Estimating the 12-Hour Serum Lithium Level (eLi_{12}): Development and Two Proof-of-Concept Studies

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Abstract

Objective: Most serum lithium (se-Li) tests do not comply with the required timing (12 hours after lithium intake). We aimed to develop an equation estimating 12-hour se-Li levels when lithium blood tests are taken at other time points than 12 hours.

Methods: The equation was developed via secondary analyses using data from the Bipolar Clinical Health Outcomes Initiative in Comparative Effectiveness (CHOICE) trial and verified in 2 separate proof-of-concept studies. Bipolar CHOICE included 122 lithium-treated patients (192 se-Li measurements), who had se-Li levels measured and self-reported the time since lithium intake. The proof-of-concept studies tested the accuracy of the equation by measuring se-Li concentrations at different time points up to 24 hours after lithium intake and were performed in Boston, US (5 patients, 10 se-Li measurements) and Aarhus, Denmark (21 patients, 159 se-Li measurements).

Results: We present a simple equation calculating the estimated 12-hour se-Li level (eLi_{12}) based on the measured se-Li level at the patient-reported time for intake of the last lithium dose. The accuracy was confirmed in both proof-of-concept studies, where eLi_{12} showed a mean deviation from the 12-hour se-Li level of 10% compared to 25% for the measured se-Li ($P < .0001$). For 99 out of 102 (97%) blood tests taken between 3 and 24 hours after the last lithium dose, eLi_{12} was closer to the 12-hour level than the actual measured se-Li level.

Conclusion: eLi_{12} provides clinicians with more accurate 12-hour se-Li estimations and gives patients flexibility as to when to show up for lithium blood tests.

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Lithium has for decades been a standard mood-stabilizing treatment option for patients with bipolar disorder.[1–4] Dosing of lithium is based on the clinical effect, side effects, and monitoring of serum-lithium (se-Li) levels.[4,5] Clinical efficacy is dose-dependent and correlates with se-Li levels,[5] which can be measured easily and accurately. Guidelines recommend measuring se-Li levels during titration but also regularly when a stable dose has been achieved.[4,6,7] In addition to influencing clinical treatment decisions, se-Li levels are measured to avoid high se-Li levels and hence potential side effects of lithium treatment. Lithium can adversely affect the kidneys[8–12] and the thyroid gland[11–13] and has a narrow therapeutic window.[3,4,14]

Standard practice is that se-Li levels should be measured 12 hours after the patient took the most recent lithium dose,[15] with most guidelines recommending a window between 8 and 14 hours.[4,6,7] Optimally, the patient should take the lithium dose in the evening, and the blood test should be conducted the next morning before a possible morning dose. However, adherence to lithium treatment is low,[16] regular therapeutic drug monitoring often not performed,[17,18] and many patients do not take their lithium 12 hours before a blood test. Because these issues create a time-lag between the last lithium dose and se-Li measurement, the se-Li level may not reflect the actual 12-hour se-Li level, which could lead to clinical problems. For example, a falsely low se-Li level may lead to up-titration of lithium dosage, increasing the risk for side effects.

Despite the necessity of assaying the 12-hour se-Li level, only a few small studies[15,19] have explored how deviating from 12 hours affects se-Li levels. Studies on large samples of patients seen in clinical settings are missing. Furthermore, while methods have been proposed to calculate the estimated lithium dosage requirement[20,21] or an a priori se-Li level,[22,23] no study has tried to estimate 12-hour se-Li levels for patients who

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Clinical Points

- Lithium blood tests should be conducted 12 hours after the last lithium dose, but it is difficult to comply with this strict timing.
- We developed a simple tool to estimate the 12-hour serum lithium concentration when the lithium blood test was taken at a different time point.
- We will test whether it is possible and feasible to implement eLi_{12} in everyday clinical work.

had a different time interval between the last lithium dose and the blood test.

To fill this gap, the present study sought to create a useful clinical tool that would enable back-calculation of an approximate 12-hour se-Li level (termed eLi_{12}) based on the patients' self-reported time since lithium intake and the measured se-Li level.

METHODS

Development of eLi_{12}

Setting. eLi_{12} was developed based on secondary analysis using data from the Bipolar CHOICE study,[24] a 6-month multisite, randomized trial comparing lithium to quetiapine for bipolar disorder. Participants provided verbal and written informed consent prior to participation, and all Institutional Review Boards approved the study protocol (for Methods, see reference 24).

Participants. A total of 482 patients aged 18–62 years were randomized, 240 to lithium carbonate. Bipolar CHOICE applied broad inclusion and limited exclusion criteria. Participants had a *DSM-IV-TR* diagnosis of bipolar disorder, assessed with the extended Mini-International Neuropsychiatric Interview and a Clinical Global Impression Scale for Bipolar Disorder score ≥3.[25] Clinical interviews obtained demographic information and medical history.

