The Lithium ALS Worldwide Study: 3 Month Preliminary Report

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1 Abstract

In February 2008 Fornai et al. (2008) reported results of a small human trial indicating that patients taking lithium plus riluzole had a disease progression that was only one third as fast as patients taking riluzole alone. The trial ran for a total of 15 months, but a separation in progression rates between the treatment and control groups was seen as early as the third month. Given the importance of the results and the need for ALS patients to obtain rapid and accurate evaluation of new treatments, an international online trial, led by patient and family volunteers, was quickly started to test the findings of Fornai et al. (2008). A total of 191 patients signed up for the trial between January and May 2008. All trial participants took lithium and attempted to obtain blood levels of between 0.4 and 0.8 mmol/l, as specified in the protocol of Fornai et al. (2008). 60% of participants also chose to take riluzole. Patient progress was tracked via the ALSFRS-R (ALS Functional Rating Score-Revised (Cedarbaum et al. 1999)) which was computed on an online calculator by the patient or caregiver. As of June 12, 2008 ALSFRS-R scores have been recorded for 142 PALS (Patients with ALS) after one month on lithium, 116 after two months, 91 after three months, 42 after four months, 14 after five months, and 1 after 6 months. 82 of the patients reporting scores at 3 months also provided sufficient initial data that their projected progression rates, had they not been taking lithium, could be estimated. Here we present an analysis of the first three months of data, with some initial analysis of the four month data. Cumulatively over the first three months the mean rate of progression of patients on lithium was 20% slower than a group of control patients taken from the PatientsLikeMe (PLM) data base, an online site where patients also calculate and record their own ALSFRS-R scores, and whose patients have similar profiles to those participating in the online lithium trial. The 20% difference, however, is not statistically significant, and a Kolmogorov-Smirnoff (K-S) test demonstrates a high similarity between the distribution of ALSFRS-R point losses of the experimentals and controls (89% probability that the two data sets come from the same parent distribution, or only an 11% probability that there is a difference between the groups). These statistics do not include data from the 26 patients who stopped taking lithium before the three month point (this represents 20% of the total patients who started lithium > 3 months ago and who provided full initial data.) The 20% decrease in progression rate seen also appears to come primarily from the first two months on treatment; month to month data shows a decrease in disease progression for the first two months, followed by a return to initial progression rates in months 3 and 4. Those taking riluzole with lithium showed a faster progression than those taking lithium alone at the three month mark, but the difference was not statistically significant and reversed at 4 months. No difference in progression rates was seen between those patients who did and did not obtain a blood level of ≥ 0.4. Statistically significant slower progression was seen at 3 months by patients who started lithium treatment later in their disease progression (starting ALSFRS-R score of < 35 out of 48 points) but this is likely because patients starting with lower scores were more likely to drop out or not report data, and the improvement disappears at 4 months. 49% of patients reported side effects from lithium, with 12% reporting severe side effects. At

least 2 patients experienced dangerously high blood lithium levels on relatively low doses, because their disease interfered with proper intake of sodium and fluids. Three patients passed away during the first three months of the study, with cause of death given as an embolism, heart failure, and unknown cause after returning home from hospitalization for dehydration. One patient went on a ventilator. On the more positive side relief from painful cramping, clearly associated with taking lithium, was reported by 6 patients. The relief from cramping was experienced at low doses and blood levels of lithium (300 mg, 0.2 mmol/l blood concentration). Five patients reported a decrease in previously strong fasciculations (although others had temporary increases), four patients reported more flexibility/less spasticity, and one reported relief from emotional lability. The findings to date indicate that low levels of lithium may be useful in treatment of some symptoms of ALS, but that lithium or lithium plus riluzole does not produce significant slowing of disease progression at the 3 and 4 month marks.

All of the data collected for our trial is freely available online at http://alslithium.atspace.com

Special note: The main statistics for this three month report were tabulated as of June 12. The figures, however, were re-made on July 3, 2008 so that they contain more current data. Thus some numbers reported throughout the text are quoted as of June 12 and others are quoted as of July 3. The main statistical conclusions did not change as a result of the data collected between these two dates.

2 Introduction

In February 2008 Fornai et al. (2008) published a report that lithium significantly slowed the progression Amytrophic Lateral Sclerosis (ALS, or Lou Gehrig's Disease) in a mouse model and in a small human trial. The human trial contained 44 subjects; 16 received lithium plus riluzole, the remaining received riluzole only. Lithium blood levels in the experimentals were maintained between 0.4 and 0.8 mmol/l, on reported dosages of 300 mg or 450 mg/day. Fornai et al. (2008) evaluated their subjects with the ALSFRS-R (Cedarbaum et al. 1999), Norris, and MRC functionality scales, and by percent survival and FVC (Forced Vital Capacity). Slower declines were seen in the lithium group by the 3 and 6 month marks, with statistical significance in the ALSFRS-R score difference at 6 months. At the end of 15 months, one third of the control group had died, while all of the experimentals had survived. Throughout the experiment PALS (People with ALS) on lithium experienced ALSFRS-R point loss at a rate that was about 2/3 less than the rate of decline of the controls.

