

What's new in the pharmacological treatment of bipolar disorder?

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Bipolar Disorder

1 in 100 people
Highly recurrent
Suicidality 30%

Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology

GM Goodwin¹, PM Haddad², IN Ferrier³, JK Aronson⁴, TRH Barnes⁵, A Cipriani¹, DR Coghill⁶, S Fazel¹, JR Geddes¹, H Grunze⁷, EA Holmes⁸, O Howes⁹, S Hudson¹⁰, N Hunt¹¹, I Jones¹², IC Macmillan¹³, H McAllister-Williams³, DR Miklowitz¹⁴, R Morriss¹⁵, M Munafò¹⁶, C Paton¹⁷, BJ Saharkian¹⁸, KEA Saunders¹, JMA Sinclair¹⁹, D Taylor²⁰, E Vieta²¹ and AH Young²²



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1–59

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Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology



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1-59

Table 1. Traditional evidence categories.

Evidence categories	Treatment studies	Observational studies
I	Meta-analysis of RCTs, at least one large, good-quality, RCT or replicated, smaller RCTs	Large representative population samples
II	Small, non-replicated RCTs, at least one controlled study without randomization or evidence from at least one other type of quasi-experimental study	Small, well designed but not necessarily representative samples
III	Non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies	Non-representative surveys, case reports
IV	Expert committee reports or opinions and/or clinical experience of BAP expert group	

Randomized Controlled Trials (RCTs) must have an appropriate control treatment arm; for primary efficacy this should include a placebo condition although for psychological treatments this may not be met. BAP: British Association for Psychopharmacology.

Table 2. Grades of recommendation and their relationship with supporting levels of evidence.

Grade of recommendation	Underlying methodology	Symbol
High	RCTs or double upgraded observational studies	****
Moderate	Downgraded RCTs or upgraded observational studies	***
Low	Double downgraded RCTs or observational studies	**
Very low	Triple downgraded RCTs or downgraded observational studies or case series/reports	*

PHASES OF TREATMENT

ACUTE



Control of acute symptoms

CONTINUATION



Maintain control of
acute episode

MAINTENANCE



Prevent or attenuate
new episodes

Goodwin FK, Jamison KR: *Manic-Depressive Illness*; 1990.

PHASES OF TREATMENT

ACUTE MANIC
EPISODE

ACUTE
DEPRESSIVE
EPISODE

CONTINUATION

CONTINUATION

LONG-TERM TREATMENT
PREVENTION

ACUTE MANIC EPISODES

OVERVIEW POINTS

- Most patients with mania will require short term treatment with medicines in an appropriate setting. (I)
- Evidence from network meta-analysis is coherent.
- Choice of drug should reflect the balance of benefit and harm for a given individual.
- If successful treatment has been initiated for mania, long term treatment should be considered. (S)
- Drug discontinuation should be planned in relation to the need for maintenance treatment. (S) Remission will often occur within 3 months (I) but mood stability may require 6 months or more to achieve.

ACUTE MANIC EPISODES

NOT ALREADY TAKING LONG-TERM TREATMENT

SEVERE MANIC EPISODES

- Oral administration of dopamine antagonist. ****
- Alternatives
 - Valproate
 - Lithium
 - Aripiprazole
 - Carbamazepine
- Parenteral dopamine antagonists/partial agonists and GABA modulator use should follow established protocols.
- To promote sleep, consider GABA modulating drugs. ***
- Drugs for depression should usually be tapered and discontinued in a manic episode. **

HYPOMANIA

- Treatment can be extrapolated from practice in mania.

ACUTE MANIC EPISODES

WHILST TAKING LONG-TERM TREATMENT

INADEQUATE SYMPTOM CONTROL

- Ensure the highest well-tolerated dose of current treatment offered.
- Increases in dose may be sufficient for those taking dopamine antagonists/partial antagonists or valproate.
- Lithium Check serum concentrations.
 - Consider aiming for higher end of 0.6-0.8 mmol/L.
 - Concentrations of 0.8-1.0 may be more effective but carry risks in the long term.
 - Consider adding a dopamine antagonist/partial agonist/valproate.

POOR ADHERENCE

- Establish the cause and offer an appropriate intervention.
- With deliberate poor adherence, lithium use may not be indicated.

ACUTE MANIC EPISODES

OTHER CONSIDERATIONS

INADEQUATE RESPONSE TO FIRST-LINE MEDICINE

- Consider the combination of lithium or valproate with a dopamine antagonists or partial agonist * * * *
- Consider clozapine in more refractory illness. * *
- ECT may be considered for:
 - Those who express a preference for it.
 - Patients whose mania is particularly severe or treatment resistant.
 - Patients with severe mania in pregnancy. * * *

MIXED FEATURES

- DSM-5 would have us identify mixed features rather than mixed episodes.
- Treatment as for mania would be appropriate.

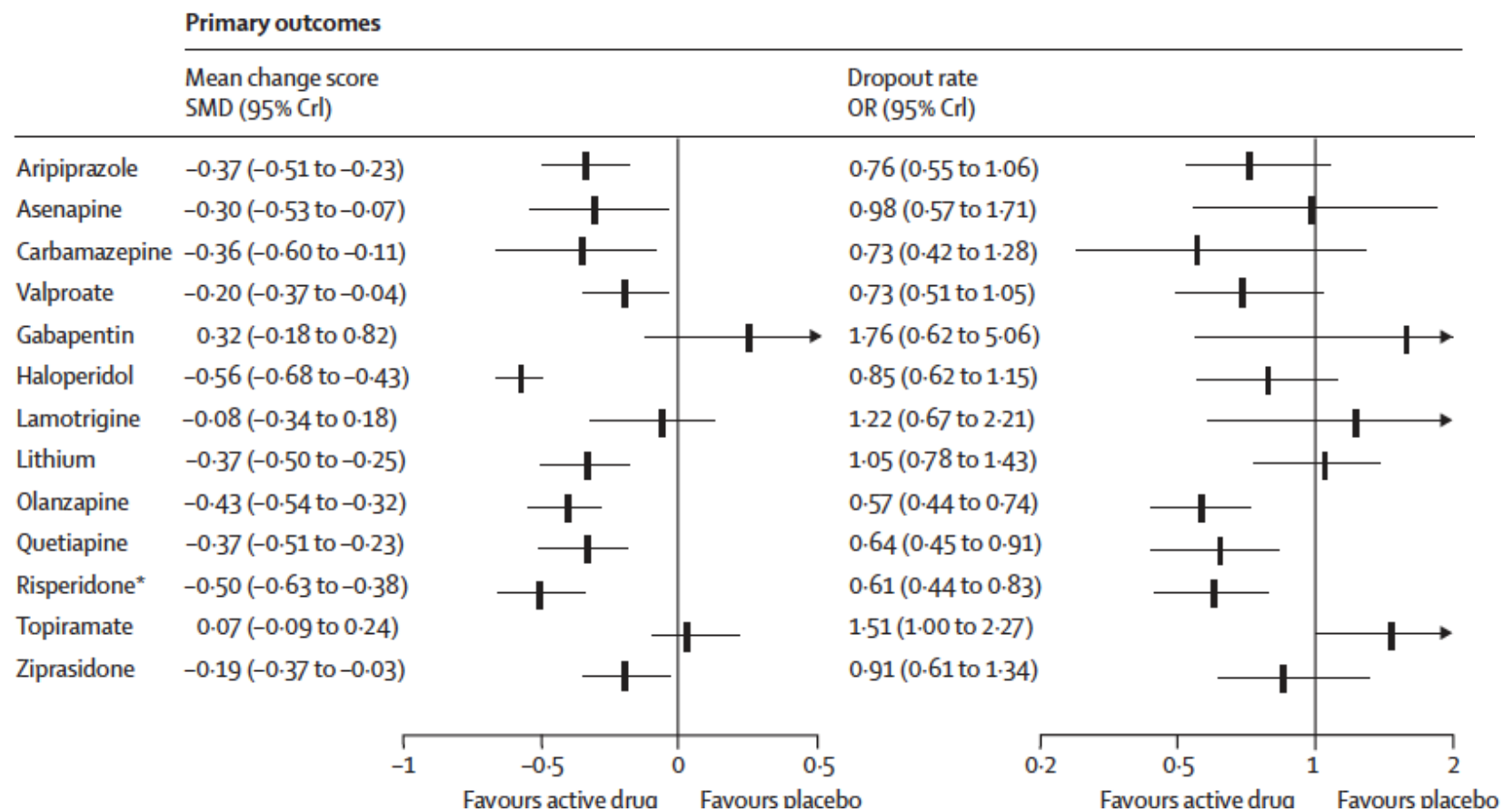


Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

Andrea Cipriani, Corrado Barbui, Georgia Salanti, Jennifer Rendell, Rachel Brown, Sarah Stockton, Marianna Purgato, Loukia M Spineli, Guy M Goodwin, John R Geddes

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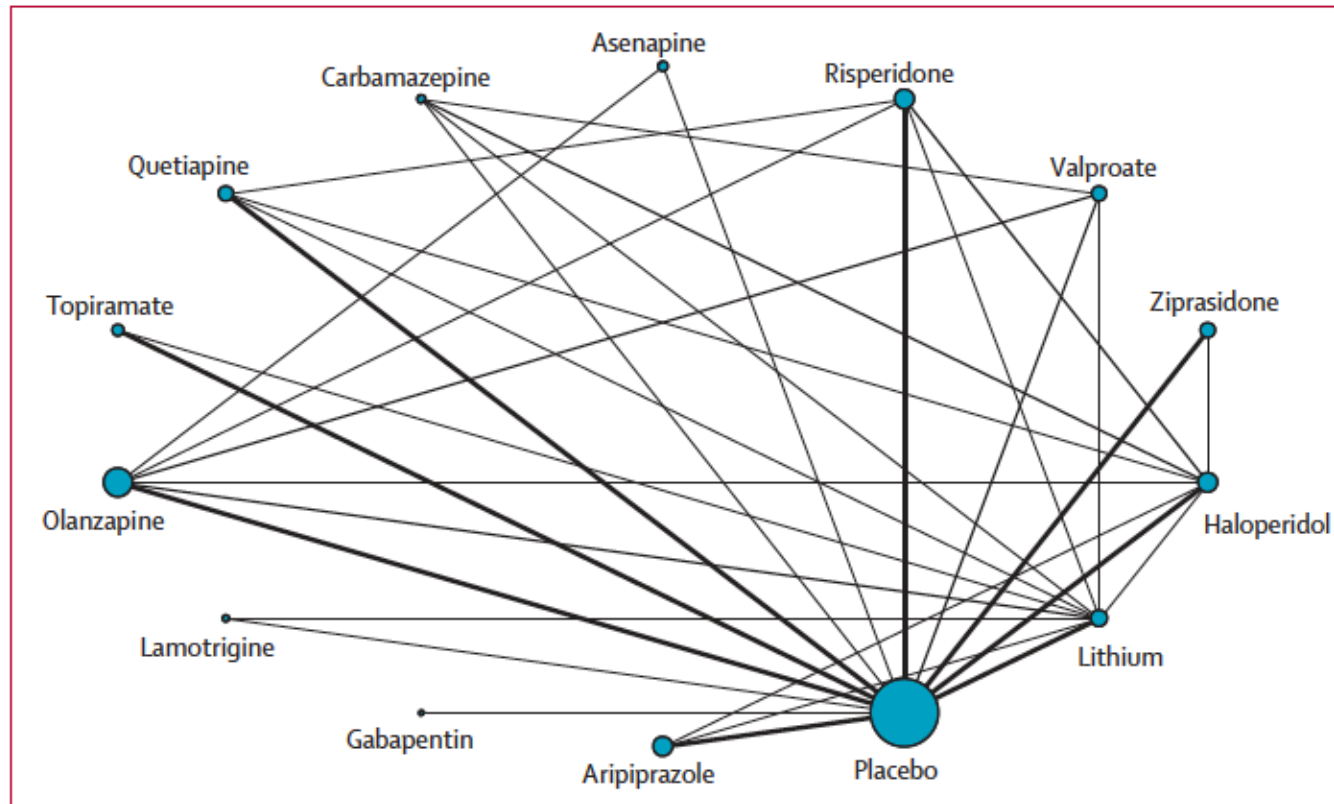
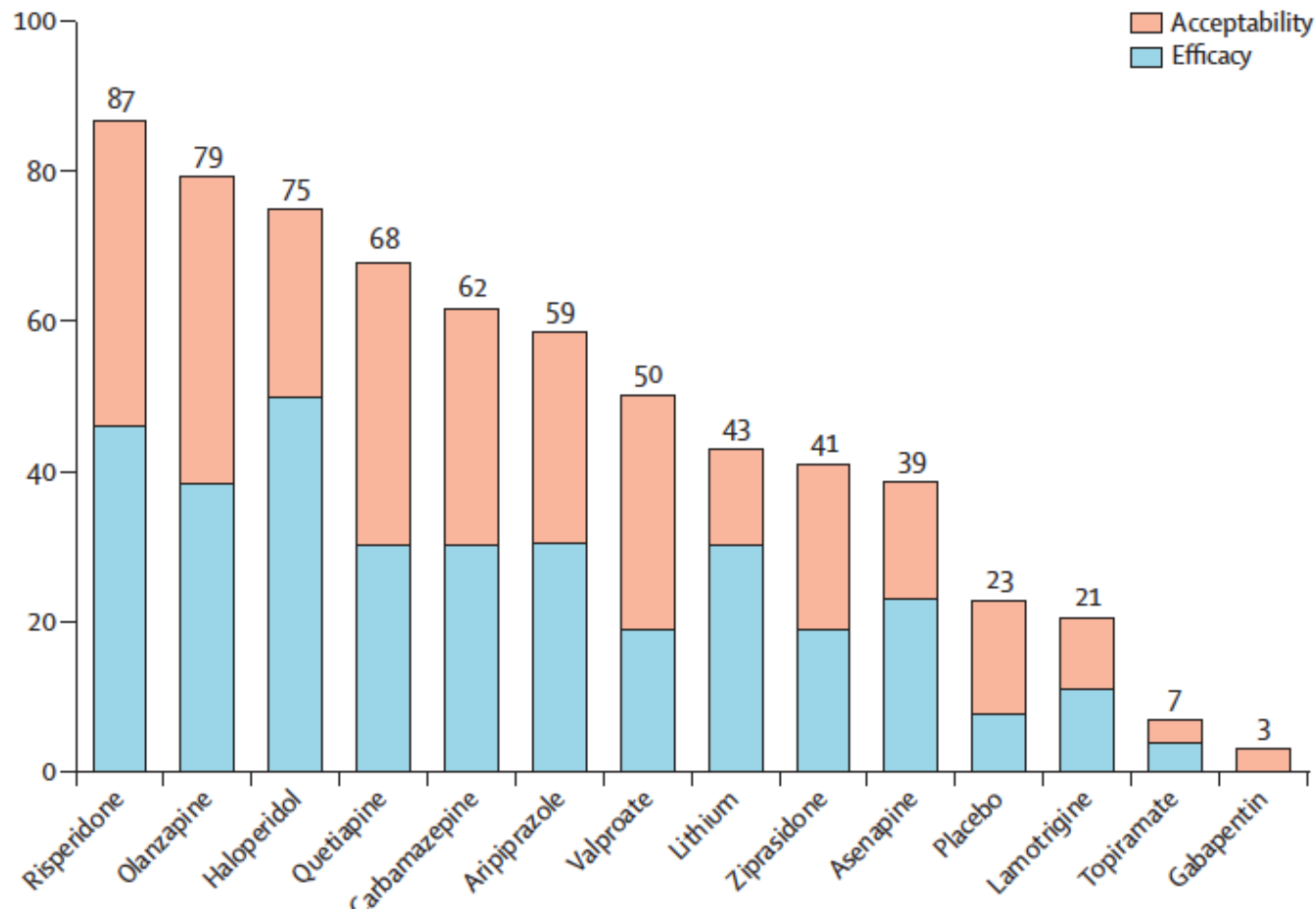