Se-Li levels and time since last lithium dose. Among the 240 patients randomized to lithium carbonate, se-Li levels (in milliequivalents per liter, mEq/L) were measured via an antecubital vein blood sample after 2, 16, and 24 weeks of treatment. At the same visits, patients reported the number of hours between their last lithium dose and the blood test. We included the 145 participants with this information.

The target se-Li was 0.6 mEq/L, corresponding to an approximate dose of 900 mg lithium. Patients started with lithium treatment at study entry; hence, the 2-week visit was during up-titration. Most patients were on their stable maintenance dose at weeks 16 and 24. Creatinine and blood urea nitrogen (BUN) were measured at weeks 0, 16, and 24. Thyroid-stimulating hormone (TSH) was measured at weeks 0 and 24.

Statistical analysis. All analyses were performed using STATA 14.0. To test whether the included and excluded lithium-treated participants differed on clinical and sociodemographic characteristics, we performed Fisher exact test for continuous variables and analysis of variance (ANOVA) for categorical variables.

We used Gaussian regression to estimate 12-hour se-Li levels from the measured se-Li level and the time since the most recent intake of lithium. Because se-Li levels were not normally distributed, we used the square root of se-Li levels as the dependent variable (Supplementary Figure 1). We assessed for a nonlinear development over time between the last lithium dose and included its interactions with sex, NSAID use, creatinine, and BUN.

We grouped patients based on the time since their most recent lithium intake: <8, 8–12, 12–14, 14–16, 16–20, and >20 hours. We performed ANOVA using the guideline-recommended group of 8–12 hours as the reference group. Bonferroni, Scheffe, and Sidak multiple comparisons were performed to investigate differences between all groups separately.

As a first sensitivity analysis, we added data from the week 2 visit, although this was a time during up-titration for most patients. Additional sensitivity analyses excluded individuals with increased serum creatinine >1.2, NSAID use at any point during the study, treated hypertension, or any self-reported kidney disease, as these might affect se-Li levels. Because some patients supplied more than one data point, all observations were not statistically independent of one another. We addressed this issue by using robust standard errors, clustering on patient.

First Proof-of-Concept Study

Setting. To test the accuracy of the eLi_{12} equation, we performed a pilot proof-of-concept study at the Massachusetts General Hospital bipolar disorder outpatient clinic (Boston, MA). Participants provided verbal and written informed consent prior to participation, and the Institutional Review Board approved the study protocol.

Participants. We recruited 5 patients aged 18–65 years with a diagnosis of bipolar disorder treated with lithium. Exclusion criteria were inability to provide informed consent, pregnancy, and involuntary hospital admission.

Se-Li levels and time since most recent lithium dose. We took 2 blood tests from each participant via standard antecubital vein blood sample. The first was 12 hours after their self-reported time of most recent lithium intake; the second was between 15 and 18 hours after the self-reported time of intake.

Statistical analysis. We calculated eLi_{12} using the equation developed in the discovery study. To compare the eLi_{12} value from the second blood test to the 12-hour se-Li level, we calculated the absolute and percent deviation between these two values.

Second Proof-of-Concept Study

Setting. We performed a larger proof-of-concept study at Aarhus University Hospital Psychiatry, Aarhus, Denmark (EudraCT number: 2022-000034-42). Participants provided verbal and written informed consent, and the Central Denmark Region Research Ethics Committee approved the study (reference number: 1-10-72-28-22).

Participants. We recruited 23 inpatients according to the following criteria:

Inclusion criteria:

1. Age ≥18 years.
2. Treatment with lithium.
3. On a stable lithium dose, ie, no dose change within the past 5 days.
4. Lithium prescribed as one daily dose administered in the evening.

Exclusion criteria:

1. Lacking ability to provide informed consent.
2. Any current coercive measure (eg, involuntarily admission).
3. Patients under forensic sanctions.
4. Reduced renal clearance, defined as estimated glomerular filtration rate (eGFR) <60 within the previous month.
5. Severe mania (as per clinical judgment).
6. Clinical condition that precludes participation, eg, severe suicidality (as per clinical judgment).
7. Pregnancy (pregnancy test).