These results generated great excitement in the ALS community. Since lithium is an approved drug for the treatment of bipolar disorder, it was immediately available for off-label prescription and a number of ALS patients quickly began lithium treatment. ALS patients often lose control of all voluntary muscles over a time span of months to several years, and so patients often do not have the 2 to 3 years to wait for formal follow up studies to be performed and published. Therefore the worldwide web was used by the patients and their families to rapidly gather and analyze data on whether lithium was working. In January 2008 Humberto Macedo, an ALS patient living in Brazil, initiated an online spreadsheet for PALS on lithium to track their dosage, blood levels, side effects, and change in ALSFRS-R scores for each month on lithium. The data tracking and analysis effort was soon joined by Karen Felzer, whose father was diagnosed with ALS in August 2007. A website was set up at http://alslithium.atspace.com, which provides information on taking

lithium for ALS, information on joining the study, and links to the study spreadsheet and graphs, where all data is made available in real time. On March 8 the spreadsheet project joined forces with PatientsLikeMe, an online site where ALS patients track their symptoms, ALSFRS-R score progressions, and treatments. PatientsLikeMe provides a wealth of control data that, like the spreadsheet data, is compiled online and reported by patients themselves. This study represents a strong example of how motivated patients and the tools made available by the world wide web can be used to rapidly and rigorously evaluate the effectiveness of proposed treatments that use already approved drugs or over-the-counter supplements.

PALS on lithium signed up on the spreadsheet over a period of time, from January until May 12, when new enrollment was closed at a total enrollment of 191. PALS wishing to participate after that date entered data only on the PatientsLikeMe site. As of June 12, 2008 168 of spreadsheet participants had provided dates of ALS diagnosis, and ALSFRS-R scores for their time of diagnosis and the date on which they started lithium. These dates and scores allow for estimates of each PALS progression rate prior to starting lithium. This is critical, as ALS is characterized by a wide range of progression rates. Also as of June 12, 2008 142 PALS had reported their ALSFRS-R scores after one month on lithium, 116 their scores after two months, 91 their scores at the three month mark, 42 their scores at the four month mark, 14 their scores at the five month mark, and one person reported a six month data point. Of the 91 patients reporting 3 month data 82 also provided sufficient background data to estimate their pre-lithium progression rate. For this report we present our statistical analysis of the first three months of lithium treatment and preliminary analysis of the fourth month. Sufficient data is not yet available for months 5 and 6.

3 Methods

ALS patients for the online lithium and riluzole trial were recruited through online discussion forums, the PatientsLikeMe website, and the study website, http://alslithium.atspace.com. Patients worked with their own doctors to take baseline health tests before starting lithim, obtain prescriptions for lithium (in the vast majority of cases in the form of lithium carbonate), and monitor lithium blood levels, kidney and thyroid function, and other potential health issues. In accordance with personal communication from S. Ruggieri, an author on Fornai et al. (2008), patients were advised to start with 150 mg of lithium carbonate taken twice daily (300 mg/day) and to increase to 150 mg taken 3 times daily if a blood level of 0.4 mmol/l of lithium was not obtained after two weeks. Fornai et al. (2008) indicated that all patients attained a blood level of 0.4 to 0.8 mmol/l (with the majority between 0.4 and 0.6 mmol/l, Fornai et al. (2008)) on doses of either 300 or 450 mg/day. We found, however, that in many cases higher doses were required. As of June 12, 2008 101 of the initial 191 patients who signed up had attained blood levels of at least 0.4 mmol/l; 35% did so on doses of 450 mg/day or less; the remaining 65% required more (Figure 1). 33% of patients required 600 mg/day to reach 0.4 mmol/l. 25% of patients needed more than 600 mg/day, with a total of 5% needing to take more than 900 mg/day (the maximum dose taken was 1200 mg/day). Patients who did not reach 0.4 mmol/l in general either could not tolerate the dose needed to obtain this blood level, stopped taking lithium before reaching this level, were advised by their doctors to stay at a lower level, or were lost to follow up. The need for many patients in our study to take a dose higher than 450 mg/day to reach 0.4 mmol/l blood concentration may reflect differences in the diets of our patients and patients in the Italian study, as sodium, liquid, and food acidity, among many other dietary factors, will influence lithium excretion. For comparison, patients with bipolar disorder usually taken 450 to 1200 mg/day, with a goal of obtaining blood lithium concentrations of 0.6 to 1.0 mmol/l.

All data for our study was collected via email. Patients were first sent a questionnaire which collected their background data and starting lithium date and dosage and ALSFRS-R score. E-mails were then sent once a month to each participant to collect their current ALSFRS-R score, any lithium side effects, lithium

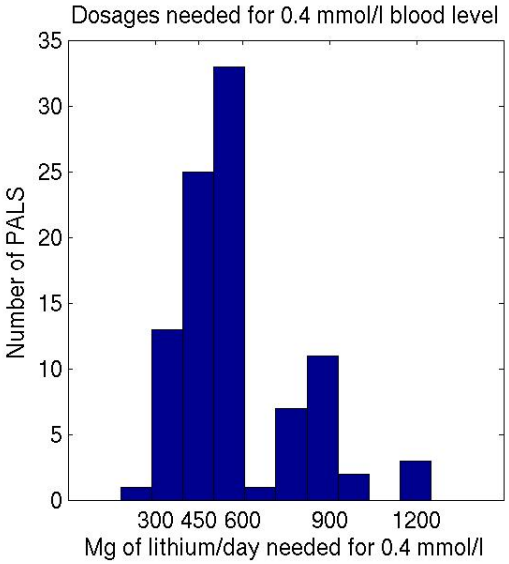

Figure 1: The distribution of dosages taken by patients who achieved 0.4 mmol/l blood concentration of lithium. Although Fornai et al. (2008) indicated that doses of only 300 or 450 mg/day were necessary, these dosages worked for only 35% of the patients in the current study who achieved a 0.4 mmol/l lithium concentration. Another 33% of patients achieved the recommended blood level on a dose of 600 mg/day, and the remaining patients required higher doses.

