

66 Jahre Lithium – Entdeckungen, heutiger Stellenwert und Ausblick

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Lithium: einzigartiges Element & Medikament in der Psychiatrie

Lithium containing lepidolite



Pure lithium in paraffin



along an independent segment of the San Andreas transform fault. Zhabuye Lake (17°N, 81°E) is one of a family of closed basins in the Tibetan plateau on the upper plate of the Himalayan-Tibetan collisional orogen; in detail, it is a Neogene graben at high angles to the structural grain of the orogen. Curiously, and due partly to extreme aridity, most of these example deposits are in globally exceptional tectonic settings: the Basin and Range is the world's widest extensional province, the Altiplano is the highest sector of a continental-margin arc, and Tibet is the largest and highest syncollisional plateau.

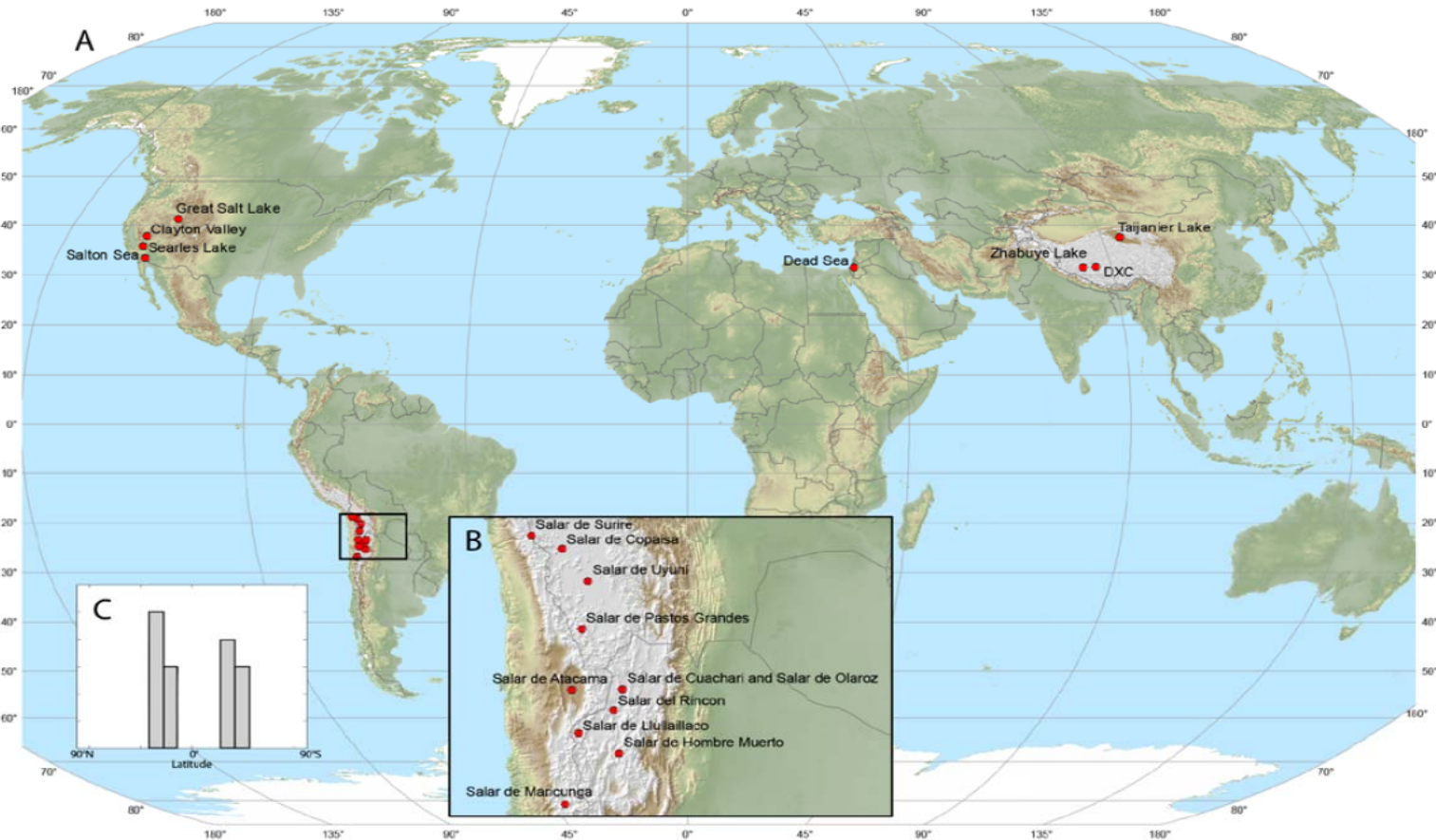


Figure 2. (A) World map of lithium brine deposits (red dots). (B) Detail in South America. (C) Histogram showing the bimodal latitudinal distribution of Li brine deposits in northern and southern arid belts.

Atacama Desert (Northern Chile)



66 Jahre Lithium Geschichte

- **Wichtige Substanz in der Psychopharmakologie seit über 60 Jahren (1949 Cade)**
- **Manie (1950s) – antimanische Aktivität**
- **Rezidivprophylaxe – Rückfallverhinderung bipolare und unipolare affektive Störungen (1960s)**
- **Depression (1980-90s)– Augmentation von Antidepressiva**
- **Suizidverhinderung (1990s) – antisuizidale Aktivität**
- **Neuroprotektion (2000) – neuroprotektive Aktivität**

Lithium

- Akut antimanisch +++
- Akut antidepressiv – Mono +
- Akut antidepressiv – Augmentation +++
- Rezidivprophylaktisch – Manie +++
- Rezidivprophylaktisch – Depression ++
- Antisuizidal ++
- Rapid cycling +
- Mischformen (Mixed) +
- Prädiktion der Li-Response bei excellenten Lithium-Respondern 1. Grades ++

Lithium: Bedeutung bei Affektiven Störungen

Rezidivprophylaxe

Antisuizidale Aktivität

**Augmentation
Antidepressiva**

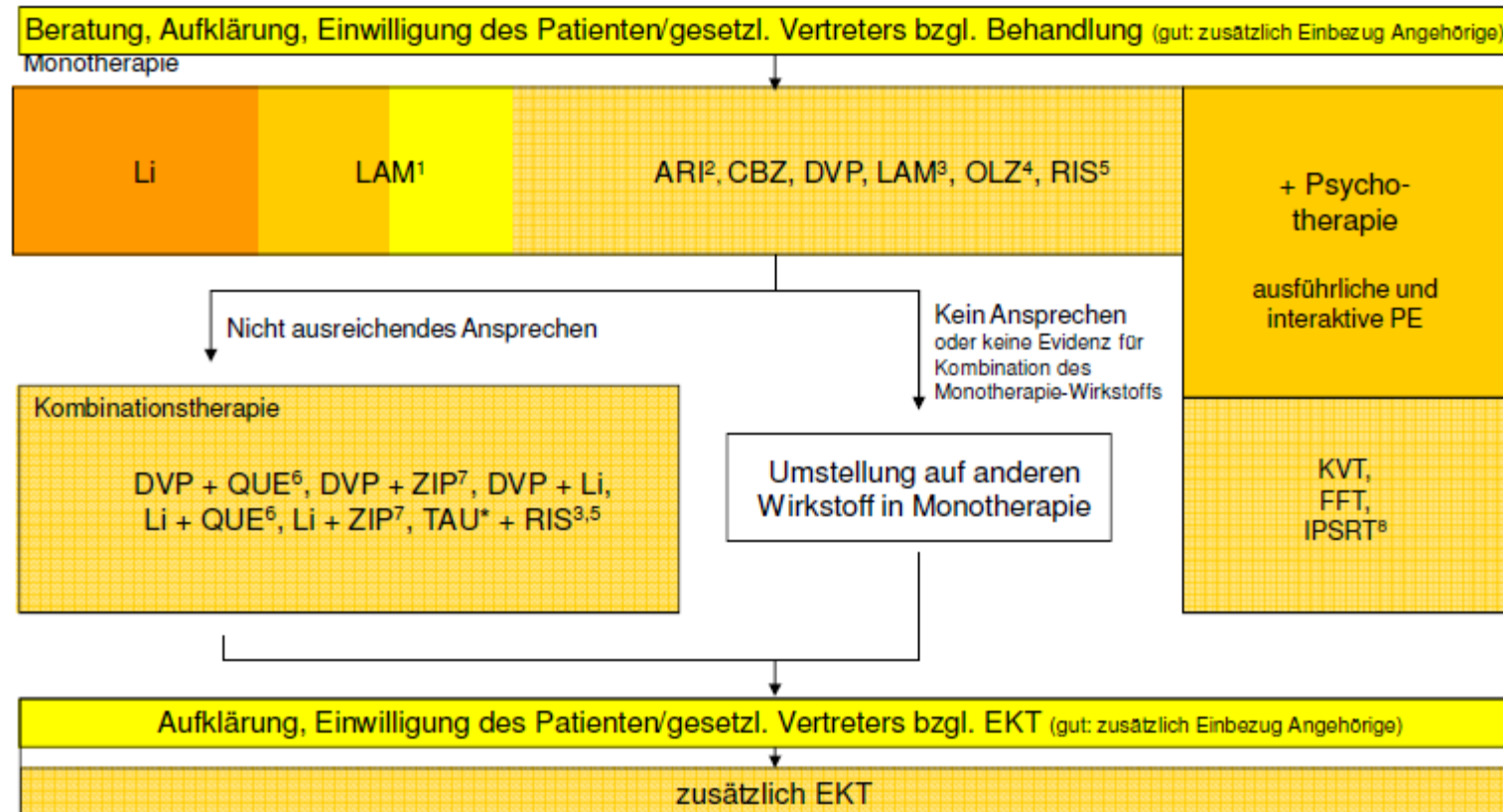
5.4.7 Algorithmus

Im Folgenden ist ein Algorithmus abgebildet, der die Empfehlungen zur Phasenprophylaxe bei Bipolaren Störungen zusammenfasst.

Algorithmus 5: Phasenprophylaxe bei Bipolaren Störungen

Phasenprophylaxe bei bipolaren Störungen

Die Schattierung entspricht dem Empfehlungsgrad (Legende rechts unten). Die Wirkstoffe sind innerhalb einer Empfehlungsgrad-Stufe alphabetisch geordnet.



¹gegen depr. E. bei Ansprechen in Akutphase, KKP für Einsatz gegen depressive Episoden auch ohne Ansprechen in Akutphase,

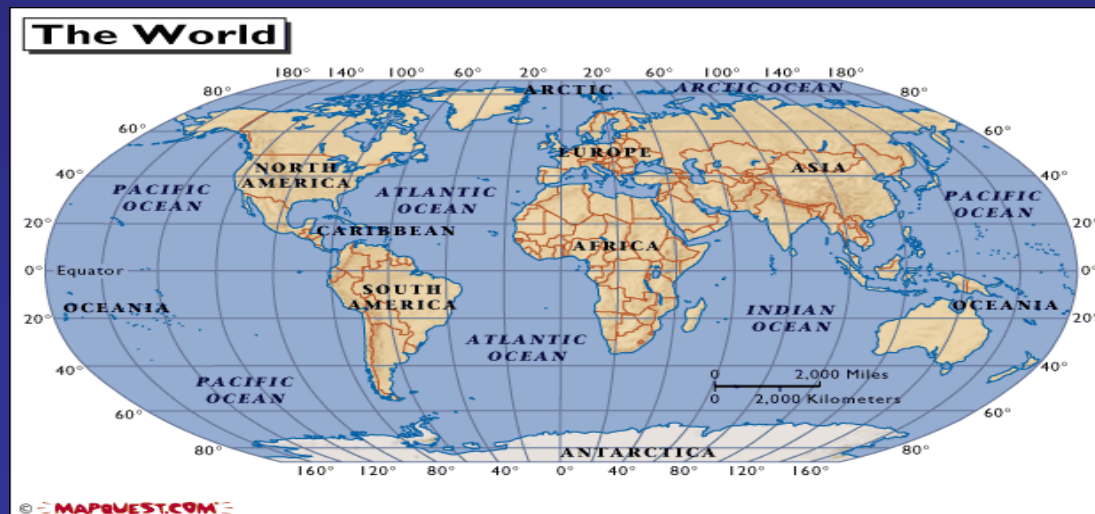
²gegen manische Episoden bei Ansprechen in Manie, ³bei Rapid Cycling, ⁴bei Ansprechen in Manie, ⁵Depotpräparat, bei Ansprechen in Akutphase, ⁶bei Ansprechen auf diese Kombination in Akutbehandlung, ⁷bei Ansprechen auf ZIP in Manie, ⁸bei Beginn in akuter Phase und längerfristiger Planung, *Behandlung wie üblich: jede Monotherapie und Kombination von Antidepressiva, Stimmungsstabilisierern und Anxiolytika erlaubt

