# Lithium augmentation

## Tortoise or hare?

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# OVERVIEW

## THIS PRESENTATION WILL COVER

- Lithium use in major depressive disorder
- Early observations to practice guidelines
- Mechanisms and models of onset of action
- Future directions

# MAJOR DEPRESSIVE DISORDER

- High prevalence and often recurrent
- Substantial morbidity and mortality
- Only 40-60% of patients respond to their initial antidepressant monotherapy

If there is no (or minimal improvement) with initial treatment, typical guideline recommendations include:

- Dose increase
- Switching antidepressants
- Augmentation/combination treatment

# A NOTE ON STRATEGIES

**COMBINATION**

Two or more antidepressant drugs taken together

**AUGMENTATION**

Antidepressant drug together with a ‘non-antidepressant drug’

**ACCELERATION**

Simultaneous initiation of two drugs to hasten response

# LITHIUM: ACUTE ANTIDEPRESSANT EFFECTS

| Study | Comparator | N | Duration (weeks) | Outcome |
|---|---|---|---|---|
| Mendels 1972 | Desipramine | 24 | 3 | Lithium = desipramine |
| Watanabe 1975 | Imipramine | 45 | 3 | Lithium = imipramine |
| Worrall 1979 | Imipramine | 29 | 3 | Lithium > imipramine |
| Khan 1981 | Amitriptyline | 25 | 3 | Lithium = amitriptyline |
| Arieli 1981 | Clomipramine Placebo | 33 | 3 | Lithium = clomipramine > placebo |
| Khan 1987 | Placebo | 31 | 6 | Lithium > placebo |
| Linder 1989 | Clomipramine | 22 | 4 | Lithium = clomipramine |

= Comparable efficacy
> Greater efficacy

Onset of action of lithium was similar to comparator drugs

Table reproduced from Bauer et al 2006

# LITHIUM: ACUTE ANTIDEPRESSANT EFFECTS

## PREDICTORS OF FAVOURABLE OUTCOME AS MONOTHERAPY IN ACUTE UNIPOLAR DEPRESSION

- Family history of bipolar disorder
- Mood fluctuations and ‘light’ hypomania
- Cyclothymic personality
- ‘Endogenous’ type of depression
- Early onset of illness
- Postnatal depression

**LATENT BIPOLAR DISORDER?**

Inoue 2011; Birkenhager 2021

# LITHIUM: AUGMENTATION

## Lithium Induces Rapid Relief of Depression in Tricyclic Antidepressant Drug Non-Responders

C. DÉ MONTIGNY, F. GRUNBERG, A. MAYER and J.-P. DESCHENES

Summary: Eight patients suffering from a major unipolar depression and having failed to respond to treatment for three weeks or more with tricyclic antidepressants were given lithium. All eight patients experienced a remarkable relief of their depression within 48 hours. This rapid antidepressant effect of lithium in 'treatment-resistant' patients might be due to the enhancement of the efficacy of the central serotoninergic system, unveiling the tricyclic anti-depressant-induced sensitization of the serotoninergic postsynaptic receptors.

