Lithium Augmentation of Antidepressants in Treatment-Refractory Depression

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The use of lithium to convert antidepressant nonresponders to responders is reviewed. Although there is little doubt that lithium is effective in a sizable percentage of patients who do not respond to tricyclic antidepressants (TCAs) and serotonin selective reuptake inhibitors (SSRIs), much remains obscure about this effect. Does it work preferentially on antidepressants that act primarily on serotonergic neurons, or is it equally effective with agents that act upon other neurotransmitter systems? When should lithium, compared with other strategies, be utilized in antidepressant nonresponders? Are certain subtypes of depression more likely than others to respond to lithium augmentation? The available literature highlights the efficacy of lithium as an augmenting agent in refractory depression and serves as an impetus for additional neurobiological and clinical studies of this phenomenon.

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A substantial number of patients diagnosed with depression are generally acknowledged to be treatment-resistant, though the definition of *treatment resistance* varies considerably from study to study. As many as 30% of patients do not respond to an initial course of antidepressant treatment, and 5% to 10% of patients who have undergone many therapeutic interventions remain chronically depressed.[1]

Lithium has been used to augment the efficacy of antidepressant medications for more than 15 years. The impetus for using lithium as an adjunct for treatment-resistant depression was derived from laboratory animal studies in which lithium was demonstrated to enhance the synthesis and release of serotonin (5-HT).[2–4] Previously, chronic administration of tricyclic antidepressants (TCAs) had been demonstrated to increase postsynaptic sensitivity to 5-HT in forebrain neurons.[5] De Montigny and Aghajanian hypothesized that coadministration of a TCA and lithium would enhance serotonergic transmission to a sensitized postsynaptic membrane, thereby providing an overall increase in 5-HT neurotransmission and a subsequently enhanced antidepressant effect.

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The first study to test this hypothesis in humans was carried out by de Montigny et al.[6] Eight patients diagnosed with major depression, unipolar subtype, who had failed to respond to at least 3 weeks of TCA treatment received 900 mg of lithium daily for 2 days. Within 48 hours, all eight patients showed substantial improvement, as measured by a significant decline in the Hamilton Rating Scale for Depression (HAM-D) score. This improvement was posited to be a result of potentiation of the action of the TCA by lithium on the efficacy of 5-HT neurotransmission.

Whether or not changes in 5-HT neurotransmission underlie the now well-documented effect of lithium to convert nonresponders to responders, however, remains controversial. Normally, prolactin levels increase after administration of L-tryptophan by increasing brain 5-HT synthesis and availability; thus, measuring prolactin levels in response to L-tryptophan provides an indirect measure of 5-HT availability in the hypothalamus. The increase in plasma prolactin concentrations is further enhanced if L-tryptophan is administered to patients treated with lithium.[7] The prolactin response to administration of L-tryptophan in patients who underwent lithium augmentation after failing to respond to a TCA has been studied.[8] Lithium treatment did, in fact, facilitate 5-HT neurotransmission, as assessed by an increase in prolactin concentrations. However, the magnitude of this increase did not correlate with clinical outcome; some lithium-augmentation responders showed little increase in prolactin release while other lithium-augmentation responders had a much greater prolactin response. Thus, both preclinical and clinical evidence demonstrate that lithium augmentation increases 5-HT neurotransmission; it remains unclear whether enhanced 5-HT neurotransmission is the major

mechanism by which lithium acts to potentiate the effects of antidepressants.

Regardless of the neurobiological mechanism involved in the effect of lithium, the dramatic improvement described by de Montigny et al.[6] in their pilot study has led to a number of case reports, open studies, and placebo-controlled, double-blind studies that have assessed the efficacy of lithium augmentation in patients who have failed to respond to one or another antidepressant. Overall, the majority of the studies conducted since 1981 have demonstrated substantial efficacy of lithium augmentation in antidepressant nonresponders. However, many of these studies are uncontrolled and/or methodologically flawed, and statistical improvement after lithium augmentation does not necessarily translate into dramatic clinical improvement.

Table 1[6,9–24] summarizes reports of lithium augmentation of antidepressants published between 1981 and 1996. These studies differ widely in methodology, patient population, definition of nonresponse, and statistical analyses, which renders it difficult to make comparisons between studies. Among the differences in methodology and study design are the following: (1) Some studies excluded and others included bipolar depressed and psychotically depressed patients; (2) the length of time antidepressant treatment continued despite a suboptimal clinical response varied from weeks to months; (3) the antidepressant dose was variable, as were the classes of antidepressants used; (4) the definition of *treatment-refractory* varied widely; (5) the severity, length of episode, and past history of depression in a single study ranged from a single episode to multiple episodes, and length of illness from a few weeks to over a year; (6) the dose, plasma level, and duration of lithium treatment was not consistent; (7) the definition of *clinical response* after lithium augmentation was not consistent, making it difficult to assess the overall efficacy of lithium augmentation (some studies used a > 50% HAM-D reduction, others used a cut-off HAM-D score such as ≤ 7 as criterion for response, and still others used global scales such as the Clinical Global Impressions [CGI] scale).

