Lithium for Schizophrenia Revisited: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Clinicians frequently use lithium to augment antipsychotic medication in schizophrenia. Therefore, we undertook a systematic review and meta-analysis of the use of lithium in the treatment of schizophrenia.

Data sources and study selection: Randomized controlled trials examining lithium (as a sole or an adjunctive compound) in participants with schizophrenia or related disorders were searched in the register of the Cochrane Schizophrenia Group. No language restrictions were applied. The Boolean phrase [*lithium** or *lithicarb* or *eskalith* or *lithobid* or *lithane* or *cibalith-s* or *quilonum* or *hypnorex*] was used to locate articles. The search strategy initially identified 90 references. The authors of the included studies were contacted to obtain original patient data. The data were combined in a meta-analysis. The main outcome parameters were the number of patients with a clinically significant response and the number of patients leaving the studies early.

Results: The meta-analysis includes 20 studies (N = 611). The evidence shows that lithium as a sole agent is ineffective in the treatment of schizophrenia. Eleven trials examined the augmentation of antipsychotics with lithium. More patients who received lithium augmentation than those who received antipsychotics alone were classified as responders. However, the superiority was not consistent across different response thresholds, and when patients with prominent affective symptoms were excluded from the analysis, the advantage of lithium augmentation was not significant (p = .07). Significantly more patients taking lithium left the trials early, suggesting a lower acceptability of lithium augmentation compared with that of taking antipsychotics alone.

Conclusion: Despite some evidence in favor of lithium augmentation, the overall results are inconclusive. A large trial of lithium augmentation of antipsychotic medications will be required in order to detect a benefit of small effect size in patients with schizophrenia who lack affective symptoms.

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Despite the introduction of several "atypical" antipsychotic agents over recent years, many patients with schizophrenia have suboptimal responses. While there is evidence showing that clozapine is effective for treatment-resistant patients,[1] many other interventions used in this group lack sufficient evidence. For example, recent systematic reviews and meta-analyses found no significant benefits of augmentation with carbamazepine or beta-blockers.[2,3]

One of the most long-standing and widely used clinical interventions for treatment-resistant psychosis is the addition of lithium to antipsychotic medication (lithium augmentation). In the early 1970s, randomized controlled studies examined the utility of lithium in the treatment of schizophrenia and schizoaffective disorder.[4–6] Several of the early, smaller studies provided evidence in support of lithium augmentation. These studies[7,8] probably influenced the recommendations in several narrative reviews published in the last decade.[9–11] The use of lithium augmentation in schizophrenia has been codified in recent treatment guidelines such as the American Psychiatric Association guideline,[12] the Schizophrenia Patient Outcomes Research Team (PORT),[13] and the Texas Medication Algorithm Project (TMAP),[14] albeit the level of evidence is typically described as "not robust" or "very little." Many psychiatrists follow these recommendations. For example, 43% of the inpatients with schizophrenia of the New York State psychiatric hospitals received a mood

stabilizer in 1998,[15] although in recent years, there has been a shift to valproate (an intervention that has a smaller evidence base compared with lithium).

In recent years, several randomized controlled studies examining the utility of lithium augmentation in treatment-resistant schizophrenia have been published (e.g., references 16–18). In contrast to the early studies, most of these studies did not support improved clinical outcomes associated with lithium augmentation (see Table 1). While most of the studies in this field have been too small to allow the detection of small to moderate quantitative differences,[19] meta-analysis enables the results of individual trials to be combined, which increases the statistical power for detecting significant effects. Furthermore, the conclusions of traditional reviews may be affected by publication biases,[20] language biases,[21] and the personal opinion of the reviewers.

In order to provide guidance for clinicians, we undertook a systematic review and meta-analysis on the use of lithium as a sole agent and as an adjunct to antipsychotics for schizophrenia. In order to optimize the analysis, we sought the individual patient data of the relevant randomized controlled trials.

METHOD

Search

All published and unpublished randomized controlled trials that assessed the effectiveness of lithium in the treatment of schizophrenia and schizophrenia-like psychoses (schizoaffective, schizophreniform, and delusional disorder) were searched using the register of randomized controlled trials of the Cochrane Schizophrenia Group (March 2002). This register is compiled by methodical searches of BIOSIS, CINAHL, dissertation abstracts, EMBASE, LILACS, MEDLINE, PSYNDEX, PsycINFO, RUSSMED, Sociofile supplemented with hand searching of 30 journals, and conference proceedings (American Psychiatric Association, American Association of Geriatric Psychiatry, Association of European Psychiatrists, Biological Psychiatry, Collegium Internationale Neuropsychopharmacologicum, European College of Neuropsychopharmacology, European Federation of Neurological Sciences, Institute on Psychiatric Services, Royal College of Psychiatrists Winter Meeting, Schizophrenia: Breaking Down the Barriers, International Congress on Schizophrenia Research, World Congress of Psychiatry, World Congress of Neurology). No language restrictions were applied. The following phrase was used: [*lithium** or *lithicarb* or *eskalith* or *lithobid* or *lithane* or *cibalith-s* or *quilonum* or *hypnorex*]. All references in the articles selected for inclusion were searched for further relevant trials, and the first author of each included study was contacted for information regarding unpublished trials. The search strategy identified 90 references.