blood test results, and any changes in dosage. Some participants also voluntarily provided data at more frequent intervals. If a participant did not respond within 7 days a second email reminder was sent out. If a patient reported stopping lithium they were not sent another query for data until the 6 month mark. The loss of patients from the study may have impact on the results, as discussed below. All reported data was recorded as soon as possible (generally within several days) on an online spreadsheet that is accessible to the public, making it possible for all patients and anyone else interested to have full access to all of the data in real time. Patients were identified on this spreadsheet by a username of their choice. Of all those who started lithium as of June 12, 2008 77% of those who started over a month ago provided 1 month ALSFRS-R scores; 68% of those starting over 2 months ago provided 2 month scores, 68% of those starting over 3 months ago provided 3 month scores, 79% of those starting over 4 months ago provided 4 month scores, and 72% of those starting over 5 months ago provided 5 month scores. Reasons for not providing scores were either unknown or the participant had stopped taking lithium (As of June 12, 2% of study participants had stopped taking lithium before the 1 month mark, 6% before the 2 month mark, 13% before the three month mark, and 16% before the 4 month mark). By July 12, 2008 a total of 24% of the original participants had stopped lithium and overall data collection rates were lower - see Figure 5. In some cases participants did not respond on time because they were out of town or hospitalized. ALSFRS-R scores were calculated by the patient or a family member using an online calculator.

3.1 Data Analysis

Since all of the patients in the trial are on lithium, data is analyzed by comparing participants to their own pre-lithium progression rates and by comparing patients to PALS on PLM (PatientsLikeMe) who did not take lithium.

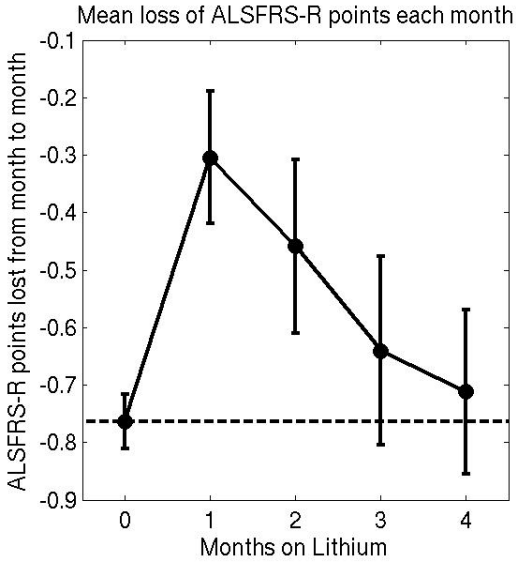

Figure 2: The mean change in ALSFRS-R score from month to month for patients on lithium. The error bars give standard error (one standard deviation) on the confidence of the mean. The data used is from all patients that provided data for at least two consecutive months as of July 3, 2008. This includes 138 PALS who provided data for month 0 and month 1, 109 who reported for month 1 and month 2, 91 who reported for month 2 and month 3, and 61 who reported for month 3 and month 4. The month 0 data point gives the average loss of ALSFRS-R points per month between diagnosis and the start of lithium, and is constrained by data from 170 study participants.

Self comparison of the study population to itself was done first by calculating the mean loss of ALFRS-R points per month between diagnosis and the start of lithium to the change from month to month while lithium was being taken. This particular method is not statistically rigorous as patients do not generally follow a linear progression along the entire ALSFRS-R scale, but it gives a general and straightforward measure of the results. A plot of the average monthly ALSFRS-R change for the first four months, along with the standard error on the population mean, is given in Figure 2 . It can be seen that ALSFRS-R point loss slowed for the first month on lithium, but returned towards baseline on months 3 – 4. The decreased progression rate for the first two months may be real; a few patients posted strong initial improvements, and ten patients noted steep decreases in cramping and spasticity. It should be noted, however, that a decrease in ALS progression rate is often seen for the first two months after a patient starts on a promising new treatment (J. Heywood, personal communication).

Changes in the mean ALSFRS-R point change provide a good general picture but do not tell us about the underlying distribution – did a subset of patients experience benefits at the 3 month mark while others actually experienced faster progression? Figure 3 provides histograms of the month to month change for each patient over the first four months; it is clear that there is a wide spread in the results. Determining whether this spread is normal in ALS progression and rigorously determining whether lithium has any effect on progression rates requires comparison against a control group. Since a placebo effect may be occurring for the first two months on lithium, we do a comparison between experimentals and controls only at the three month mark.

