The Use of Lithium to Augment Antidepressant Medication

F. Rouillon, M.D.;
and Philip Gorwood, M.D., Ph.D.

Lithium is one of the most studied agents used to augment the pharmacologic effect of antidepressant drugs, particularly in refractory depression. We reviewed 22 case reports, 22 open trials, 5 open comparison studies, and 9 placebo-controlled studies of lithium augmentation and 6 studies in which antidepressants were added to, or coadministrated with, lithium. The efficacy of the augmentation therapeutic strategy is supported by these analyses, involving 969 patients. The optimal dose and the most effective blood levels of lithium are unclear, but a reasonable strategy would be to start with low doses (600–900 mg/day) and, if necessary, to increase the doses to obtain a level in accordance with the usual therapeutic range of blood levels (0.8–1.2 mEq/L). Some patients respond quickly, but others need a long and combined treatment; it is thus advantageous to prescribe lithium for at least 3 to 6 weeks. Despite the fact that the mechanism of action of lithium augmentation is still unknown, all refractory depressed patients can potentially be treated by lithium augmentation, particularly bipolar patients, to obtain full prophylactic effect as soon as possible.

(J Clin Psychiatry 1998;59[suppl 5]:32–39)

Among the numerous therapeutic approaches to treat refractory depression, such as higher dosages, alternative antidepressant medications, combinations of antidepressant therapies, intravenous drugs, or electroconvulsive therapy, is the use of adjunct treatments. Many agents have been proposed to augment the pharmacologic effect of antidepressants, including stimulants such as methylphenidate, amino acids such as L-tryptophan, thyroid or gonadal hormones, anxiolytics such as buspirone, carbamazepine, and lithium.

Lithium salts, which were proposed by Cade in the treatment of manic depressive illness in 1949, were recognized as an effective drug against mania[1–3] and as a prophylactic drug in long-term treatment of both unipolar and bipolar illnesses.[4,5] Lithium originally seemed to have a poor antidepressant effect, but its antidepressant efficacy has been recently supported by many controlled studies.[6] Lithium augmentation is a new stage of the lithium story.

From the Department of Psychiatry, Louis Mourier Hospital, Colombes Cedex, France.

Presented at the symposium "Augmentation of Antidepressant Medication," February 6, 1997, New York, N.Y., which was supported by an unrestricted educational grant from Bristol-Myers Squibb.

Reprint requests to: F. Rouillon, M.D., Department of Psychiatry, Louis Mourier Hospital, 178, rue des Renouillers, 92701 Colombes Cedex, France.

HISTORY OF THE USE OF LITHIUM AUGMENTATION

Zall and colleagues[7] were the first to describe the benefit of adding lithium to antidepressant drugs by observing the synergistic effect of lithium coadministration with tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs). Himmelhoch et al.[8] proposed an empirical justification with the first open trial with tranylcypromine added to lithium. At the same time, O'Flanagan[9] concluded that there is a more rapid improvement and a better tolerance when lithium is used in conjunction with clomipramine.

In 1978, the Montreal Group proposed a rationale for the use of lithium augmentation[10] and conducted the first trial in eight refractory depressed patients.[11] In this study, a dramatic improvement was reported 48 hours after addition of lithium to a previously ineffective tricyclic treatment. Over the last 20 years, many case reports, open studies, and controlled studies have observed that around two thirds of patients respond to a greater or lesser extent to this therapeutic strategy. Most of these reports have been reviewed by Katona,[12] Schöpf,[13] Schou,[14] and de Montigny,[15] who all concluded that despite methodological limitations of many studies, evidence suggests efficacy of lithium augmentation.

Two meta-analyses[16,17] of placebo-controlled studies supported this positive conclusion. The first by Austin et al.[16] stressed the considerable variations among studies for

Table 1. Case Reports (≤ 5 Cases) of Lithium Augmentation

Author	N(Sex/Age)	Antidepressant	Time to Response
Nelson and Byck (1982)[20]	3 (F 41 y, 51 y; M 75 y)	Phenelzine	≤ 5 d
Birkhimer et al (1983)[21]	1 (M 45 y)	Trazodone	7 d
Joyce et al (1983)[22]	1	Mianserin	2 d
Weaver (1983)[23]	1 (F 73 y)	Maprotiline	No response
Schrader and Levien (1985)[24]	1 (M 73 y)	Clomipramine	1 wk
Pande and Max (1985)[25]	1 (F 82 y)	Imipramine added to lithium	2 d
Roy and Pickar (1985)[26]	3 (M 26 y, 52 y; F 32 y)	Imipramine	10 d–2 wk
Madakasira (1986)[27]	3	Amitriptyline-phenelzine	3–10 d
Pai et al (1986)[28]	5 (F 38 y, 59 y; M 64 y, 69 y, 72 y)	Amitriptyline-dothiepin	1–2 wk
Garbutt et al (1986)[29]	4	Amitriptyline-imipramine	2 d–1 wk
Delisle (1986)[30]	1 (F 39 y)	Imipramine	2 d[a]
Kushnir (1986)[31]	5 (F 87 y, 78 y; M 65 y, 83 y, 93 y)	Trazodone-desipramine-maprotiline	1–2 wk
Tariot et al (1986)[32]	1	Tryptophan	2 d
Cerra et al (1986)[33]	1 (M 47 y)	Alprazolam	2 wk
Lieff and Herrmann (1988)[34]	1 (F 71 y)	Phenelzine + doxepin	1 wk
Manning and Connor (1994)[35]	2 (F 35 y; M 28 y)	Fluoxetine-nortriptyline	72 h–2 wk
Fein et al (1988)[36]	4 (M 56 y, 67 y; F 40 y, 67 y)	Phenelzine	5 d–weeks
Yuvarajan and Yousufzai (1988)[37]	1 (F 57 y)	Imipramine then maprotiline	Mania induced then remitted
Conte (1988)[38]	2 (M 48 y, 20 y)	Imipramine + tryptophan	≤ 1 wk
Feder (1988)[39]	1 (M 25 y)	Clomipramine	2 wk
Pope et al (1988)[40]	5 (M 19 y, 20 y, 20 y; F 34 y, 26 y)	Fluoxetine	weeks or months
Price et al (1988)[41]	1	Desipramine	1 wk

