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Lithium Augmentation in Antidepressant-Resistant Patients
A Quantitative Analysis

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A quantitative analysis was used to examine the efficacy of lithium augmentation in the acute treatment of depressed patients resistant to a standard trial of an antidepressant. Effect sizes were measured by the odds ratio using the Mantel–Haenszel method. Only controlled trials were included in order to minimise bias in method. A highly statistically significant effect for lithium augmentation was found, the pooled odds ratio being 0.146 and its 95% confidence interval 0.05–0.44 (i.e. the odds of remaining ill are reduced by between 56% and 95% with the use of lithium treatment). While these results support the case for lithium augmentation in treatment-resistant depression, there remains considerable uncertainty over the duration of treatment necessary to see and sustain the treatment response.

Treatment-resistant depression is a common and well known clinical problem. While 70–80% of depressed patients respond within three weeks to a tricyclic antidepressant and a further proportion may respond within another 3–4 weeks to a second-line antidepressant (Nolen *et al*, 1988), 10–30% of patients with a major depressive illness do not respond to antidepressants given at an adequate dose and for an adequate period of time (Nolen *et al*, 1988).

Pharmacological augmentation of the effects of either re-uptake inhibitors or monoamine oxidase inhibitors (MAOIs) is an attractive second-line approach to the management of treatment-resistant depressed patients. To achieve it, a variety of agents have been proposed, including L-tryptophan (Pare, 1963), stimulants (Wharton *et al*, 1971), triiodothyronine (Goodwin *et al*, 1982) and reserpine (Price *et al*, 1987). However, positive results have been most extensively reported with lithium. Himmelhoch *et al* (1972) were the first to describe the benefits of adding lithium to an antidepressant. Initially, the justification for lithium augmentation was an empirical one, but improved understanding of the mechanism of action of antidepressants gave a better rationale for its use (de Montigny & Aghajanian, 1978). The first trial of lithium augmentation in resistant patients was reported by de Montigny *et al* (1981). In this study, a dramatic improvement was reported in eight depressed patients, 48 hours after the addition of lithium to a previously ineffective tricyclic regime. There have now been 49 case reports and open studies (as listed by Dinan & Barry, 1989; Thase *et al*, 1989; Schou, 1990), with some 387 patients given lithium in addition to a tricyclic or MAOI. No less than 243 responded to a greater or lesser extent to the addition of lithium, often within 48 hours as de Montigny *et al* (1981) had claimed. While these findings may have been clinically convincing, they cannot be taken as conclusive without controlled evaluation of lithium augmentation.

To date there have only been seven double-blind, placebo-controlled trials of lithium augmentation in patients resistant to a standard course of an antidepressant. Although traditional qualitative reviews of the literature (Schöpf, 1989; Schou, 1990) have supported the benefits of this approach, they also highlight the difficulty of drawing firm conclusions based on the results of several small studies, none of which is conclusive in itself and some of which are actually negative. Since the efficacy of this approach to treatment-resistant depression is of considerable clinical importance, and trials of an adequate size are difficult to perform, there is a need to extract as much quantitative information from the existing data as possible. The objective of this study was to review the usefulness of lithium augmentation in patients resistant to standard antidepressant treatment by means of a 'meta-analysis'. Quantitative analysis or 'meta-analysis' (Glass, 1977) can combine the results of different trials of similar method to improve the quantitative basis of our understanding of a given treatment effect. Furthermore, it shifts the focus to size of effect rather than levels of significance in the evaluation of therapeutic efficacy (Gardner & Altman, 1990).

Method

An attempt was made to gather data from all controlled trials of lithium augmentation in antidepressant-resistant patients. The relevant references were obtained using a computer-aided search, and an informal search through *Index Medicus*, recent journal reviews and published studies. Direct contact with authors was made when details of interest were not available from the published data.