All citations identified by the searches were independently inspected by 2 reviewers before inclusion. As most trials were incompletely reported and did not provide the information necessary to allow meta-analytic calculations, all relevant authors were contacted for the individual patient data.

Quality Assessment

Empirical research has shown that lack of adequate allocation concealment in randomized trials is associated with bias.[22] Concealment of the allocation prevents the possibility of conscious or subconscious manipulation of individual assignments. Inadequate concealment undermines the principle of randomization, because participants may then be allocated to a treatment according to prognostic variables rather than by pure chance. For this reason, a rating was given for each trial based on the 3 quality categories as described in the Cochrane Collaboration Handbook,[22] and only studies reaching a criterion of low or moderate risk of bias (category A or B, respectively) were included. Two reviewers independently evaluated the quality of the included trials.

Outcome Parameters

Meta-analytic calculations of continuous outcomes require that the data be normally distributed. Since data distribution is difficult to assess in small trials (as was often the case in this review), the use of dichotomous variables was preferred. These dichotomous variables were either provided in the original publication or were derived from original patient data by defined cutoff points. The main outcomes of interest were acceptability of treatment as measured by the number of participants leaving the study early ("dropouts"), relapse as defined by the original studies, and the number of participants without a clinically significant improvement as defined by the original studies. When the latter did not specify a response criterion, a less than 50% reduction of the score of a rating scale, such as the Brief Psychiatric Rating Scale (BPRS),[23] or a rating of less than "much improved" according to the Clinical Global Impressions scale (CGI)[24] was used. However, since there is an uncertainty about which cutoff is optimal, we also analyzed a rather small degree of improvement (less than 20% BPRS score reduction) and an intermediate degree of improvement (less than 35% BPRS score reduction). Other outcomes of interest were specific aspects of the mental state such as positive symptoms, negative symptoms, and mood. Finally, we attempted to analyze general and lithium-specific side effects.

Dropouts and Crossover Studies

Dichotomous data were analyzed on an intention-to-treat basis, which means that everyone allocated to treatment was counted irrespective of whether he or she completed follow-up. When a participant dropped out, it was

assumed that the participant had no change in condition unless otherwise stated. Continuous data were reported as presented in the original studies without any assumptions about those lost to follow-up. Furthermore, in order to exclude the potential additive effect in the second or a later stage of crossover trials, only data from the first stage were analyzed.

Meta-Analytic Calculations

The outcome data found were combined into a meta-analysis. For dichotomous data, the relative risk (RR), that is, the ratio of the risk of an unfavorable outcome among "experimental" treatment-allocated participants to the corresponding risk among those in the control group, was calculated for each study: $RR = (a/n_1)/(c/n_2)$, where a = the number of patients with an event in the experimental group, n_1 = total number of patients in the experimental group, c = number of patients with an event in the control group, and n_2 = total number of patients in the control group. Whereas some years ago many meta-analysts preferred to use odds ratios, it has been shown that RR is more intuitive[25] and that odds ratios tend to be interpreted as RR by clinicians.[26] This misinterpretation then leads to an overestimate of the magnitude of the effect.

To pool the results of the single studies, the standard Mantel-Haenszel fixed-effects model was used in the case of homogeneous outcomes and the Der-Simonian-Laird random-effects model[27] was used in the case of heterogeneous outcomes. The random-effects model is usually considered more conservative than the fixed-effects model because it takes into account the variability between studies. Therefore, homogeneous outcomes were also checked with this method in a sensitivity analysis.

For the assessment of continuous outcomes, tentative standardized mean differences (SMD), which allow the combination of the results of different scales used to assess the same outcome, were calculated. Study heterogeneity was sought by visual inspection of the graphs and with a chi-square test of heterogeneity. Because this test is relatively insensitive, results with p values < .1 were considered to suggest significant heterogeneity. The mean RRs are presented along with their 95% confidence intervals (CI), calculated as: CI = log RR–SE (log RR) Φ (0.975), to log RR + SE (log RR) Φ (0.975), where phi is the standard normal deviate and SE is the standard error. Values below 1 indicate effects favoring the new antipsychotic. The overall test statistic is given by z = log RR/SE (log RR). In the case of statistically significant results (p < .05), the number of participants needed to treat (NNT) or the number of participants needed to harm (NNH) were calculated as the inverse of the risk difference.

The evidence for lithium as an effective agent for the treatment of bipolar affective disorder is robust.[28,29] Thus, in order to rule out the possibility that any superiority of lithium was related to the improvement of manic or depressive symptoms, patients with schizoaffective disorder or predominant affective symptoms were excluded in a second sensitivity analysis.

