Lithium Augmentation Therapy in Refractory Depression: Clinical Evidence and Neurobiological Mechanisms

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Objective: This systematic review examines the evidence and discusses the clinical relevance of lithium augmentation as a treatment strategy for refractory major depressive episodes. It also examines hypotheses on the mode of action of lithium augmentation, with a focus on serotonin (5-HT) and neuroendocrine systems, and proposes recommendations for future research.

Method: We searched the Medline computer database and the Cochrane Library for relevant original studies published in English from January 1966 to February 2003. The key words were as follows: lithium, augmentation strategies, lithium augmentation, major depression, refractory depression, treatment-resistant depression, neuroendocrinology, and serotonin.

Results: Of 27 prospective clinical studies published since 1981, 10 were double-blind, placebo-controlled trials, 4 were randomized comparator trials, and 13 were open-label trials. Five of 9 acute-phase placebo-controlled trials demonstrated that lithium augmentation had substantial efficacy. In the acute-treatment trials, the average response rate in the lithium group was 45%, and in the placebo group, 18% ($P < 0.001$). One placebo-controlled trial showed the efficacy of lithium augmentation in the continuation-phase treatment. Summarizing the open and controlled data, approximately 50% of patients responded to lithium augmentation within 2 to 6 weeks. Animal studies offer robust evidence that lithium augmentation increases 5-HT neurotransmission, possibly by a synergistic action of lithium and the antidepressant on brain 5-HT pathways.

Conclusions: Augmentation of antidepressants with lithium is the best-documented augmentation therapy in the treatment of refractory depression. Emerging data from animal studies suggest that the 5-HTergic system is involved in the augmentatory effect of lithium.

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Clinical Implications

- Lithium augmentation should be considered a first-line treatment strategy for patients with a major depressive episode that does not adequately respond to standard antidepressant treatment.
- In responders, lithium augmentation should be continued for a minimum of 12 months.
- More studies are required to examine the efficacy of lithium augmentation in patients refractory to antidepressants that act mainly on the noradrenergic system.

Limitations

- This is a narrative review.
- Only a few placebo-controlled trials examined lithium's efficacy with newer antidepressants (for example, the selective serotonin, selective norepinephrine, and selective serotonin-norepinephrine reuptake inhibitors).
- It remains to be examined whether the response to lithium augmentation is a true, synergistic augmentation effect or whether it is owing to the antidepressant effect of lithium alone.

Key Words: *major depression, lithium augmentation, lithium, serotonin, neuroendocrine tests, DEX–CRH test, cortisol, treatment-resistant depression, refractory depression*

Although there are many drugs available to treat major depression, the overall treatment outcome among depression patients is usually far from optimal. Regardless of the initial choice of antidepressant, about 30% to 50% of patients with a major depressive episode (MDE) will not respond sufficiently to adequately performed first-line treatment and will not return to premorbid levels of functioning (1). Various treatment strategies have been proposed for patients not responding or responding partially to a monotherapy trial with an antidepressant. The major strategies employed are as follows: 1) switching to a new antidepressant, either from within the same pharmacologic class or from a different class, 2) combining 2 antidepressants from different classes, 3) augmenting the antidepressant with other agents to enhance antidepressant efficacy, and 4) combining the antidepressant with a psychotherapeutic intervention (1).

These strategies have been studied with various agents and combinations, but most have not been subjected to rigorous scientific investigation or have only included small study groups (1,2). Currently, there is no consensus about which strategy should be favoured for nonresponding patients, since to date no rigorous trial with a randomized, double-blind design has been conducted to answer this question (3). Some authors have argued in favour of augmentation strategies because they eliminate the period of transition between antidepressants and build on the partial response. When they work, augmentation strategies can be rapidly effective. Further, patients who have had some response may be reluctant to risk losing that improvement, and in this situation, augmentation may be beneficial.

Lithium salts have been used to augment the efficacy of antidepressant medications for more than 20 years. The first study to test the hypothesis in patients with major depression was performed by de Montigny and associates in 1981 (4). The researchers reported a dramatic response—within 48 hours—when lithium was added to the regime of 8 patients who had not responded to at least 3 weeks of treatment with tricyclic antidepressants (TCAs) (4). The efficacy of the combination and the rapid response have since led many clinical research groups to study this treatment intervention further.

