Lithium in bipolar disorders.

S. Mehdi Samimi Ardestani M.D.

✓ **Department of Psychiatry , Shahid Beheshti University of Medical Science , Behavioral science research center**

✓ **Iranian psychiatric association, section of "Mood disorders"**

Disclosure /conflict of interest:

- Participation in scientific conferences sponsored by some pharmaceutics as guest or speaker(Sanofi, Novartis, AstraZeneca, Actover, Cobel)

- Bipolar disorders specially bipolar spectrum is the main conflict of interest

Lithium is a classic mood stabilizer forever:

- Substance that is effective for 1 pole without inducing the other: **lithium**, carbamazepine, valproate, probably lamotrigine and some atypical antipsychotics.

- Substance that is effective for both poles of the illness: **lithium**, carbamazepine, quetiapine, olanzapine .

- Substance that is effective for both poles of the illness and for prophylaxis of recurrences: **lithium**.

Efficacy of Lithium: Placebo-Controlled Studies With Bipolar Patients

Study	Year	Duration (Months)	Lithium (% Relapses)	Placebo (% Relapses)
Baastrup	1970	5	0	55
Melia	1970	24	57	78
Cundall	1972	12	33	83
Coppen	1971	4-26	18	95
Stallone	1973	8-22	44	93
Prien	1973	24	43	80

Lithium Reduces Frequency and Severity of Bipolar Episodes

	Lithium	Placebo
Patients, N	25	27
Mean years in study	1.84	0.68
Manic episodes per patient-year	0.11	0.86
Depressive episodes per patient-year	0.24	0.70

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Predictors of Poor Long-Term Response With Lithium

- Psychosis
- Substance abuse
- Rapid cycling
- More than 3 episodes
- Mixed mania (depression and mania)
- Poor compliance

These are not straightforward

Lithium response may be a genetic entity

(comparing offspring of lithium responders and non responders):

- The difficulties of offspring of lithium responders: **episodic course** and in adolescence present mostly as **mood disorders**.