[a]Mania induced within a short delay.

criteria of refractoriness, lithium response, previous exposure to antidepressants, and duration of trials. The authors concluded, however, that the number of responders is significantly ($p < .01$) larger with lithium (18/50) than with placebo (6/49). Some authors nevertheless considered that there were insufficient data[17] or not enough methodologically sound studies[18] to draw unequivocal conclusions. Notwithstanding, Katona[19] published a second meta-analysis that pooled the results of Austin et al.[16] and their own data. They also showed a significant superiority of lithium over placebo ($p < .001$).

CASE REPORTS AND OPEN STUDIES

There are, to our knowledge, 22 publications of case reports, each with five patients or less (Table 1), representing a total of 48 refractory depressed patients treated by lithium augmentation. Depressed patients had previously been treated, before lithium addition, by different antidepressants: tricyclics (e.g., amitriptyline, imipramine, desipramine, clomipramine), MAOIs (phenelzine), serotonin selective reuptake inhibitors (SSRIs), other antidepressants (e.g., mianserin, maprotiline), and a triazolobenzodiazepine (alprazolam), here considered as an antidepressant. The delay of response varied from 2 days to 2 or 3 weeks, but improvement was often rapid and marked. As negative findings are obviously less frequently published in such papers, it is difficult to draw conclusions from such studies.

Some cases of lithium augmentation have been reported in other psychiatric disorders: obsessive-compulsive disorder (OCD),[42] panic disorder,[43] comorbid depression and OCD plus panic attack,[39] schizoaffective disorder and depression associated with OCD or bulimia nervosa,[40] and major depressive episode associated with OCD.[44]

A therapeutic effect of lithium augmentation was described in the 22 open studies presented in Table 2, which represent a total of 518 patients. There are considerable variations with respect to number of patients (range, 5–84), duration of treatment (range, 2 days–6 weeks), and response rates (range, 44%–100%). Nevertheless, we have to consider the bias inherent to open studies.

OPEN COMPARISON STUDIES

There are five open comparison studies. The oldest study compared 22 patients treated with lithium and L-tryptophan to 22 patients treated with amitriptyline during 4 weeks. No statistical difference was found between the response rates, which were, respectively, 82% and 71%.[65] In their study, Garbutt et al.[29] observed that four patients responded to lithium added to a TCA after withdrawal of triiodothyronine (T_3), which had failed to increase the antidepressant effect of the same TCA. Joffe[66] conducted a study in which patients were successively treated with T_3 or lithium added to imipramine or desipramine for 3 weeks. There were no statistical differences between the response rates of lithium augmentation (23%) and T_3 augmentation (36%). Some patients (36%) did not respond to either lithium or T_3, and 5% responded to both of them. Thase et al.[61] compared 20 patients who had coadministration of lithium and imipramine with a control group of 20 patients selected from the population of the Pittsburgh study.[67] They observed a significant ($p = .03$) superiority of lithium augmentation after 6 weeks. In a comparison study of lithium and TCA versus ECT, Dinan and Barry[68] found no statistical difference between the response rates of these two treatments after 3 weeks (respectively, 66% vs. 73%). The onset of efficacy with lithium addition seemed to be more rapid than with ECT.

Table 2. Open Trials of Lithium Added to Antidepressant (N > 5 in Each Trial)*

Author	Design	N	Duration	Dosage (mg/d)	Response
Neubauer and Bermingham (1976)[45]	Lithium subst. for antidepressant	20	. . .	. . .	100%
de Montigny et al (1981)[11]	TCA + lithium	8	2 d	900	100% (within 48 h)
de Montigny et al[a] (1983)[46]	TCA + lithium	39	2 d	900	77% (≥ 50% improvement)
de Montigny et al[b] (1983)[46]	Amitriptyline/placebo + lithium	5 + 5	2 d	900	100% (versus 20% placebo)
Price et al (1983)[47]	[TCA + neuroleptic] + lithium	6	21 d	900–1200	50% marked; 34% partial
Heninger et al[c] (1983)[48]	Switch to lithium from placebo	7	24 d	900	86% (significant decrease)
Alvarez et al (1984)[49]	Case method	10	. . .	. . .	70%
Bellwald (1984)[50]	Case method	8	. . .	. . .	100%
Louie and Meltzer (1984)[51]	Case method	7/2[d]	1–6 wk	1200	44%
de Montigny et al (1985)[52]	Iprindole + lithium	7	2 d	900	86% (≥ 50% improvement)
Joyce (1985)[53]	Case method	6	2–21 d	500–750	66%
Price et al (1986)[54]	Lithium added to TCA, adinazolam, bupropion, fluvoxamine, mianserin, trazodone	73/11[d]	21 d	900–1500	31% marked; 25% partial response; 44% no change/adverse effect
Charney et al (1986)[55]	Desipramine/tranylcypromine + lithium	12/2[d]	4 wk	. . .	79%
Nelson and Mazure (1986)[56]	[TCA + neuroleptic] + lithium	12/9[d]	Retrospective	600–1200	52% (89% bipolar/25% unipolar)
Hale et al (1987)[57]	[Clomipramine + tryptophan] + lithium	6	6 wk	400–800	100% ≈ 3 d–6 wk
Delgado et al (1988)[58]	Fluvoxamine + lithium (+ perphenazine)	16/2[d]	3 wk	. . .	56%
Ryan et al (1988)[59]	Adolescents with refractory depression	14	. . .	. . .	43% marked; 21% partial
Cohen et al (1988)[60]	Lithium + imipramine	74	. . .	. . .	67%
Thase et al (1989)[61]	Lithium + imipramine	20	42 d	900	65%
Fontaine et al (1991)[62]	Lithium + desipramine or fluoxetine	60	14 wk	600 then adjusted	58% fluoxetine ≈ desipramine
Rybakowski and Matkowski (1992)[63]	Lithium + antidepressant	37/14[d]	28 d	500–1500	55%
McCance-Katz et al (1992)[64]	Lithium + antidepressant	23/3[d]	7 d	900	38% marked; 50% partial