Studies with negative results are less likely to be published than are studies with significant results. The possibility of such publication bias was examined with a "funnel-plot" method described by Clarke and Oxman.[22] All calculations were done with Review Manager 4.1,[30] the meta-analytic software used by the Cochrane Collaboration; the exact formulas have been reported there. A detailed protocol has been described elsewhere.[31]

RESULTS

Search

Of the 90 references initially identified, 45 merited further inspection. Of these, 31 studies had to be excluded because they were not randomized. One of these was the study by Lerner and Mintzer,[32] which could not be included because the authors used alternate allocation, which is not considered to be an adequate randomization method.[22] Five studies did not make relevant comparisons, and 5 did not include patients with schizophrenia. Four further studies did not present any data suitable for meta-analysis. Gerlach et al.[33] and Jus et al.[34] studied the therapeutic effects of lithium on tardive dyskinesia in stable patients. Carman et al.[8] and Growe[7] were small double-blind crossover studies examining lithium augmentation; however, the data required for our meta-analysis (outcomes after first stage only) were not available. Furthermore, it is not clear whether the study by Growe[7] was randomized. Finally, it was possible to include data drawn from 20 randomized controlled studies on lithium for schizophrenia in the meta-analysis (Table 1).

The studies could be classified according to 3 different comparisons: (1) lithium as a sole treatment versus placebo (3 studies), (2) lithium as a sole treatment versus antipsychotics (8 studies), and (3) lithium as an adjunct to antipsychotics versus placebo (or no treatment) added to antipsychotics (11 studies). It was possible to use Johnstone et al.[37] for all 3 comparisons. Comparisons 1 and 2 were important, because if lithium were effective as a sole agent, this would make add-on effects more likely. Funnel plots revealed no obvious likelihood for the existence of unpublished trials.

Study Characteristics

Most studies used a parallel-group design, but Simpson et al.,[35] Garver et al.,[36] Small and Kellams,[42] Small et al.,[18] and Terao et al.[47] were crossover studies. Sample sizes in the individual trials were small, with numbers ranging between 10 and 84. In total, the studies included 611 participants. Most participants had schizophrenia, although there were also participants with schizoaffective disorder

Table 1. Characteristics of Controlled Studies of Lithium for Schizophrenia

Study	Study Design	Participants: Diagnosis	Participants: N	Participants: Age, Mean, y	Intervention	Overall Efficacy Result
Lithium as a sole agent versus placebo						
Simpson et al[35]	Double-blind, crossover, 12 wk, inpatients	Long-term hospitalized patients (mostly schizophrenia) tardive dyskinesia	11	~ 72	Lithium as a sole treatment (levels maintained between 0.6 and 1.0 mmol/L) Placebo as a sole treatment	No effect of lithium on symptoms
Garver et al[36]	Double-blind, crossover, flexible duration, inpatients	Acute schizophrenia, schizophreniform, and schizoaffective disorder (DSM-III and RDC criteria)	15	N/A	Lithium (target level = 0.8–1.4 mmol/L): responders later crossed over to placebo Placebo: nonresponders later crossed over to lithium	Lithium > placebo
Johnstone et al[37]	Double-blind, parallel, 4 wk (+ 6-y maintenance extension)	"Functional psychoses" with schizophrenia (-like) psychoses (DSM-III)[c]	84	~ 35	Lithium alone (levels between 0.5 and 1.2 mmol/L) Placebo	Lithium only effective on mood
Lithium as a sole agent versus antipsychotics						
Johnson et al[6]	Double-blind, parallel, 3 wk, inpatients	Acutely ill, excited schizoaffectives and schizophrenics	17	~ 39	Lithium (all patients, level > 1.0 mmol/L) Chlorpromazine (200–2000 mg/d)	Chlorpromazine > lithium (NS)
Shopsin and Kim[5]	Double-blind, parallel, 5 wk, inpatients	Acute schizophrenia and schizoaffective disorder (clinical diagnosis)	21	21–61	Lithium (level < 1.5 mmol/L) Chlorpromazine (maximum dose = 1200 mg/d)	Chlorpromazine > lithium
Prien et al[4]	Double-blind, parallel, 3 wk, inpatients	Excited schizoaffective disorder (DSM-II)	83	~ 39	Lithium (level < 2.0 mmol/L) Chlorpromazine (mean dose = 1100 mg/d)	Chlorpromazine > lithium (except only mildly active subgroup)
Brockington et al[38]	Double-blind, parallel, 4 wk	Schizomania (PSE)	19	N/A	Lithium (maximum dose = 2500 mg/d) Chlorpromazine (range, 400–1000 mg/d)	Lithium = chlorpromazine
Dube[39]	Double-blind, parallel, 7 wk, inpatients	Schizophrenia (ICD-9)	60	N/A	Lithium (mean dose = 827 mg/d) Chlorpromazine (mean dose = 992 mg/d)	Chlorpromazine > lithium
Braden[40]	Double-blind, parallel, 3 wk, inpatients	Drug-free patients with various psychotic disorders, all with at least 2 manic symptoms (DSM-III, RDC, Feighner)	12[a]	N/A	Lithium (target level = 1.6 mmol/L) Chlorpromazine (mean dose all patients = 796 mg/d)	Chlorpromazine > lithium (except subgroup without overactivity)
Mattes[41]	Double-blind, parallel, 1 y, outpatients	Mainly schizophrenic schizoaffectives (RDC)	14	26	Placebo + lithium (levels > 0.6 mmol/L) Placebo + fluphenazine (5–20 mg/d)	Fluphenazine > lithium
Johnstone et al[37]	Double-blind, parallel, 4 wk (+ 6-y maintenance extension)	"Functional psychoses" with schizophrenia (-like) psychoses (DSM-III)[c]	84	~ 35	Lithium alone (levels between 0.5 and 1.2 mmol/L) Pimozide alone (16 mg/d)	Pimozide > lithium
Lithium versus placebo as an adjunct to antipsychotics						
Small and Kellams[42]	Double-blind, crossover (4 phases), 16 wk, inpatients	Treatment-resistant schizophrenia or schizoaffective disorder (Feighner)	22	~ 36	Antipsychotics (constant dose) + lithium (level = 0.6–1.2 mmol/L) Antipsychotics (constant dose) + placebo	Lithium > placebo
Biederman et al[43]	Double-blind, parallel, 5 wk, inpatients	Acute schizophrenic or affective schizoaffectives with elevated mood or hyperactivity (RDC)	39	~ 30	Haloperidol (10–60 mg/d) + lithium (mean level = 0.99 mmol/L) Haloperidol (8–70 mg/d) + placebo	Lithium > placebo
Huang and Bowden[44]	Double-blind, parallel, 10 wk, inpatients	Schizophrenia, bipolar depression, mania (DSM-III-R)	10[b]	~ 34	Haloperidol + lithium (target level = 0.6–1.2 mmol/L) Haloperidol + placebo	Not indicated; focus was MAO activity

