Acceleration and Augmentation of Antidepressants With Lithium for Depressive Disorders: Two Meta-Analyses of Randomized, Placebo-Controlled Trials

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Objective: The delayed onset of therapeutic response and the high number of nonresponders to antidepressants remain major clinical problems in depressive disorders. Among the strategies to overcome both dilemmas, the additional treatment with lithium has been suggested as a viable method. The authors determined in 2 separate meta-analyses the efficacy of lithium in accelerating and in augmenting clinical response in patients with depression.

Study Selection and Data Sources: Two meta-analyses of randomized, double-blind, placebo-controlled trials including subjects with unipolar or bipolar disorder, depressive phase, assessed the concomitant administration of lithium and antidepressant to accelerate or augment clinical response in the acute treatment phase of depression. Data were obtained from searching the following databases: MEDLINE (1966 to July 2006), EMBASE (1989 to July 2006), and The Cochrane Central Register of Controlled Trials (The Cochrane Library 2006, Issue 3). For the accelerating meta-analysis, subject headings including *depressive disorder, bipolar disorder, antidepressive agents,* and *lithium* and text words such as *depress*, lithium,* and *antidepress** were used. For the augmentation meta-analysis, subject headings included *depressive disorder, bipolar disorder, antidepressive agents, lithium, drug therapy,* and *combination,* and text words included *augment*, refract*,* and *resistant*. Outcomes investigated included response rates and depression scale rates.

Data Synthesis: Five acceleration studies (231 participants) adding lithium to tricyclics and tetracyclics and 10 augmentation studies (269 participants) adding lithium to various antidepressants including selective serotonin reuptake inhibitors were incorporated. In the acceleration meta-analysis, a statistical trend in favor of lithium was found (standardized mean difference of –0.43, 95% CI = –0.93 to 0.07). In the augmentation meta-analysis, lithium was significantly more effective than placebo (odds ratio = 3.11, 95% CI = 1.80 to 5.37).

Conclusion: There is firm evidence for lithium as an effective augmentation strategy but only modest evidence for lithium to accelerate response to antidepressants in patients with depressive disorders.

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Despite the progress in the treatment of depressive disorders during the past decade, the delayed onset of therapeutic response and the high number of nonresponders to antidepressants remain major concerns in clinical practice.[1] With respect to the delayed onset of response to antidepressants, to date no antidepressant has yielded any apparent benefit before the second or third week of treatment; reducing this latency time would markedly reduce the suffering and impairment associated with depression. Furthermore, regardless of the initial choice of antidepressant, about 30% to 50% of patients with a major depressive episode will not respond sufficiently to adequately performed first-line treatment.[1]

Among the strategies to overcome the aforementioned problems, the additional treatment with lithium has been suggested as a viable method. The combination of lithium with an antidepressant has been used in depressed patients with a double purpose: first, as an acceleration strategy,[2] speeding up the time for response to antidepressants, and second, as an augmentation strategy in which lithium added to antidepressant treatment after a partial response or nonresponse can potentiate the therapeutic effect. The evidence supporting the role of lithium as an augmentation

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agent is supported by a meta-analysis performed in 1999 by 1 of the authors (M.B.) and a colleague.[3] The recent publication of a study showing a negative effect of lithium augmentation therapy has raised some concern about the current status of the evidence.[4] Therefore, we performed 2 separate meta-analyses that would refer to the augmentation and acceleration effects of lithium, the latter not being addressed by a systematic review or meta-analysis in the past.

METHOD

Inclusion and Exclusion Criteria

For both meta-analyses, only randomized controlled trials including subjects with unipolar or bipolar disorder, depressive phase, treated with any antidepressant plus lithium in any dose or with placebo were included. Studies had to use an accepted criterion for depressive episode and report their outcomes in a clearly defined, dichotomous classification and/or with a valid depression scale. In trials that used multiple treatment arms, only the data from the lithium and placebo arms were included. Preliminary reports of trials were excluded if the final version was published in the meantime. Authors were contacted if information was not available or, if this was not possible at the time of writing, data were extracted from figures and/or, assuming the largest standard deviation for the statistical significance, reported when no measure of variance was presented. For the accelerating meta-analysis, studies had to include only subjects without previous appropriate treatment for the depressive episode. For the augmentation meta-analysis, studies had to include patients not responding to conventional antidepressants.

