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Supplementary Material

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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SUPPLEMENTARY MATERIAL FOR

Developing a method to estimate the 12-hour serum-lithium level, eLi$_{12}$:

Discovery and two proof-of-concept trials

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Supplementary Table 1: Characteristics at baseline and during follow-up of the included 145 individuals from the Bipolar CHOICE trial compared to the 95 excluded individuals.

	Included (N=145)	Excluded (N=95)
BASELINE		
Mean age	39.3 ±11.9	37.6 ±12.2
Female gender	59.4%	56.7%
Ethnicity other than hispanic or latino	83.5%	86.7%
Marital status		
Single	39.2%	42.3%
Divorced or separated	18.9%	21.7%
Married	35.7%	30.9%
Widowed	2.8%	0%
Never Married	3.5%	5.2%
Employment		
Employed	40.6%	37.1%
Unemployed	32.9%	33.0%
Disability recipient	16.1%	15.5%
Student	6.3%	9.3%
Retired	2.8%	1.0%
Other	1.4%	4.1%
Educational level		
Less than high school	4.2%	6.2%
High school	20.3%	15.5%
Some college	28.7%	32.0%
Technical school	14.0%	11.3%
Bachelor's degree	22.4%	30.9%
Graduate or professional degree	10.5%	4.1%
Household income		
24,999 or less	51.8%	51.0%
25,000-49,999	19.6%	20.8%

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25,000-74,999	14.0%	10.4%
75,000 or greater	14.7%	17.7%
Current major depressive episode	72.7%	69.1%
Current manic episode	18.2%	17.5%
Age at first depressive episode	16.2 ±8.7	16.2 ±8.1
Age at first manic episode	19.7 ±10.3	19.2 ±9.1
Lifetime depressive episodes	36.0 ±35.0	38.7 ±41.3
Lifetime manic episodes	36.0 ±42.8	41.6 ±67.0
Taking psychotropic drugs at baseline	77.6%	79.4%
Previous psychiatric hospitalized	44.8%	48.5%
No. of previous psychiatric hospitalizations	4.0 ±7.7	2.4 ±1.9
Previous suicide attempt	37.8%	40.2%
Mean MADRS	23.2 ±9.8	24.4 ±9.8
Mean CGI-BP	4.5 ±0.9	4.5 ±0.8
Mean FISER side effects	0.67 ±1.22	0.78 ±1.28
Mean TSH	1.66 ±0.91	1.76 ±1.54
Mean creatinine	83.8 ±0.18	84.4 ±0.18
Mean BUN	11.9 ±3.72	12.0 ±4.16
WEEK 2		
Mean lithium dose	663 ±235	711 ±213
No. of psychotropic medications	1.8 ±0.92	2.0 ±1.17
Mean MADRS	14.0 ±9.3	17.7 ±10.6
Mean CGI-BP	3.5 ±1.1	3.9 ±1.1*
Mean FISER side effects	1.45 ±1.63	1.53 ±1.78
WEEK 16		
Mean lithium dose	964 ±274	944 ±389
No. of psychotropic medications	2.1 ±1.0	2.4 ±1.3
Mean creatinine	0.90 ±0.22	0.87 ±0.22
Mean BUN	11.3 ±4.26	12.1 ±5.08
Mean MADRS	10.6 ±9.2	12.9 ±10.9*
Mean CGI-BP	3 ±1.4	3 ±1.4
Mean FISER side effects	1.36 ±1.59	1.35 ±1.56
WEEK 24		
Mean lithium dose	995 ±266	949 ±428
No. of psychotropic medications	2.2 ±1.05	2.4 ±1.22
Mean TSH	2.69 ±1.85	2.10 ±1.18
Mean creatinine	0.89 ±0.22	0.89 ±0.21
Mean BUN	11.4 ±4.32	11.9 ±4.25
Mean MADRS	10.4 ±9.8	11.3 ±8.7
Mean CGI-BP	2.9 ±1.3	3.1 ±1.3
Mean FISER side effects	1.14 ±1.51	0.87 ±1.29

Values are presented as mean ±SD (standard deviation) or as percentages.

Variables between the two groups were compared with Fisher´s exact test for categorical variables or oneway ANOVA analysis for continuous variables. * indicate a p-value < 0.05.

