The Lithium ALS Worldwide Study: Six Month Update

Karen Felzer and Humberto Macedo

November 16, 2008

1 Summary

In January, 2008 an international web-based patient and family led study (http://alslithium.atspace.com) was initiated to test the results of (Fornai et al. 2008) that lithium, and/or lithium plus riluzole, slowed the progression of ALS (Amyotrophic Lateral Sclerosis). The study started with 191 participants and ran for six months. Patients were followed via self-reported ALSFRS-R scores (ALS Functional Rating Scores, Revised) (Cedarbaum et al. 1999) which were calculated on an online calculator (http://www.outcomes-umassmed.org/als/alsscale.cfm). 60% of the patients self-elected to take riluzole with the lithium, while 40% decided to take lithium by itself. All patients initially tried to obtain the 0.4 mmol/l blood concentration of lithium advised by Fornai et al. (2008), and patients were monitored by their personal doctors. The patients on lithium were compared to 66 comparable patients in the PatientsLikeMe data base (http://www.patientslikeme.com) who did not take lithium. Of the initial study participants 71 decided to stop taking lithium before the six months had elapsed because of side effects, lack of efficacy, or doctor's advice. 37 of these patients reported their ALSFRS-R scores six months after their original lithium start date. Of the patients who remained on lithium, 77 reported a three month ALSFRS-R score and 50 reported a 6 month ALSFRS-R score. At least 7 patients passed away in the course of the study, and at least 3 went on ventilators.

Contrary to the findings of Fornai et al. (2008), lithium alone or lithium plus riluzole was not found to be effective at slowing the progression of ALS over the six month study period. Some decrease in progression rate was found during the first two months on treatment, but this was followed by a return to progression rates similar to those seen by the controls. Progression rates were also not influenced by whether or not patients obtained a 0.4 mmol/l blood level of lithium, whether they took riluzole with the lithium, or by whether patients were early or late in disease progression at the time that lithium was started.

In addition to the lack of efficacy seen for lithium on ALS progression it is also important to investigate whether taking lithium did any harm. There is no statisically significant indication that lithium sped up ALS progression, but several patients reported an apparent faster decline as their reason for stopping lithium, and those patients who decided to stop had a non-significant stronger progression at six months than those who remained on the treatment, indicating that they may have begun to progress more quickly at the time that they stopped. Furthermore, as reported in the three month report, lithium also produced side effects, with 49% reporting some side effect and 12% reporting a severe side effect. Common side effects experienced that are known side effects of lithium included increased urination and urination urgency, stomach upset, increased fatigue, increased weakness, skin problems, headache, temporary depression, hypothyroidism, a strange taste in the mouth, and weight gain. A few patients experienced a sudden increase in breathing difficulties, which is not a known side effect of lithium, so it is not known whether this was due to to the lithium or to ALS progression. In addition, two patients reported serious infections after about 6 months on lithium, with one pericarditis and one severe bladder and kidney infection that involved the diaphragm

and right lung. Two regular bladder infections were also reported. It is not known whether lithium was involved in these infections, but lithium may cause the body to excrete more water (diabetes insipidus) and thus increase the probability of urinary tract infections in patients who are not or cannot, because of swallowing difficulties, maintain adequate fluid intake. The failure to maintain adequate fluid intake can also lead to dangerous concentrations of lithium in the body, and at least 2 incidences of high lithium levels were reported.

On the more positive side low doses of lithium did help alleviate ALS symptoms for some patients, including alleviation of painful cramping and reduction of fasciculations for a few. Some patients also found that problems such as slurring of speech, drooling, and fasiculations suddenly became worse when they stopped taking lithium and abated when they went back on a low dose of 150 mg/day. It is not known, however, whether lithium was treating these symptoms (e.g. they would have been worse had the patients never taken lithium) or whether lithium withdrawal caused the symptoms to appear.

Based on these results we find that low doses (150 mg/day) of lithium might be tried primarily for the relief of painful cramps, but that lithium should not be recommended for most ALS patients.

What follows is a series of figures summarizing the progression rates seen by patients over the 6 months of the trial. For further detail on the study, side effects, and quantitative comparison of the study and control populations please see our three month report (http://alslithium.atspace.com).