Dé Montigny et al BJPsych 1981; 138:252-256

# LITHIUM: AUGMENTATION

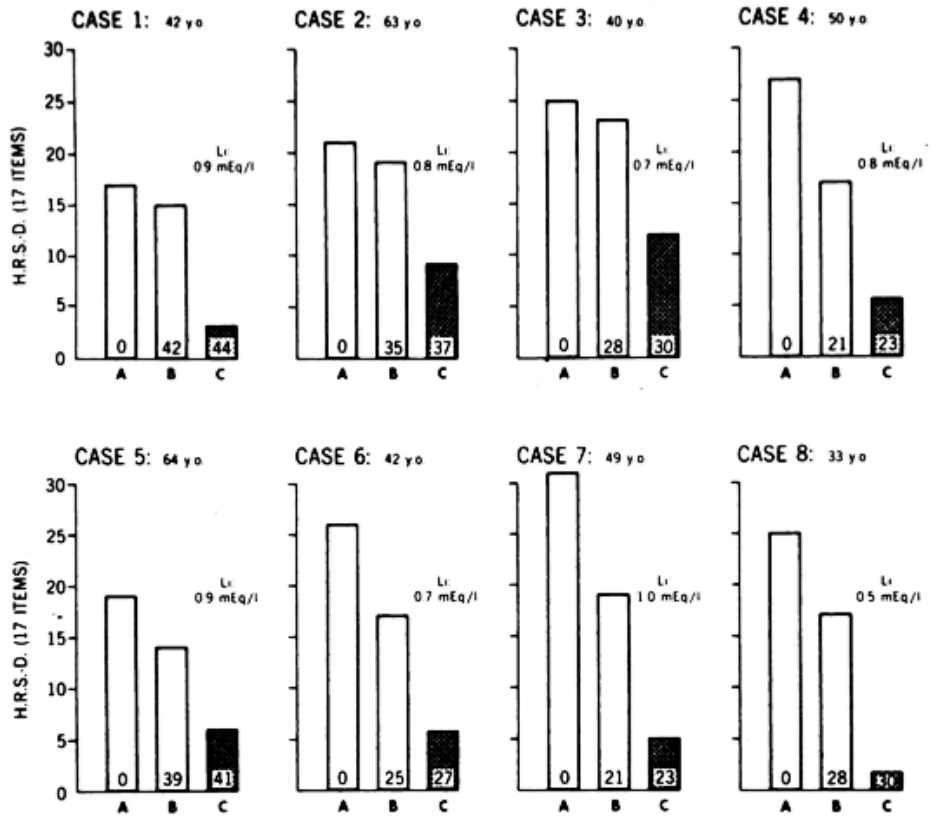



FIG 1.—Total scores on the 17-item Hamilton Rating Scale for Depression for each patient obtained before treatment (A), after a three week or more treatment with a TCA drug (B), and 2 days after the addition of lithium to their therapeutic regimens (C). Lithium was added immediately after evaluation B. The date of the evaluation (in days) is indicated in the bottom of each column. The lithium plasma concentration indicated is that obtained on the morning of evaluation C.

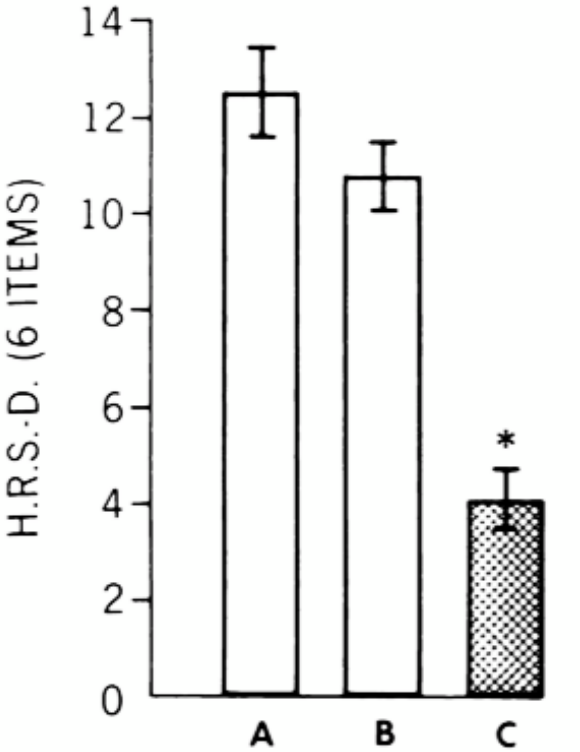



FIG 2.—Average scores (±s.e.m.) of the eight patients reported on the 6-item Hamilton subscale of Bech *et al* (Items 1, 2, 7, 8, 10 and 13) obtained before treatment (A), after a three week or more treatment with TCA (B), and 48 hours after the addition of lithium to their therapeutic regimen (C). *P <0.001 (one way analysis of variance).

Dé Montigny et al BJPsych 1981; 138:252-256

# LITHIUM: AUGMENTATION

## KEY EARLY STUDIES

**Heninger et al 1983**
RCT of lithium added to various TCA, reporting improvement at 2 days but considered clinically significant at 7-12 days.

**DéMontigny et al 1983**
Argued for true augmentation rather than the antidepressant effects in three small studies.

- Confirmed rapid effect of augmentation.
- Augmentation more marked in those pretreated with amitriptyline compared to those pretreated with placebo.
- 50% relapse on discontinuation

**Price LH et al 1986:**
Augmentation of various antidepressants with lithium (n=84, 11 of which BD).
Response in 56%, with 31% (n=26) having a marked response.
2/26 responded in 1-6 days
16/26 responded in 19-24 days