ARI: Aripiprazol, CBZ: Carbamazepin, DVP: Valproat, EKT: Elektrokonvulsionstherapie, FFT: familienfokussierte Therapie, IPSRT: interpersonelle und soziale Rhythmustherapie, KVT: kognitive Verhaltenstherapie, LAM: Lamotrigin, Li: Lithium, OLZ: Olanzapin, PE: Psychoedukation, QUE: Quetiapin, RIS: Risperidon, ZIP: Ziprasidon

Empfehlungsgrade: A, B, O, KKP (Klinischer Konsenspunkt)

Lithium 'Gold Standard' in Internationalen Leitlinien

- Lithium has demonstrated efficacy in preventing relapse of mania¹ and bipolar depression² in patients with bipolar disorder³



¹Prien et al 1973a; ²Prien et al 1973b, WFSBP 2002

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

 International Journal of
Bipolar Disorders
a SpringerOpen Journal

RESEARCH

Open Access

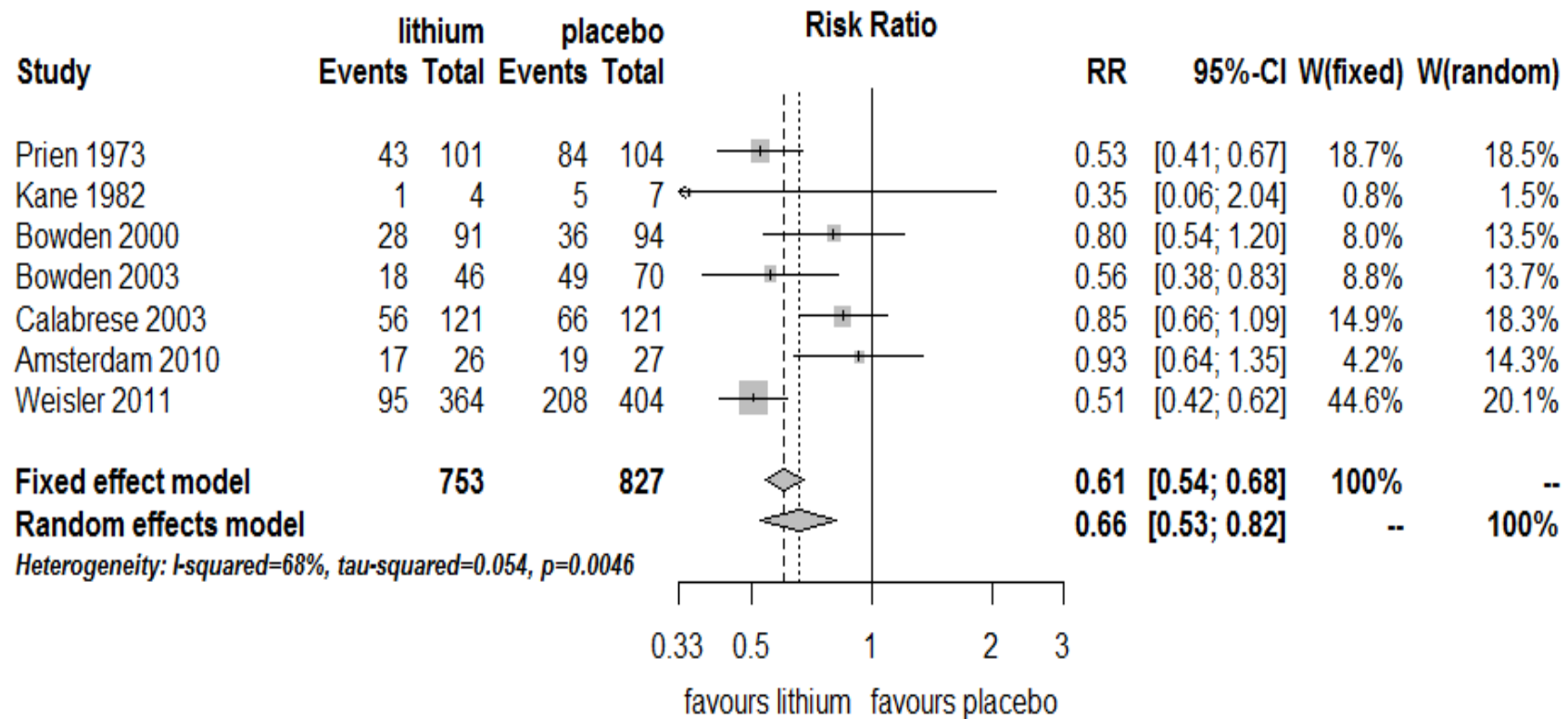
Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis

Emanuel Severus^{1*†}, Matthew J Taylor^{2†}, Cathrin Sauer¹, Andrea Pfennig¹, Philipp Ritter¹, Michael Bauer¹
and John R Geddes³

Lithium for prevention of relapse in bipolar disorder

Placebo-controlled RCTs

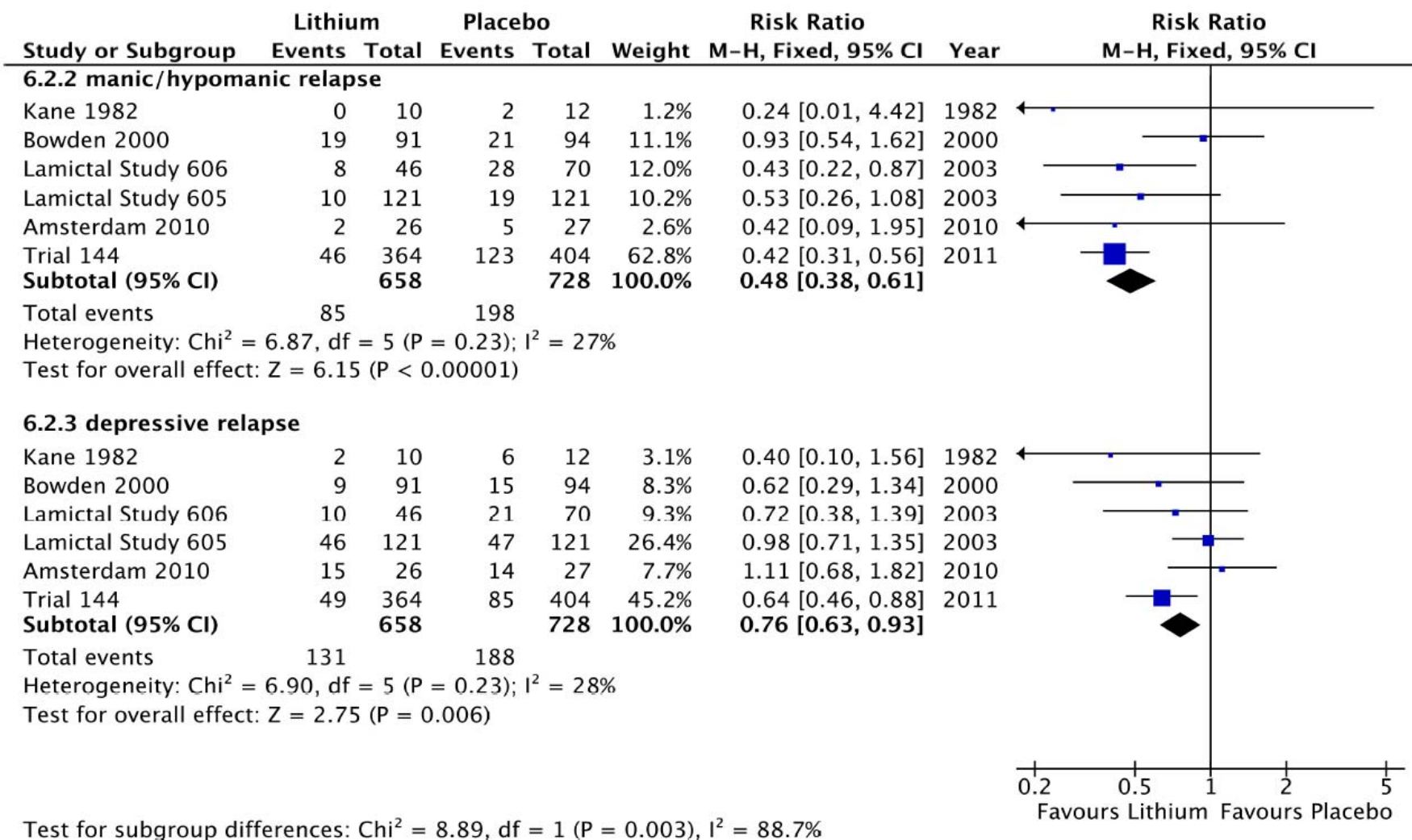
Prevention of any type of episode (mania and depression)



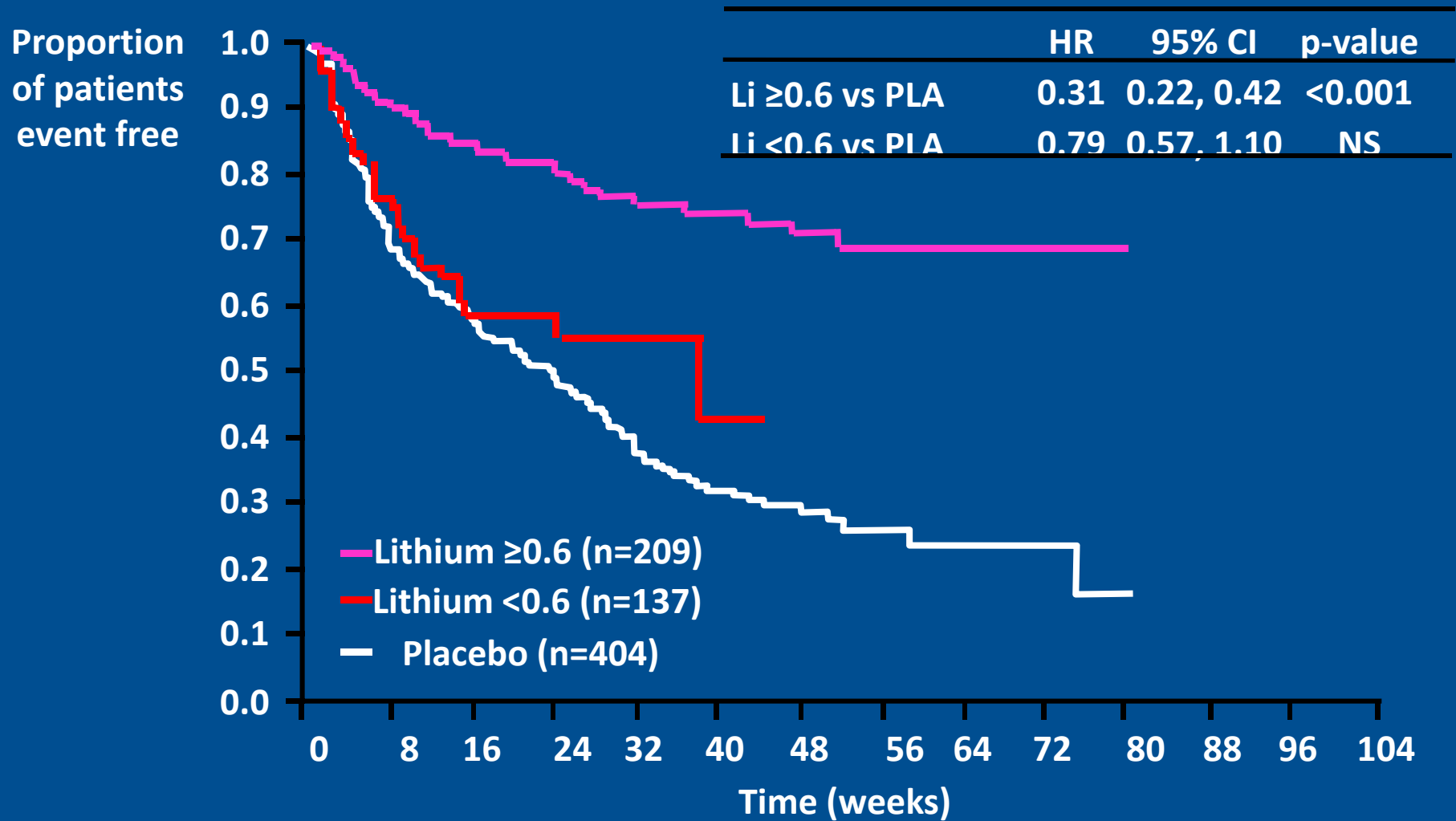
Lithium for prevention of relapse in bipolar disorder