DEFINING *TREATMENT-REFRACTORY*

The definition of *treatment-refractory* is arguably the most important consideration both in assessing the lithium augmentation literature and in determining when to clinically employ lithium augmentation. A patient must have had an adequate antidepressant trial before being identified as treatment-refractory. An adequate antidepressant trial consists of using an adequate dose for an adequate duration.[1]

Antidepressant dosages of all antidepressants should be therapeutic, and, for the TCAs, plasma levels should be measured. Plasma levels of all antidepressants can also be used to ascertain compliance, a major problem in depressed outpatients. Although many of the studies of lithium augmentation measured plasma TCA levels, few used these levels in defining an adequate dose of medication. Moreover, a recent study by Fava et al.,[22] suggested that partial responders to fluoxetine (who may actually fit the diagnosis of treatment-refractory for many studies) may respond better to an increased dose of the serotonin selective reuptake inhibitor (SSRI) medication than to lithium augmentation or combined fluoxetine-desipramine therapy. Thus, one option for antidepressant nonresponders is to maximize the antidepressant dose. Few studies have systematically examined the effects of increasing the antidepressant dose, particularly of the newer agents, on clinical response.

In many of the lithium augmentation studies, the duration of treatment with the antidepressant has been modeled on the original 1981 study by de Montigny and colleagues,[6] in which *treatment-refractory* was defined as a decrease of less than 40% on the HAM-D after 3 weeks of treatment with a TCA. Three weeks of treatment, however, is almost certainly an insufficient period of time to evaluate true treatment-refractoriness. Current recommendations include maintaining a patient for at least 4–6 weeks on a given antidepressant medication,[25] and some psychiatrists suggest a minimum of 8 weeks.[1] In addition, recent evidence suggests that patients who respond partially to antidepressant therapy may benefit from prolonged treatment[1,26]; few of the studies on lithium augmentation have compared partial responders with nonresponders. Moreover, certain groups of patients, such as the elderly, are known to respond more slowly to antidepressant treatment. In any case, to augment with lithium after only 3 weeks leaves it unclear whether the antidepressant effect is due to lithium augmentation or to a delayed response to the antidepressant medication. This problem highlights the need for a placebo-control group in designing lithium augmentation studies.

RECENT LITHIUM AUGMENTATION STUDIES

Once a depressed patient is determined to be treatment-refractory, lithium augmentation becomes a viable strategy with proven efficacy. A meta-analysis[27] of lithium augmentation for treatment-refractory depression included five controlled trials[10,13–15,18]; the likelihood of remaining ill after lithium augmentation was reduced 56% to 96%. Since publication of this meta-analysis, several additional controlled studies have been added to the lithium augmentation literature, and these are described below.

Katona et al.[23] published the results of a placebo-controlled trial of lithium augmentation in patients refractory to treatment with fluoxetine or lofepramine. Interestingly, the initial analysis used a HAM-D score of 13 or less to define treatment response and found no difference

Table 1. Studies of Lithium Augmentation of Antidepressants in Treatment-Refractory Patients*