# LITHIUM: AUGMENTATION

Table 2. Randomized Double-Blind Lithium Augmentation Studies

| Study | Subjects | Antidepressant Treatment | Lithium Dosage (serum level) and Duration | Response Criteria |
|---|---|---|---|---|
| Heninger et al (1983)[26] | 14 UP, 1 BP, 12 F, 3 M, mean age = 50 y | Various TCAs and tetracyclics | 900–1200 mg/d (0.5–1.1 mmol/L), 12 d | Decrease of 2 or more points on SCRS |
| Kantor et al (1986)[22] | 7 UP, sex NR, mean age NR | Various TCAs | 900 mg/d, 48 h | ≥ 40% decrease in HAM-D |
| Zusky et al (1988)[23] | 16 UP, 13 F, 3 M, mean age = 45 y | Various TCAs and MAOIs | 300 mg/d first week, 900 mg/d second week, 14 d | Final HAM-D ≤ 7 |
| Schöpf et al (1989)[28] | 18 UP, 9 BP, 19 F, 8 M, mean age = 54 y | Various antidepressants | 600–800 mg/d (0.6–0.8 mmol/L), 7 d | ≥ 50% decrease in HAM-D |
| Browne et al (1990)[29] | 14 UP, 3 BP, 10 F, 7 M, mean age = 42 y | Various TCAs and tetracyclics | 900 mg/d, 48 h | ≥ 50% decrease in HAM-D |
| Stein and Bernadt (1993)[24] | 34 UP, 27 F, 7 M, mean age = 47 y | Various TCAs | 250 mg/d, 21 d | ≥ 50% decrease in HAM-D |
| Joffe et al (1993)[25] | 33 UP, 18 F, 15 M, mean age = 37 y | Various TCAs | 900 mg/d (> 0.55 mmol/L), 14 d | ≥ 50% decrease in HAM-D |
| Katona et al (1995)[30] | N = 61, polarity NR, 35 F, 26 M, mean age = 40 y | SSRIs and TCAs | 800 mg/d (0.6–1 mmol/L), 42 d | ≥ 50% decrease in HAM-D |
| Baumann et al (1996)[27] | 23 UP, 1 BP, 17 F, 7 M, mean age = 41 y | Citalopram | 800 mg/d (0.5–0.8 mmol/L), 7 d | ≥ 50% decrease in HAM-D |
| Nierenberg et al (2003)[4] | 35 UP, 16 F, 19 M, mean age = 38 y | Nortriptyline | 900 mg/d | ≥ 50% decrease in HAM-D |

Abbreviations: BP = bipolar, F = female, HAM-D = Hamilton Rating Scale for Depression, M = male, MAOI = monoamine oxidase inhibitor, NR = not reported, SCRS = Short Clinical Rating Scale, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, UP = unipolar.

Predominantly TCA augmentation

Lithium duration ranging from 2 to 42 days

Crossley & Bauer J Clin Psych 2007; 68:935-40

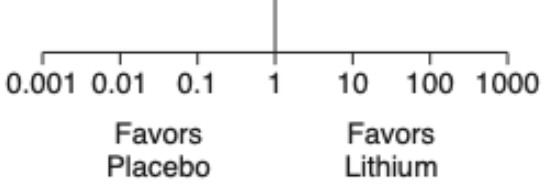
# LITHIUM: AUGMENTATION

## Meta-Analysis of Lithium Augmentation Studies[a]

| Study | Lithium, N/N | Control, N/N | Fixed Effects OR and 95% CI | Fixed Effects OR (95% CI) |
|---|---|---|---|---|
| Heninger et al (1983)[26] | 5/8 | 0/7 | | 23.57 (1.00 to 556.08) |
| Kantor et al (1986)[22] | 1/4 | 0/3 | | 3.00 (0.09 to 102.05) |
| Zusky et al (1988)[23] | 3/8 | 2/8 | | 1.80 (0.21 to 15.41) |
| Schöpf et al (1989)[28] | 7/14 | 0/13 | | 27.00 (1.35 to 541.57) |
| Browne et al (1990)[29] | 3/7 | 2/10 | | 3.00 (0.35 to 25.87) |
| Stein and Bernadt (1993)[24] | 2/16 | 4/18 | | 0.50 (0.08 to 3.19) |
| Joffe et al (1993)[25] | 9/17 | 3/16 | | 4.88 (1.01 to 23.57) |
| Katona et al (1995)[30] | 15/29 | 8/32 | | 3.21 (1.09 to 9.48) |
| Baumann et al (1996)[27] | 6/10 | 2/14 | | 9.00 (1.27 to 63.89) |
| Nierenberg et al (2003)[4] | 2/18 | 3/17 | | 0.58 (0.08 to 4.01) |
| Total | 53/131 | 24/138 | | 3.11 (1.80 to 5.37) |

Test for Heterogeneity: $\chi^2 = 11.90$, df = 9, p = .22, $I^2 = 24.4\%$

Test for Overall Effect: Z = 4.06, p < .0001




[a]Pooling of patients responding to augmentation therapy. Fixed effects model used.[9]

Crossley & Bauer J Clin Psych 2007; 68:935-40

# MORE RECENT STUDIES

**Bauer et al 2013**
Lithium augmentation comparable to quetiapine augmentation of antidepressants

**Schindler 2007**
Lithium non-significantly better than lamotrigine augmentation

**Stepped treatment studies**
STAR*D: 16% reached remission with lithium at step 3 of 4
Birkenhager: 59% response rate at step 2 of 4

**Systematic reviews and meta-analysis**
Recent publications including MMA have focused on treatment refractory depression, finding no significant effect of mood stabilisers.
Only two lithium augmentation studies included.