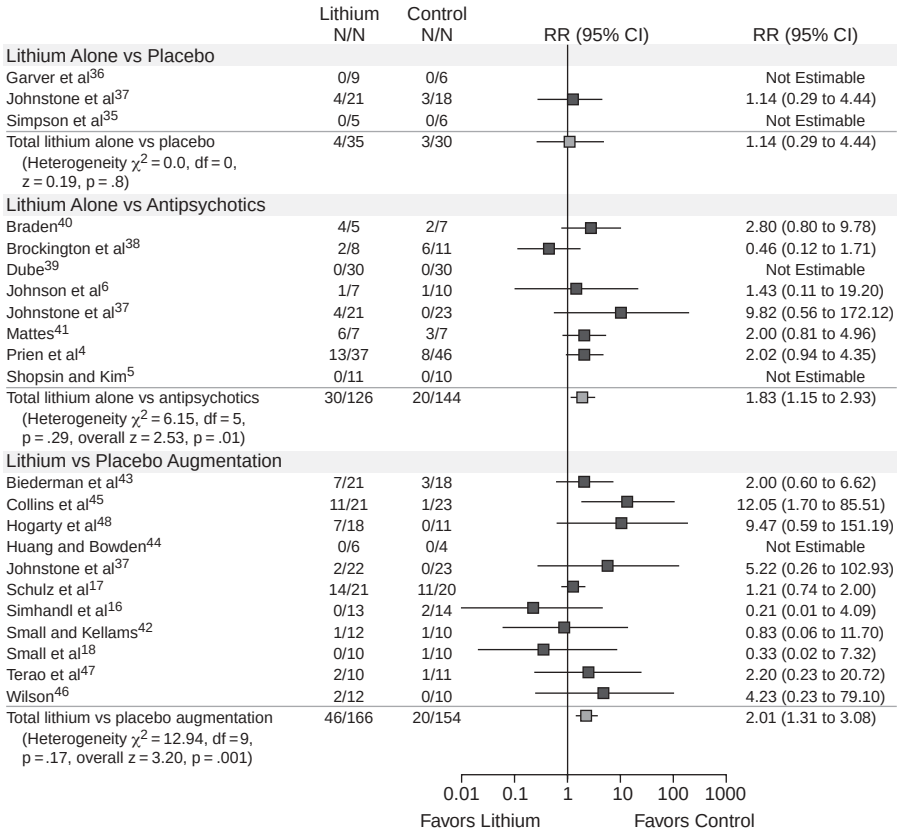
continued

Table 1. Characteristics of Controlled Studies of Lithium for Schizophrenia (cont.)