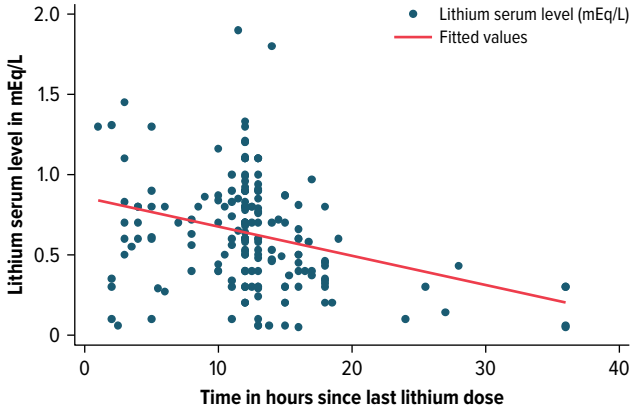
Se-Li levels and time since most recent lithium dose. Participation involved up to 9 antecubital vein blood samples during 24 consecutive hours. The daily lithium dose was given in the evening, mostly at 8 PM. The first blood sample was taken immediately before this lithium dose. The remaining 8 blood samples were taken at 2, 4, 9, 11, 12, 14, 20, and 24 hours after the first blood sample, respectively. Some samples were taken at slightly different time points if preferred by the patient, eg, a 10-hour level at 6 AM instead of 5 AM for the 9-hour level. Blood samples were centrifuged (most directly after sampling, some were at room temperature for up to 6 hours), stored at −80°C, and se-Li levels were measured in all samples at the same time to minimize measurement bias.

Power calculation. Based on the data from the Bipolar CHOICE trial, we assumed a power of 80%, a SD of 0.3 (which was the SD for the mean se-Li levels as a function of time (hours) since the most recent lithium intake), and a width of 0.1 (assuming a rather narrow confidence interval), which resulted in 154 required blood samples.

Statistical analysis. The primary end point was whether eLi_{12} could estimate a 12-hour se-Li level within an acceptable range of the measured 12-hour se-Li level without giving falsely high or low se-Li values. All se-Li data from participants with a measured se-Li level at 12 hours and at least 1 other time point were included for analyses.

Figure 1.

Dot Plot of the Association Between the Time in Hours Since the Last Lithium Dose and the Se-Li Level Among 122 Patients[a] From the Bipolar CHOICE Trial



[a]The dataset included a total of 192 se-Li measurements after 16 (n = 103) and 24 weeks (n = 89) of lithium treatment, respectively. Individuals with serum lithium levels of 0 (N = 3) and those with >36 hours since last lithium dose (N = 2) were excluded.

We calculated the mean differences including SD between the eLi_{12} from the different time points and the measured 12-hour se-Li level in absolute and relative (ie, percentage) terms. We performed paired *t* tests to calculate the difference between the mean eLi_{12} and the mean measured se-Li levels.

RESULTS

Development of eLi_{12}

The 145 included patients did not differ from the remaining 95 patients (Supplementary Table 1). The same was the case for the 122 patients who were on a stable maintenance dose, ie, after 16 or 24 weeks of treatment, that were used for the primary analyses.

The 122 patients (mean age 39.2, 59.4% females) yielded 192 se-Li level measurements. The mean se-Li was 0.63 mEq/L (SD = 0.33; range = 0.05–1.9) while the median was 0.60 (interquartile range [IQR] = 0.35–0.81). The mean lithium carbonate dose was 1,002.0 mg (SD = 259.7; range = 150–1,500). The mean time from the most recent lithium dose to the blood sampling was 13.1 hours (SD = 5.6; range = 1–36), while the median was 12 hours (IQR = 11–14). The 53 (27.6%) who reported that they took their most recent lithium dose 12 hours before blood sampling had a mean se-Li level of 0.74 (SD = 0.29) and a mean lithium dose of 1,062.2 mg (SD = 270.1).

Regression model of the association between last lithium dose and se-Li level. Figure 1 shows the plot between se-Li levels and the time since the last dose (Pearson correlation = −0.30; $P < 0.0001$).

When compared to participants with blood samples taken 8–12 hours after the most recent lithium dose, patients with 14–16 hours ($P = .018$), 16–20 hours ($P = .021$), and >20 hours ($P < .001$) had significantly lower se-Li levels (Table 1). Patients with 8–12 hours since the last lithium dose had a more than 3-fold higher (0.72 vs 0.21 mEq/L) se-Li compared to patients with >20 hours. We found no statistically significant differences between the groups regarding mean lithium dose or levels of TSH, creatinine, and BUN (Table 1).

Gaussian regression found a statistically significant association between the time since the most recent lithium dose with lower se-Li levels (β-coefficient = −0.013; 95% CI, −0.018, −0.007; $P < .001$). The Pearson correlation between the actual and predicted square root of se-Li level was 0.34 ($P < .0001$). We found similar results when including week 2 se-Li levels, resulting in 145 patients with 284 se-Li measurements (Supplementary Figure 2).

Based on the Gaussian regression model predicting se-Li level from time since last dose, we present the following equation for calculating the estimated 12-hour se-Li level:

$$\mathrm{eLi}_{12} = (\sqrt{\text{se-Li}} + \beta * (12 - h))2$$

where eLi_{12} is the estimated 12-hour se-Li level. se-Li is the actual measured se-Li level at the patient-reported hour (h) after the last lithium dose, √ is the square root operator, and β is the coefficient from the regression model, ie, −0.013. The equation uses the square root of the serum Li level because we used the square root transformation in our regression analysis.