We have currently been able to select 63 controls from PatientsLikeMe; more will hopefully be selected as our study progresses. Controls were selected as PALS who had ALSFRS-R data points recorded between

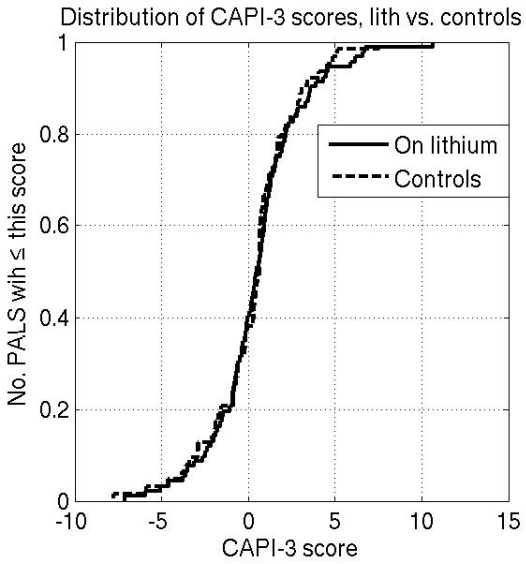

Figure 3: Comparison of the distribution of CAPI-3 scores for patients on lithium for three months vs. PALS not taking lithium who reported ALSFRS-R scores on the PatientsLikeMe website. The CAPI-3 score is a measure of progression over a three month period corrected for the PALS previous rate of progression (see text). Calculation of the score requires an ALSFRS-R score at least three months before the start of lithium (usually given for the time of ALS diagnosis), and scores at lithium start and 3 months later. As of July 3, 2008 CAPI-3 scores could be calculated for 93 PALS on lithium and 63 controls. The distribution of CAPI-3 scores for the lithium and control populations are extremely similar; a Kolmogorov-Smirnoff test indicates an 89% probability that the two data sets come from the same parent distribution, indicating an 89% probability that lithium has no effect (either positive or negative) on ALS progression rate at the 3 month mark.

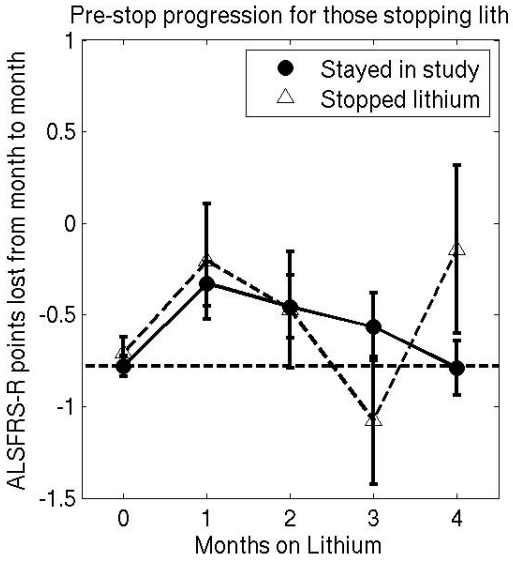

Figure 4: The mean change in ALSFRS-R score from month to month for patients still taking lithium as of July 3, 2008, vs. the data for those who stopped taking lithium at some point before July 3. The error bars give standard error (one standard deviation) on the confidence of the mean. The data used is from all patients that provided data for at least two consecutive months as of July 3, 2008. This includes 108, 90, 79, and 57 patients who stayed on lithium for the 1 through 4 month data points, vs. 31, 19, 12, and 4 patients who dropped lithium for the 1 through 4 month data points. There are no statistically significant 98%) confidence in the month to month progression rates for those who stayed on vs. decided to stop taking lithium. As faster progression or weakness was often given as as reason for stopping lithium, however, the PALS who stopped may have experienced faster progression during the month that they stopped taking lithium and stopped providing data.

2.5 - 4 months apart and who had an additional point that was at least three months before this point, and near the time of diagnosis, from which prior progression rate could be estimated. Average progression rate and age were very similar between the experimentals and controls (see details in Table 1). The controls started at a lower initial ALSFRS-R score, which we correct for, as described below. The controls also had a different gender mix, with a higher percentage of women to men than in the experimentals. However as gender was not seen to influence progression rates on lithium, this factor was not corrected for. For the three month report we use for the main analysis the 82 PALS who had reported a three month ALSFRS-R score by June 12, 2008 and who reported ALSFRS-R scores for their lithium start data and for at least one other date at least three months prior to this (generally this data point was reported for the time of diagnosis). Note that this does not include the 26 PALS who dropped out before the 3 month mark as of June 12. An inspection of the patients who stopped taking lithium shows that they were progressing similarly to other patients for the first two months, but progressed more quickly at month 3; the most popular time for dropping the study was also between the third and fourth months (Figures 4, 5). Faster progression or weakness was one of the reasons patients gave for stopping lithium, so it is possible that some experienced even faster progression in the month that they stopped taking lithium and providing ALSFRS-R scores.

To maximize the sensitivity of our statistical analysis we transform the change in ALSFRS-R points to a score corrected for previous progression rate, that we call the three month Corrected ALS Progression Index, or CAPI-3 score. The score is given by:

Group	Age	Gender	Mean decline pre-lith.	ALSFFRS-R at lith. start
On Lithium	52.1 ± 11.2	82% male	-0.7 ± 0.57	33.4 ± 9
Controls	51.9 ± 9.6	59% male	-0.75 ± 0.96	28.5 ± 9.6

Table 1: Comparison between the 63 controls and 82 PALS on lithium for three months as of June 12. Values given are the means $\pm$ one standard deviation. The mean decline pre-lithium is the mean loss of ALSFRS-R points per month between diagnosis and the start of lithium treatment. For controls this is the average loss was calculated to the start of the three months of data that we used for each control.