Figure 2: Network of eligible comparisons for the multiple-treatments meta-analysis for efficacy
The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomised participants (sample size). The networks of eligible comparisons for acceptability analysis (dropout rate) and for efficacy as binary outcome are similar (webappendix pp 26–27).

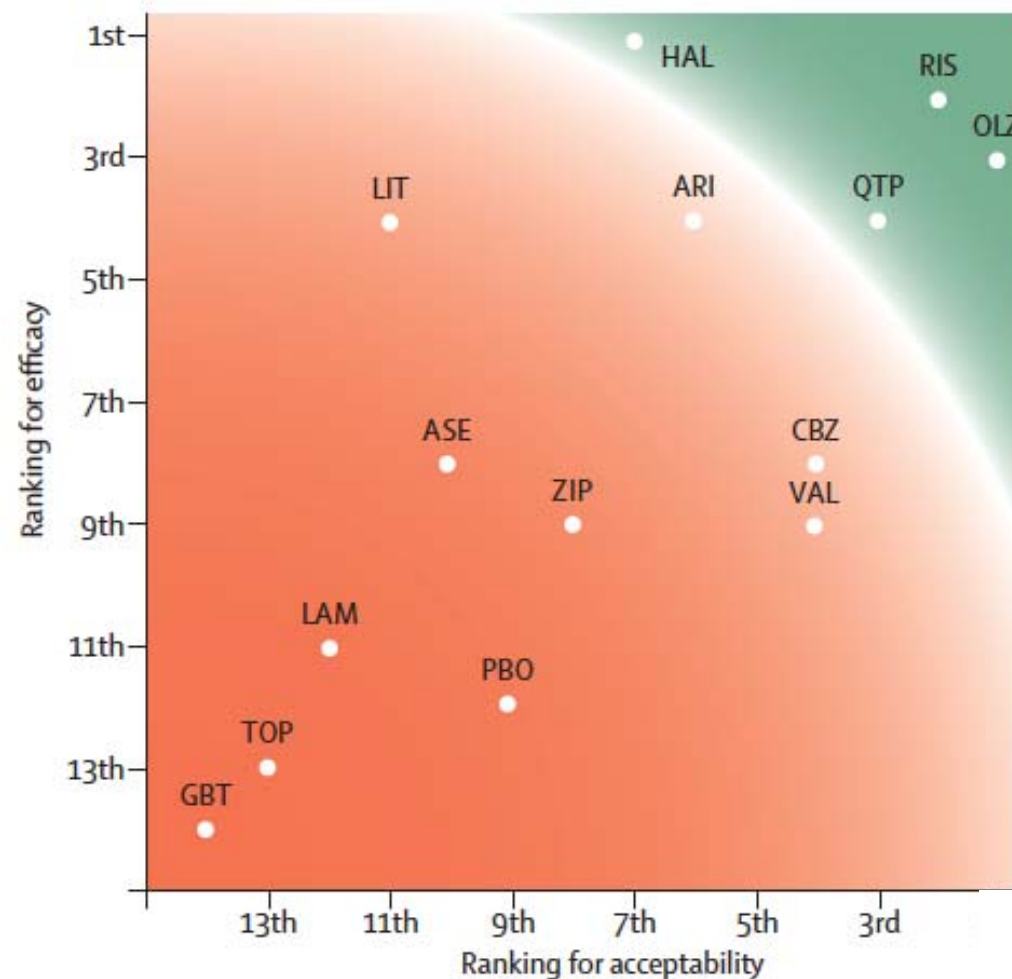
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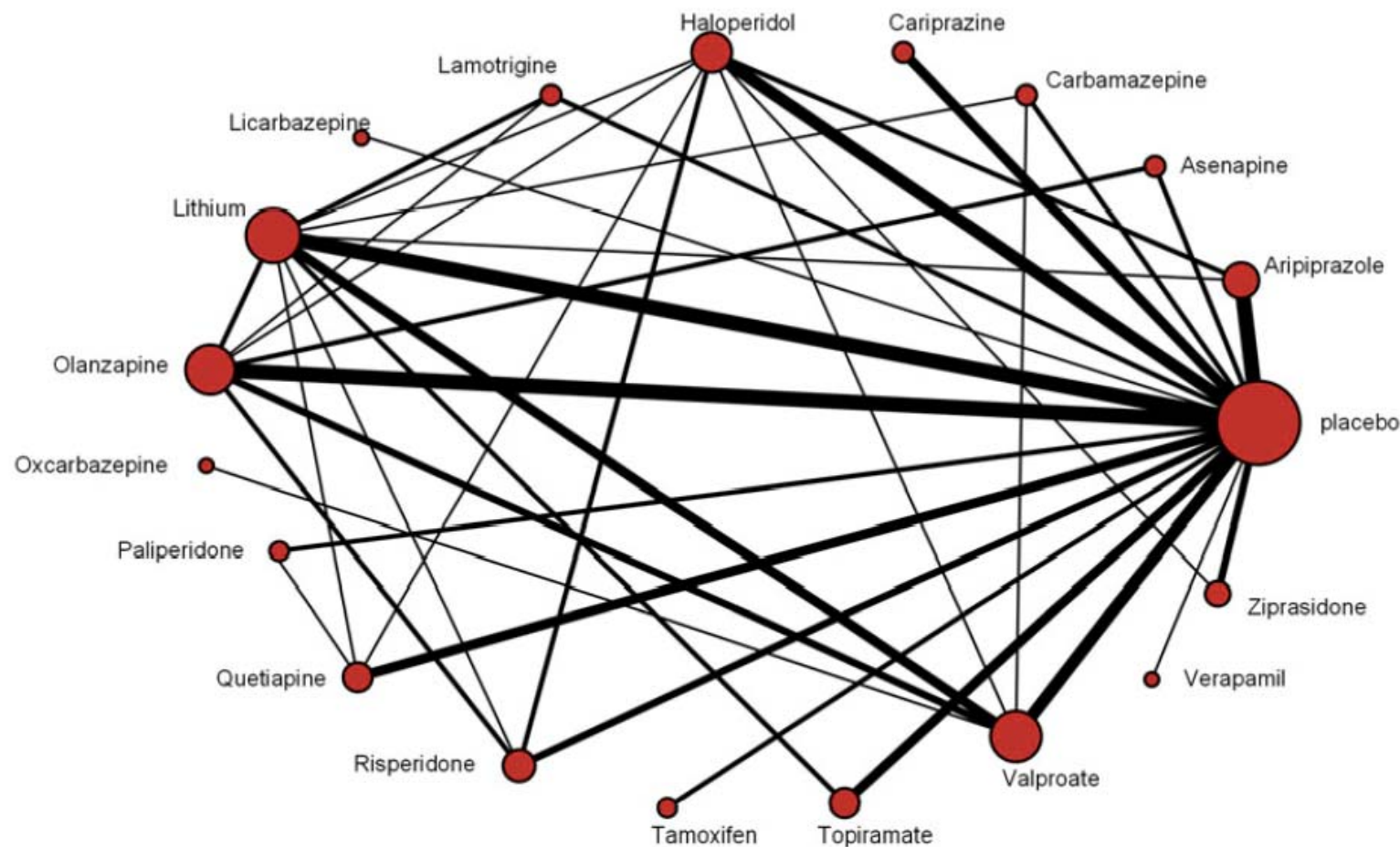
Andrea Cipriani, Corrado Barbui, Georgia Salanti, Jennifer Rendell, Rachel Brown, Sarah Stockton, Marianna Purgato, Loukia M Spineli, Guy M Goodwin, John R Geddes



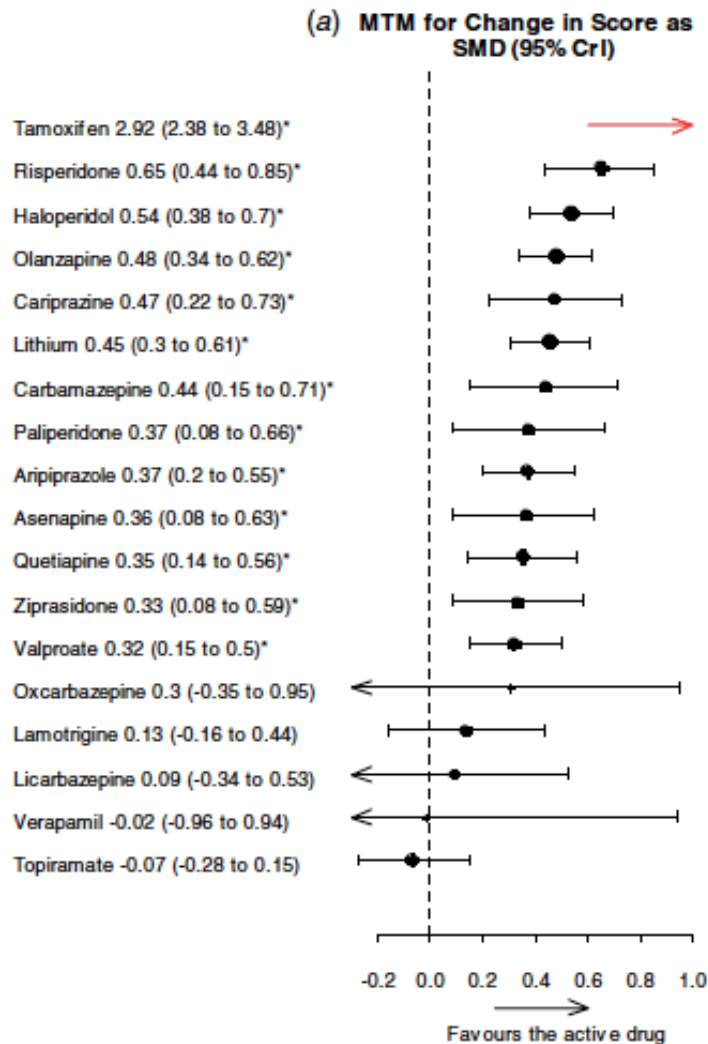
Lancet 2011; 378: 1306-15

A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania

A. Yildiz^{1,2*}, M. Nikodem³, E. Vieta^{2,4}, C. U. Correll⁵ and R. J. Baldessarini^{2,6}



A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania



This updated network by differential exclusion of all add-on or combination trials ($N = 15$ RCTs, 32 study arms, 13 treatments), and also four apparently single-agent trials ($N = 4$, eight study arms, Lerer *et al.* 1987; Brown *et al.* 1989; Ortega Soto, 1993; Pfizer, 2008); along with further consideration of three recent cariprazine (Knesevich *et al.* 2009; Bose *et al.* 2012; Calabrese *et al.* 2013), one licarbazepine (Novartis, 2007), two tamoxifen (Zarate *et al.* 2007; Yildiz *et al.* 2008), and one verapamil (Janicak *et al.* 1998) trials ($N = 7$ RCTs, 13 study arms, four new treatments), is different than the previous one in 53 data points deriving from 29 comparisons (Cipriani *et al.* 2011).

The present total of 57 studies, reported up to 15 January 2014, involved 95 direct comparisons with 14256 randomized participants.

