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## Original Article

# The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: a post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144)

Nolen WA, Weisler RH. The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: a post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144). *Bipolar Disord* 2013; 15: 100–109. © 2012 John Wiley & Sons A/S. Published by Blackwell Publishing Ltd.

**Objectives:** There is no robust proof that the efficacy of lithium in the prevention of manic and depressive episodes in bipolar disorder depends on its plasma level. This analysis aimed to compare the effect of lithium within the presumed therapeutic range of 0.6–1.2 mEq/L and below 0.6 mEq/L with that of placebo.

**Methods:** We carried out a post hoc analysis of a double-blind trial in which patients aged  $\geq 18$  years with bipolar I disorder (DSM-IV) who had achieved stabilization from a manic, depressive, or mixed episode during open-label treatment with quetiapine were randomized to continue quetiapine or to switch to lithium or placebo for up to 104 weeks. Of patients randomized to lithium, 201 obtained median lithium levels between 0.6 and 1.2 mEq/L, and 137 obtained median lithium levels  $< 0.6$  mEq/L. Their outcomes were compared with those of patients receiving placebo ( $n = 404$ ). The primary outcome was time to recurrence of any mood event; additional outcomes included time to recurrence of a manic or depressive event.

**Results:** Times to recurrence of any mood event as well as a manic or depressive event were significantly longer for the lithium 0.6–1.2 mEq/L group versus placebo and versus lithium  $< 0.6$  mEq/L, with no differences between lithium  $< 0.6$  mEq/L and placebo.

**Conclusions:** The results support and expand previous findings that lithium should be dosed high enough to achieve plasma levels  $\geq 0.6$  mEq/L in order to achieve an effect in the prevention of both manic and depressive recurrences of bipolar I disorder. A major limitation is that the composition of the two lithium groups was not based on randomization.

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**Clinical trial registration information:** Quetiapine Fumarate Bipolar Maintenance Monotherapy (SPaRCLe); D1447C00144; <http://clinicaltrials.gov/ct2/show/NCT00314184?cntry1=SA%3ACO&rank=29>.

Portions of these data were presented in poster format at the Eighth International Conference on Bipolar Disorders, June 25–27, 2009, Pittsburgh, PA, USA and at the 22nd ECNP Congress, September 12–16, 2009, Istanbul, Turkey.

Bipolar I disorder is characterized by recurrent manic and depressive episodes. Therefore, treatment should be aimed not only at reducing the symptoms of acute manic and depressive episodes, but also at preventing further recurrences (maintenance treatment). In the 1970s, lithium was the first drug approved in the USA as well as many other countries for the maintenance treatment of bipolar disorder. Although, since then, several other drugs have become available for the maintenance treatment of bipolar disorder (such as valproate, olanzapine, quetiapine, aripiprazole, and lamotrigine) (1–11), lithium has remained a first-line option (12–14). This position was supported by a systematic review and meta-analysis of five randomized controlled trials ( $n = 770$ ) that compared lithium with placebo in the maintenance treatment of bipolar disorder, excluding trials that randomly assigned patients who had been stable on long-term lithium to continue or discontinue lithium. The review found efficacy for lithium in the prevention of any mood episode and manic episodes, but less unequivocal results regarding the prevention of depressive episodes (15).

A disadvantage of lithium is its small therapeutic window. At higher dosages leading to lithium plasma levels above 1.2 mEq/L, there is an increased risk of adverse effects and even toxicity. On the other hand, too-low dosages and corresponding too-low lithium levels are associated with insufficient effect. Therefore, guidelines recommend monitoring lithium levels in patients for an optimal effect and tolerance (12, 13). It is still unclear, however, what the most efficacious and, especially, what the minimum lithium level should be.

While Schou and Bastrup (16), who developed the use of lithium in the maintenance treatment of bipolar disorder, recommended treating patients with lithium levels of at least 0.6 mEq/L, they never evaluated the optimum lithium level in a controlled study. A recent review (17) identified five randomized, controlled studies ( $N = 266$ ) that addressed this question, although with different methodologies. In four studies, patients ( $n = 197$ ) were randomized to low or high lithium levels after having received open treatment with lithium; in the fifth study, patients ( $n = 69$ ) were directly randomized in four groups. The results suggest that lithium levels  $< 0.4$  mEq/L are ineffective, while lithium levels  $> 0.75$  mEq/L may not confer additional advantage. The conclusions of the review are hampered by various methodological limitations: (i) differences in whether patients had already received lithium prior to randomization; (ii) different lithium levels being compared; (iii) different outcome parameters; (iv) not all studies used

intent-to-treat (ITT) analysis; and (v) none of the studies had a placebo arm. Furthermore, the poorer outcome of lower lithium levels in some patients may have resulted from acute reduction of lithium level in patients who were randomized to low lithium levels after receiving lithium at higher levels prior to randomization (18).