Study	Design	N	Diagnoses Included	Antidepressant		Lithium			Response		Response Correlation	
				Agent	Duration	Dose (mg/d)	Levels (mEq/L)	Duration	Rate	Latency (d)	Lithium Levels	Severity of Depression
de Montigny et al (1981)	Open	8	Unipolar, psychotic (N = 1)	Amitriptyline, imipramine, doxepin, iprindole	≥ 3 wk	900	Not reported	2 d	100%	2	No	Not assessed, but psychosis resolved
de Montigny et al (1983)	Open, placebo-controlled (mixed)	42	Unipolar, psychotic (N = 2)	Amitriptyline, imipramine, doxepin, trimipramine, iprindole	≥ 3 wk	900	0.4–1.2	2 d	74%	2	No	No, but most dramatic responses among most severely depressed
Heninger et al (1983)	Double-blind, placebo-controlled	15	Unipolar, bipolar (N = 1)	Amitriptyline, desipramine, mianserin	≥ 3 wk	900–1200	0.5–1.1	12–24 d	80%	6–18	No	Not assessed
de Montigny et al (1985)	Open	7	Unipolar, psychotic (N = 2)	Iprindole	3 wk	900	0.4–1.2	2 d	86%	2	No	Not assessed, but psychosis resolved
Price et al (1986)	Open	84	Unipolar, bipolar, psychotic	Desipramine, amitriptyline, adinazolam, bupropion, fluvoxamine, mianserin, trazodone	4–6 wk	900–1500	0.5–1.3	≥ 10 d	56% 31% marked 25% partial	≤ 21	Not assessed	Yes; psychotic < nonmelancholic < melancholic
Kantor et al (1986)	Placebo-controlled, double-blind	7	Unipolar	Amitriptyline, amoxapine, imipramine, doxepin	≥ 21 d	900	Not assessed	2 d	14%	2	Not assessed	Not assessed
Zusky et al (1988)	Double-blind, placebo-controlled	16	Unipolar	Amitriptyline, trazodone, imipramine, desipramine, maprotiline, doxepin, nortriptyline, phenelzine	2–36 mos (mean 9.2 mos)	300–900	0.1–0.8	3 wk	38% lithium 25% placebo	21	Not assessed	Patients less depressed and treated for longer with antidepressant than other studies
Schopf et al (1989)	Double-blind, placebo-controlled, randomized	27	Unipolar, bipolar, psychotic (N = 3)	Amitriptyline, maprotiline, clomipramine, fluvoxamine dibenzepin	≥ 3 wk	600–800	0.19–0.82 (mean 0.75)	2 wk	48%	≤ 14	No	No
Dinan and Barry (1989)[a]	Randomized (parallel group design)	30	Unipolar, bipolar, psychotic (N = 3)	Amitriptyline or equivalent	≥ 4 wk	600–800	0.5–0.7	3 wk	67% lithium 73% electroconvulsive therapy	≤ 21	Not assessed	Not assessed
Fontaine et al (1991)	Open	60	Unipolar	Desipramine, fluoxetine	6 wk	600	0.3–1.2	6 or 14 wk	67% desipramine/lithium 60% fluoxetine/lithium	≤ 42	Not assessed	Not assessed
Stein and Bernadt (1993)	Double-blind, placebo-controlled	34	Did not specify unipolar or bipolar; included psychotic	Amitriptyline or equivalent	≥ 3 wk	250 or 750		6–9 wk	44% lithium (750 mg) 22% placebo 18% lithium (250 mg)	≤ 21	Not assessed	Not assessed
Dinan (1993)	Open	11	Unipolar	Sertraline	≥ 6 wk	400 or 800	0.26 (400) and 0.6 (800)	1 wk	67% lithium (400 mg) 43% lithium (800 mg)	≤ 7	No	Not assessed
Joffe et al (1993)[b]	Randomized, double-blind, placebo-controlled	50	Unipolar	Desipramine, imipramine	≥ 5 wk	900–1200	> 0.55	2 wk	59% triiodothyronine 53% lithium 19% placebo	≤ 14	No	Not assessed
Hoencamp et al (1994)[c]	Double-blind, randomized	51	Bipolar, unipolar, dysthymia, depression, not otherwise specified, psychosis	Maprotiline	6 wk	600–1200	0.6–1.10	6 wk	30% maprotiline + lithium 23.8% brofaromine	≤ 42	Not assessed	Not assessed, except patients were depressed average of 18.9 mo; may be longer than other studies
Fava et al (1994)[d]	Randomized	41	Did not specify unipolar or bipolar	Fluoxetine	8 wk	300–600	Not assessed	4 wk	53% high dose fluoxetine 25% desipramine 29% lithium	≤ 28	Not assessed	Not assessed
Katona et al (1995)	Placebo-controlled, double-blind	62	Unipolar, bipolar	Fluoxetine, lofepramine	6 wk	400–800	> 0.4	6 wk	52% lithium 25% placebo	≤ 42	Concluded that need > 0.4 for response	Not assessed
Baumann et al (1996)	Double-blind, placebo-controlled	24	Bipolar, unipolar, dysthymia	Citalopram	4 wk	800	0.5–0.8	7–14 d	58% lithium 14% placebo	≤ 14	Not assessed	Not assessed

*Data from references 6, 9–16. [a]Compared lithium with electroconvulsive therapy. [b]Compared lithium with triiodothyronine. [c]Compared lithium and maprotiline with brofaromine. [d]Compared lithium with desipramine and high-dose fluoxetine.

between lithium augmentation and placebo augmentation. A reanalysis defining *treatment response* as having a HAM-D score of 10 or less did show a significant advantage of lithium as an augmenting agent compared with placebo. Thus, lithium augmentation may convert partial antidepressant responders into complete responders.

