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SPECIAL ISSUE

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Lithium augmentation therapy in refractory depression – Update 2002

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Abstract Lithium has been used to augment the efficacy of antidepressant medications for more than 20 years. The present study examines whether evidence exists to support the clinical efficacy of lithium augmentation in refractory, treatment resistant depression. Studies were identified by searching Medline (1980 to August 2002) and by scanning the references of published reviews and standard textbooks. Studies were selected if they were open-labeled or double-blind, placebo-controlled or comparator trials that involved patients who had not responded to conventional antidepressants. 27 prospective studies were identified that included a total of 803 depressed patients displaying the following designs: 10 double-blind, placebo-controlled trials, 2 randomized, double-blind comparator trials, 2 randomized, open comparator trials, and 13 open-label trials. The majority of randomized controlled trials has demonstrated substantial efficacy of lithium augmentation in partial and non responders to antidepressant treatment. In the placebo-controlled trials, the response rate in the lithium group was 45 % and in the placebo group 18 % ($p < 0.001$). Summarizing all open and controlled studies, approximately 50 % of patients responded to lithium augmentation within 4 weeks. In conclusion, lithium is the foremost and most well-documented augmentation strategy in refractory depression. Therefore, it should be considered a first-line treatment strategy in patients with major depression who do not adequately respond to standard antidepressants.

Key words major depression · lithium augmentation · treatment resistant depression · response prediction · refractory depression

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Introduction

Antidepressants remain the staple treatment of depression, yet as many as 30–40 % of patients treated with them will fail to make a satisfactory improvement, and 10–15 % of these may develop chronic depression (Nierenberg and Amsterdam 1990; Paykel 1994; Scott 1988; Bauer et al. 2002a, b). Therefore, non-response and resistance to antidepressant therapy is one of the challenging issues in the treatment of depressive disorders.

The antidepressant activity of lithium

In contrast to its widespread use in the prophylaxis of affective disorders and in the acute treatment of mania (Bauer et al. 2002b; Müller-Oerlinghausen et al. 2002), lithium has not been well established as an antidepressant agent in the acute treatment of major depression. In the early 1970s several controlled studies tested the hypotheses that lithium alone has superior efficacy than placebo and equivalent antidepressant activity com-

pared to established tricyclic antidepressants (reviewed in: Mendels 1976, Adli et al. 1998). Although these early studies had some methodological flaws, e. g., small sample sizes, there was some evidence in support of these hypotheses from a meta-analysis that included 6 randomized double-blind comparison studies by Souza and Goodwin (1991). Today, although not being a first-line antidepressant, lithium has been recommended for the treatment of mild depressive episodes in patients with bipolar disorder, particularly in those with a history of switching easily into mania during administration of classical antidepressants (Adli et al. 1998).

Lithium augmentation: mechanisms of action

Later, another strategy involving lithium in the treatment of depression opened a new field of basic and clinical research. This strategy, so-called lithium augmentation, involves the addition of lithium to an antidepressant in the treatment of depressed patients who failed to respond satisfactorily to monotherapy with an antidepressant. Lithium has now been used to augment the efficacy of antidepressant medications for more than 20 years. The impetus for using lithium as an adjunct or augmentor for treatment resistant depression was initially derived from animal studies in which lithium has been demonstrated to enhance the synthesis and release of serotonin (Sangdee and Franz 1978, Treiser et al. 1981). Other animal studies showed that chronic administration of tricyclic antidepressants increased postsynaptic sensitivity to serotonin in forebrain neurons (de Montigny and Aghajanian 1978). Subsequently, the latter authors hypothesized that coadministration of a tricyclic antidepressant (TCA) and lithium should enhance serotonergic neurotransmission to a sensitized postsynaptic membrane, thus providing an overall increase in serotonin neurotransmission followed by an enhanced antidepressant effect.

The first study to test this hypothesis in patients with unipolar major depression was performed by de Montigny et al. (1981) who reported a dramatic response within 48 hours to the addition of lithium in 8 patients who had not responded to at least 3 weeks of treatment with tricyclic antidepressants. It was the efficacy of the combination and rapidity of the response that has since led many clinical research groups to further study this novel treatment intervention.

The goal of this article is 1) to review the literature on the use of lithium augmentation conducted during the past 20 years including prospective, open-label and randomized controlled trials (RCTs), and 2) to determine whether evidence exists to support the clinical efficacy of lithium augmentation in depressed patients who do not adequately respond to antidepressants.

Methods

An attempt was made to identify all prospective, open-label and controlled trials of lithium augmentation in treatment resistant (refractory) depression. The studies have been extracted from the following sources:

- A computerized literature search of MEDLINE from 1980 – August 2002 using the key-words "lithium augmentation", "lithium addition", "lithium with augmentation" and "lithium with depression".
- An intensive hand search using the references of published reviews on lithium augmentation and standard textbooks on refractory depression.