Literature Search

An effort was made to identify all pertinent randomized controlled trials addressing each of the 2 questions. A computer-based search was performed using the following databases: MEDLINE (1966 to July 2006), EMBASE (1989 to July 2006), and The Cochrane Central Register of Controlled Trials (The Cochrane Library 2006, Issue 3). No language constraints were applied. For the accelerating meta-analysis, subject headings including *depressive disorder, bipolar disorder, antidepressive agents,* and *lithium* and text words such as *depress*, lithium,* and *antidepress** were used. For the augmentation meta-analysis, subject headings included *depressive disorder, bipolar disorder, antidepressive agents, lithium, drug therapy,* and *combination,* and text words included *augment*, refract*,* and *resistant*. This last search was performed only from June 1997 (date until which the previous meta-analysis searched[3]). References of the identified studies and published reviews on lithium acceleration or augmentation were also searched.[5–8]

Statistical Analysis

The primary outcome measure for the acceleration meta-analysis was changes in depression scales' ratings at 1 to 2 weeks after treatment. Standardized differences between the rating scales of the placebo and lithium groups were calculated using Hedges' adjusted g. The number of patients responding at 1 or 2 weeks was a secondary outcome measure in this meta-analysis, because it was expected to show less sensitivity to minor changes.

For the augmentation meta-analysis, the main outcome measure was odds ratios (ORs) of patients responding, which were extracted from the last measurement provided in the original article.

Heterogeneity was evaluated using the χ^2 test, using $p < .1$ as statistically significant. If heterogeneity was present, a random effect method for pooling was used.[9] If this was not the case, a fixed effect model was chosen.[10] Possible bias was evaluated with Egger's test,[11] using $p < .1$ as statistically significant. This test regresses the standardized effect size (OR divided by its standard error) against its precision (the inverse of its standard error). Since small-sample trials will have low precision and small standardized effect sizes, the line should run through the origin. If bias is present and small trials systematically overestimate or underestimate the effect size, the intercept of this line would significantly deviate from zero. Egger's test is exactly the intercept of this line. For the continuous variable used in the acceleration meta-analysis, standardized mean differences (SMDs) were used instead of OR. Analyses were done using Cochrane RevMan software, version 4.2 (Cochrane Collaboration, http://www.cc-ims.net/RevMan/download.htm), and MATLAB, version 6.5 (The MathWorks, Natick, Mass.).

RESULTS

Lithium Acceleration Meta-Analysis

Nine studies were identified for further evaluation.[12–20] Four articles were excluded due to lack of explicit randomization,[12] inclusion of subjects with resistant depression,[13] duplication,[14] and use of the Brief Psychiatric Rating Scale for measuring depressive symptoms, which was considered to be inadequate.[15] Antidepressants used were various tricyclics, except in 1 study[17] in which maprotiline, a tetracyclic antidepressant, was also used (Table 1). Lithium doses used achieved plasma levels in most studies between 0.7 and 1.0 mmol/L, with the exception of the study by Lingjaerde et al.,[16] which used levels up to 1.3 mmol/L.

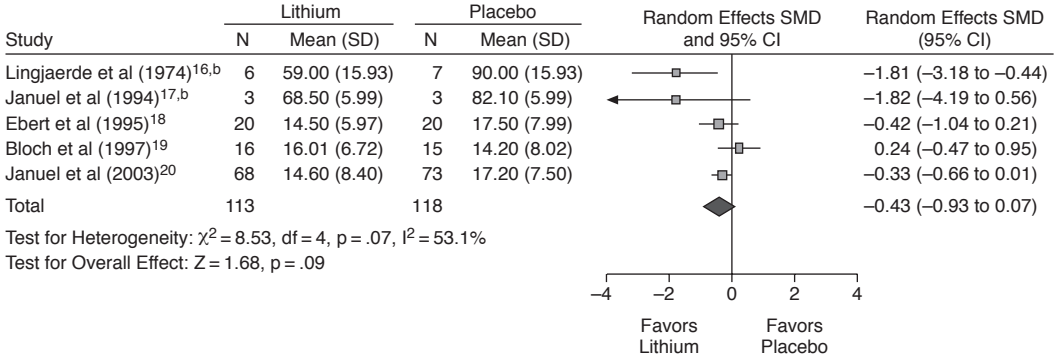
Normalized depressive scores of the 5 studies[16–20] and their pooling are shown in Figure 1. The random effect model was used since heterogeneity was present. A statistical trend in favor of lithium was found (SMD = –0.43, 95% CI = –0.93 to 0.07; test for overall effect, p = .09). Pooling of the number of subjects defined as responders