Further analysis, and follow up of patients past the six month point, will be provided by the research staff at PatientsLikeMe (http://www.patientslikeme.com/).

Acknowledgements We are extremely grateful to all of the PALS on the lithium spreadsheet who not only went through the process of trying lithium on themselves but also put in the time and effort to provide their data for the benefit of the ALS community. We are also extremely grateful to the staff and members of PatientsLikeMe who made the critical control data available and who are working together with us on this study. Tremendous gratitude also to our families who helped us with this project and made it possible for us to do this work: A. Felzer, L. Felzer, M. Harrington, A. Harrington, T. Harrington, M. Nerdi, and all of H. Macedo's "little" family, especially Dandara Macedo, Arthur Maravalhas, Daniel Macedo, and Amanda Maravalhas. We are also grateful to A. Michael for important discussions and support.

References

Cedarbaum, J. M., N. Stambler, E. Malta, C. Fuller, D. Hilt, B. Thurmond, and A. Nakanishi (1999). The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J. Neurol. Sci. 169*, 13–21.

Fornai, F., P. Longone, L. Cafaro, O. Kastsiuchenka, M. Ferrucci, M. L. Manca, G. Lazzeri, A. Spalloni, N. Bellio, P. Lenzi, N. Modugno, G. Siciliano, C. Isidoro, L. Murri, S. Ruggieri, and A. Paparelli (2008). Lithium delays progression of amyotrophic lateral sclerosis. *Proc. Natl. Acad. Sci. 105*, 2052–2057.

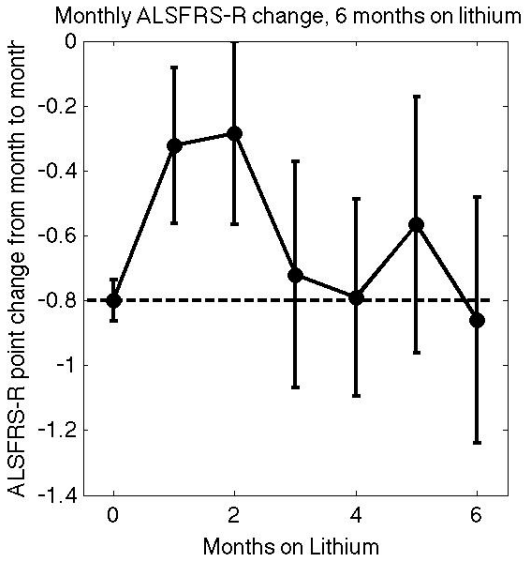

Figure 1: The mean change in ALSFRS-R score from month to month for patients who remained on lithium for at least 6 months. The dotted line gives the average monthly rate of ALSFRS-R point loss between diagnosis and when lithium was started. Error bars are given at the 98% confidence level. After an initial slowing of progression for two months, progression rates returned to the previous average for the rest of the trial.

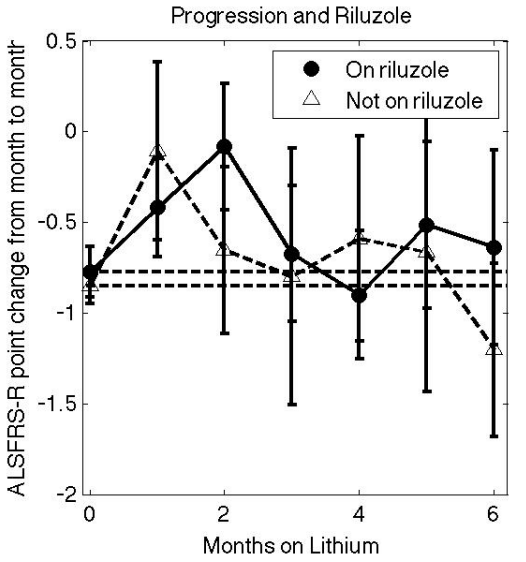

Figure 2: The mean change in ALSFRS-R score from month to month for patients who remained on lithium for at least 6 months, as a function of whether or not the patient chose to take Riluzole. The flat dashed lines give the initial average monthly loss of ALFRS-R points from diagnosis to lithium start for each group. Errors are given at 98% confidence. No significant difference is seen between the two groups.