# LITHIUM AND SEROTONIN

## AUGMENTATION RATIONALE

TCA were thought to **increase the sensitivity of post-synaptic 5HT receptors** in the forebrain whilst lithium potentiates serotonergic systems presynaptically

## EVIDENCE

**Preclinical**

- Acute: increases uptake of tryptophan
- Acute and chronic: enhancement of 5HT release
- **Hippocampus** appears particularly sensitive to the effects of lithium

**Clinical**

- Assessed using the prolactin response to intravenous l-tryptophan
- Acute effects consistent with original hypothesis of action

# LITHIUM AND SEROTONIN

## CLINICAL EVIDENCE

**Healthy volunteers**

- Prolactin response to L-tryptophan increased by short- and long-term administration of lithium.

**Patients with depression**

- Endocrine response to Li-tryptophan diminished but rectified by lithium.
  - Cowen et al 1991: at 4 days and 4 weeks
  - Price et al 1990: at 3 days but not 3 weeks
- Not clearly related to improvements in mood.

**Medication studies**

- McCance-Katz et al 1992: antidepressants (6 weeks) did not affect prolactin response to L-tryptophan, but the addition of lithium enhanced it compared to placebo.
- Walsh et al 1991: pretreatment with lithium does not attenuate the effects of gepirone ($5HT_{1A}$ agonist) in healthy volunteers.

# LITHIUM AND SEROTONIN

## NON-SEROTONERGIC ANTIDEPRESSANTS

Most augmentation trials studied TCA with known 5HT reuptake inhibition properties

RCT augmenting nortriptyline with lithium (900 mg/day) versus placebo for 42 days reported that lithium was not superior to placebo (Nierenberg et al 2003)

## SSRI AUGMENTATION

**Placebo controlled studies augmenting SSRIs**

Lithium superior when added to citalopram (Baumann et al 1996) and subjects taking TCA or SSRI (Katona et al 1995)

Short term improvements with lithium not as marked when added to SSRIs compared to augmentation of TCA (Birkenhager et al 2004; Zullino 2001 review)

The SSRI class may not induce post-synaptic serotonin receptor sensitivity to the same degree as TCAs (Bijak et al 1994)

# LITHIUM: ACCELERATION THERAPY

Table 1. Randomized Double-Blind Lithium Acceleration Studies

| Study | Subjects | Antidepressant Treatment | Lithium Dosage or Serum Level (SL) | Length of Treatment, wk | Depression Scale and Day of Assessment |
|---|---|---|---|---|---|
| Lingjaerde et al (1974)[16] | 37 UP, 8 BP, 35 F, 10 M, mean age = 49 y | Various TCAs | SL = 0.8–1.3 mmol/L | 4 | HAM-D, 7 d |
| Januel et al (1994)[17] | 6 UP, 3 F, 3 M, age range = 21–51 y | Clomipramine, maprotiline, or tianeptine | 750 mg/d | 3 | HAM-D, 14 d |
| Ebert et al (1995)[18] | 40 BP, 40 M, mean age = 39 y | Amitriptyline | 900 mg/d | 5 | HAM-D, 14 d |
| Bloch et al (1997)[19] | 29 UP, 2 BP, 17 F, 14 M, mean age = 47 y | Desipramine | SL = 0.7–1.0 mmol/L | 5 | HAM-D, 14 d |
| Januel et al (2003)[20] | 149 UP, 92 F, 57 M, mean age = 44 y | Clomipramine | 750 mg/d | 6 | MADRS, 11 d |

Abbreviations: BP = bipolar, F = female, HAM-D = Hamilton Rating Scale for Depression, M = male, MADRS = Montgomery-Asberg Depression Rating Scale, TCA = tricyclic antidepressant, UP = unipolar.

Acceleration effect of lithium revisited after an open report of 3 subjects responding in 2 weeks to the simultaneous initiation of lithium and a TCA *(Austin 1990)*

Studies are of varying quality and underpowered
In some, serum lithium levels were high and side effects marked

Nick et al 1976 not included in meta-analysis (reported significance levels only)

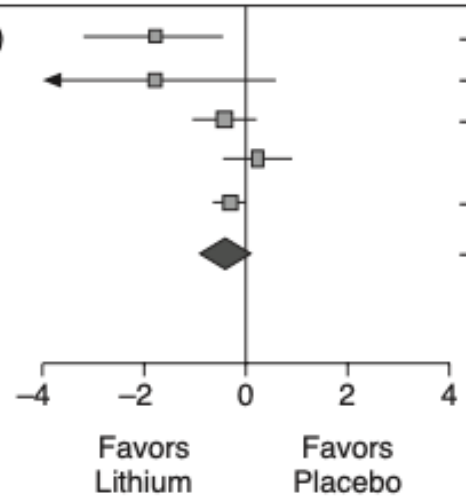
Crossley & Bauer J Clin Psych 2007; 68:935-40