This article reviews the evidence and discusses the clinical relevance of lithium augmentation as a treatment strategy for refractory major depression. It also examines hypotheses regarding the mode of action of lithium augmentation, with a focus on serotonin (5-HT) and neuroendocrine systems.

Clinical Studies in Major Depression

We identified 27 studies and a total of 803 patients. Of these, 9 were randomized, double-blind, placebo-controlled studies (RCTs) in the acute-treatment phase (5–13). The remaining 18 trials included 13 open trials (4,14–25); 3 randomized, double-blind comparator trials (26–28), 1 randomized, open comparator trial (29), and 1 placebo-controlled trial in the continuation-treatment phase (30). In these studies, most patients (more than 90%) suffered from unipolar depression.

Acute-Treatment Phase: Randomized Placebo-Controlled Studies

Nine RCTs (5–13) conducted during the acute-treatment phase and involving 234 patients were recently included in a metaanalysis (31). The mean ages of patients in these studies ranged from 37 to 54 years and the male-to-female ratio was 4:7. Lithium carbonate dosages ranged from 250 to 1200 mg daily, with some studies allowing titration to a serum lithium level (usually 0.5 mmol/L or more). Duration of augmentation therapy was as short as 2 days up to as long as 42 days (Table 1). The response rates in the lithium group ranged from 18% to 62.5% (mean 45%); in the placebo group, response rates ranged from 0% to 25% (mean 18%) (Figure 1).

The combined results of these 9 RCTs showed that lithium augmentation led to a higher response rate than was observed with the placebo ($P < 0.001$). When RCTs were entered into a cumulative metaanalysis in the order of increasing dosage, the effect was statistically significant at a lithium carbonate dosage of 600 to 800 mg daily, and results did not change with higher dosages. A cumulative metaanalysis of RCTs entered in the order of increasing treatment duration showed a statistically significant effect at 7 days (31).

There was a significant heterogeneity in the design and outcome of the studies. All studies presented some limitations in quality. Assuming a relation between quality and outcome, we performed a cumulative metaanalysis of studies arranged by descending quality scores (Figure 2). Study quality was evaluated independently by 2 investigators according to the Quality Assessment Scale (32). Differences in assessment were discussed and settled by consensus. Quality was expressed as a percentage of achievable scores. The cumulative metaanalysis allows an increasing estimate of treatment effects as studies with lower-quality scores are added to the previous higher-score studies. The analysis suggests that the benefit of lithium augmentation can still be demonstrated when studies of lesser quality are added to the pooled analysis (Figure 2).

Acute-Treatment Phase: Open and Comparator Studies

A total of 438 depression patients (mean age 43 years) were included in 17 trials that used an open-label or a comparator design (4,14–29). The duration of antidepressant pretreatment ranged between 3 and 7 weeks (mean, 4.5 weeks); the subsequent lithium augmentation therapy lasted between 2 days and 14 weeks (mean duration, 29 days). The antidepressants used in the trials included agents from different groups, including selective serotonin reuptake inhibitors (SSRIs),