In another attempt to investigate whether the effect of lithium depends on its level, Severus et al. (19) performed a post hoc analysis of a study in which patients who had remitted from a manic episode during treatment with the combination of olanzapine and lithium were subsequently randomized to continue double-blind treatment with either olanzapine ( $n = 217$ ) or lithium alone ( $n = 214$ ) (20). Lithium levels were aimed to be between 0.6 and 1.2 mEq/L, but actual lithium levels at randomization were  $< 0.6$  mEq/L ( $n = 14$ ), 0.6–0.8 mEq/L ( $n = 70$ ), and  $> 0.8$  mEq/L ( $n = 128$ ). The lithium  $< 0.6$  mEq/L group had a significantly increased risk for manic/mixed, but not depressive, episodes compared with the combined lithium 0.6–1.2 mEq/L group, suggesting that lithium levels should be above 0.6 mEq/L to be efficacious, at least against mania. A major limitation of this study is that it had no placebo arm.

The objective of the current paper is to describe the results of a post hoc analysis of a randomized, controlled, double-blind trial in which bipolar I disorder patients who achieved stabilization on open-label quetiapine (300–800 mg/day) over 4–24 weeks were randomized to continue quetiapine or to switch to lithium (0.6–1.2 mEq/L) or placebo for up to 104 weeks (21). Both continuation of quetiapine and switching to lithium significantly increased time to recurrence of any mood episode (the primary outcome criterion) as well as time to manic or depressive episodes when compared with switching to placebo. Of the 418 patients randomized to lithium in this trial, 54 were excluded from the ITT population due to inadequate monitoring of their lithium level. Of the remaining 364 patients, 163 patients did not have a median lithium level within the predefined range of 0.6–1.2 mEq/L; in most of these cases lithium levels were  $< 0.6$  mEq/L. This created the opportunity to compare two groups of patients receiving lithium (with lithium levels  $< 0.6$  mEq/L and 0.6–1.2 mEq/L) against those receiving placebo.

## Methods

In this paper, we describe only a part of Trial 144: the outcome of patients who were randomized to switch to lithium or placebo. The study design,

including key inclusion and exclusion criteria and the per-protocol amendment that led to premature discontinuation of the study after interim analysis showed a positive outcome for quetiapine versus placebo, is described in detail elsewhere (21).

The study was conducted in 15 countries in Asia, Europe, Central and South America, and the USA; adhered to the current amendment of the Declaration of Helsinki and International Conference on Harmonisation/Good Clinical Practice guidelines; and was approved by the ethical review boards of participating centers. Written informed consent was obtained from all patients after complete description of the study.

#### Patients

In short, 2438 patients aged  $\geq 18$  years with bipolar I disorder (DSM-IV) with  $\geq$  one previous episode in the last two years and a current (or documented recent) manic, depressive, or mixed episode started open-label treatment with quetiapine (300–800 mg/day, depending on efficacy and tolerance) for up to 24 weeks. Exclusion criteria included intolerance or lack of response to quetiapine or lithium and regular contraindications to lithium. Patients who achieved stabilization by at least week 20 and who maintained stability for at least four subsequent weeks [defined by a Young Mania Rating Scale (YMRS) total score  $\leq 12$  (22) and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score  $\leq 12$  (23)] subsequently entered the double-blind, randomized phase, which was planned for up to 104 weeks. During this phase, patients either continued quetiapine or were gradually switched to placebo or lithium.

#### Study medication

Study medications (quetiapine, lithium, or placebo) were administered twice daily using a double-dummy design. The quetiapine tablets used during the prerandomization phase were systematically replaced with placebo tablets during the first two weeks following randomization. Lithium was started at 600 mg/day and increased to 900 mg/day at day 4. Blood samples were taken for determination of trough serum lithium levels after two weeks and subsequently at every visit, and lithium doses were adjusted to obtain lithium levels between 0.6 and 1.2 mEq/L. To ensure blinding of lithium treatment, a programmed automatic system sent a reply for each blood sample and suggested a change in medication dosage for lithium or dummy recommendations for placebo.