Study	Study Design	Participants: Diagnosis	Participants: N	Participants: Age, Mean, y	Intervention	Overall Efficacy Result
Lithium versus placebo as an adjunct to antipsychotics (cont.)						
Johnstone et al[37]	Double-blind, parallel, 4 wk (+ 6-y maintenance extension)	"Functional psychoses" with schizophrenia (-like) psychoses (DSM-III)[c]	84	~ 35	Lithium alone (levels between 0.5 and 1.2 mmol/L) Pimozide alone (16 mg/d) Placebo Lithium + pimozide	Pimozide = pimozide + lithium
Collins et al[45]	Single-blind, parallel, 4 wk, inpatients	Treatment-resistant schizophrenia (DSM-III-R and PSE)	44	N/A	Antipsychotics (flexible dose, mean = 1452 mg/d CPZ equ) + lithium (target level = 0.4–1.0 mmol/L) Antipsychotics (flexible dose, mean 1154 mg/d CPZ equ) + no additional treatment	Lithium = placebo
Wilson[46]	Double-blind, parallel, 6 wk baseline, 8 wk experimental phase, inpatients	Treatment-resistant schizophrenia (DSM-III-R) without a major affective disorder	22[d]	34	After a 6-week baseline period with haloperidol, nonresponders received haloperidol (constant dose, mean = 19.0 mg/d) + lithium (target level = 1.0 mmol/L) or haloperidol (mean dose = 25.9 mg/day) + placebo	Lithium = placebo
Terao et al[47]	Double-blind, crossover, 19 wk (interventions withdrawn between crossover phases), inpatients	Schizophrenia with persistent symptoms despite long-term antipsychotic treatment (DSM-III-R)	21	~ 47	Antipsychotics (constant dose, mean ~ 27 mg haloperidol equ) + lithium (target level = 0.4 mmol/L) Antipsychotics (constant dose, mean ~ 27 mg haloperidol equ) + placebo	Lithium = placebo
Hogarty et al[48]	Double-blind, parallel, 12 wk, outpatients	Schizophrenia or schizoaffective disorder (RDC) "persistently distressed by anxiety"	29	~ 36	Fluphenazine (constant dose, mean = 13.6 mg IM biweekly) + lithium (target level = 0.4–0.8 mmol/L) Fluphenazine (constant dose, mean = 16.4 mg IM biweekly) + placebo	Lithium > placebo for anxiety
Simhandl et al[16]	Double-blind, parallel, 8 wk, hospital	Treatment-resistant schizophrenia (DSM-III-R)	27	~ 35	Antipsychotics (constant dose, mean N/A) + lithium (level = 0.6–1.0 mmol/L) Antipsychotics (constant dose, mean N/A) + placebo[e]	Lithium > placebo (only on CGI)
Schulz et al[17]	Double-blind, parallel, 8 wk, inpatients	Patients with schizophrenia, schizophreniform, or schizoaffective disorder (DSM-III-R) who could not be stabilized on depot antipsychotics	41	~ 29	Fluphenazine (constant dose, mean N/A) + lithium (level = 0.8–1.0 mmol/L) Fluphenazine (constant dose, mean N/A) + placebo	Lithium = placebo
Small et al[18]	Double-blind, crossover (4 phases), 16 wk, inpatients	Patients with schizophrenia or schizoaffective disorder (DSM-IV) with insufficient response to clozapine	20	~ 37	Clozapine (constant dose, mean ~ 400 mg/d) + lithium (level at least 0.5 mmol/L) Clozapine (constant dose, mean ~ 400 mg/d) + placebo	Lithium = placebo (some improvement in schizoaffective subgroup)

[a]Overall, there were 78 patients with different diagnoses, but only dropout rates of patients with schizophrenia according to RDC could be extracted for our analyses.
[b]The numbers relate to the patients with schizophrenia.
[c]Overall, the study included 120 patients with "functional psychoses." The authors sent us the original patient data so that patients with pure affective disorders could be excluded. N and mean age relate to the whole population included in this study.
[d]Seven further patients dropped out before randomization.
[e]There was also a third group that received augmentation with carbamazepine.
Abbreviations: CGI = Clinical Global Impressions scale, CPZ = chlorpromazine, equ = equivalent, ICD-9 = *International Classification of Diseases*, Ninth Edition, IM = intramuscular, MAO = monoamine oxidase, N/A = data not available, NS = not statistically significant, PSE = Present State Examination, RDC = Research Diagnostic Criteria.

Figure 1. Controlled Studies of Lithium for Schizophrenia: Number of Patients Leaving the Studies Early



Abbreviations: CI = confidence interval, RR = relative risk.

(N = 196 [155 schizomanics]), schizophreniform disorder (N = 22), atypical psychoses (N = 7), and delusional disorder (N = 5), and there were 29 participants whose diagnosis was not clearly indicated. Most studies used some form of standardized diagnostic criteria; however, since studies from a large time period were reviewed, these criteria varied considerably. With respect to treatment resistance, 7 of the 11 lithium augmentation studies (comparison 3) included only treatment-resistant patients. The lithium dose was commonly adjusted to yield levels considered to be therapeutic for affective disorders. Whereas with 2 exceptions (Mattes,[41] fluphenazine and Johnstone et al.,[37] pimozide), all studies in the lithium as a sole agent versus antipsychotics section used chlorpromazine as a comparator, and of the augmentation studies, 3 used haloperidol,[43,44,46] 2 used fluphenazine,[17,48] 1 each used pimozide[37] or clozapine,[18] and 3 used various antipsychotic drugs.[16,42,45,47] Table 1 shows that a wide range of antipsychotic doses was used.