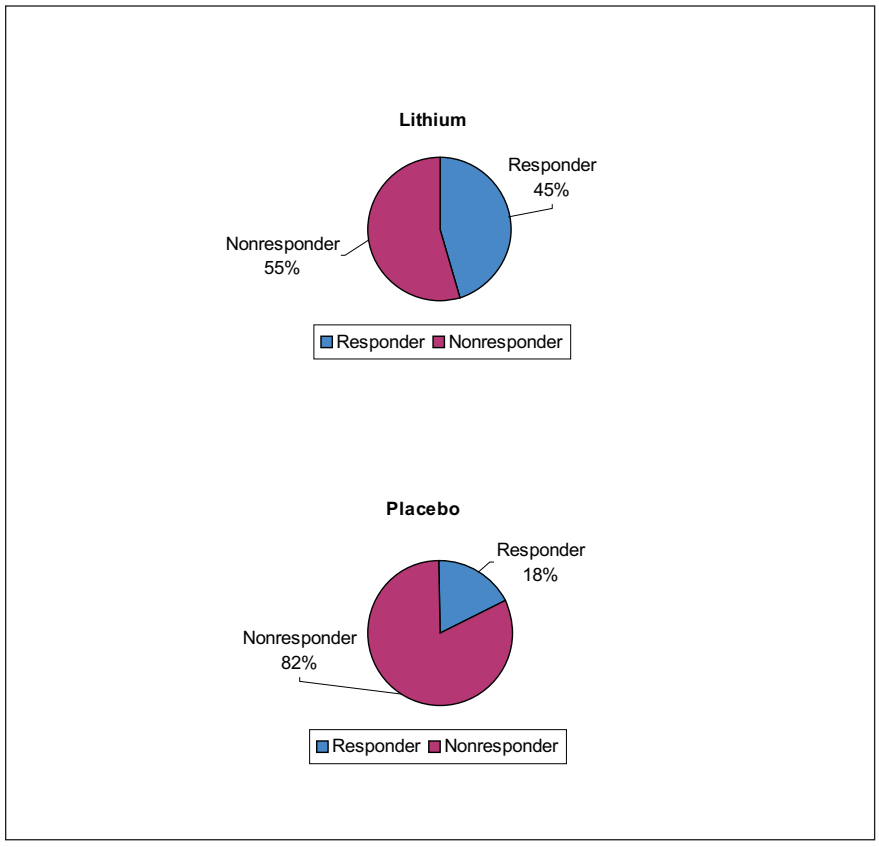
Table 1 Double-blind, placebo-controlled studies of lithium augmentation in treatment-resistant depression

Study	Study subjects (*n*)	Class of antidepressant	Duration and dosages[a] of lithium augmentation therapy	Results	Quality score (%)[b]
Heninger and others 1983 (5)	14 UP, 1 BP; 12 F, 3 M	Various TCA and tetracyclics	12–14 days Lithium 900–1200 mg daily	Lithium: 62.5% Placebo: 0%	46
Kantor and others 1986 (6)	7 UP sex, nr	Various TCA	2 days Lithium 900 mg daily	Lithium: 25.0% Placebo: 0%	39
Zusky and others 1988 (7)	16 UP 13 F, 3 M	Various TCA and MAOI	14 days Lithium 300–900 mg daily	Lithium: 38.0% Placebo: 25.0%	57
Schöpf and others 1989 (8)	18 UP, 9 BP 19 F, 8 M	Various AD	14 days Lithium 600–800 mg daily	Lithium: 50.0% Placebo: 0%	68
Browne and others 1990 (9)	14 UP, 3 BP 10 F, 7 M	Various TCA and tetracyclics	2 days Lithium 900 mg daily	Lithium: 43.0% Placebo: 20.0%	67
Joffe and others 1993 (10)	33 UP 18 F, 15 M	Various TCA	14 days Lithium 900–1200 mg daily	Lithium: 52.0% Placebo: 18.7%	86
Stein and Bernadt 1993 (11)	34 UP 27 F, 7 M	Various TCA	Day 1–21: Lithium 250 mg daily Day 22–42: Lithium 250 mg daily vs 750 mg daily	Lithium (250mg): 18.0% Lithium (750mg): 44.0% Placebo: 22.0%	77
Katona and others 1995 (12)	61, polarity nr 35 F, 26 M	SSRI and TCA	42 days Lithium: 400–800 mg daily	Lithium: 53.0% Placebo: 25.0%	93
Baumann and others 1996 (13)	23 UP, 1 BP; 17 F, 7 M	SSRI	14 days Lithium 800 mg daily	Lithium: 58.0% Placebo: 14.0%	86

[a]Lithium dosages refer to lithium carbonate; [b]According to the Quality Assessment Scale by Detsky and others (32)

Abbreviations: AD = antidepressants; BP = bipolar disorder; MAOI = monoamine oxidase inhibitors; nr = not reported; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; UP = unipolar disorder