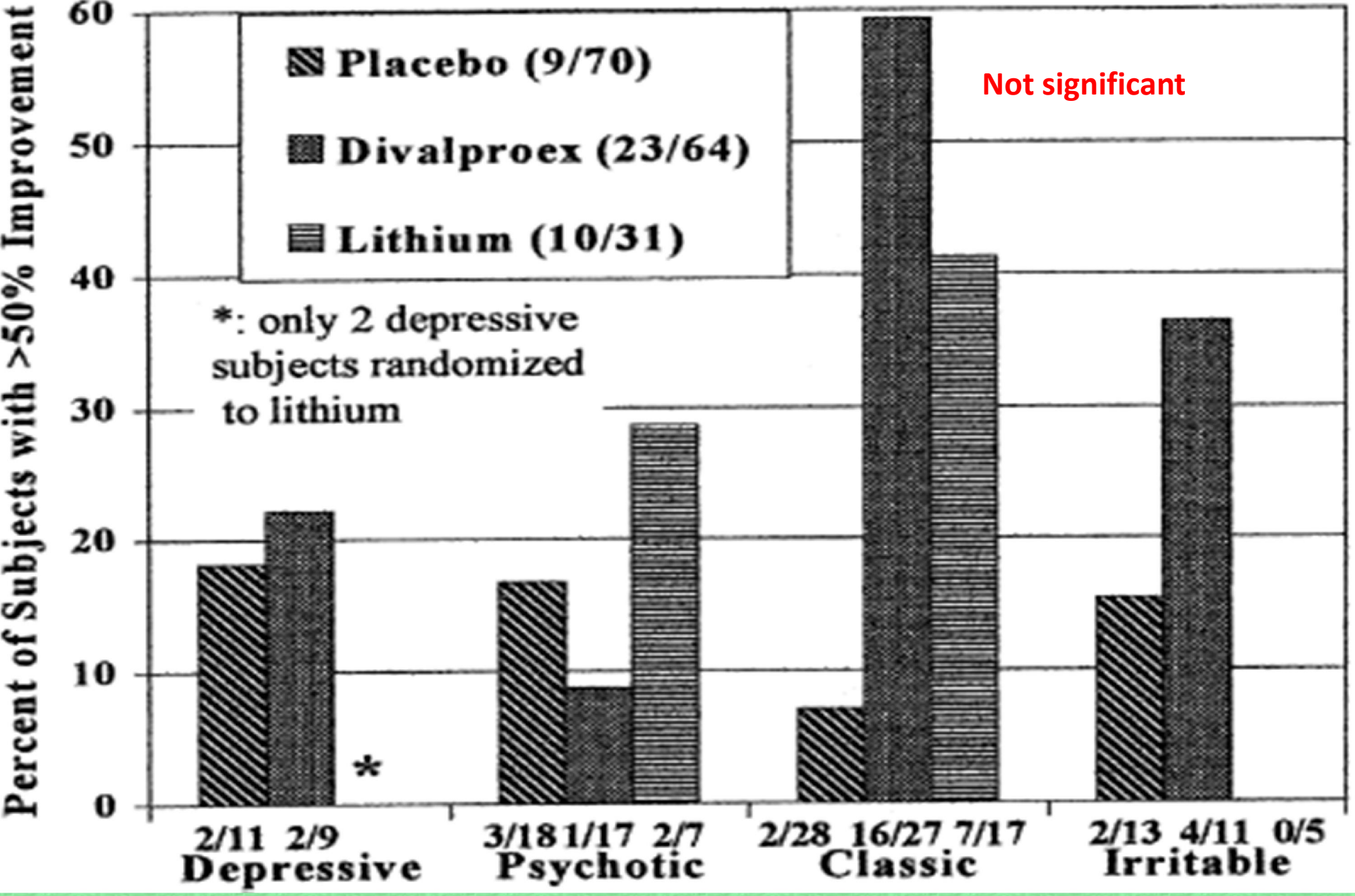
- offspring of non-responders: show either partially **remitting** or **non-remitting** fluctuating course of illness and not infrequently manifest **cluster A traits** (social inhibition, odd thinking) and **cognitive problems** diagnosed as **attentional problems** and **learning disabilities**

Grof P: Acta Psychiatr Scand 2009: 120: 378–385

three-week, double-blind, comparison of treatments of primary acute manic episodes

	Placebo 66	Divalproex 61	Lithium 28	F
Impulsivity	- 0.08 ± 1.24 L or V >P	0.69 ± 1.13	0.70 ± 1.37	5.93 (0.003)
Anxious pessimism	0.03 ± 0.86	0.051 ± .07	0.02 ± 0.78	0.18
Hyperactivity	0.39 ± 1.16 L or V >P	0.94 ± 1.13	1.0 ± 11.46	5.77 (0.004)
Distressed Appearance	0.15 ± 0.87	0.03 ± 0.90	0.06 ± 1.06	0.40
Hostility	0.13 ± 1.32 V > P	0.31 ± 1.16	0.22 ± 0.98	3.40 (0.04)
Delusions	0.05±1.14	0.24±1.22	0.27±1.27	0.84

NEUROPSYCHOPHARMACOLOGY2002–VOL.26,NO.4



Percentages of subjects with over 50% improvement in Manic Syndrome Score

- Patients in the classic subtype improved more with divalproex or with lithium than with placebo.

- Patients in the irritable subtype responded significantly better to divalproex than to lithium or placebo.

- There were significant improvements during treatment with divalproex in the psychotic, *classic and irritable subtypes*