First Proof-of-Concept Study

The 5 participants (mean age 29.2 years [range 19–53], 20% female, mean lithium carbonate dose 600 mg) provided 1 blood test 12 hours after the self-reported most recent lithium intake and another between 14.9 and 18.2 hours after lithium intake. Table 2 shows that for all patients, except #6, eLi_{12} was closer to the self-reported 12-hour level compared with the measured level. For #6, the deviation was the same for both. The mean deviation of eLi_{12} compared to the 12-hour level was 0.044 mEq/L (mean of 0.552 vs 0.508), while it was 0.11 mEq/L for the measured se-Li at other time points.

Second Proof-of-Concept Study

The 23 participants (17 with bipolar disorder and 6 with unipolar depression) were all treated with lithium citrate (mean age 41.6 years [range = 21–72], 61% female, and mean lithium dose 19.8 mmol) and provided 163 blood tests. For 2 participants, it was not possible to draw blood at 12 hours, leaving data from 21 participants with 159 blood tests for analysis. The mean 12-hour se-Li level of the 21 participants was 0.57 mEq/L (SD = 0.16, range = 0.27–0.81).

Figure 2 shows the measured se-Li levels and the eLi_{12} levels during the 24 hours after the lithium dose for each of the 21 participants. Ideally, the eLi_{12} lines (Figure 2B) should each be horizontal as they aim to each estimate the same 12-hour se-Li level. They are not perfectly horizontal, but much closer to horizontal than the actual se-Li levels (Figure 2A).

The measured se-Li and eLi_{12} levels including the absolute and percentage deviations between these measures are presented in Table 3. When including all blood tests (excluding those at 0 and 12 hours), the mean difference from the measured se-Li compared to the 12-hour se-Li level was 0.14 mEq/L, while the difference was 0.07 mEq/L for eLi_{12} ($P < .0001$). The difference between the measured se-Li and the 12-hour level was larger at the more extreme time points, eg, at 4, 19, or 20 hours, with eLi_{12} being notably closer to the 12-hour se-Li level even at these extreme time points. For example, after 20 hours, the measured mean se-Li was 0.21 (34%) lower than the 12-hour se-Li level, while the mean eLi_{12} was only 0.07 (12%) lower.

For the 117 blood levels not taken at 0 or 12 hours, eLi_{12} was closer to the true 12-hour level in 105 blood tests (90%), while for 2 blood tests, eLi_{12} was identical with the measured se-Li. Those 10 blood tests, where eLi_{12} was not closer to the 12-hour level, were all taken within 2 hours after the last lithium dose. In these cases, eLi_{12} estimated se-Li levels lower than the measured se-Li. Hence, among blood tests taken between 3 and 24 hours after the most recent lithium dose, 99 out of 102 (97%) eLi_{12} estimations were closer to the 12-hour se-Li compared to the measured se-Li concentrations. At no time point did eLi_{12} estimate an unexpectedly high 12-hour se-Li level.

DISCUSSION

This study presents a new method to estimate more accurate 12-hour se-Li levels independent of when the lithium blood test is taken, which has the potential to improve real-world lithium treatment. eLi_{12} is based on data from 3 separate clinical studies; the discovery study using data from a US multisite randomized trial and 2 proof-of-concept studies conducted in the US and Denmark, respectively. Based on the findings of the present study, eLi_{12} can provide the clinician with a better metric for adjusting the patient's lithium dose than the current 12-hour se-Li, since deviations in the timing of blood sampling by only a few hours from the 12-hour blood test results in clinically relevant differences in se-Li levels. In addition, eLi_{12} offers greater flexibility for the patient as blood tests are not required to be taken exactly 12 hours after the last lithium dose. Thereby, the present study lays the foundation for future

Table 1.

Data From the Bipolar CHOICE Trial: Patient Characteristics (mean ± SD) by Time Since Most Recent Lithium Dose

	Time in hours since last lithium dose					
	<8 (N = 28)	8–12 (N = 80)	12–14 (N = 39)	14–16 (N = 21)	16–20 (N = 16)	>20 (N = 8)
Se-Li, mEq/L	0.68 ± 0.37	0.72 ± 0.31	0.64 ± 0.36	0.47 ± 0.25[a]	0.44 ± 0.21[a]	0.21 ± 0.14[a]
Lithium[b] dose, mg	1,021 ± 216	1,034 ± 262	1,017 ± 291	945 ± 228	842 ± 256	950 ± 225
TSH[c,d], µU/mL	2.3 ± 1.7	3.1 ± 1.8	2.6 ± 1.3	2.3 ± 2.3	2.8 ± 1.4	2.2 ± 0.1
Creatinine[d], mg/dL	0.97 ± 0.22	0.91 ± 0.21	0.96 ± 0.28	0.86 ± 0.14	0.82 ± 0.11	0.81 ± 0.18
BUN[d], mg/dL	10.6 ± 4.3	11.3 ± 4.3	11.8 ± 5.8	11.6 ± 3.7	12.2 ± 4.4	11.0 ± 4.5