Clinically relevant response and remission outcomes in cariprazine-treated patients with bipolar I disorder

Willie Earley^{a,*}, Suresh Durgam^a, Kaifeng Lu^a, Adam Ruth^{b,1}, György Németh^c, István Laszlovszky^c, Lakshmi N. Yatham^d

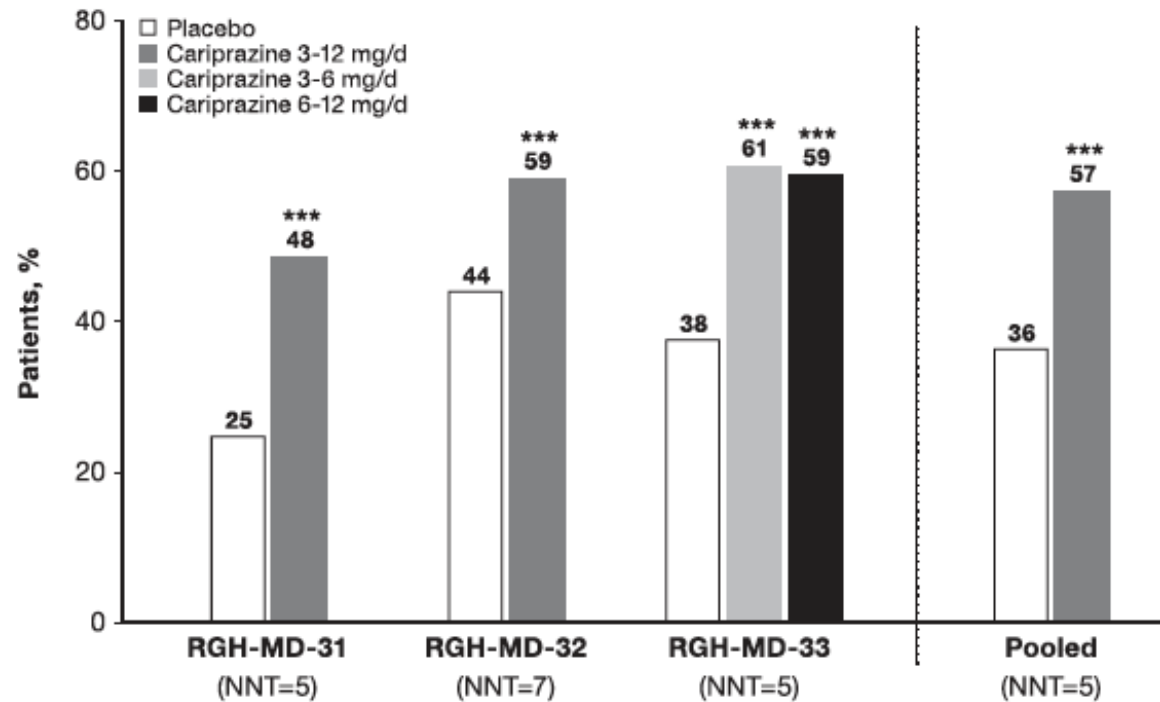


Fig. 1. Rate of response at week 3 ($\geq 50\%$ improvement in YMRS total score). Response in RGH-MD-31, RGH-MD-32, and RGH-MD-33 was based on logistic regression, with treatment group and baseline YMRS total score as explanatory values. Missing values were imputed using last observation carried forward (LOCF). *** $P < .001$. NNT, number needed to treat; YMRS, Young Mania Rating Scale.

GERI-BD: A Randomized Double-Blind Controlled Trial of Lithium and Divalproex in the Treatment of Mania in Older Patients With Bipolar Disorder

Objective: Clinicians treating older patients with bipolar disorder with mood stabilizers need evidence from age-specific randomized controlled trials. The authors describe findings from a first such study of late-life mania.

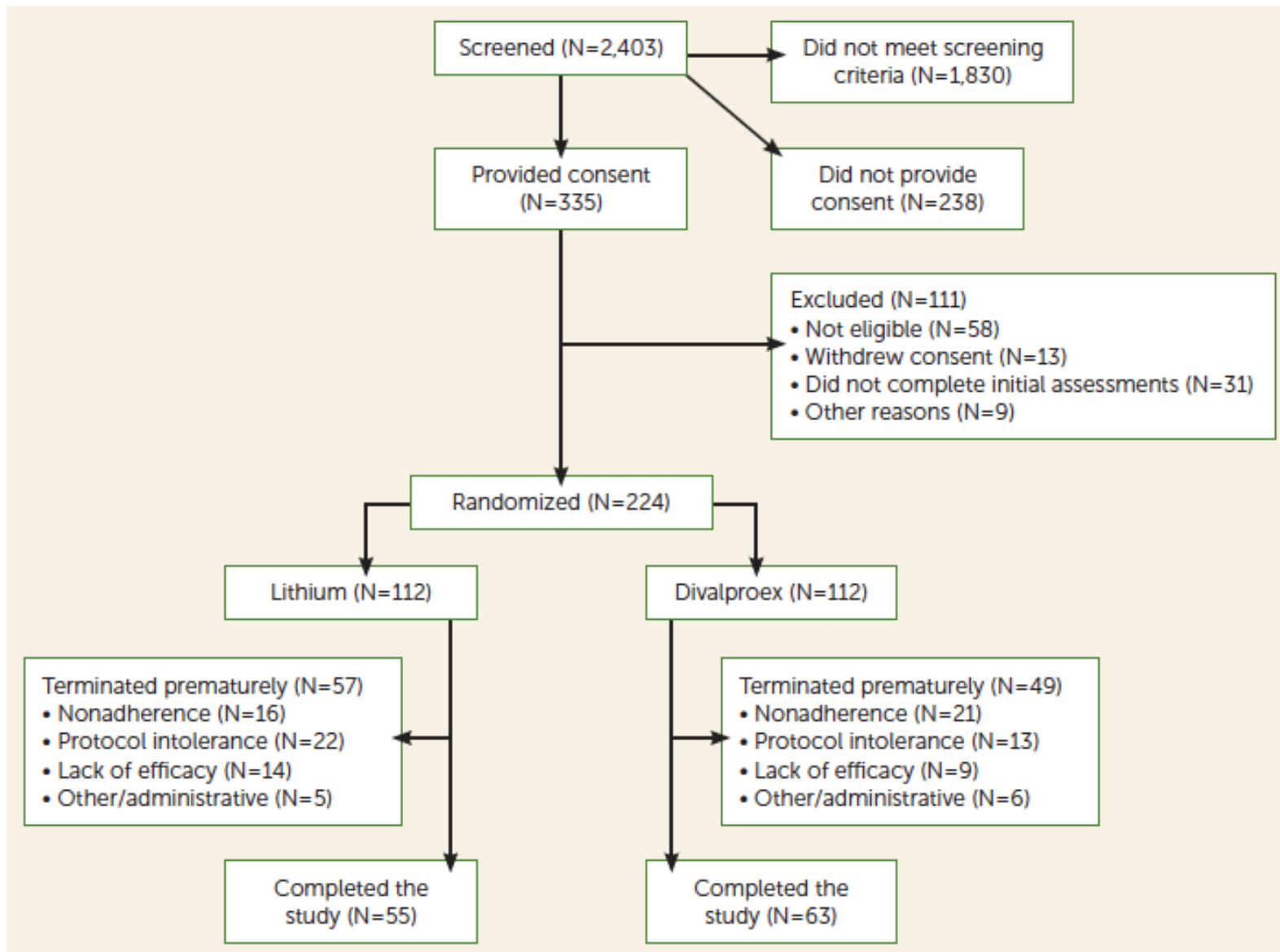
Method: The authors compared the tolerability and efficacy of lithium carbonate and divalproex in 224 inpatients and outpatients age 60 or older with bipolar I disorder who presented with a manic, hypomanic, or mixed episode. Participants were randomly assigned, under double-blind conditions, to treatment with lithium (target serum concentration, 0.80–0.99 mEq/L) or divalproex (target serum valproate concentration, 80–99 µg/mL) for 9 weeks. Participants with an inadequate response after 3 weeks received open adjunctive risperidone. The authors hypothesized that divalproex would be better tolerated and more efficacious than lithium. Tolerability was assessed based on a measure of sedation and on the proportions of participants achieving target concentrations. Efficacy was assessed with the Young Mania Rating Scale (YMRS).

Results: Attrition rates were similar for lithium and divalproex (14% and 18% at week 3 and 51% and 44% at week 9, respectively). The groups did not differ significantly in sedation. Participants in the lithium group tended to experience more tremor. Similar proportions of participants in the lithium and divalproex groups achieved target concentrations (57% and 56%, respectively). A longitudinal mixed model of improvement (change from baseline in YMRS score) favored lithium (change in score, 3.90; 97.5% CI=1.71, 6.09). Nine-week response rates did not differ significantly between the lithium and divalproex groups (79% and 73%, respectively). The need for adjunctive risperidone was low and similar between groups (17% and 14%, respectively).

Conclusions: Both lithium and divalproex were adequately tolerated and efficacious; lithium was associated with a greater reduction in mania scores over 9 weeks.

Am J Psychiatry 2017; 174:1086–1093; doi:10.1176/appi.ajp.2017.15050657

FIGURE 1. CONSORT Chart for a Trial of Lithium and Divalproex for the Treatment of Mania in Older Patients With Bipolar Disorder^a



GERI-BD: A Randomized Double-Blind Controlled Trial of Lithium and Divalproex in the Treatment of Mania in Older Patients With Bipolar Disorder

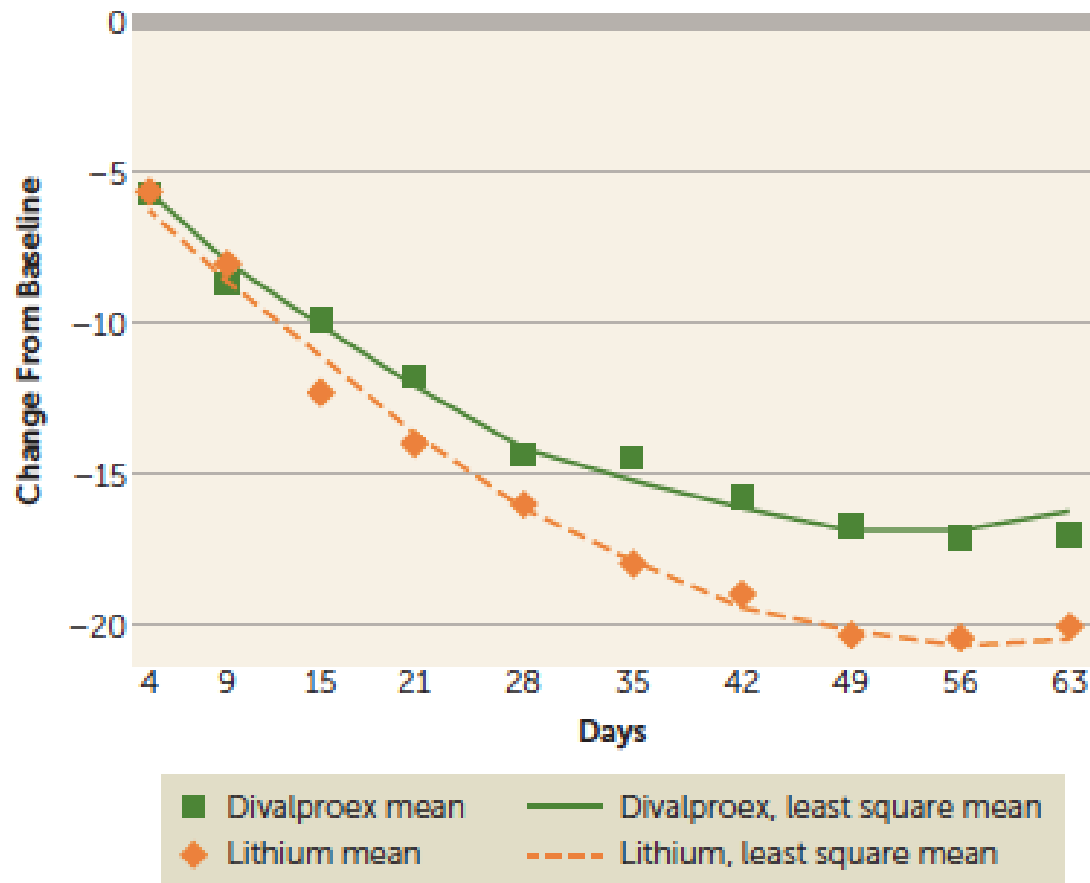


FIGURE 2. Change From Baseline in Young Mania Rating Scale Score in a Trial of Lithium and Divalproex for the Treatment of Mania in Older Patients With Bipolar Disorder^a

Am J Psychiatry 174:11, November 2017

ACUTE DEPRESSIVE EPISODES

OVERVIEW POINTS

- The evidence from network meta-analysis of available RCTs supports the efficacy of a limited range of individual medicines.
- Networks may not be stable
 - rankings strongly influenced by inclusion criteria
 - indirect comparisons sometimes contradict direct comparisons
- The medicines have different pharmacologies and weights of evidence.
- There remains uncertainty over the option of using drugs for depression (antidepressants) in bipolar disorder.
- If successful treatment has been initiated for depression, long term treatment should be considered. (S)

ACUTE DEPRESSIVE EPISODES

NOT ALREADY TAKING LONG-TERM TREATMENT

- Consider quetiapine, lurasidone or olanzapine. ***
- Antidepressants have not been adequately studied in bipolar disorder.
 - only olanzapine/fluoxetine in combination has support as a specific treatment. ***
 - if antidepressants are used, they should be co-prescribed with a drug for mania.
- Consider lamotrigine (incremental dosing) usually as an addition to agents preventing recurrence of mania.****
- Consider ECT for:
 - high suicide risk
 - treatment resistance
 - psychosis
 - severe depression in pregnancy
 - life-threatening inanition***
- Lithium may be considered in less severe cases (limited evidence but prelude to long-term treatment) **

ACUTE DEPRESSIVE EPISODES

WHILST TAKING LONG-TERM TREATMENT

- Ensure that the current choice of long-term treatment is likely to protect the patient from manic relapse.
- Check doses are adequate and that serum concentrations of lithium are in the therapeutic range. (S)
- Address current stressors, if any. (S)
- If episode fails to respond to optimisation, follow recommendations outlined for depressive episode.

