IGSLi
International Group for the Study of Lithium Treated Patients

Founded 1988 by Mogens Schou, MD

Tratamiento con litio: Estado del Arte 2017

Educación Médica Continua SOCHITAB

18 Mayo 2017 Hotel Intercontinental Santiago

Dr. Jorge Cabrera

Prof. Adjunto Psiquiatría U. De Chile

Programa Enfermedades Afectivas

Instituto Psiquiátrico Dr. José Horwitz

¿Cómo se acumula el litio en el salar?

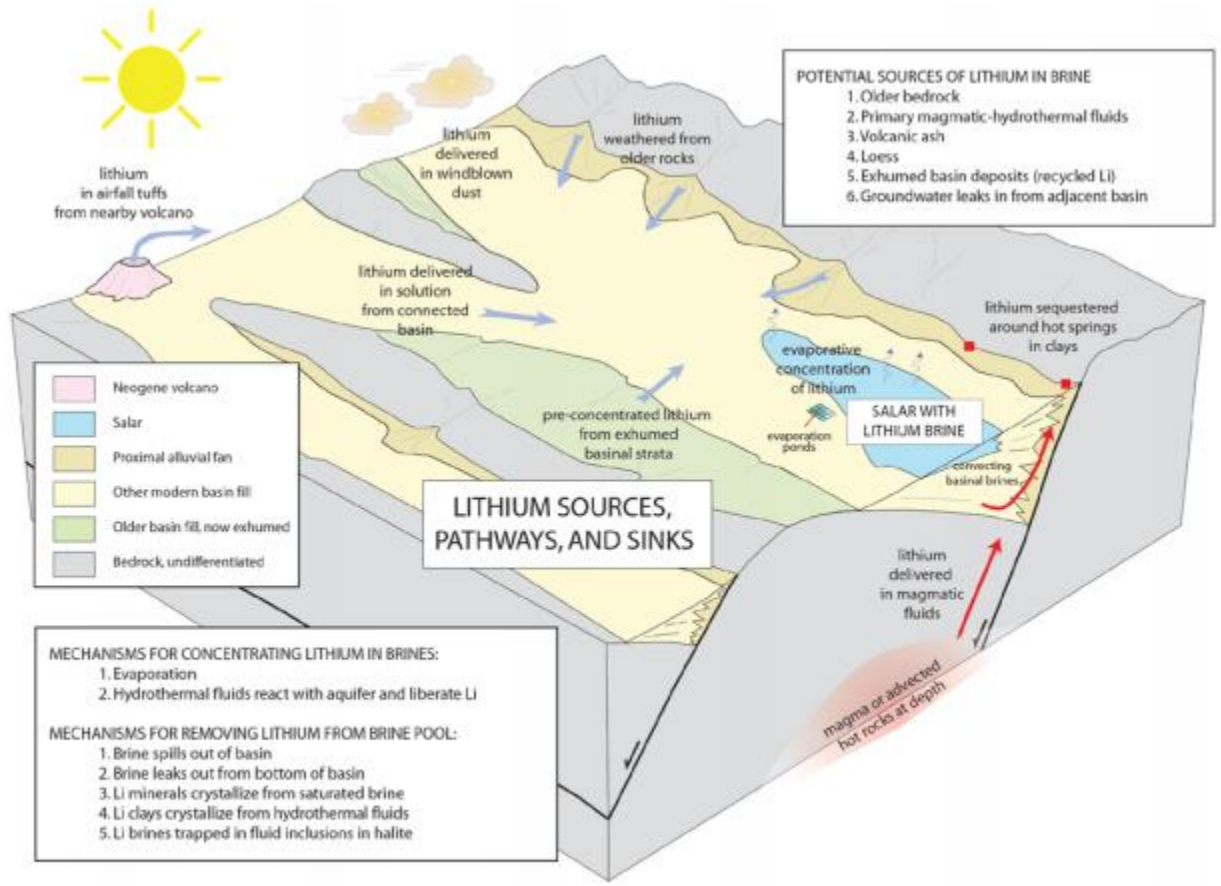
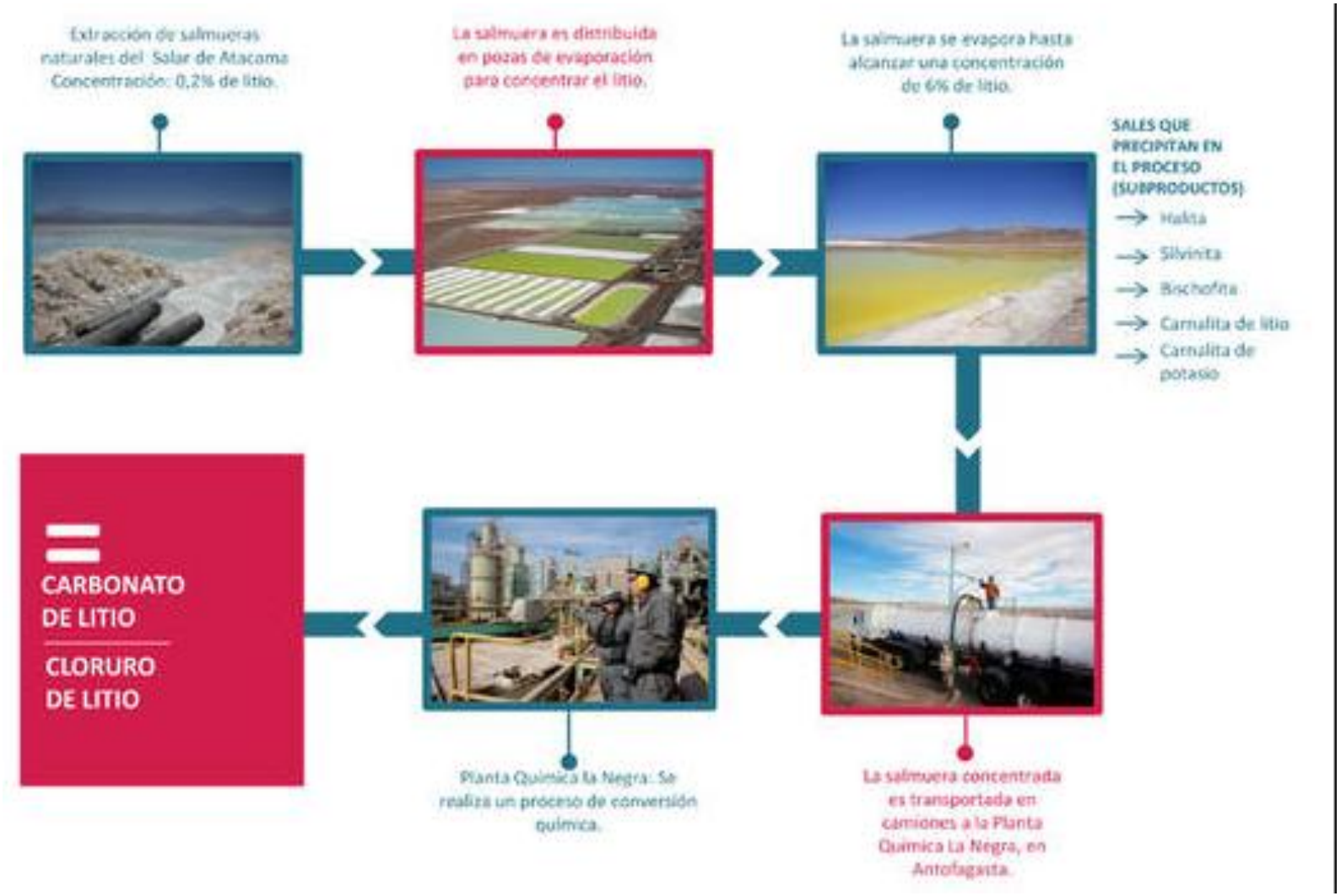


Figure 1. Schematic deposit model for lithium brines showing part of a closed-basin system consisting of interconnected subbasins. The subbasin containing the salar is the lowest.

Extracción de litio desde Salar de Atacama



Un viaje desde el Pasado al Futuro: 68 años de investigación con litio

- Efecto antimaníaco (Cade, 1949)
- Efecto en prevención de recaídas en trastornos del ánimo recurrentes (Schou, Baastrup, 1950s/60s)
- Potenciación en depression resistente (de Montigny, 1981)
- Actividad antisuicida (IGSLi, Müller-Oerlinghausen, Baldessarini (1990s)
- Efecto neuroprotector (Manji, 2000)

Bauer M, Grof P, Müller-Oerlinghausen (Eds.) (2006) Lithium in Neuropsychiatry – The Comprehensive Guide. Informa Healthcare, Abingdon, UK

Litio 2017 – ¿Dónde estamos ahora?

- Efecto antimaníaco (1949/50s) +++
- Efecto preventivo de recaídas en trastornos del ánimo recurrente (desde 1950s/60s) +++
- Depresión bipolar (1970s) +
- Potenciación en depresión (1981) ++(+)
- Efecto antisuicida (1990s) ++
- Efecto neuroprotector (2000) ++básico +clínico

+++ evidencia muy buena; ++ evidencia buena; + evidencia baja

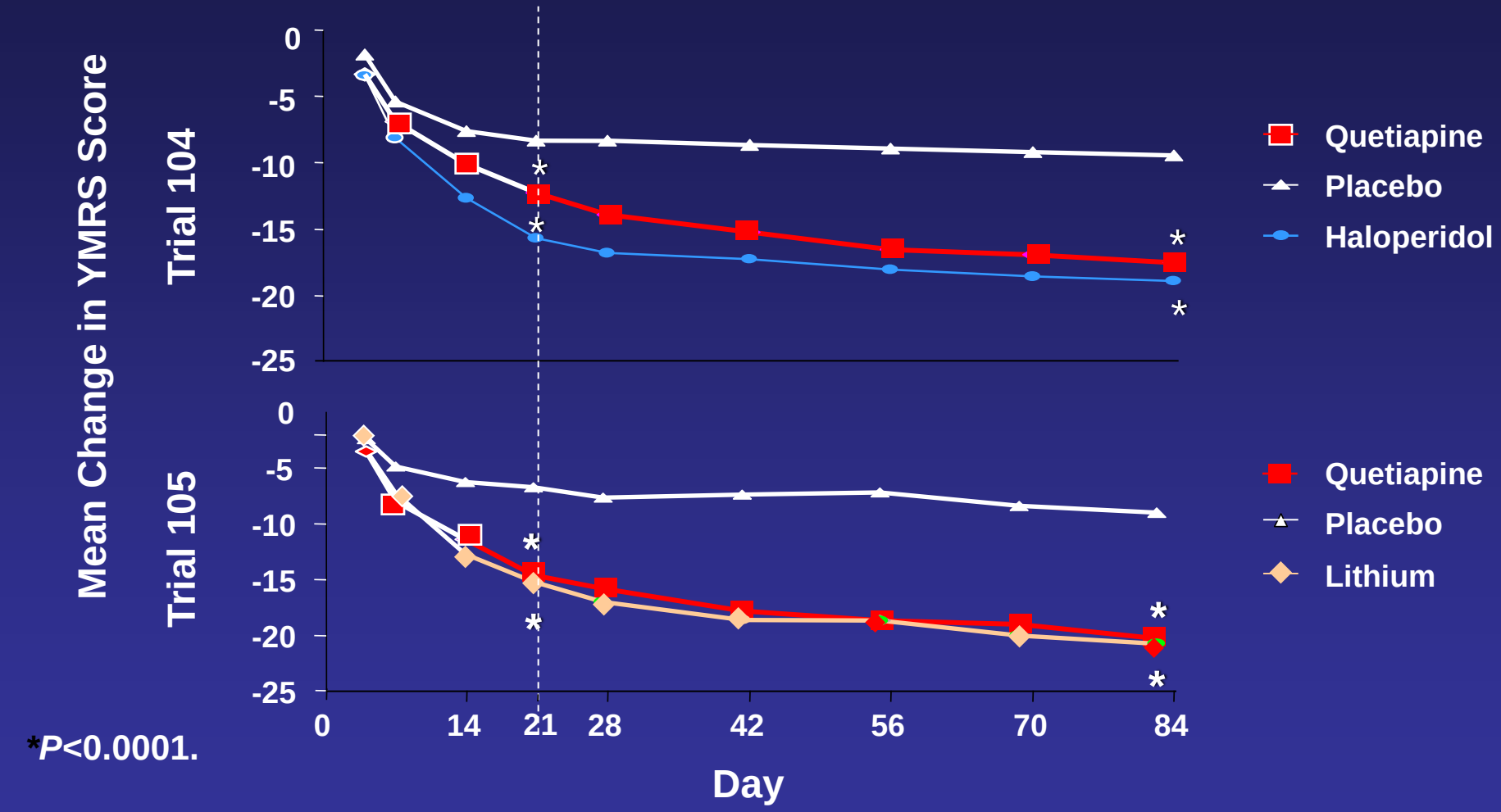
Litio en el tratamiento de la manía

Mogens Schou

- 1920-2005 Aarhus, Dinamarca
- Fundador de la investigación científica en la psiquiatría moderna
- Realizó el primer estudio doble ciego de litio controlado con placebo en manía aguda en 1954, y de prevención de recaídas en 1967
- Lithiumbehandling af manio-depressiv sygdom 1978. Information fur Arzt und Patienten