[a]ANOVA with 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.
[b]$P = .18$ for difference between the 6 groups in mean lithium dose based on 1-way ANOVA analyses.
[c]TSH levels were only measured after 24 weeks but not after 16 weeks.
[d]ANOVA comparison between the different groups, using those with 8–12 hours as the reference group, showed $P = 0.13$ for creatinine, $P = 0.67$ for TSH, and $P = 0.89$ for BUN.
Abbreviations: BUN = blood urea nitrogen, TSH = thyroid-stimulating hormone.

Table 2.

Results From the Boston Proof-of-Concept Trial Assessing the Accuracy of the eLi_{12} Equation

ID	Age	Sex	Last dose	Hours after 12-hour level (h)	12-Hour se-Li level	12 + h se-Li level	eLi_{12}	Absolute deviation[a]	Percent deviation[b]
1	19.5	Female	450 mg	2.9	1.09	0.9	0.97	0.12	0.11
2	53.5	Male	900 mg	4	0.44	0.35	0.41	0.03	0.06
4	32.1	Male	600 mg	3.9	0.61	0.5	0.57	0.04	0.06
6	46.8	Male	300 mg	4.17	0.31	0.28	0.34	−0.03	−0.10
7	24.2	Male	750 mg	6.17	0.31	0.18	0.25	0.06	0.18
Mean	29.2		600	4.2	0.552	0.442	0.508	0.056	10.2

[a]Absolute deviation: the difference between predicted and self-reported 12-hour se-Li levels.
[b]Percent deviation: the difference as a percentage of the self-reported 12-hour se-Li level.
Abbreviation: eLi_{12} = estimated 12-hour se-Li level.

studies to develop a tool that can help to improve lithium treatment in everyday clinical settings.

Our findings have actionable, clinical implications for several reasons. First, both research[16,26] and clinical experience indicate that most se-Li tests do not comply with the 12-hour requirement. This may be due to missed doses,[27] waiting time, logistical challenges, or insufficient knowledge about the 12-hour level. Second, even slightly higher se-Li levels can increase the long-term risk for potentially severe side effects and even kidney damage,[8–13] which is why guidelines have re-evaluated their recommended se-Li target levels in order to avoid high levels.[4,6,7] The importance of an approximate 12-hour se-Li level is further emphasized as patients often take lithium for years or decades and often are followed in nonspecialized settings without expert knowledge.[26] Third, estimated values of clinically important measurements are used broadly. A well-known example is the eGFR, representing a widely used blood test estimating kidney function based on creatinine, age, sex, and race.[28–30]