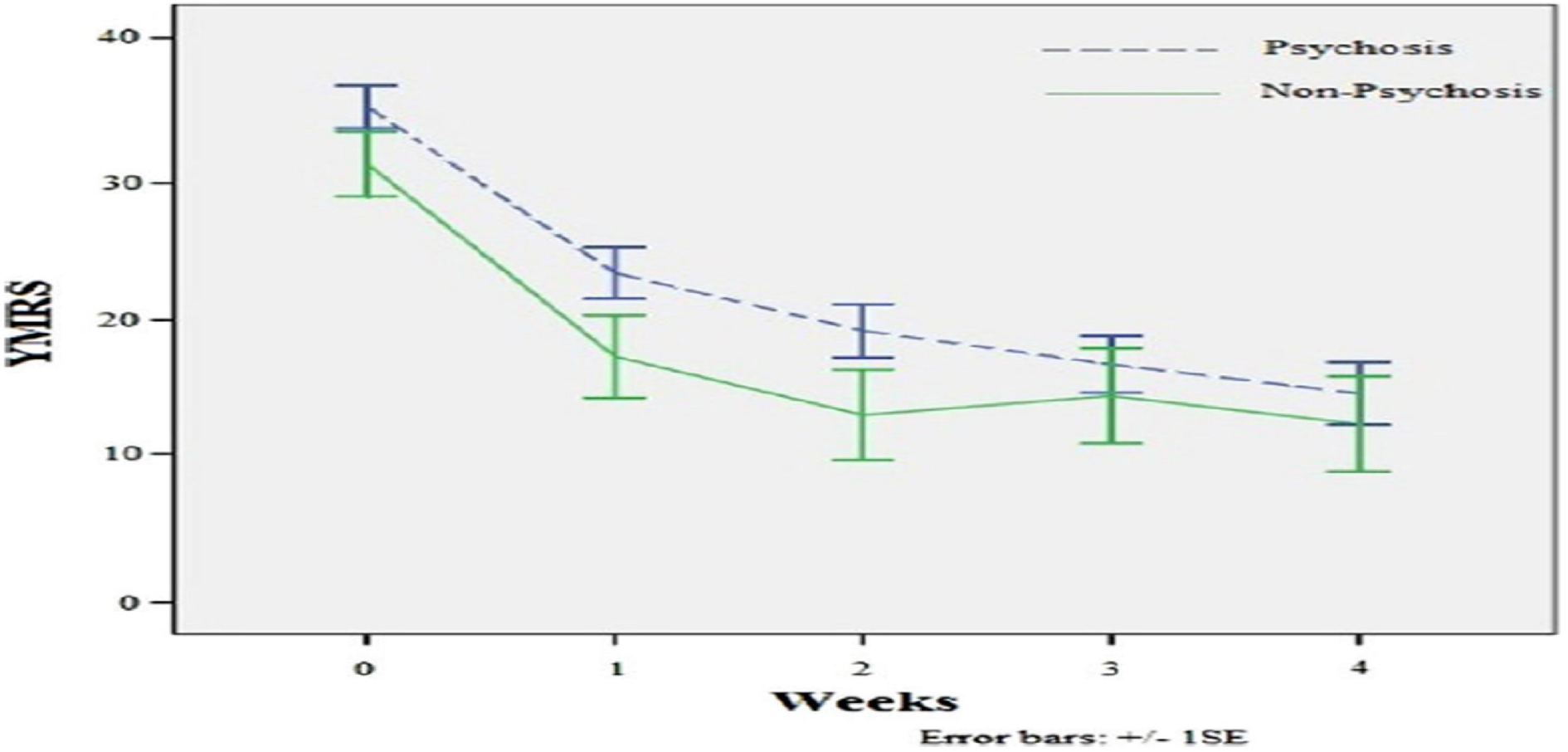
- There were significant improvements with lithium in the psychotic and classic *subtypes.*

Lithium response in psychotic mania:

Rafael T. de Sousaa, J Psychiatr Res. 2012 December.

	Psychosis (*n = 32)*	Non-psychosis (*n = 14)*
Response	63%	64%
Remission (YMRS ≤ 12)	50%	64%
Remission (YMRS ≤ 7)	34%	50%

significant improvement of manic symptoms in the both groups from baseline to endpoint