All studies that involved participants who had been treated with lithium addition after not responding to conventional antidepressants were included in this review. Inclusion criteria were the use of accepted criteria for depression (DSM-III, DSM-IV; ICD-9, or ICD-10), and response criteria based on acceptable measurement of depression as an outcome variable. In placebo-controlled trials with multiple treatment arms, only the data from the lithium and placebo arms were included in the overview of response rates. The following data were extracted from the studies: study design, study population, antidepressant dose and duration of treatment, lithium dosages, duration of augmentative treatment and treatment response. Only studies with 5 or more participants were included in this review.

Results

27 studies were identified with a total of 803 patients. Ten of these were double-blind placebo-controlled studies (Heninger et al. 1983; Kantor et al. 1986; Zusky et al. 1988; Schöpf et al. 1989; Browne et al. 1990; Joffe et al. 1993b; Stein et al. 1993; Katona et al. 1995; Baumann et al. 1996; Bauer et al. 2000). Their main results are shown in Table 1. The remaining 17 trials included 13 open trials (De Montigny et al. 1981; De Montigny et al. 1983; De Montigny et al. 1985; Price et al. 1986; Delgado et al. 1988; Fontaine et al. 1991; Dinan 1993; Flint and Rifat 1994; Hawley et al. 1994a; Hawley et al. 1994b; Uehlinger et al. 1995; Sluzeska et al. 1997; Hoencamp et al. 2000), 2 randomized, double-blind, comparator trials (Hoencamp et al. 1994; Fava et al. 2002) and 2 randomized, open comparator trials (Dinan and Barry 1989; Fava et al. 1994) (Table 2). The majority of patients (> 90 %) in these studies were diagnosed with unipolar depression.

Double-blind, placebo-controlled trials

Nine of 10 randomized, double-blind, placebo-controlled trials (RCTs) were conducted during the acute treatment phase (Table 1). In one study, the double-blind, placebo-controlled phase was performed during the continuation phase treatment (Bauer et al. 2000). Those 9 RCTs during the acute treatment phase involving 234 patients were recently subjected to a meta-analysis (Bauer and Döpfmer 1999). The mean ages of patients included in this meta-analysis ranged from 37–54 years and the male to female ratio was approximately 4:7. Lithium carbonate doses ranged from 250 mg a day to 1200 mg a day, with some studies allowing titration to a serum lithium level (usually 0.5 mmol/L or more); du-

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

Study, Year	Subjects	Study Design	Study Therapy[1]	Response
Heninger et al. 1983	14 UP, 1 BP; 12 F, 3 M; mean age, 50 y	R, DB, P	amitriptyline 150–300 mg/d, desipramine 150–300 mg/d, mianserin 90–120 mg/d) (≥ 21 d) plus lithium/P (900–1200 mg/d) (12–14 d)	Lithium: 62.5 % Placebo: 0 %
Kantor et al. 1986	7 UP gender, n. r.; mean age, n. r.	R n. r., DB, P	various TCA (≥ 100–250 mg/d) (≥ 3 wks) plus lithium/P (900 mg/d) (48 h)	Lithium: 25 % Placebo: 0 %
Zusky et al. 1988	16 UP 13 F, 3 M; mean age, 45 y	R, DB, P	imipramine or equivalent ≥ 150 mg/d; phenelzine or equivalent ≥ 60 mg/d (≥ 4 wks) plus lithium/P (14 d); 1st week 300 mg lithium/plc, 2nd week 3x300 mg/d possible, according to response	Lithium: 38 % Placebo: 25 %
Schöpf et al. 1989	18 UP, 9 BP 19 F, 8 M; mean age, 54 y	R, DB, P	maprotiline, fluvoxamine ≥ 150 mg/d, dibenzepine ≥ 480 mg/d or lower dose when high serum levels (≥ 3 wks) plus lithium/P (600/800 mg/d) (14 d)	Lithium: 50 % Placebo: 0 %
Browne et al. 1990	14 UP, 3 BP 10 F, 7 M; mean age, 42 y	R, DB, P	TCA (150–300 mg/d) or maprotiline (150–200 mg/d) (≥ 3 wks) plus lithium/P (900 mg/d) (48 h)	Lithium: 43 % Placebo: 20 %
Joffe et al. 1993	33 UP 18 F, 15 M; mean age, 37 y	R, DB, P	desipramine or imipramine (5 wks) lithium/P (900 mg/d) (14d) 2nd wk: lithium/plc dose increased to 1200 mg/d	Lithium: 52 % Placebo: 18.7 %
Stein and Bernadt 1993	34 UP 27 F, 7 M; mean age, 47 y	R, DB, P	amitriptyline or equivalent (≥ 150 mg/d) (≥ 3 wks) plus lithium/P (250 mg/d) (3 wks); followed by lithium (250 mg/d) vs. lithium (750 mg/d) (3 wks)	Lithium (250 mg): 18 % Lithium (750 mg): 44 % Placebo: 22 %
Katona et al. 1995	61, polarity n. r. 35 F, 26 M; mean age, 40 y	R, DB, P	fluoxetine (20 mg/d) or lofepramine (140–210 mg/d) (6 wks) plus lithium/P (day 1–2: 400 mg/d, day 3–7: 800 mg/d) (42 d)	Lithium: 53 % Placebo: 25 %
Baumann et al. 1996	23 UP, 1 BP; 17 F, 7 M; mean age, 41 y	R, DB, P	citalopram (40–60 mg/d) (4 wks) plus lithium/P (800 mg/d) (7–14 d)	Lithium: 58 % Placebo: 14 %
Bauer et al. 2000[2]	29 UP; 17 F, 12 M; mean age, 47 y	R, DB, P	Previous antidepressant plus lithium (intended serum level: 0.5–1.0 mmol/L), 2–4 week stabilization period after remission, then randomization to lithium or placebo for a 4 month period; antidepressant continued throughout study	Relapse, continuation phase: Lithium: 0 %, Placebo: 47 %