Data Reporting

The reporting of most studies was incomplete. However, concerning the studies on augmentation with lithium, reporting was considerably improved by direct correspondence with authors, as 5 of 11 sent original individual patient data for their studies.[16,18,37,46,47]

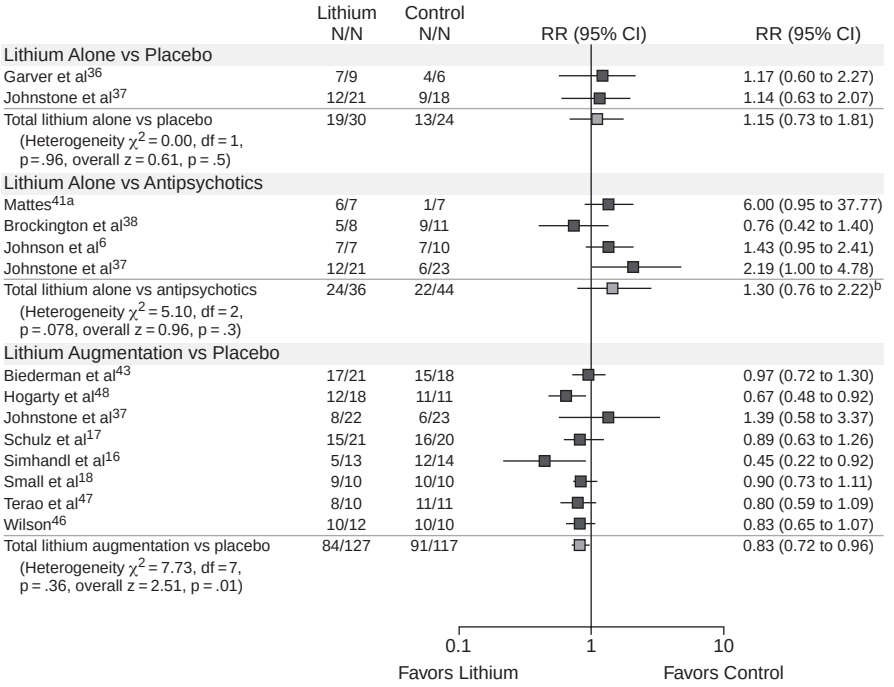
Comparison 1: Lithium as a Sole Agent Versus Placebo

Three trials fell under this category (Table 1). There was no significant difference in terms of leaving the studies early (N = 65, RR = 1.1, CI = 0.3 to 4.4, p = .8; Figure 1). One of the studies[35] examined lithium as a treatment for tardive dyskinesia and found no effect. The other 2 trials[36,37] compared lithium with placebo in acutely ill patients. A similar number of patients treated with lithium and placebo had no clinically significant improvement, defined as less than 50% reduction of the baseline value (see Figure 2). Furthermore, no significant differences were found when lower response criteria (20% or 35% reduction in score) were analyzed (data not shown).

Comparison 2: Lithium as a Sole Agent Versus Antipsychotics

Eight studies compared lithium as a sole agent with antipsychotics. Significantly more patients who received

Figure 2. Controlled Studies of Lithium for Schizophrenia: Number of Patients Without a Clinically Significant Response



[a]Number of patients relapsed not used for the mean effect size.
[b]Since the results were statistically significantly heterogeneous, a random-effects model was used here.
Abbreviations: CI = confidence interval, RR = relative risk.

lithium left the studies prematurely than did those who received antipsychotic drugs (N = 270, RR = 1.8, CI = 1.2 to 2.9, NNH = 9, CI = 5 to 33, p = .01; Figure 1). According to the results of 4 trials,[4,5,39,41] this difference is due to dropouts because of inefficacy of treatment (N = 178, RR = 3.0, CI = 1.2 to 7.8, NNH = 10, CI = 5 to 50, p = .02).

Only 3 studies provided data for the primary outcome "no clinically significant improvement" and there was no group difference between lithium alone versus antipsychotics (N = 80, RR = 1.3, CI = 0.8 to 2.2, p = .3; Figure 2). The results were statistically significantly heterogeneous, mainly due to the study by Brockington et al.,[38] which showed a trend in favor of lithium. In contrast to the other 2 studies, Brockington et al.[38] included only patients with schizoaffective disorder. Since 2 other studies[5,39] provided only data for continuous outcomes, a standardized mean difference of the endpoint mean values of scales was calculated, which showed that lithium was significantly inferior compared with antipsychotic medication (N = 136, SMD = 0.8, CI = 0.5 to 1.2, p < .001). The largest study, by Prien et al.,[4] did not indicate standard deviations, which are necessary for the calculations; however, this study also reported that lithium was significantly inferior compared with chlorpromazine. In the only long-term study, by Mattes,[41] more patients taking lithium than fluphenazine relapsed, and this was of borderline statistical significance (N = 14, RR = 6.00, CI = 0.95 to 37.8, p = .06).