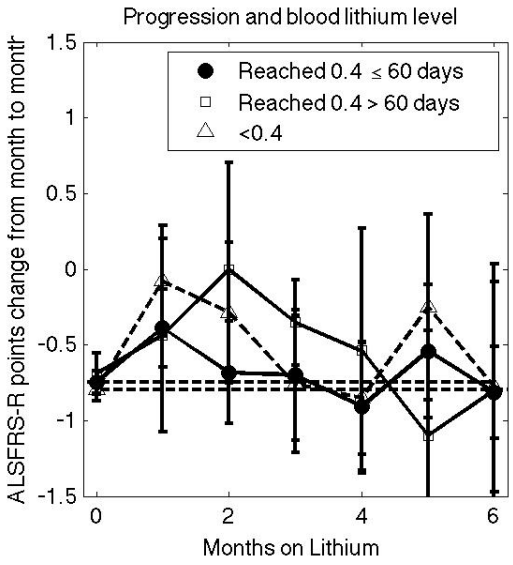

Figure 3: The mean change in ALSFRS-R score from month to month for patients who remained on lithium for at least 6 months as a function of lithium blood level achieved. The different curves give patients who reached lithium blood levels of 0.4 in the first 60 days, who reached 0.4 after 60 days, and who remained at lower blood levels for the full six months. The flat dashed line gives the average monthly rate of ALSFRS-R point loss between diagnosis and when lithium was started. Error bars are given at the 98% confidence level. No significant difference is seen in progression rates as a function of lithium blood level.

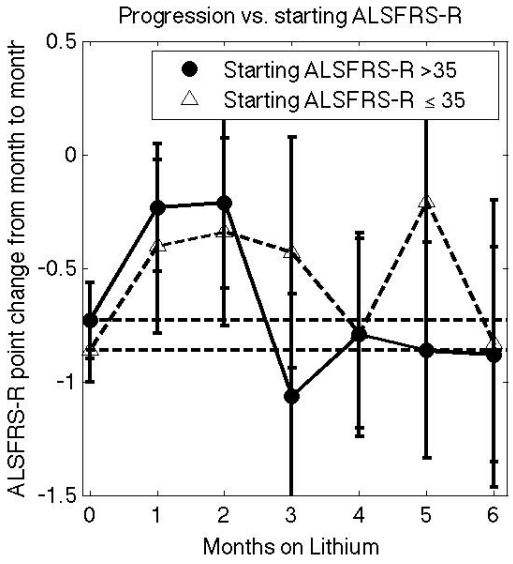

Figure 4: The mean change in ALSFRS-R score from month to month for patients as a function of whether their ALSFRS-R score was above or below 35 points at the start of lithium. The flat dashed lines show the average ALSFRS-R point loss per month from the time of diagnosis to the start of lithium for each group. Error bars are given at 98% confidence. No significant difference is seen in the effect of lithium as a function of initial ALSFRS-R score.

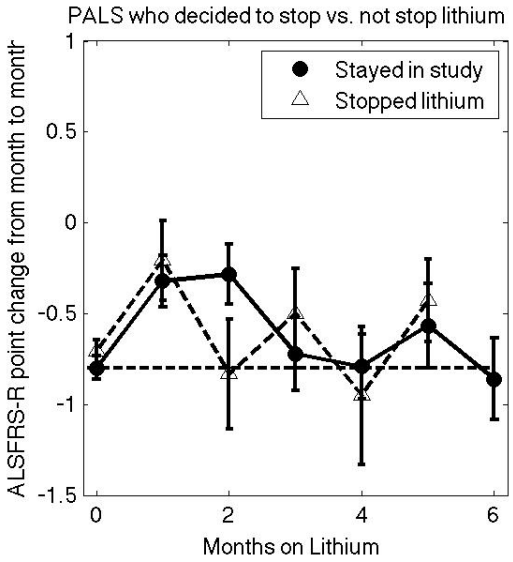

Figure 5: The mean change in ALSFRS-R score from month to month for patients who stopped taking lithium before 6 months vs. patients who remained on lithium for at least 6 months. Data points are only taken from the times when the patients who dropped out were still taking lithium. The data indicates that patients who dropped out did significantly worse than other patients during the second month on lithium, but that after this progression rates were comparable during the time that the patients who stopped taking lithium were still in the study. This suggests that bias created by either generally faster or or more slowly progressing patients preferentially dropping the study was not considerable.