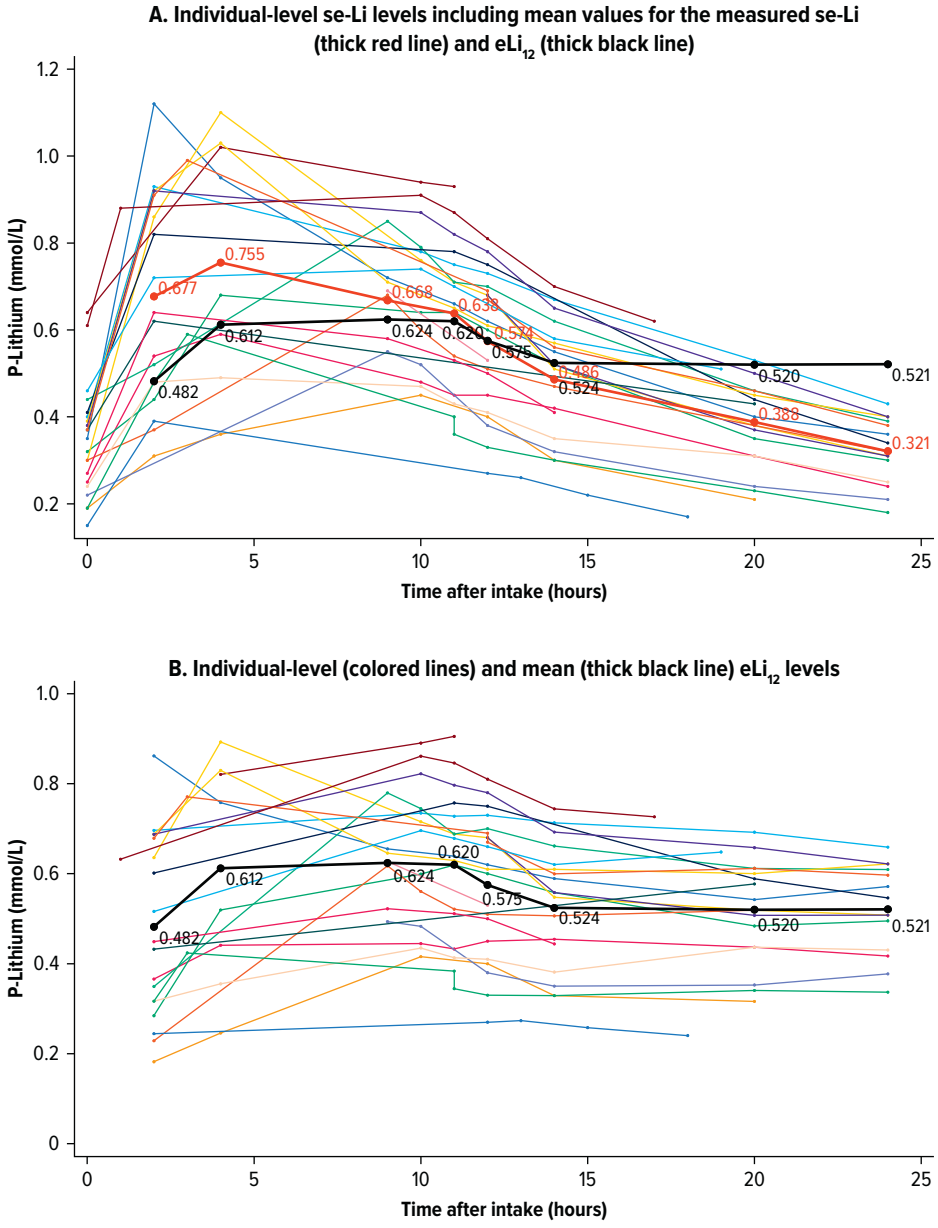
Our equation provides information similar to eGFR. By only requiring the patient-reported time for intake of the last lithium dose, eLi_{12} provides an estimated 12-hour se-Li level that could help clinicians to better evaluate the measured se-Li level. Furthermore, this gives an entirely new flexibility to the patient, as the lithium blood test can be taken at other time points than 12 hours. In addition, eLi_{12} could support the use of lithium for patients where clinicians else would prefer other drugs without the need for specific blood test timing.

Strengths and Limitations

Strengths include the large study population of Bipolar CHOICE and that we performed 2 separate proof-of-concept studies in 2 countries with very

Figure 2.

Data from the Aarhus eLi_{12} Proof-of-Concept Study: Plots of (A) Individual-Level Actual Measured Se-Li levels and (B) eLi_{12} Level Based on the Time in Hours Since the Last Lithium Dose



different health care systems. Also, it is reassuring that the validity of eLi_{12} was supported in settings where patients self-reported the time of the most recent lithium intake (discovery and first proof-of-concept study) and where this time was monitored by research staff (second proof-of-concept study). Furthermore, the validity of eLi_{12} was supported both by studies using lithium carbonate (discovery and first proof-of-concept study) and lithium citrate (second proof-of-concept study).

Regarding limitations, it can be argued that the relatively weak linear relationship between the time since the most recent lithium intake and the measured se-Li level in the Bipolar CHOICE data speaks against the validity of estimating 12-hour se-Li levels using a linear model, but both prospective proof-of-concept studies confirmed the validity of this approach. Second, the validity of eLi_{12} is undetermined for patients (1) younger than 18 years, (2) older than 70 years, (3) with severe

Table 3.

Findings From the Second Proof-of-Concept Trial Conducted in Aarhus, Denmark, to Test the Final Accuracy of the Developed eLi_{12} Equation