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The trials included in the review were required to have random assignment to lithium or placebo and double-blind evaluation. In addition, all studies included in this analysis defined treatment-resistant patients as those not responding to a minimum of 150 mg/day of a tricyclic antidepressant (or an equivalent antidepressant) given for three weeks or more. Patients were required to have a minimum lithium level of 0.4 mmol/l at the time of assessment of treatment response (Blier & de Montigny, 1985). In spite of its small number, the Kantor *et al* (1986) study was included as we wished to analyse the maximum number of patients. Two studies were excluded, the first, by de Montigny *et al* (1983), was excluded due to its use of a lithium rather than a placebo control group, and the second, by Cournoyer *et al* (1984), did not lend itself to this type of analysis because of its cross-over design and lack of sufficient raw data to allow inclusion of the results of the first phase of the trial. In the study by Stein & Bernadt (1988) the lithium levels in the double-blind placebo-controlled phase were $\leqslant 0.4$ mmol/l. It was worth analysing, however, because of the relatively large number of patients studied. Effect sizes were therefore calculated with and without this study. With Stein's study included, 99 patients were analysed in total.

Statistical procedure

Both the significance and the magnitude of effect are readily determined for categorical data from 2×2 tables (e.g. lithium/placebo × responder/non-responder) using the Mantel–Haenszel method (Mantel & Haenszel, 1959). For the effect size, the odds ratio together with its associated confidence interval has been advocated as both intuitively comprehensible and statistically elegant (Yusuf *et al*,1985). The expected number of failures in the lithium augmentation group, E, was contrasted with the observed number of failures, O, as follows.

	Responders	Non-responders	Total
Lithium	a	b	$a+b$
Placebo	c	d	$c+d$
Total	$a+c$	$b+d$	n

gives

$$E = \frac{(b+d)(a+b)}{n}$$

where $b+d$ is the number of patients not responding in the lithium and placebo groups, $a+b$ is the number of patients in the lithium group, and n is the total number of patients in the trial.

If treatment were beneficial $O-E$ would tend to be negative. If, on the other hand, treatment were wholly without effect, the quantity $O-E$ would differ only randomly from zero, with variance V and standard error $\sqrt{V}$, where variance was given by

$$V = \frac{(a+b)(c+d)(a+c)(b+d)}{n^2\,(n-1)}$$

For i individual studies, $\Sigma(O_i-E_i)$ would differ randomly from zero if treatment were without effect (with variance equal to the sum of individual variances, ΣV_i). $\Sigma(O_i-E_i)$ would be negative if treatment were effective. Statistical significance was expressed as two-tailed P values, where $P=0.05$ corresponds to $(O-E)/\sqrt{V}=1.96$. $(O-E)/\sqrt{V}$ and the $\Sigma(O_i-E_i)/\sqrt{\Sigma V_i}$ were assumed to be normally distributed. The odds of failure for patients on lithium augmentation compared with the odds of failure for patients on placebo was chosen as the main measure of risk, and was given by the odds ratio $\pm$95% confidence intervals: $\exp((O-E)/V \pm 1.96/\sqrt{V})$ (Yusuf *et al*, 1985).

The χ^2 of association tests for between-treatment differences in efficacy once study effects are removed: it was given with one degree of freedom by $[\Sigma(O_i-E_i)]^2/\Sigma V_i$. The χ^2 of heterogeneity tests whether between-study differences are significant: it was given by the difference between the total χ^2 and the χ^2 of association with $n-1$ degrees of freedom, where the total χ^2 was given by $\Sigma[(O_i-E_i)^2/V_i]$.

