. If more patients were treated for longer periods of time at therapeutic concentrations of lithium, a small benefit of the drug might have been seen. In the Italian pilot study, how quickly and what proportion of patients achieved therapeutic lithium concentrations are unclear;[1] however, significant benefits of lithium treatment were reported on the Norris scale, the ALSFRS-R, and forced vital capacity after 3 months. The long-term effects of

lithium on ALS progression might be established from other ongoing controlled studies.

Our study includes three key features: the use of a time-to-event endpoint as the primary outcome measure rather than a conventional random effects model evaluating slope of ALSFRS-R decline; blinded crossover to the active compound for participants initially assigned to placebo once they reach the prespecified event; and multiple planned interim analyses for futility and efficacy. We have shown the feasibility of the time-to-event design for ALS trials. Time-to-event endpoints convert an interval scaling measure into a binary measure, which means that clinical relevance is incorporated into the endpoint. If the study is positive, conversion of the results into an estimate of number needed to treat is also straightforward. This design can be analysed by survival analysis, as we did with our primary analysis, or by use of a random-effects model, as we did in our secondary analysis. A conventional fixed time design could also be analysed in both these ways. We studied the four combinations of design by simulation; in most cases there is a small power loss associated with use of time-to-failure design but more power loss with survival analysis rather than the random-effects model. There is also a small power loss when a futility rule for stopping is used. The stopping rule depends on the alternative hypothesis: the probability of stopping early if the alternative is true. This trial was designed with an alternative that specified that lithium was superior to placebo, and the chance of stopping for futility if this had been the case was very small. However, if the benefit of lithium was moderate, for example 30%, as we assumed for celecoxib,[23] then the likelihood of stopping the trial because of futility would be much higher and there would be a larger loss of power compared with a trial without futility stopping. This trial did not use a futility design: the study was designed to enrol 250 patients unless early results showed that continuation of the trial was futile based on predefined stopping rules.

Given the lack of effect of lithium in 84 patients, it is unlikely that enrolling more patients would have changed the result. However, whether the time-to-failure endpoint was a major determinant in reaching futility is unclear. More studies are needed to investigate whether the time-to-failure endpoint improves the sensitivity of futility analyses.

This design was chosen in part to increase acceptance of a placebo-controlled trial by patients in the setting of intense patient interest and easy availability of lithium outside the trial. The inclusion of a placebo group and masking in a randomised clinical trial is necessary to control for the placebo effect in ALS and is required to detect mild to moderate treatment effects. The time-to-event design was thought to be attractive to potential participants in that patients would be exposed to placebo for an average of only 7 months and those with a rapid progression in the placebo group would receive active compound earlier in the course of their disease. This trial design provides a good compromise between the need to assess therapeutic efficacy and the desire to limit the period of time participants are on placebo. This design should be considered for future trials in patients with ALS, especially when the active compound is easily accessible.

In conclusion, this randomised, double-blind, placebo-controlled trial failed to show a significant slowing of disease progression in patients with ALS treated with lithium. Whether smaller beneficial effects of lithium in ALS are still possible and whether compounds that target induction of autophagy have therapeutic potential in this disease needs to be assessed in future studies. At this time, there remains no convincing evidence for the use of lithium as a treatment for patients with ALS.

Contributors

SPA, LZ, RAC, DS, JS, and MC participated in conception and design of the study. ES, JM, KEJ, and HP provided project management and assisted with data collection and resolution of site queries. SPA, LZ, ES, DS, JS, and MC contributed to analysis and interpretation of data, and writing of the paper.

Northeast ALS and Canadian ALS consortia

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Conflicts of interest

We have no conflicts of interest.

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