Hours after lithium	N	12-Hour se-Li	Measured, mean ± SD (range or 12-h se-Li)	Actual difference to 12-h se-Li (%)	eLi_{12}, mean ± SD (range)	eLi_{12} difference to 12-h se-Li (%)	Difference eLi_{12} actual (%)
12	21	0.57 ± 0.16 (0.27–0.81)	0.57 ± 0.16 (0.27–0.81)	0	0.57 ± 0.16 (0.27–0.81)	0	
2	18	0.58 ± 0.16	0.68 ± 0.24 (0.31–1.12)	0.10 ± 0.17	0.48 ± 0.20 (0.18–0.86)	0.1 ± 0.14	0
3	2	0.53 ± 0.19	0.79 ± 0.28	0.27 ± 0.05 (53)	0.60 ± 0.25 (0.42–0.77)	0.07 ± 0.01 (22)	0.2 (31)
4	7	0.53 ± 0.13	0.74 ± 0.29 (0.36–1.1)	0.2 ± 0.18 (37)	0.58 ± 0.25 (0.24–0.89)	0.04 ± 0.15 (22)	0.16 (15)
9	7	0.55 ± 0.16	0.68 ± 0.10 (0.55–0.85)	0.13 ± 0.04 (25)	0.62 ± 0.10 (0.49–0.78)	0.07 ± 0.04 (13)	0.06 (12)
10	12	0.59 ± 0.15	0.67 ± 0.16 (0.45–0.91)	0.08 ± 0.03 (14)	0.63 ± 0.16 (0.41–0.86)	0.03 ± 0.03 (6)	0.05 (8)
11	15	0.60 ± 0.16	0.64 ± 0.14 (0.4–0.87)	0.03 ± 0.01 (5)	0.62 ± 0.14 (0.38–0.85)	0.01 ± 0.01 (2)	0.02 (3)
13	1	0.27	0.26	0.01 (4)	0.27	0.003 (1)	0.007 (3)
14	18	0.58 ± 0.16	0.50 ± 0.13 (0.3–0.7)	0.08 ± 0.04 (14)	0.54 ± 0.13 (0.33–0.74)	0.04 ± 0.04 (7)	0.04 (7)
15	1	0.27	0.22	0.05 (19)	0.26	0.01 (4)	0.04 (15)
17	1	0.81	0.62	0.19 (23)	0.73	0.08 (10)	0.11 (13)
18	1	0.27	0.17	0.1 (37)	0.24	0.03 (11)	0.07 (26)
19	1	0.66	0.51	0.15 (23)	0.65	0.01 (2)	0.14 (21)
20	16	0.58 ± 0.16	0.38 ± 0.10 (0.21–0.53)	0.21 ± 0.07 (34)	0.51 ± 0.11 (0.32–0.69)	0.07 ± 0.07 (12)	0.14 (22)
24	15	0.59 ± 0.14	0.32 ± 0.08 (0.18–0.43)	0.27 ± 0.09 (45)	0.52 ± 0.10 (0.34–0.66)	0.07 ± 0.08 (12)	0.2 (33)
Mean				0.14 ± 0.10 (25)		0.07 ± 0.07 (10)	

physical illness, (4) with poor kidney function (ie, abnormal creatinine levels), and (5) who are pregnant. Third, eLi_{12} does not, directly, take renal function and the dose of lithium into account, which would likely provide more accurate estimates of the 12-hour se-Li levels. Fourth, in clinical practice, eLi_{12} will rely on patients being able to validly report the time interval between the most recent lithium dose and the blood sampling, which may be difficult for some patients, particularly the most severely ill. Fifth, the 2 proof-of-concept studies were small ($n = 5$ and $n = 23$, respectively).

CONCLUSION

Based on 3 studies from USA and Denmark, we provide an equation to estimate the 12-hour se-Li level, which we term eLi_{12}. This approach can be compared to eGFR, a frequently used test in clinical settings estimating kidney function. eLi_{12} has the potential to improve lithium treatment by providing clinicians with a more accurate estimate of the 12-hour se-Li level and giving lithium-treated patients and hospital services flexibility regarding timing of blood testing. A study examining the feasibility of implementing eLi_{12} in clinical practice is warranted.

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Author Contributions: Drs Köhler-Forsberg, Faraone, and Nierenberg developed the concept of eLi_{12} based on the Bipolar CHOICE study, where Drs Köhler-Forsberg and Faraone performed all statistical analyses. Dr Nierenberg designed and conducted the first proof-of-concept study in Boston, Massachusetts. Drs Köhler-Forsberg, Wiuff, Devantier, and Østergaard designed and performed the second proof-of-concept study in Aarhus, Denmark. Dr Köhler-Forsberg wrote the first draft of the manuscript, which was subsequently revised for important intellectual content by the remaining authors. All authors approved the manuscript prior to submission. Dr Köhler-Forsberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary Material

Article Title: Estimating the 12-Hour Serum-Lithium level (eLi_{12}): Development and Two Proof-of-Concept Studies

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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.

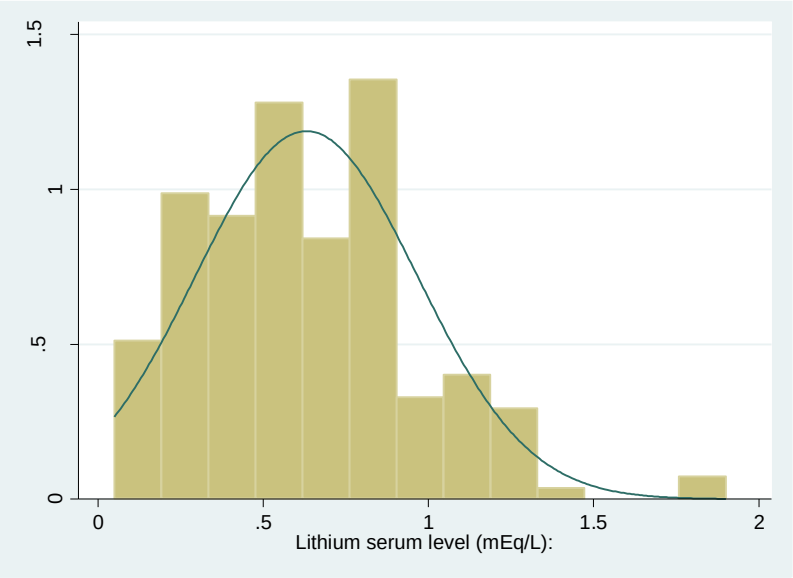
	Included (N=145)	Excluded (N=95)
BASELINE		
Mean age	39.3 ±11.9	37.6 ±12.2
Female gender	59.4%	56.7%
Ethnicity other than hispanic or latino	83.5%	86.7%
Marital status		
Single	39.2%	42.3%
Divorced or separated	18.9%	21.7%
Married	35.7%	30.9%
Widowed	2.8%	0%
Never Married	3.5%	5.2%
Employment		
Employed	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%