*Symbols: . . . = not specified. ≈ = approximately.
[a]First phase of de Montigny study.
[b]Second phase of de Montigny study.
[c]Seven patients from the placebo group of the double-blind Heninger study were switched to active lithium carbonate after 12 days of placebo/lithium comparison that revealed no therapeutic effect.
[d]Unipolar/bipolar.

STUDIES OF ANTIDEPRESSANTS ADDED TO OR INITIATED WITH LITHIUM

Some studies are not, strictly speaking, lithium augmentation studies, because lithium and antidepressant medication were simultaneously prescribed as first-line treatment, or because antidepressant medication was added to lithium that was previously prescribed. For example, Zall[69] observed the efficacy of the coadministration of isocarboxazid and lithium for four depressed patients unsuccessfully treated by other antidepressants alone. Similarly, Himmelhoch et al.[8] have shown 52% remission and 24% partial remission in 13 bipolar and 8 unipolar patients previously resistant to TCA medication and treated by tranylcypromine added to lithium. Lingjaerde et al.[70] compared in a double-blind study TCA plus lithium with TCA plus placebo in 45 endogenous depressed patients during 4 weeks of treatment. The response rate was greater with TCA plus lithium (82%) than with TCA plus placebo (57%), and the difference was statistically significant ($p = .04$). On the other hand, Nick et al.[71] found no statistical difference between clomipramine plus lithium (response rate = 80%) and clomipramine plus placebo (response rate = 75%) compared in double-blind conditions during 3 weeks of treatment. There was a 92% response rate in an open trial of tranylcypromine added to lithium for 2 bipolar and 10 unipolar patients who had not responded to the addition of lithium to desipramine, adinazolam, or bupropion during a mean period of 3.2 weeks.[72] In this Yale University Group study, 8 of the 11 patients who showed a significant improvement were blindly judged much or very much improved. Finally, Ebert et al.[73] found a statistically significant ($p < .05$) superiority of amitriptyline plus lithium (response rate = 85%) in comparison with amitriptyline plus placebo (response rate = 60%) in a double-blind study that included 40 bipolar depressed patients.

PLACEBO-CONTROLLED STUDIES OF LITHIUM AUGMENTATION

Six of the nine placebo-controlled studies of lithium augmentation are more or less conclusive. The first study

Table 3. Placebo-Controlled Studies of Lithium Augmentation

Author	N	Duration (d)	Dosage (mg/d)	Response		p Value
				Lithium	Placebo	
de Montigny et al (1983)[46]	10	Lithium add to amitriptyline or placebo 2	900	Lithium + amitriptyline (100%)	Lithium + placebo (20%)	< .001
Heninger et al (1983)[48]	1 bipolar 14 unipolar	12	900–1200	62%	0%	< .014
Cournoyer et al (1984)[74]	12	Crossover 2	900	Statistically significant improvement in lithium period but not after placebo		. . .
Kantor et al (1986)[75]	7 unipolar	2	900	25%	0%	NS
Zusky et al (1988)[76]	16	14	≥ 300	37%	25%	NS
Schöpf et al (1989)[77]	9 bipolar 18 unipolar	7	≥ 800	100%	0%	< .005
Kramlinger and Post (1989)[78]	13 bipolar 2 unipolar	21	300–600	53%	. . .	. . .
Stein and Bernadt (1993)[79]	34	21 × 3	250	18%	22%	NS
			750	44%	. . .	. . .
Katona et al (1995)[80]	62	42	800 + adjustment	52%	25%	< .05

presented in Table 3 is not a placebo-controlled study but a double-blind comparison of amitriptyline versus placebo when coadministered with lithium.[46] In this trial conducted by the Montreal Group, lithium was added for 48 hours after 3 weeks of treatment with amitriptyline (N = 5) or placebo (N = 5). All five patients receiving amitriptyline showed a greater than 50% improvement in contrast to only one in the placebo group. The Heninger et al.[48] study is not blind because lithium was prescribed to patients in alternate order with active treatment versus placebo. Nevertheless, its results (62% response rate with lithium versus 0% with placebo) have been included in the meta-analysis of Austin et al.[16] Crossover studies by Cournoyer et al.[74] and Schöpf et al.[77] showed a statistically significant superiority of lithium and a fast onset of action.

The Kramlinger and Post[78] study was a single-blind trial in which lithium was substituted for placebo for patients who had not responded to double-blind treatment with carbamazepine; 53% of them showed a good response to lithium. The last double-blind study[80] is one of the most important to confirm that lithium augmentation is a useful strategy. It was conducted for 6 weeks on 62 depressed patients who had failed to respond to a controlled trial of fluoxetine or lofepramine. Response was defined by a final score on the Hamilton Rating Scale for Depression of less than 10 and was more frequent in the lithium group (52%) than in the placebo group (25%), the difference being statistically significant ($p < .05$).