Placebo-controlled RCTs

Prevention of depressive and manic episodes



Sparcle-Studie: Behandlungserfolg hängt signifikant vom Lithium-Serumspiegel ab
(Nolen et al. Bipolar Disord 2012 Dec 10. doi: 10.1111/bdi.12027. [Epub ahead of print])



BALANCE Studie 3 x 110 Patienten

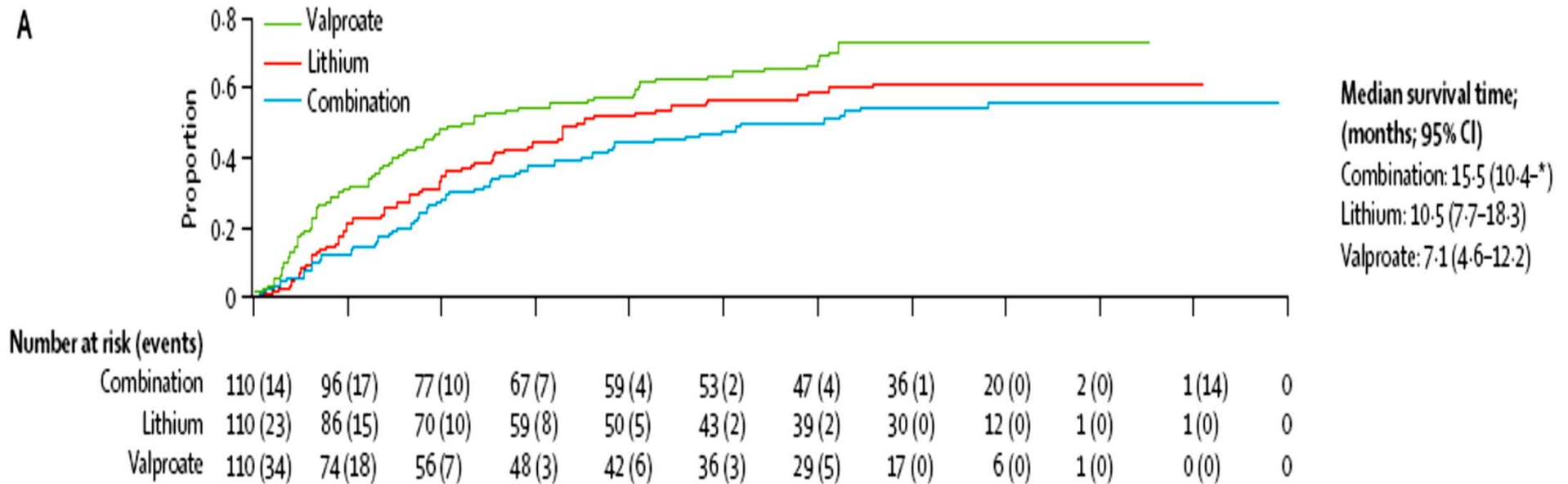


Figure 2: Time to event outcome measures

(A) First admission or adjuvant treatment for emerging mood episode. (B) First admission to hospital. (C) First added treatment. (D) First episode of depression. (E) First manic episode. (F) Stopping trial treatment. *Survival curve does not extend sufficiently far to allow calculation of upper limit of 95% CI.

Hazard ratios:

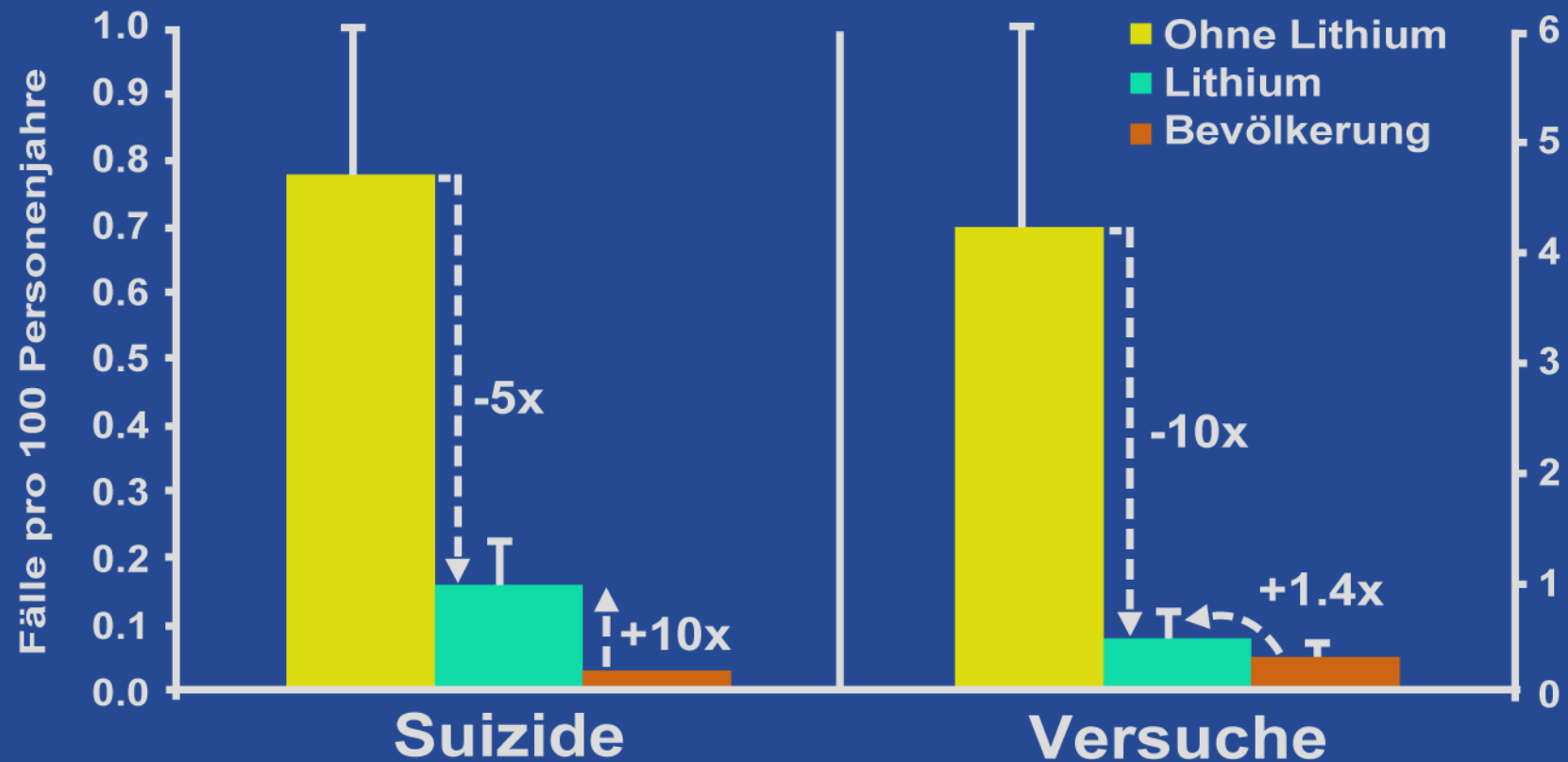
combination vs valproate 0.59 (95% CI 0.42–0.83, p=0.0023)
 combination vs lithium 0.82 (0.58–1.17, p=0.27)
 lithium vs valproate 0.71 (0.51–1.00, p=0.0472)

The BALANCE investigators and collaborators: Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2009

Prädiktoren für gutes Ansprechen der Rezidivprophylaxe mit Lithium

- **“Klassische” manisch-depressive Erkrankung**
- **Bipolar Typ 1**
- **Typischer Verlauf: interepisodische Remission**
- **Kein Rapid cycling**
- **Synthyme Wahnthemen**
- **Positive Familienanamnese einer Lithium Response**

Lithium reduziert Suizidrisiko bei affektiven Störungen

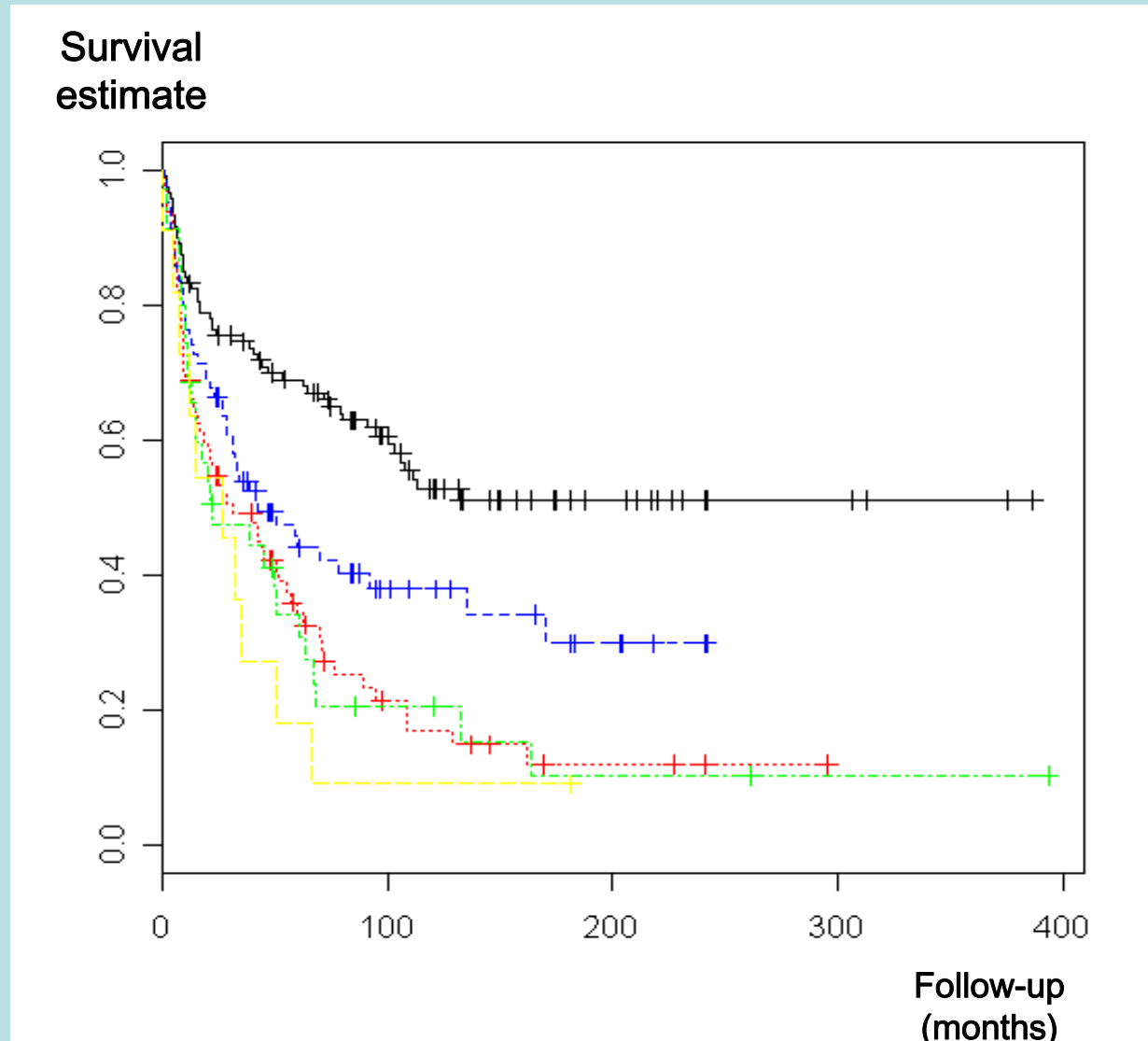


Baldessarini, R. J.; APA 2003

IGSLI Scale of Typical and Atypical Features

Typical Bipolar Disorder	<input type="checkbox"/>	Atypical Bipolar Disorder	<input type="checkbox"/>
Core features			
No comorbidity	<input type="checkbox"/>	Comorbidity (lifetime diagnosis of anxiety, substance abuse, etc)	<input type="checkbox"/>
Only mood-congruent psychotic features	<input type="checkbox"/>	Mood-incongruent psychotic features	<input type="checkbox"/>
Full interepisodic remission	<input type="checkbox"/>	Residual symptoms	<input type="checkbox"/>
No. of depressive episodes > no. of manic episodes before index episode	<input type="checkbox"/>	No. of manic episodes > no. of depressive episodes before index episode	<input type="checkbox"/>
Optional features			
Normal MMPI profile	<input type="checkbox"/>	Normal MMPI profile with subthreshold precarious findings	<input type="checkbox"/>
Frequency of episodes ≤ 2 per year before index episode	<input type="checkbox"/>	Rapid cycling > 4 episodes per year before index episode	<input type="checkbox"/>
No rebound after discontinuation	<input type="checkbox"/>	Rebound after discontinuation	<input type="checkbox"/>
Positive family history of bipolar disorder	<input type="checkbox"/>	Family history of nonepisodic disorder	<input type="checkbox"/>