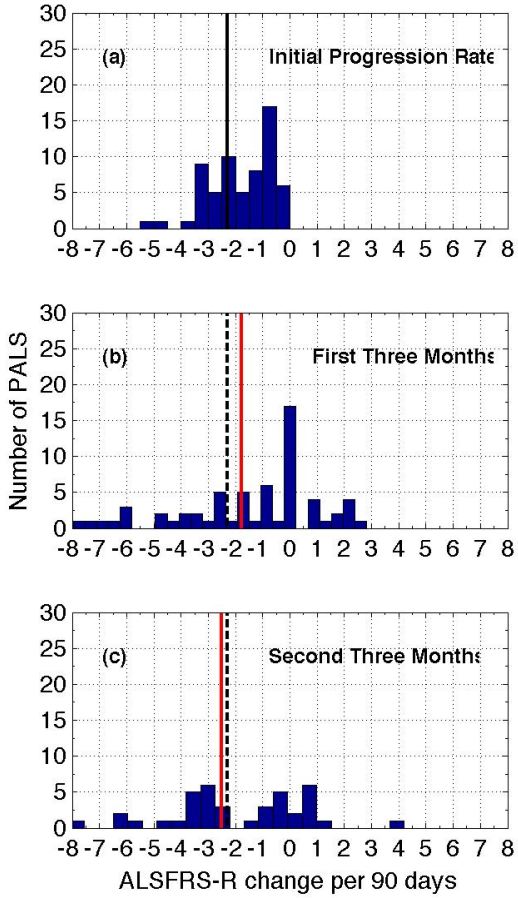

Figure 6: The distribution of changes in ALSFRS-R score over 3 month periods for control patients (ALS patients not taking lithium) taken from the PatientsLikeMe data base. Control patients were intially chosen for the three month report and were taken as 66 PALS who had recently entered 2 ALSFRS-R data points 2 - 4 months apart and a data point around the time of diagnosis that preceded the other two points by at least 3 months. Panel (a) gives the spread and average (black line) 90 day ALSFRS-R point change from the time of diagnosis to the first data point that was used. Panel (b) gives the ALSFRS-R point change over the next 90 day period. The mean change is given by the red line, and the dashed black line gives the original mean progression rate from (a). Since data points may actualy have been entered at 60 - 120 day separations the 90 day change is estimated from linear interpolation/extrapolation if necessary. (c) ALSFRS-R point change over the next 90 days for the 42 control patients who entered an additional data point at 2 - 4 months. Again the mean change in the panel is given by the red line and the mean initial progression rate from (a) is given by the dashed black line. It can be seen that the average rate of ALSFRS-R point loss between diagnosis and the six month study period agrees well with the mean rate of ALSFRS-R point change over the next six months.