Schou M et al J Neurol Neurosurg Psychiat 1954; 17:250-260
Baastrup PC, Schou M Arch Gen Psychiat 1967; 16:162-172
Schou M Nervenarzt 1971;42:1-10
Schou Mogens. Rev Chil Neuro Psiquiat 1990; 28: 3-11
Schou M. Rev. Psiquiatría Chil 1991; 8: 669-674

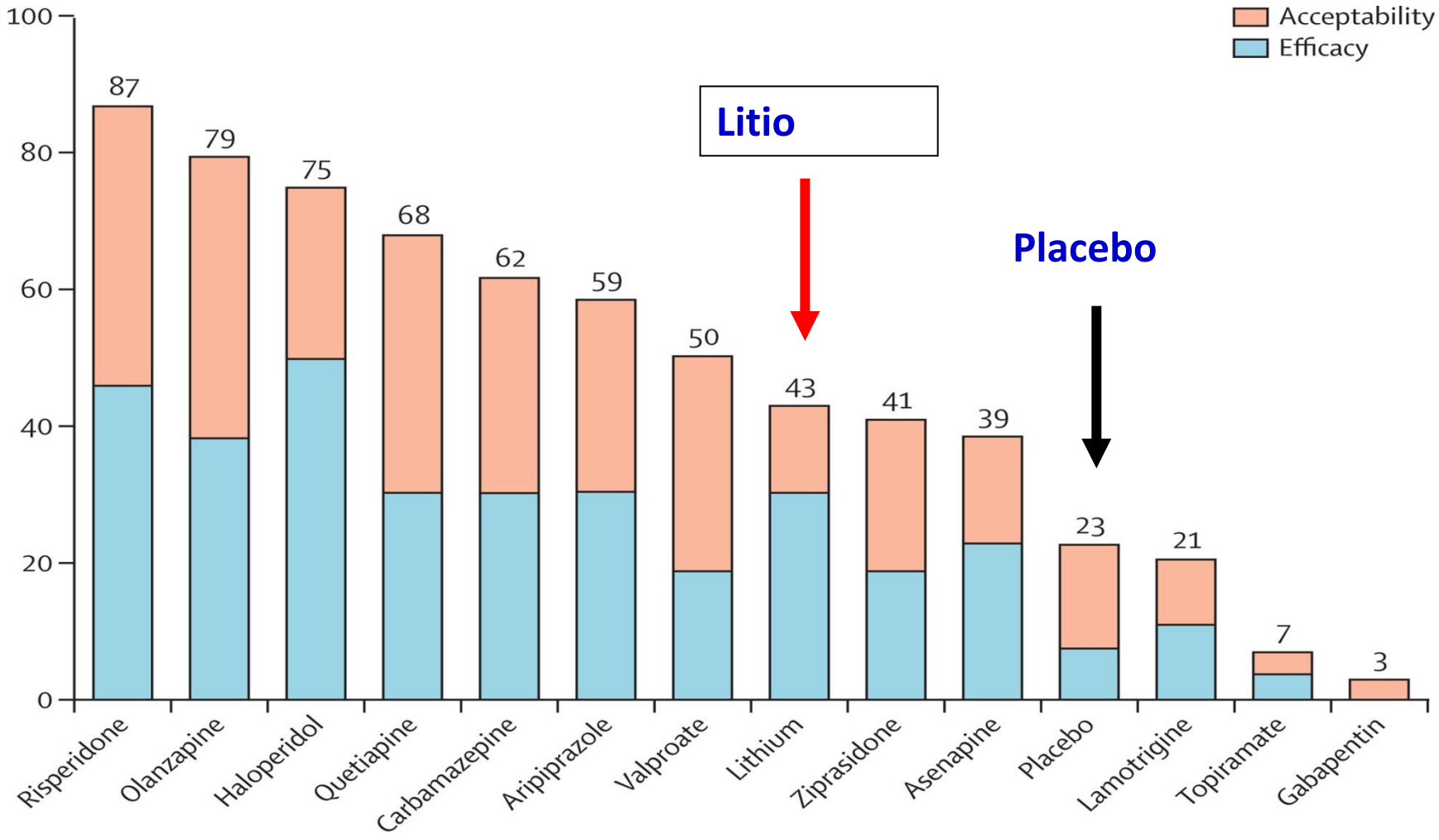
Quetiapine vs placebo en manía versus haloperidol y litio (validadores internos)



*$P<0.0001$.

Jones et al. 2003

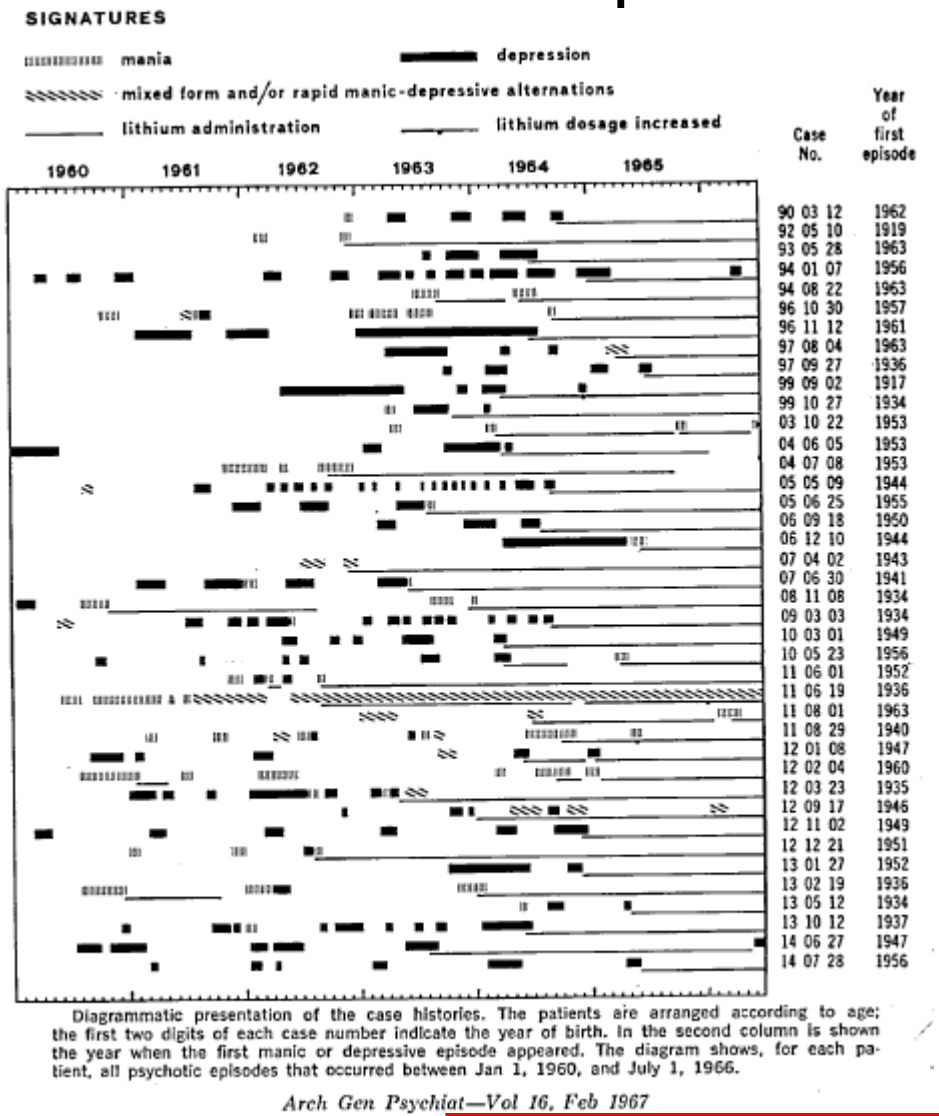
Eficacia comparativa y aceptabilidad de medicamentos en manía aguda: un metaanalisis de múltiples tratamientos



[1]Cipriani et al. Lancet 2011. Published online 17 August 2011

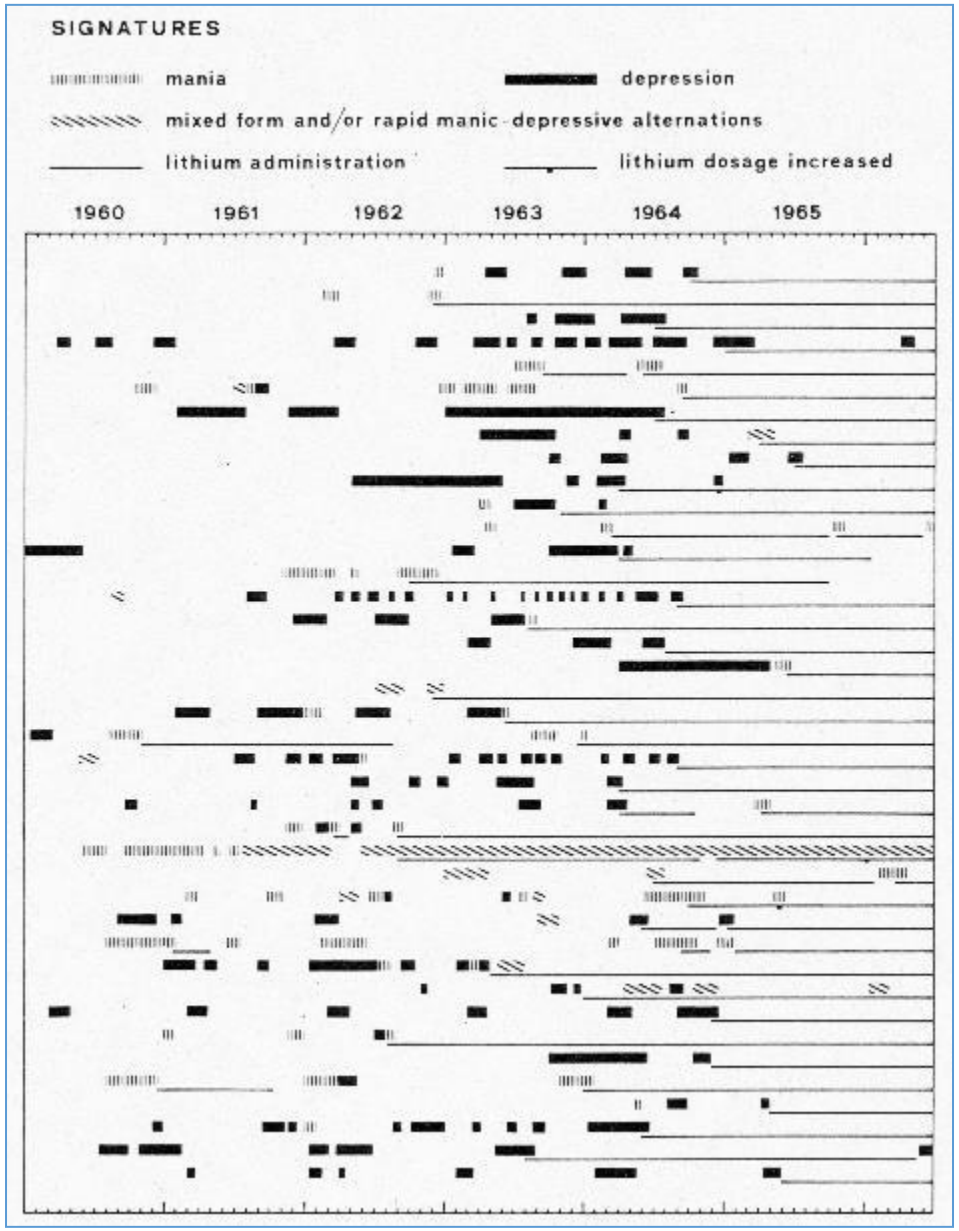
Litio en la prevención de recaídas del trastorno bipolar

Litio en prevención de Recaídas



Diagrammatic presentation of the case histories. The patients are arranged according to age; the first two digits of each case number indicate the year of birth. In the second column is shown the year when the first manic or depressive episode appeared. The diagram shows, for each patient, all psychotic episodes that occurred between Jan 1, 1960, and July 1, 1966.