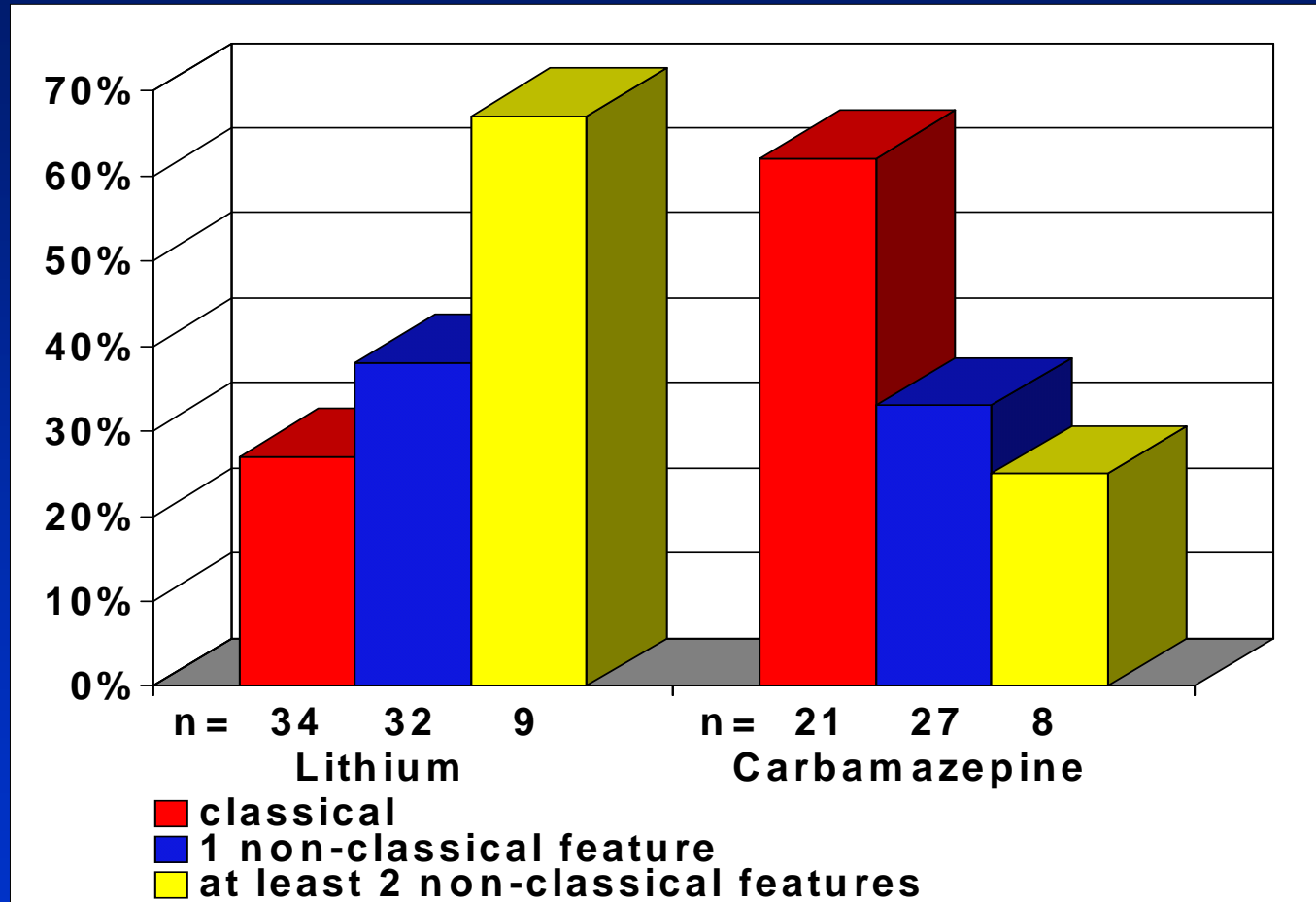
Relationship between time to first recurrence and number of core atypical features



- 0 features
- 1 feature
- 2 features
- 3 features
- 4 features

MAP Study (RCT, 2.5 yrs) in Bipolar Disorder

Hospitalisation Rates

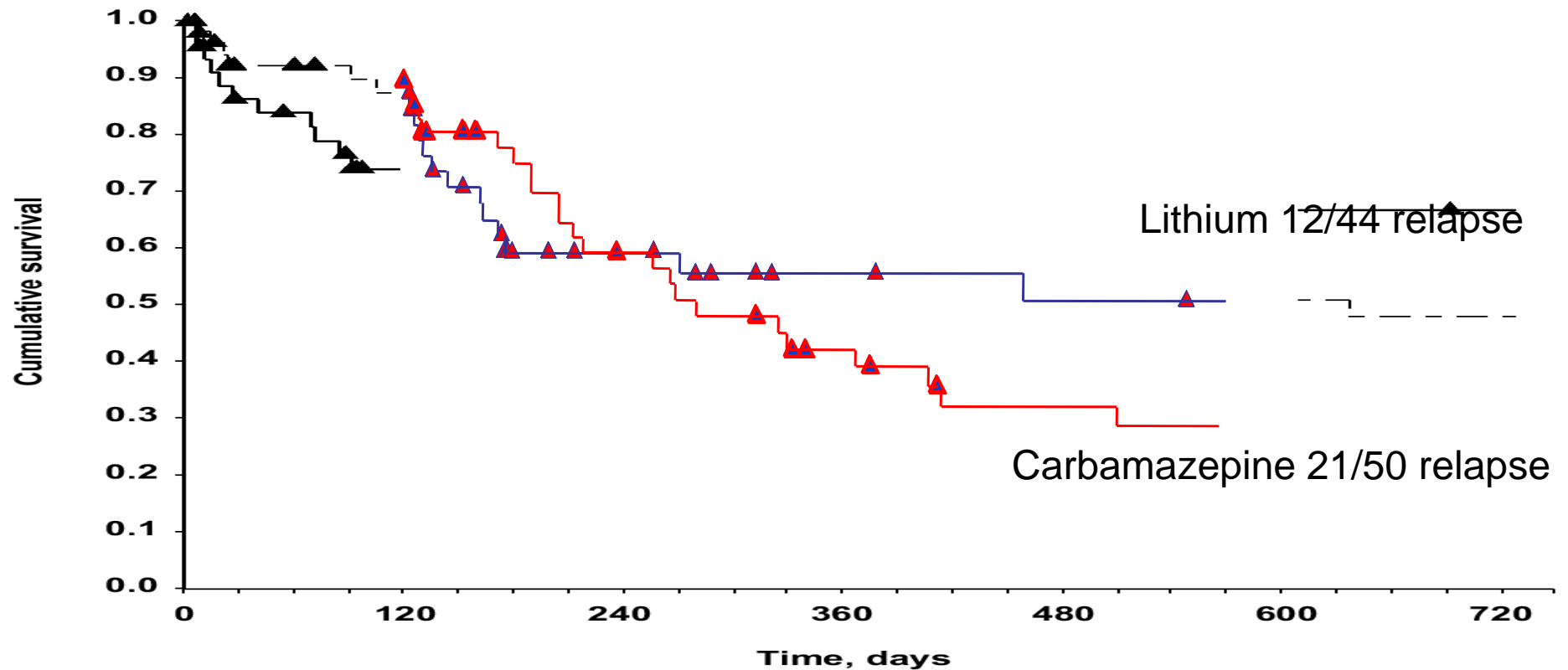


Greil et al. (1998) J Clin Psychopharmacol 18: 455-460

Prophylaxe Lithium vs. Carbamazepin

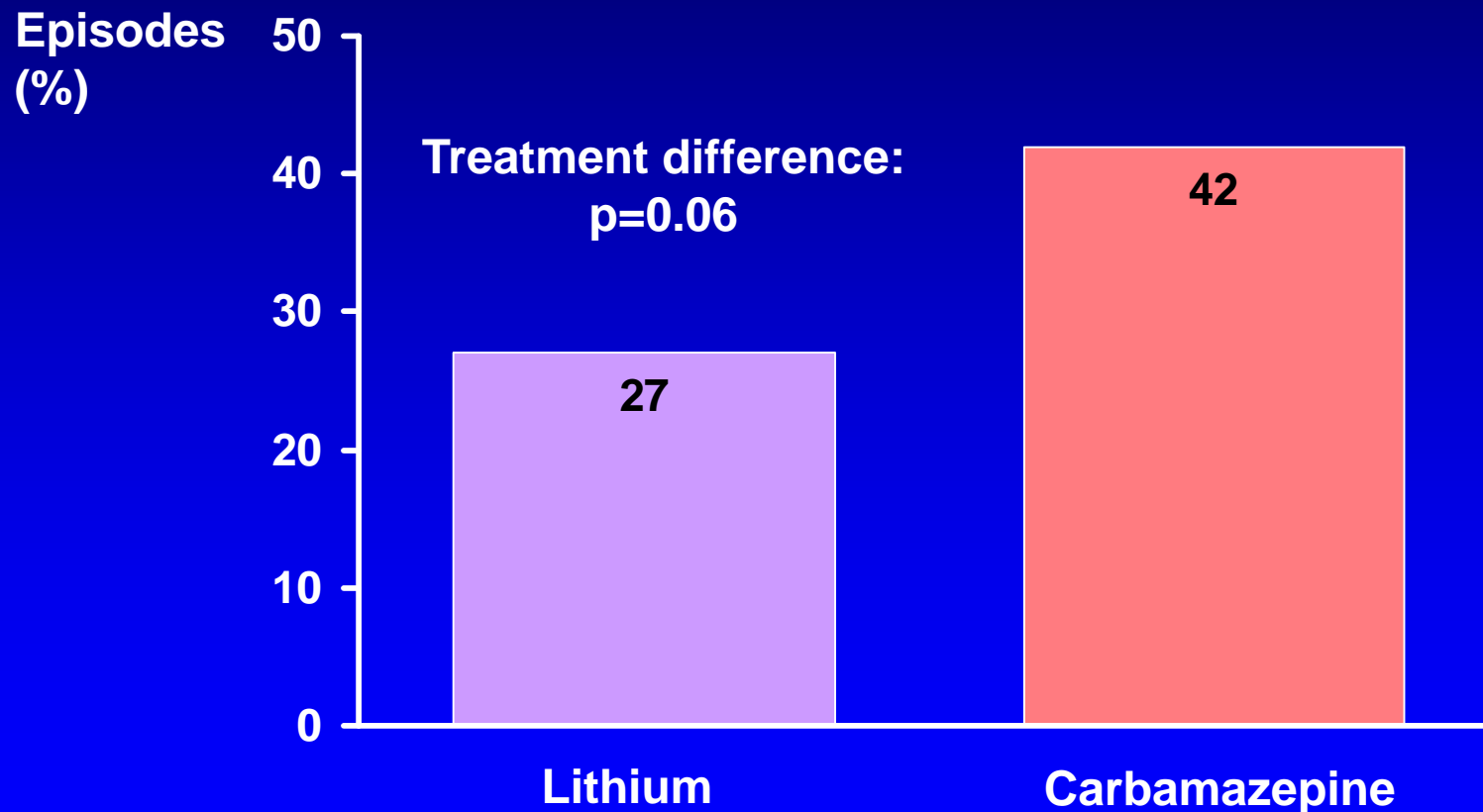
- Dutch LitCar Group (Hartong et al.)
- 2 Jahre, doppelblind, randomisiert
- in Remission, bislang prophylaktisch unbehandelte bipolare Patienten (n=94)
- Manische/Hypomanische Indexepisode:
Efficacy Li > CBZ

Cumulative Survival on Lithium and Carbamazepine (mood episodes = terminal events)



Carbamazepine: less effective than lithium

Prophylaxis in patients in remission (2-year trial)