Results

Table 1 gives details of patient entry criteria, and lithium duration, dose and serum levels. Either lithium or placebo was added to an antidepressant in all studies. Most studies reported on unipolar patients, except for Schöpf *et al* (1989), where a third of patients were bipolar. All patients met either DSM-III or RDC criteria for major depressive disorder/episode. There was a wide range of scores on the Hamilton Rating Scale for Depression (HRSD) (Table 1), suggesting that the studies included patients with a wide spectrum of illness severity. While all patients had been on an antidepressant for three weeks or more, illness duration at the time of entry into the trial was somewhat unclear, with the exception of Zusky *et al* (1988) and Schöpf *et al* (1989), who gave a mean illness duration of six months. In Table 1, 'Duration' refers to the period during which the trial was double-blind and placebo-controlled. This period was different in most cases from the full duration of the trial, which in Heninger *et al* (1983) was 24 days; in Zusky *et al* (1988) 21 days; and in Schöpf *et al* (1989) 14 days.

Table 2 shows the findings of these studies. Schöpf *et al* (1989) and Stein & Bernadt (1988) defined responders as patients with a $\geqslant$50% drop in HRSD, and Kantor *et al* (1986) used a $\geqslant$40% drop in HRSD. Heninger *et al* (1983) used a decrease of 2 or more points on the Short Clinical Rating Scale (SCRS; a 15-point nurse-rated 'psychopathology' scale) as their measure of response, while Zusky *et al* (1988) defined responders as those with an HRSD score of 7 or less. Only half the studies were said to be 'significant' ($P<0.05$), but all the studies (except Stein & Bernadt, 1988) showed a positive treatment effect as indicated by negative $O-E$ values. Indeed, when pooled significance values were considered, these results were unlikely to have occurred by chance ($P<0.001$).

Figure 1 illustrates both individual and pooled effect sizes and confidence intervals. The pooled odds ratio is 0.146, with a 95% confidence interval ranging from 0.05 to 0.44. The pooled $O-E$ value is -6.5, which means that 13 out of 34 patients, or nearly 40%, were 'responders' when treated with lithium.

The χ^2 of heterogeneity was 2.5 (NS), indicating that the studies did not significantly differ in the results they

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Table 1
Controlled trials of lithium augmentation

	Study	Patient entry criteria	Duration	Lithium dose and serum level
(a)	Heninger *et al*, 1983	Unipolar: 14/15 Mean HRSD: 34.5±10.4	12 days	900–1200 mg/day 0.5–1 mmol/l
(b)	Kantor *et al*, 1986	Mean HRSD: 23.3±3.8	48 hours	900 mg/day Levels not available
(c)	Zusky *et al*, 1988	Patients with HRSD≥12 Mean HRSD: 22.6±8.9 Episode duration: 9 months	14 days	⩾300 mg/day ⩾0.4 mmol/l in 2nd week
(d)	Schöpf *et al*, 1989	Patients with HRSD≥15 Unipolar: 18/27 Mean HRSD: 20±4.9 Episode duration: 8 months	7 days	⩾800 mg/day 0.6–0.8 mmol/l
	Stein & Bernadt, 1988	Mean HRSD: 25.1±5.2	3 weeks	250 mg/day Mean level 0.23 mmol/l

obtained. When Stein & Bernart's (1988) study was included, the χ^2 of heterogeneity was 8.5, giving a P value of 0.005, thereby highlighting its differences in method from the rest of the studies. With inclusion of this study, the pooled odds ratio increased to 0.29, while the 95% confidence intervals became 0.12–0.73 – a significant increase in width, as one would expect.

Discussion

No statistical synthesis can overcome flaws in method inherent in the studies themselves. Firstly, while most authors chose to use the de Montigny *et al* (1981) definition of treatment-resistant depression (⩾150 mg/day of a tricyclic antidepressant given for ⩾3 weeks leading to an HRSD score decrease of less than 40%), many clinicians would favour the World Psychiatric Association (1974) definition, which requires that a patient be treated for between four and six weeks with a tricyclic antidepressant at a dose ⩾150 mg/day in order to be defined as treatment-resistant. Nevertheless, it is doubtful that many clinicians would in practice wait more than four weeks before changing to another treatment if no response was seen.