Arch Gen Psychiat—Vol 16, Feb 1967



Baastrup & Schou, Arch Gen Psychiat Vol 16, Feb 1967
Schou Mogens. Rev Chil Neuro Psiquiat 1990; 28: 3-11

Representación episodios entre Enero 1960 y Julio 1966 Primeros dos dígitos año de nacimiento y 2da col. año primer episodio

Severus *et al. International Journal of Bipolar Disorders* 2014, **2**:15
http://www.journalbipolardisorders.com/content/2/1/15

International Journal of Bipolar Disorders
a SpringerOpen Journal

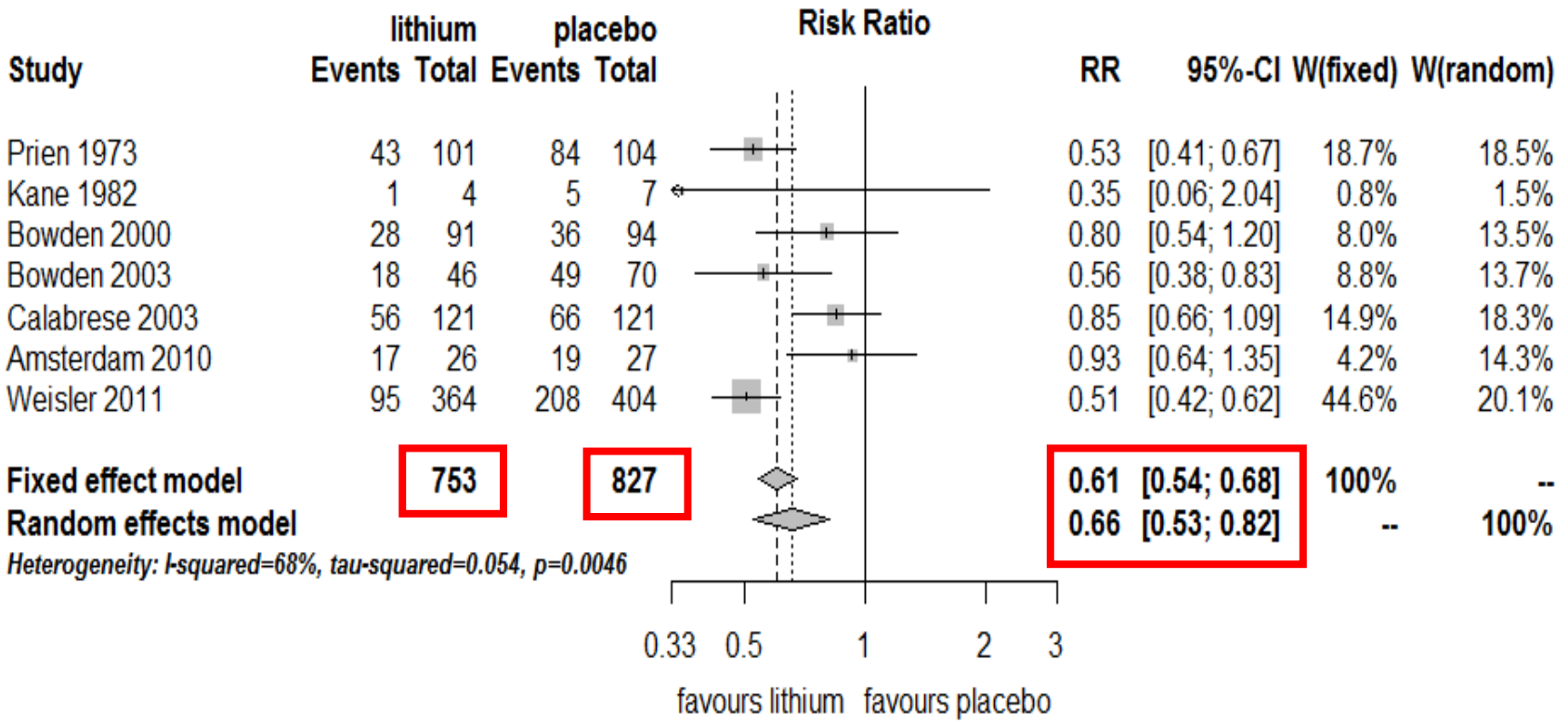
RESEARCH Open Access

Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis

Emanuel Severus[1*†], Matthew J Taylor[2†], Cathrin Sauer[1], Andrea Pfennig[1], Philipp Ritter[1], Michael Bauer[1] and John R Geddes[3]

Severus et al. Int J Bipolar Disord 2014 2:15

Litio en la prevención de recaídas del trastorno bipolar
RCTs controlados con placebo
Prevención de cualquier tipo de episodio (manía y depresión)



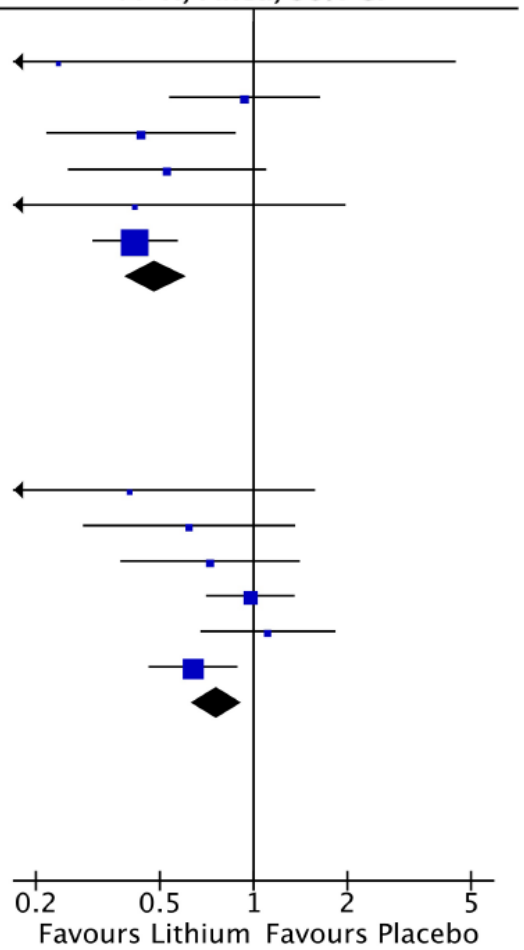
Severus et al. Int J Bipolar Disord 2014 2:15

Litio en la prevención de recaídas en trastorno bipolar

RCTs controlados con Placebo

Prevención de episodios depresivos y maníacos

Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
6.2.2 manic/hypomanic relapse							
Kane 1982	0	10	2	12	1.2%	0.24 [0.01, 4.42]	1982
Bowden 2000	19	91	21	94	11.1%	0.93 [0.54, 1.62]	2000
Lamictal Study 606	8	46	28	70	12.0%	0.43 [0.22, 0.87]	2003
Lamictal Study 605	10	121	19	121	10.2%	0.53 [0.26, 1.08]	2003
Amsterdam 2010	2	26	5	27	2.6%	0.42 [0.09, 1.95]	2010
Trial 144	46	364	123	404	62.8%	0.42 [0.31, 0.56]	2011
Subtotal (95% CI)		**658**		**728**	**100.0%**	**0.48 [0.38, 0.61]**	
Total events	85		198				
Heterogeneity: $Chi^2 = 6.87$, df = 5 (P = 0.23); $I^2 = 27\%$							
Test for overall effect: Z = 6.15 (P < 0.00001)							
6.2.3 depressive relapse							
Kane 1982	2	10	6	12	3.1%	0.40 [0.10, 1.56]	1982
Bowden 2000	9	91	15	94	8.3%	0.62 [0.29, 1.34]	2000
Lamictal Study 606	10	46	21	70	9.3%	0.72 [0.38, 1.39]	2003
Lamictal Study 605	46	121	47	121	26.4%	0.98 [0.71, 1.35]	2003
Amsterdam 2010	15	26	14	27	7.7%	1.11 [0.68, 1.82]	2010
Trial 144	49	364	85	404	45.2%	0.64 [0.46, 0.88]	2011
Subtotal (95% CI)		**658**		**728**	**100.0%**	**0.76 [0.63, 0.93]**	
Total events	131		188				
Heterogeneity: $Chi^2 = 6.90$, df = 5 (P = 0.23); $I^2 = 28\%$							
Test for overall effect: Z = 2.75 (P = 0.006)							



Test for subgroup differences: $Chi^2 = 8.89$, df = 1 (P = 0.003), $I^2 = 88.7\%$

Severus et al. Int J Bipolar Disord 2014 2:15

Estudio BALANCE prevención de episodios pacientes bipolares comparó litio, valproato y combinación

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Articles

Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial

The BALANCE investigators and collaborators‡

- Método
- 330 pacientes mayores de 16 años fueron reclutados en 41 sitios en Inglaterra, Francia, USA e Italia y asignados en forma aleatoria a monoterapia con litio (litemia entre 0;4-1.0 mmol/l, n=110); monoterapia con valproato (750-1250mg, n=110), o ambos agentes combinados (n=110), después de una fase inicial de 4-8 semanas de prueba de tolerancia a la combinación.
- La randomización se hizo con un programa computacional y los participantes y los investigadores fueron informados del grupo asignado. Diseño no enriquecido
- La medida de evaluación primaria fue el inicio de una nueva intervención para tratar un nuevo episodio del ánimo

Geddes, JR, Goodwin GM al et *Lancet Psychiatry* 2010; 375:385-395

Resultados

	Combination (n=110)*	Lithium (n=110)	Valproate semisodium (n=110)
New intervention for mood episode			
Number of patients with event (%)	59 (54%)	65 (59%)	76 (69%)
HR (95% CI)	1·00	0·82 (0·58–1·17)	0·59 (0·42–0·83)
p value	..	0·27	0·0023
Adjusted HR† (95% CI)	1·00	0·80 (0·57–1·15)	0·57 (0·40–0·80)
p value	..	0·23	0·0014
Hospital admission			
Number of patients with event (%)	16 (15%)	22 (20%)	25 (23%)
HR (95% CI)	1·00	0·78 (0·39–1·33)	0·59 (0·32–1·11)
p value	..	0·28	0·10
Adjusted HR† (95% CI)	1·00	0·72 (0·38–1·38)	0·51 (0·27–0·96)
p value	..	0·32	0·0383
New drug treatment for mood episode			
Number of patients with event (%)	58 (53%)	64 (58%)	75 (68%)
HR (95% CI)	1·00	0·82 (0·57–1·17)	0·60 (0·42–0·84)
p value	..	0·27	0·0031
Adjusted HR† (95% CI)	1·00	0·80 (0·56–1·14)	0·57 (0·40–0·80)
p value	..	0·21	0·0014
New treatment for mania			
Number of patients with event (%)	30 (27%)	40 (36%)	49 (45%)
HR (95% CI)	1·00	0·67 (0·42–1·08)	0·51 (0·32–0·80)
p value	..	0·10	0·0034
Adjusted HR† (95% CI)	1·00	0·66 (0·41–1·07)	0·50 (0·31–0·79)
p value	..	0·09	0·0030
New treatment for depression			
Number of patients with event (%)	39 (35%)	35 (32%)	50 (45%)
HR (95% CI)	1·00	1·12 (0·71–1·76)	0·70 (0·46–1·07)
p value	..	0·63	0·10
Adjusted HR† (95% CI)	1·00	1·06 (0·67–1·67)	0·71 (0·46–1·08)
p value	..	0·81	0·11