BALANCE Studie 3 x 110 Patienten

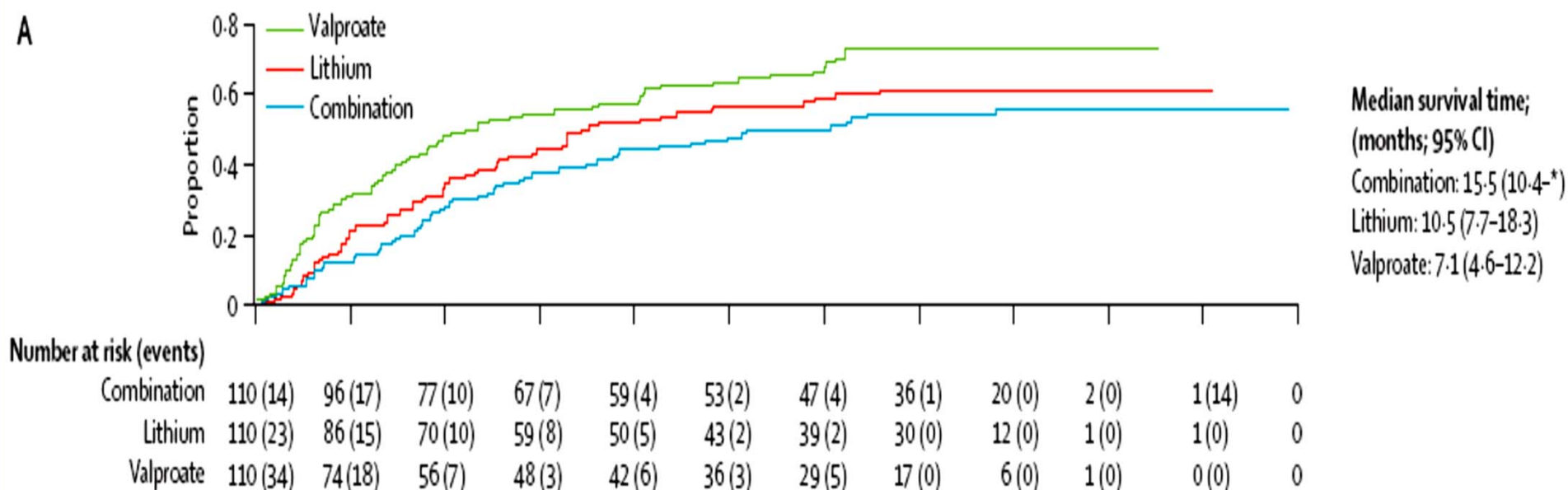


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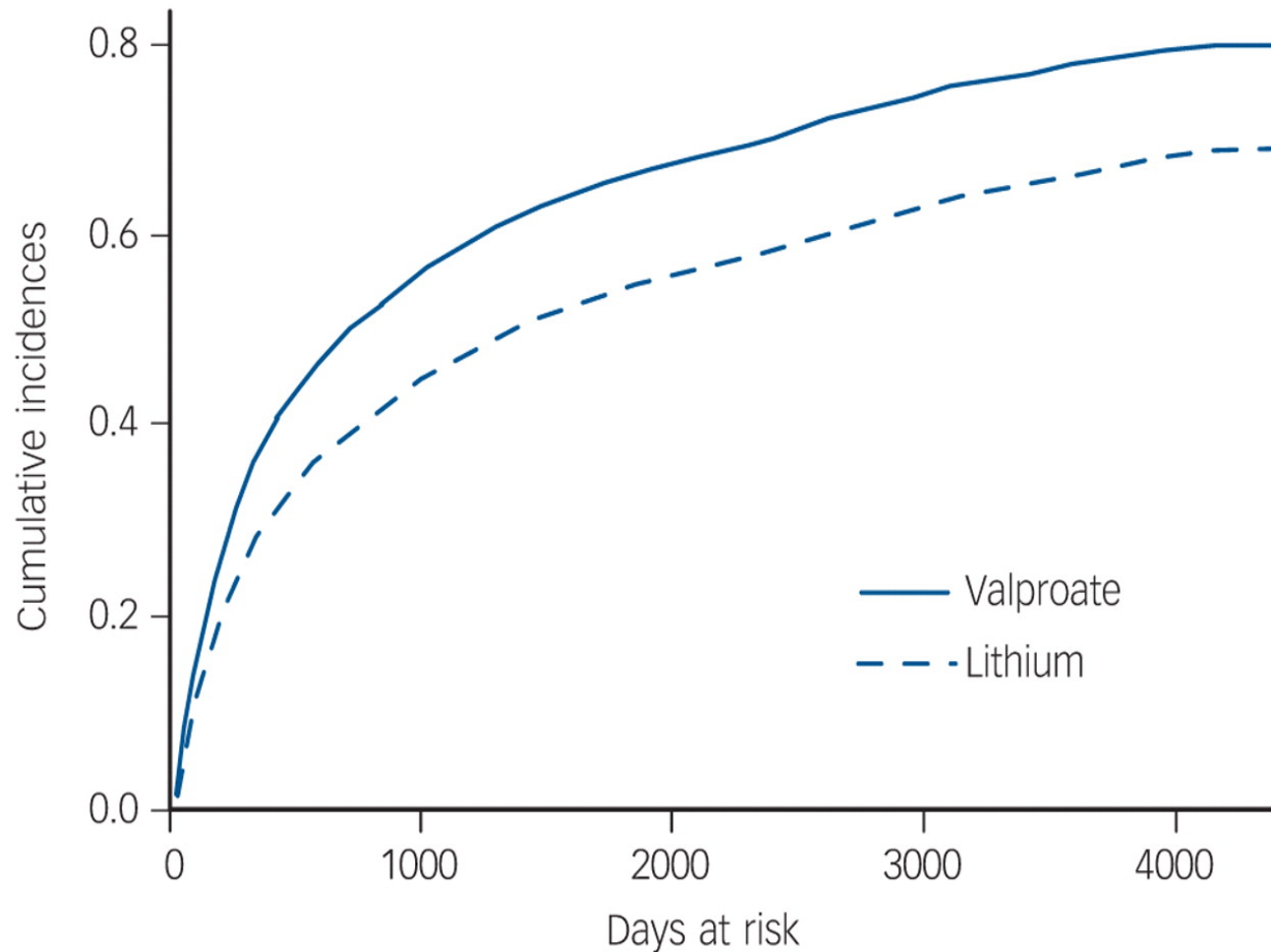
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Valproate v. lithium in the treatment of bipolar disorder in clinical practice: observational nationwide register-based cohort study

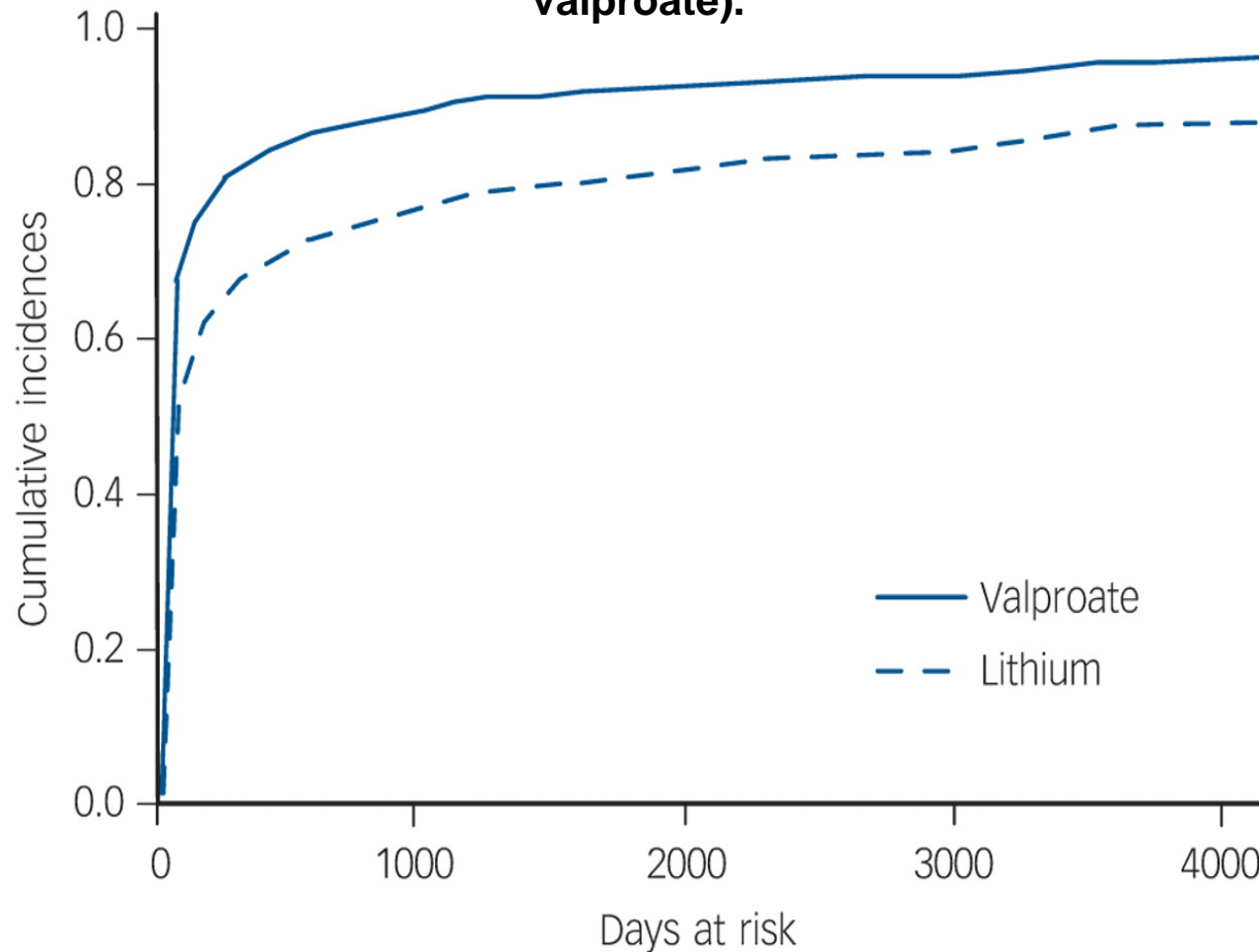
**Kessing, L. V. et al.
The British Journal of Psychiatry 2011;199:57-63**

Fig. 1 Cumulative incidence curves for the risk of psychiatric hospital admissions in people with bipolar disorder treated with valproate v. lithium (uncorrected).



Kessing, L. V. et al. The British Journal of Psychiatry 2011;199:57-63

Fig. 2 Cumulative incidence curves for the risk of switch to or add on of another psychotropica in people with bipolar disorder treated with valproate v. lithium in monotherapy (uncorrected). a. Another psychotropic: the opposite drug of interest (lithium or valproate), antidepressants, antipsychotics or anticonvulsants (other than valproate).

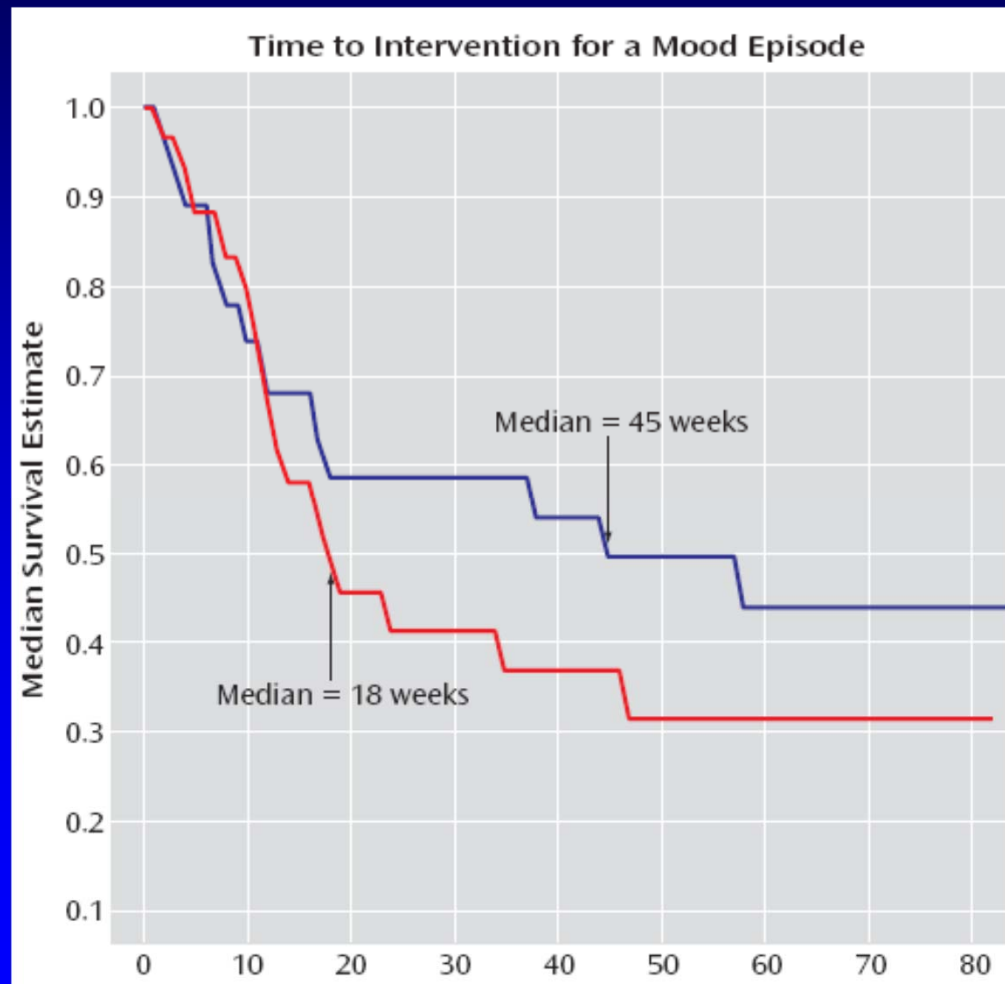


Kessing, L. V. et al. The British Journal of Psychiatry 2011;199:57-63

THE BRITISH JOURNAL
OF PSYCHIATRY

Kessing et al. (2011)