Three studies did not reach a level of statistical significance: in the first of those, published by Kantor et al.,[75] there was a 25% response with lithium (versus none with placebo), but the small sample size (N = 7) could explain a type II error. In the second study,[76] the doses of lithium were low or patients were less depressed and possibly treated for a longer period than in the other studies. These differences may explain the comparable lithium (37%) and placebo (25%) response rates. The third inconclusive study was the first step (comparing 250 mg of lithium with placebo) of a study that then compared 750 mg with 250 mg of lithium. During the first phase (3 weeks), the response rate was 18% in the lithium group and 22% in the placebo group. Response rate was 44% when the lithium dose was increased from 250 mg to 750 mg.[79]

LITHIUM DOSAGE, PLASMA LEVELS, AND RESPONSE RATES

The lithium dosage usually prescribed is around 900 mg/day, and the mean plasma lithium level ranges between 0.4 and 1.1 mEq/L (Table 4).

Findings regarding the correlation between plasma levels of lithium and responsiveness to lithium augmentation treatment are rather contradictory. Some studies observed a higher plasma level in responders than in nonresponders or an improvement after increasing the dose of lithium in some patients.[34,40,50,79] Others showed no significant correlation between plasma levels and improvement or differences between responders and nonresponders.[56,65,78] Similarly, Rybakowski and Matkowski[63] found the same response rate with plasma levels < 0.7 or ≥ 0.7 mEq/L of lithium. Thase et al.,[61] on the other hand, observed higher plasma lithium levels in nonresponders (0.83 mEq/L) than in responders (0.56 mEq/L) ($p < .01$). Moreover, they found that plasma levels were lower in patients who improved during the first 2 weeks than during the third to sixth weeks. Similarly, Kushnir[31] reported a 100% response rate to lithium augmentation with low plasma lithium levels (0.15–0.40 mEq/L) in geriatric patients.

Nevertheless, Zusky et al.[76] stressed that low plasma lithium levels could explain the insufficient response rate in their study. Katona et al.[80] also observed a better response rate when patients with inadequate plasma lithium level (< 0.40 mEq/L) were excluded (62.5% vs. 52%).

Table 4. Plasma Lithium Levels in Lithium Augmentation Studies*

Author	Level mEq/L (mean or range)
Lingjaerde et al (1974)[70]	0.6–1
Nick et al (1976)[71]	0.35–1.1
Worrall et al (1979)[6]	0.86–0.93
de Montigny et al (1981)[11]	0.5–1
Honore et al (1982)[65]	0.67–1
de Montigny et al (1983)[46]	0.4–1.20
Heninger et al (1983)[48]	0.50–1.07
Price et al (1983)[47]	0.4–1.20
Weaver (1983)[23]	0.72–1.12
Bellwald (1984)[50]	0.45–0.95
Louie and Meltzer (1984)[51]	0.70–1.20
Price et al (1984)[81]	1.07–1.31
de Montigny et al (1985)[52]	0.40–1.20
Price et al (1985)[72]	0.63–1.28
Schrader and Levien (1985)[24]	0.75
Cerra et al (1986)[33]	0.91
Delisle (1986)[30]	0.5
Garbutt et al (1986)[29]	0.46–1.10
Kushnir (1986)[31]	0.15–0.40
Madakasira (1986)[27]	0.18–0.70
Nelson and Mazure (1986)[56]	0.82 (nr)–0.75 (r)
Pai et al (1986)[28]	0.50–1.00
Price et al (1986)[54]	0.50–1.30
Tariot et al (1986)[32]	0.70
Conte (1988)[38]	0.52
Lieff and Herrmann (1988)[34]	0.32 (nr)–0.86 (r)
Pope et al (1988)[40]	0.40–1.20
Price et al (1988)[41]	0.60
Yuvarajan and Yousufzai (1988)[37]	0.22–0.24
Zusky et al (1988)[76]	0.10–0.80
Kramlinger and Post (1989)[78]	0.69 (nr)–0.67 (r)
Dinan and Barry (1989)[68]	0.50–0.70
Schöpf et al (1989)[77]	0.41–1.28
Thase et al (1989)[61]	0.83 (nr)–0.56 (r)
Rybakowski and Matkowski (1992)[63]	0.44–0.97
Stein and Bernadt (1993)[79]	0.65–0.78
Ebert et al (1995)[73]	0.61–0.66
Katona et al (1995)[80]	adequate level (≤ .40)

*Abbreviations: r = responders, nr = nonresponders.

Thus, it could be recommended that adequate plasma lithium levels are necessary to get a better efficacy of lithium augmentation.

DELAY OF ACTION AND DURATION OF TREATMENT

Some studies found a very short delay of action when lithium was added to antidepressant medication. Others reported an improvement after a medium or long delay of action. Thirty-three studies among the 64 reviewed mention, more or less, delay of action. For 198 of the 374 patients treated in those studies, the response is sufficiently documented to class them in three categories:

1. 73 patients (37.0%) responded quickly (≤ 48 hours)
2. 72 patients (36.5%) responded in a period from 2 days to 2 weeks
3. 53 patients (27.5%) responded after a longer time (> 2 weeks)

There is no clear explanation for this variation. De Montigny[15] speculated that more intensive and prolonged antidepressant therapy may be associated with a slower response. For example, in the study by Thase et al.,[61] the initial treatment consisted of a high dosage of imipramine for 12 weeks. Unlike findings of previous studies, only 1 patient had a clinically significant response during the first week of lithium augmentation, and 38% of responders did not improve until the fifth or sixth week of lithium addition. These results suggest that lithium augmentation be used for at least 1 month.

