Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials

**ABSTRACT**

**Objective:** To assess whether genetic subgroups in recent amyotrophic lateral sclerosis (ALS) trials responded to treatment with lithium carbonate, but that the treatment effect was lost in a large cohort of nonresponders.

**Methods:** Individual participant data were obtained from 3 randomized trials investigating the efficacy of lithium carbonate. We matched clinical data with data regarding the UNC13A and C9orf72 genotype. Our primary outcome was survival at 12 months. On an exploratory basis, we assessed whether the effect of lithium depended on the genotype.

**Results:** Clinical data were available for 518 of the 606 participants. Overall, treatment with lithium carbonate did not improve 12-month survival (hazard ratio [HR] 1.0, 95% confidence interval [CI] 0.7–1.4; p = 0.96). Both the UNC13A and C9orf72 genotype were independent predictors of survival (HR 2.4, 95% CI 1.3–4.3; p = 0.006 and HR 2.5, 95% CI 1.1–5.2; p = 0.032, respectively). The effect of lithium was different for UNC13A carriers (p = 0.027), but not for C9orf72 carriers (p = 0.22). The 12-month survival probability for UNC13A carriers treated with lithium carbonate improved from 40.1% (95% CI 23.2–69.1) to 69.7% (95% CI 50.4–96.3).

**Conclusions:** This study incorporated genetic data into past ALS trials to determine treatment effects in a genetic post hoc analysis. Our results suggest that we should reorient our strategies toward finding treatments for ALS, start focusing on genotype-targeted treatments, and standardize genotyping in order to optimize randomization and analysis for future clinical trials.

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**GLOSSARY**

ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-revised; CI = confidence interval; GWAS = genome-wide association studies; HR = hazard ratio; IPD = individual participant data; SNP = single nucleotide polymorphism.

Despite considerable efforts, riluzole is still the only drug that has been shown to increase survival in patients with amyotrophic lateral sclerosis (ALS). Phenotypic, genetic, and pathophysiologic heterogeneity form a plausible explanation for the large number of negative trials in ALS. Although the mechanisms underlying ALS are not fully understood, it is clear that genetic variation plays an important role in both familial and sporadic ALS. It is reasonable to hypothesize that mutations in many different genes may act through several different pathways, but that they all cause motor neurodegeneration and manifest with an ALS phenotype. It

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may, therefore, be conceivable that different subtypes of ALS respond differently to disease-modifying therapies and multiple individually tailored therapies may need to be developed to treat the disease effectively.

Within the field of oncology, the treatment for a specific type of malignancy often depends on the genetic tumor characteristics. For instance, patients with melanoma and BRAF gene mutations have significantly improved rates of overall and progression-free survival when treated with a BRAF kinase inhibitor. It seems that therapeutic strategies for ALS are also moving toward precision medicine and ground-breaking targeted trials for SOD1-related ALS have already been undertaken or are underway with antisense oligonucleotides, arimoclomol (ClinicalTrials.gov NCT00706147), and pyrimethamine. In this study, we explore the possibility that patients with genetic subgroups of ALS may have responded to treatment in previously conducted negative trials evaluating lithium carbonate, but that a proportionally larger cohort of nonresponders diluted the treatment effect in the overall analysis.

METHODS Study design. When performing post hoc analyses according to genotype and re-estimating treatment effects for genetic subgroups, it is important to recognize that several problems will arise. First, the sample size within each subgroup will decrease dramatically and statistical power to detect treatment differences is severely reduced. Second, obtaining DNA samples and genetic screening is not standard practice in ALS clinical trials, thus one can expect that genetic data will be missing. Finally, over 30 genes have been associated with ALS. This may further reduce the statistical power by multiple testing, but more importantly, will inflate the false-positive risk. To overcome these issues, we performed an individual participant data (IPD) meta-analysis of randomized controlled trials with lithium carbonate in ALS; multiple trials with this compound have been performed and, therefore, a large sample size could be obtained. Moreover, an IPD meta-analysis enabled us to reduce the false-positive risk by validating trends in independent cohorts of patients and improve generalizability. Genetic post hoc analyses were limited to (1) genes in which variation is relatively common in order to ensure sufficient numbers and (2) genesanalyses were limited to (1) genes in which variation is relatively common in order to ensure sufficient numbers and (2) genes analyzed to reduce the false-positive risk by validating trends in independent cohorts of patients and improve generalizability. Genetic post hoc analyses were limited to (1) genes in which variation is relatively common in order to ensure sufficient numbers and (2) genes analyzed to reduce the false-positive risk by validating trends in independent cohorts of patients and improve generalizability.