ACUTE DEPRESSIVE EPISODES

OTHER CONSIDERATIONS

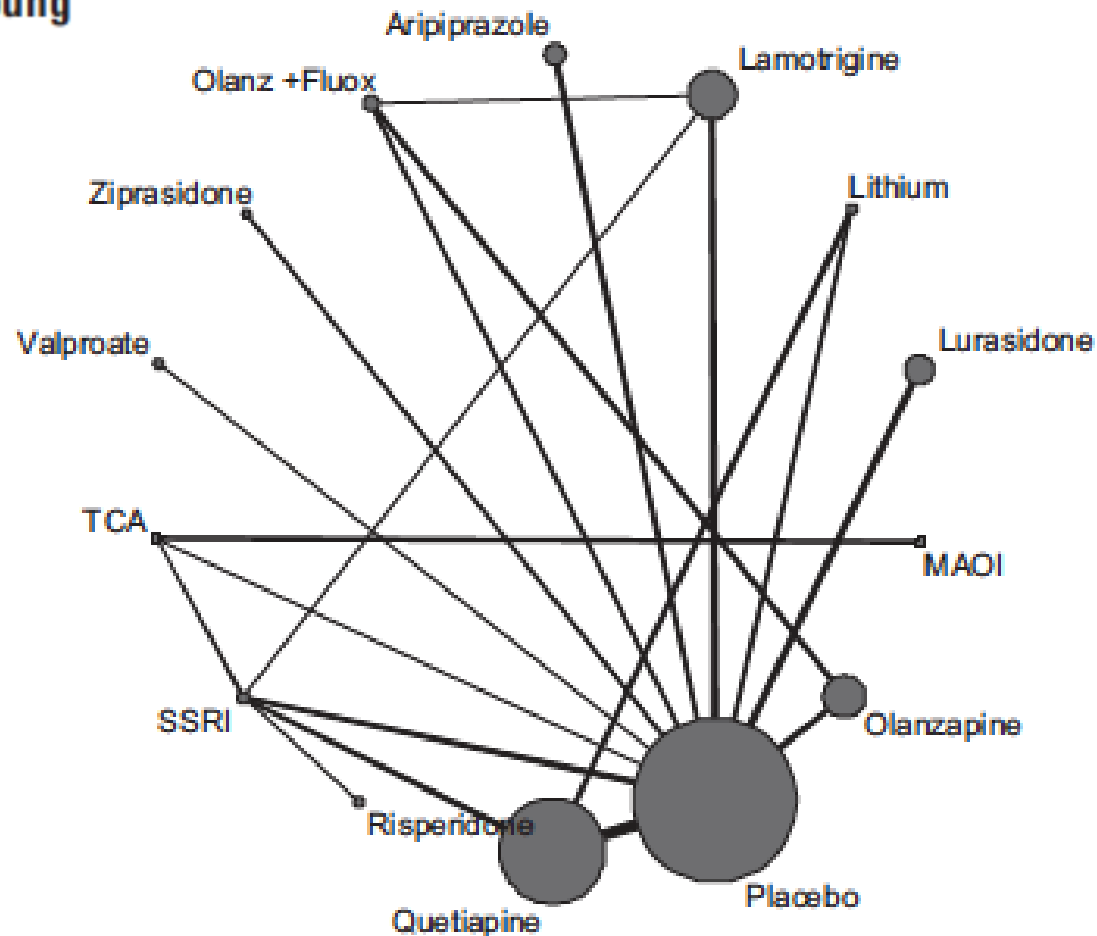
TREATMENT RESISTANT BIPOLAR DEPRESSION

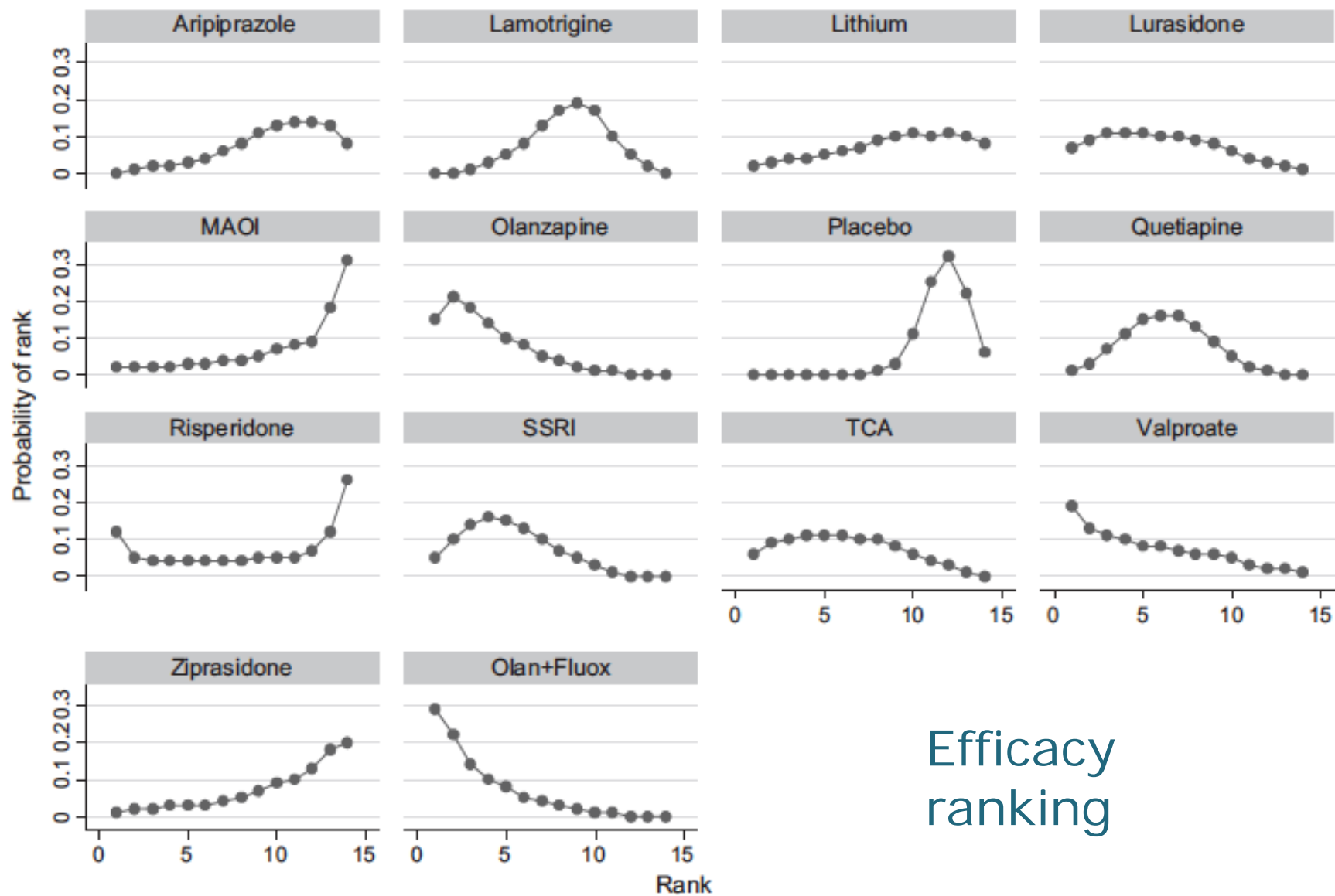
Treatment resistant bipolar depression lacks operational criteria.

- Known to occur (I) and suggested as a failure to respond not just to an antidepressant but also quetiapine, olanzapine, lurasidone and lamotrigine singly and in combination.
- Little trial evidence to support options:
 - ECT can be considered.***
 - Augmentation can be extrapolated from unipolar depression but not before evidence based bipolar disorder options exhausted.
 - Antimanic cover will be necessary

Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis

D. M. Taylor^{1,2}, V. Cornelius³,
L. Smith⁴, A. H. Young⁵





Efficacy
ranking

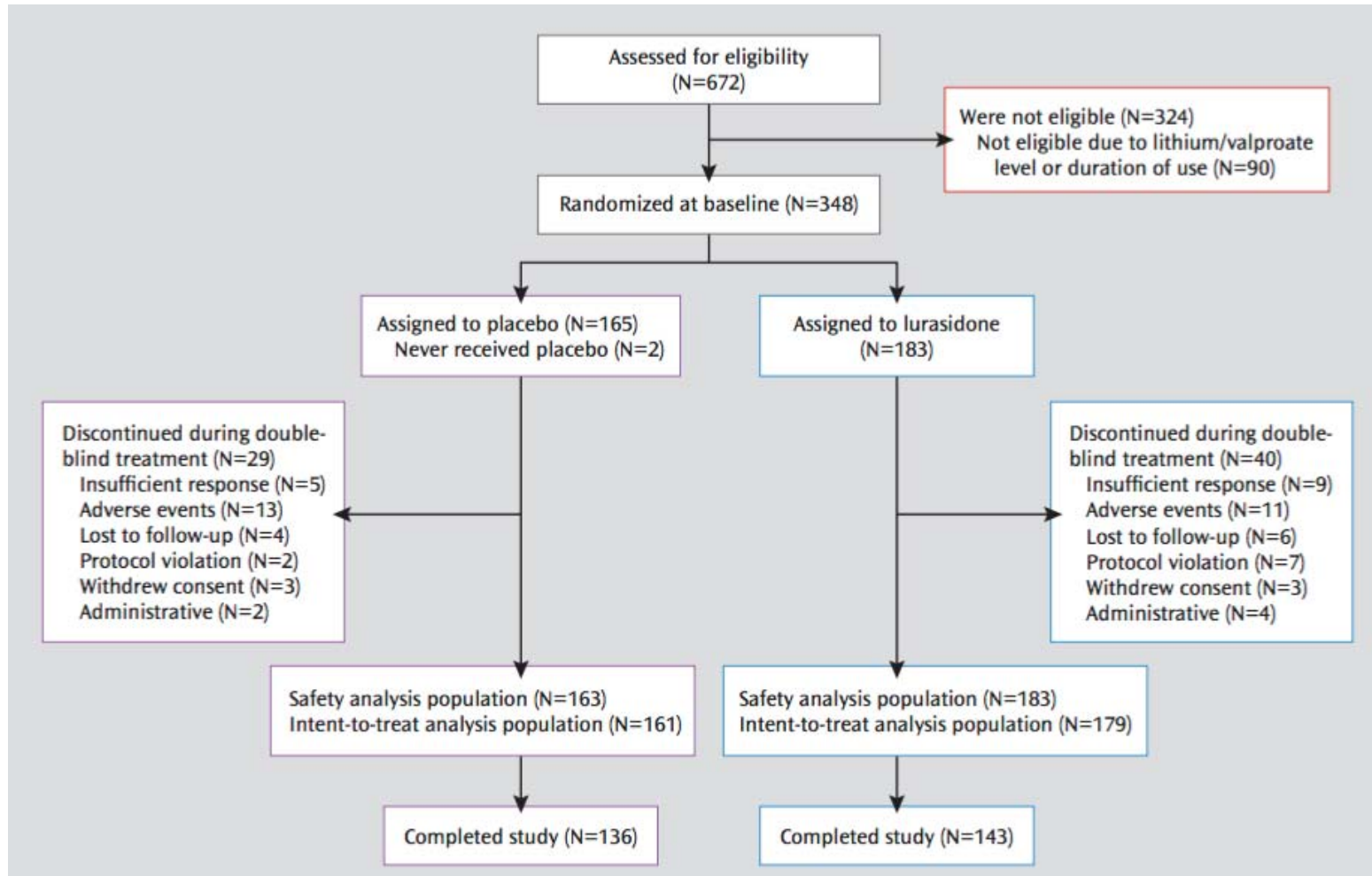
Fig. 3. 'Rankogram' showing the probability of rank for efficacy (SMD) by treatment. Higher probability of lower rank (i.e. 1) is favourable.



Switch to mania ranking

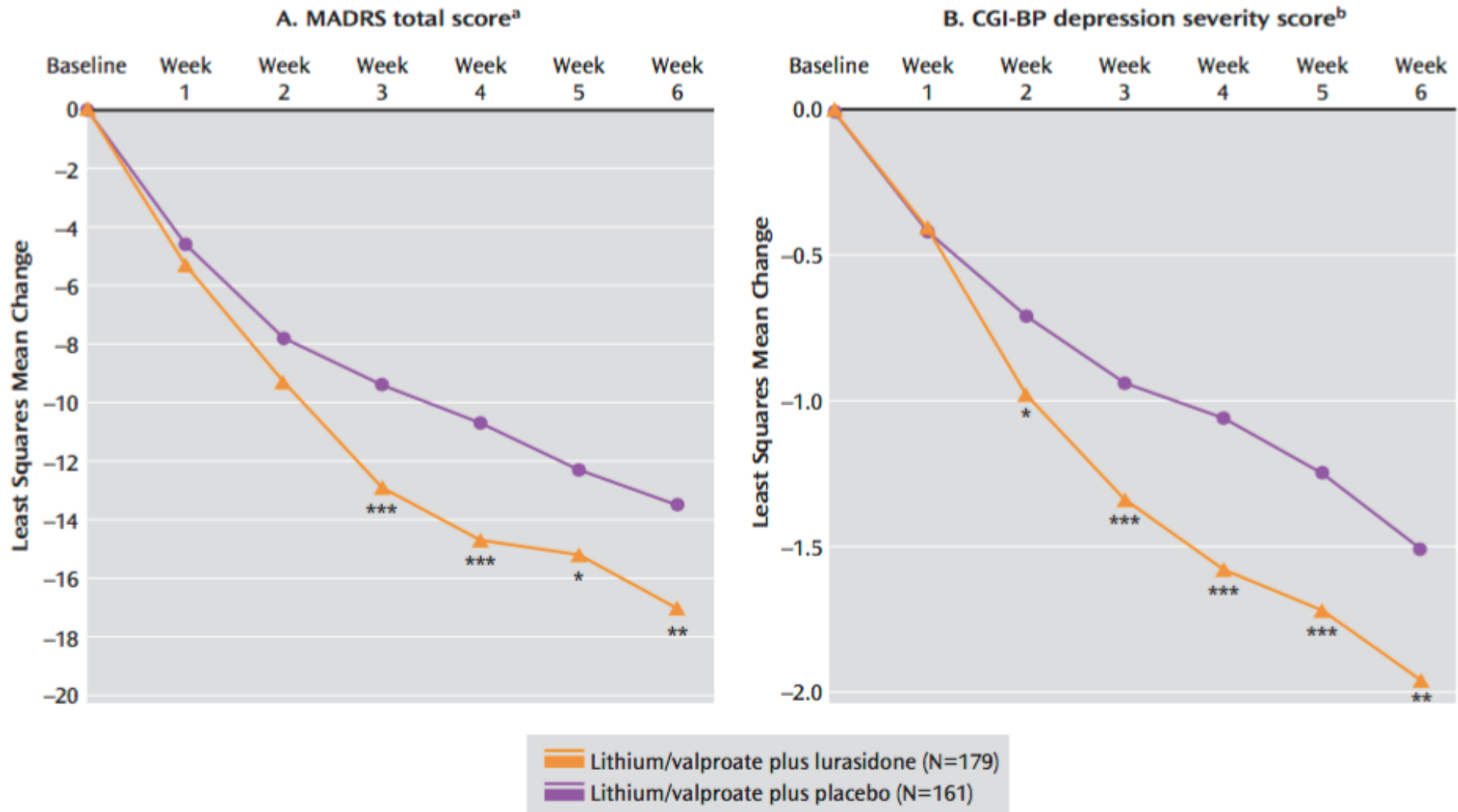
Fig. 5. 'Rankogram' showing probability of rank of 'switch to mania' by treatment. Higher probability of lower rank (i.e. 1) is favourable.