Patients were allowed to continue medications for non-psychiatric illnesses unless these medications were associated with known significant interactions with study medications. Low doses of zolpidem tartrate (maximum 10 mg/day), zaleplon (maximum 20 mg/day), zopiclone (maximum 7.5 mg/day), and chloral hydrate (maximum 1 g/day) for insomnia; lorazepam (maximum 2 mg/day) for anxiety; and anticholinergic medications for extrapyramidal symptoms were permitted throughout the study. No other psychoactive medications were allowed in the four weeks prior to randomization or during the randomized phase.

#### Outcome measures

The primary outcome measure was the time to recurrence of any mood event (manic, depressive, or mixed). *Recurrence* was defined as at least one of the following: initiation of an antipsychotic, antidepressant, anxiolytic (other than lorazepam), or other medication to treat a mood event; hospitalization for a mood event; YMRS score  $\geq 20$  (mania) or MADRS score  $\geq 20$  (depression) at two consecutive assessments or final assessment if the patient discontinued; or discontinuation from the study if this, according to the investigator, was due to a mood event.

Secondary outcome measures included time to recurrence of a manic or depressive event, time to all-cause discontinuation (defined as premature discontinuation due to a mood event or any other reason), and interepisodic mood symptoms [via assessment of severity of manic and depressive symptoms using YMRS, MADRS, and Clinical Global Impression-Bipolar (CGI-BP) Severity of Illness and Global Improvement rating scales (24)]. Assessments during the randomized phase were performed at weeks 0, 1, 2, 4, 6, and 8, and thereafter every four weeks to week 104. For the complete overview of all secondary outcome measures, see the primary publication of the study (21).

#### Adverse events

The incidence and severity of adverse events and withdrawals due to adverse events were recorded at each assessment based on the total population that received medication. Adverse events were reported using Medical Dictionary for Regulatory Activities terminology (<http://www.meddransso.com/>).

Safety measures (laboratory assessments, vital signs, weight and body mass index, electrocardiogram, movement disorders, and suicidality) are not reported here; for the overall results, see the primary publication (21).



## Statistical analyses

Time to recurrence of any mood event, manic event, or depressive event was analyzed by Cox proportional hazards modeling, with geographical region included as covariate (patients with mixed symptoms were allocated by investigators to groups according to predominance of manic or depressive symptoms). Hazard ratios (HRs) for time to recurrence, with corresponding 95% confidence intervals (CIs), were determined between treatment arms. The time to event was censored when a patient completed or discontinued the study without experiencing a manic or depressive event. Times to any mood, manic, and depressive events and time to all-cause discontinuation were additionally explored by Kaplan–Meier estimates and curves. Patients not experiencing an event before the end of the trial (including those who discontinued after interim analysis) were censored.

YMRS, MADRS, and CGI-BP scores were analyzed using analysis of covariance. Importantly, as no patients in the lithium <0.6 mEq/L group even remained in the study after 44 weeks, a mixed-model repeated measures analysis, as described in the primary publication (21), could not be performed. The mean of all assessments between randomization and up to, but excluding, the visit where a mood event was recorded was analyzed. Treatment and geographic region were included in the model as fixed effects and score at randomization as covariate. The ITT population was used for all efficacy analyses.

Descriptive statistics were used to report adverse events and included all patients who received treatment during the randomized phase.

All statistical tests are two-tailed and a  $p$ -value <0.05 is considered statistically significant. No adjustment for multiplicity was carried out and all  $p$ -values are nominal; thus, caution should be exercised when analyzing the results.

## Results

In total, 2438 patients were enrolled in the pre-randomization phase ( $n = 1174$  manic;  $n = 710$  depressive;  $n = 554$  mixed-index episode), of whom 1226 (50.3%) were randomized and 1172 (95.6%) were included in the total ITT population ( $n = 404$  quetiapine;  $n = 364$  lithium;  $n = 404$  placebo) (Fig. 1). In this paper, we focus on the results in the patients who were switched to lithium and who obtained a median lithium level <0.6 mEq/L (lithium <0.6 group;  $n = 137$ ) or between 0.6 and 1.2 mEq/L (lithium 0.6–1.2 group;  $n = 201$ ) versus

those in patients who were switched to placebo ( $n = 404$ ). Eight patients with a median lithium level >1.2 mEq/L were not included in the analysis, as well as 18 patients who did not have any lithium assessment.