Definitions and outcome measures. Based on previous literature, patients with the UNC13A C/C genotype were classified as UNC13A carriers in the subsequent analyses; the remaining patients with the UNC13A A/C or A/A genotype were classified as noncarriers. Patients with more than 30 repeats in the C9orf72 gene were considered to be C9orf72 carriers. Our a priori primary measure of treatment efficacy was death from any cause at 12 months after randomization. Due to the high adverse event and nonadherence rate, setting the follow-up to 12 months was thought to best capture a possible therapeutic effect and minimize the risk of diluting the effect by the intention-to-treat principle of analysis.

Statistical analysis. All outcomes were analyzed according to the intention-to-treat principle of analysis. We chose to analyze the IPD from the 3 trials using a one-step meta-analytic approach.
### Table 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Revised El Escorial category</th>
<th>Study (year)</th>
<th>Patients, n</th>
<th>Study design</th>
<th>Lithium dose, mEq/L</th>
<th>Primary outcome</th>
<th>Risk of bias</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fornai et al. (2008)</td>
<td>44</td>
<td>Randomized, single-blind</td>
<td>0.4–0.8</td>
<td>Death of any cause</td>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aggarwal et al. (2010)</td>
<td>88</td>
<td>Randomized, double-blind</td>
<td>0.2–0.4 mEq/L</td>
<td>Death of any cause</td>
<td>Low</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chio et al. (2010)</td>
<td>171</td>
<td>Randomized, double-blind</td>
<td>6–36</td>
<td>Death of any cause</td>
<td>Low</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verstraete et al. (2010)</td>
<td>1.71</td>
<td>Randomized, double-blind</td>
<td>&gt;36</td>
<td>Death of any cause</td>
<td>Low</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UKMND–LiCALS Study Group (2013)</td>
<td>214</td>
<td>Randomized, double-blind</td>
<td>6–36</td>
<td>Death of any cause</td>
<td>Low</td>
<td>A</td>
</tr>
</tbody>
</table>

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–revised; NIV = noninvasive ventilation.

Risk of bias and level of evidence was assessed for each study; results are presented in table e-1.

#### Results

Data were available for 518 participants in 3 randomized clinical trials evaluating the efficacy of lithium carbonate; study characteristics are given in table 1. Individual data were not available from 1 of the 4 clinical trials (study by Aggarwal et al.24), which involved 88 participants. Baseline characteristics of the participants included in the analysis are given in table 2. Complete data regarding the main prognostic confounders were available for 98.5% of the participants (8 patients had an unknown date of onset). In total, 261 (50.4%) patients received lithium carbonate and 257 (49.6%) patients were allocated to the control arm, in which 174 patients received placebo (67.4%) and 83 patients a subtherapeutic dose of lithium carbonate (32.3%). The baseline characteristics were well-balanced between the lithium carbonate and control groups.

Age, Amyotrophic Lateral Sclerosis Functional Rating Scale–revised (ALSFRS-R) slope, and vital capacity at baseline were predictors for survival at 12 months (all $p < 0.001$) and were adjusted for in all
subsequent analyses (table e-2). Overall, 75.3% (95% confidence interval [CI] 69.9–81.2) of the patients in the control arm and 74.7% (95% CI 69.1–80.6) in the lithium arm were still alive at 12 months, corresponding to an adjusted hazard ratio (HR) of 1.0 (95% CI 0.7–1.4; \( p = 0.96 \)); figure 1A). Excluding the subtherapeutic control group from the analysis did not change the treatment effect (HR 1.3, 95% CI 0.9–2.1; \( p = 0.21 \)). Next, we evaluated the pre-specified genetic subgroup interactions in all patients with genetic data (\( n = 269 \)); the baseline characteristics are given in tables 3 and e-3. Both the \textit{UNC13A} and \textit{C9orf72} genotype were independent predictors for 12-month survival, with an adjusted HR of 2.4 (95% CI 1.3–4.3; \( p = 0.006 \)) and HR 2.5 (95% CI 1.1–5.2; \( p = 0.032 \)), respectively (figure 1B). The overall effect of lithium carbonate in the patients with genetic data remained futile (HR 0.8, 95% CI 0.4–1.4; \( p = 0.39 \)).