(Continues on next page)

Geddes, JR, Goodwin GM al et *Lancet Psychiatry* 2010; 375:385-395

Interpretación de los resultados por los autores

- Para los pacientes con trastorno bipolar I con indicación de terapia de mantenimiento, tanto la combinación de litio más valproato como la monoterapia con litio, son más probable que prevengan las recaídas que la monoterapia con valproato.
- Estos beneficios parecen ser independientes de la severidad de la enfermedad y se mantienen por dos años.
- El estudio BALANCE no pudo confiablemente confirmar ni refutar un beneficio de la combinación comparado con el litio

Geddes, JR, Goodwin GM al et *Lancet Psychiatry* 2010; 375:385-395

Metaanálisis tratamiento de mantenimiento del trastorno bipolar

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis

Tomofumi Miura, Hisashi Noma, Toshi A Furukawa, Hiroshi Mitsuyasu, Shiro Tanaka, Sarah Stockton, Georgia Salanti, Keisuke Motomura, Satomi Shimano-Katsuki, Stefan Leucht, Andrea Cipriani, John R Geddes, Shigenobu Kanba

Summary

Background Lithium is the established standard in the long-term treatment of bipolar disorder, but several new drugs have been assessed for this indication. We did a network meta-analysis to investigate the comparative efficacy and tolerability of available pharmacological treatment strategies for bipolar disorder.

Methods We systematically searched Embase, Medline, PreMedline, PsycINFO, and the Cochrane Central Register of Controlled Trials for randomised controlled trials published before June 28, 2013, that compared active treatments for bipolar disorder (or placebo), either as monotherapy or as add-on treatment, for at least 12 weeks. The primary outcomes were the number of participants with recurrence of any mood episode, and the number of participants who discontinued the trial because of adverse events. We assessed efficacy and tolerability of bipolar treatments using a random-effects network meta-analysis within a Bayesian framework.

Findings We screened 114 potentially eligible studies and identified 33 randomised controlled trials, published between 1970 and 2012, that examined 17 treatments for bipolar disorder (or placebo) in 6846 participants. Participants assigned to all assessed treatments had a significantly lower risk of any mood relapse or recurrence compared with placebo, except for those assigned to aripiprazole (risk ratio [RR] 0·62, 95% credible interval [CrI] 0·38–1·03), carbamazepine (RR 0·68, 0·44–1·06), imipramine (RR 0·95, 0·66–1·36), and paliperidone (RR 0·84, 0·56–1·24). Lamotrigine and placebo were significantly better tolerated than carbamazepine (lamotrigine, RR 5·24, 1·07–26·32; placebo, RR 3·60, 1·04–12·94), lithium (RR 3·76, 1·13–12·66; RR 2·58, 1·33–5·39), or lithium plus valproate (RR 5·95, 1·02–33·33; RR 4·09, 1·01–16·96).

Interpretation Although most of the drugs analysed were more efficacious than placebo and generally well tolerated, differences in the quality of evidence and the side-effect profiles should be taken into consideration by clinicians and patients. In view of the efficacy in prevention of both manic episode and depressive episode relapse or recurrence and the better quality of the supporting evidence, lithium should remain the first-line treatment when prescribing a relapse-prevention drug in patients with bipolar disorder, notwithstanding its tolerability profile.

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Lancet Psychiatry 2014; 1: 351–59

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See Comment page 321

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- 33 estudios controlados
- Realizados entre 1970 y 2012
- 6876 pacientes
- 17 tratamientos trastorno bipolar

Miura T et al et *Lancet Psychiatry* 2014; 1:351-359

Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis

Tomofumi Miura, Hisashi Noma, Toshi A Furukawa, Hiroshi Mitsuyasu, Shiro Tanaka, Sarah Stockton, Georgia Salanti, Keisuke Motomura, Satomi Shimano-Katsuki, Stefan Leucht, Andrea Cipriani, John R Geddes, Shigenobu Kanba

Lancet Psychiatry 2014; 1: 351–59

Published Online September 16, 2014

Summary

Background Lithium is the established standard in the long-term treatment of bipolar disorder, but several new drugs have been assessed for this indication. We did a network meta-analysis to investigate the comparative efficacy and tolerability of available pharmacological treatment strategies for bipolar disorder.

Tolerability (discontinuation due to adverse event; 95% CrI) | Comparison | Efficacy (any mood episode relapse; 95% CrI)

ARP+VPA	0·04 (0·00–1·64)	0·07 (0·00–2·01)	0·13 (0·00–3·56)	0·04 (0·00–1·01)	0·15 (0·00–5·77)	0·02 (0·00–1·88)	0·06 (0·00–1·49)	0·04 (0·00–1·69)	0·12 (0·01–2·40)	0·09 (0·00–2·87)	0·04 (0·00–1·33)	0·23 (0·01–7·41)	0·14 (0·00–4·88)	0·06 (0·00–9·80)	0·16 (0·00–4·28)	0·11 (0·00–4·93)	1·15 (0·01–>100)
0·71 (0·22–2·27)	LIT+OXC	1·82 (0·24–12·20)	3·24 (0·44–23·26)	0·97 (0·11–8·77)	3·80 (0·33–44·39)	0·45 (0·01–19·81)	1·54 (0·26–9·16)	0·85 (0·05–13·79)	2·95 (0·34–25·00)	2·23 (0·24–19·23)	1·10 (0·14–8·78)	5·78 (0·65–50·00)	3·37 (0·29–40·00)	1·41 (0·02 to 134·69)	3·98 (0·60–27·00)	2·65 (0·17–45·65)	28·57 (0·51–>100)
0·58 (0·22–1·55)	0·81 (0·40–1·63)	OLZ	1·78 (0·64–6·13)	0·53 (0·13–2·67)	2·08 (0·35–13·89)	0·25 (0·01–7·58)	0·84 (0·40–2·19)	0·47 (0·05–4·43)	1·62 (0·42–7·58)	1·22 (0·36–4·55)	0·61 (0·17–2·47)	3·17 (0·84–13·63)	1·85 (0·33–11·76)	0·77 (0·01–48·91)	2·18 (0·95–6·13)	1·45 (0·15–14·28)	15·52 (0·43–>100)
0·55 (0·20–1·49)	0·77 (0·38–1·57)	0·96 (0·66–1·34)	QTP	0·30 (0·07–1·38)	1·17 (0·18–7·13)	0·14 (0·00–4·24)	0·48 (0·19–1·14)	0·26 (0·03–2·25)	0·91 (0·21–4·02)	0·69 (0·16–2·79)	0·34 (0·09–1·34)	1·78 (0·44–6·99)	1·04 (0·19–5·71)	0·44 (0·01–27·06)	1·23 (0·57–2·73)	0·82 (0·09–7·77)	8·74 (0·23–>100)
0·55 (0·20–1·49)	0·77 (0·37–1·64)	0·96 (0·62–1·48)	1·00 (0·64–1·60)	LIT+VPA	3·91 (0·45–31·69)	0·46 (0·01–16·35)	1·58 (0·45–5·37)	0·88 (0·08–10·06)	3·03 (0·83–11·11)	2·29 (0·36–13·51)	1·14 (0·22–5·61)	5·95 (1·02–33·33)	3·46 (0·43–27·78)	1·45 (0·02–>100)	4·09 (1·01–16·96)	2·72 (0·24–31·22)	29·41 (0·65–>100)
0·55 (0·18–1·62)	0·76 (0·33–1·77)	0·95 (0·54–1·66)	0·99 (0·56–1·77)	0·99 (0·52–1·86)	ARP+LTG	0·12 (0·00–5·05)	0·41 (0·07–2·24)	0·22 (0·02–3·13)	0·78 (0·10–6·29)	0·59 (0·08–4·41)	0·29 (0·04–2·17)	1·52 (0·47–5·13)	0·89 (0·09–8·70)	0·37 (0·00–31·25)	1·05 (0·20–5·84)	0·70 (0·05–10·42)	7·46 (0·23–>100)
0·46 (0·16–1·32)	0·65 (0·30–1·41)	0·81 (0·49–1·30)	0·84 (0·51–1·39)	0·84 (0·48–1·44)	0·85 (0·43–1·65)	LIT+IMP	3·41 (0·12–89·12)	1·89 (0·04–94·44)	6·54 (0·20–>100)	4·95 (0·15–>100)	2·45 (0·07–73·77)	12·82 (0·37–>100)	7·46 (0·18–>100)	3·13 (0·10–84·61)	8·82 (0·31–>100)	5·87 (0·11–>100)	62·50 (0·43–>100)
0·47 (0·18–1·21)	0·65 (0·34–1·26)	0·81 (0·62–1·03)	0·84 (0·64–1·13)	0·84 (0·58–1·21)	0·85 (0·51–1·44)	1·00 (0·66–1·53)	LIT	0·55 (0·07–4·64)	1·92 (0·60–6·37)	1·45 (0·39–5·32)	0·72 (0·25–2·04)	3·76 (1·13–12·66)	2·19 (0·41–11·90)	0·92 (0·02–54·05)	2·58 (1·33–5·29)	1·72 (0·20–15·00)	18·52 (0·54–>100)
0·46 (0·16–1·36)	0·65 (0·28–1·49)	0·80 (0·46–1·38)	0·84 (0·48–1·46)	0·84 (0·44–1·56)	0·85 (0·41–1·70)	1·00 (0·52–1·93)	0·99 (0·59–1·66)	ARP	3·46 (0·30–38·46)	2·62 (0·23–29·41)	1·30 (0·12–13·89)	6·80 (0·65–66·67)	3·95 (0·33–47·62)	1·66 (0·02–>100)	4·67 (0·64–34·26)	3·11 (0·16–55·56)	33·33 (0·61–>100)
0·46 (0·18–1·16)	0·64 (0·32–1·29)	0·79 (0·56–1·13)	0·83 (0·58–1·23)	0·83 (0·58–1·19)	0·84 (0·47–1·50)	0·98 (0·61–1·62)	0·98 (0·77–1·28)	0·99 (0·56–1·78)	VPA	0·76 (0·12–4·29)	0·38 (0·08–1·79)	1·96 (0·36–10·76)	1·14 (0·14–8·79)	0·48 (0·01–34·54)	1·35 (0·35–5·32)	0·90 (0·08–10·83)	9·61 (0·23–>100)
0·45 (0·17–1·24)	0·63 (0·31–1·32)	0·79 (0·55–1·10)	0·82 (0·56–1·22)	0·82 (0·50–1·32)	0·83 (0·46–1·49)	0·98 (0·58–1·64)	0·97 (0·70–1·34)	0·98 (0·55–1·75)	0·99 (0·66–1·47)	RisLAI	0·50 (0·09–2·66)	2·59 (0·50–14·35)	1·51 (0·22–11·13)	0·63 (0·01–42·48)	1·78 (0·54–6·41)	1·19 (0·09–14·18)	12·70 (0·32–>100)
0·43 (0·15–1·22)	0·60 (0·27–1·30)	0·74 (0·45–1·19)	0·77 (0·46–1·27)	0·77 (0·44–1·32)	0·78 (0·40–1·51)	0·92 (0·51–1·65)	0·91 (0·66–1·38)	0·92 (0·47–1·78)	0·93 (0·56–1·51)	0·94 (0·55–1·57)	CBZ	5·24 (1·07–26·32)	3·05 (0·44–21·74)	1·28 (0·02–83·33)	3·60 (1·04–12·94)	2·40 (0·22–27·78)	25·64 (0·62–>100)
0·38 (0·14–1·01)	0·53 (0·27–1·06)	0·66 (0·48–0·89)	0·69 (0·50–0·96)	0·68 (0·44–1·04)	0·69 (0·43–1·10)	0·81 (0·51–1·31)	0·81 (0·64–1·02)	0·82 (0·47–1·41)	0·83 (0·59–1·15)	0·83 (0·59–1·19)	0·89 (0·56–1·44)	LTG	0·58 (0·08–4·20)	0·24 (0·00–17·78)	0·69 (0·21–2·35)	0·46 (0·04–5·18)	4·90 (0·19–>100)
0·34 (0·12–0·99)	0·48 (0·22–1·05)	0·60 (0·37–0·94)	0·63 (0·39–1·01)	0·62 (0·36–1·08)	0·63 (0·33–1·20)	0·74 (0·42–1·34)	0·74 (0·48–1·13)	0·75 (0·39–1·41)	0·76 (0·46–1·22)	0·76 (0·47–1·25)	0·81 (0·45–1·47)	0·91 (0·58–1·43)	PAL	0·42 (0·01–31·12)	1·18 (0·26–5·47)	0·79 (0·06–10·78)	8·41 (0·19–>100)
0·30 (0·11–0·84)	0·43 (0·20–0·89)	0·53 (0·34–0·80)	0·55 (0·36–0·86)	0·55 (0·33–0·90)	0·56 (0·30–1·03)	0·66 (0·43–1·00)	0·65 (0·46–0·92)	0·66 (0·36–1·21)	0·67 (0·43–1·01)	0·67 (0·42–1·06)	0·72 (0·42–1·23)	0·80 (0·54–1·20)	0·88 (0·51–1·50)	IMP	2·82 (0·05–>100)	1·88 (0·02–>100)	20·00 (0·09–>100)
0·29 (0·11–0·76)	0·40 (0·21–0·79)	0·50 (0·39–0·63)	0·52 (0·40–0·68)	0·52 (0·35–0·77)	0·53 (0·32–0·88)	0·62 (0·40–0·96)	0·62 (0·53–0·72)	0·62 (0·38–1·03)	0·63 (0·47–0·83)	0·64 (0·48–0·85)	0·68 (0·44–1·06)	0·76 (0·62–0·94)	0·84 (0·56–1·24)	0·95 (0·66–1·36)	PLB	0·67 (0·08–5·62)	7·14 (0·21–>100)
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	FLX	10·75 (0·19–>100)
..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	VPA+LTG