Demographic baseline disease characteristics did not differ between patients in the two lithium groups and the placebo group (Table 1). Use of lorazepam, sleep medication, and anticholinergic drugs was similar across treatment groups.

The means of the patients' individual median lithium levels were 0.33 [standard deviation (SD) = 0.15] mEq/L in the lithium <0.6 group (with 56 patients between 0.4 and <0.6 mEq/L, and 81 patients <0.4 mEq/L) and 0.77 (SD = 0.13) mEq/L in the lithium 0.6–1.2 group.

## Efficacy measures

The time to recurrence of any mood event (the primary outcome measure), as well as of a manic or depressive event, was significantly longer in the lithium 0.6–1.2 group compared with the placebo group as well as the lithium <0.6 group, while these measures were not different between the lithium <0.6 group and the placebo group (Table 2 and Figs. 2–4). The HR for the time to recurrence of any mood event for lithium 0.6–1.2 versus placebo was 0.32 (95% CI: 0.23–0.44;  $p < 0.0001$ ), corresponding to a risk reduction of 68%. There were no significant differences between lithium <0.6 and placebo on these outcome measures. On the recommendation of the reviewers, we also performed a multivariate Cox regression analysis with inclusion of potential confounders (gender, type of index episode, rapid cycling, and YMRS and MADRS score at randomization) that were not distributed equally over the three groups. This analysis yielded essentially the same results (Table 2).

When data were stratified by index episode (manic, depressive, or mixed), lithium 0.6–1.2 mEq/L was significantly more effective than placebo in six of the nine outcome measures and was more effective than lithium <0.6 mEq/L in three of the nine outcome measures, while lithium <0.6 mEq/L was not different from placebo (*see Supplementary Table 1*).

Lithium 0.6–1.2 mEq/L was also associated with significant improvements, compared with placebo, in interepisode scores on the YMRS, MADRS, CGI-BP Severity of Illness, and CGI-BP Global Improvement scales and, compared with lithium <0.6 mEq/L, on the CGI-BP Severity of Illness scale (*see Supplementary Table 2*). Again,