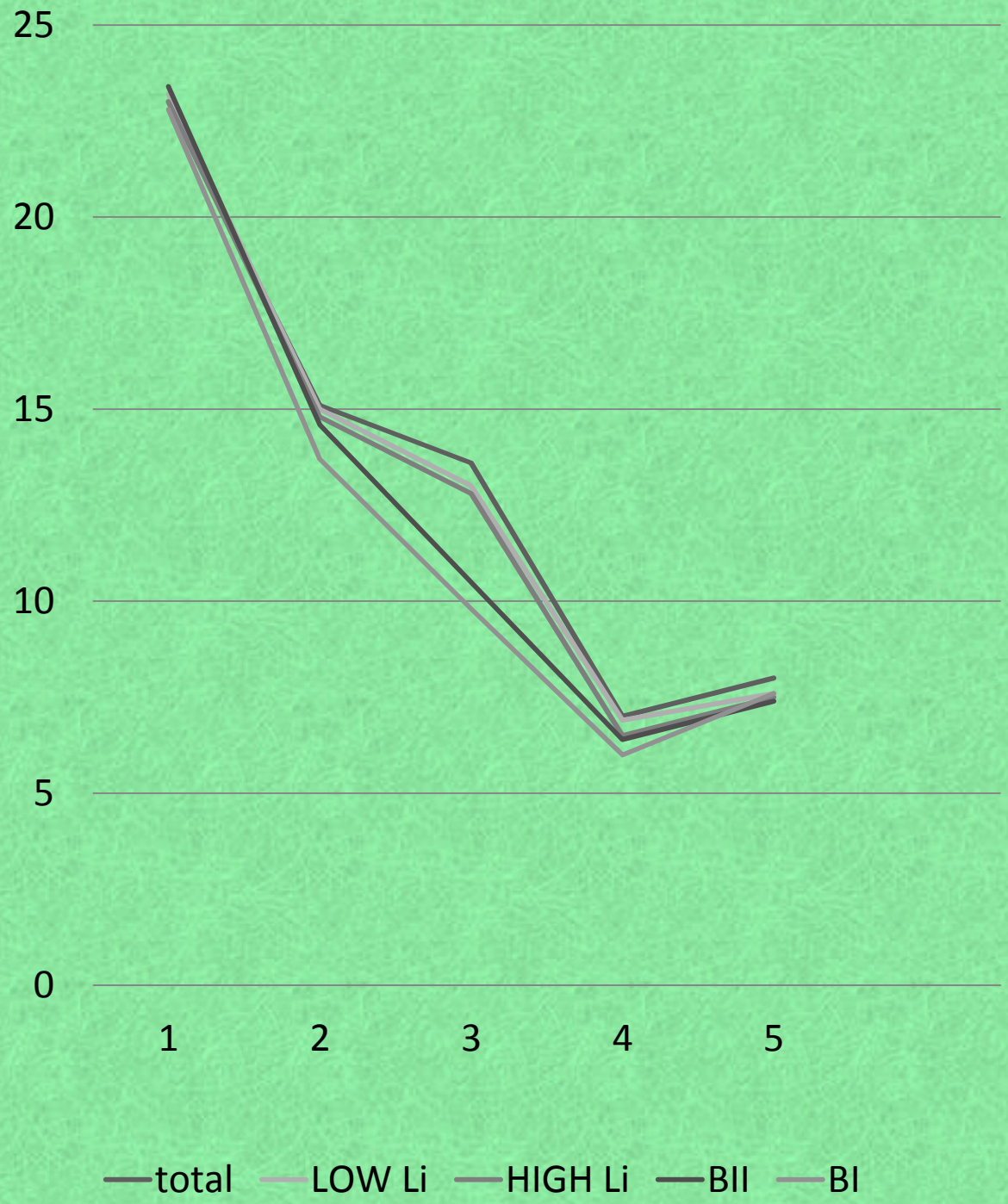


No significant difference in response between psychotic and non psychotic patients

Lithium in bipolar depression:

Characteristics	Bipolar I (n=11)	Bipolar II (n=18)	P-value
Age (years)	29.1±6.3	27.9±5.	0.592
Female gender	9 (81.8)	12 (66.7)	0.376
Duration of illness (months)	43.3±20.3	31.6±18.3	0.121
History of psychosis	4 (36.4)	0 (0%)	0.006
Naïve to treatment at week 0	6 (54.5)	15 (83.3)	0.092
Medication-free at week 0	8 (72.7)	17 (94.4)	0.100
HAM-D score at baseline	22.2±4.5	22.8±2.9	0.669
Ham-D score at week 6	7.5±5.7	7.1±6.1	0.852
YMRS score at baseline	6.4±6.3	5.9±5.3	0.982
YMRS score at week 6	5.2±13.2	2.9±4.0	0.912
Response rate at week 6	8 (72.7)	17 (94.4)	0.100
Remission rate at week 6	7 (63.6)	11 (61.1)	0.892
Levels of lithium at week 6 (mmol/l)	0.51±0.21	0.48±0.19	0.729

EXPERIMENTAL AND THERAPEUTIC MEDICINE 8: 1205-1208, 2014



No significant difference was observed when comparing low (<0.5 mEq/l) and high (>0.5 mEq/l) blood lithium levels with regards to antidepressant efficacy.

The diagnosis of bipolar disorder I (BI) or bipolar disorder II (BII) did not significantly influence the clinical outcome

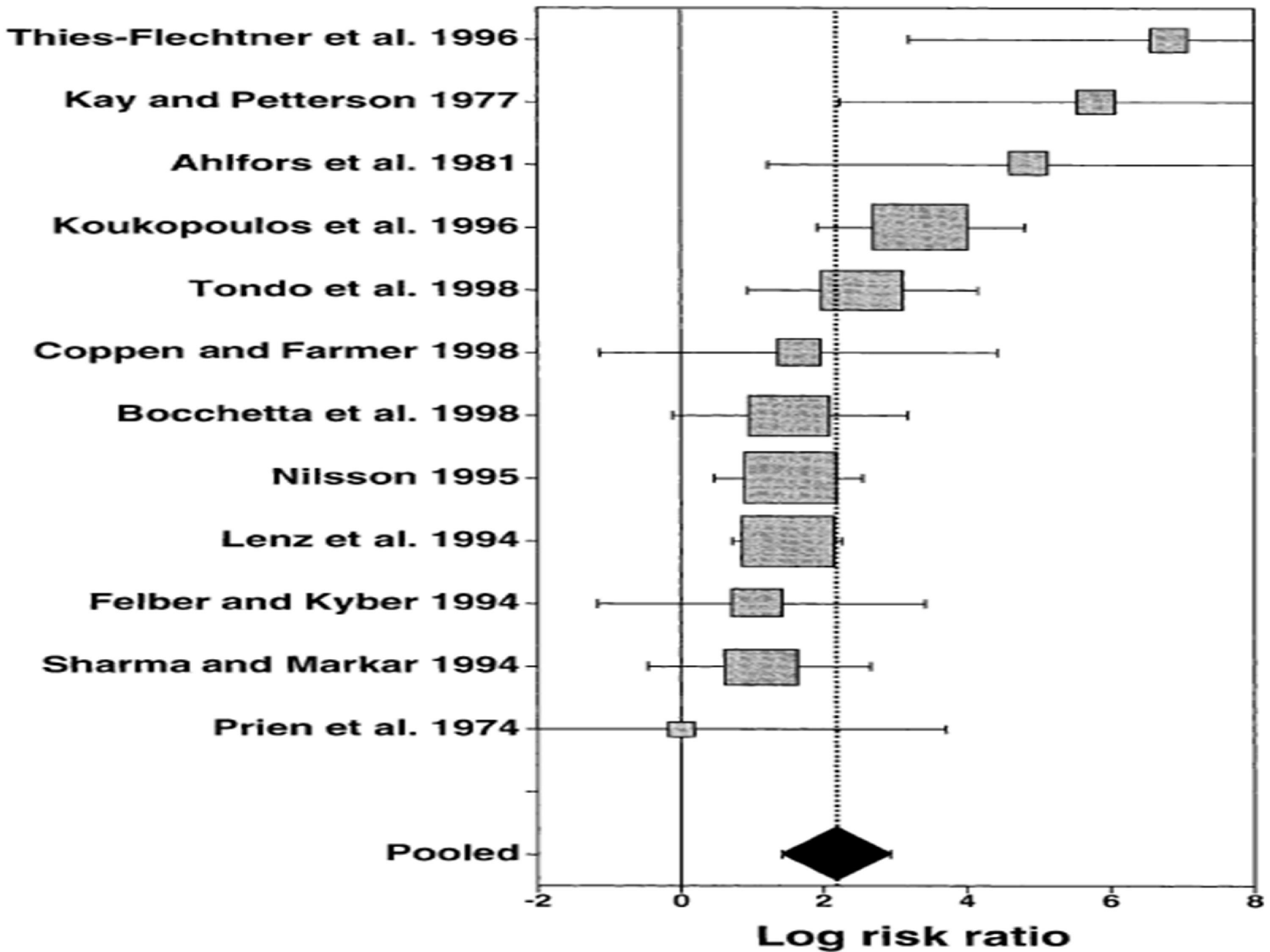
Lithium and suicide reduction:

- patients diagnosed with bipolar manic-depressive, or bipolar subjects admixed with major affective, or schizoaffective disorder subjects

- Among 5647 patients (33 473 patient-years of risk) in 22 studies, suicide was **82% less frequent** during lithium-treatment **(0.159 vs. 0.875 deaths/100 patient-years).**

- The computed risk-ratio in studies with rates on/off lithium was 8.85 (95% CI, 4.12–19.1; P<0.0001).

Tondo L, et al Acta Psychiatr Scand 2001: 104: 163–172.


Thies-Flechtner et al. 1996
Kay and Petterson 1977
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Nilsson 1995
Lenz et al. 1994
Felber and Kyber 1994
Sharma and Markar 1994
Prien et al. 1974
Pooled
-2
0
2
4
6
8
Log risk ratio

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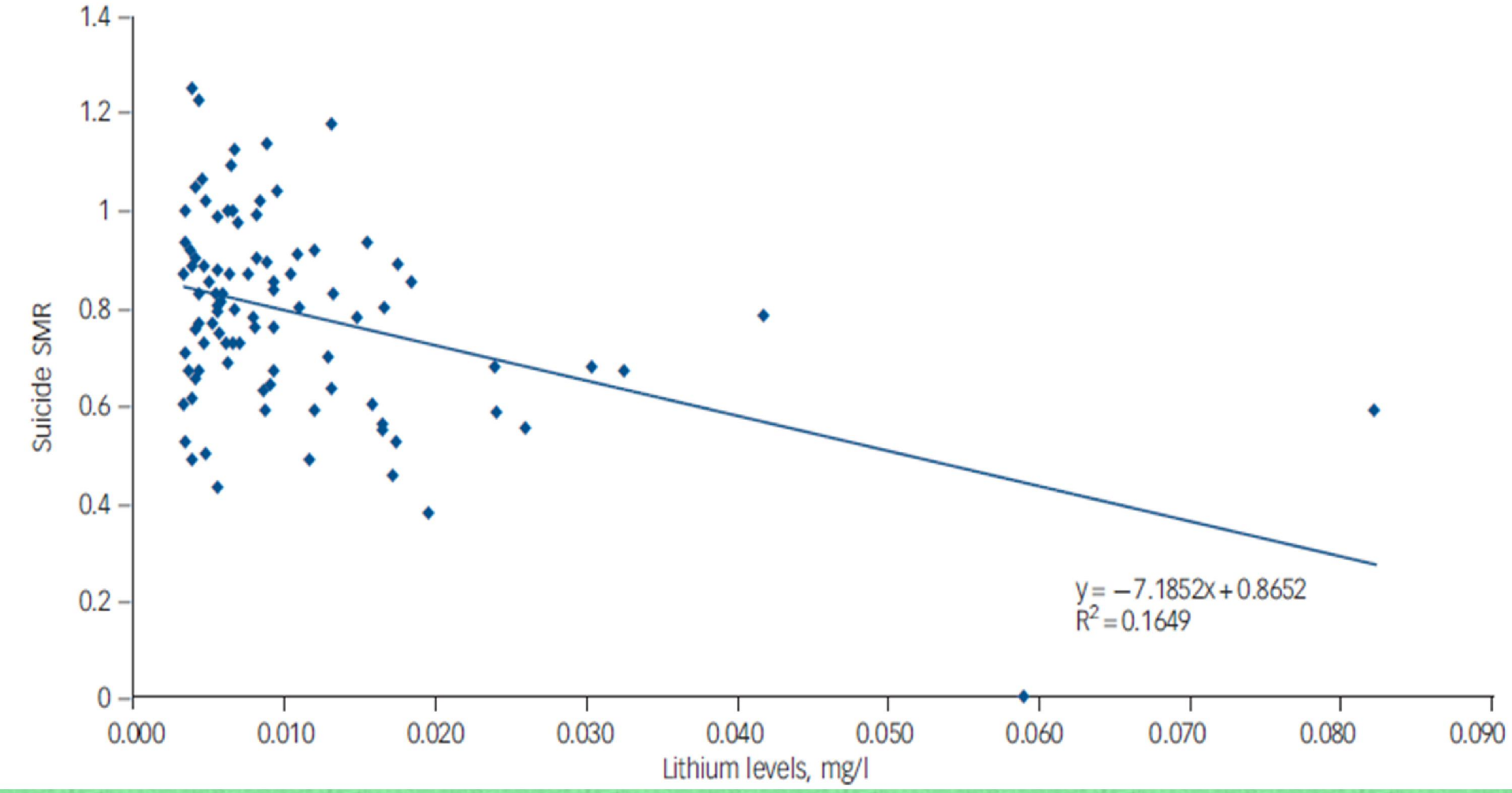
The British Journal of Psychiatry
BJPsych