A 20-Month, Double-Blind, Maintenance Trial of Lithium Versus Divalproex in Rapid-Cycling Bipolar Disorder



kein signifikanter Unterschied in Zeit bis zu Behandlungsmaßnahme

Relapse: YMRS ≥ 15 oder
HAMD-24 ≥ 20 für 8 Wo,
Lithium Spiegel: 0.93 mEq/L,
Valproat Spiegel: 67 μ g/ml

Depression – Augmentation

1980-90s

de Montigny and others



25 Years of Lithium Augmentation

- Large database in support of this strategy
- 10 placebo-controlled double-blind trials
- 8 comparator-controlled trials
- 13 open, large-scale prospective studies
- Numerous case series and small studies

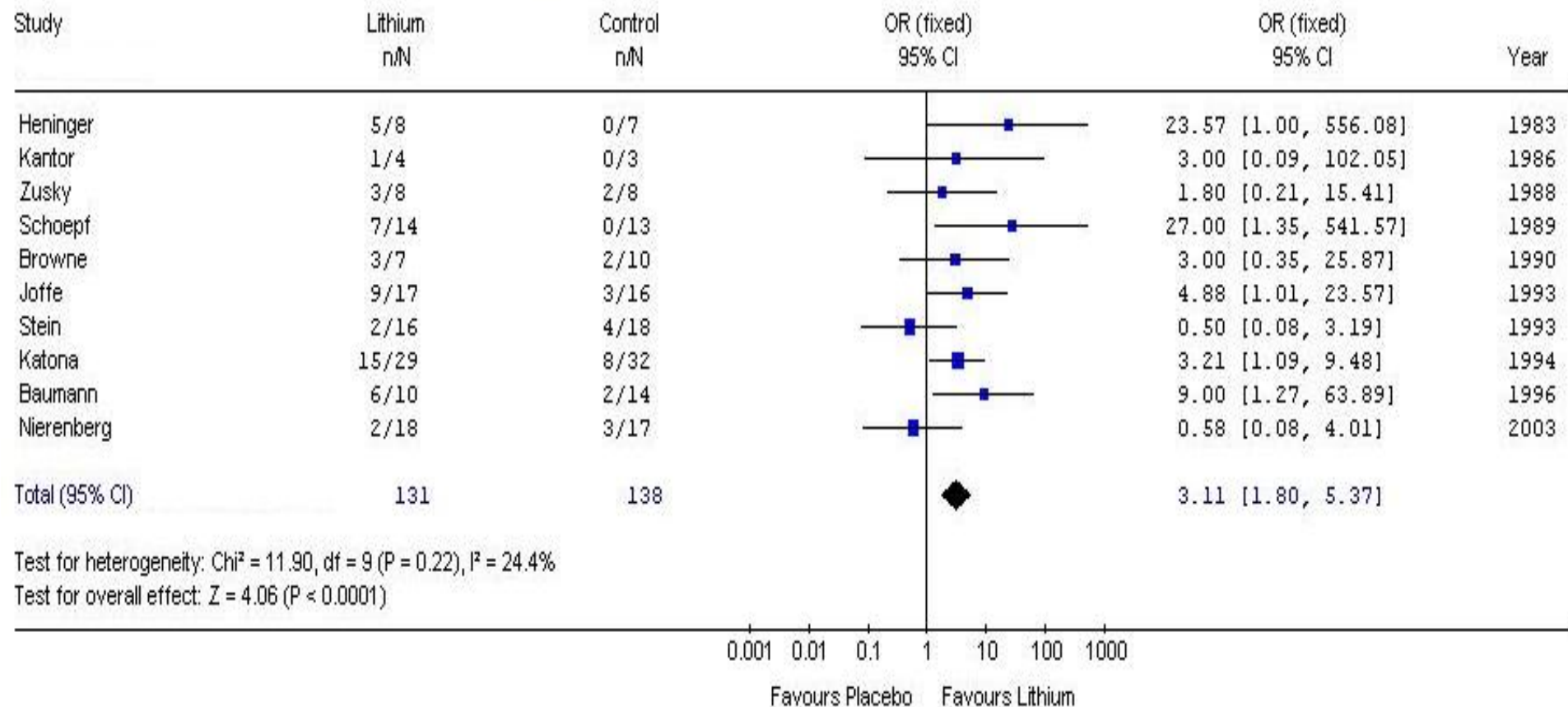
Bauer M et al. The acute antidepressive effects of lithium: from monotherapy to augmentation. In: Bauer M, Grof P, Müller-Oerlinghausen (Eds.) (2006) Lithium in Neuropsychiatry – The Comprehensive Guide. Informa Healthcare, Abingdon, UK, pp. 109-128

10 Placebo-RCTs of Lithium Augmentation

- Various antidepressants
- One positive study with citalopram (Baumann et al. 1996)
- One positive study with SSRIs and TCAs (Katona et al. 1995)

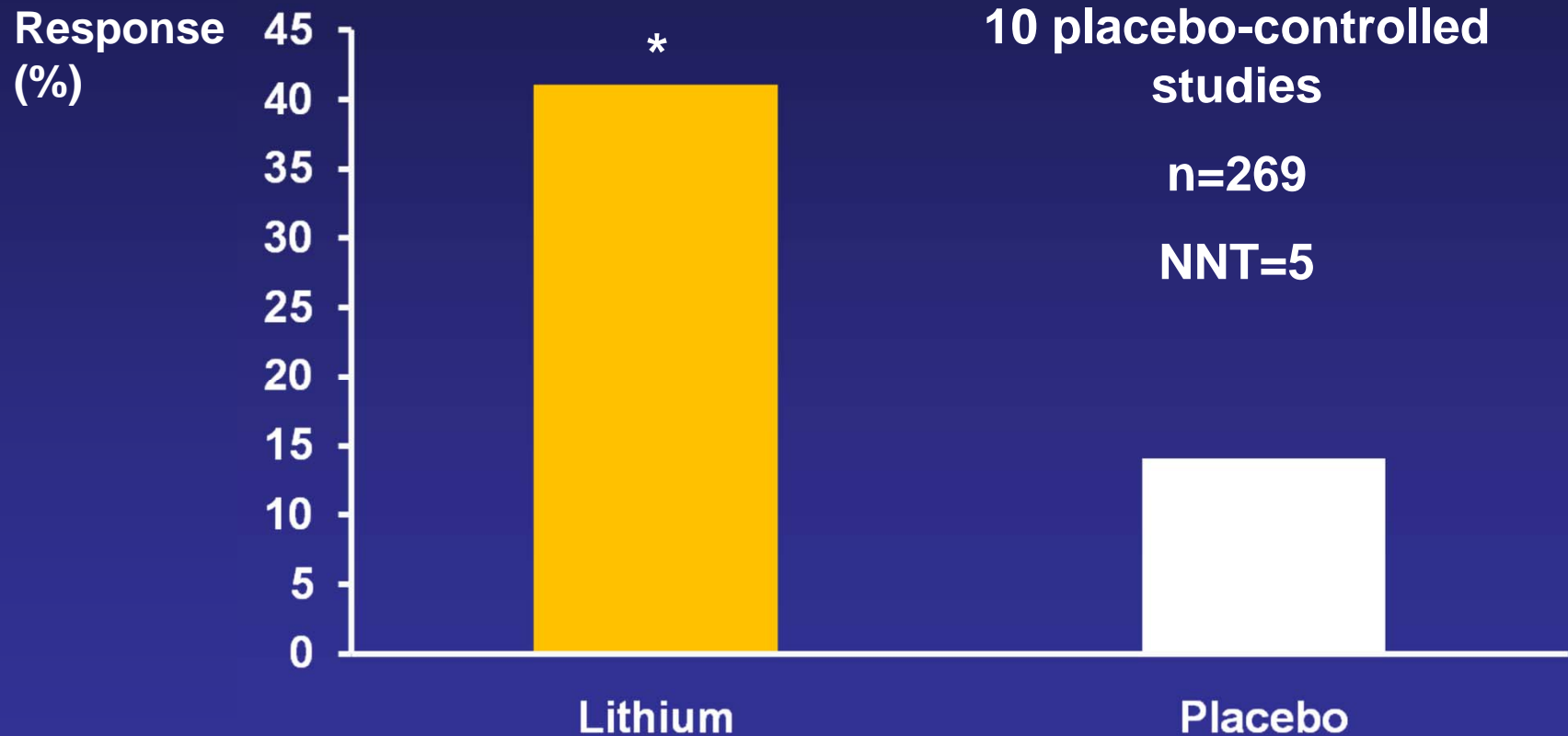
Bauer M et al. The acute antidepressive effects of lithium: from monotherapy to augmentation. In: Bauer M, Grof P, Müller-Oerlinghausen (Eds.) (2006) Lithium in Neuropsychiatry – The Comprehensive Guide. Informa Healthcare, Abingdon, UK, pp. 109-128

Refined Meta-Analysis: Lithium Augmentation in Refractory Depression (10 RCTs)



Crossley and Bauer, 2005

Meta-analysis of RCTs lithium augmentation vs placebo



*p < 0.001

Crossley and Bauer 2007

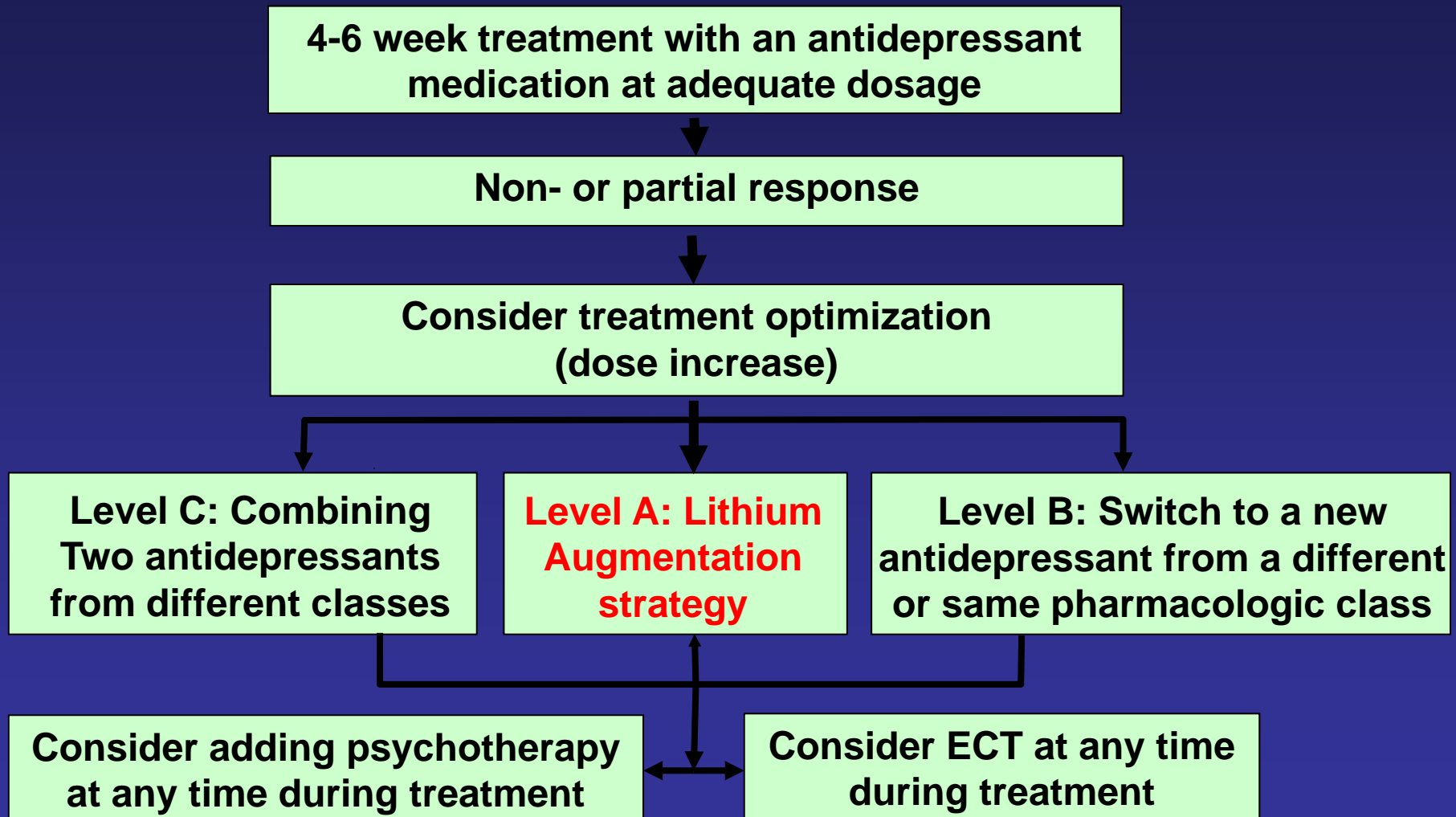
Augmentation Strategies for Refractory Depression