***Figure 3*: Efficacy (any mood episode relapse or recurrence) and tolerability (discontinuation due to adverse event) according to the network meta-analysis**
Comparisons between treatments should be read from left to right and the estimates are in the cell in common between the column-defining treatment and the row-defining treatment. Drugs are reported in order of efficacy (any mood episode relapse or recurrence) ranking estimated by SUCRA (surface under the cumulative ranking curve). For tolerability, a risk ratio (RR) lower than 1·00 favours the row-defining treatment. For any mood episode relapse or recurrence, a RR lower than 1·00 favours the column-defining treatment. Significant results are in bold. The RR of drug B over drug A can be obtained by calculating the inverse of the RR of drug A over drug B. ARP=aripiprazole. CBZ=carbamazepine. CrI=credible interval. FLX=fluoxetine. IMP=imipramine. LIT=lithium. LTG=lamotrigine. OLZ=olanzapine. QTP=quetiapine. OXC=oxcarbazepine. PAL=paliperidone. PLB=placebo. RisLAI= risperidone longacting injection. VPA=valproate.

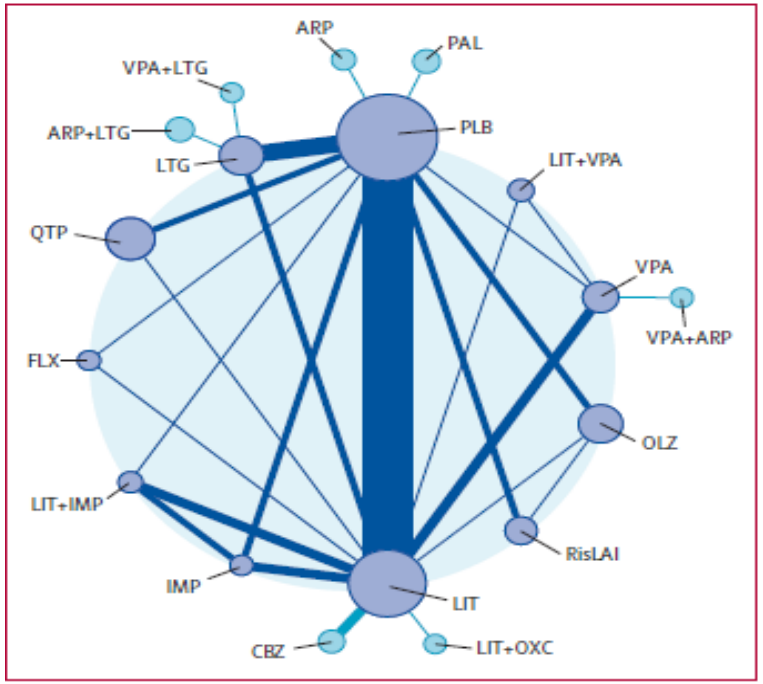
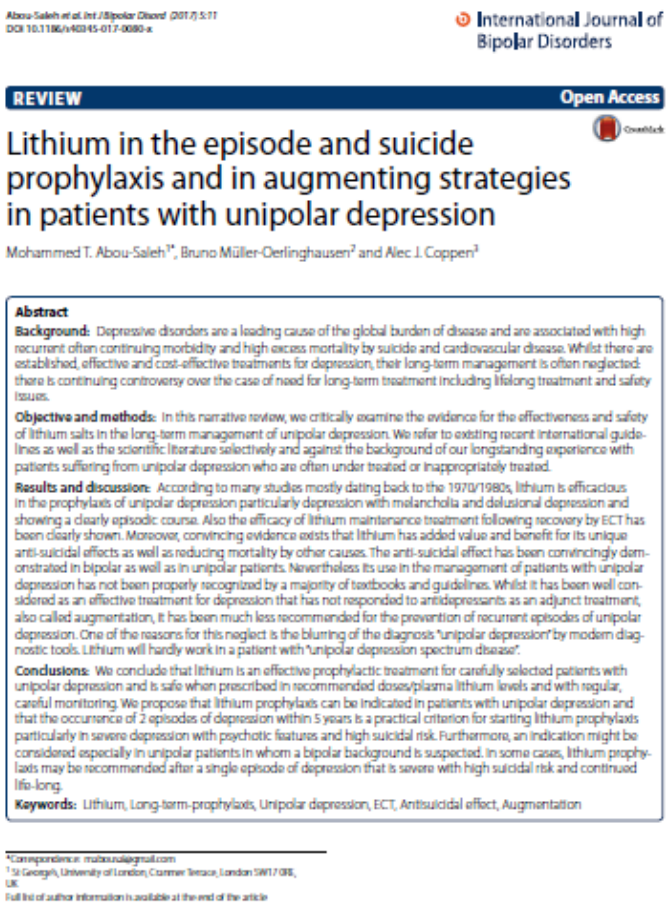


***Figure 2*: Network of all eligible comparisons for the network meta-analysis**
Each node (circle) corresponds to a drug included in the analysis, with the size proportional to the number of participants randomly assigned to that drug. Each line represents direct comparisons between drugs, with the width of the lines proportional to the number of trials comparing each pair of treatments. The treatment nodes in the closed-loop network are purple, whereas single-standing nodes and their connections are light blue. All the monotherapies, except for ARP, PAL, and CBZ, were compared with at least two other treatment nodes (ie, were in the closed-loop network). 12 (50%) of 24 comparisons for the primary efficacy outcome and seven (29%) of 24 comparisons for tolerability were done in more than one trial. ARP=aripiprazole. CBZ=carbamazepine. FLX=fluoxetine. IMP=imipramine. LIT=lithium. LTG=lamotrigine. OLZ=olanzapine. OXC=oxcarbazepine. PAL=paliperidone. PLB=placebo. QTP=quetiapine. RisLAI=risperidone longacting injection. VPA=valproate.

Miura T et al *Lancet Psychiatry* 2014; 1:351-359

Litio en prevención de recaídas depresión unipolar

Litio en la prevención de recaídas en depresión unipolar



Abou-Saleh et al. Int J Bipolar Disord (2017) 5:11
DOI 10.1186/s40345-017-0080-x

International Journal of Bipolar Disorders

REVIEW Open Access

Lithium in the episode and suicide prophylaxis and in augmenting strategies in patients with unipolar depression

Mohammed T. Abou-Saleh[1*], Bruno Müller-Oerlinghausen[2] and Alec J. Coppen[3]

Abstract

Background: Depressive disorders are a leading cause of the global burden of disease and are associated with high recurrent often continuing morbidity and high excess mortality by suicide and cardiovascular disease. Whilst there are established, effective and cost-effective treatments for depression, their long-term management is often neglected: there is continuing controversy over the case of need for long-term treatment including lifelong treatment and safety issues.

Objective and methods: In this narrative review, we critically examine the evidence for the effectiveness and safety of lithium salts in the long-term management of unipolar depression. We refer to existing recent international guidelines as well as the scientific literature selectively and against the background of our longstanding experience with patients suffering from unipolar depression who are often under treated or inappropriately treated.

Results and discussion: According to many studies mostly dating back to the 1970/1980s, lithium is efficacious in the prophylaxis of unipolar depression particularly depression with melancholia and delusional depression and showing a clearly episodic course. Also the efficacy of lithium maintenance treatment following recovery by ECT has been clearly shown. Moreover, convincing evidence exists that lithium has added value and benefit for its unique anti-suicidal effects as well as reducing mortality by other causes. The anti-suicidal effect has been convincingly demonstrated in bipolar as well as in unipolar patients. Nevertheless its use in the management of patients with unipolar depression has not been properly recognized by a majority of textbooks and guidelines. Whilst it has been well considered as an effective treatment for depression that has not responded to antidepressants as an adjunct treatment, also called augmentation, it has been much less recommended for the prevention of recurrent episodes of unipolar depression. One of the reasons for this neglect is the blurring of the diagnosis "unipolar depression" by modern diagnostic tools. Lithium will hardly work in a patient with "unipolar depression spectrum disease".

Conclusions: We conclude that lithium is an effective prophylactic treatment for carefully selected patients with unipolar depression and is safe when prescribed in recommended doses/plasma lithium levels and with regular, careful monitoring. We propose that lithium prophylaxis can be indicated in patients with unipolar depression and that the occurrence of 2 episodes of depression within 5 years is a practical criterion for starting lithium prophylaxis particularly in severe depression with psychotic features and high suicidal risk. Furthermore, an indication might be considered especially in unipolar patients in whom a bipolar background is suspected. In some cases, lithium prophylaxis may be recommended after a single episode of depression that is severe with high suicidal risk and continued life-long.