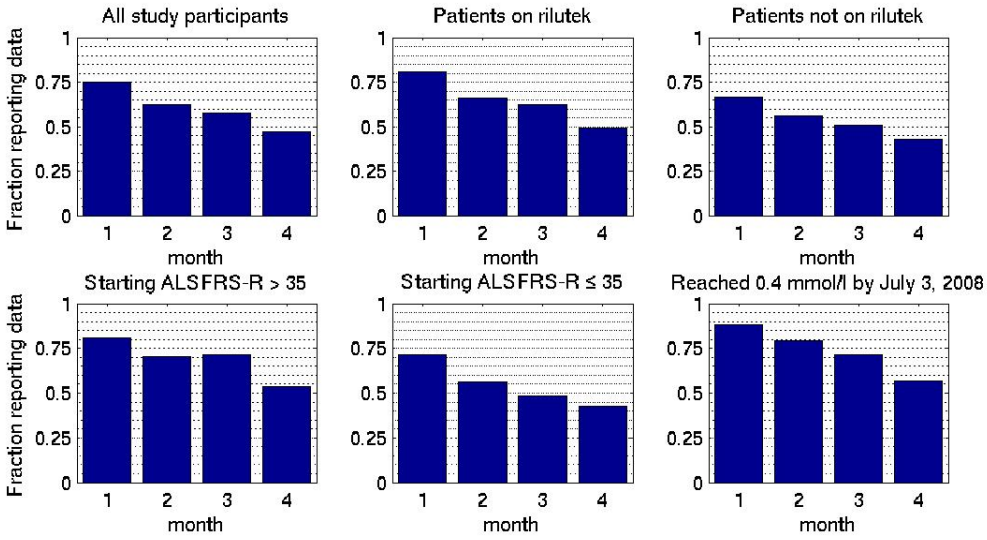

Figure 5: Fraction of patients reporting data each month. The top right plot gives the fraction of all study participants; other plots look at subgroups of patients on and off of rilutek, with an ALSFRS-R score at the beginning of the study of above and below 35 points, and patients reaching 0.4 mmol/l blood lithium concentration by July 3, 2008. By July 3, 2008 24% of initial patients reported quitting lithium and another 26% had not reported their 4 month data. Incidence of non-reporting or late reporting has increased during the summer months due to summer travel.

$$CAPI-3 = FRS_{3ME} - FRS_{3MO} - 3/FRS_{init} \quad (1)$$

where FRS_{3ME} is the expected ALSFRS-R change over three months, found via linear extrapolation from the average rate of ALSFRS-R change per month from diagnosis to the beginning of the three month period, and FRS_{3MO} is the observed change in ALSFRS-R points over the 3 month period. FRS_{init} is the ALSFRS-R score at the beginning of the three month period. The last term is an empirical correction for a small negative correlation found between the CAPI-3 score and FRS_{init}.

The more positive the CAPI-3 score the slower the progression (less points lost than expected by linear extrapolation), while a more negative CAPI-3 score indicates a faster progression over the tested three month period. Since control patients were those simply reporting ALSFRS-R scores at will at a period somewheres between 2.5 - 4 months, vs. experimentals who were queried at three months for their score, the ALSFRS-R score change reported by the controls was corrected to a three month estimated point change via linear extrapolation or interpolation, as needed.

For control patients with initial ALSFRS-R point loss rates between diagnosis and the beginning of the three month measurement period ('start of placebo') of < 2 points per month, which represents 95% of the control population, there is no correlation between the previous progression rate and CAPI-3 score over the three month trial period ($r = 0.01$, $n = 60$). This indicates that the CAPI-3 score provides a useful metric by which groups of PALS on different treatments may be compared to each other even if initial progression rates are not precisely matched (although a gross mis-match in progression rates may, of course, still prove to be problematic). For the three controls initial progression rates faster than 2 points lost per month there is a strong negative correlation, indicating, thankfully, that progression that starts at a very rapid pace often does not maintain such speed. With the empirical correction given above included in the equation there is also no correlation between the CAPI-3 score and the ALSFRS-R score at the beginning of the three month period ($r = 0.008$,$n = 63$).

Although the CAPI-3 scores do not correlate with previous progression rates or starting ALSFRS- R values they do show a wide range, varying from about -8 to +8 for both the controls and experimentals, which illustrates the general volatility of ALS progression rates over three month periods. The mean CAPI-3 score for the controls was 0.3 ± 0.3 (standard error, or 67% confidence) while the mean CAPI-3 score for the experimentals was 0.64 ± 0.3. This indicates a 50% overlap of the standard error ranges of the mean progressions. Cumulative distribution function (CDF) plots for the two CAPI-3 distributions show significant overlap (Figure 3) and a Kolmogorov-Smirnoff (K-S) test indicates an 89% probability that the two distributions come from the same parent distribution. That is, there is only an 11% chance that we can reject the null hypothesis that lithium has no effect on ALS progression – far below the usual standard of 95% or 98% confidence before a treatment is declared effective.