Lurasidone as Adjunctive Therapy With Lithium or Valproate for the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study



(Am J Psychiatry 2014; 171:169–177)

FIGURE 2. Change From Baseline in Key Efficacy Measures



(Am J Psychiatry 2014; 171:169–177)

Lurasidone Monotherapy in the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study

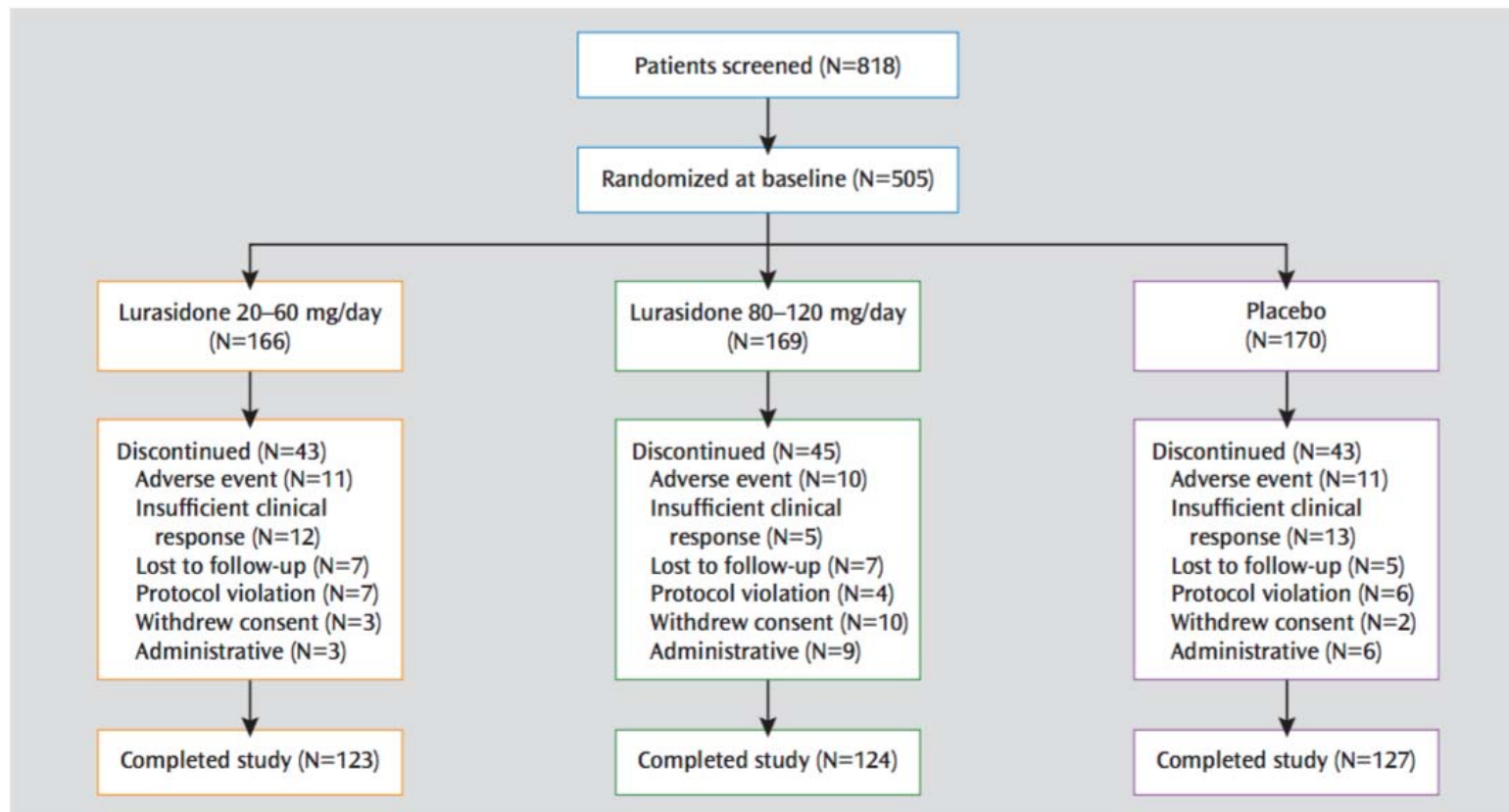
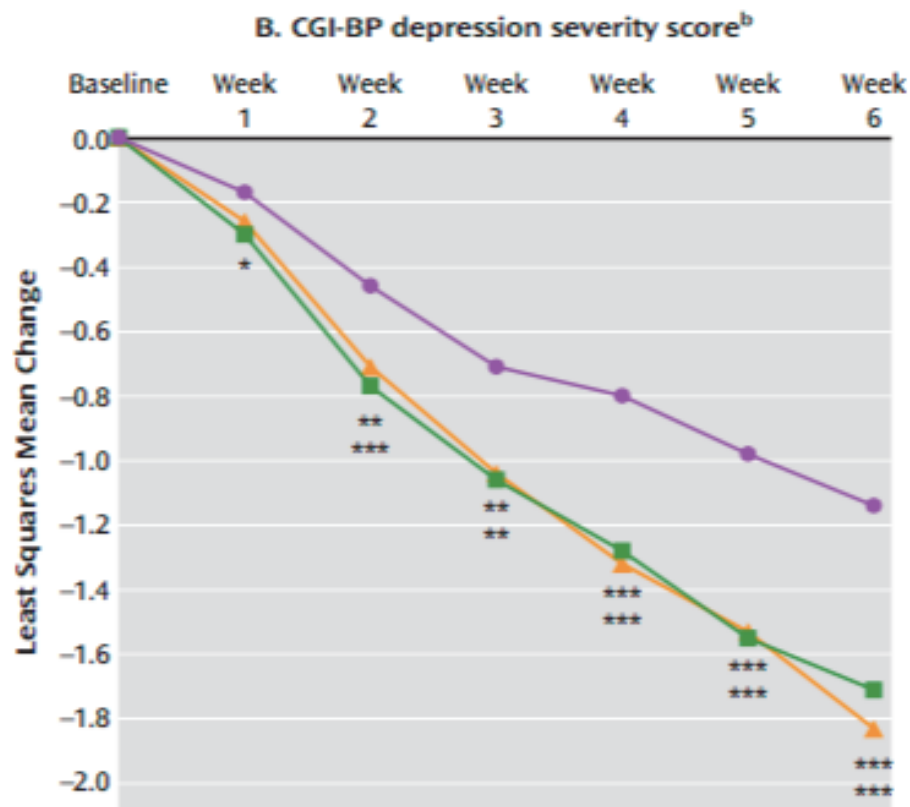
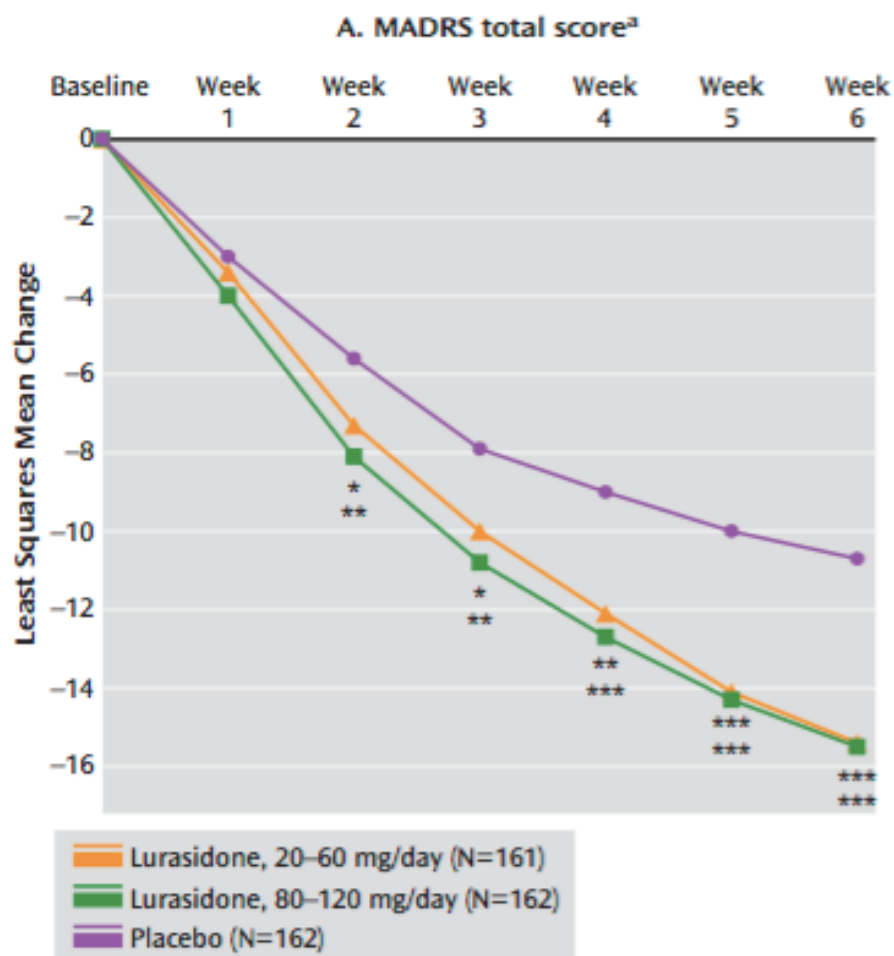


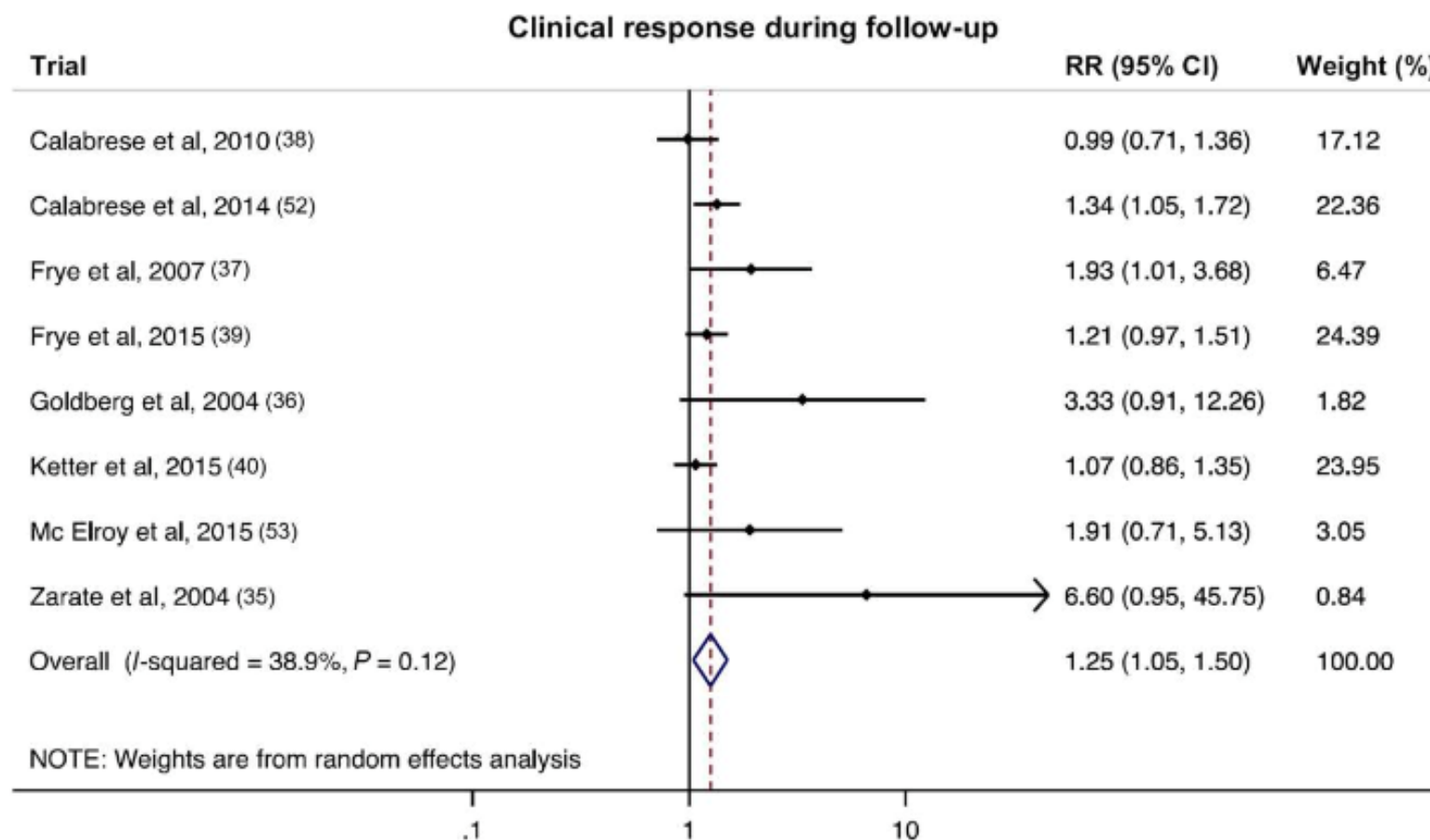
FIGURE 2. Change From Baseline in Key Efficacy Measures