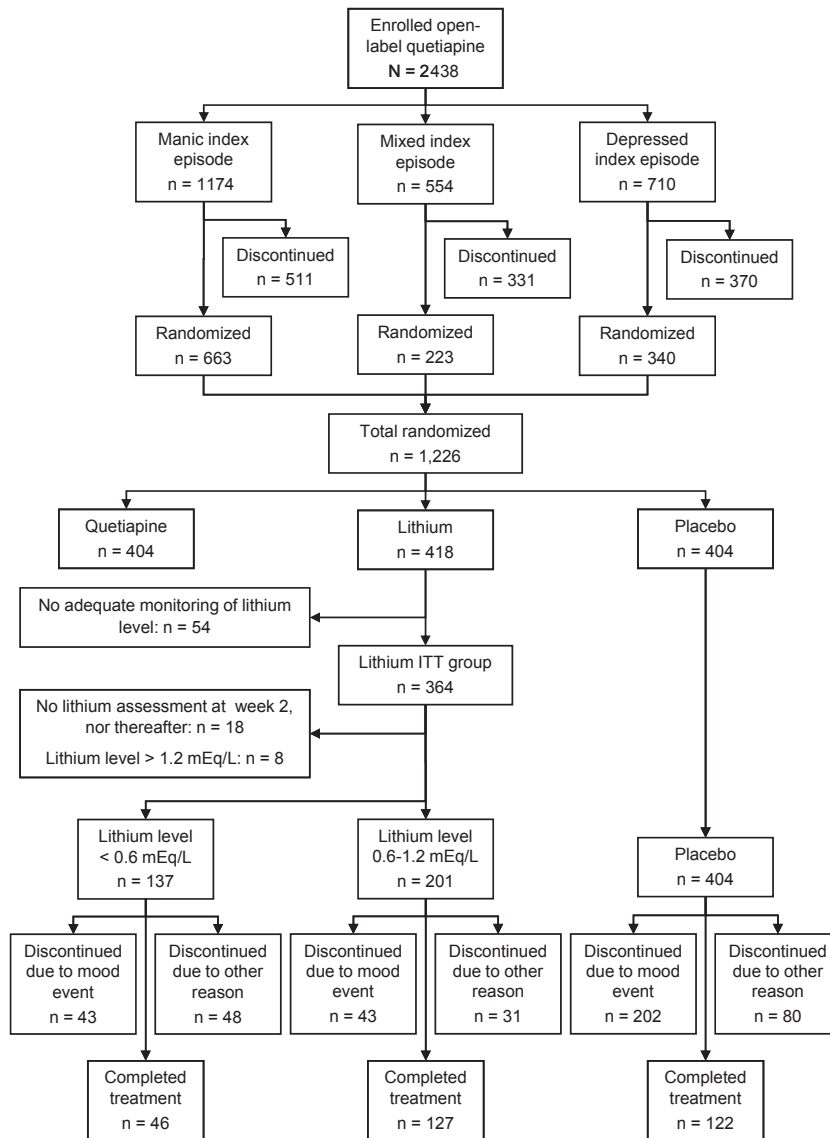


Fig. 1. Flowchart of the study. ITT = intent-to-treat.

lithium <0.6 mEq/L was not different from placebo.

Time to all-cause discontinuation showed a different pattern: it was longest in the lithium 0.6–1.2 group (median 169 days), shortest in the lithium <0.6 group (median 57 days), and intermediate for the placebo group (median 76 days) (Fig. 5).

In addition to the cutoff of 0.6 mEq/L, our data also allow comparisons of patients using other cutoffs, for example, patients with a median lithium level <0.4 (n = 81, 22.3%), between 0.4 and <0.6 (n = 56, 15.4%), between 0.6 and <0.8 (n = 118, 32.4%), between 0.8 and <1.0 (n = 68, 18.7%), and between 1.0 and 1.2 mEq/L (n = 15, 4.1%). On the primary outcome measure (recurrence of any mood event), the HRs versus

placebo were 0.66 (95% CI: 0.42–1.03; p = 0.065) for lithium <0.4 mEq/L; 1.05 (95% CI: 0.67–1.63; p = 0.85) for lithium 0.4 to <0.6 mEq/L; 0.35 (95% CI: 0.23–0.52; p < 0.0001) for lithium 0.6 to <0.8 mEq/L; 0.24 (95% CI: 0.14–0.42; p < 0.0001) for lithium 0.8 to <1.0 mEq/L; and 0.50 (95% CI: 0.21–1.22; p = 0.13) for lithium 1.0–1.2 mEq/L.

#### Safety and tolerability measures

During the randomized phase, 111 (62.0%) patients in the lithium <0.6 group and 126 (59.2%) patients in the lithium 0.6–1.2 group reported an adverse event, versus 228 (56.4%) patients receiving placebo. These events were considered drug-related in 67 (37.4%), 68 (31.9%), and 102 (25.2%)

## Lithium maintenance treatment in BD (Trial 144)

Table 1. Demographic and current illness characteristics of all patients at enrollment and of patients in the two lithium groups (<0.6 mEq/L and 0.6–1.2 mEq/L) and the placebo group at randomization

	Prerandomization phase (open-label quetiapine)	Randomized phase		
	Patients enrolled (N = 2438)	Lithium <0.6 mEq/L (n = 137)	Lithium 0.6–1.2 mEq/L (n = 201)	Placebo (n = 404)
Gender, n (%)				
Male	1131 (46.4)	48 (35.0)	99 (49.3)	210 (52.0)
Female	1307 (53.6)	89 (65.0)	102 (50.7)	194 (48.0)
Age, years, mean (SD)	38.4 (12.3)	36.9 (11.7)	39.3 (12.8)	40.0 (12.9)
Most recent episode, n (%)				
Mania	1174 (48.2)	56 (40.9)	122 (60.7)	223 (55.2)
Depression	710 (29.1)	41 (29.9)	53 (26.4)	115 (28.5)
Mixed	554 (22.7)	40 (29.2)	26 (12.9)	66 (16.3)
With rapid-cycling course, n (%)				
Yes	470 (19.3)	25 (18.2)	22 (10.9)	47 (11.6)
Unknown	2 (0.1)	1 (0.7)	0 (0)	0 (0)
YMRS total score at randomization, mean (SD)				
Overall	15.8 (10.0)	4.2 (3.5)	3.3 (3.4)	3.7 (3.6)
Index episode				
Mania <sup>a</sup>	20.9 (8.8)	5.1 (3.8)	3.8 (3.5)	4.2 (3.8)
Depression <sup>b</sup>	6.3 (5.7)	3.1 (3.3)	2.0 (2.9)	2.3 (2.7)
Mixed <sup>c</sup>	17.3 (7.8)	4.0 (2.9)	3.5 (3.4)	4.4 (3.4)
MADRS total score at randomization, mean (SD)				
Overall	15.1 (11.1)	4.4 (3.8)	2.6 (3.1)	3.4 (3.4)
Index episode				
Mania <sup>a</sup>	6.8 (5.8)	2.8 (3.2)	1.9 (2.6)	2.4 (2.7)
Depression <sup>b</sup>	24.4 (8.3)	5.5 (3.8)	3.9 (3.3)	4.8 (3.9)
Mixed <sup>c</sup>	20.9 (9.6)	5.4 (3.8)	3.4 (3.8)	4.3 (3.6)