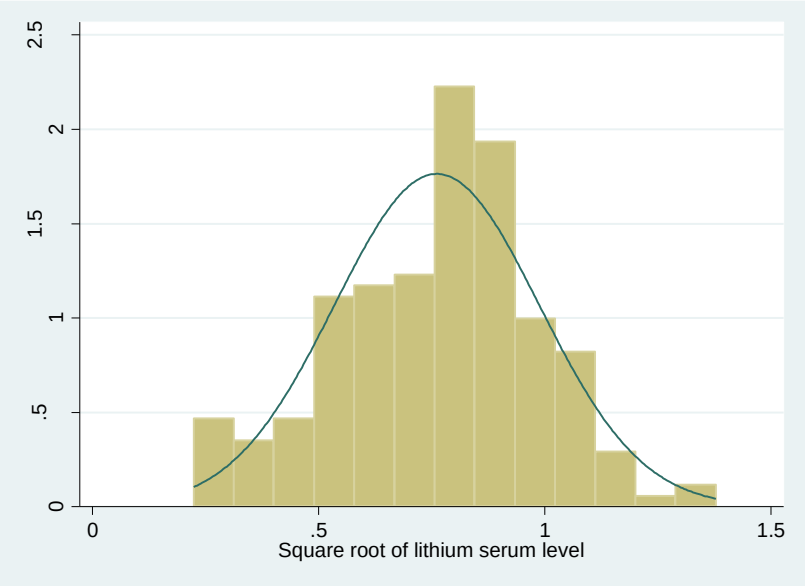
25,000-74,999	14.0%	10.4%
75,000 or greater	14.7%	17.7%
Current major depressive episode	72.7%	69.1%
Current manic episode	18.2%	17.5%
Age at first depressive episode	16.2 ±8.7	16.2 ±8.1
Age at first manic episode	19.7 ±10.3	19.2 ±9.1
Lifetime depressive episodes	36.0 ±35.0	38.7 ±41.3
Lifetime manic 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.

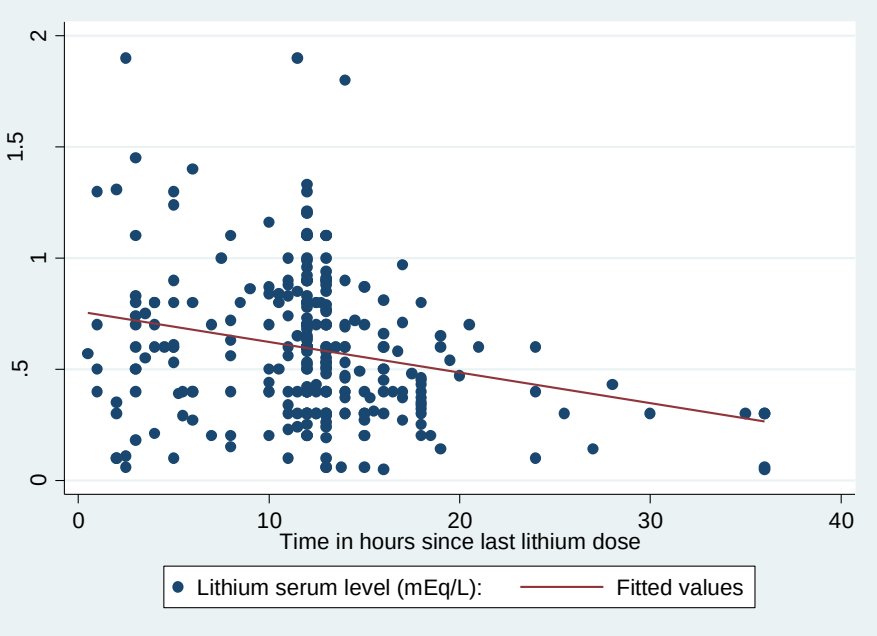
Variables between the two groups were compared with Fisher´s exact test for categorical variables or oneway ANOVA analysis for continuous variables. * indicate a p-value < 0.05.

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.