The treatment effect was different for the \textit{UNC13A} carriers (\( n = 46; p = 0.027 \)) but not for the \textit{C9orf72} carriers (\( n = 25; p = 0.22 \)). Lithium carbonate in \textit{UNC13A} carriers resulted in a 70% reduction in the number who died during the 12-month follow-up period as compared to the placebo group (HR 0.3, 95% CI 0.1–0.9), whereas the non-carriers did not benefit from lithium carbonate (HR 1.2, 95% CI 0.6–2.3; figure 2). The significant treatment interaction with \textit{UNC13A} genotype remained after correcting for the interaction between the \textit{C9orf72} genotype and lithium (\( p = 0.020 \)) or excluding the control group from the LITALS study (\( p = 0.047 \)). The interaction between lithium treatment and \textit{UNC13A} was homogenous across the 3 different studies (3-way interaction Cox model; \( p = 0.99 \); figure e-2). Baseline characteristics of the \textit{UNC13A} carriers are given in table e-3 (\( n = 46 \)). The crude Kaplan-Meier estimate of 12-month survival probability for \textit{UNC13A} carriers improved from 40.1% (95% CI 23.2–69.1) in the control group (\( n = 26 \)) to 69.7% (95% CI 50.4–96.3) in the lithium group (\( n = 20 \); \( p = 0.056 \)). When we adjusted for baseline inequalities (vital capacity and sex), lithium treatment was effective (\( p = 0.039 \)), and remained so when we additionally corrected for age and ALSFRS-R slope (\( p = 0.040 \)).

**DISCUSSION** In this study, we have shown the importance of including genetic information in clinical trials for ALS. Our results reveal that even within a well-defined and selected trial population, considerable differences in the primary outcome can be expected for patients with either the \textit{UNC13A} \textit{C/C} genotype or \textit{C9orf72} repeat expansion. Interestingly, we showed that the overall meta-analysis of trials with lithium carbonate in ALS is futile, but that a genetic subgroup of patients (\textit{UNC13A} \textit{C/C} genotype) may benefit from this treatment. Due to the small sample size of this genetic subgroup (fewer than 20% of the cases), the signal indicating response may have been lost within the large group of nonresponders.

Although our genetic knowledge about causative and disease-modifying genes in ALS is growing exponentially,\(^5\) we have not yet managed to translate these novel findings into effective therapeutic strategies. To date, only 2 targeted (phase I) genetic trials have been completed and a number of targeted trials are currently underway.\(^5,6\) By showing that genetic variation in ALS genes significantly influences the primary outcome measure of a clinical trial and may alter treatment response, we have demonstrated the importance of incorporating genetic data in the analysis of ALS trials. Unequally balanced genotypes across treatment and control groups, especially in smaller studies, may greatly influence the false-positive and false-negative rates and the validity of clinical trials in ALS as a whole. For instance, the probability of an imbalance larger than 10% between treatment arms, if the prognostic factor is present in 15% of the cases (like \textit{UNC13A} \textit{C/C} genotype), is 0.24 and 0.10 for trial sizes \( n = 50 \) and \( n = 100 \), respectively.\(^25\) It might therefore even be conceivable that the high false-positive rate of the phase II trial in ALS\(^2\) is partially caused by an imbalance of disease-modifying genetic