Secondly, one must question whether a response to lithium augmentation given for only 48 hours can be regarded as fully meaningful. The rationale for the original design of the de Montigny *et al* (1981) trial was based on the hypothesis that 'chronic' administration of tricyclic antidepressants leads to increased sensitivity of forebrain neurons to 5-HT and that the acute administration of lithium releases 5-HT on to these receptors to form the basis of antidepressant efficacy. This acute pre-synaptic enhancement of transmitter release has been shown to occur at lithium concentrations ⩾0.4 mmol/l (Blier & de Montigny, 1985). Some authors do report a therapeutic effect after 48 hours of lithium augmentation at appropriate concentrations (de Montigny *et al*, 1983; Cournoyer *et al*, 1984; Schöpf *et al*, 1989), but others report little or no effect until one week after commencement of lithium (Heninger *et al*, 1983). Schöpf *et al* (1989)

Table 2
Results of controlled trials of lithium augmentation[1]

Study	Lithium		Placebo		$O-E$	V	P
	Responders	Non-responders	Responders	Non-responders			
(a) Heninger *et al*, 1983	5	3	0	7	−2.3	0.88	<0.014
(b) Kantor *et al*, 1986	1	3	0	3	−0.4	0.24	NS
(c) Zusky *et al*, 1988	3	5	2	6	−0.5	0.92	NS
(d) Schöpf *et al*, 1989	7	7	0	13	−3.3	1.34	<0.005
Total	16	18	2	29	−6.5	3.38	<0.001
Stein & Bernadt, 1988	2	14	4	14	+0.8	1.27	NS
Total + Stein & Bernadt	18	32	6	43	−5.7	4.65	<0.008

1. $O-E$ is the observed minus expected number of failures in the lithium group; V is the variance of $O-E$; P is the two-tailed probability corresponding to each normal deviate given by $(O-E)/\sqrt{V}$.

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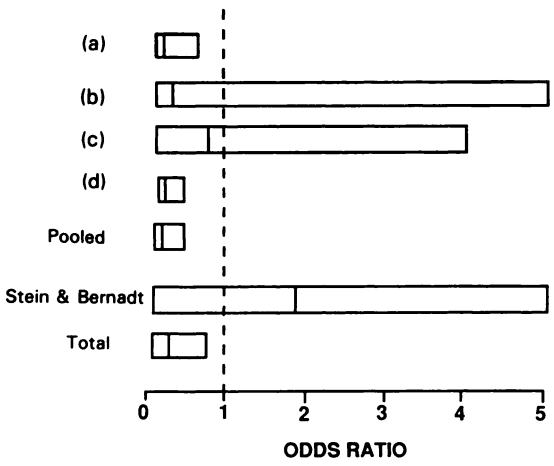


Fig. 1 The odds ratio with the 95% confidence intervals for individual and pooled data from lithium augmentation studies. Studies (a)–(d) are as in Table 1. The left side (< 1) favours a positive effect of lithium augmentation and the right side (> 1) favours no effect. Some studies have 95% confidence intervals which extend beyond 5 and are not drawn in full (Kantor *et al* (1986), 0.004 to 11.6; Stein & Bernadt (1988), 0.22 to 15.8). 'Pooled' refers to pooled results of studies (a)–(d).

report an increase in the proportion of responders from about 20% responding at 48 hours to 40% responding within two weeks.