How long should one continue treatment with lithium? There are few data to give an answer to this practical question. De Montigny et al.,[11] in a follow-up of 3 to 9 months, observed relapse in one patient for whom lithium was discontinued after 1 week for side effects and in one among five patients for whom lithium was discontinued after 1 month. In another study of nine patients, de Montigny et al.[46] discontinued lithium after 48 hours and found five patients who relapsed within 1 week and four patients who remained well while receiving only tricyclic antidepressant medication. Sixty-six patients (88%) of the original cohort, which comes from the Yale Study,[41] were included in a longitudinal retrospective naturalistic study for 29 ± 15 months by Nierenberg et al.[83] They showed a positive correlation ($p < .03$) between the percentage of favorable long-term outcome and the degree of short-term response to lithium augmentation:

1. for poor outcome (29%): 58% had no response, 32% partial response, 11% marked response;
2. for fair outcome (23%): 20% had no response, 33% partial response, 47% marked response;
3. for favorable outcome (48%): 34% had no response, 19% partial response, 47% marked response.

These findings indicate that lithium is able to stop the episode of illness in some patients. Those patients remained well after withdrawal of antidepressant or lithium or both. But other patients remained well under combined therapy, and in isolated cases depressive recurrences were observed even if associated therapy had been continued.

ADVERSE EFFECTS

Side effects of lithium, such as hand tremor, nausea, polyuria, and weight gain, can occur during lithium treatment.[61,76] A lithium toxicity has also been observed in association with tricyclic antidepressants. Confusion,[79] ataxia and memory deficit,[84] seizure,[85] ectopic electrocardiogram (ECG) activity,[86] and myoclonus[87] have been observed. Moreover, a serotonin syndrome has been described with combination of SSRIs and lithium. Salama and Shafey[88] described cases of confusion, tremor, and hyperthermia with the conjunction of lithium and SSRI medication. Absence seizure was observed by Sacristan et

al.,[89] and somnolence by Evans and Marwick.[90] But lithium and antidepressants are usually well tolerated when given together, particularly if lower doses of lithium are used in the elderly.

Lithium has a well-known mood-stabilizing and antimanic action; it is therefore surprising that manic and hypomanic episodes were reported during lithium augmentation treatment for bipolar patients receiving phenelzine or imipramine,[30,51] fluoxetine,[91] and for bipolar II patients receiving tricyclic antidepressant medication.[81] Yuvarajan and Yousufzai[37] observed a manic episode in a unipolar patient treated with lithium added to imipramine and then maprotiline. There were, nevertheless, few cases of mania or hypomania reported in comparison with the great number of patients treated with lithium augmentation.

WHO WILL RESPOND?

Sociodemographic factors (e.g., gender, age) have not been shown to exert any influence on the outcome of lithium augmentation treatment.

Among clinical data, results are controversial. The ratio of responsiveness in bipolar and unipolar patients approximated that described for lithium when used as a primary antidepressant. Rybakowski and Matkowski[63] found a response rate of 79% for bipolar versus 46% for unipolar patients. Furthermore, Nelson and Mazure[56] described nearly the same ratio of 89% versus 25%. Price et al.[54] found, on the other hand, a greater percentage of response with unipolar patients (59%) than with bipolar patients (37%), and others found no difference.[8,70,72] Price et al.[54] showed a better ($p < .04$) efficacy for melancholic (50%) versus nonmelancholic depressed patients (13%), but Rybakowski and Matkowski[63] found a greater ($p < .001$) response rate in moderate depression (78%) than in severe depression (30%). Similarly, lithium augmentation was similar in either delusional or nondelusional depression, in either isolated or recurrent depression, in depression with either acute or insidious onset, and in depressed patients either with or without familial history. Likewise, the response rate is not correlated with the number of previous episodes or with duration of illness or episode.

The type of previous antidepressant does not seem to play an essential role in response rate. Nevertheless, Kramlinger and Post[78] calculated in their review a better response rate with tricyclics (77%), tetracyclics (88%), or MAOI treatment (90%) than with other antidepressants (55%) or with carbamazepine (53%). Louie and Meltzer[51] suggested that the efficacy of nortriptyline may not be increased by lithium, and Price et al.[54] found a greater response rate with TCA medication (69%) or mianserin (83%) than with bupropion (43%), trazodone (22%), fluvoxamine (45%), or adinazolam (30%). In this review, we calculated a more or less similar efficacy of compounds with selective reuptake of norepinephrine (desipramine, amoxapine, maprotiline: 71%), compared with those without clear preference of reuptake inhibition (amitriptyline, dothiepin, doxepin, imipramine, nortriptyline: 81%), with SSRIs (60%), or with antidepressants with no action on reuptake (bupropion, iprindole, mianserin, or trimipramine: 65%).

The influence of other therapeutic factors (e.g., additional medication, sequence of drug administration, previous treatment with T_3) is still unclear. Nevertheless, the results of Thase et al.[61] suggest that the shorter the duration of prior treatment, the more rapid the onset of response. Moreover, Rybakowski and Matkowski[63] found a better response ($p < .001$) when improvement occurred during the first week (91%) than later (28%). Biological data that have been studied as possible prognostic factors do not seem to clearly predict the therapeutic response of lithium augmentation. The prognostic value of the dexamethasone suppression test found by Alvarez et al.[49] was not confirmed by Rybakowski and Matkowski,[63] Price et al.,[54] or Joyce.[53] The ratio of T_3 to T_4 and the level of thyroid-stimulating hormone (TSH) and ΔTSH can predict lithium augmentation response,[77] as does the methylphenidate test.[53] Price et al.[54] and Zusky et al.[76] found no correlation between response rate and level of MHPG. Finally, McCance-Katz et al.[64] did not observe a correlation between prolactin response to intravenous tryptophan and response to lithium augmentation, but they found a greater prolactin response after lithium addition than after placebo addition or with antidepressant alone.