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**Table 2** Clinical characteristics of patients included in pooled analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LITALS (( n = 171 ))</th>
<th>LICALS (( n = 214 ))</th>
<th>LITRA (( n = 133 ))</th>
<th>Total (( n = 518 ))</th>
<th>Lithium (( n = 261 ))</th>
<th>Control (( n = 257 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization, y</td>
<td>58 (11)</td>
<td>60 (11)</td>
<td>58 (12)</td>
<td>59 (11)</td>
<td>58 (12)</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Female</td>
<td>71 (42)</td>
<td>66 (31)</td>
<td>53 (40)</td>
<td>190 (37)</td>
<td>96 (37)</td>
<td>94 (37)</td>
</tr>
<tr>
<td>Disease duration at randomization, mo</td>
<td>19 (10)</td>
<td>19 (8)</td>
<td>15 (8)</td>
<td>18 (9)</td>
<td>18 (9)</td>
<td>18 (9)</td>
</tr>
<tr>
<td>Bulbar site of onset</td>
<td>41 (24)</td>
<td>47 (22)</td>
<td>38 (29)</td>
<td>126 (24)</td>
<td>62 (24)</td>
<td>64 (25)</td>
</tr>
<tr>
<td>Predicted upright vital capacity</td>
<td>85 (21)</td>
<td>91 (18)</td>
<td>95 (17)</td>
<td>90 (19)</td>
<td>90 (19)</td>
<td>90 (19)</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>37 (6)</td>
<td>38 (6)</td>
<td>40 (5)</td>
<td>38 (6)</td>
<td>39 (6)</td>
<td>38 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-revised. Data are mean (SD) or n (%).
variants between treatment arms in these studies. The false-positive risk may be further inflated by the limited sample size often used for phase II ALS trials.

Lithium for ALS first came into the spotlight after an initial report that suggested an important improvement of survival following lithium treatment.26 Our study, combining the results of 3 randomized placebo-controlled trials, excludes an overall treatment effect similar to riluzole. We had 89% power to detect a 10% absolute increase in survival.27 We found, however, that the treatment effect of lithium carbonate was not homogenous across patients. The
observation that patients with ALS homozygous for
the C allele of rs12608932 in UNC13A may benefit
from lithium may warrant further research. The
UNC13A protein is involved in synaptic vesicle mat-
uration and neuronal outgrowth. Lithium has been
shown to influence many pathways, including the

Table 3 Comparison of the baseline characteristics between patients with and without genetic data

<table>
<thead>
<tr>
<th></th>
<th>Patients without genetic data (n = 249)</th>
<th>Patients with genetic data</th>
<th>Total (n = 269)</th>
<th>Lithium (n = 129)</th>
<th>Control (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization, y</td>
<td>60 (11)</td>
<td>58 (11)</td>
<td>57 (11)</td>
<td>59 (11)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>83 (33)</td>
<td>107 (40)</td>
<td>54 (42)</td>
<td>53 (38)</td>
<td></td>
</tr>
<tr>
<td>Disease duration at randomization, mo</td>
<td>17 (8)</td>
<td>18 (9)</td>
<td>18 (9)</td>
<td>19 (9)</td>
<td></td>
</tr>
<tr>
<td>Bulbar site of onset</td>
<td>66 (27)</td>
<td>60 (22)</td>
<td>27 (21)</td>
<td>33 (24)</td>
<td></td>
</tr>
<tr>
<td>Predicted upright vital capacity</td>
<td>88 (19)</td>
<td>92 (19)</td>
<td>92 (19)</td>
<td>91 (19)</td>
<td></td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>38 (6)</td>
<td>39 (6)</td>
<td>39 (6)</td>
<td>39 (6)</td>
<td></td>
</tr>
<tr>
<td>C9orf72 expansion carriers</td>
<td>249 (48)*</td>
<td>25 (9)</td>
<td>14 (11)</td>
<td>11 (8)</td>
<td></td>
</tr>
<tr>
<td>LICALS</td>
<td>157 (73)*</td>
<td>6 (11)</td>
<td>2 (7)</td>
<td>4 (13)</td>
<td></td>
</tr>
<tr>
<td>LITALS</td>
<td>73 (57)*</td>
<td>8 (8)</td>
<td>5 (10)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>LITRA</td>
<td>19 (14)*</td>
<td>11 (10)</td>
<td>7 (13)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>UNC13A C/C genotype carriers</td>
<td>249 (48)*</td>
<td>46 (17)</td>
<td>20 (16)</td>
<td>26 (19)</td>
<td></td>
</tr>
<tr>
<td>LICALS</td>
<td>157 (73)*</td>
<td>11 (19)</td>
<td>6 (22)</td>
<td>5 (17)</td>
<td></td>
</tr>
<tr>
<td>LITALS</td>
<td>73 (57)*</td>
<td>18 (18)</td>
<td>9 (19)</td>
<td>9 (18)</td>
<td></td>
</tr>
<tr>
<td>LITRA</td>
<td>19 (14)*</td>
<td>17 (15)</td>
<td>5 (9)</td>
<td>12 (20)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–revised.
Data are mean (SD) or n (%). Three patients had both risk variants of UNC13A and C9orf72.