Figure 1 Response rates in 9 placebo-controlled trials on the efficacy of lithium augmentation of antidepressant medication in patients with major depression

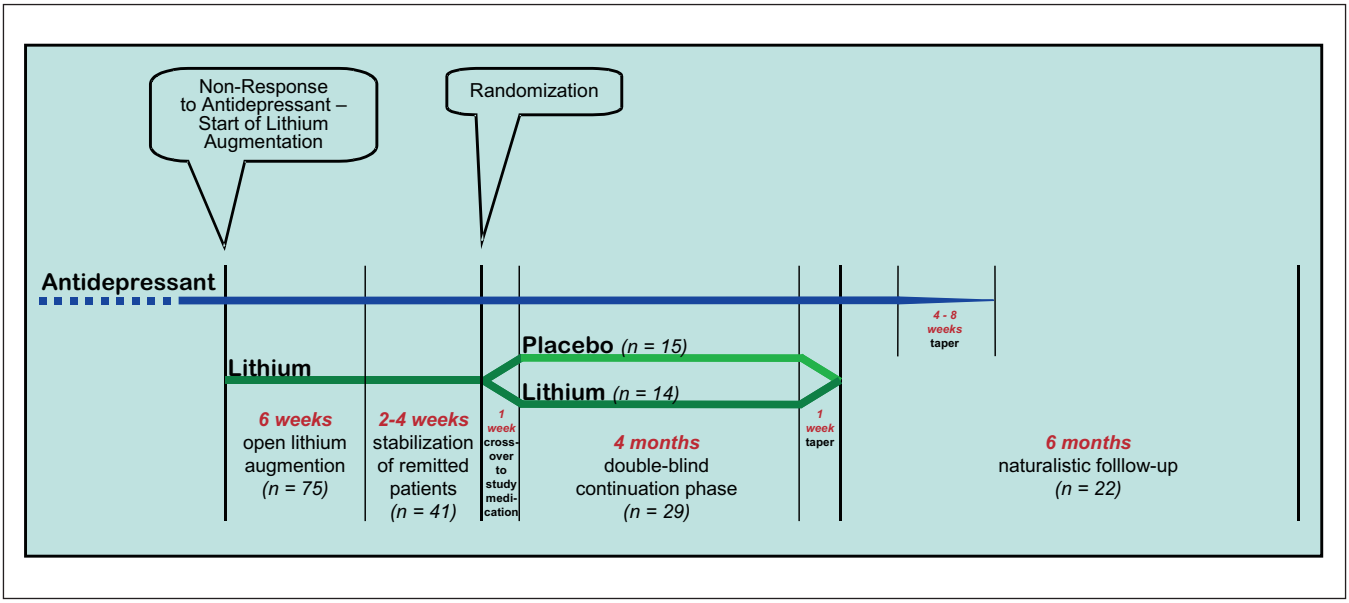


serotonin-norepinephrine reuptake inhibitors (SNRI), tri- and tetracyclic antidepressants, and monoamine oxidase inhibitors (MAOIs). The antidepressant dosages used were not reported in all trials. The dosages of lithium carbonate ranged between 300 and 1500 mg daily. The response rates ranged widely between 23.5% and 100% (median, 56%); 10/17 studies found response rates to lithium augmentation of 50% or more.

Continuation-Treatment and Discontinuation Studies

In one study, the authors examined the efficacy of lithium augmentation in the continuation treatment of unipolar major depressive disorder (MDD) (30). The study sample comprised 29 patients with a refractory MDE that had responded to acute lithium augmentation therapy during a 6-week open study. After a stabilization period of 2 to 4 weeks, these patients were randomized for another 4 months to a double-blind continuation treatment with either lithium (n = 14) or placebo (n = 15), while the antidepressant was continued at

Figure 2 Acute and continuation phases of a study on the effectiveness of lithium augmentation of antidepressant medication in patients with major depression



Adapted from Bauer and others (31) and Bschor and others (33)

the same dosage (30) (Figure 3). Of the 15 patients who received a placebo, 7 suffered a relapse (5 depressive and 2 manic) during the double-blind study phase; no patients from the lithium group relapsed. Even more patients relapsed during the 6-month open phase that followed the double-blind phase (33). The researchers concluded that patients who respond to lithium augmentation should be maintained on lithium augmentation for a minimum of 12 months, or even longer (33).