CONCLUSION

The efficacy of lithium augmentation of antidepressant response is supported by many case reports and open trials that constitute a body of evidence and is strongly confirmed by methodologically sound studies. Several mechanisms have been proposed to explain the cojoint actions of lithium. In vitro studies have demonstrated that low plasma levels of lithium (0.1 mEq/L) enhance serotonin turnover and induce a short-term effect.[92,93] A synergistic effect or potentiation involving another monoamine other than serotonin (e.g., norepinephrine, acetylcholine) could also be suggested. Moreover, a primary antidepressant effect of lithium cannot be excluded as suggested by the long latency of response for some patients. In fact, the antidepressant effect of lithium has generally been underestimated, although it had once been found to be around 60%,[12] an effect which may also be explained by the efficacy of the antidepressant previously prescribed.[82] Pharmacokinetic interaction is an unlikely explanation, as plasma antidepressant concentrations are unmodified after lithium addition.[46,52,61]

Lithium augmentation is far from being a universal panacea for refractory depression and can induce some side effects. All refractory depressed patients can, never-

theless, be treated by lithium augmentation. Moreover, lithium augmentation may have another beneficial effect: achievement of an early and full prophylactic effect of lithium can reduce the risk of a switch to mania in bipolar patients.

Drug names: adinazolam (Deracyn), alprazolam (Xanax), amitriptyline (Elavil and others), amoxapine (Asendin), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), clomipramine (Anafranil), desipramine (Norpramin and others), dexamethasone (Decadron), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), iprindole (Tertran), isocarboxazid (Marplan), L-tryptophan (Trofan and others), maprotiline (Ludiomil), methylphenidate (Ritalin), nortriptyline (Pamelor and others), perphenazine (Trilafon), phenelzine (Nardil), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil).

REFERENCES

1. Schou M. Lithium in psychiatric therapy and prophylaxis. J Psychiatr Res 1968;6:67–95
2. Gershon S. Lithium in mania. Clin Pharmacol Ther 1970;11:168–187
3. Prien RF, Caffey EM, Klett CJ. Relationship between serum lithium level and clinical response in acute mania treated with lithium. Br J Psychiatry 1972;120:409–414
4. Baastrup PC, Poulsen JC, Schou M, et al. Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. Lancet 1970;2:326–330
5. Angst J, Weiss P, Grof P, et al. Lithium prophylaxis in recurrent affective disorders. Br J Psychiatry 1970;116:604–614
6. Worrall EP, Moody JP, Peet M, et al. Controlled studies of the acute antidepressant effect of lithium. Br J Psychiatry 1979;135:255–262
7. Zall H, Therman PG, Myers JM. Lithium carbonate: a clinical study. Am J Psychiatry 1968;125:549–555
8. Himmelhoch JM, Detre T, Kupfer DJ, et al. Treatment of previously intractable depressions with tranylcypromine and lithium. J Nerv Ment Dis 1972; 155:216–220
9. O'Flanagan P. Clomipramine infusion and lithium carbonate: a synergistic effect? [letter] Lancet 1973;2:974
10. de Montigny C, Aghajanian GK. Tricyclic antidepressants: long term treatment increases responsivity of rat forebrain neurons to serotonin. Science 1978;202:1303–1306
11. de Montigny C, Grunberg F, Mayer A, et al. Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. Br J Psychiatry 1981;138:252–256
12. Katona CLE. Lithium augmentation in refractory depression. Psychiatric Developments 1988;2:153–171
13. Schöpf J. Treatment of depressions resistant to tricyclic antidepressants related drugs or MAO inhibitors by lithium addition: review of literature. Pharmacopsychiatry 1989;22:174–182
14. Schou M. Lithium and treatment resistant depression: a review. Lithium 1990;1:3–8
15. de Montigny C. Lithium addition in treatment-resistant depression. Int Clin Psychopharmacol 1994;9:31–35
16. Austin MPV, Souza FGM, Goodwin GM. Lithium augmentation in antidepressant-resistant patients: a quantitative analysis. Br J Psychiatry 1991; 159:510–514
17. Flint A. Lithium augmentation in antidepressant resistant patients [letter]. Br J Psychiatry 1992;160:710
18. Patten SB, Lupin DA, Boucher SA, et al. Pharmacologic management of refractory depression. Can Med Assoc J 1992;146:483–487
19. Katona CLE. Refractory depression: a review with particular reference to the use of lithium augmentation. Eur Neuropsychopharmacol 1995;5 (suppl):109–113
20. Nelson JC, Byck R. Rapid response to lithium in phenelzine non-responders. Br J Psychiatry 1982;141:85–86