[1] lithium doses refer to lithium carbonate
[2] double-blind phase during continuation treatment; study not included in meta-analysis (see result section)
UP unipolar disorder; *BP* bipolar disorder; *DB* double-blind; *R* randomized; *P* placebo; *n. r.* not reported

ration of augmentation therapy was as little as two days to as long as 42 days. The response rate in the lithium group ranged from 12.5 % to 62.5 % with a median of 50 %. The response rate in the placebo group ranged from 0 % to 50 % (median: 18.7 %).

The combined results of these 9 RCTs showed that lithium augmentation led to a higher response rate than did placebo ($p < 0.001$) (Table 2). When RCTs were entered into a cumulative meta-analysis in the order of increasing dose, the effect was statistically significant at a lithium carbonate dose of 600 to 800 mg/day, and results did not change with higher doses. A cumulative meta-analysis of RCTs entered in the order of increasing treatment duration showed a statistically significant effect at 7 days (Bauer and Döpfmer 1999).

In the continuation treatment phase study, 29 patients with unipolar major depression who had responded to lithium augmentation were randomized af-

Table 2 Meta-analysis[1] – Treatment response for lithium augmentation versus placebo in refractory depression

Trial type	No. of trials	Response rates Improved/Total (%) with		Relative benefit (95 % CI)	NNT (95 % CI)
		Lithium	Placebo		
Sufficient lithium carbonate dose (minimum 800 mg/day) and duration (min. 2 weeks)	3	27/54 (50 %)*	13/56 (23 %)*	2.2 (1.3 to 3.7)	3.7 (2.3 to 11)
All trials	9	50/113 (45 %)**	21/121 (18 %)**	2.5 (1.6 to 3.8)	3.8 (2.6 to 6.6)

[1] modified from Bauer and Döpfmer (1999)
* $p = 0.002$; ** $p < 0.001$
NNT number needed to treat

ter a 2–4-week stabilization period to a double-blind continuation treatment for another 4 months with either lithium (N = 14) or placebo (N = 15) while the antidepressant was continued at the same dosage (Bauer et al. 2000). Seven of the 15 patients who received placebo suffered from a relapse (5 depressive and 2 manic) during the double-blind study phase, while none patient from the lithium group relapsed. Even more patients relapsed during the open 6-month phase that followed the double-blind phase (Bschor et al. 2002b). It was concluded from these studies that lithium augmentation should be maintained in responders to that strategy for a minimum of 12 months (Bschor et al. 2002b).

Comparator and open trials

A total of 438 depressed patients with a mean age of 43 years were included in 17 trials that used an open-label or a comparator design (Table 3). The duration of antidepressant pre-treatment ranged between 3 and 7 weeks with a mean of 4.5 weeks, and of the subsequent lithium augmentation therapy between 2 days and 14 weeks with a mean duration of 29 days. The antidepressants used in the trials included agents from different groups, among them were SSRIs, tri- and tetracyclic antidepressants and MAO inhibitors. The dosages of the antidepressants used were not reported in all trials. The dosages of lithium carbonate ranged between 300 and 1500 mg/day. The response rates ranged widely between 100 % and 23.5 % with a median of 56 %; 10 of 17 open

Table 3 Comparator and open-label studies of lithium augmentation in treatment resistant depression