Keywords: Lithium, Long-term-prophylaxis, Unipolar depression, ECT, Antisuicidal effect, Augmentation

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Abou-Saleh M, Muller-Oerlinghausen B, Coppen A al et *Int J. Bipolar Disord (2017) 5:11*

Litio en potenciación de depresión 1980-90

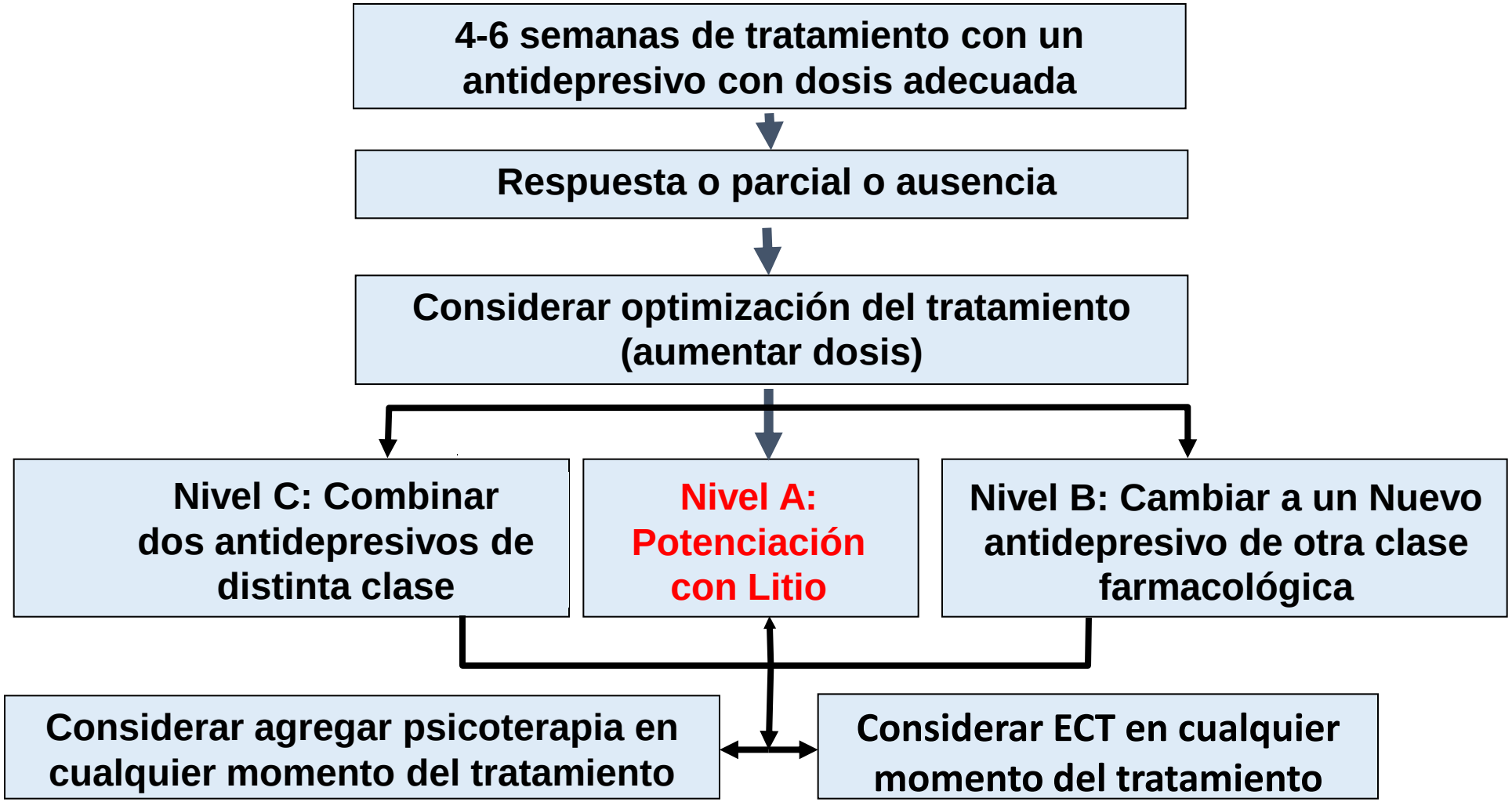
De Montigny y otros

Treinta años de potenciación con litio

- Gran cantidad de data apoya esta indicación
- 10 estudios doble-ciego controlado con placebo
- 8 estudios controlados con comparador
- 13 estudios abiertos prospectivos
- Numerosos series clínicas y reporte casos clínicos

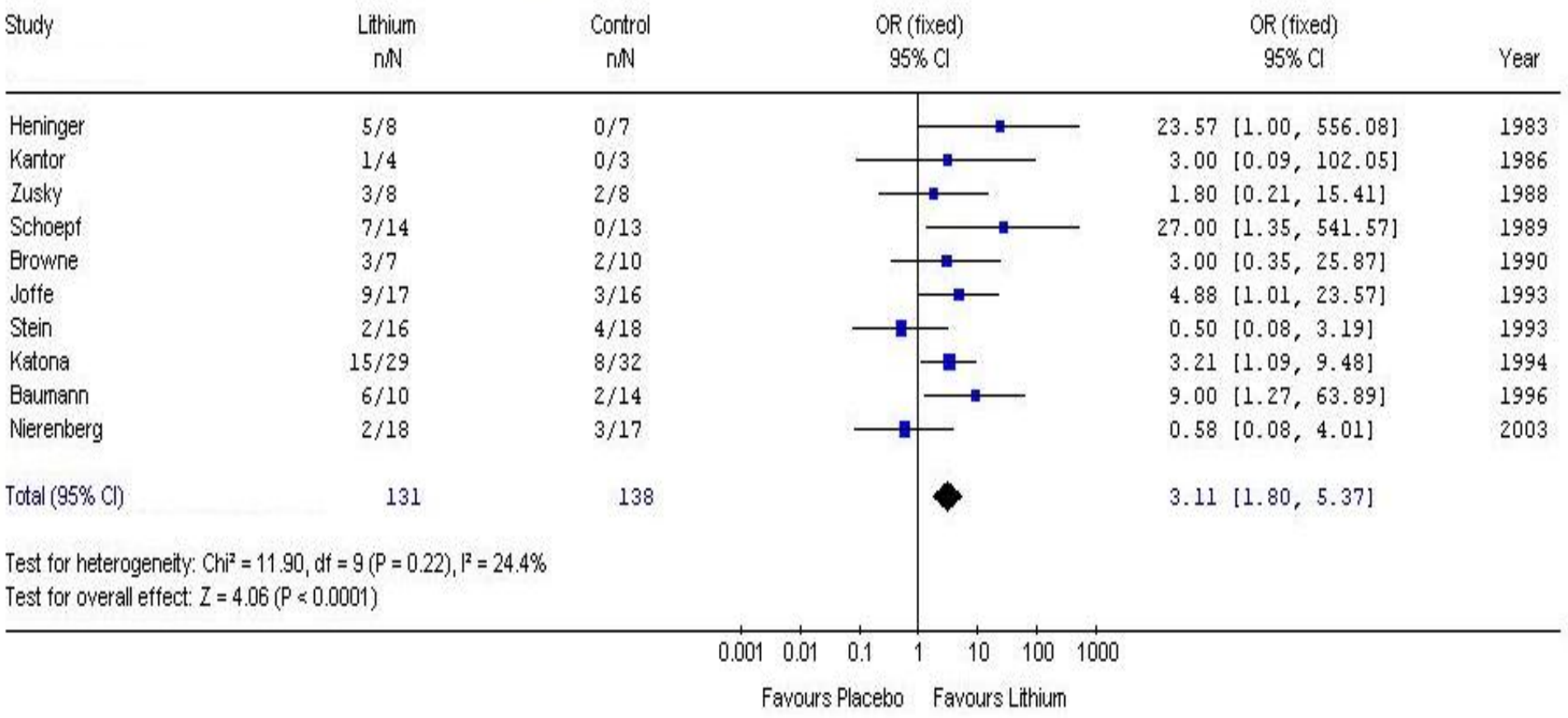
Bauer M et al. The acute antidepressive effects of lithium: from monotherapy to augmentation. en: Bauer M, Grof P, Müller-Oerlinghausen (Eds.) (2006) Lithium in Neuropsychiatry – The Comprehensive Guide. Informa Healthcare, Abingdon, UK, pp. 109-128

Estrategia de Tratamiento para la Depresión: Guía WFSBP



Bauer et al 2002/2007

Metaanalisis: Potenciación con Litio en Depresión Refractaria Refractory (10 RCTs)



Crossley and Bauer, 2005

Estrategia de Potenciación para la Depresión Refractaria – Guía WFSBP Update 2013

	Nivel-Evidencia
• Litio	A
• Triyodotironina (T3)	B
• Antipsicóticos Atípicos	A/B/C
• (Quetiapina, Aripiprazole)	
• L-Thyroxine	C
• Anticonvulsantes	C
• Estrogenos	C
• Agonistas de Dopamina	C
• Psicoestimulantes	C

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 (2013) *Bauer, Whybrow, Angst, Möller World J Biol Psychiatr*

Double-Blind, Placebo-Controlled Trial of the Use of Lithium to Augment Antidepressant Medication in Continuation Treatment of Unipolar Major Depression

Michael Bauer, Ph.D., M.D.

Tom Bschor, M.D.

Dieter Kunz, M.D.

Anne Berghöfer, M.D.

Andreas Ströhle, M.D.

Bruno Müller-Oerlinghausen, M.D.

Objective: Use of lithium to augment antidepressant medication has been shown to be beneficial in the acute treatment of depression. The authors examined the efficacy of lithium augmentation in the continuation treatment of unipolar major depressive disorder.

Method: Thirty patients with a refractory major depressive episode who had responded to acute lithium augmentation during an open 6-week study participated in a randomized, parallel-group, double-blind, placebo-controlled trial of lithium augmentation during continuation treatment. After a 2–4-week stabilization period following remission, patients were randomly assigned to receive either lithium or placebo for a 4-month period. Antidepressant medication was continued throughout the study.

Results: Relapses (including one suicide) occurred in seven (47%) of the 15 patients who received placebo in addition to antidepressants. None (0%) of the 14 patients who received lithium augmentation with antidepressants suffered a relapse during the double-blind phase of the study. Five of the seven relapsing patients in the placebo group developed a depressive episode, and the other two experienced a manic episode.

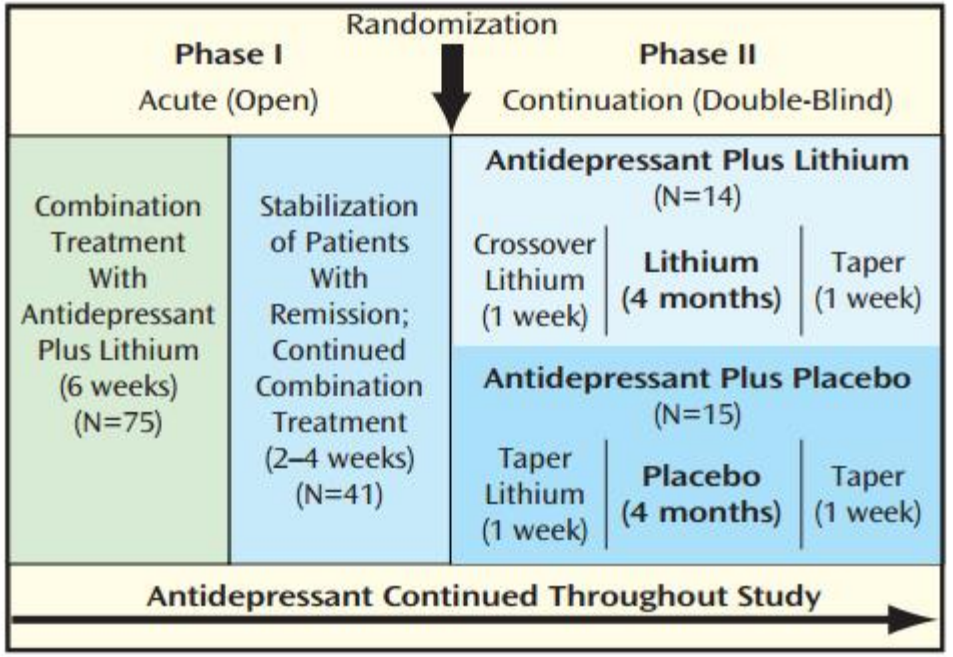
Conclusions: Lithium augmentation in the continuation phase of treatment of unipolar major depressive disorder effectively protects patients against a relapse. Patients who respond to lithium augmentation should be maintained on lithium augmentation for a minimum of 6 months or even longer.