We can also do a straight comparison of how patients in the lithium and control group did over the three month period in comparison to a linear extrapolation of their average progression rate from diagnosis to lithium/placebo start. The controls had an average linear projection of 2.39 ALSFRS-R points over the three months and lost an average of 1.87 points, or 78% of the linear extrapolation, while those on lithium had an average linear extrapolated loss of 2.1 points and lost an average of 1.32, or 63%. Based on this, the lithium patients may be said to have progressed about 80% as quickly as the controls over the three month period, or 20% slower. From the statistical comparisons above, however, it must be noted that the differences between the lithium and control groups are not statistically significant. In addition, any slower progression in the lithium group is primarily due to slower progression during months 1 and 2; by month 4 the average month to month point loss is very close to pre-lithium levels (Figure 2).

4 Population subsets: Riluzole, blood levels, and disease status

Although patients taking lithium as a whole do not show any statistically significant change in expected ALS progression rates at the 3 and 4 month marks it is important to ask whether any subset of the patient population might be doing differently. In particular, does it make any difference whether or not a patient takes riluzole with the lithium? Whether or not they have achieved a lithium blood level of at least 0.4 mmol/l? Whether they start lithium early or later on in the disease progression?

We first look at riluzole usage. Of the 82 patients who provided complete 3 month and background data as of June 12, 54, or 66% reported taking riluzole with the lithium, while 28 reported not taking riluzole. The mean CAPI-3 scores of those on riluzole was lower than those not on riluzole (0.38 vs. 1.46) indicating that those on riluzole actually did worse; however the difference between the two groups is not statistically significant at 98% confidence (63% chance that the two distributions are the same, using the K-S test). Month to month progression comparisons of those on and not on riluzole is given in Figure 6 and shows that while those on riluzole did worse in month 3 they actually did better in month 4. This volatility may be caused by the observation that patients on riluzole were more likely to quit the study (Figure 5). In summary this is data that we need to continue to watch, but at this point there is no clear indication that it is helpful to take riluzole with lithium.

We next compare patients who did or did not achieve lithium blood levels of 0.4 mmol/l by the three month mark. Of the 82 three month patients 21 achieved 0.4 mmol/l by the end of the first month on lithium, 40 by the end of the second month, and 49 by the end of the third month. 29 patients were still below 0.4 mmol/l at the three month mark, in some cases because they could not tolerate higher doses of lithium. Comparing the 40 patients who reached 0.4 mmol/l at least 30 days before the 3 month mark and the 29 patients who had not reached 0.4 mmol/l before 90 days we find that those who remained below 0.4 mmol/l did better (mean CAPI-3 score of 0.91 vs. 0.34) but again the difference between the two groups is not statistically significant (24% chance that the two distributions come from the same parent distribution using the K-S test). Month to month progression comparisons of those who did or did not reach 0.4 mmol/l by at least 30 days before the 3 month mark is given in Figure 7.

Finally we look at the effect of a PALS' ALSFRS-R value when they started taking lithium. Of the 82 patients reporting three months of data by June 12, 2008 40 started lithium at ALSFRS-R scores of > 35 (out of a total of 48 possible points) and 42 started at 35 or less. The patients with a starting ALSFRS-R score of < 35 actually did significantly better at the three month mark at 98% confidence than those starting out with higher ALSFRS-R scores (mean CAPI-3 of 1.23 vs. 0.24; the K-S test indicates less than a 0.3% chance that the two distributions are the same). The patients starting with ALSFRS-R scores of < 35 also do significantly better than the < 35 control population, at 98% confidence. When we look at the month to month plot of patients starting above and below an ALSFRS-R score of 35, however, we see that this statistic is only because of a strong difference between the two groups at 3 months (Figure 8); the difference is not very strong at 1 or 2 months, and the two groups are close to each other again at the 4 month mark. Thus the difference does not appear to be a real or lasting effect. It is most likely caused by the increased propensity of patients with lower starting ALSFRS-R scores to drop out of the study before the three month mark, and the fact that the difference between drop out rates of those starting with ALSFRS-R scores above and below 35 is strongest at the 3 month mark (Figure 5). The starting score of those who dropped before the three month mark is 29 ± 2.3 while the mean starting ALSFRS-R score of those staying the course was 33.2 ± 1 (standard errors given). One might imagine that those starting with lower ALSFRS-R scores had tried different treatments before, and were thus quicker to stop a new treatment in the absence of obvious benefit. One might further imagine that those who felt themselves doing more poorly at three months were more likely to drop out. This would explain why the mean of those remaining in the study at three months would suddenly show improvement. Further note that the largest attrition rate occurred between the second