# LITHIUM: ACCELERATION THERAPY

## Meta-Analysis of Lithium Acceleration Studies[a]

| Study | Lithium N | Lithium Mean (SD) | Placebo N | Placebo Mean (SD) | Random Effects SMD and 95% CI | Random Effects SMD (95% CI) |
|---|---|---|---|---|---|---|
| Lingjaerde et al (1974)[16,b] | 6 | 59.00 (15.93) | 7 | 90.00 (15.93) | | –1.81 (–3.18 to –0.44) |
| Januel et al (1994)[17,b] | 3 | 68.50 (5.99) | 3 | 82.10 (5.99) | | –1.82 (–4.19 to 0.56) |
| Ebert et al (1995)[18] | 20 | 14.50 (5.97) | 20 | 17.50 (7.99) | | –0.42 (–1.04 to 0.21) |
| Bloch et al (1997)[19] | 16 | 16.01 (6.72) | 15 | 14.20 (8.02) | | 0.24 (–0.47 to 0.95) |
| Januel et al (2003)[20] | 68 | 14.60 (8.40) | 73 | 17.20 (7.50) | | –0.33 (–0.66 to 0.01) |
| Total | 113 | | 118 | | | –0.43 (–0.93 to 0.07) |

Test for Heterogeneity: $\chi^2 = 8.53$, df = 4, p = .07, $I^2 = 53.1\%$
Test for Overall Effect: Z = 1.68, p = .09




[a]Pooling of depression scale ratings at 7 to 14 days for lithium versus placebo group. Hedges' adjusted g were pooled using DerSimonian and Laird model.[10]
[b]Percentage of baseline score shown.
Abbreviation: SMD = standardized mean difference.

Crossley & Bauer J Clin Psych 2007; 68:935-40

# LITHIUM: DURATION OF AUGMENTATION

## DISCONTINUATION OBSERVATIONS

**Dé Montigny 1981/83**

55% relapse if lithium discontinued after 1 week

20% relapse if stopped after 1 month

## DISCONTINUATION STUDIES

**Bauer et al 2000**

Refractory MDD (n=29) responded to lithium augmentation in open 6-week study. Following a further 2–4 weeks of stabilization, randomized to continuation of lithium (4 months) or placebo. Relapse in 7/15 placebo and 0/14 lithium treated.

**Bschor et al 2002**

Relapses observed during the 6 month open follow up once lithium was stopped in those previously receiving it for approximately 6 months (in Bauer et al 2000 study).

**Hardy et al 1997**

Placebo controlled gradual discontinuation (n=12) of lithium in elderly responders. 2/6 in each group relapsed

# TRANSLATION TO GUIDELINES

# Pharmacological Augmentation in Unipolar Depression: A Guide to the Guidelines

Rachael W. Taylor, Lindsey Marwood, Emanuella Oprea, Valeria DeAngel, Sarah Mather, Beatrice Valentini, Roland Zahn, Allan H. Young, Anthony J. Cleare

**Background:** Pharmacological augmentation is a recommended strategy for patients with treatment-resistant depression. A range of guidelines provide advice on treatment selection, prescription, monitoring and discontinuation, but variation in the content and quality of guidelines may limit the provision of objective, evidence-based care. This is of importance given the side effect burden and poorer long-term outcomes associated with polypharmacy and treatment-resistant depression. This review provides a definitive overview of pharmacological augmentation recommendations by assessing the quality of guidelines for depression and comparing the recommendations made.

**Methods:** A systematic literature search identified current treatment guidelines for depression published in English. Guidelines were quality assessed using the Appraisal of Guidelines for Research and Evaluation II tool. Data relating to the prescription of pharmacological augmenters were extracted from those developed with sufficient rigor, and the included recommendations compared.

**Results:** Total of 1696 records were identified, 19 guidelines were assessed for quality, and 10 were included. Guidelines differed in their quality, the stage at which augmentation was recommended, the agents included, and the evidence base cited. Lithium and atypical antipsychotics were recommended by all 10, though the specific advice was not consistent. Of the 15 augmenters identified, no others were universally recommended.

**Conclusions:** This review provides a comprehensive overview of current pharmacological augmentation recommendations for major depression and will support clinicians in selecting appropriate treatment guidance. Although some variation can be accounted for by date of guideline publication, and limited evidence from clinical trials, there is a clear need for greater consistency across guidelines to ensure patients receive consistent evidence-based care.