Only Prien et al.[4] and Shopsin and Kim[5] provided adverse events data suitable for this review: Somnolence was significantly more frequent in the chlorpromazine group (N = 83, RR = 0.2, CI = 0.04 to 0.7, NNH = 4, CI = 3 to 10, p = .02), whereas toxic confusion (N = 104, RR = 9.3, CI = 1.2 to 70.6, NNH = 7, CI = 4 to 17, p = .03) and increased white blood cell count (N = 21, RR = 17.4, CI = 1.1 to 265.4, NNH = 1, CI = 0.9 to 2.0, p = .04) were more frequent in the lithium group. For all other adverse events, no significant differences could be derived from these limited data.

Comparison 3: Lithium Versus Placebo as an Adjunct to Antipsychotics

Eleven studies compared lithium augmentation of antipsychotics with placebo. In terms of acceptability of treatment, significantly more patients with lithium augmentation than with placebo left the studies prematurely (N = 320, RR = 2.0, CI = 1.3 to 3.1, NNH = 7, CI = 4 to 14, p = .001; Figure 1). Unfortunately, the quality of the reporting in these studies did not allow more detailed analyses of the reasons underlying this finding.

There was a significant superiority of lithium augmentation in terms of the number of patients without a clinically significant improvement. Since, with 1 exception,[46]

no study provided an a priori definition of response, a less than 50% reduction of a scale[16,17,37,42,46,47] or a CGI rating less than much improved[43,48] was used as the criterion (N = 244, RR = 0.8, CI = 0.7 to 0.9, NNT = 8, CI 4 to 33, p = .01, Figure 2). Using a less than 20% reduction of a scale or a CGI rating less than minimally improved as a criterion, there was no significant difference (N = 244, RR = 0.9, CI = 0.7 to 1.2, p = .6). Analyzing the results of single scales showed that, compared with those on antipsychotic medication alone, those on lithium augmentation were significantly more likely to be at least minimally improved according to the CGI (4 studies[16,18,43,48]: N = 115, RR = 0.6, CI = 0.4 to 0.9, NNT = 5, CI = 3 to 20, p = .02) and to have a 50% reduction in BPRS scores (5 studies[16–18,46,47]: N = 131, RR = 0.8, CI = 0.7 to 0.9, NNT = 5, CI = 3 to 14, p = .004). There was a superiority of lithium using 35% BPRS score reduction (N = 131, RR = 0.8, CI = 0.6 to 1.0, p = .05), but not using 20% BPRS score reduction as a response threshold (N = 131, RR = 0.9, CI = 0.7 to 1.2, p = .4). Johnstone et al.[37] was the only study to use the Manchester Scale[49] instead of the BPRS and showed no significant differences between groups in the 3 response criteria. A tentative analysis of the mean values of the scales at endpoint also showed no significant difference (5 studies[16–18,37,47]: N = 147, SMD = –0.16, CI = –0.48 to 0.17, p = .4).

Only a limited number of trials provided data on positive, negative, and mood symptoms. Alone and in combination, these studies showed no statistically significant differences or clear trends in any specific aspect of the mental state (data not shown); thus this review is not able to provide more fine-grained detail about the pattern of clinical response to lithium augmentation. Again, adverse events were generally poorly reported; however, the analyses revealed no significant group differences.

Sensitivity Analysis: Exclusion of Patients With Affective Symptoms and Random-Effects Model

In order to rule out the possibility that the superiority of lithium augmentation was merely due to an effect on mood symptoms, patients with schizoaffective disorder or predominant affective symptoms were excluded in a sensitivity analysis for the primary outcomes: All patients in Biederman et al.[43] had schizoaffective disorder, and all patients in Hogarty et al.[48] were persistently distressed by anxiety and/or depression and had few positive symptoms. Five patients from Johnstone et al.[37] and 10 patients from Small et al.[18] were excluded because they had schizoaffective disorder. Schulz et al.[17] and Small and Kellams[42] included a number of schizoaffective patients. Since individual patient data from these studies[17,42] were not available, both trials had to be excluded completely from the sensitivity analysis. Again, significantly more patients left the studies early (7 studies[16,18,37,44–47]: N = 174, RR = 3.5, CI = 1.4 to 8.8, NNH = 6, CI = 4 to 17, p = .007). When the results of 5 trials[16,18,37,46,47] that had data suitable for the "no significant response" outcome were pooled, compared with antipsychotic medication alone, patients on lithium augmentation had better outcomes; however, this difference did not reach the p = .05 level of significance (N = 120, RR = 0.8, CI = 0.6 to 1.0, p = .07).

In order to examine the stability of the findings, we assessed the data using a random-effects model. With this more conservative model, 2 previously significant findings attained only a borderline degree of significance: The higher rates of leaving the studies early among the patients who received lithium as a sole agent compared with antipsychotics (RR = 1.8, CI = 1.01 to 3.1, p = .05) and the higher rates of leaving the studies early among the patients who received lithium augmentation compared with monotherapy with antipsychotics (RR = 1.9, CI = 0.9 to 3.8, p = .08).