Study, Year	Subjects	Study Design	Study Therapy[1]	Response
De Montigny et al. 1981	UP; N = 8	Open	Amitriptyline, Imipramine, Doxepin, Iprindole (3 weeks) plus lithium (900 mg) (2 days)	100 %
De Montigny et al. 1983	UP; N = 42	Open	Amitriptyline, Imipramine, Doxepin, Iprindole, Trimipramine (3 weeks) plus lithium (900 mg) (2 days)	74 %
De Montigny et al. 1985	UP; N = 7	Open	Iprindole (3 weeks) plus lithium (900 mg) (2 days)	86 %
Price et al. 1986	UP, BP; N = 84	Open	Desipramine, Amitriptyline, Adinazolam, Bupropion, Fluvoxamine, Mianserin, Trazodon (4–6 weeks) plus lithium 900–1500 mg (> 10 days)	56 % (31 % marked, 25 % partial)
Delgado et al. 1988	UP; N = 5	Open	Fluvoxamine (300 mg) (4–6 weeks) plus lithium (3 weeks)	44 %
Dinan and Barry 1989	UP, BP; N = 30	Open, R, COM	Amitriptyline or equivalent (> 4 weeks) randomized to lithium (600–800 mg) or electroconvulsive therapy (ECT) (3 weeks)	Lithium: 67 % ECT: 73 %
Fontaine et al. 1991	UP; N = 60	Open	Desipramine, fluoxetine (6 weeks) plus lithium (600 mg) (6 or 14 weeks)	Desipramine + lithium: 67 % Fluoxetine + lithium: 60 %
Dinan 1993	UP; N = 11	Open	Sertraline (> 6 weeks) plus lithium (400 or 800 mg) (1 week)	Lithium (400 mg): 67 % Lithium (800 mg): 43 %
Hoencamp et al. 1994	BP, UP, Dysthymia; N = 51	DB, R, COM	Maprotiline (6 weeks) randomized to lithium (600–1200 mg) or brofaromine (MAO-A-inhibitor) (6 weeks)	Maprotiline + lithium: 30 % Brofaromine: 23.8 %
Fava et al. 1994[1]	UP, BP; N = 41	Open, R, COM	Partial or nonresponders to fluoxetine (20 mg) (8 weeks) randomized to fluoxetine (40–60 mg) or lithium (300–600 mg) or desipramine (25–50 mg) (4 weeks)	High-dose fluoxetine: 53 % Lithium: 29 % Desipramine: 25 %
Flint and Rifat 1994	UP; N = 21	Open	Fluoxetine (mean 35 mg) or Nortriptyline (6 weeks) plus lithium (> 2 weeks)	24 %
Hawley et al. 1994	UP; N = 21	Open	Paroxetine (20 mg) (6 weeks) plus lithium (6 weeks)	26 %
Hawley et al. 1994	UP; N = 14	Open	Fluoxetine (20 mg) (6 weeks) plus lithium (12 weeks)	50 %
Uehlinger et al. 1995	UP; N = 5	Open	Citalopram (20–60 mg) (4 weeks) plus lithium (2 weeks)	80 %
Sluzeska et al. 1997	UP; N = 32	Open	Sertraline, Fluoxetine, Imipramine, Clomipramine, Amitriptyline, Dibenzepine, Dezipramine, Moclobemide plus lithium (4 weeks)	75 %
Hoencamp et al. 2000	UP; N = 22	Open	Venlafaxine (225 mg) (7weeks) plus lithium (600 mg) (6 weeks)	32 %
Fava et al. 2002[2]	UP; N = 101	DB, R, COM	Partial or nonresponders to fluoxetine (20 mg) (8 weeks) randomized to high-dose fluoxetine (40–60 mg) or lithium (300–600 mg) or desipramine (25–50 mg) (4 weeks)	High-dose fluoxetine: 42 % Lithium: 23.5 % Desipramine: 29.4 %

[1] lithium doses refer to lithium carbonate
[2] the Fava et al. 1994 and Fava et al. 2002 studies included different patient populations
UP unipolar disorder; *BP* bipolar disorder; *COM* comparator trial; *DB* double-blind; *R* randomized; *P* placebo

studies found response rates to lithium augmentation of 50 % or more (see Table 3 for details).