Two controlled studies (34,35) examined the effects of gradually discontinued lithium augmentation therapy in elderly depression patients; both studies found high relapse rates after lithium discontinuation. In the first, Hardy and others conducted a placebo-controlled discontinuation study in 12 geriatric patients who had responded to lithium augmentation during their most recent refractory unipolar depressive episode (34). Patients were randomized to receive either continued lithium augmentation or matching placebo. In the lithium maintenance group, 2/6 patients had a recurrence of depression at 61 and 96 weeks, respectively, immediately after a stressful life event. Similarly, in the placebo group, 2/6 patients had a recurrence at 7 and 92 weeks, respectively, without any apparent changes in life stresses. In the second study, a naturalistic discontinuation study in a cohort of elderly patients with MDD, 11 patients (52%) relapsed following discontinuation of lithium augmentation (35).

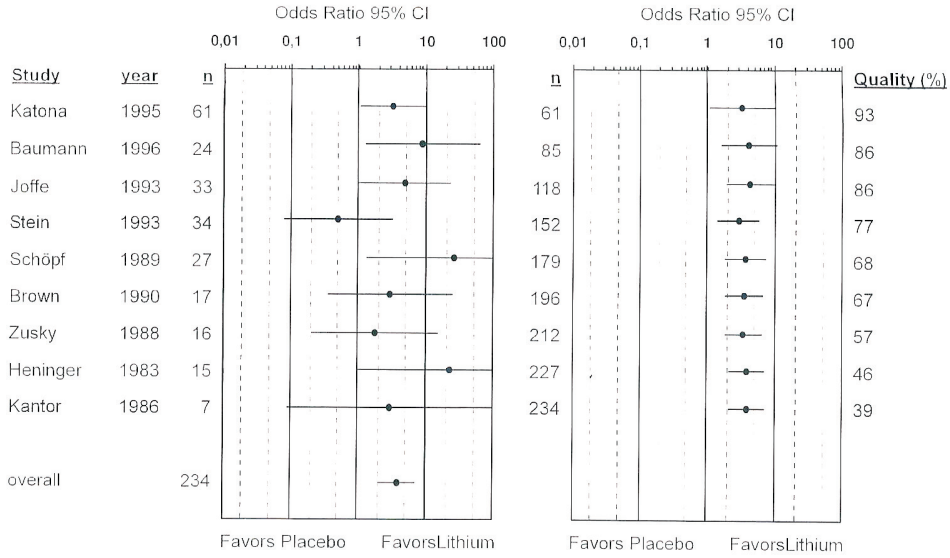
Mechanisms of Action of Lithium Augmentation: Neurobiological Basis

Treatment strategies for major depression that show well-documented effects on the outcome of patients have heuristic value for the investigation of the disorder's pathophysiology. There is strong evidence that the serotonergic (5-HTergic) system plays a key role in mood regulation (36,37), and studies indicate that lithium has a net enhancing effect on the 5-HT function (38,39). Neurochemical and neuroendocrine research based on studies in animals and humans has provided hypotheses for the mechanisms involved in lithium augmentation therapy. Arguments for a true augmentation effect result from both animal and human studies. Animal studies show that a potentiation of antidepressant treatment by lithium may be mediated through enhanced 5-HT neurotransmission. Neuroendocrine studies in humans also demonstrate that lithium augments the function of the 5-HTergic system. We outline these 2 lines of experimental evidence below.