Individual studies have other more minor variations that may limit their comparability. Heninger *et al* (1983) used a nurse-rated scale, the SCRS, to assess outcome, thus making the detail of their results less comparable with those of other studies. However, they report unambiguously the favourable clinical outcome of the study. Kantor *et al* (1986) suffered a large number of drop-outs, and due to the resulting small numbers this study, taken on its own, was entirely inconclusive. Schöpf *et al* (1989) included bipolar patients who, when depressed, appear to show a response to lithium alone. This could have increased the chance of a spurious positive response to lithium augmentation; however, the ratio of responders to non-responders in the unipolar and bipolar groups is similar at one week, and so the response to lithium does not appear to have been biased by the inclusion of bipolar patients. This similarity of response to lithium augmentation in unipolar and bipolar patients has also been reported by Price *et al* (1986). Other problems with the Schöpf *et al* (1989) study included the use of small doses of neuroleptics in a number of patients, and less than adequate doses of antidepressant in others (although tricyclic serum levels for these patients were reported to be within the therapeutic range). The limitation of small numbers in all the studies is only partly overcome by their combination to give a grand total of 99 patients in all (if Stein's study is included). Since probably up to 30% of patients treated with a tricyclic antidepressant do not respond, this remains a relatively disappointing total: these patients are not rare.

The majority of the patients included in this analysis were moderately depressed (total mean HRSD score, 24.4). Although illness severity is said not to influence response to lithium augmentation (de Montigny *et al*, 1983; Schöpf, 1989), it cannot be assumed that lithium would be efficacious in severely depressed patients. Thus the range of patients to which the favourable effect of lithium applies remains uncertain.

A binary outcome scale, required for the Mantel–Haenszel method, may appear too crude to assess an acute treatment such as lithium augmentation. However, we believe it reasonably reflects clinical decision-making. The other advantage lies in the simplification of the raw data for direct analysis; this minimises bias of method but allows optimal use of the available data by pooling all study results.

In summary, our findings suggest that lithium augmentation is effective. The pooled effect size is large and our presentation of the results illustrates the difference in emphasis between a statistical analysis based on significance levels and one based on effect size. Thus 'negative' studies (Kantor *et al*, 1986; Zusky *et al*, 1988; Stein & Bernadt, 1988) are not statistically discriminating but, equally, are not necessarily negative (in terms of effect size), as would be reported in traditional reviews (Schöpf, 1989; Schou, 1990). The difference is not a trivial one because the analyses lead to opposite conclusions: that lithium is ineffective (because 'not significant'), or that it may be effective (as shown by a significant effect size) but that the confidence interval is too great to allow certainty. We believe that the present review supports the practice of lithium augmentation in treatment-resistant patients. The odds of remaining ill are reduced by between 56% and 95% with lithium augmentation. This appears to be a worthwhile benefit. However, the present data do not offer clues as to who will respond, and we do not know for how long to continue treatment.

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References

BLIER, P. & DE MONTIGNY, C. (1985) Short-term lithium administration enhances serotonergic neurotransmission: electrophysiological evidence in the rat CNS. *European Journal of Pharmacology*, **112**, 415–418.

https://doi.org/10.1192/bjp.159.4.510 Published online by Cambridge University Press

COURNOYER, G., DE MONTIGNY, C., OUELLETE, J., *et al* (1984) Lithium addition in tricyclic-resistant unipolar depression: a placebo-controlled study. *Abstracts Collegium Internationale Neuro-Psychopharmacologicum Florence*, June 19–23, 179.

DE MONTIGNY, C. & AGHAJANIAN, G. K. (1978) Tricyclic antidepressants: long-term treatment increases responsivity of rat forebrain neurons to serotonin. *Science*, **202**, 1303–1306.

———, GRUNBERG, F., MAYER, A., *et al* (1981) Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. *British Journal of Psychiatry*, **138**, 252–256.

———, COURNOYER, G., MORISETTE, R., *et al* (1983) Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression. *Archives of General Psychiatry*, **40**, 1327–1333.

DINAN, T. G. & BARRY, S. (1989) A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic non-responders. *Acta Psychiatrica Scandinavica*, **80**, 97–100.

GARDNER, M. J. & ALTMAN, D. G. (1990) Confidence – and clinical importance – in research findings. *British Journal of Psychiatry*, **156**, 472–474.

GLASS, G. V. (1977) Integrating findings: the meta-analysis of research. *Review of Research in Education*, **5**, 351–379.