MADRS = Montgomery-Åsberg Depression Rating Scale; SD = standard deviation; YMRS = Young Mania Rating Scale.

<sup>a</sup>In the prerandomization phase, n = 1174; in the randomized phase, n = 56 for lithium <0.6 mEq/L, n = 122 for lithium 0.6–1.2 mEq/L, and n = 222 or 223 for placebo.

<sup>b</sup>In the prerandomization phase, n = 710; in the randomized phase, n = 41 for lithium <0.6 mEq/L, n = 53 for lithium 0.6–1.2 mEq/L, and n = 115 for placebo.

<sup>c</sup>In the prerandomization phase, n = 544; in the randomized phase, n = 40 for lithium <0.6 mEq/L, n = 26 for lithium 0.6–1.2 mEq/L, and n = 66 for placebo.

Table 2. Hazard ratios for time to recurrence of any mood event (primary outcome measure), manic event, or depressive event

	Recurrent event								
	Any mood event			Manic event			Depressive event		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Lithium <0.6 mEq/L versus placebo	0.79	0.57–1.10	0.1674	0.68	0.42–1.11	0.1272	0.91	0.57–1.45	0.6920
Adjusted <sup>a</sup>	0.78	0.56–1.10	0.1551	0.69	0.42–1.13	0.1370	0.88	0.54–1.41	0.5860
Lithium 0.6–1.2 mEq/L versus placebo	0.32	0.23–0.44	<0.0001	0.26	0.17–0.41	<0.0001	0.41	0.25–0.66	0.0003
Adjusted <sup>a</sup>	0.32	0.23–0.44	<0.0001	0.26	0.17–0.41	<0.0001	0.42	0.26–0.68	0.0005
Lithium < 0.6 mEq/L versus lithium 0.6–1.2 mEq/L	2.23	1.38–3.59	0.0010	2.43	1.22–4.84	0.0117	2.06	1.07–3.99	0.0309
Adjusted <sup>a</sup>	2.16	1.32–3.53	0.0021	2.23	1.11–4.49	0.0247	1.95	0.98–3.89	0.0563

CI = confidence interval; HR = hazard ratio.

<sup>a</sup>Adjusted for gender, type of index episode, rapid cycling, and Young Mania Rating Scale and Montgomery-Åsberg Depression Rating Scale scores at randomization.

patients, and led to discontinuation in seven (3.9%), eight (3.8%), and 12 (3.0%) patients, respectively. Serious adverse events were reported by five (2.8%) patients in the lithium < 0.6 group,

two (0.9%) in the lithium 0.6–1.2 group, and 11 (2.7%) in the placebo group. Detailed information on adverse events occurring in ≥5% of any group is presented in *Supplementary Table 3*, together with

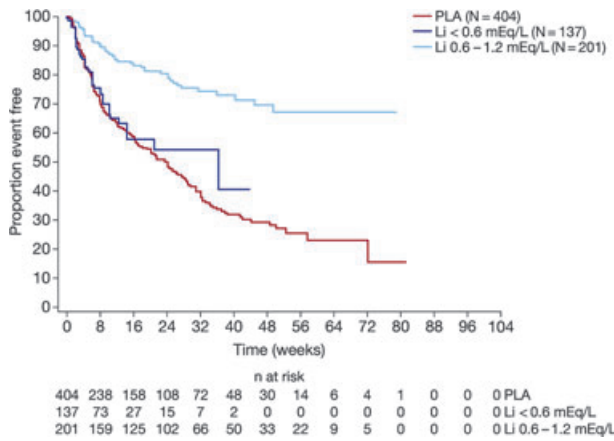


Fig. 2. Time to recurrence of any mood event (primary outcome measure, Kaplan–Meier curves). PLA = placebo; Li = lithium.