Table 1. Randomized Double-Blind Lithium Acceleration Studies

Study	Subjects	Antidepressant Treatment	Lithium Dosage or Serum Level (SL)	Length of Treatment, wk	Depression Scale and Day of Assessment
Lingjaerde et al (1974)[16]	37 UP, 8 BP, 35 F, 10 M, mean age = 49 y	Various TCAs	SL = 0.8–1.3 mmol/L	4	HAM-D, 7 d
Januel et al (1994)[17]	6 UP, 3 F, 3 M, age range = 21–51 y	Clomipramine, maprotiline, or tianeptine	750 mg/d	3	HAM-D, 14 d
Ebert et al (1995)[18]	40 BP, 40 M, mean age = 39 y	Amitriptyline	900 mg/d	5	HAM-D, 14 d
Bloch et al (1997)[19]	29 UP, 2 BP, 17 F, 14 M, mean age = 47 y	Desipramine	SL = 0.7–1.0 mmol/L	5	HAM-D, 14 d
Januel et al (2003)[20]	149 UP, 92 F, 57 M, mean age = 44 y	Clomipramine	750 mg/d	6	MADRS, 11 d

Abbreviations: BP = bipolar, F = female, HAM-D = Hamilton Rating Scale for Depression, M = male, MADRS = Montgomery-Asberg Depression Rating Scale, TCA = tricyclic antidepressant, UP = unipolar.

Figure 1. Meta-Analysis of Lithium Acceleration Studies[a]



[a]Pooling of depression scale ratings at 7 to 14 days for lithium versus placebo group. Hedges' adjusted g were pooled using DerSimonian and Laird model.[10]
[b]Percentage of baseline score shown.
Abbreviation: SMD = standardized mean difference.

between days 7 and 14 was also performed for 4 studies,[16,18–20] showing a positive but nonsignificant effect of lithium (OR = 1.37, 95% CI = 0.53 to 3.52). Egger's test was nonsignificant for bias (intercept = –0.41, 95% CI = –1.64 to 0.82).

Lithium Augmentation Meta-Analysis

The search identified 11 randomized, placebo-controlled trials.[4,21–30] Because 1 study was double-blinded only during the continuation phase treatment,[21] only 1 study[4] was added to the 9 randomized controlled trials that were included in the previous meta-analysis.[3] Details of the 10 studies included in the meta-analysis are presented in Table 2.

Pooling of the OR for subjects responding to the treatment for each of the studies was performed using a fixed effect model after testing for heterogeneity. Results of each study sorted by year of publication and pooling of the data are presented in Figure 2. Lithium had a positive effect versus placebo, with an OR of 3.11, which corresponds to a number-needed-to-treat (NNT) of 5. Egger's test was nonsignificant for bias (intercept = 10.32, 95% CI = –5.47 to 26.12). The mean response rate was 41.2% in the lithium group and 14.4% in the placebo group ($p < .001$).