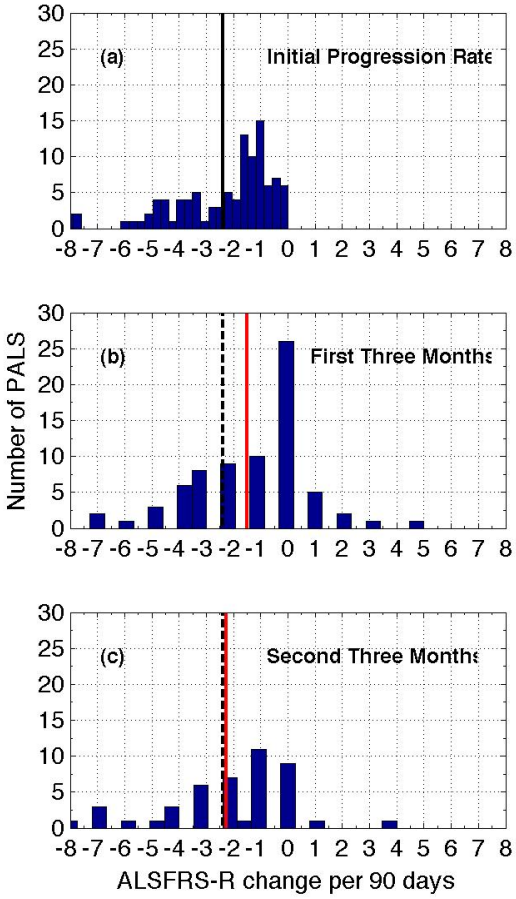

Figure 7: Histograms of ALSFRS-R score change over 3 month periods for patients who remained on lithium for the six month study duration. Panel (a) gives the spread and average (black line) 90 day ALSFRS-R point change from the time of diagnosis to the first data point that was used for 104 patients who provided this data and did not report stopping lithium over the study duration. Panel (b) gives the ALSFRS-R point change over the next 90 day period for 70 of the patients in Panel (a) who reported a 3 month data point. The mean change is given by the red line, and the dashed black line gives the original mean progression rate from (a). (c) ALSFRS-R point change over the next 90 days for the 42 patients from Panels (a) and (b) who entered a six month data point. Again the mean change in the panel is given by the red line and the mean initial progression rate from (a) is given by the dashed black line. It can be seen that although patients reported progressing more slowly in the first several months after starting lithium, progression from months 4 to 6 returned to the original rate, and is comparable to the progression seen in controls (Figure 6).

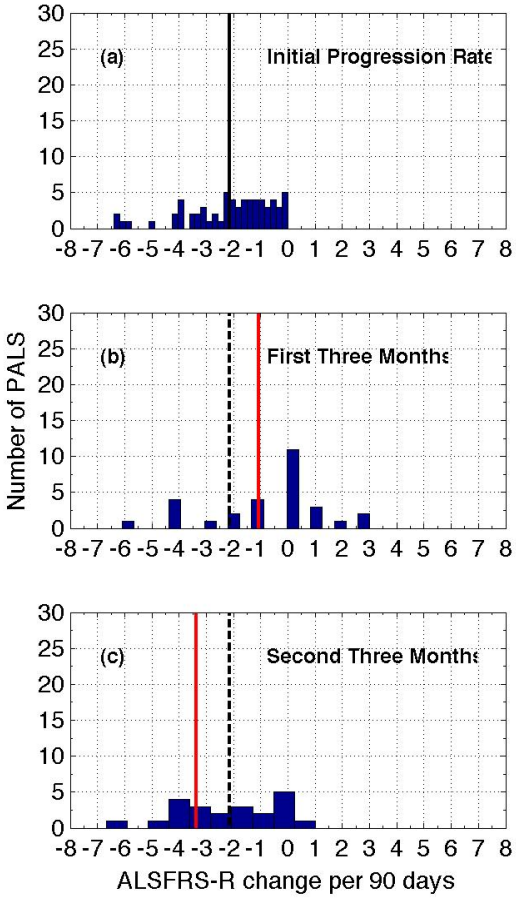

Figure 8: Histograms of ALSFRS-R score change over 3 month periods for patients who stopped taking lithium before 6 months had passed. Panel (a) gives the spread and average (black line) 90 day ALSFRS-R point change from the time of diagnosis to the first data point that was used for 65 patients who provided this data and reported stopping lithium during the study duration. Panel (b) gives the ALSFRS-R point change over the next 90 day period for 30 of the patients in Panel (a) who were still on lithium after 3 months and reported a 3 month data point. The mean change is given by the red line, and the dashed black line gives the original mean progression rate from (a). (c) ALSFRS-R point change over the next 90 days for the 22 patients from Panels (a) and (b) who had stopped lithium but sent in a six month data point. Again the mean change in the panel is given by the red line and the mean initial progression rate from (a) is given by the dashed black line. The mean progression rate in the second three months was worse than the initial rate for these patients, but given the large spread in the data and small number of patients the change is not significantly worse at the 98% confidence level from the changes reported by controls.