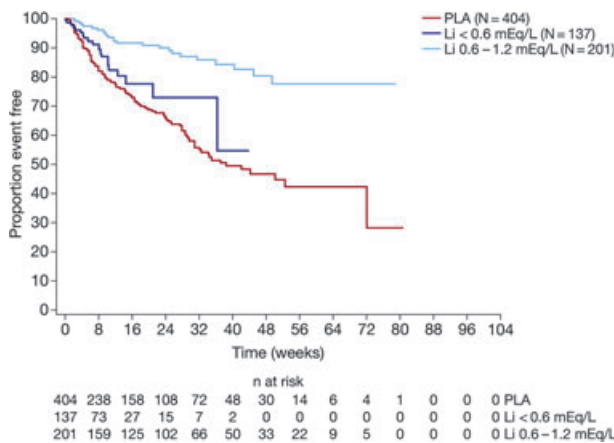


Fig. 3. Time to recurrence of a manic event (Kaplan–Meier curves). PLA = placebo; Li = lithium.

incidence densities that adjust for different durations of treatment.

**Discussion**

For the main findings of the study (both the continuation of quetiapine and switching to lithium were found to be more effective than placebo in preventing recurrence of any mood event as well as preventing manic and depressive events in patients who had responded to quetiapine for the treatment of an acute manic, depressed, or mixed episode), we refer to the primary publication (21). An interesting aspect (and problem) of the study is that 137 patients in the lithium group had median plasma levels below the predefined range of 0.6–1.2 mEq/L. This created the opportunity to compare the effect of lithium in two groups of patients, with mean plasma levels between 0.6 and 1.2 mEq/L and below 0.6 mEq/L. Moreover, we

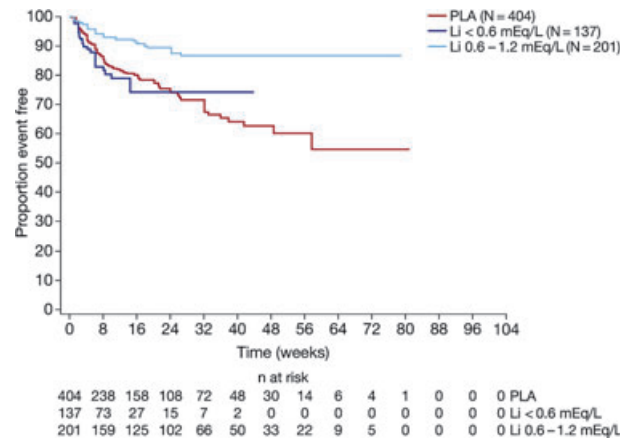


Fig. 4. Time to recurrence of a depressive event (Kaplan–Meier curves). PLA = placebo; Li = lithium.

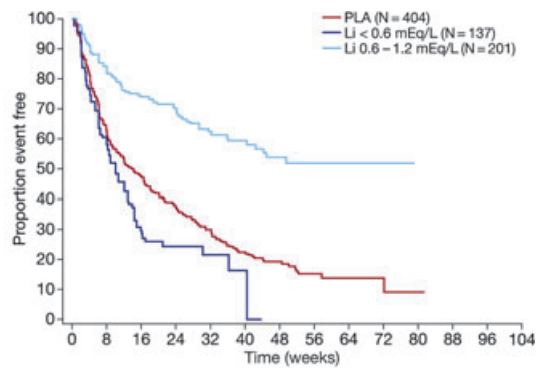


Fig. 5. Time to all-cause discontinuation (Kaplan–Meier curves). PLA = placebo; Li = lithium.

could, for the first time, compare both groups with a group receiving placebo. The major finding of these comparisons is that, compared to placebo, lithium 0.6–1.2 mEq/L prevented the recurrence of any mood event and also of a manic and a depressive event, while this was not the case in the lithium < 0.6 group. Moreover, lithium 0.6–1.2 mEq/L was more effective than lithium < 0.6 mEq/L on these outcome measures.

When further divided into smaller subgroups, both lithium 0.6 to < 0.8 mEq/L and lithium 0.8 to < 1.0 mEq/L were more effective than placebo in preventing any mood episode, while lithium < 0.4 mEq/L and lithium 0.4 to < 0.6 mEq/L were not, indicating that the cutoff for an effective plasma level of lithium is more likely to be around 0.6 mEq/L than around 0.4 mEq/L. This supports and expands the findings of meta-analyses of previous randomized studies which, however, did not have placebo arms (15, 18).