(Am J Psychiatry 2014; 171:160–168)

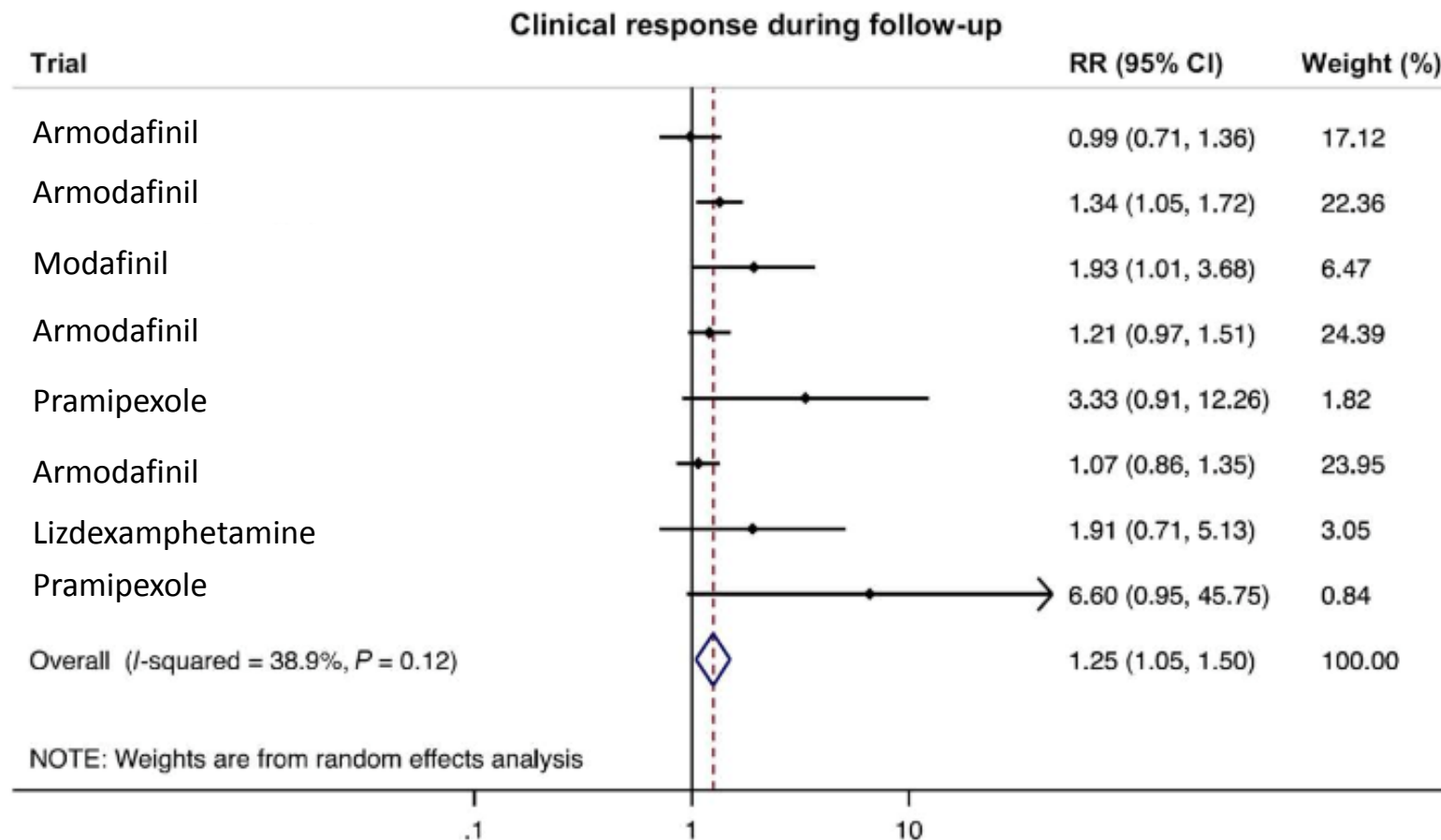
Dopaminergic agents in the treatment of bipolar depression: a systematic review and meta-analysis

Acta Psychiatr Scand 2017; 135: 527–538



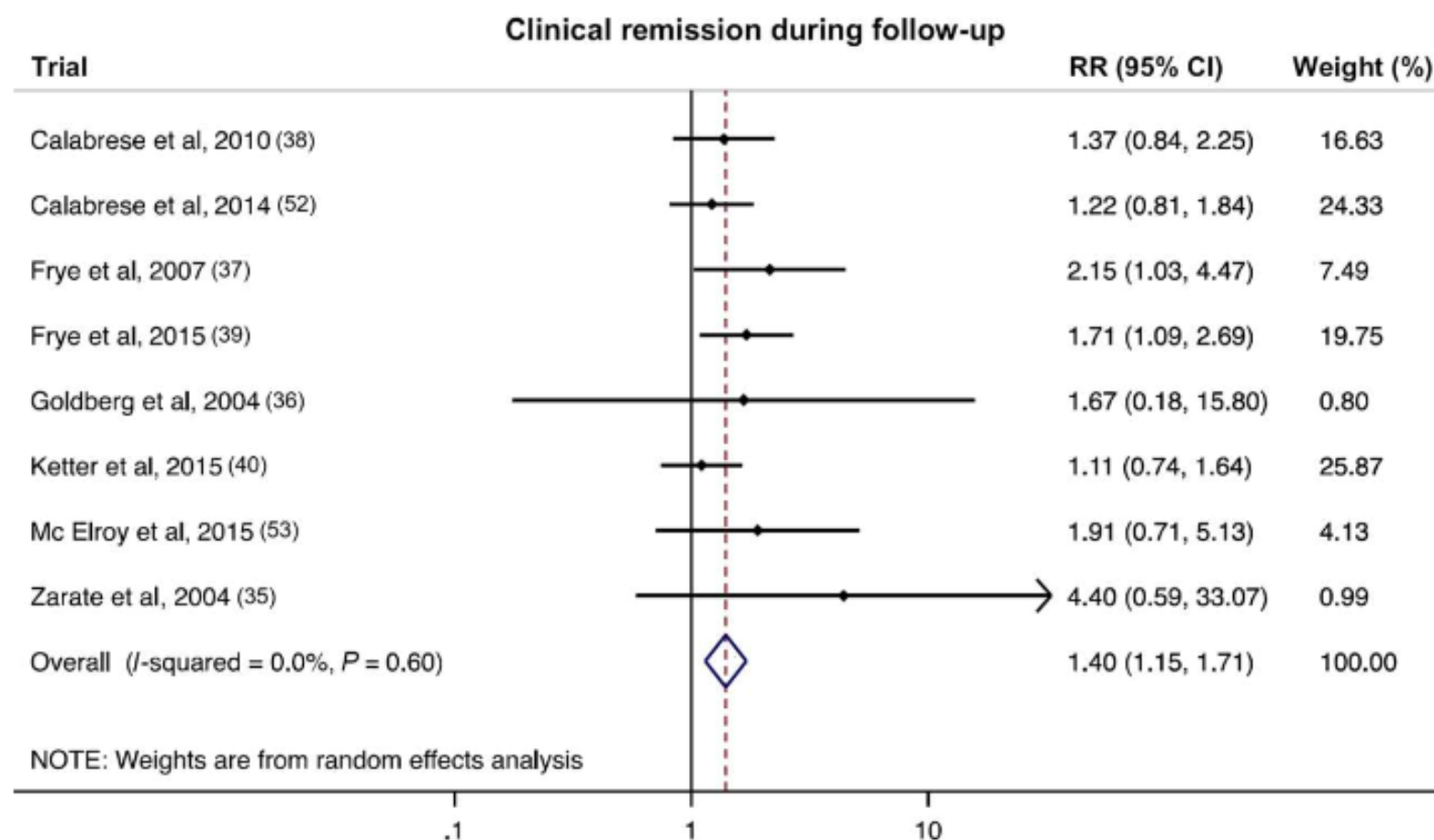
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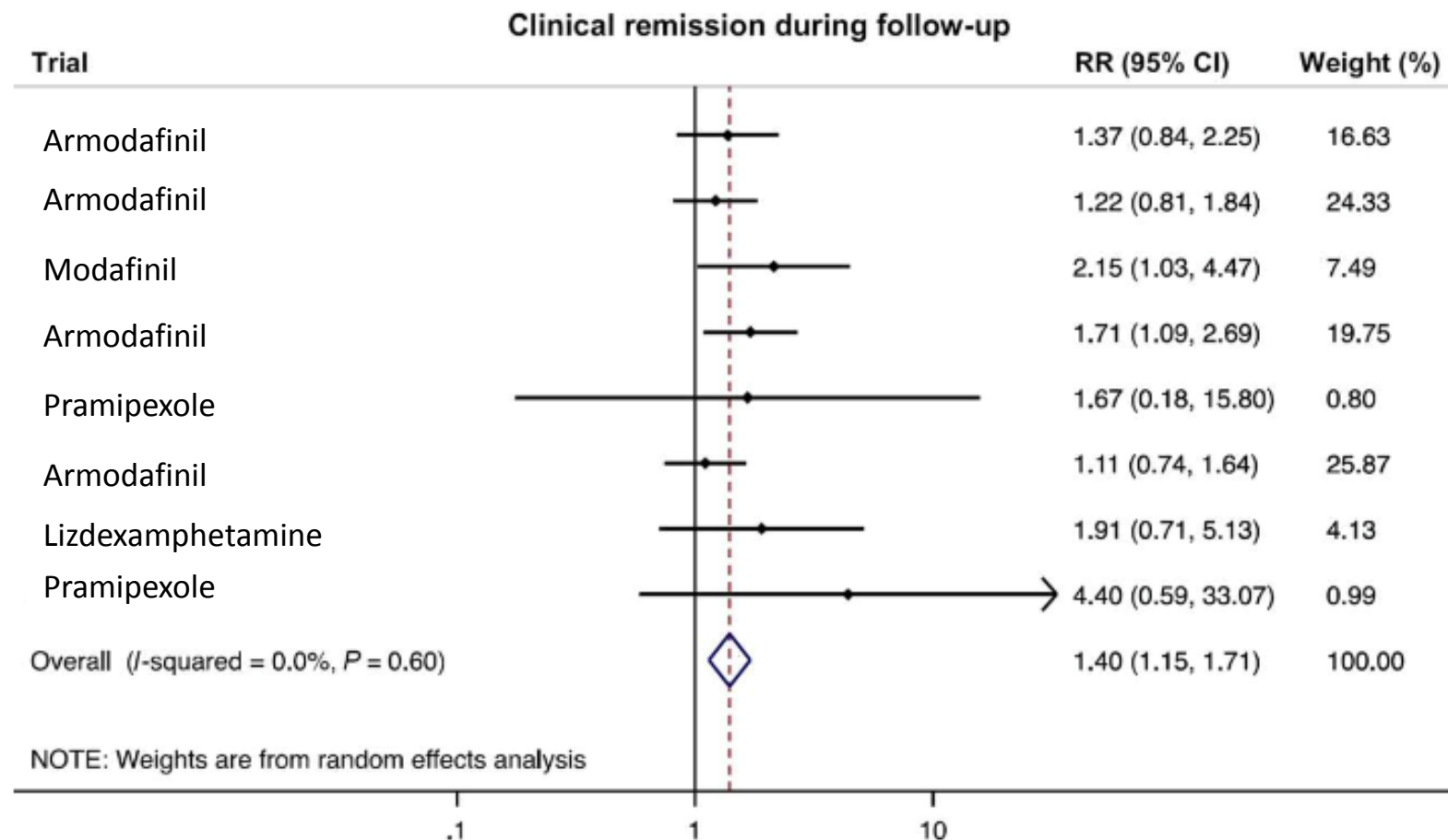
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A Placebo-Controlled Evaluation of Adjunctive Modafinil in the Treatment of Bipolar Depression

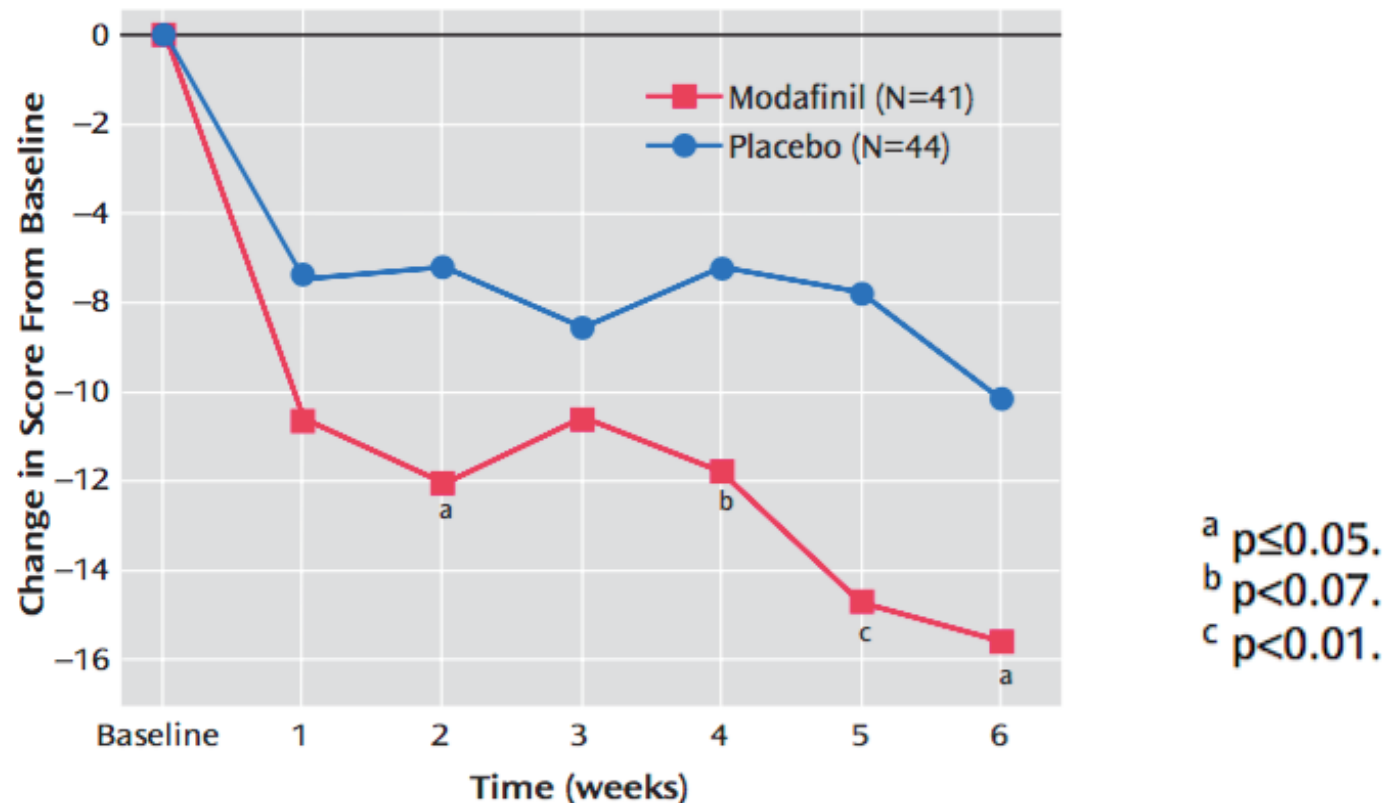


FIGURE 2. Mixed-Model Repeated-Measures Analysis of the Time Course of Antidepressant Response According to Inventory for Depressive Symptoms Score, Controlling for Baseline Score, in 85 Patients With Bipolar Depression Receiving Adjunctive Modafinil or Placebo (Intent-to-Treat Population)