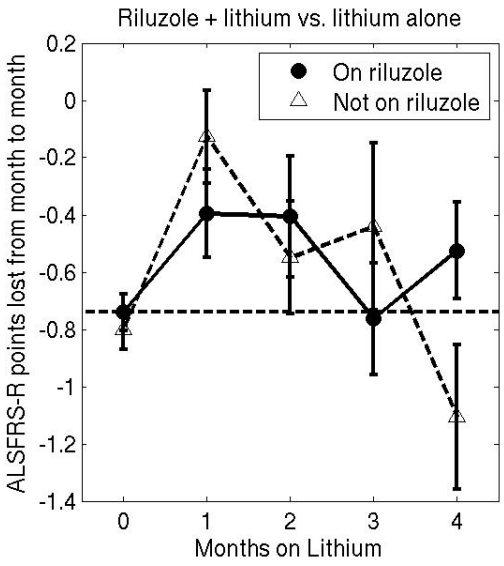

Figure 6: Comparison of month to month progression for patients taking lithium and riluzole together vs. those taking lithium alone. The plot gives the mean change in ALSFRS-R score from month to month and the standard error (one standard deviation) on the calculation of the population mean. The point at month zero gives mean ALSFRS-R point change from diagnosis to lithium start. This plot is based on data available July 3, 2008 and uses, for the patients on riluzole, 106, 91, 69, 56, and 41 patients respectively for the data at month 0, 1, 2, 3, and 4, and for those taking lithium only there are 64, 47, 40, 35, and 28 patients used for months 0, 1, 2, 3, and 4. Note that whether or not a patient was taking riluzole did not impact their rate of decline before the start of the study. Patients on riluzole do worse at the 3 month point but better at the 4 month point; neither difference is statistically significant at 98% confidence (although the 4 month difference is significant at 67% confidence, or one standard deviation). Patients on riluzole who quit the study had faster progression, on average, while on lithium (lost ALSFRS-R points at an average rate of -0.59 points/month from the time of starting to stopping lithium) whereas patients not on riluzole who stopped the study only lost an average of -0.16 points/month from the time they started to the time they stopped lithium. Patients not on riluzole were also overall more likely to drop the study (Figure 5).

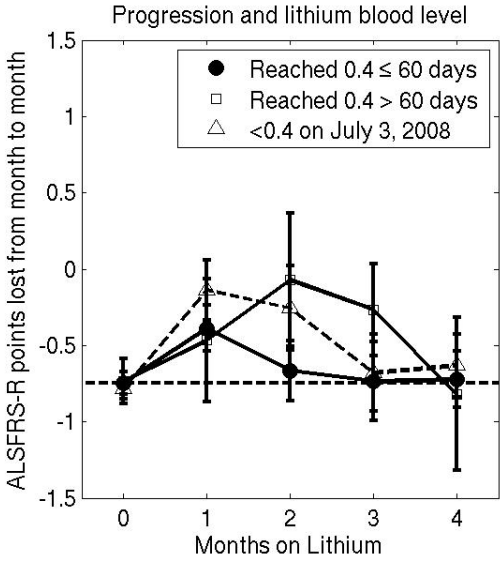

Figure 7: The mean change in ALSFRS-R score from month to month for patients who achieved blood levels of 0.4 mmol/l by the end of the second month on lithium, those who achieved it after the second month but before July 3, 2008, and those who were below 0.4 mmol/l on July 3, 2008. No significant difference is seen in the progression rates of the three groups.

and third month, when 7% of patients stopped taking lithium; only 3% dropped between months 3 and 4, which may explain why the 3 to 4 month ALSFRS-R point loss looks more similar again between the > 35 and < 35 ALSFRS-R point starting groups.

5 Side effects and morbidity

Fornai et al. (2008) reported that no participant in their study experienced side effects from the lithium, presumably because of the lower dosage and blood level target employed than for treatment of bipolar disorder. In spite of the lower dosage and blood level targets, however, 49% of participants in the current study reported side effects, with 12% of study participants reporting moderate to severe problems. Many of the side effects were strongest when lithium was started or when doses were increased and abated with time, but some side effects persisted throughout the time of lithium usage. Common side effects have included increased fasciculations, increased need and urgency of urination, sudden increased weakness, sudden increased slurring of speech, increased fatigue, stomach upset, including diarrhea and nausea, dry mouth, dry and/or irritated skin, problems with thyroid function, weight gain, strange taste in mouth, headache, increased breathing difficulties, temporary depression (upon starting lithium or increase in dose), and general feeling of unwellness. A more detailed description of side effects and their frequency is given in Table 2 and a detailed tabulation of side effect frequency and severity can also be found on the PatientsLikeMe website. There is some difficulty in knowing whether some effects, such as weakness, were due to lithium or to natural ALS progression; in general we made the assumption that effects that were reported to start within a week of lithium starting or dosage increase, and to be much stronger than anything previously experienced by the patient, to be lithium side effects. Such side effects that were clearly temporally associated with lithium, including weakness, also were generally reported to improved when lithium was decreased or discontinued.