Effects of Lithium on the 5-HT System in Animals

There is consistent evidence from animal studies that lithium enhances 5-HTergic responsiveness by actions on turnover and release (40–42). Grahame-Smith and Green reported that an increase in 5-HT transmission, produced by enhancing the function of 5-HT neurons, could be demonstrated behaviourally by the appearance of "5-HT syndrome" in rats after short-term application of lithium (43). In their study, the combination of lithium and MAOIs produced a behavioural

Figure 3 Lithium augmentation in refractory depression: metaanalysis of placebo-controlled trials



Response during lithium augmentation compared with response during placebo treatment. Odds ratios (ORs)and their respective 95%CIs for individual studies and the overall estimate are plotted on a logarithmic scale on the left-hand side of the graph. Cumulative ORs and their respective 95%CIs are plotted on the right-hand side of the graph. Studies were pooled by the Mantel–Haenszel method and were arranged individually and cumulatively by decreasing quality scores.

overactivity syndrome in rats that was indistinguishable from the overactivity evoked by MAOIs and tryptophan. This lithium-induced overactivity syndrome was blocked by prior administration of an inhibitor of 5-HT synthesis (43). Lithium administration was also shown to augment 5-HT release in the rats' dorsal hippocampus (44) and to enhance 5-HT synthesis (45). Further, short-term administration of lithium also augmented the efficacy of electrically stimulating the ascending 5-HT pathway that suppresses firing of postsynaptic neurons in rats' dorsal hippocampus (38).

Subsequently, it was postulated that a pharmacodynamic action mediated via the 5-HTergic systems may account for the synergistic effect of lithium added to a TCA (14). This hypothesis was based on several observations of the neurobiological effects of TCAs in combination with the above-described lithium effects on the 5-HT system. Initially, de Montigny and Aghajanian demonstrated that long-term TCA treatment induced a selective increase in the responsiveness to 5-HT in rats' dorsal hippocampus (46); this was later shown to be mediated by postsynaptic 5-HT_{1A} receptors (47). If also true for humans, this would mean that, in patients who fail to respond to an antidepressant, chronic TCA use may induce postsynaptic sensitization to 5-HT, as seen in animals. Second, if lithium has similar effects on 5-HT turnover in humans, lithium augmentation of antidepressant therapy may alter 5-HT neurotransmission (14,48).

Further evidence for a true augmentation effect, derived from animal studies, showed that, in contrast to lithium alone, lithium added to antidepressant treatment with an SSRI (citalopram) potentiated presynaptic 5-HTergic function in rats (49). A subchronic lithium dosage added to chronic citalopram therapy, using microdialysis techniques, further elevated basal levels of 5-HT in the rat ventral hippocampus (50).

Neuroendocrine Studies

Human neuroendocrine challenge tests have been studied repeatedly in depression patients during lithium-augmentation therapy. The pharmacologic challenge test used most frequently to assess central 5-HT function is the prolactin response to intravenous L-tryptophan (41). Cowen and others found that administering lithium increased the prolactin response to L-tryptophan after both 4 days and 4 weeks of treatment in patients receiving TCAs (51). These results provide evidence that lithium may facilitate 5-HT neurotransmission. However, the magnitude of the prolactin

increase did not correlate with the clinical outcome. Some lithium augmentation responders showed little increase in prolactin release, while others had a more pronounced prolactin response (51). McCance-Katz and others obtained similar results, reporting that primary antidepressant medication did not increase prolactin response but that lithium augmentation significantly increased prolactin response, compared with placebo pretreatment and antidepressant treatment alone (52). Further, depression severity and response to lithium augmentation did not correlate with the increase in prolactin response (52).

Another endocrine system that has been studied during lithium augmentation is the hypothalamo–pituitary–adrenocortical (HPA) system (53,54). The dexamethasone suppression–corticotropin-releasing hormone stimulating test (DEX–CRH test) is a sensitive neuroendocrinological challenge test to investigate HPA system function (55). A significant proportion of patients with major depression show an overstimulation in the DEX–CRH test (55).

The combined DEX–CRH test was given to 30 subjects with unipolar depression who had not responded to an antidepressant treatment trial of at least 4 weeks. The test was performed directly before and—depending on the response status—2 to 4 weeks after the initiation of lithium augmentation therapy (n = 24 for the second test). In contrast to results from studies in depression patients treated with TCAs (56,57), where a decline was found, the cortisol and adrenocorticotropic hormone (ACTH) response to CRH stimulation after dexamethasone pretreatment displayed a significant rise under lithium augmentation, compared with the baseline (58,59). Eleven patients responded according to the criteria applied (based on weekly ratings with the Hamilton Depression Rating Scale [HDRS]), and it is noteworthy that both responders and nonresponders demonstrated the increase. This led to the assumption that stimulation of the HPA system may be a direct effect of the lithium ion, probably mediated by the 5-HTergic actions of the pharmacon (58). Early studies in patients (60,61), as well as in animals and cell cultures (62–64), had already demonstrated a stimulating effect of lithium on cortisol or ACTH production.