(Am J Psychiatry 2007; 164:1242–1249)

Pramipexole for Bipolar II Depression: A Placebo-Controlled Proof of Concept Study

Carlos A. Zarate, Jr., Jennifer L. Payne, Jaskaran Singh, Jorge A. Quiroz, David A. Luckenbaugh, Kirk D. Denicoff, Dennis S. Charney, and Husseini K. Manji

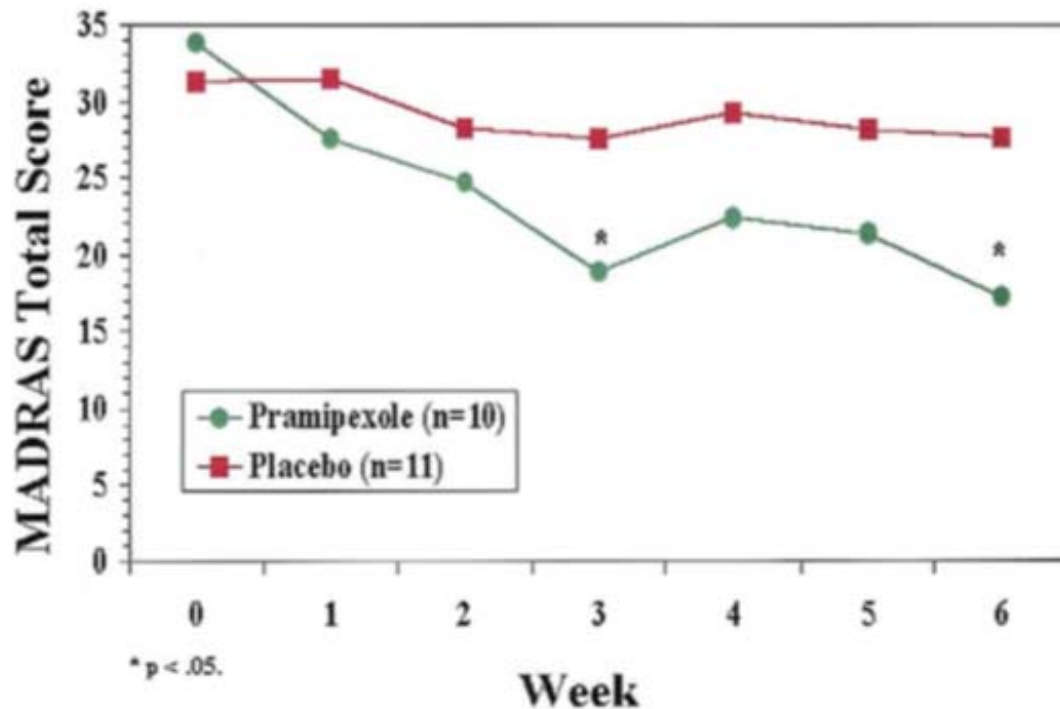
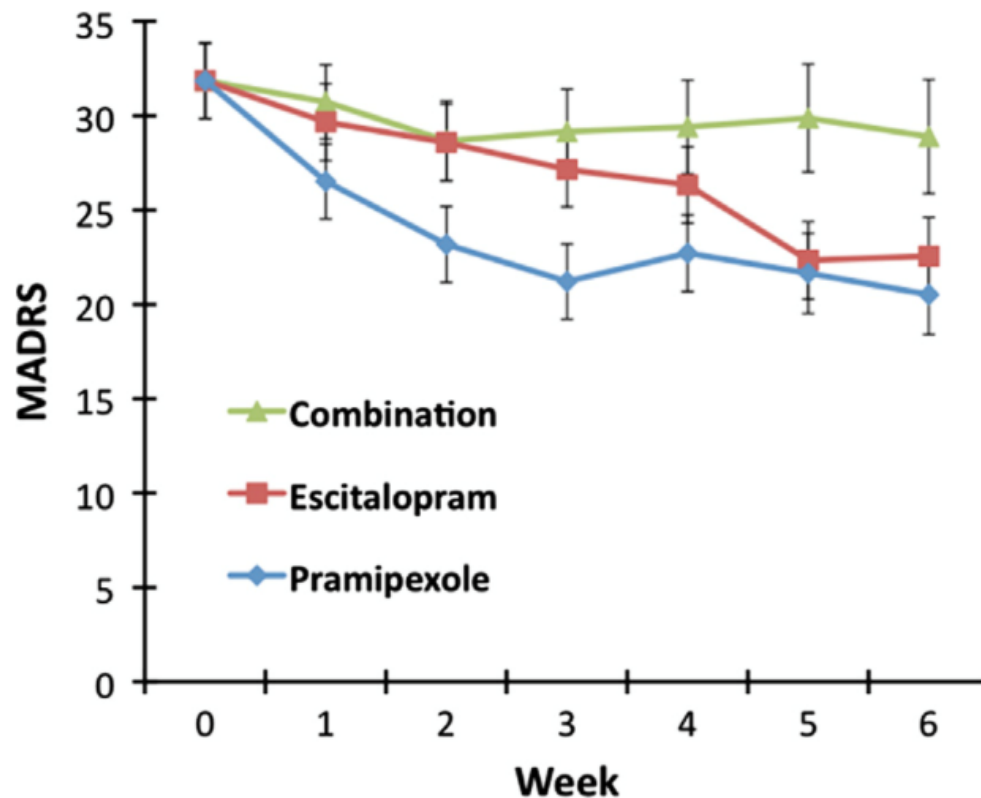


Figure 1. Mean change in MADRS total scores from baseline in patients with bipolar II depression who were treated with pramipexole or placebo for 6 weeks. MADRS, Montgomery-Asberg Depression Rating Scale.

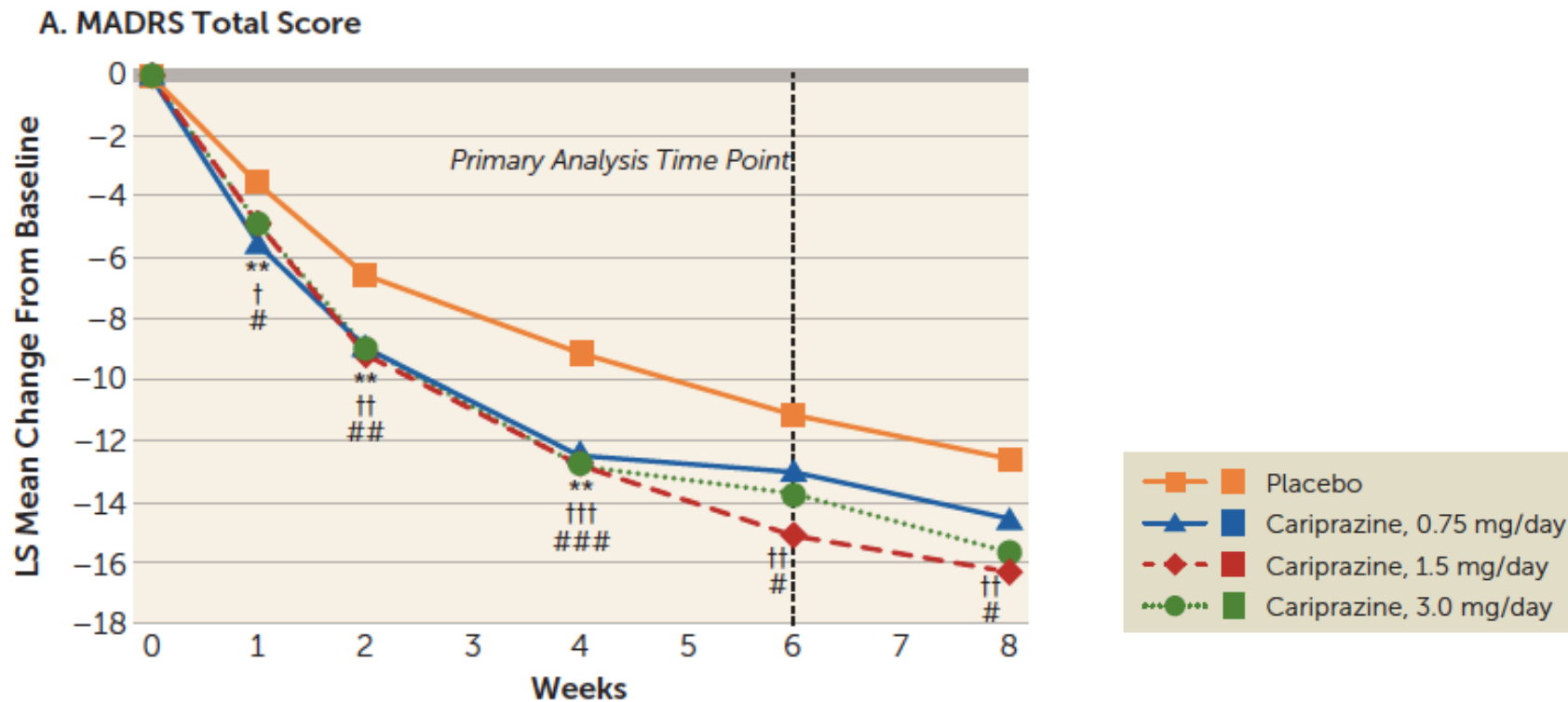
Combining a dopamine agonist and selective serotonin reuptake inhibitor for the treatment of depression: A double-blind, randomized pilot study

Jose A. Franco-Chaves^a, Camilo F. Mateus^a, David A. Luckenbaugh^a, Pedro E. Martinez^b, Alan G. Mallinger^{a,c}, Carlos A. Zarate Jr.^{a,*}



An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression

Suresh Durgam, M.D., Willie Earley, M.D., Alan Lipschitz, M.D., Hua Guo, Ph.D., István Laszlovszky, Pharm.D., György Németh, M.D., Eduard Vieta, M.D., Ph.D., Joseph R. Calabrese, M.D., Lakshmi N. Yatham, M.B.B.S., F.R.C.P.C.



Am J Psychiatry 2016; 173:271–281; doi: 10.1176/appi.ajp.2015.15020164

Aripiprazole Monotherapy in Non-Psychotic Bipolar I Depression

Results of 2 Randomized, Placebo-Controlled Studies

Michael E. Thase, MD,*† Alan Jonas, MD,‡ Arif Khan, MD,§|| Charles L. Bowden, MD,¶||
Xiaoling Wu, PhD,# Robert D. McQuade, PhD,** William H. Carson, MD,**
Ronald N. Marcus, MD,# and Randall Owen, MD#

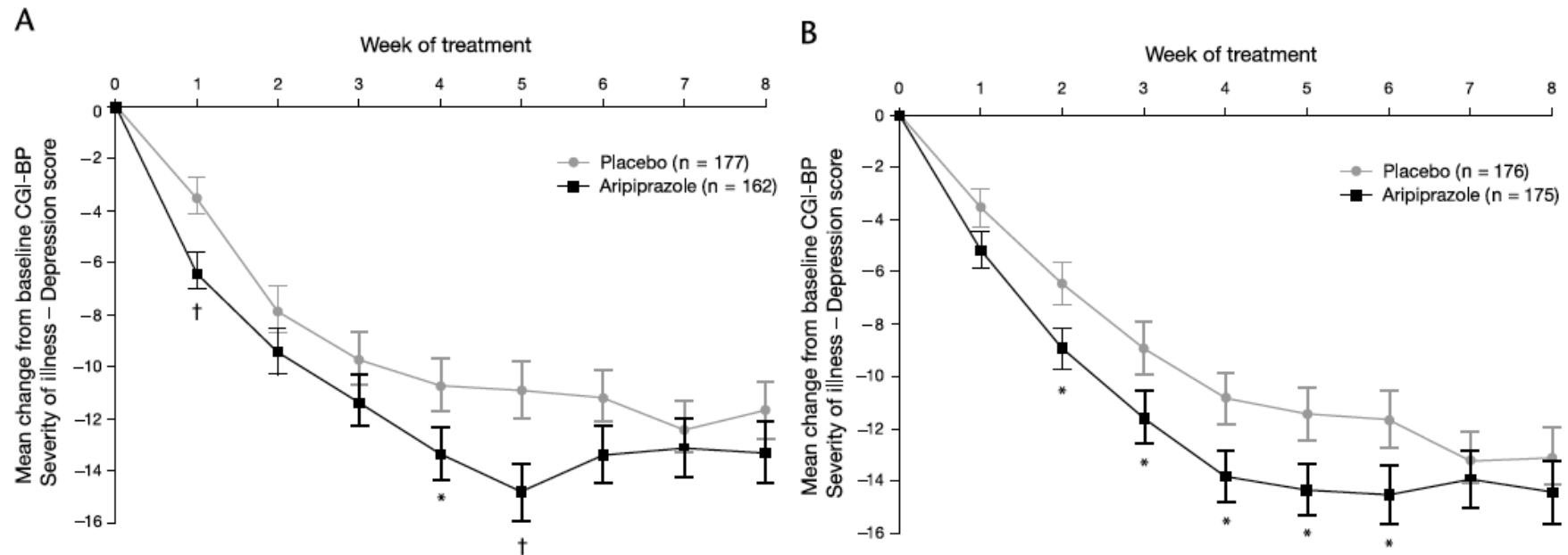


FIGURE 2. Adjusted mean \pm SE change from baseline in CGI-BP Severity of Illness Score-Depression in (A) Study 1 and (B) Study 2 (LOCF; efficacy sample). * $P \leq 0.05$ versus placebo; † $P < 0.01$ versus placebo. Baseline scores in Study 1: placebo, 4.34; aripiprazole, 4.28. Baseline scores in Study 2: placebo, 4.48; aripiprazole, 4.43.