(Am J Psychiatry 2000; 157:1429–1435)

Bauer M, Schor T, Kunz D. Muller-Oerlinghausen *Am J Pschiatry 2000; 157: 1429-1435*

LITHIUM WITH ANTIDEPRESSANTS

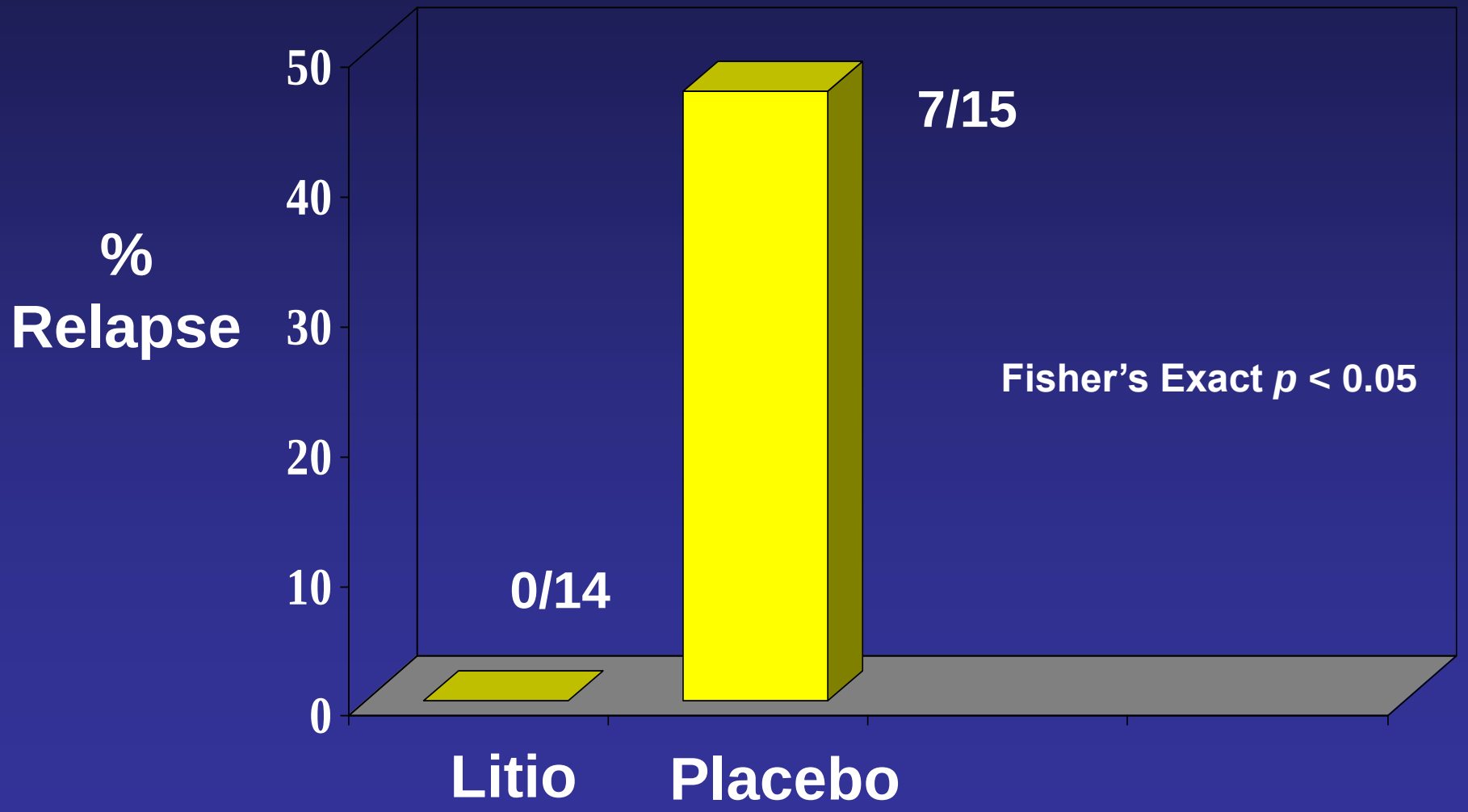
FIGURE 1. Phases of a Study on the Effectiveness of Lithium Augmentation of Antidepressant Medication in the Continuation Treatment of Depressed Patients[a]



[a] Mean period of treatment with antidepressants before phase I addition of lithium was 46.1 days (SD=29.7). Eleven of the 41 patients who experienced remission declined to participate in the continuation phase, and one additional patient dropped out before the end of the study.

Bauer M, Schor T, Kunz D. Muller-Oerlinghausen *Am J Pschiatry 2000; 157: 1429-1435*

Continuación de Potenciación con Litio Previene Recaídas

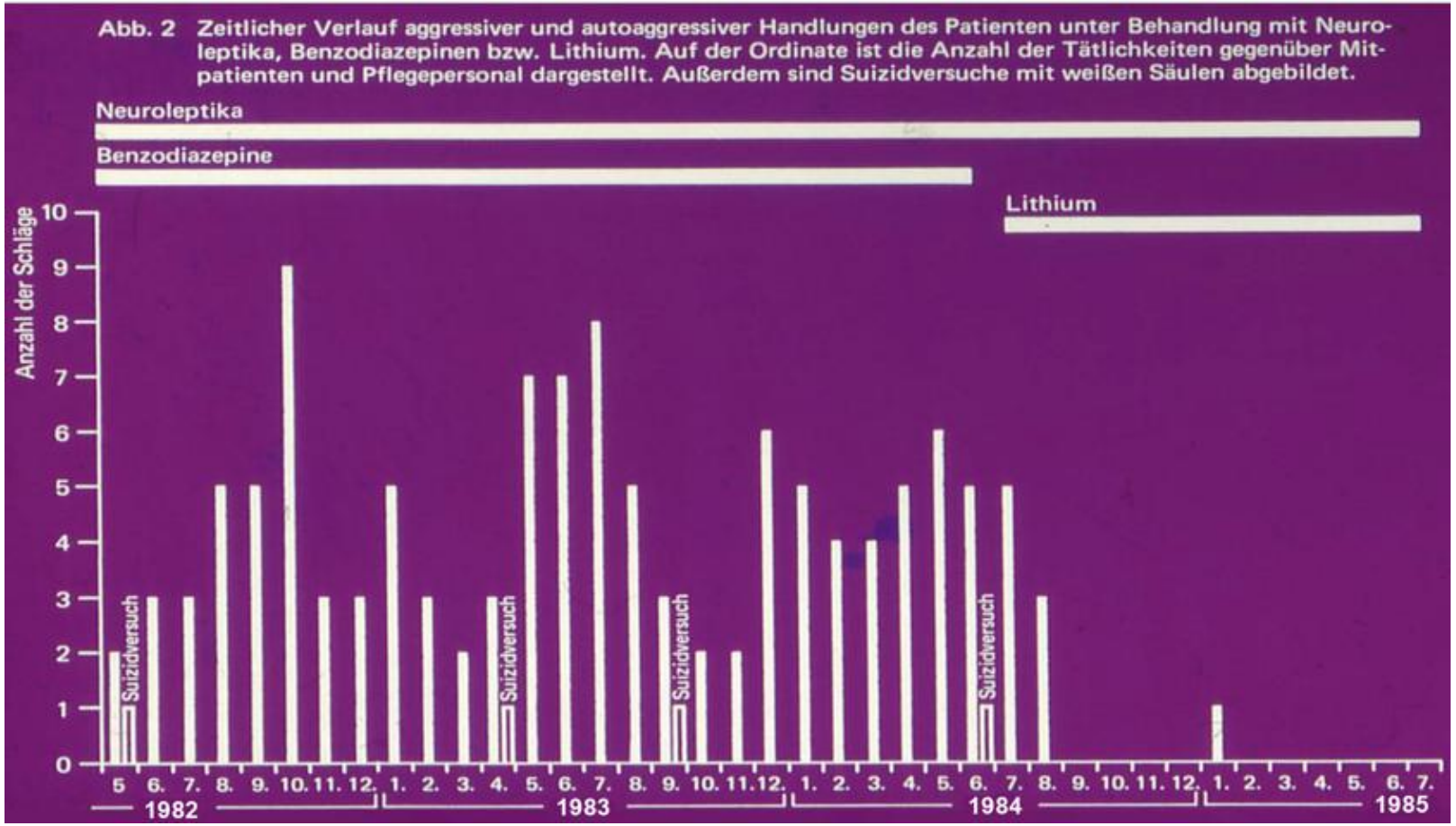


Bauer et al. (2000) Am J. Psychiatry 157:1429-1435

Efecto antisuicida del Litio

- Prof.Dr. Bruno Müller-Oerlinghausen

Disminución de auto y heteroagresión en paciente con Esquizofrenia tratado con litio



Cabrera J, Korner W, Muller-Oerlinghausen B. Nervenarzt 1985; 56:154-159

Efecto Antisuicida del Litio

- Müller-Oerlinghausen (IGSLI) 1992, 2001: 827 pacientes con trastornos del ánimo tratados con litio. Dramático efecto antisuicida – mortalidad no difirió comparada con población sana.
- Confirmación del efecto antisuicida:
  Baldessarini y Tondo 1997,
  Bocchetta et al 1998,
  Lewitzka et al 2015
- Litio posee un poderoso efecto antisuicida más allá del efecto estabilizador . Presente aún en no respondedores a litio(Müller-Oerlinghausen 2001) y en pacientes depresivos sin trastorno bipolar (Lauterbach et al 2008)

Suicidio e Intento de Suicidio en Pacientes Bipolares Randomizados a Litio o Carbamazepina (n=378)

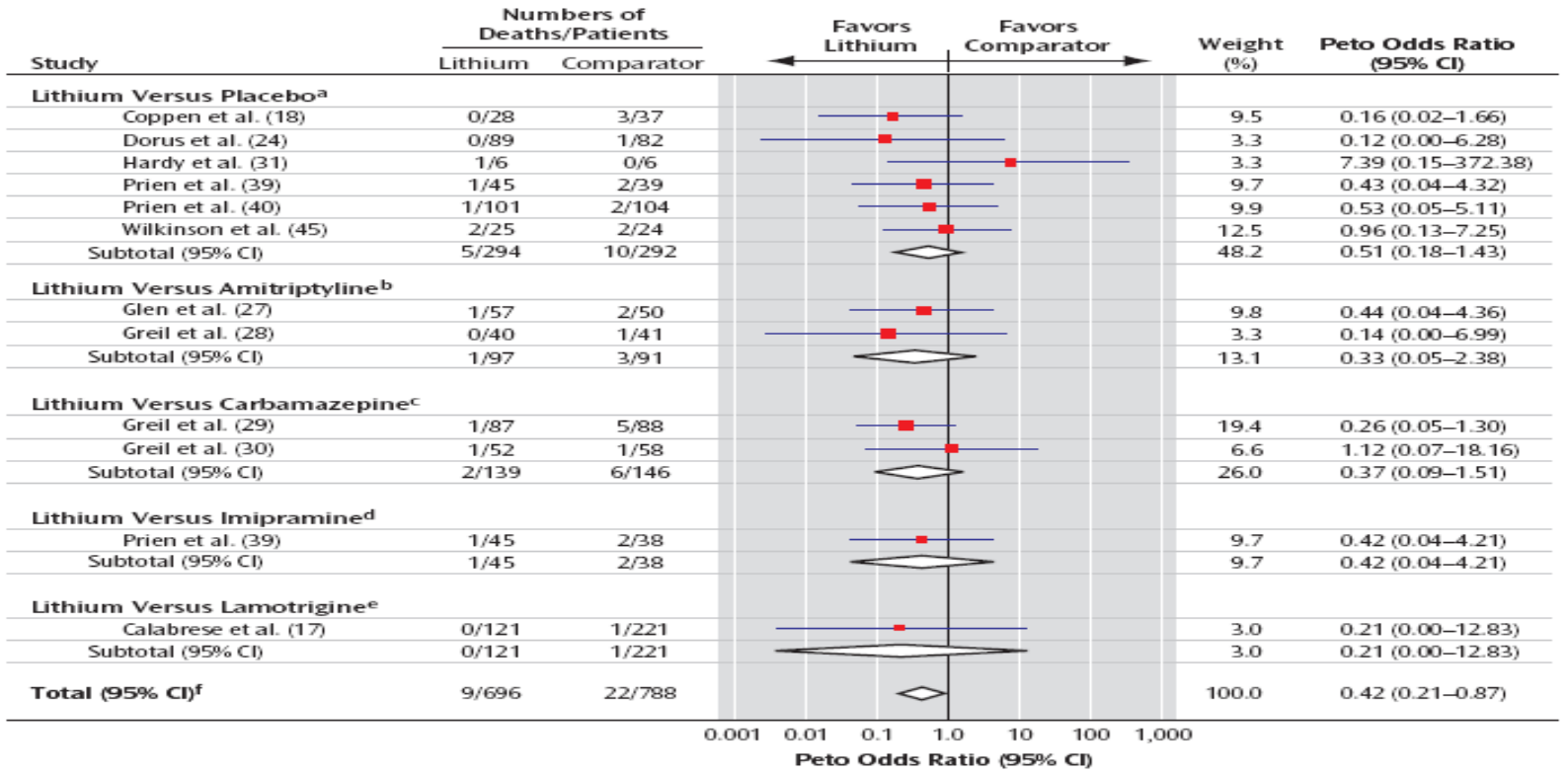
(Estudio Prospectivo-Randomizado 2.5 años)