Predictors of response and neuroendocrine mechanisms of action

Although proven effective in a series of RCTs and open-label studies, approximately 50 % of depressed patients do not respond sufficiently to lithium augmentation. Thus, it is of major clinical and theoretical interest to identify clinical and biological variables that help to predict the outcome of lithium augmentation. To date, 7 studies have investigated clinical variables in lithium augmentation trials (de Montigny et al. 1983, Price et al. 1986, Schöpf et al. 1989, Rybakowski and Matkowski 1992, Joffe et al. 1993a, Alvarez et al. 1997, Bschor et al. 2001). Consistently, age, gender, and class of augmented antidepressant were found to be not associated with response. A better response in patients with a lower depression score was reported in three studies (Joffe et al. 1993a, Rybakowski and Matkowski 1992, Alvarez et al. 1997), while three other studies (de Montigny et al. 1983, Price et al. 1986, Schöpf et al. 1989) did not find such a correlation. However, in a retrospective analysis of 71 depressed patients, refractory to a treatment trial with a tricyclic antidepressant, we demonstrated that patients with a more severe depressive syndrome (rated with the Bech-Rafaelsen Melancholia Scale (Bech and Rafaelsen 1986)) were more likely to respond to lithium augmentation (Bschor et al. 2001). This result is in line with studies on treatment with antidepressants in which more severely depressed patients showed a greater response (Möller et al. 1987). A two-step logistic regression also revealed that the duration of the index episode of responders was shorter, that their triiodothyronine serum levels were lower and that they had less frequent a neuroleptic co-medication or a co-diagnosis of personality disorder (Bschor et al. 2001).

The use of biological systems as predictors of successful lithium augmentation has rarely been studied (Bschor et al. in press). With the development and course of depression linked to central regulation impairment of the hypothalamic-pituitary-adrenocortical (HPA) system, investigation of this biological system can provide important insights into the pathophysiology and treatment of depression (Dinan 1997, Holsboer 2000). In a recent study, we conducted the combined dexamethasone/CRH test (DEX/CRH test) (Holsboer 2000), the most sensitive challenge test of the HPA system, prior to lithium augmentation in 30 patients with a major depressive episode who had not responded to an antidepressant monotherapy trial of at least 4 weeks. Eleven (37 %) patients responded to lithium augmentation within 4 weeks. Non-responders had a statistically significant higher cortisol/ACTH peak ratio compared to responders (Bschor et al. accepted). This ratio is an indicator for the sensitivity of the adrenal cortex to ACTH (Holsboer et al., 1995). The finding would be in line with the assumption of a more chronic course of depression with more pronounced biological alterations in the non-responder group, because chronic depression is known to cause enlargement of the adrenal gland with a subsequent hypersensitivity to ACTH (Amsterdam et al. 1983, Barden et al. 1995).

Also, new insights evolve from the study applying the DEX/CRH test during the course of lithium augmentation. This neuroendocrinological challenge test was repeated in 24 of the 30 patients after response was determined or, in cases of non-response, 4 weeks after initiation of lithium augmentation (Bschor et al. 2002a). In treatment studies with a tricyclic antidepressant, a normalization of the overstimulation of ACTH and cortisol secretion in the DEX/CRH test was found to go along with the clinical improvement (Heuser et al. 1996). However, during lithium augmentation the opposite effect could be demonstrated: patients had a significantly higher ACTH and cortisol response to CRH stimulation during lithium augmentation compared to the values at baseline. Because the effect was independent of the response status it was suggested that this increase reflects an effect of lithium that is independent from the psychopathological state or its change. It was speculated from a review of basic research literature that this effect might be explained by the serotonergic effects of lithium (Bschor et al. 2002a).

Discussion

This review revealed that a substantial number of RCTs and open studies has been conducted on the use of lithium augmentation in refractory depression since its first description in 1981 by de Montigny and co-workers. The majority of studies has demonstrated substantial efficacy of lithium augmentation in partial and non responders to antidepressant treatment. The results of a previous meta-analysis of 9 RCTs also provided firm evidence that lithium augmentation results in a statistically significant improvement in the antidepressant response rate as compared with the effects of placebo (Bauer and Döpfmer 1999). Overall, RCTs and open studies included, about 50 % of patients were responsive to lithium augmentation in these reports. About 20 % of patients responded within the first week (de Montigny 1994).

Lithium has been found to potentiate the therapeutic effects of a broad spectrum of antidepressants, including SSRIs (de Montigny 1994a, Bauer 1995, Baumann et al. 1996; Zullino and Baumann 2001). Lithium augmentation is generally well tolerated with all classes of antidepressants. The combination of lithium with antidepressants has not been reported to be associated with serious side effects (Rouillon and Gorwood 1998; Zullino and Baumann 2001), and therefore has been recommended by many clinicians for treatment resistant depressed patients (Adli et al. 2002, de Montigny 1994, Heit and Nemeroff 1998, Bauer et al. 2002a).

Only 6 % of patients of the studies included in a meta-analysis were reported to have bipolar depression, all other patients had unipolar depression. Therefore, no conclusion could be made whether patients with bipolar disorder respond differently to lithium augmentation than patients with unipolar depression (Bauer and Döpfmer 1999).