Evidence-Level

- **Lithium** **A**
- **Triiodothyronine (T3)** **B**
- **Atypical antipsychotics** **A/B/C**
- **(Quetiapine, Aripiprazole)**
- **L-Thyroxine** **C**
- **Anticonvulsants** **C**
- **Estrogen** **C**
- **Dopaminagonists** **C**
- **Psychostimulants** **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 (2002). *Bauer, Whybrow, Angst, Versiani, Möller World J Biol Psychiatr 2:59-69*

Treatment strategies for depression: WFSBP guidelines

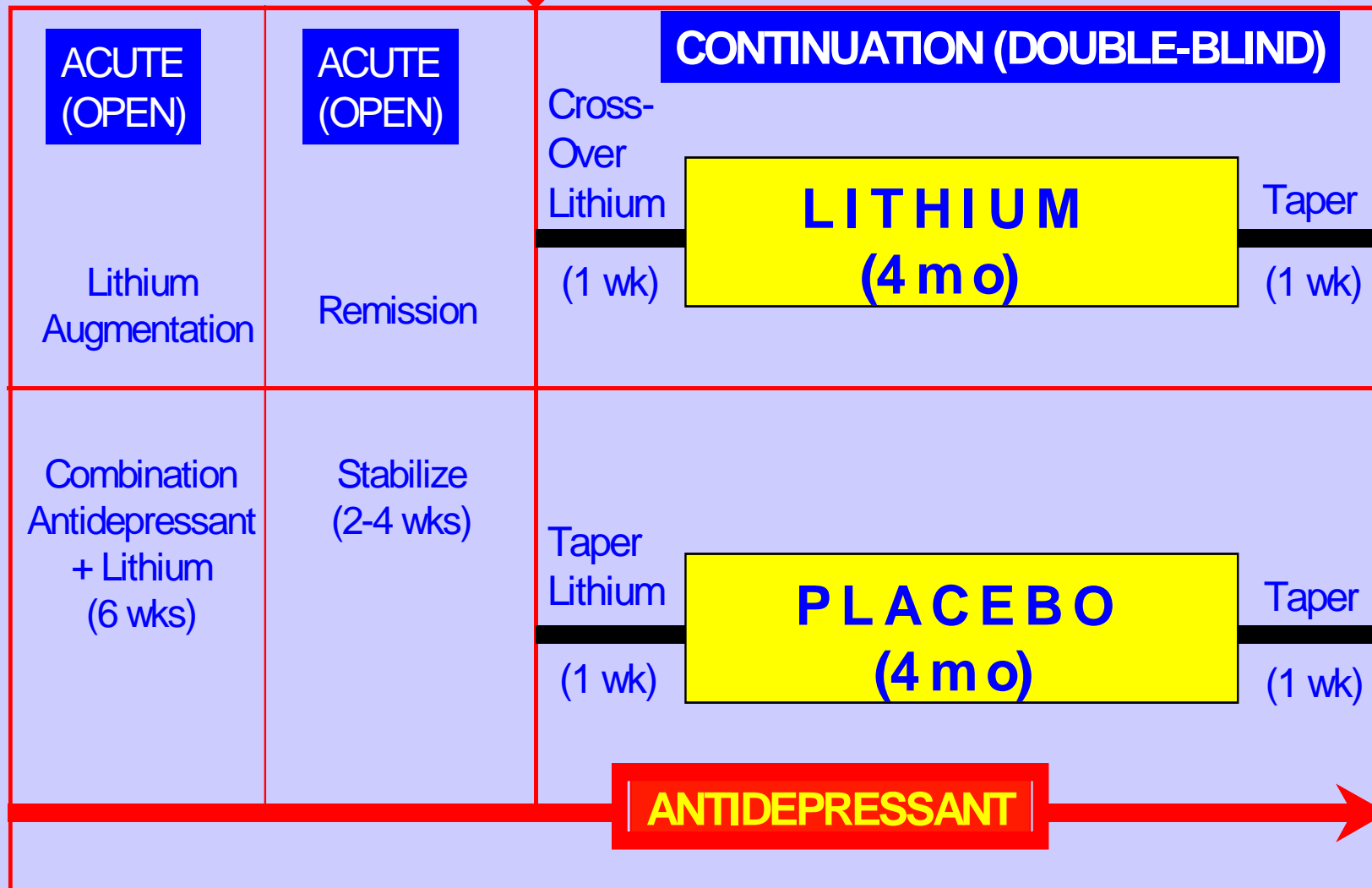


Study Design Overview

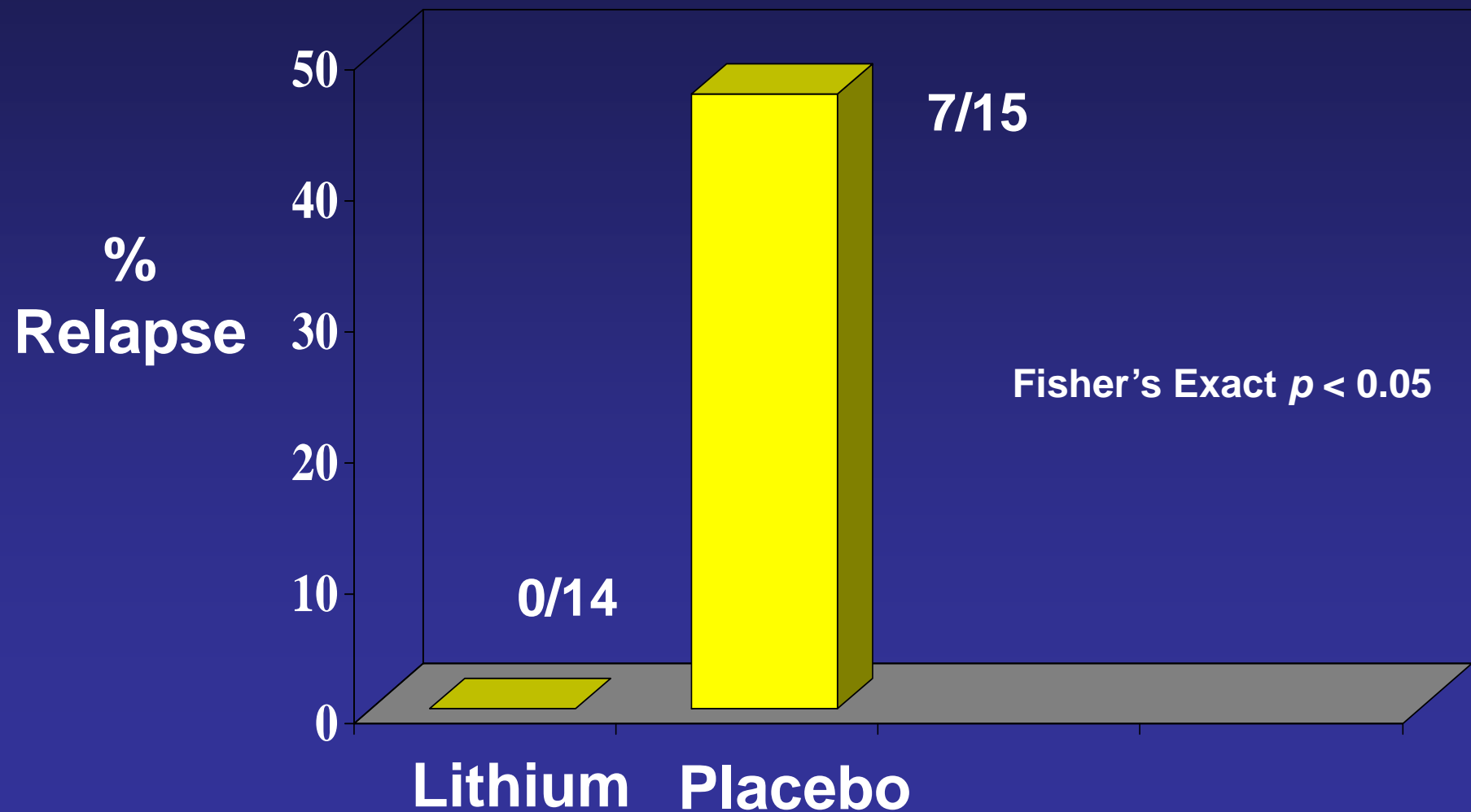
PHASE I



PHASE II



Lithium Augmentation Continuation Prevents Relapse



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



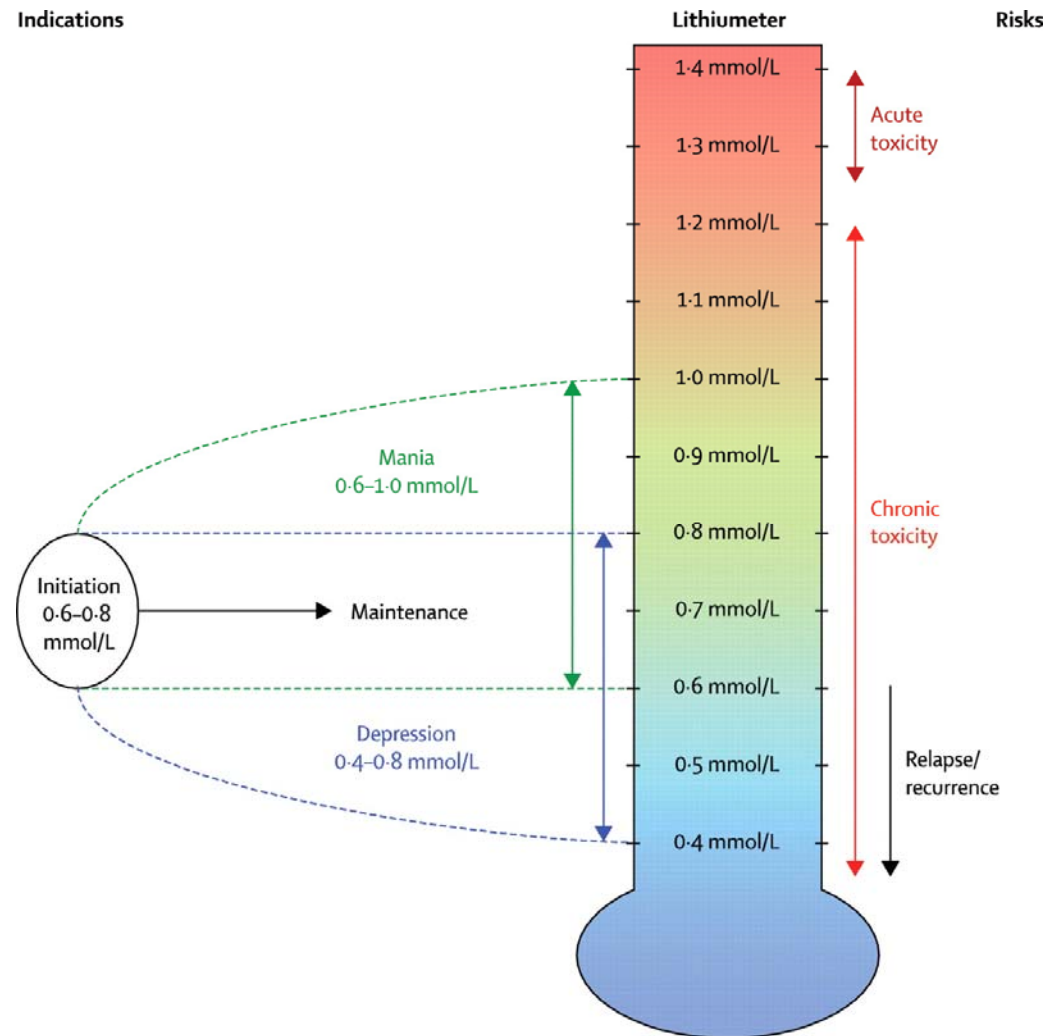
Unerwünschte Wirkungen

Lithium: Verträglichkeit und Probleme