*International Journal of Neuropsychopharmacology* (2020) 23(9): 587–625

# TRANSLATION TO GUIDELINES

## DIFFERENCES IN GUIDELINES HIGHLIGHT AREAS WHERE EVIDENCE IS LACKING

**Effectiveness of lithium augmentation**
All support the use of lithium, but some as second-line (APA and CANMAT).

**Importance of antidepressant**
Not addressed in all guidelines but BAP draws attention to the evidence being derived largely from TCA augmentation.

**Determination of response**
RANZCP states if no benefit observed in 7-10 days, alternatives should be considered.

**Duration of treatment**
Wide ranging from 4-8 weeks (APA) to 2 years or longer based on response and illness pattern. Gradual withdrawal favoured.

**Continuing as lithium monotherapy**
Most do not recommend this. WFSBP note potential for use in relapse prevention but lithium + AD better. RANZCP supports this if AD poorly tolerated. NICE precludes.

# WHAT ABOUT THE TORTOISE?

# NEUROPROTECTION AND LITHIUM

## PRECLINICAL

Compelling evidence from neuronal cell and rodent studies. (Haupt 2021)

Key enzyme substrates include

- inhibition of glycogen synthase kinase (GSK-3), directly and indirectly via Akt
- up-regulation of bcl-2
- Increases neurotrophic molecules such as BDNF (via Wnt/B-catenin pathway)

Initially variously described as neuroprotective, neurogenic or neurorestorative.
Capacity for adult neurogenesis remains a contested issue.
Neuroprotective or neurorestorative actions would be more consistent with a delayed onset of action or prevention.

Acute effects notable, but influence on rapid improvement in mood less clear.

- Post-stroke neuroprotection established in animal models with stem cell lithium enrichment enhancing therapeutic potential via TLR-4 (Haupt 2021)

# NEUROPROTECTION AND LITHIUM

## CLINICAL

Observational and trial evidence in dementia
Lithium increases BDNF levels in augmentation of antidepressants in MDD
Structural MRI and MRS suggestive of protective effect **in bipolar disorder**

# NEUROPROTECTION AND LITHIUM

## CLINICAL

Observational and trial evidence in dementia
Lithium increases BDNF levels in augmentation of antidepressants in MDD
Structural MRI and MRS suggestive of protective effect **in bipolar disorder**

Lithium augmentation increases BDNF, though not related to response

Ricken 2013

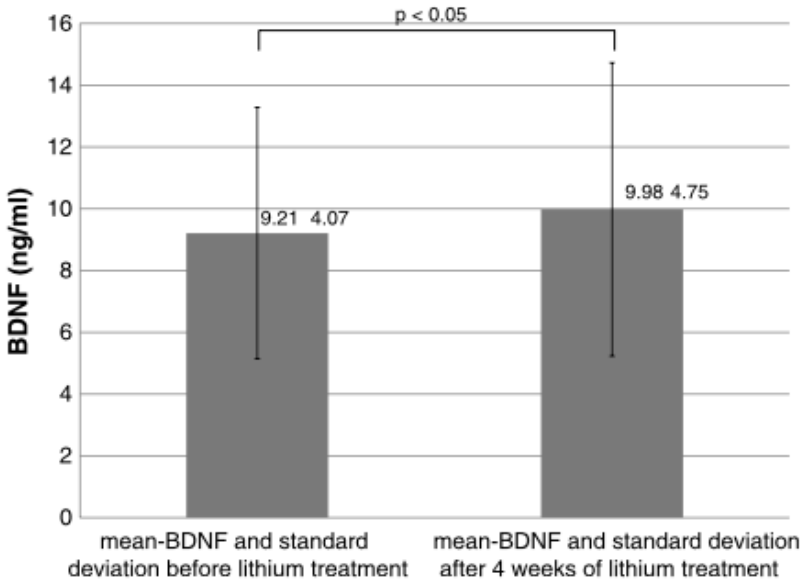



**FIGURE 1.** Brain-derived neurotrophic factor serum levels increase during 4 weeks of lithium augmentation ($F_{2,81} = 5.04$, $P < 0.05$).