	Suicidio	Intento suicidio	Total conducta suicida
Litio	0	0	0
Carbamazepina	5	4	9

Thies-Flechtner K, Muller-Oerlinghausen B .*Pharmacopsychiatry 1996 ; 29: 103-107*

Litio en Prevención de Suicidio Revisión Sistemática de Estudios Randomizados

FIGURE 4. Forest Plot Showing Meta-Analysis of Deaths From All Causes in Randomized Trials Comparing Lithium With Placebo or Active Comparators



Study	Numbers of Deaths/Patients: Lithium	Numbers of Deaths/Patients: Comparator	Weight (%)	Peto Odds Ratio (95% CI)
Lithium Versus Placebo[a]				
Coppen et al. (18)	0/28	3/37	9.5	0.16 (0.02–1.66)
Dorus et al. (24)	0/89	1/82	3.3	0.12 (0.00–6.28)
Hardy et al. (31)	1/6	0/6	3.3	7.39 (0.15–372.38)
Prien et al. (39)	1/45	2/39	9.7	0.43 (0.04–4.32)
Prien et al. (40)	1/101	2/104	9.9	0.53 (0.05–5.11)
Wilkinson et al. (45)	2/25	2/24	12.5	0.96 (0.13–7.25)
Subtotal (95% CI)	5/294	10/292	48.2	0.51 (0.18–1.43)
Lithium Versus Amitriptyline[b]				
Glen et al. (27)	1/57	2/50	9.8	0.44 (0.04–4.36)
Greil et al. (28)	0/40	1/41	3.3	0.14 (0.00–6.99)
Subtotal (95% CI)	1/97	3/91	13.1	0.33 (0.05–2.38)
Lithium Versus Carbamazepine[c]				
Greil et al. (29)	1/87	5/88	19.4	0.26 (0.05–1.30)
Greil et al. (30)	1/52	1/58	6.6	1.12 (0.07–18.16)
Subtotal (95% CI)	2/139	6/146	26.0	0.37 (0.09–1.51)
Lithium Versus Imipramine[d]				
Prien et al. (39)	1/45	2/38	9.7	0.42 (0.04–4.21)
Subtotal (95% CI)	1/45	2/38	9.7	0.42 (0.04–4.21)
Lithium Versus Lamotrigine[e]				
Calabrese et al. (17)	0/121	1/221	3.0	0.21 (0.00–12.83)
Subtotal (95% CI)	0/121	1/221	3.0	0.21 (0.00–12.83)
Total (95% CI)[f]	9/696	22/788	100.0	0.42 (0.21–0.87)

[a] Test for heterogeneity: χ^2=3.60, df=5, p=0.61; test for overall effect: z=1.28, p=0.20.
[b] Test for heterogeneity: χ^2=0.25, df=1, p=0.62; test for overall effect: z=1.10, p=0.27.
[c] Test for heterogeneity: χ^2=0.80, df=1, p=0.37; test for overall effect: z=1.38, p=0.17.
[d] Test for overall effect: z=0.74, p=0.46.
[e] Test for overall effect: z=0.74, p=0.46.
[f] Test for heterogeneity: χ^2=4.98, df=11, p=0.93; test for overall effect: z=2.35, p=0.02.

Cipriani A, Pretty H, Hawton K, Geddes JR Am J Psychiatry 2005; 162:1805 1819

Disminución del Riesgo e Intentos de Suicidio: Meta-Análisis

Review Article

Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review

Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord 2006; 8: 625–639. © Blackwell Munksgaard, 2006

Objective: To update and extend comparisons of rates of suicides and suicide attempts among patients with major affective disorders with versus without long-term lithium treatment.

Methods: Broad searching yielded 45 studies providing rates of suicidal acts during lithium treatment, including 34 also providing rates without lithium treatment. We scored study quality, tested between-study variance, and examined suicidal rates on versus off lithium by meta-analytic methods to determine risk ratios (RRs) and 95% confidence intervals (CI).

Results: In 31 studies suitable for meta-analysis, involving a total of 85,229 person-years of risk-exposure, the overall risk of suicides and attempts was five times less among lithium-treated subjects than among those not treated with lithium (RR = 4.91, 95% CI 3.82–6.31, $p < 0.0001$). Similar effects were found with other meta-analytic methods, as well as for completed versus attempted suicide, and for bipolar versus major mood disorder patients. Studies with higher quality ratings, including randomized, controlled trials, involved shorter exposures with somewhat lesser lithium superiority. Omitting one very large study or those involving lithium-discontinuation had little effect on the results. The incidence-ratio of attempts-to-suicides increased 2.5 times with lithium-treatment, indicating *reduced lethality* of suicidal acts. There was no indication of bias toward reporting positive findings, nor were outcomes significantly influenced by publication-year or study size.

Conclusions: Risks of completed and attempted suicide were consistently lower, by approximately 80%, during treatment of bipolar and other major affective disorder patients with lithium for an average of 18 months. These benefits were sustained in randomized as well as open clinical trials.

Ross J Baldessarini[a,b], Leonardo Tondo[b,c], Paula Davis[a], Maurizio Pompili[b,d], Frederick K Goodwin[a] and John Hennen[a,b]

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Key words: bipolar disorder – lithium – major affective disorders – meta-analysis – suicide

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Long-term lithium treatment has been associated with reduced risk of suicide and suicide attempts in patients with bipolar disorder (BPD) or other major affective disorders (1–8). In a previous meta-analysis that included only 22 studies reporting on completed suicides, we found an 82%

RJB consults or engages in collaborative research with companies that produce medicines used to treat major psychiatric disorders (Eli Lilly & Co., IFI SpA, Janssen, JDS, Novartis). LT has served as a consultant to IFI SpA. MP has received research support from Eli Lilly & Co. JH had received grant or contract support from Eli Lilly & Co., JDS and Novartis. PD and JH received contract support from JDS Pharmaceuticals, a manufacturer of lithium products that helped in the preparation of an FDA petition on this topic. FKG has no reported conflict of interest. No author holds any equity positions in pharmaceutical corporations.

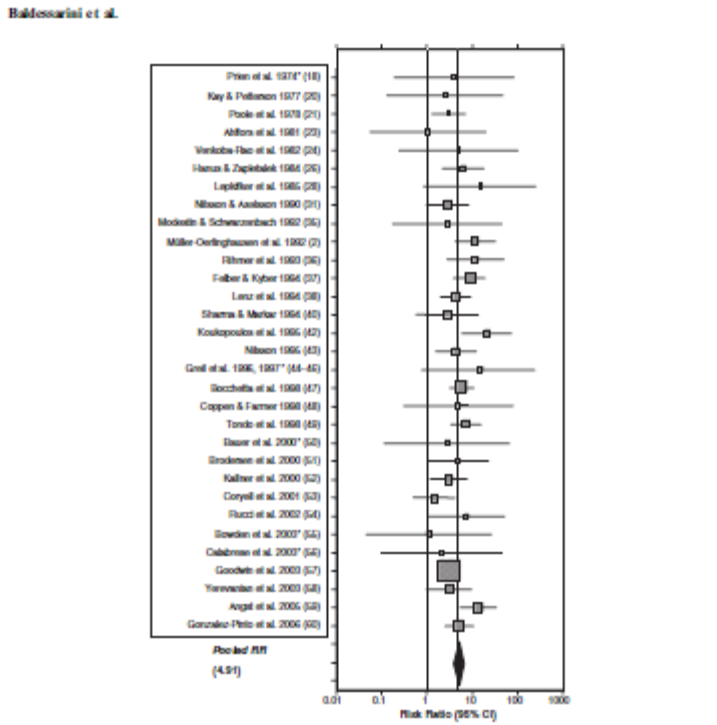

Fig. 1. Forest plot Risk Ratios (RR) as shaded squares proportional to study weight and their 95% confidence intervals (CI) based on random-effects meta-analysis of suicidal risk [rates of suicides and/or attempts per 100 person-years (%/year)] in 31 studies, with two arms (with and without lithium treatment) and non-zero suicidal risk in at least one arm (see Table 1) (2, 18, 20, 21, 23, 24, 26, 28, 31, 35–38, 40, 42–60). The computed pooled risk ratio (RR) (black diamond) = 4.91 (95% CI 3.82–6.31, $z = 12.5$, $p < 0.0001$). *Randomized, controlled trials.

Baldessarini RJ, Tondo L, Goodwin F K, et al Bipolar Disord 2006;8:625-639

Tratamiento coadyuvante con litio en la prevención de conducta suicida: estudio randomisado, controlado con placebo, durante 1 año

- Estudio controlado,multicentrico, prospectivo, Alemania
- Pacientes con intento de suicidio reciente (3 meses)
- Trastorno del espectro afectivo (n = 167)
- Litio vs. placebo, add-on a tratamiento usual

Lauterbach et al. (2008) Acta Psychiatr Scand 118(6):469-79

Tratamiento coadyuvante con litio en la prevención de conducta suicida: estudio randomisado, controlado con placebo, durante 1 año

- Sin diferencia en el número de intentos suicidio (7 en cada grupo
- Análisis post-hoc:
- Un número significativamente mayor cometió suicidio en el grupo placebo (3 versus 0 en el con litio; p=0,049

Lauterbach et al. (2008) Acta Psychiatr Scand 118(6):469-79

Cómo aumentar seguridad en uso de litio

- Investigar cómo prevenir el daño renal
- Programas de educación continua cómo usar litio de manera adecuada y seleccionar el paciente respondedor (características típicas vs atípicas)
- Cómo prevenir y tratar la intoxicación con litio
- Pedir calcemia y hormona paratiroídes

Litio: áreas de investigación a futuro

- Mejor estabilizador disponible pero; existe una marcada subutilización (mayoría de los países): sólo 10-40% de los pacientes que tienen indicación lo reciben
- Desarrollo de formulaciones distintas que la oral (E.V o I.M.) y medición de litemia por el paciente (chip)
- Investigación del efecto antisuicida ¿agudo?
- Efecto neuroprotector: ¿a quienes beneficia? ¿Es el efecto independiente den la prevención de recaídas?
- Aumentar seguridad: efecto en riñón:

  -prevención daño renal e insuficiencia, detección precoz de candidatos de daño renal

Recomendaciones monitoreo en tratamiento prolongado con litio ISBD

Base	- TSH, Calcemia, Creatinemia
Litemia	- Luego de 5 días de iniciado el litio tratamiento, -Dos mediciones consecutivas dentro de rango con la misma dosis - Luego de cambio de dosis - Cada 3-6 meses
Longitudinal	-Creatinemia, BUN cada 3-6 meses durante tto. -Clearance de creatinina cada 3-9 meses -Tasa de filtración glomerular cada 3-9 meses -T3, T4, TSH cada 6-12 meses - Calcemia, HPT(paratiroides) anual - P/A, Hemograma, Electrolitos cada 6 meses -Peso, ECG, Glicemia anual

ISBD Guidelines for the safety monitoring of bipolar treatment 2009:11:559-595
Bauer, M,Gitlin M. The esencial guide to lithium treatment Edit Springer, 2016 pag,117

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