The main conclusion drawn from this review and meta-analysis is that lithium augmentation is effective and may be recommended as the first-choice treatment procedure for depressed patients who fail to respond to antidepressant monotherapy. This conclusion is based upon several reasons: first, for treatment resistant depression lithium augmentation is the strategy that has been investigated most frequently in placebo-controlled, double-blind studies. Second, results from the large, placebo-controlled and methodologically sound trials are positive (Joffe et al. 1993b, Katona et al. 1995, Baumann et al. 1996).

Although proven effective, not all patients do benefit from the lithium augmentation strategy. It can be estimated from the large number of controlled and open studies that approximately 50 % of refractory patients do not respond to this intervention. Thus, it is of major clinical and theoretical interest, to identify clinical and biological variables that help to predict the outcome during lithium augmentation. Our own results indicate lithium augmentation seems to be of particular value for the more severely ill depressed patient. Future studies designed as prospective studies to identify predictors of response to this intervention should extend to those variables that are presumably involved in the pathophysiology of depression, e. g., the serotonergic and noradrenergic systems.

Although there is convincing evidence that lithium augmentation is more effective than "placebo augmentation", it remains unsolved whether the response to lithium augmentation is a "true" augmentation effect, results from synergistic effects or is simply the antidepressant effect of lithium alone. 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 depressed patients compared to placebo-pretreated patients who showed no improvement after a 3-week treatment (de Montigny et al. 1983). On the other hand, it has been well documented in a series of controlled studies in the 1970s that lithium alone exerts antidepressant effects (Souza and Goodwin 1991, Adli et al. 1998). Ten of 13 controlled studies reviewed by Fieve and Peselow (1994) indicated that lithium is superior to placebo or is as effective as tricyclic antidepressants, particularly for bipolar depressed patients. Therefore, only a randomized, double-blind study that controls for the effects of lithium alone compared to those in combination with an antidepressant will yield a definite answer to this query.

Conclusions

Augmentation with lithium is the most well-documented studied augmentation therapy in the treatment of major depressive disorders to date. Most double-blind, placebo-controlled studies showed a significant benefit for lithium augmentation with response rates of about 40 % to 50 % across studies. Therefore, with respect to efficacy, adding lithium to ongoing antidepressant treatment is recommended as the first choice treatment procedure for depressed patients who do partially or do not respond to antidepressant monotherapy. Lithium has been found to augment the therapeutic effects of a broad spectrum of antidepressants including TCAs and SSRIs. About 20 % of patients have been reported to respond during the first week. Lithium augmentation should be administered for at least 2 to 4 weeks to allow assessment of the patient's response. Serum lithium levels of 0.6 to 0.8 mmol/L are recommended that are characteristically achieved at a lithium carbonate dose of 800–1200 mg/day (equivalent to approximately 24–36 mmol/day). In patients who respond to lithium augmentation, effective lithium doses should be continued in combination with the antidepressant for at least 12 months after remission.

References

1. Adli M, Berghöfer A, Linden M, Helmchen H, Müller-Oerlinghausen B, Mackert A, Stamm T, Bauer M (2002) Effectiveness and feasibility of a standardized stepwise drug treatment regimen algorithm for inpatients with depressive disorders: results of a two-year observational algorithm study. J Clin Psychiatry 63:782–790
2. Adli M, Bschor T, Canata B, Döpfmer S, Bauer M (1998) Lithium in the treatment of acute depression. [Article in German] Fortschr Neurol Psychiatr 66:435–441
3. Alvarez E, Pérez-Solá V, Pérez-Blanco J, Queraltó JM, Torrubia R, Noguera R (1997) Predicting outcome of lithium added to antidepressants in resistant depression. J Affect Disord 42:179–186
4. Amsterdam JD, Winokur A, Abelman E, Lucki I, Rickels K (1983) Cosyntropin (ACTH alpha 1–24) stimulation test in depressed patients and healthy subjects. Am J Psychiatry 140:907–909
5. Barden N, Reul JM, Holsboer F (1995) Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? Trends Neurosci 18:6–11
6. Bauer M (1995) The combined use of lithium and SSRIs. J Serotonin Res 2:69–76
7. Bauer M, Bschor T, Kunz D, Berghöfer A, Ströhle A, Müller Oerlinghausen B (2000) Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry 157:1429–1435
8. Bauer M, Döpfmer S (1999) Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. J Clin Psychopharmacol 19:427–434
9. Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ (2002a) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorders, Part 1: Acute and continuation treatment of major depressive disorder. World J Biol Psychiatr 3:5–43

10. Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ (2002b) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorders, Part 2: Maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depressions. World J Biol Psychiatr 3:67–84
11. Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, Uehlinger C, Kasas A, Amey M, Jonzier-Perey M (1996) A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: A clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol 16:307–314
12. Bech P, Rafaelsen OJ (1986) The melancholia scale: development, consistency, validity and utility. In: Sartorius N, Ban PA (eds) Assessment of depression. Springer, Berlin Heidelberg New York, pp 259–269
13. Browne M, Lapierre YD, Hrdina PD, Horn E (1990) Lithium as an adjunct in the treatment of major depression. Int Clin Psychopharmacol 5:103–110
14. Bschor T, Adli M, Baethge C, Eichmann U, Ising M, Uhr M, Modell S, Künzel H, Müller-Oerlinghausen B, Bauer M (2002a) Lithium augmentation increases the ACTH and cortisol response in the combined DEX/CRH test in unipolar major depression. Neuropsychopharmacol 27:470–478
15. Bschor T, Baethge C, Adli M, Eichmann U, Ising M, Uhr M, Modell S, Künzel H, Müller-Oerlinghausen B, Bauer M (2003) Association between response to lithium augmentation and the combined DEX/CRH test in major depressive disorder. J Psychiatr Res 37:135–143
16. Bschor T, Baethge C, Adli M, Lewitzka U, Eichmann U, Bauer M (2003) Hypothalamic-pituitary-thyroid system activity during lithium augmentation in unipolar major depression. J Psychiatr & Neuroscience 28:210–216
17. Bschor T, Berghöfer A, Ströhle A, Kunz D, Adli M, Müller-Oerlinghausen B, Bauer M (2002b) How long should the lithium augmentation strategy be maintained? A 1-year follow-up of a placebo-controlled study in unipolar refractory major depression. J Clin Psychopharmacol 22:427–430
18. Bschor T, Canata B, Müller-Oerlinghausen B, Bauer M (2001) Predictors of response to lithium augmentation in tricyclic antidepressant-resistant depression. J Affect Disorders 64:261–265
19. Delgado PL, Price LH, Charney DS Heninger GR (1988) Efficacy of fluvoxamine in treatment refractory depression. J Affect Disorder 15:55–60
20. De Montigny C (1994) Lithium addition in treatment-resistant depression. Int Clin Psychopharmacol 9 (Suppl 2):31–35
21. De Montigny C, Aghajanian GK (1978) Tricyclic antidepressants: long-term treatment increases responsivity of rat forebrain neurons to serotonin. Science 202:1303–1306
22. De Montigny C, Cournoyer G, Morisette R (1983) Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression: correlations with the neurobiologic actions of tricyclic antideoressant drugs and lithium on the serotonin system. Arch Gen Psychiatry 40:1327–1334
23. De Montigny C, Elie R, Caille G (1985) Rapid response to the addition of lithium in iprindole-resistant unipolar depression: a pilot study. Am J Psychiatry 142:220–223
24. De Montigny C, Grunberg F, Mayer A, Deschenes JP (1981) Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. Br J Psychiatry 138:252–256
25. Dinan TG (1993) Lithium augmentation in sertraline-resistant depression: a preliminary dose-response study. Acta Psychiatr Scand 88:300–301
26. Dinan TG (1997) Neuroendocrinology of mood disorders. Curr Opin Psychiatry 10:84–87
27. Dinan TG, Barry S (1989) A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic nonresponders. Acta Psychiatr Scand 80:97–100
28. Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, Worthington J, Baer L, Rosenbaum JF (2002) Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. J Clin Psychopharmacol 22:379–387
29. Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM (1994) Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry 151:1372–1374
30. Fieve RR, Peselow ED (1994) Lithium: clinical applications. In: Burrows GD (ed) Psychiatry Series. Elsevier, Amsterdam, pp 277–321
31. Flint AJ, Rifat SL (1994) A prospective study of lithium augmentation in antidepressant-resistant geriatric depression. J Clin Psychopharmacol 14:353–356
32. Fontaine R, Ontiverod A, Elie R, Vézina M (1991) Lithium carbonate augmentation of desipramine and fluoxetine in refractory depression. Biol Psychiatry 29:946–948
33. Hawley CJ, Roberts AG, Baldwin DS (1994a) Tolerability of combined treatment with lithium and fluoxetine: 14 cases treated under open conditions. Int Clin Psychopharmacol 9:31–33
34. Hawley CJ, Roberts AG, Walker MH (1994b) Tolerability of combined treatment with lithium and paroxetine: 19 cases treated under open conditions. Int Clin Psychopharmacol 8:266–267
35. Heninger GR, Charney DS, Sternberg DE (1983) Lithium carbonate augmentation of antidepressant treatment. Arch Gen Psychiatry 40:1335–1342
36. Heit S, Nemeroff CB (1998) Lithium augmentation of antidepressants in treatment-refractory depression. J Clin Psychiatry 59 (suppl 6):28–33
37. Heuser IJE, Schweiger U, Gotthardt U, Schmider J, Lammers CH, Dettling M, Yassouridis A, Holsboer F (1996) Pituitary-adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. Am J Psychiatry 153:93–99
38. Hoencamp E, Haffmans PMJ, Dijken WA (1994) Brofaromine versus lithium addition to maprotiline: a double blind study in maprotiline refractory depressed outpatients. J Affect Disord 30:219–227
39. Hoencamp E, Haffmans PMJ, Dijken WA, Huijbrechts IPAM (2000) Lithium augmentation of venlafaxine: an open-label trial. J Clin Psychiatry 20:538–543
40. Holsboer F (2000) The corticosteroid receptor hypothesis of depression. Neuropsychopharmacol 23:477–501
41. Holsboer F, Lauer Ch J, Schreiber W, Krieg JC (1995) Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology 62:340–347
42. Joffe RT, Levitt AJ, Bagby RM, MacDonald C, Singer W (1993a) Predictors of response to lithium and triiodothyronine augmentation of antidepressants in tricyclic non-responders. Br J Psychiatry 163:574–578
43. Joffe RT, Singer W, Levitt AJ, MacDonald C (1993b) A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Arch Gen Psychiatry 50:387–393
44. Kantor D, McNevin S, Leichner P, Harper D, Krenn M (1986) The benefit of lithium carbonate adjunct in refractory depression – fact or fiction? Can J Psychiatry 31:416–418
45. Katona CLE, Abou-Saleh MT, Harrison DA, Nairac BA, Edwards DRL, Lock T, Burns RA, Robertson MM (1995) Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. Br J Psychiatry 166:80–86
46. Mendels J (1976) Lithium in the treatment of depression. Am J Psychiatry 133:373–378
47. Möller HJ, Fischer G, Zerssen vD (1987) Prediction of therapeutic response in acute treatment with antidepressants. Results of an empirical study involving 159 endogenous depressive patients. Eur Arch Psychiatr Neurol Sci 236:349–357