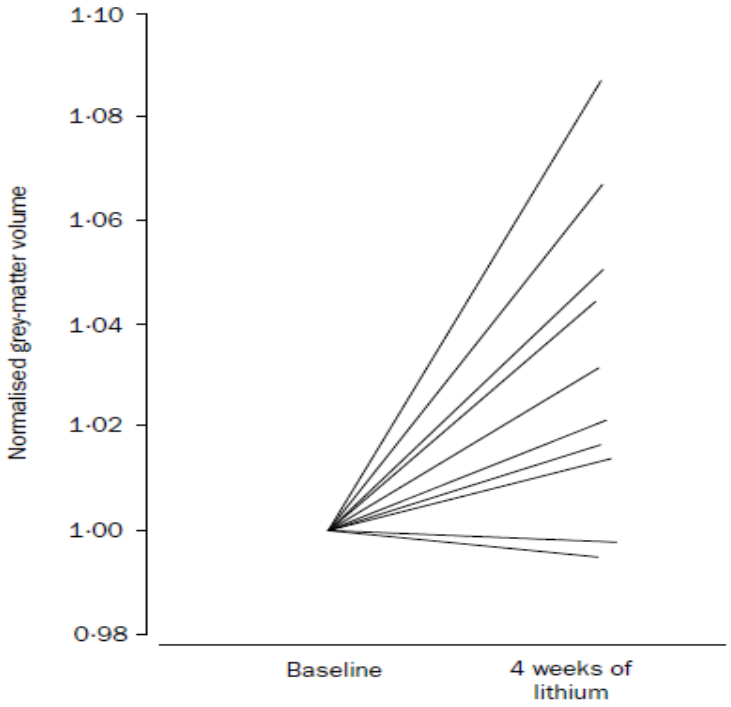
# NEUROPROTECTION AND LITHIUM

## CLINICAL

Observational and trial evidence in dementia
Lithium increases BDNF levels in augmentation of antidepressants in MDD
Structural MRI and MRS suggestive of protective effect **in bipolar disorder**

Lithium increases grey matter volume by 3% in **bipolar disorder**

Moore 2000



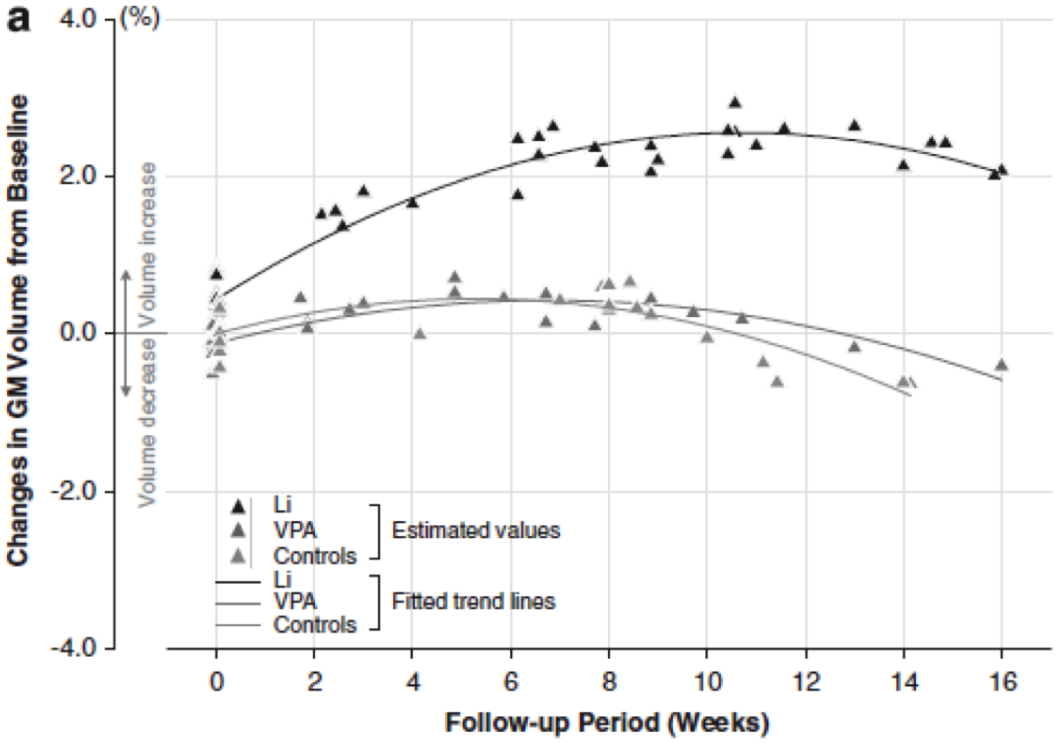
# NEUROPROTECTION AND LITHIUM

## CLINICAL

Observational and trial evidence in dementia
Lithium increases BDNF levels in augmentation of antidepressants in MDD
Structural MRI and MRS suggestive of protective effect **in bipolar disorder**