We consider these findings especially important as, for lithium, the study did not have a so-called enriched design; patients were not selected for prior response to lithium, but were all responders to



quetiapine. Thus, these results are quite a fair analysis of lithium efficacy, with no bias at all in favor of lithium per se. Nevertheless, the results must also be interpreted with care, as a major limitation of this study is that patients were not randomized to either lithium  $<0.6$  mEq/L or lithium 0.6–1.2 mEq/L; the composition of these groups was the result of how dosing and adherence transpired in a study that aimed to obtain lithium levels between 0.6 and 1.2 mEq/L in all patients who were switched to lithium. Therefore, the possibility exists that channeling occurred, i.e., there may have been a common underlying reason(s) why patients who failed to reach predefined levels also had a poorer outcome. However, a multivariate Cox regression analysis with inclusion of potential confounders (gender, type of index episode, rapid cycling, and YMRS and MADRS scores at randomization) indicates that at least the unequal distribution of these patient characteristics over the three groups does not explain the differences found between the three groups.

It is not completely clear why so many patients receiving lithium ( $n = 137$ ; 37.6%) did not reach predefined lithium levels. With a mean and median stay in the study of about two months in the lithium  $<0.6$  group, one would expect that more patients would have reached predefined levels. In a normal clinical setting, when the clinician can decide on dosing based on full information on the actual lithium level, this is possible within several weeks. We tend to believe that procedures specific to blinded dose adjustments in this study might have played a role. For instance, achieving predefined levels was possible in another double-blind study comparing lithium with carbamazepine, which were both dosed according to predefined plasma levels (25). In that study, clinicians received blinded information on plasma levels in  $x$  U/L, corresponding to either  $0.x$  mEq/L for lithium or  $x$  mg/L for carbamazepine, after which the clinician could decide to increase the number of blinded medications (either lithium or carbamazepine and dummy placebos). This method resulted in lithium levels outside the predefined range in six out of 44 patients (13.6%) after 30 days and in only two patients (4.6%) after 60 days. The advantage of the latter study is that it was performed in 15 sites from one small country (The Netherlands), while the current study involved 128 sites in 15 countries.

Nonadherence to study medication is also thought to be implicated in the failure to achieve predefined lithium levels, based on the observation that the dropout rate (indicated by a shorter mean time to all-cause discontinuation) was greater in the lithium  $<0.6$  group than in the lithium 0.6–1.2

group. A related explanation is that adverse events in the lithium  $<0.6$  group may have prevented some clinicians from increasing the dose as recommended based on the (blinded) lithium level assessments. This is, however, not supported by the occurrence of adverse events that led to early discontinuation, which was low (below 4%) in all three groups. Nevertheless, it is possible that some patients were very sensitive to adverse events, had their dose reduced, and ultimately were maintained on lower levels, suggesting that individual patients might be managed on lower levels.

A remarkable result of the overall analysis of patients receiving lithium (the ITT group) is that lithium prevented both manic and depressive events (21). This contrasts with the results of the meta-analysis by Geddes et al. (15) of previous long-term studies with lithium, reporting significant efficacy for lithium in the prevention of manic but not depressive episodes. When this new study was added to this meta-analysis, the prevention of depressive episodes also became significant (J. R. Geddes, personal communication).

In conclusion, despite the fact that the current data are the result of a post hoc analysis and therefore formally need to be replicated in another study before definite conclusions can be drawn, the results clearly support and expand previous findings that lithium should be dosed high enough to achieve plasma levels of at least 0.6 mEq/L—if tolerated and not contra-indicated—in order to achieve a clinically significant effect in the prevention of manic as well as depressive episodes of bipolar I disorder. Patients and their families need to be educated about this in order for them to benefit from the preventive effect of lithium, and advised that failure to achieve and maintain such levels can result in poorer health outcomes and higher total medical costs (26).

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**Author contributions**

WAN developed the idea, designed the analysis, and wrote the manuscript. RHW contributed to the acquisition, analysis, and interpretation of data, and critically reviewed and approved the manuscript.

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### Supporting information

Additional Supporting information may be found in the online version of this article:

**Table S1.** Recurrence rates and hazard ratios for time to recurrence of any mood event, manic event, or depressive event stratified according to index episode.

**Table S2.** Least square mean estimated differences (standard error) [95% confidence interval] of changes in interepisode<sup>a</sup> scores for secondary outcome measures.

**Table S3.** Incidence and incidence density<sup>a</sup> of adverse events ( $\geq 5\%$  in any group) during the randomized phase (randomized safety population).