DISCUSSION

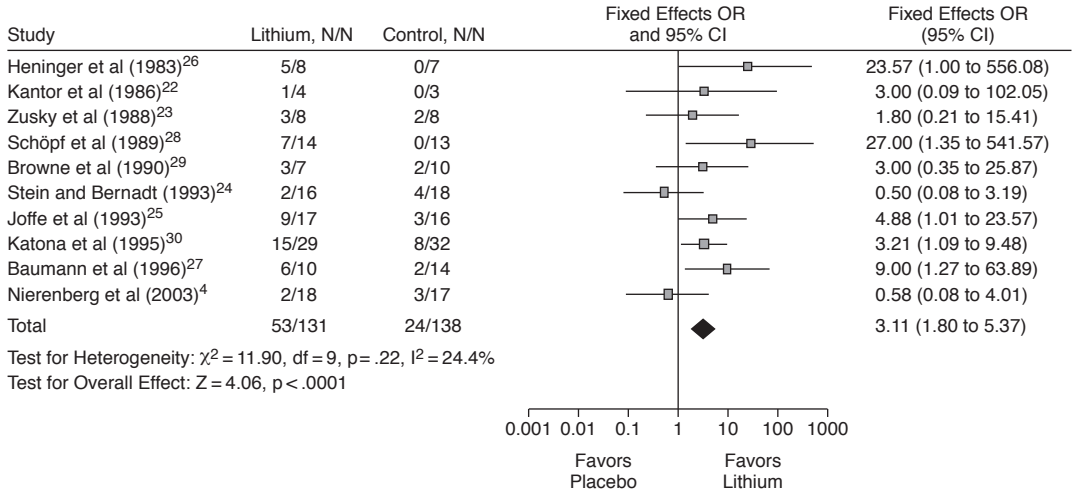
In the lithium acceleration meta-analysis, a positive but nonsignificant trend ($p = .09$) was found in support of lithium. Also, the number of patients classified as responders at study end was not significant. The effect size of –0.43 standard deviations can be translated to a Montgomery-Asberg Depression Rating Scale score (using the data from the largest study pooled[20]) giving a difference of approximately 3 points at 2 weeks. It is difficult to interpret the clinical importance of these modest effects of lithium acceleration. Subjects with recurrent mood disorders who would benefit from long-term prophylaxis therapy with lithium[31] might be good candidates

Table 2. Randomized Double-Blind Lithium Augmentation Studies

Study	Subjects	Antidepressant Treatment	Lithium Dosage (serum level) and Duration	Response Criteria
Heninger et al (1983)[26]	14 UP, 1 BP, 12 F, 3 M, mean age = 50 y	Various TCAs and tetracyclics	900–1200 mg/d (0.5–1.1 mmol/L), 12 d	Decrease of 2 or more points on SCRS
Kantor et al (1986)[22]	7 UP, sex NR, mean age NR	Various TCAs	900 mg/d, 48 h	≥ 40% decrease in HAM-D
Zusky et al (1988)[23]	16 UP, 13 F, 3 M, mean age = 45 y	Various TCAs and MAOIs	300 mg/d first week, 900 mg/d second week, 14 d	Final HAM-D ≤ 7
Schöpf et al (1989)[28]	18 UP, 9 BP, 19 F, 8 M, mean age = 54 y	Various antidepressants	600–800 mg/d (0.6–0.8 mmol/L), 7 d	≥ 50% decrease in HAM-D
Browne et al (1990)[29]	14 UP, 3 BP, 10 F, 7 M, mean age = 42 y	Various TCAs and tetracyclics	900 mg/d, 48 h	≥ 50% decrease in HAM-D
Stein and Bernadt (1993)[24]	34 UP, 27 F, 7 M, mean age = 47 y	Various TCAs	250 mg/d, 21 d	≥ 50% decrease in HAM-D
Joffe et al (1993)[25]	33 UP, 18 F, 15 M, mean age = 37 y	Various TCAs	900 mg/d (> 0.55 mmol/L), 14 d	≥ 50% decrease in HAM-D
Katona et al (1995)[30]	N = 61, polarity NR, 35 F, 26 M, mean age = 40 y	SSRIs and TCAs	800 mg/d (0.6–1 mmol/L), 42 d	≥ 50% decrease in HAM-D
Baumann et al (1996)[27]	23 UP, 1 BP, 17 F, 7 M, mean age = 41 y	Citalopram	800 mg/d (0.5–0.8 mmol/L), 7 d	≥ 50% decrease in HAM-D
Nierenberg et al (2003)[4]	35 UP, 16 F, 19 M, mean age = 38 y	Nortriptyline	900 mg/d	≥ 50% decrease in HAM-D

Abbreviations: BP = bipolar, F = female, HAM-D = Hamilton Rating Scale for Depression, M = male, MAOI = monoamine oxidase inhibitor, NR = not reported, SCRS = Short Clinical Rating Scale, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, UP = unipolar.