Response Prediction

Approximately 50% of depression patients do not respond sufficiently to lithium augmentation, despite its proven superiority over placebo. Efforts have been undertaken to identify clinical and biological variables that allow prediction of lithium augmentation outcome. We analyzed the HPA system status with regard to its predictive value and found that subsequent nonresponders to lithium augmentation showed a statistically significant higher cortisol–ACTH peak ratio in the combined DEX-CRH test, compared with subsequent responders (65). This ratio is considered to indicate the sensitivity of the adrenal cortex to ACTH (66). The higher ratio in nonresponders eventually points to a more chronic depression course with more marked biological changes, since chronic depression was found to result in enlargement of the adrenal gland with an increased sensitivity to ACTH (67,68).

In depression patients treated with antidepressants, a significant association has been demonstrated between a high cortisol reaction in the combined DEX–CRH test at admission from hospital and a depressive relapse in the continuation-treatment phase (69,70). However, after lithium augmentation, a follow-up study detected no correlation between the DEX–CRH test results and a depressive relapse. The mean follow-up interval was 18 months (range 12 to 28 months). Only 48% of the 23 patients studied had a favourable follow-up, defined as no occurrence of a major depressive syndrome. Favourable or unfavourable course was not correlated to any demographic, clinical, or therapeutic variable (Bschor and others, unpublished observation).

Discussion

This review revealed substantial evidence for the efficacy of lithium augmentation therapy in the treatment of MDEs. It has been well established in controlled trials that approximately one-half of all treatment-refractory depression patients respond when lithium is added to their ongoing antidepressant regimen. The level of evidence for the efficacy of lithium augmentation is higher than that for other augmentation strategies (1). Therefore, lithium augmentation should be considered a first-line treatment strategy in patients with an MDE that does not adequately respond to standard antidepressant treatment. In responders, lithium augmentation should be continued for a minimum of 12 months (32,33).

However, it remains to be examined whether the response to lithium augmentation represents true augmentation resulting from synergistic effects or whether the response is simply owing to the antidepressant effect of lithium itself. Arguments for a true augmentation effect derive from a controlled clinical trial showing that the antidepressant effects of lithium addition were significantly higher in amitriptyline-pretreated depression patients, compared with placebo-pretreated patients, who showed no improvement after a 3-week treatment (14). Conversely, it has been well documented in a series of controlled studies undertaken in the 1970s that lithium alone exerts antidepressant effects (71,72). Therefore, a randomized, double-blind study that controls for the effects of lithium alone, compared with lithium in combination with an antidepressant, is warranted.

Previous placebo-controlled studies used either various antidepressants with different pharmacologic profiles or SSRIs. None of the prior studies exclusively used a selective

norepinephrine inhibitor. Postulating that lithium augmentation has a 5-HTergic mode of action (14,48), one may speculate that lithium augmentation does preferentially work with 5-HTergic antidepressants but that it does not work, or works insufficiently, with antidepressants acting mainly on the noradrenergic system. Therefore, a controlled lithium augmentation study using a highly selective norepinephrine inhibitor (for example, reboxetine) and including a placebo or an SSRI, or both, as a comparator drug would be of great theoretical and clinical interest.

Neuroendocrine studies of the effects of lithium augmentation on the HPA system showed an unexpected and marked increase in the ACTH and cortisol response in the combined DEX–CRH test (58,59). These results contrast with the established decline of HPA-system activity during treatment with TCAs and, therefore, question the paradigm that in major depression the normalization of HPA-system overstimulation in the combined DEX–CRH test is a necessary prerequisite for recovery (57). To elucidate lithium's effects on the HPA system, studies are needed to investigate the effects of lithium monotherapy on the HPA system in healthy control subjects, as well as in subjects with major depression during the acute depressed state and during remission.