One of the most recent controlled studies[24] compared lithium and placebo in patients who were treatment-refractory to citalopram, an SSRI not currently available in the United States. The researchers found that the overall response rate to lithium augmentation was 58%.

Although most of the studies conducted over the past 2 decades have examined lithium augmentation of TCAs, some of the more recent studies, including the citalopram study,[24] have evaluated the utility of lithium augmentation in SSRI nonresponders. A case report described a patient who had been treatment refractory to paroxetine but who had improved significantly after lithium augmentation.[28] An open, prospective study[19] compared dosages of lithium added to sertraline-resistant patients; the investigator demonstrated significant improvement with both low-dose (400 mg) and higher-dose (800 mg) lithium augmentation. Fontaine et al.[17] compared lithium augmentation in patients refractory to a 6-week trial of either desipramine or fluoxetine; lithium augmentation significantly improved 60% of patients in both groups as defined by a decrease in CGI scores.

There are reports that lithium augmentation is successful in patients who are refractory to treatment with monamine oxidase inhibitors (MAOIs),[29,30] trazodone,[12,31] and bupropion,[12] as well as with TCAs or SSRIs.

LITHIUM AUGMENTATION COMPARED WITH OTHER STRATEGIES

A few studies have compared lithium augmentation with other strategies for treating patients with treatment-refractory depression. Dinan and Barry[16] compared ECT with a combination of lithium and TCA in 30 TCA nonresponders; both augmenting strategies were effective, and there were no statistical differences in efficacy between the two groups, though the lithium/TCA group improved more rapidly than the ECT-treated group. Joffe et al.[20] conducted a controlled study comparing the efficacy of lithium, triiodothyronine (T_3), and placebo in patients failing to respond to a TCA. Both lithium- and T_3-treated patients exhibited significant improvement in HAM-D scores compared with placebo, but there was no significant difference in response rates between T_3 and lithium, indicating comparable efficacy as augmenting agents.

Hoencamp et al.[21] compared the efficacy of lithium augmentation in maprotiline nonresponders with discontinuing the heterocyclic and treating with a selective MAOI, brofaromine. They reported that 30% of the maprotiline-plus-lithium group and 23.8% of the brofaromine group improved, a nonsignificant difference in efficacy.

A recent study examined lithium- versus TCA-augmentation of fluoxetine.[22] Patients were categorized as nonresponders or partial responders to treatment with 20 mg of fluoxetine daily for 8 weeks. High-dose fluoxetine (40–60 mg) was the more effective treatment among partial responders. High-dose fluoxetine and lithium augmentation of fluoxetine were equally efficacious among nonresponders, and both of these treatments were more effective than TCA augmentation of fluoxetine nonresponders. A significant flaw in the experimental design of this study, however, was that the dosages of both lithium and the TCA were inadequate. Lithium was administered at a dose of 300 to 600 mg/day and desipramine at a dose of 25 to 50 mg/day. These insufficient doses preclude definitive conclusions about the efficacy of augmenting fluoxetine with lithium versus a TCA.

VARIABLES REQUIRING STUDY

It has not yet been determined if there are subgroups of patients who respond or do not respond to lithium augmentation, and this is a question worth considering. Price et al.[12] obtained a standard dexamethasone suppression test (DST) on patients undergoing lithium augmentation and did not find any difference in nonsuppression rates between lithium-augmentation responders and nonresponders.

It is clear that there are subgroups of patients who respond either slowly or rapidly to lithium augmentation, but the biological mechanisms that underlie such differences remain obscure. The length of time it takes to achieve a salutary response to lithium augmentation varies from study to study. Both the original de Montigny et al.[6] study and a second study published 2 years later[9] showed a very rapid response—of less than 48 hours—to lithium augmentation. Studies conducted since then have shown more varied rates of response. Fontaine et al.[17] reported that some patients responded to lithium augmentation within 1 week (fast responders), and others responded after 1 to 6 weeks of lithium treatment (slow responders). Other studies have reported little or no effect until at least 1 week after beginning lithium augmentation.[10,15] Katona et al.[23] suggest that it is necessary to treat antidepressant nonresponders with lithium for 6 weeks before determining that it is ineffective.