Figure 2 Cox proportional hazards model of 12-month survival and the interaction of lithium carbonate with
UNC13A genotype

Incorporating interaction terms between treatment arm (control or active) and UNC13A carrier status revealed that the
effect of lithium carbonate significantly depended on the UNC13A carrier status (p = 0.027). Lithium carbonate improved
the 12-month survival in individuals with the UNC13A C/C genotype, but had no effect in noncarriers.
induction of sprouting of pyramidal neurons in the corticospinal tract and the promotion of synaptogenesis, and plays a role in autophagy.29 All these mechanisms are potentially relevant to ALS. However, it has also been shown that rs12608932 influences the expression of the nearby KCNN1 gene,30,31 which encodes a potassium calcium-activated channel. It is therefore also possible that lithium influences KCNN1 or acts through other pathways.

Without a solid understanding of the biological interaction between the treatment and pathophysiological pathway, it is challenging to robustly identify the responder group, without increasing the risk of drawing false-positive or false-negative conclusions.32 We reduced this likelihood by only testing 2 prespecified pharmacogenetic interactions and selecting genotypes that are relatively commonly occurring in the general ALS population. Moreover, by using data from 3 independent cohorts, we could assess whether the signal is consistent across studies. Nevertheless, the evidence we provide regarding the interaction between UNC13A and lithium carbonate is still exploratory and hypothesis-generating. This finding does, however, warrant further exploration of lithium carbonate in a well-balanced, blinded, randomized clinical trial specifically targeted at patients with ALS and the UNC13A C/C genotype. Such a trial, and future genetic trials for ALS in general, will require intensive international cooperation to obtain large sample sizes of patients with ALS with a specific genotype. For instance, the prevalence of the UNC13A C/C genotype is 12.2%–19.5%9,12,15 among patients with ALS. This would result in a screening failure rate of 80.5%–87.8% on genotype alone. Large numbers of patients will need to be approached to ensure an acceptable phase III clinical trial sample size. For instance, 140 UNC13A carriers would be required to detect a HR of 0.62 by a 2-sided log-rank test with 90% power, assuming a 1-year survival of 50% in the placebo group, indicating that in the worst case (UNC13A prevalence of 12.2%), approximately 1,100 patients need to be genotyped.

ALS is both clinically and genetically a highly heterogeneous disease and it is this complexity that seems to complicate the development of effective treatment for our patients. Even in carefully selected trial populations, the genotype significantly affected the primary outcome measure—survival—in ALS trials. The assumption of a homogenous treatment effect across patients with ALS, for lithium specifically and ALS trials in general, seems no longer tenable and genetic subgroups of patients may modify the treatment effect. The results from this study suggest that we should reorient our strategies toward finding treatments for ALS and start focusing on genotype-targeted treatments and standardize genotyping in order to optimize randomization and analysis in ALS clinical trials.

AUTHOR CONTRIBUTIONS

M.A.v.E. was responsible for the study concept. The chief investigators of randomized trials of lithium carbonate in patients with ALS were A.A.-C. (LiCALs), A.C. (LiTALS), and L.H.v.d.B. (LiTRA). R.P.a.V.E., M.A.v.E., and A.A.-C. wrote the protocol. A.R.J., A.S., P.J.S., P.N.L., C.A.Y., C.E.S., G.M., J.M., G.B., P.V., F.P.D., W.v.R., and E.V. contributed substantially to data acquisition and interpretation of the analysis. R.P. A.v.E., M.A.v.E., and M.J.C.E. analyzed the data. M.A.v.E. and R.P. A.v.E. drafted the final manuscript, which was reviewed, edited, and approved by all the authors.

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