The lithium augmentation strategy is derived from de Montigny's heuristic proposal that the enhancement of ascending presynaptic 5-HTergic function would translate into the potentiation of antidepressant efficacy (14). Evidence from both basic and clinical studies clearly demonstrates that lithium augmentation increases 5-HT neurotransmission, possibly by a synergistic action of lithium and the antidepressant on brain 5-HT pathways. However, it remains to be seen whether enhanced 5-HT neurotransmission is the major mechanism by which lithium acts to potentiate the effects of antidepressants (73).

Over the past decade, studies of lithium's action in receptor-mediated phosphoinositide signalling in the brain have opened up new lines of investigation that derive from lithium's inhibition of the enzyme inositol monophophatase (74). Considerable recent basic research has shown that lithium can affect neurotrophic signalling cascades, and it has been suggested that these effects may also underlie its efficacy in potentiating the efficacy of various classes of antidepressants (73). Specifically, lithium acts upon various neurotransmitter systems at multiple signalling levels in the brain—for example, by altering neurotransmitter receptor regulation, second messenger generating systems, protein kinase C (PKC) regulation, and gene expression (reviewed in 73,75). Among the most recent discoveries in this new area of research are findings that lithium markedly increased the levels of the neuroprotective protein, bcl-2, in rat frontal cortex and hippocampus and also increased the expression of the major PKC substrate, myristoylated alanine-rich C-kinase substrate (MARCKS) (76). Beyond these neuroprotective effects, it has recently been demonstrated that lithium also exerts regenerative effects on axons of retinal ganglion cells, enhances hippocampal neurogenesis, and protects neurons from proapoptotic stimuli (77–79). In summary, these molecular studies have demonstrated that lithium's action has novel cellular target sites; they may therefore have a major impact on our understanding of the pathophysiology of affective illness.

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Résumé : Augmentation du lithium dans la dépression réfractaire : les preuves cliniques et les mécanismes neurobiologiques

Objectif : Cette étude méthodique examine les preuves et discute de la pertinence clinique de l'augmentation du lithium comme stratégie de traitement pour les épisodes de dépression majeure réfractaire. Elle étudie également les hypothèses sur le mode d'action de l'augmentation du lithium, plus précisément sur la sérotonine (5-HT) et les systèmes neuroendocriniens, et propose des recommandations pour la recherche future.

Méthode : Nous avons cherché dans la base de donnée électronique Medline et dans la Cochrane Library les études originales pertinentes publiées en anglais entre janvier 1966 et février 2003. Les mots clés étaient les suivants : lithium, stratégies d'augmentation, augmentation du lithium, dépression majeure, dépression réfractaire, dépression réfractaire au traitement, neuroendocrinologie et sérotonine.

Résultats : Sur les 27 études cliniques prospectives publiées depuis 1981, 10 étaient des essais à double insu, contrôlés contre placebo, 4 étaient des essais comparateurs aléatoires, et 13 étaient des essais ouverts. Cinq des 9 essais contrôlés contre placebo en phase aiguë démontraient que l'augmentation du lithium avait une efficacité substantielle. Dans les essais de phase aiguë du traitement, le taux de réponse moyen du groupe lithium était de 45 %, et dans le groupe placebo, de 18 % ($P < 0{,}001$). Un essai contrôlé contre placebo a démontré l'efficacité de l'augmentation du lithium dans la phase de continuation du traitement. Pour résumer les données ouvertes et contrôlées, environ 50 % des patients ont répondu à l'augmentation du lithium en 2 à 6 semaines. Les études animales offrent des preuves tangibles que l'augmentation du lithium accroît la neurotransmission 5-HT, possiblement par l'action synergique du lithium et de l'antidépresseur sur les voies 5-HT du cerveau.

Conclusions : L'augmentation des antidépresseurs avec le lithium est la thérapie d'augmentation la mieux documentée dans le traitement de la dépression réfractaire. Les données issues des études animales indiquent une participation du système 5-HT dans l'effet augmentatif du lithium.