Figure 2. Meta-Analysis of Lithium Augmentation Studies[a]



[a]Pooling of patients responding to augmentation therapy. Fixed effects model used.[9]

for receiving lithium from the beginning. An important limitation of this acceleration meta-analysis is also the lack of data on lithium's effects when added to selective serotonin reuptake inhibitors or other newer antidepressants, nowadays the de facto first-line antidepressant agents in depression.

Confirming the results of our previously published meta-analysis,[3] our now updated meta-analysis of 10 randomized lithium augmentation trials found lithium to be effective, with an OR of 3.11, an NNT of 5, and a significantly higher rate of responders compared with placebo treatment (41.2% vs. 14.4%). Considering the number of randomized trials and the results from this meta-analysis, lithium is the foremost and most well-documented augmentation strategy for depressed patients not responding to antidepressants.

Possible reasons for the negative results in some of the augmentation trials have been discussed previously,[3] ranging from clearly insufficient lithium doses (e.g., only 250 mg/day in 1 study, leading to a mean lithium serum level of 0.25 mmol/L[24]) to inappropriate duration of treatment (e.g., only 48 hours in 2 studies[22,29]). For the new

study[4] included in this meta-analysis, a noradrenergic profile of the antidepressant used (nortriptyline) may be a possible explanation for its negative outcome.[32] To our knowledge, no study has used lithium augmentation with a selective noradrenergic antidepressant with a selective serotonergic antidepressant used as a comparator. This would be of theoretical and clinical interest and address the question of the specificity of lithium augmentation according to the pharmacologic profile of the antidepressant used. An alternative explanation for the negative outcome in the study by Nierenberg et al.[4] may be that patients refractory to multiple antidepressants were included. Similarly, recently published results from the STAR*D trial (a prospective, randomized, but not placebo-controlled, trial) also showed a minimal response (13.2%) and remission rate (15.9% after a mean of 9.6 weeks) with lithium augmentation as a third-step treatment for patients with major depressive disorder.[33] This latter low remission rate might, alternatively, be attributable to the lack of systematic assessment and serial monitoring of lithium levels under naturalistic treatment conditions.[33] Similar to the conflicting results of placebo-controlled studies, some studies without a placebo control group,[34] but not the majority, also showed minimal response with lithium augmentation; for a review, see reference 8.

The diagnostic specificity of the augmentation strategy has raised some concern in the past.[5,8] Most of the placebo-controlled studies included mixed depressed populations with predominantly unipolar subjects, with only 14 patients in total clearly describing bipolar depression. Because several studies,[22–24] moreover, did not explicitly exclude depressed patients with a history of bipolar disorder, and 1 larger study did not report the polarity (unipolar or bipolar) at all,[30] we decided not to conduct a separate meta-analysis for diagnostic specificity. Obviously, a separate meta-analysis in bipolar depression was not feasible given that none of the studies included patients with bipolar depression exclusively.

The available data do not allow an answer to the question of whether the augmentation effect gets lost if lithium is started right at the beginning of antidepressant treatment. For both strategies it also remains to be examined whether the response to lithium acceleration or augmentation represents a true effect resulting from synergistic effects or whether the response is simply owing to the antidepressant effect of lithium itself.[35] A randomized, double-blind study that controls for the effects of lithium alone for each strategy compared with lithium in combination with an antidepressant is warranted.

In conclusion, these meta-analyses reinforce the firm evidence for lithium as an effective augmentation strategy but demonstrate only modest evidence for lithium to accelerate response to antidepressants in patients with depressive disorders.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), lithium (Eskalith, Lithobid, and others), nortriptyline (Pamelor, Aventyl, and others).

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