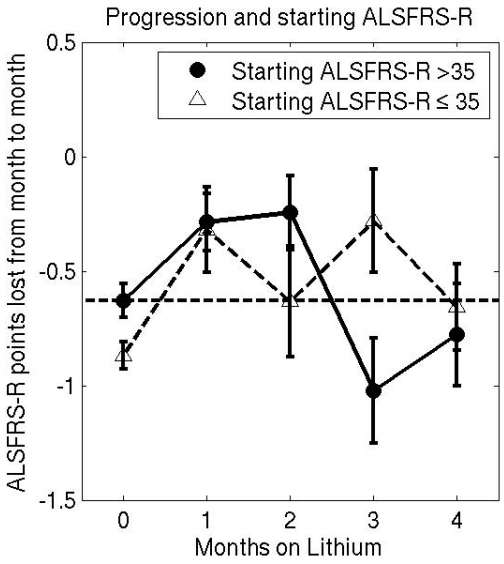

Figure 8: Comparison of month to month progression for patients starting the lithium study with ALSFRS-R scores above and below 35 points. The plot gives the mean change in ALSFRS-R score from month to month and the standard error (one standard deviation) on the calculation of the population mean. The point at month zero gives mean ALSFRS-R point change from diagnosis to lithium start. This plot is based on data available July 3, 2008 and uses, for the patients at a starting ALSFRS-R > 35, 75, 63, 49, 43, and 27 patients respectively for the data at month 0, 1, 2, 3, and 4, and for those with starting ALSFRS-R ≤ 35 there are 102, 75, 60, 46, and 32 patients used for months 0, 1, 2, 3, and 4. Patients with starting ALSFRS-R ≤ 35 do significantly better at the 3 month mark but the gap closes again at 4 months. Patients with a starting ALSFRS-R below 35 were more likely to drop out and overall less likely to report data as the study progressed; at month 3 71% of those with starting ALSFRS-R > 35 reported data while only 49% of those with a starting ALSFRS-R 35 did so; at 4 months the percentage of patients reporting was closer at 54% vs. 43%, respectively (Figure 5). Assuming that those patients who are doing better are more likely to report back data at any one time, the fact that many ALSFRS-R 35 patients, presumably those who were doing the worst, did not report in at 3 months may explain why the average scores for those who did report was higher.

Side Effect	Number of patients reporting
breathing difficulties	2
constipation	3
diarrhea	7
dizziness	1
dry mouth	5
increase in fasciculations	25
fatigue	15
foot pain	1
hand tremor	5
headache	14
increased saliva	7
increased urination	17
irregular bowel	2
itchy feet	1
loss of appetite	4
low thyroid	3
loss of hair	1
muscle cramps	3
nausea	8
poor concentration	3
skin irritation	8
slurred speech	4
stiffness	2
strange taste in mouth	8
swallowing difficulties	2
swollen feet	1
thirsty	3
upset stomach	5
weakness	20
weight gain	1
vision problems, eye pain	2

Table 2: This table provides a list of side effects reported by patients taking lithium and the number of patients reporting each side effect. Please also see the side effect tables on the PatientsLIkeMe website, which includes indications of severity. The side effects reported by 10 or more patients were increase in fasciculations, fatigue, headache, increased urination, and increased weakness.

Several patients experienced symptoms of lithium toxicity, and in some cases lithium levels did rise dangerously high in the blood. These patients were not on exceptionally high doses of lithium, but they were not eating or drinking very much as a result of ALS induced swallowing difficulties (one patient was waiting for a feeding tube). The lack of sufficient fluid and sodium intake is presumably what caused the high lithium levels, as without adequate fluids and sodium the kidneys cannot adequately excrete lithium from the body. Patients were clearly advised that intake of sufficient sodium and fluids was necessary, but patients did not necessarily stop taking lithium when their disease progression made swallowing very difficult.

To our knowledge no patients died in this study as a result of lithium toxicity, but 3 patients were lost during the first three months of the trial. Causes of death were given as probable embolism, heart failure during a transfer, and unknown causes after returning home from hospital treatment for dehydration. At least one patient went on a ventilator during the first 4 months of lithium treatment.

6 Benefits of lithium

Although our numbers currently show that lithium does not affect ALS progression, some patients did report relief from some ALS symptoms as a result of taking lithium. Symptomatic relief included a decrease in fasciculations (4 patients), a strong decrease in painful cramping (6 patients), increased flexibility/less spasticity (4 patients), and relief from emotional lability (1 patient). The symptom relief generally occurred soon after the patients started lithium, and before they reached 0.4 mmol/l; doses of 300 mg/day and blood levels of 0.2 mmol/l were generally sufficient to provide the benefit. It is not clear at this time, however, whether the benefits will be long-lasting; on June 27 we received reports of returning cramps from one patient who had initially experienced some of the strongest relief from lithium treatment.

7 Summary and conclusions

In summary we see no statistically significant impact of lithium on the rate of ALS progression for PALS who reported ALSFRS-R scores at the 3 and 4 month mark. PALS on lithium are progressing at rates that are consistent with their previous rates of progression, as determined by comparison with ALS controls. The one important caveat to this is that 3 and 4 month ALSFRS-R scores were not taken from patients who decided to stop taking lithium before these points, because they were no longer under lithium treatment. If these patients had remained in the study it is possible that we would have seen lithium negatively affecting ALS progression. The ALSFRS-R scores of all patients who started the study is currently being collected at the 6 month mark, whether those patients remained on lithium or not, so that the progression of the group stopping lithium can also be tracked.

Even if lithium does not accelerate ALS progression, it resulted in side effects for nearly half of study participants, with serious side effects for about 12% of patients. Given the lack of any clear positive benefit of lithium on ALS progression and this incidence of unpleasant side effects, lithium cannot be recommended at this time as treatment for ALS, except for in cases where small doses of lithium (300 mg/day, or blood levels of 0.2 mmol/l) are shown to be effective in individuals for treatment of cramps, fasciculations, or spasticity.

The big question is why our results differ so strongly from those of Fornai et al. (2008), who found such a clear benefit of lithium in slowing ALS progression. We do not know the reason for the discrepancy but hypothesize that since the Fornai et al. (2008) treatment group was so small (15 patients), it may have been disproportionally made up of slow progressors. It is difficult to think of any other error which may have been made in the study, although it is also worth noting that the lithium mouse study results reported by Fornai

et al. (2008) also could not be repeated by ALS TDI (the ALS Therapy Development Institute; lithium study results can be seen by following the links from http://www.als.net/research/ or http://alslithium.atspace.com).

We plan to continue collecting data from study participants through the 6 month mark. At that point we will write up our final analysis and submit for publication. Further follow up and analysis may be conducted after that point by the reasearch staff at PatientsLikeMe.

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