48. Müller-Oerlinghausen B, Berghöfer A, Bauer M (2002) Bipolar disorder. Lancet 359:241–247
49. Nierenberg AA, Amsterdam JD (1990) Treatment-resistant depression: definition and treatment approaches. J Clin Psychiatry 51 (suppl 6):39–47
50. Paykel ES (1994) Epidemiology of refractory depression. In: Nolen WA, Zohar J, Roose SP, Amsterdam JD (eds) Refractory Depression. Current Strategies and Future Directions. London: John Wiley & Sons Ltd, pp 3–17
51. Price LH, Charney DS, Henninger GR (1986) Variability of response to lithium augmentation in refractory depression. Am J Psychiatry 143:1387–1392
52. Rouillon F, Gorwood P (1998) The use of lithium to augment antidepressant medication. J Clin Psychiatry 59 (suppl 5):32–39
53. Rybakowski J, Matkowski K (1992) Adding lithium to antidepressant therapy: factors related to therapeutic potentiation. Eur Neuropsychopharmacol 2:161–165
54. Sangdee C, Franz DN (1978) Lithium-induced enhancement of 5-HT transmission at a central synapse. Comm Psychopharmacol 2:191–198
55. Schöpf J, Baumann P, Lemarchand T, Rey M (1989) Treatment of endogenous depressions resistant to tricyclic antidepressants or related drugs by lithium addition. Results of a placebo-controlled double-blind study. Pharmacopsychiatry 22:183–187
56. Scott J (1988) Chronic depression. Br J Psychiatry 153:287–297
57. Sluzeska A, Sobieska M, Rybakowski JK (1997) Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. Biol Psychiatry 35:123–127
58. Souza FG, Goodwin GM (1991) Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. Br J Psychiatry 158:666–675
59. Stein G, Bernadt M (1993) Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. Br J Psychiatry 162:634–640
60. Treiser SL, Cascio CS, O'Donohue TL, Keilar K (1981) Lithium increases serotonin release and decreases serotonin receptors in the hippocampus. Science 213:1529–1531
61. Uehlinger C, Nil R, Amey M, Baumann P, Dufour H (1995) Citalopram-lithium combination treatment of elderly depressed patients: a pilot study. Int J Ger Psychiatry 10:281–287
62. Zusky PM, Biederman J, Rosenbaum JF, Manschreck TC, Gross CC, Weilberg JB, Gastfriend DR (1988) Adjunct low dose lithium carbonate in treatment-resistant depression: a placebo-controlled study. J Clin Psychopharmacol 8:120–124
63. Zullino D, Baumann P (2001) Lithium augmentation in depressive patients not responding to selective serotonin reuptake inhibitors. Pharmacopsychiatry 34:119–127