Lithium in drinking water and suicide mortality

Nestor D. Kapusta, Nilufar Mossaheb, Elmar Etzersdorfer, Gerald Hlavin, Kenneth Thau, Matthäus Willeit, Nicole Praschak-Rieder, Gernot Sonneck and Katharina Leithner-Dziubas

BJP 2011, 198:346-350.
Access the most recent version at DOI: 10.1192/bjp.bp.110.091041

Suicide mortality was significantly correlated with mean lithium levels per district



The univariate regression parameters for the untransformed lithium levels as the independent variable

lithium and dementia:

BJPsych | The British Journal of Psychiatry (2011)
198, 336–337. doi: 10.1192/bjp.bp.110.082875

Editorial

More good news about the magic ion: lithium may prevent dementia†

Allan H. Young

Summary
Lithium is an established treatment for affective disorders with good evidence of antisuicidal properties. Alzheimer's disease rates are relatively reduced in patients with bipolar disorder on lithium and a recent trial of lithium in amnestic minimal cognitive impairment is indicative of potential benefits. This should stimulate further, larger-scale studies.

Declaration of interest
None.

Evidence for the neuroprotective effects of lithium:

- lower risk for incident **dementia**, in particular of **AD**, in bipolar patients after long-term lithium use

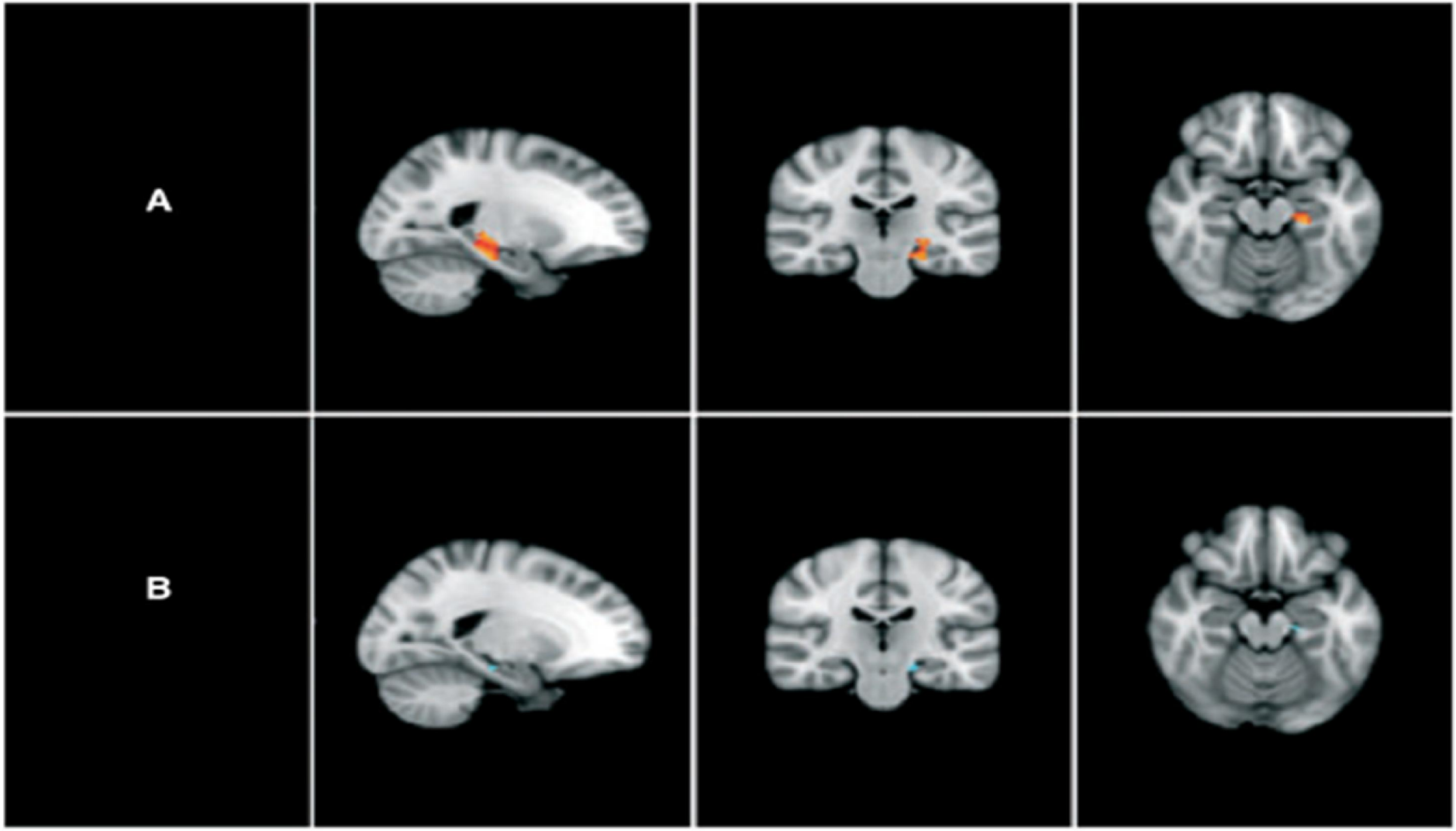
Kessing LV, *Bipolar Disord. 2010;12(1):87–94.*

- Patients on chronic lithium treatment showed lower rates of **cognitive decline** as measured by the Mini-Mental State Examination

Terao, *Neuropsychopharmacol Biol Psychiatry. 2006;30(6):1125–1128*

- Older bipolar patients on chronic lithium treatment had a significantly lower incidence of **AD** compared to those with no lithium exposure.

Nunes PV, *Br J Psychiatry. 2007;190:359–360*



(A) Non-lithium (non-Li) participants with bipolar disorder (BD) versus controls; a **significant hippocampal volume decrease in non-Li relative to control participants** (corrected $p < 0.05$).

(B) Non-Li BD participants versus lithium (Li)-treated BD patients; a trend for hippocampal volume decrease in non-Li relative to Li-treated BD patients (corrected $p < 0.1$)

Conclusion:

- Use lithium to treat mania episodes.
- Use lithium to treat bipolar depressive episodes.
- Use lithium to prevent manic episodes.
- Use lithium to prevent bipolar depressive episodes.
- Use lithium to treat treatment resistant depression.
- Use lithium to prevent suicide.
- Use lithium to prevent Alzheimer disease. ?????

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mesamimi@yahoo.com