Lithium specific and asymptote 8-12 weeks

**Lyoo 2010**



# IMAGING LITHIUM IN MDD

## NOT COMPREHENSIVELY INVESTIGATED

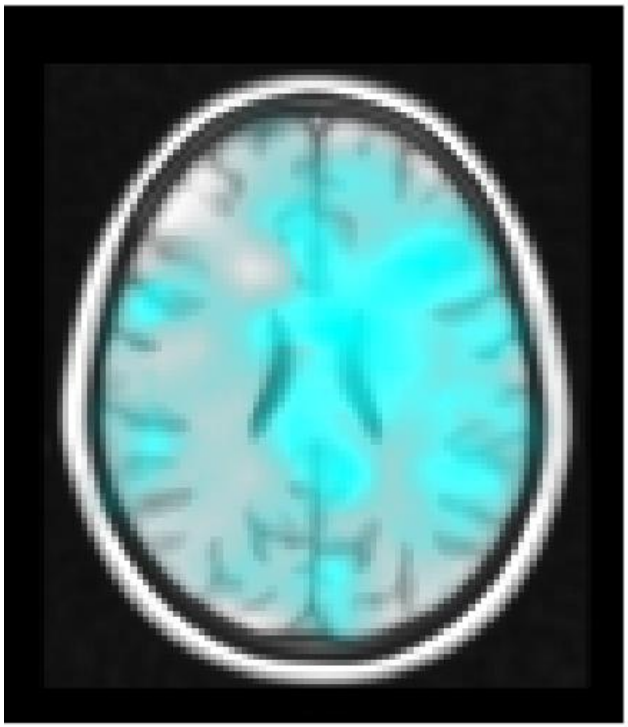
Compared to bipolar disorder, the effect of lithium treatment on brain imaging measures in MDD has not been investigated.

MDD consistently associated with reduced hippocampal volumes, notably in those with recurrent illness (Schmaal et al 2016).

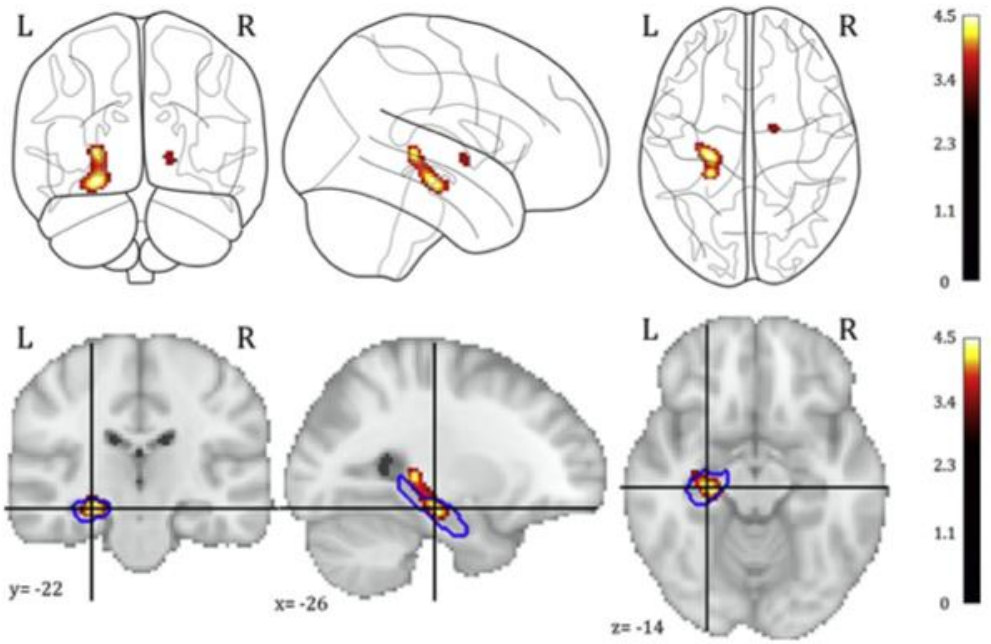
# IMAGING LITHIUM IN MDD

## NOT COMPREHENSIVELY INVESTIGATED

Longitudinal examination of hippocampal volumes with respect to response to augmentation would be valuable, given sites of lithium concentration



$^{7}$Li-MRI in bipolar disorder
Smith et al 2018




$^{7}$Li-MRI in bipolar disorder – VBM analysis 7T
Stout et al 2018

# FUTURE DIRECTIONS

## FUTURE AVENUES OF INVESTGATION

- Comparison of lithium versus antidepressant augmented by lithium (Bauer 2006)
- RCT of lithium augmentation of NA/DA antidepressant (Bauer 2007)
- Imaging correlates of lithium augmentation in major depressive disorder

## STUDIES CURRENTLY UNDERWAY

**LITHIUM VERSUS QUETIAPINE IN DEPRESSION (LQD)**

Parallel group, multi-centre, pragmatic, open-label, patient randomised clinical trial comparing lithium with quetiapine augmentation in treatment resistant depression (Marwood 2017)

**RESPONSE TO LITHIUM NETWORK (R-LINK)**

Longitudinal EU multi-centre study aiming to identify predictive biosignatures of response to lithium in bipolar disorder using multimodal imaging, digital phenotyping and ‘omics’ analysis.