The length of time that a patient should be maintained on lithium augmentation has not been well-studied. Nierenberg et al.[32] assessed the longitudinal course of 66 patients who were treated with lithium augmentation over a mean ± SD period of 29 ± 15.3 months, in a retrospectively designed study that used face-to-face interviews, phone interviews, and a review of medical records. They found that 29% of patients had poor, 23% had fair, and

48% had beneficial outcomes. Interestingly, an acute and markedly positive response to lithium augmentation predicted a good subsequent course. Responders to lithium augmentation were less likely to have a recurrent depression; nonresponders to lithium augmentation were more likely to have subsequently attempted suicide, completed suicide, or required hospitalization for depression. Because the 66 patients had continued on lithium augmentation for varying lengths of time, however, it is impossible to conclusively recommend how long a given patient should be treated with lithium augmentation. A prospectively designed study is clearly needed to evaluate this important question.

Another important but unresolved issue is the plasma lithium concentration needed for augmentation of antidepressant nonresponders. In most studies, investigators have attempted to maintain lithium levels between 0.4 and 1.2 mEq/L.[10,12,15,20,21,33] When an association between lithium levels and response was sought, none has been found, though in most of these studies, as indicated above, lithium levels were at least 0.4 mEq/L. One report concluded that a lithium level above 0.4 mEq/L was necessary to ensure an adequate response,[23] though other published studies and case reports have shown that some patients respond to levels as low as 0.2 to 0.3 mEq/L.[19,28] Stein and Bernadt[18] compared two doses of lithium (750 mg vs. 250 mg per day). They reported that 750 mg, but not 250 mg, of lithium, had a significant augmenting effect with a response rate of 44%, using a 50% decline in HAM-D score as the criterion for responsiveness. The lower dose of lithium attained a mean plasma lithium level of 0.25 mEq/L, and the higher dose attained 0.65 to 0.78 mEq/L. The use of magnetic resonance spectroscopy to measure regional brain lithium concentrations may help distinguish lithium-augmentation responders from nonresponders.

The effect of the severity of depression on the response to lithium augmentation has been examined. Price et al.[12] in an open study used lithium augmentation in 84 treatment-refractory depressed patients and obtained an overall positive response rate of 56%; this was comprised of a partial response rate of 25% and a marked response rate of 31%. Interestingly, melancholic patients had a higher marked response rate (50%) than nonmelancholic patients (23%). Psychotically depressed patients, however, exhibited a marked response rate of only 16%; none of the psychotically depressed patients were concomitantly prescribed antipsychotic medications. These results suggest that lithium augmentation may be more beneficial in moderate-to-severe depression without psychotic features. Whether lithium augmentation may be effective in antipsychotic-drug/antidepressant-drug nonresponders is worthy of a controlled, double-blind study.

Indeed, in a case report series, Price et al.[34] found lithium augmentation to be effective in antidepressant/antipsychotic refractory delusional depression in three of six patients. These were patients with complicated comorbid medical illnesses, which renders the results difficult to interpret. In a study with geriatric patients,[35] there was a trend toward greater response in patients with recurrent depression compared with those with a single episode, but this study was limited by its retrospective design. In the comprehensive study by de Montigny et al.,[9] no significant correlation was found between the depression severity and the magnitude of response to lithium augmentation; the most dramatic responses, however, were seen among the most severely depressed patients. Two patients with delusional depression showed marked improvement, including disappearance of delusions, after 48 hours of lithium augmentation.

The adverse effects of lithium in combination with other antidepressants are fairly benign; they are most commonly observed in the elderly. Furthermore, when lithium is combined with fluoxetine (and perhaps other SSRIs), a central 5-HT syndrome characterized by confusion, tremors, and hyperthermia was reported to develop in one patient.[36] The elderly develop lithium-induced side effects at a higher rate than younger people, with up to 50% of elderly patients developing dose-limiting neuromuscular or neurologic side effects.[33]

CONCLUSION

Using lithium augmentation for treatment-refractory depression will increase the likelihood of the patient responding to the antidepressant. It is still unclear, however, whether there is a subgroup of patients who respond to lithium augmentation. Other seminal questions remain, including: (1) how long lithium augmentation takes to work; (2) the length of time a lithium-augmentation responder should remain on lithium therapy; and (3) what plasma levels of lithium are most effective in augmentation. Clarification is also needed as to when a clinician should use lithium augmentation versus another strategy for treating the antidepressant-refractory patient. Whether bipolar depression or patients with a bipolar family history preferentially respond to lithium augmentation also remains unclear. Further research is urgently needed to answer these and other questions.

Drug names: adinazolam (Deracyn), amitriptyline (Elavil and others), amoxapine (Asendin), bupropion (Wellbutrin), clomipramine (Anafranil), desipramine (Norpramin and others), dexamethasone (Decadron and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), maprotiline (Ludiomil), nortriptyline (Pamelor and others), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others), triiodothyronine (Cytomel and Triostat), trimipramine (Surmontil).

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