GOODWIN, F. K., PRANGE, A. J., POST, R. M., *et al* (1982) Potentiation of antidepressant effects by L-triiodothyronine in tricyclic non-responders. *American Journal of Psychiatry*, **139**, 34–38.

HENINGER, G. R., CHARNEY, D. S. & STERNBERG, D. E. (1983) Lithium carbonate augmentation of antidepressant treatment: an effective prescription for treatment-refractory depression. *Archives of General Psychiatry*, **40**, 1335–1342.

HIMMELHOCH, J. M., DETRE, T., KUPFER, D. J., *et al* (1972) Treatment of previously intractable depressions with tranylcypromine and lithium. *Journal of Nervous and Mental Disease*, **155**, 216–220.

KANTOR, D., MCNEVIN, S., LEICHNER, P., *et al* (1986) The benefit of lithium carbonate adjunct in refractory depression: fact or fiction? *Canadian Journal of Psychiatry*, **31**, 416–418.

MANTEL, N. & HAENSZEL, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute*, **22**, 719–748.

NOLEN, W. A., VAN DE PUTTE, J. J., DIJKEN, W. A., *et al* (1988) Treatment strategy in depression – I. Non-tricyclic and selective reuptake inhibitors in resistant depression: a double-blind partial cross-over study on the effects of oxaprotiline and fluvoxamine. *Acta Psychiatrica Scandinavica*, **718**, 668–675.

PARE, C. M. B. (1963) Potentiation of monoamine oxidase inhibitors by tryptophan. *Lancet*, *i*, 527–528.

PRICE, L. H., CHARNEY, D. S. & HENINGER, G. R. (1986) Variability of response to lithium augmentation in refractory depression. *American Journal of Psychiatry*, **143**, 1387–1392.

——— & ——— (1987) Reserpine augmentation of desipramine. *Psychopharmacology*, **92**, 431–437.

SCHÖPF, J. (1989) Treatment of depressions resistant to tricyclic antidepressants, related drugs or MAO-inhibitors by lithium addition: review of the literature. *Pharmacopsychiatry*, **22**, 174–182.

———, BAUMANN, P., LEMARCHAND, T., *et al* (1989) Treatment of endogenous depressions resistant to tricyclic antidepressants or related drugs by lithium addition. *Pharmacopsychiatry*, **22**, 183–187.

SCHOU, M. (1990) Lithium and treatment-resistant depressions: a review. *Lithium*, **1**, 3–8.

STEIN, G. & BERNADT, M. (1988) Double blind trial of lithium carbonate in tricyclic resistant depression. In *Lithium: Inorganic Pharmacology and Psychiatric Use* (ed. N. J. Birch). Oxford: IRL Press.

THASE, M. E., KUPFER, D. J., FRANK, E., *et al* (1989) Treatment of imipramine-resistant recurrent depression: II. An open clinical trial of lithium augmentation. *Journal of Clinical Psychiatry*, **50**, 413–417.

WHARTON, R. N., PEREL, J. M., DAYTON, P. G., *et al* (1971) A potential clinical use for methylphenidate (Ritalin) with tricyclic antidepressants. *American Journal of Psychiatry*, **127**, 1619–1625.

WORLD PSYCHIATRIC ASSOCIATION (1974) Symposium on therapy-resistant depression. *Pharmacopsychiatry*, **7**, 69–224.

YUSUF, S., PETO, R., LEWIS, J., *et al* (1985) Beta-blockade during and after myocardial infarction: an overview of the randomised trials. *Progress in Cardiovascular Diseases*, **27**, 335–371.

ZUSKY, P. M., BIEDERMAN, J., ROSENBAUM, J. F., *et al* (1988) Adjunct low dose lithium carbonate in treatment-resistant depression: a placebo-controlled study. *Journal of Clinical Psychopharmacology*, **8**, 120–124.

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