21. Birkhimer LJ, Alderman AA, Schmitt CE, et al. Combined trazodone-lithium therapy for refractory depression. Am J Psychiatry 1983;140: 1382–1383
22. Joyce PR, Hewland HR, Jones AV. Rapid response to lithium in treatment resistant depression. Br J Psychiatry 1983;142:204–206
23. Weaver KEC. Lithium for delusional depression. Am J Psychiatry 1983; 140:962–963
24. Schrader GD, Levien HEM. Response to sequential administration of clomipramine and lithium carbonate in treatment resistant depression. Br J Psychiatry 1985;147:573–575
25. Pande AD, Max P. A lithium-tricyclic combination for treatment of depression. Am J Psychiatry 1985;142:1228–1229
26. Roy A, Pickar D. Lithium potentiation of imipramine in treatment resistant depression. Br J Psychiatry 1985;147:582–583
27. Madakasira S. Low dose potency of lithium in antidepressant augmentation. Psychiatric Journal of the University of Ottawa 1986;11:107–109
28. Pai M, White AC, Deane AG. Lithium augmentation in the treatment of delusional depression. Br J Psychiatry 1986;148:736–738
29. Garbutt JC, Mayo JP Jr, Gillette GM, et al. Lithium potentiation of tricyclic antidepressants following lack of T_3 potentiation. Am J Psychiatry 1986; 143:1038–1039
30. Delisle JD. Rapid switch in a bipolar patient during lithium tricyclic therapy. Am J Psychiatry 1986;143:1326–1327
31. Kushnir SL. Lithium-antidepressant combinations in the treatment of depressed, physically ill geriatric patients. Am J Psychiatry 1986;143: 378–379
32. Tariot PN, Murphy DL, Sunderland T, et al. Rapid antidepressant effect of addition of lithium to tranylcypromine. J Clin Psychopharmacol 1986;6: 165–167
33. Cerra D, Meacham T, Coleman J. A possible synergistic effect of alprazolam and lithium carbonate [letter]. Am J Psychiatry 1986;143:552
34. Lieff S, Herrmann N. Combined drug therapy for an elderly depressed patient [letter]. Am J Psychiatry 1988;145:1034–1035
35. Manning JS, Connor PD. Antidepressant augmentation with lithium. J Fam Pract 1994;39:379–383
36. Fein S, Paz V, Rao N, et al. The combination of lithium carbonate and an MAOI in refractory depressions. Am J Psychiatry 1988;145:249–250
37. Yuvarajan R, Yousufzai NM. Mania induced by lithium augmentation: a case report. Br J Psychiatry 1988;153:828–830
38. Conte G. Lithium, imipramine and hydroxytryptophan in resistant depression [letter]. Br J Psychiatry 1988;152:720
39. Feder R. Lithium augmentation of clomipramine [letter]. J Clin Psychiatry 1988;49:458
40. Pope HG, McElroy SL, Nixon RA. Possible synergism between fluoxetine and lithium in refractory depression. Am J Psychiatry 1988;145: 1292–1294
41. Price LH, Delgado PL, Charney DS, et al. Sequence of drug administration in lithium augmentation: a case study. J Clin Psychiatry 1988;49:161–162
42. Rasmussen SA. Lithium and tryptophan augmentation in clomipramine resistant obsessive-compulsive disorder. Am J Psychiatry 1984;141: 1283–1285
43. Cournoyer G. Rapid response of a disorder to the addition of lithium carbonate: panic resistant to tricyclic antidepressants. Can J Psychiatry 1986; 31:335–338
44. Howland RH. Lithium augmentation of fluoxetine in the treatment of OCD and major depression: a case report. Can J Psychiatry 1991;36:154–155
45. Neubauer H, Bermingham P. A depressive syndrome responsive to lithium: an analysis of 20 cases. J Nerv Ment Dis 1976;163:276–281
46. de Montigny C, Cournoyer G, Morissette R, et al. Lithium carbonate addition in tricyclic antidepressant resistant unipolar depression: correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system. Arch Gen Psychiatry 1983;40:1327–1334
47. Price LH, Conwell Y, Nelson JC. Lithium augmentation of combined neuroleptic tricyclic treatment in delusional depression. Am J Psychiatry 1983; 140:318–322
48. Heninger GR, Charney DS, Sternberg DE. Lithium carbonate augmentation of antidepressant treatment: an effective prescription for treatment refractory depression. Arch Gen Psychiatry 1983;40:1335–1342
49. Alvarez E, Udina C, Queralto JM, et al. Factors indicating the favourable response of lithium added to the treatment of resistant depression [abstract]. Collegium International of Neuro-psychopharmacology 1984;14: 75
50. Bellwald J. Lithium/Antidepressiva-Kombinations-Therapie bei endogenen Depressionen. Inaugural Dissertation [abstract]. Zurich, Switzerland: University of Zurich; 1984
51. Louie AK, Meltzer HY. Lithium augmentation of antidepressant treatment. J Clin Psychopharmacol 1984;4:316–321
52. de Montigny C, Elie R, Gaille G. Rapid response to the addition of lithium