DISCUSSION

We present the first systematic review and meta-analysis examining the clinical utility of lithium in the treatment of schizophrenia. There are 3 main findings in this study: (1) There is a small evidence base to show that lithium alone is ineffective in the treatment of schizophrenia when compared with placebo. (2) There is a moderately sized and relatively consistent evidence base demonstrating that, compared with antipsychotic medication alone, the use of lithium alone is less effective. On the basis of this finding, we advise against the use of lithium as a sole treatment for schizophrenia. (3) Compared with antipsychotic medication alone, there is some inconsistent evidence in favor of lithium augmentation; however, it appears that this effect may be explained in part by subjects with schizoaffective disorders. In addition, lithium augmentation is associated with subjects leaving the trials early—a finding in keeping with the known adverse event profile of this compound.

It was important to assess the efficacy of lithium as a sole agent first, because effectiveness as a sole agent would make add-on effects more likely. In 2 small trials, lithium as a sole agent was not more effective than placebo. No statistically significant difference concerning the number of patients without a clinically meaningful response was found in the comparisons of lithium as a sole agent with antipsychotics because 3 relatively large trials[4,5,39] did not provide usable data. However, when 2 of these studies were included in a tentative analysis of the mean BPRS total score at endpoint, a consistent superiority of antipsychotic drugs was found. Therefore, there is little evidence for any efficacy of lithium as a sole agent; this result is further supported by the finding that significantly more patients who received lithium left the studies earlier than did patients who received antipsy-

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chotic drugs. Indeed, as a monotherapy, electroconvulsive therapy is the only effective alternative to antipsychotic drugs.[50]

The most important question of this meta-analysis is the effectiveness of lithium augmentation. A conventional review would have found that only a minority of the studies showed a significant superiority of lithium augmentation, and the reviewers might have concluded that it is not effective. This meta-analysis allows a more differentiated interpretation. Of the 8 studies, 2 studies found a significant effect, and 5 studies found a numerical but nonsignificant benefit for lithium augmentation (Figure 2). This benefit became statistically significant when the results were meta-analytically combined. Of the 8 studies, the only study that found a nonsignificant benefit for antipsychotic medication alone was the trial by Johnstone et al.[37] That study excluded treatment-resistant patients, whereas all but 1 of the other trials[43] focused on nonresponders. However, the superiority in efficacy was not significant across all different thresholds for response or when pooling the mean symptom scale scores at endpoint. This result shows that the effect was not robust.

Furthermore, this meta-analysis was unable to identify which particular symptoms responded to lithium augmentation. On the basis of a more limited number of trials and patients, no statistically significant differences in terms of positive, negative, or affective symptoms between groups could be found. It is therefore possible that any superiority relates more to general symptoms (e.g., anxiety, mood, or somatic preoccupation) than to the core symptoms of the disorder (e.g., hallucinations, delusions, or negative symptoms). When participants with schizoaffective disorder or other prominent affective symptoms were excluded, only a trend in favor of lithium augmentation was found ($p = .07$). Four further randomized controlled studies provided no efficacy data for meta-analytic calculations. It is difficult to estimate how they would have affected the global result. Three of the studies (Small and Kellams,[42] Growe,[7] Carman et al.[8]) found advantages of lithium augmentation, whereas 1 did not (Collins et al.[45]). The data of the quasi-randomized trial by Lerner and Mintzer,[32] for which we had received original patient data, were consistent with the findings of our meta-analysis, since they showed a trend in favor of lithium.

Finally, any superiority in terms of efficacy might be outweighed by a lower acceptability of treatment, because significantly more patients with lithium augmentation left the studies early. Although the reasons for leaving the studies early were rarely specified, adverse reactions are a likely explanation. Dropouts due to inefficacy of treatment are an unlikely explanation, because lithium turned out to be more effective in our analysis.

We conclude that there is no evidence for the effectiveness of lithium as a sole therapy for those with schizophrenia—neither for the acute phase nor for maintenance treatment. Augmentation of antipsychotic drugs with lithium might somewhat increase efficacy; however, in light of the issues outlined above, we recommend caution in the interpretation of the data. The evidence base is too weak to support the widespread use of mood stabilizers reported by Citrome et al.,[15] and it has been shown that subsequent trials using large sample numbers often change the results of a meta-analysis.[51]

Furthermore, there is no proof that the superiority of lithium is related to the core symptoms of schizophrenia. We therefore suggest that at least 1 further large randomized controlled study, preferably using an atypical antipsychotic, be carried out. On the basis of the results of this meta-analysis, in order to confidently detect an effect (80% power, 2-sided test of significance, $p = .05$), 220 patients would need to be randomly allocated to 2 groups of equal size.

Drug names: carbamazepine (Tegretol, Epitol, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), pimozide (Orap).

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