Supplementary Figure 1: Histograms of serum lithium levels (top) including the square root distribution (bottom) of serum lithium levels.
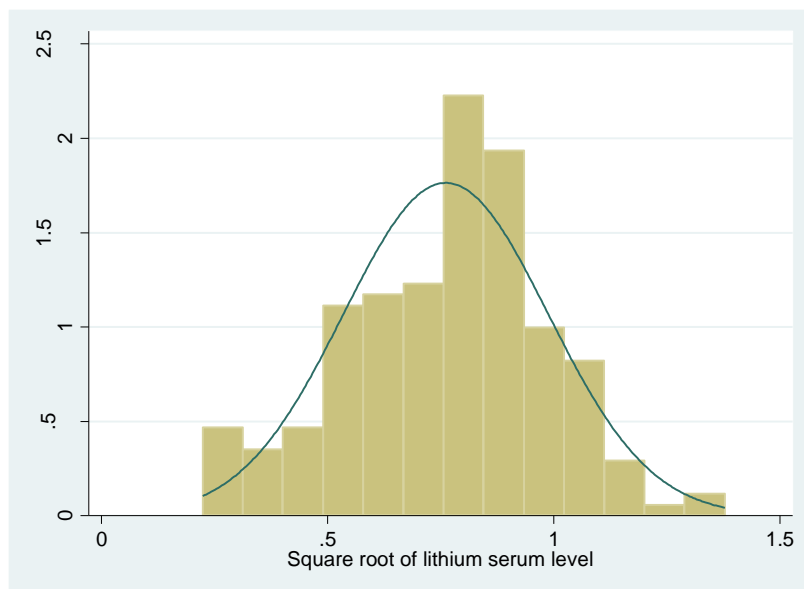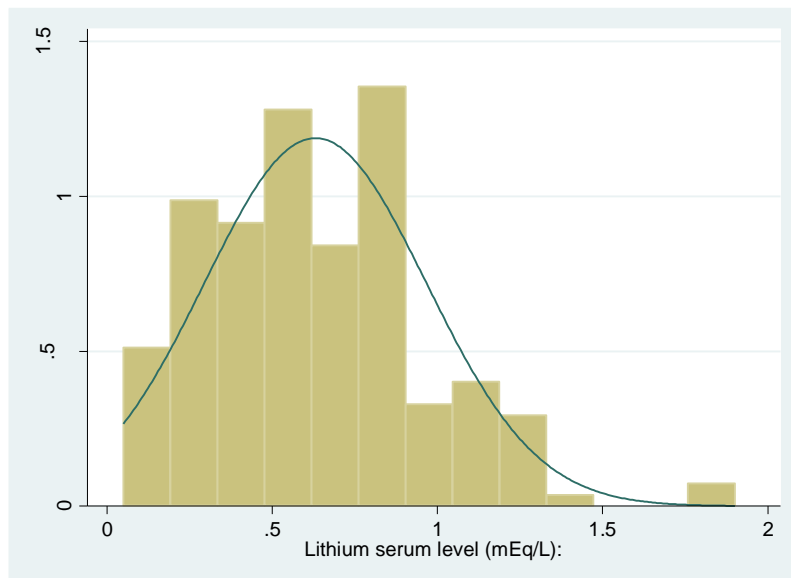
Supplementary Figure 2: Association between the time since the last lithium dose and the lithium serum level among 145 patients yielding 284 measurements after 2, 16 and 24 weeks of treatment.
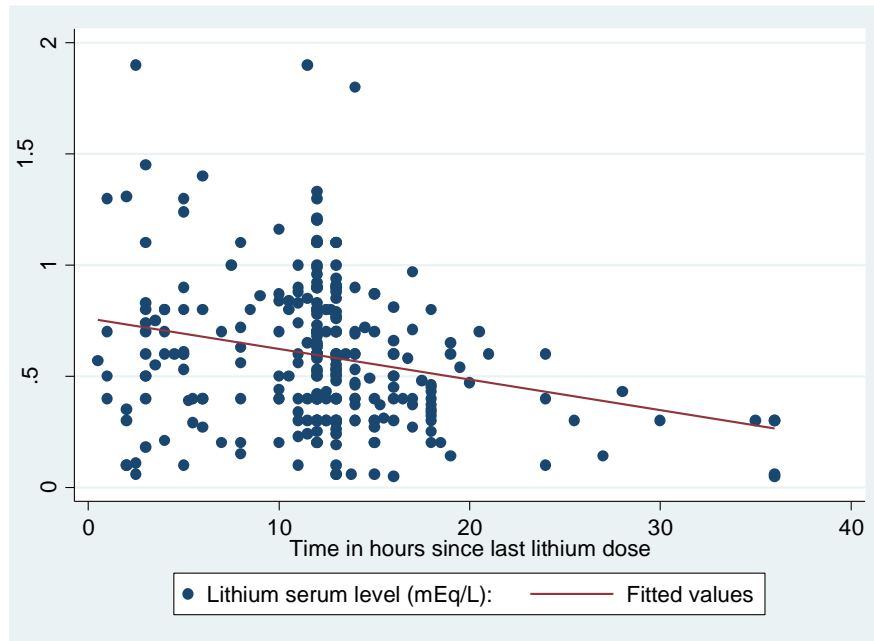
	Time in hours since last lithium dose					
	<8 (N=53)	8-12 (N=104)	12-14 (N=63)	14-16 (N=24)	16-20 (N=26)	>20 (N=15)
Mean[1] ±SD serum lithium level (mEq\L)	0.64 ±0.40	0.67 ±0.31	0.59 ±0.32	0.45 ±0.24[2]	0.44 ±0.19[2]	0.33 ±0.20[2]
Mean[3] ±SD lithium dose (mg)	852 ±300	937 ±304	892 ±318	867 ±303	776 ±242	784 ±260

Individuals with lithium serum levels of 0 (N=4) and those with >36 hours since last lithium dose (N=3) were excluded for the plot and the analyses.

[1] Linear regression analyses show a significant decrease in serum lithium depending on a longer time since the last lithium dose, as indicated by a coefficient of -0.013; 95%CI=-0.019, -0.007; $p<0.001$.

[2] Bonferroni, Scheffe and Sidak multiple comparison corrections showed that individuals with 14-16, 16-20 and >20 hours since the last lithium dose had significantly lower serum lithium levels compared to individuals with 8-12 hours since the last lithium dose.

[3] P=0.15 for oneway ANOVA analysis regarding the difference in mean lithium levels between the six different groups.