in iprindole-resistant unipolar depression: a pilot study. Am J Psychiatry 1985;142:220–223
53. Joyce PR. Mood response to methylphenidate and the dexamethasone suppression test as predictors of treatment response to zimelidine and lithium in major depression. Biol Psychiatry 1985;20:598–604
54. Price LH, Charney DS, Heninger GR. Variability of response to lithium augmentation in refractory depression. Am J Psychiatry 1986;143: 1387–1392
55. Charney DS, Price LH, Heninger GR. Desipramine-yohimbine combination treatment of refractory depression: implications for the β-adrenergic receptor hypothesis of antidepressant action. Arch Gen Psychiatry 1986; 43:1155–1161
56. Nelson JC, Mazure CM. Lithium augmentation in psychotic depression refractory to combined drug treatment. Am J Psychiatry 1986;143:363–366
57. Hale AS, Procter AW, Bridges PK. Clomipramine, tryptophan and lithium combination for resistant endogenous depression: seven case studies. Br J Psychiatry 1987;151:213–217
58. Delgado PL, Price LH, Charney DS, et al. Efficacy of fluvoxamine in treatment refractory depression. J Affect Disord 1988;15:55–60
59. Ryan ND, Meyer V, Dachille S, et al. Lithium antidepressant augmentation in TCA refractory depression in adolescents. J Am Acad Child Adolesc Psychiatry 1988;145:1317–1318
60. Cohen LS, Heller VL, Rosenbaum JF, et al. Adjuvant lithium carbonate in refractory depression. In: New Research Program and Abstracts of the 141st Annual Meeting of the American Psychiatric Association; May 1988
61. Thase ME, Kupfer DJ, Frank E, et al. Treatment of imipramine-resistant recurrent depression, II: an open clinical trial of lithium augmentation. J Clin Psychiatry 1989;50:413–417
62. Fontaine R, Ontiveros A, Elie R, et al. Lithium carbonate augmentation of desipramine and fluoxetine in refractory depression. Biol Psychiatry 1991; 29:946–948
63. Rybakowski J, Matkowski K. Adding lithium to antidepressant therapy: factors related to therapeutic potentiation. Eur Neuropsychopharmacol 1992;2:161–165
64. McCance-Katz E, Price LH, Charney DS, et al. Serotoninergic function during lithium augmentation of refractory depression. Psychopharmacology (Berl) 1992;108:93–97
65. Honore P, Moller SE, Jorgensen A. Lithium + L-tryptophan compared with amitriptyline in endogenous depression. J Affect Disord 1982;4:79–82
66. Joffe RT. T_3 and lithium potentiation to tricyclic antidepressants [letter]. Am J Psychiatry 1988;145:1317–1318
67. Thase ME, Kupfer DJ, Jarrett DB. Treatment of imipramine-resistant recurrent depression, I: an open clinical trial of adjunctive L-triiodothyronine. J Clin Psychiatry 1989;50:385–388
68. Dinan TG, Barry S. A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic nonresponders. Acta Psychiatr Scand 1989;80:97–100
69. Zall H. Lithium carbonate and isocarboxazid: an effective drug approach in severe depression. Am J Psychiatry 1971;127:1400–1403
70. Lingjaerde O, Edlund AH, Gormsen CA, et al. The effect of lithium carbonate in combination with tricyclic antidepressants in endogenous depression. Acta Psychiatr Scand 1974;50:233–242
71. Nick J, Luaute JP, Des Lauriers A, et al. L'association clomipramine lithium: essai contrôlé. L'Encéphale 1976;2:5–16
72. Price LH, Charney DS, Heninger GR. Efficacy of lithium tranylcypromine treatment in refractory depression. Am J Psychiatry 1985;142:619–623
73. Ebert D, Jasper A, Murata H, et al. Initial lithium augmentation improves the antidepressant effects of standard TCA treatment in non resistant depressed patients. Psychopharmacology 1995;118:223–225
74. Cournoyer G, de Montigny C, Ouellette J, et al. Lithium addition in tricyclic resistant unipolar depression: a placebo controlled study. Collegium International of Neuro-Psychopharmacology 1984;14:F17
75. Kantor D, McNevin S, Leichner P, et al. The benefit of lithium carbonate adjunct in refractory depression: fact or fiction? Can J Psychiatry 1986;31: 416–418
76. Zusky PM, Biederman J, Rosenbaum JF, et al. Adjunct low dose lithium carbonate in treatment resistant depression: a placebo controlled study. J Clin Psychopharmacol 1988;8:120–124
77. Schöpf J, Baumann P, Lemarchand T, et al. Treatment of endogenous depressions resistant to tricyclic antidepressants or related drugs by lithium addition. Pharmacopsychiatry 1989;22:183–187
78. Kramlinger KG, Post R. The addition of lithium to carbamazepine: antidepressant efficacy in treatment-resistant depression. Arch Gen Psychiatry 1989;46:794–800
79. Stein G, Bernadt M. Lithium augmentation therapy in tricyclic-resistant depression: a controlled trial using lithium in low and normal doses. Br J Psychiatry 1993;162:634–640
80. Katona CLE, Abou-Saleh MT, Harrison DA, et al. Placebo controlled trial of lithium augmentation of fluoxetine and lofepramine. Br J Psychiatry 1995;166:80–86
81. Price LH, Charney DS, Heninger GR. Manic symptoms following addition of lithium to antidepressant treatment. J Clin Psychopharmacol 1984;4: 361–362
82. Khan MC, Wickham EA, Reed JV. Lithium versus placebo in acute depression: a clinical trial. Int Clin Psychopharmacol 1987;2:47–54
83. Nierenberg AA, Price LH, Charney DS, et al. After lithium augmentation: a retrospective follow-up of patients with antidepressant refractory depression. J Affect Disord 1990;18:167–175
84. Austin LS, Arana GW, Melvin JA. Toxicity resulting from lithium augmentation of antidepressant treatment in elderly patients. J Clin Psychiatry 1990;51:344–345
85. Solomon JG. Seizures during lithium amitriptyline therapy. Postgrad Med 1979;163:276–281
86. Mahapatra RK, Paul SK, Mahapatra D, et al. Cardiovascular effects of polycyclic antidepressants. Angiology 1986;37:709–717
87. Devanand DP, Sacheim HA, Brown RP. Myoclonus during combined tricyclic antidepressant and lithium treatment. J Clin Psychopharmacol 1988;8: 446–447
88. Salama AA, Shafey M. A case of severe lithium toxicity induced by combined fluoxetine and lithium carbonate [letter]. Am J Psychiatry 1989;146: 278
89. Sacristan JA, Iglesias C, Arellano F, et al. Absence seizures induced by lithium: possible interaction with fluoxetine. Am J Psychiatry 1991;148 146–147
90. Evans M, Marwick P. Fluvoxamine and lithium: an unusual interaction [letter]. Br J Psychiatry 1990;156:286
91. Hadley A, Cason MP. Mania resulting from lithium fluoxetine combination [letter]. Am J Psychiatry 1989;146:1637–1638
92. Grahame-Smith DG, Green AR. The role of brain 5 hydroxytryptamine in the hyperactivity produced in rats by lithium and monoamine oxydase inhibition. Br J Pharmacology 1974;52:19–26
93. Broderick P, Lynch V. Behavioural and biochemical changes induced by lithium and L-tryptophan in muricidal rats. Neuropharmacology 1982;21: 671–679

DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for treatment of depression: alprazolam, neuroleptics, triiodothyronine.

The following agent mentioned in this article is *not* indicated for treatment of obsessive-compulsive disorder, panic disorder, panic attack, or bulimia nervosa: lithium.