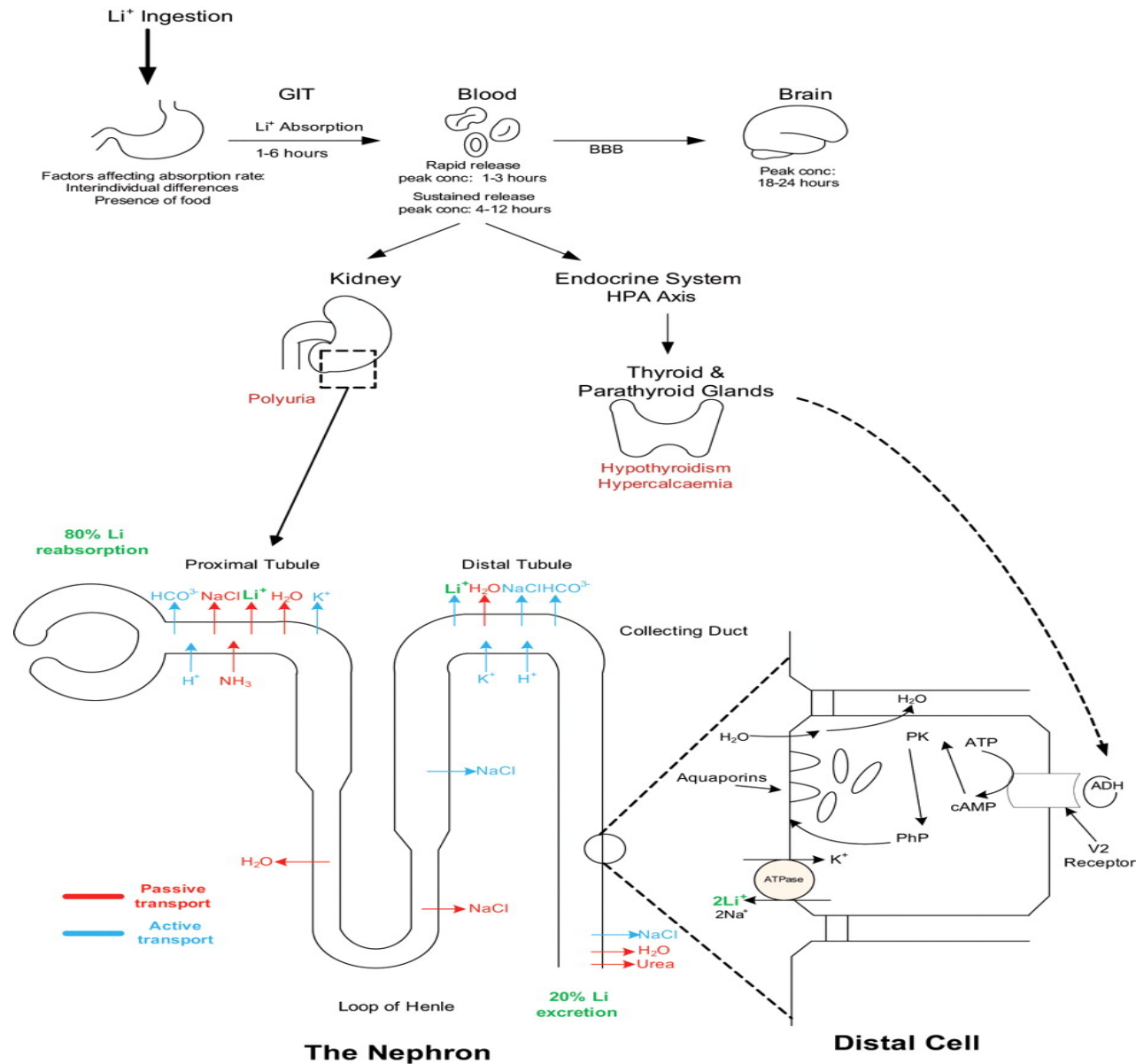
- Enges therapeutisches Fenster
- Risiko der Intoxikation (Niere!)
- Tremor, Polyurie, gastrointestinale NW
- Schilddrüse (Struma, Hypothyreose)
- Niere
- Handhabung komplizierter
- Höherer Aufwand an Psychoedukation und Kontrolluntersuchungen

The lithiumeter

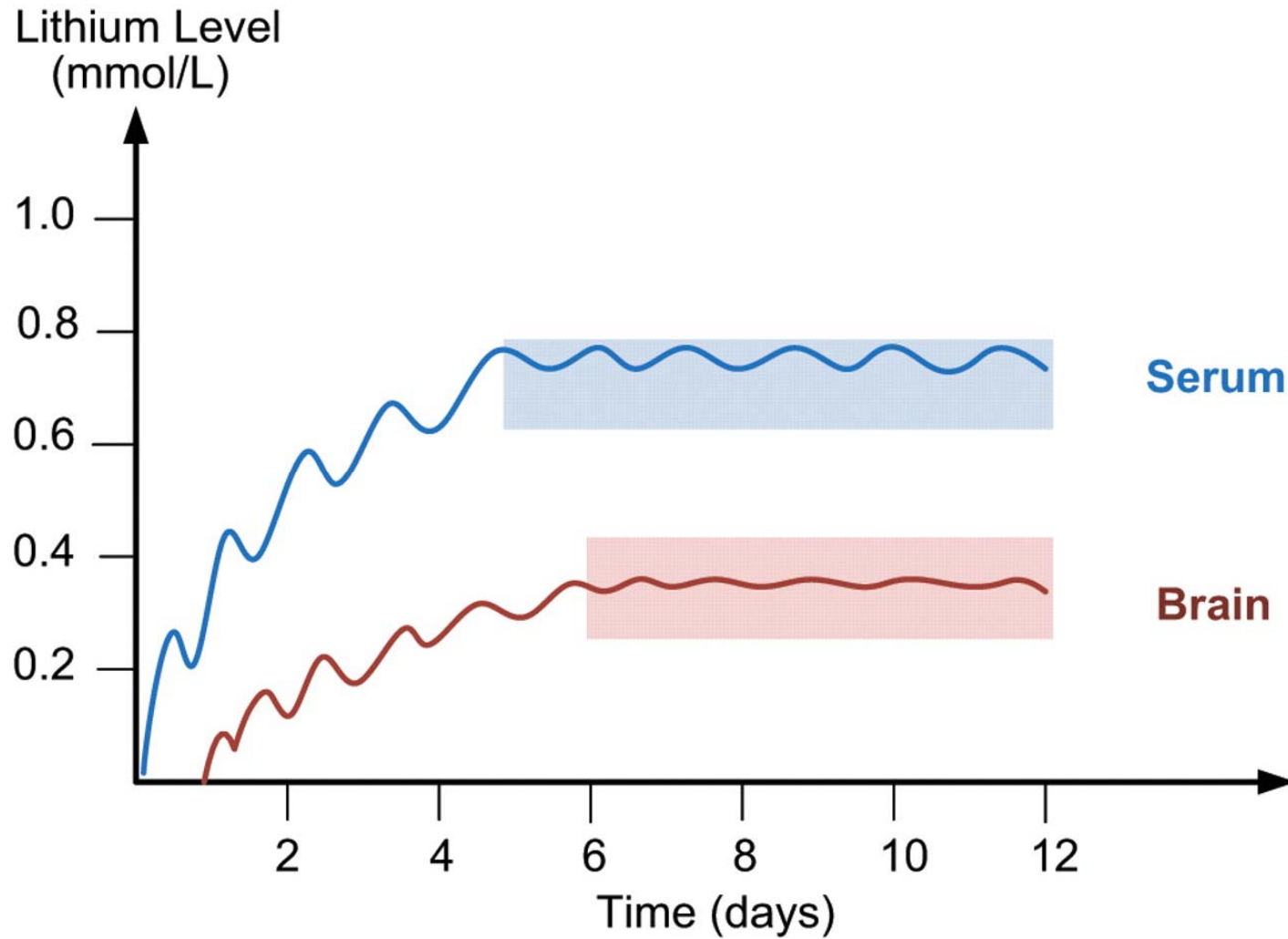
indications and risks associated with lithium according to its blood levels



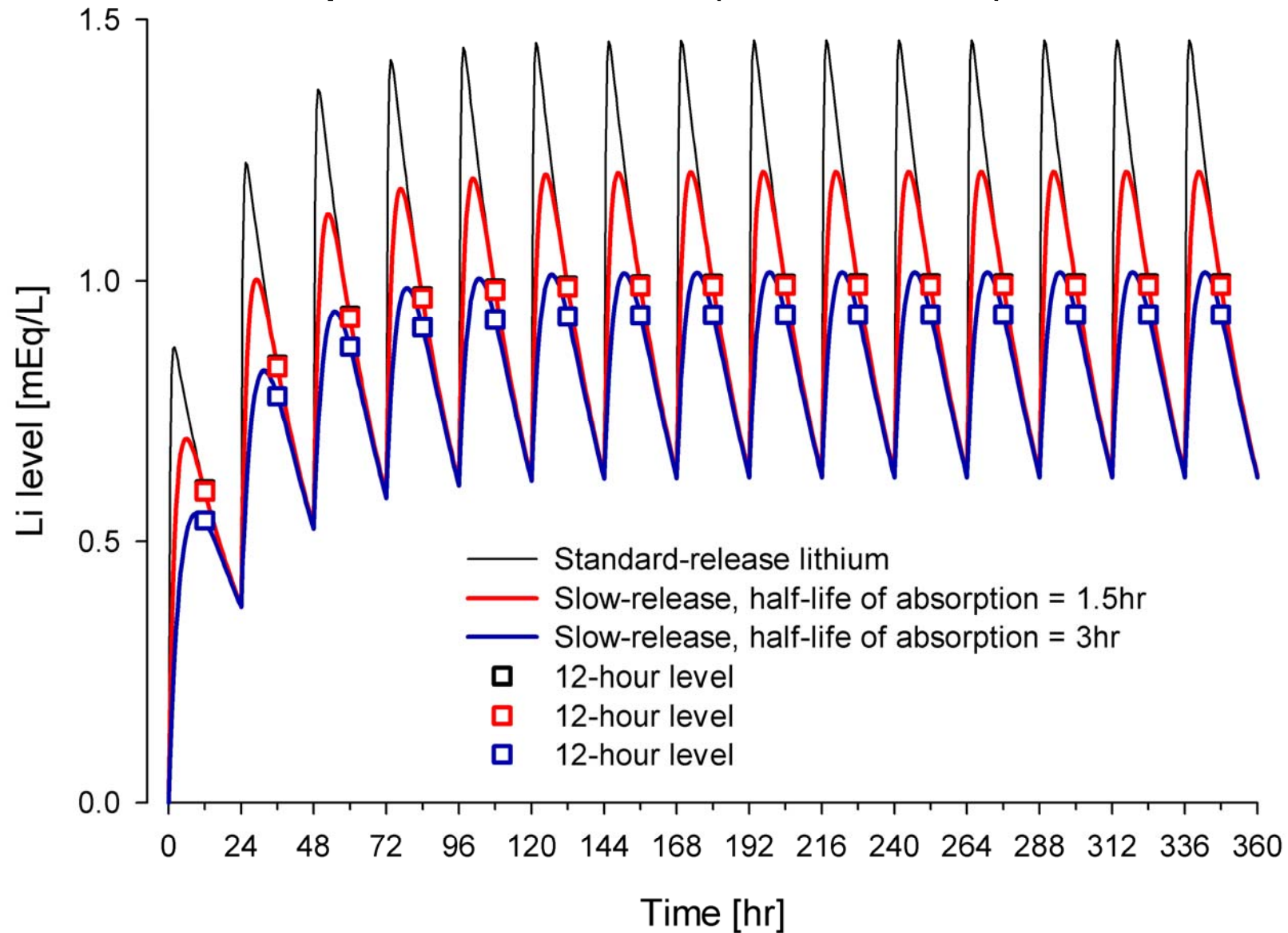
Pharmacokinetics and pharmacodynamics actions of lithium: the effects of lithium on particular organs in the body as well as its movement through the nephron



Plasma and brain lithium levels



Effect of absorption rate on the course of lithium plasma levels (Alda 2006)



Influence of Lithium on Peripheral Thyroid Physiology