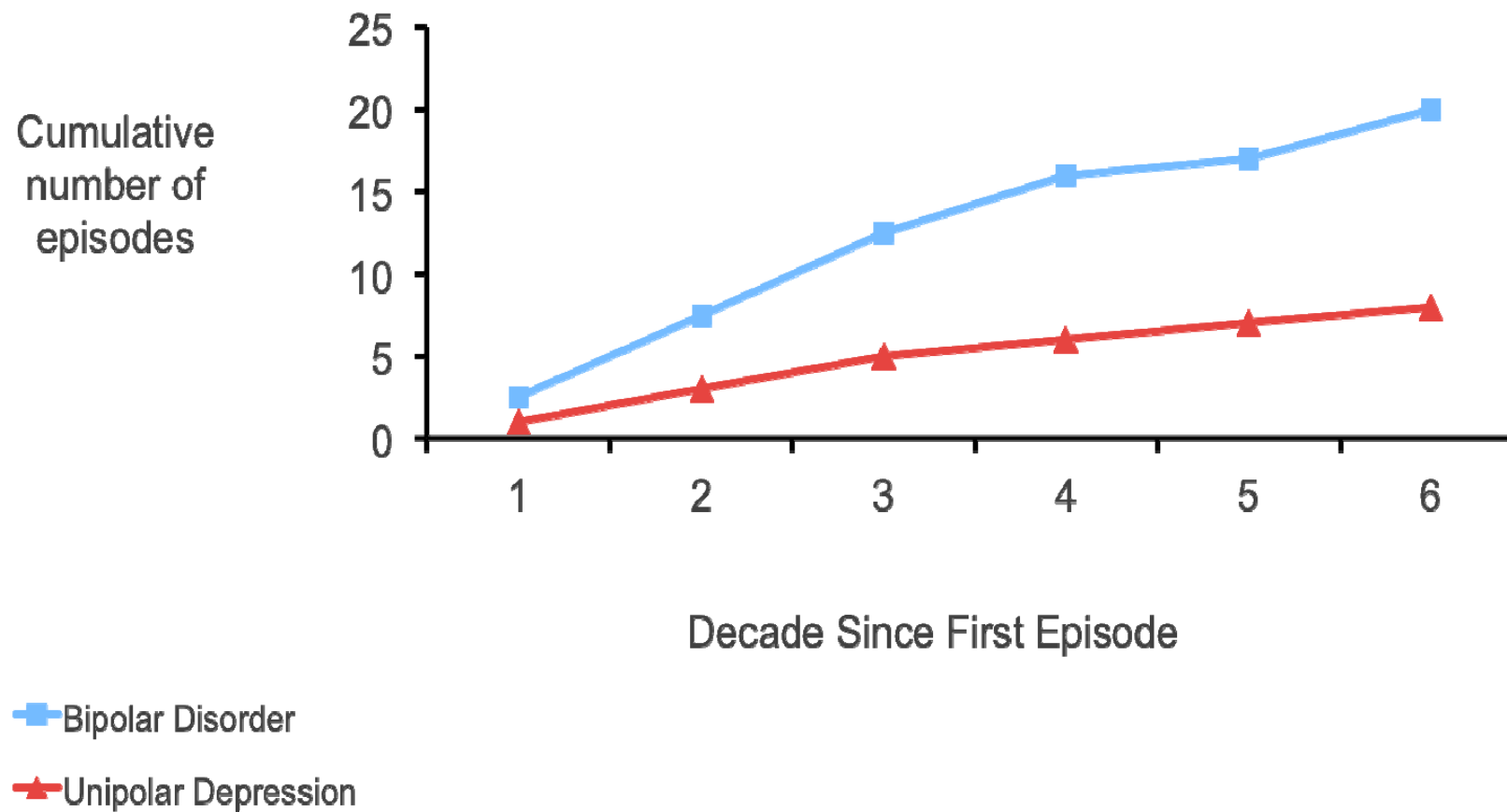
(*J Clin Psychopharmacol* 2008;28:13–20)

LONG TERM TREATMENT

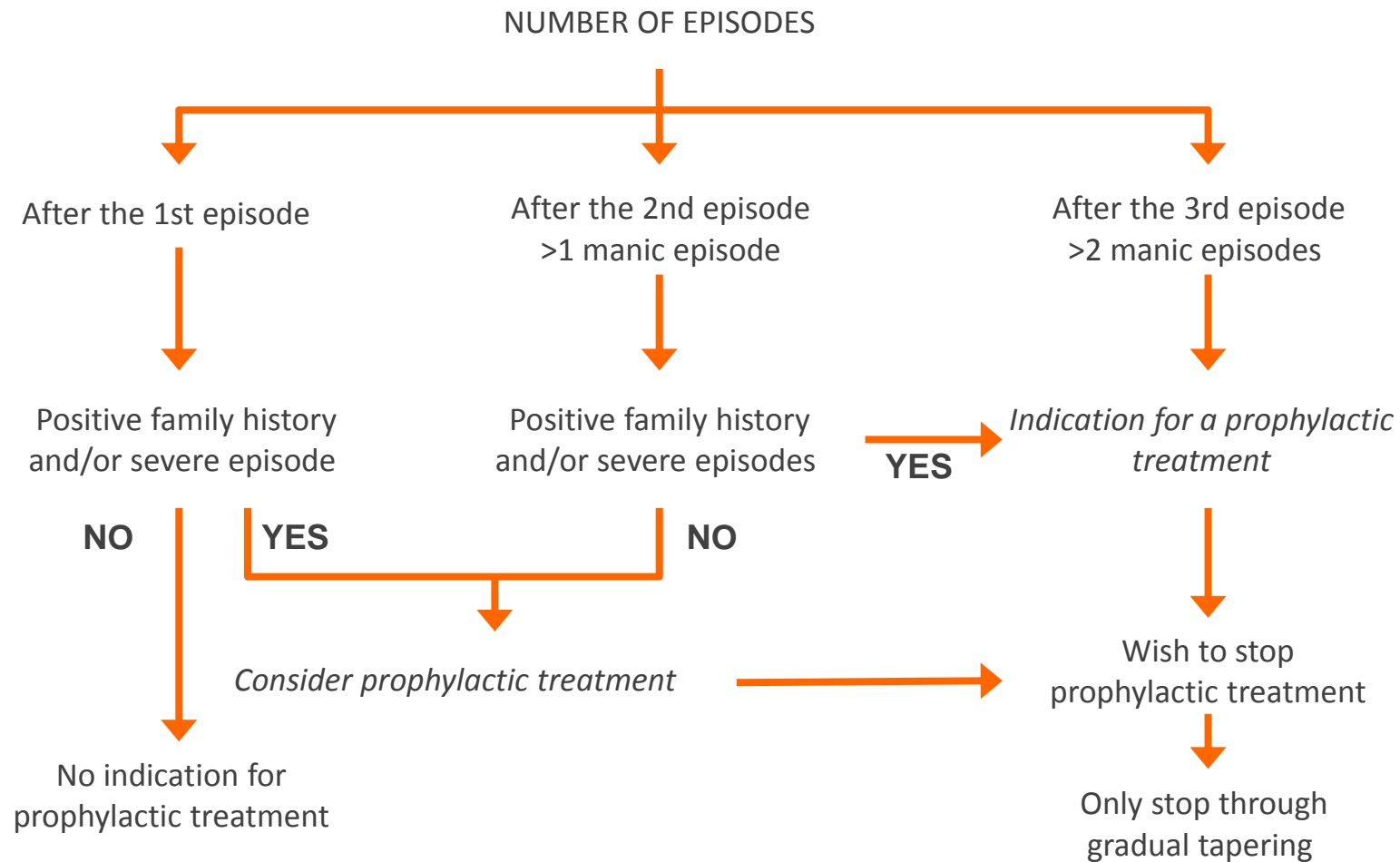
OVERVIEW POINTS

- Consider long-term treatment following a single severe manic episode. ***
- Without acceptance of the need for long-term treatment, adherence may be poor. (I).
- At present, continuous treatment is preferred to intermittent oral medications to prevent new episodes. Consider supplying add-on medications for imminent stressors or signs of relapse.
- When a patient has accepted treatment for several years and remains well, they should be advised to continue indefinitely because the risk of relapse remains high. ***
- Consider extrapolating from bipolar I to bipolar II disorder. **

ILLNESS BURDEN



GUIDELINES – DUTCH ALGORITHM



LONG TERM TREATMENT

EVIDENCE CAVEATS

- The evidence from network meta-analysis of available RCTs supports the efficacy of a limited range of individual medicines.
- Relatively few patients remain in trials for as long as 6 months.
- Many RCT designs are enriched for acute response to the drug under investigation. Lithium is a notable exception to this.

LONG TERM TREATMENT

MEDICATION OPTIONS

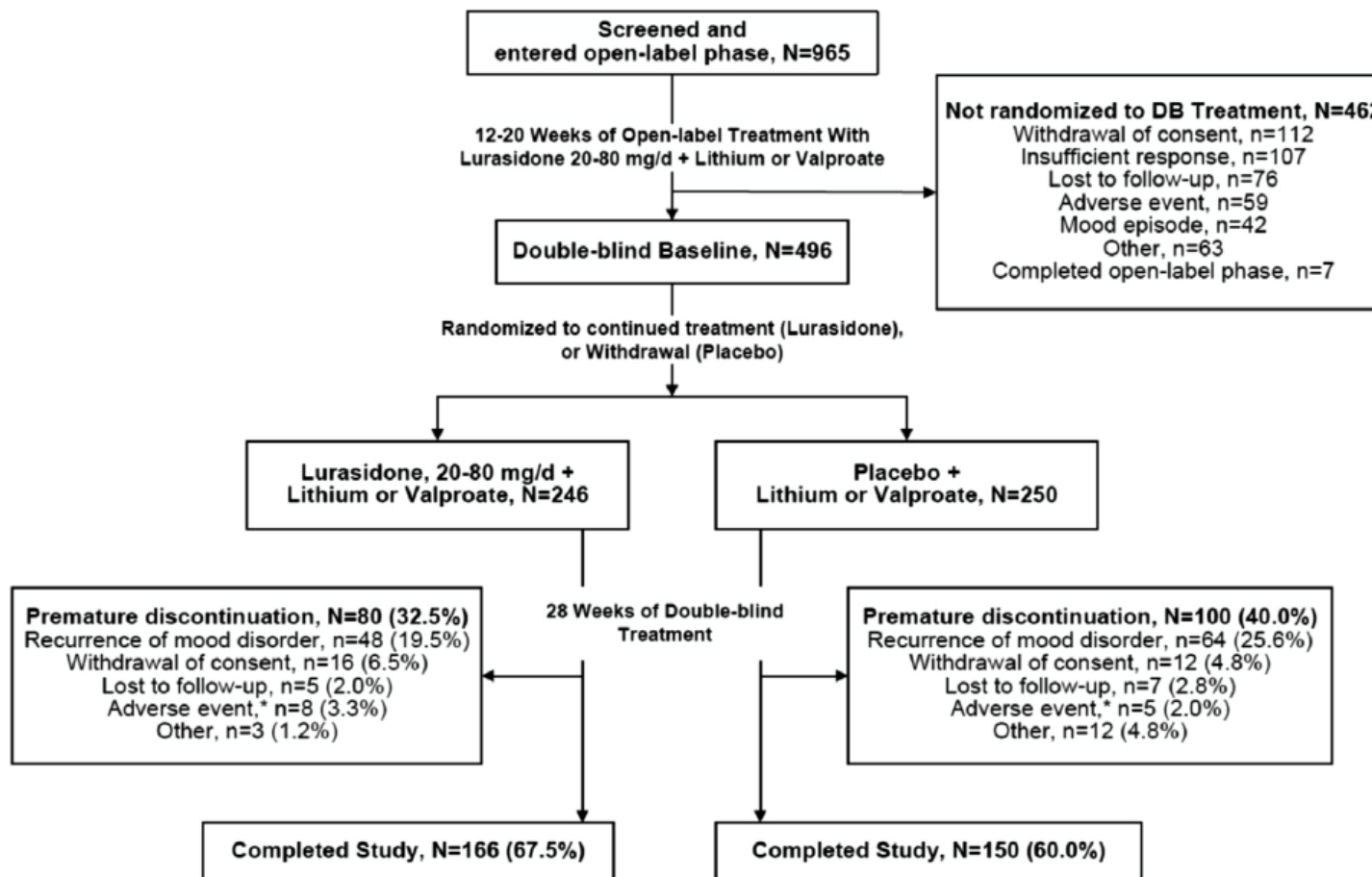
PREVENTION OF MANIA

- Network meta-analysis supports: lithium
olanzapine
quetiapine
risperidone LAI
valproate (marginal)

PREVENTION OF DEPRESSION

- Network meta-analysis supports: lithium
lamotrigine
quetiapine
- Lurasidone prevents relapse to depression

Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder [☆]



*does not include recurrence of a mood event

Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder ☆

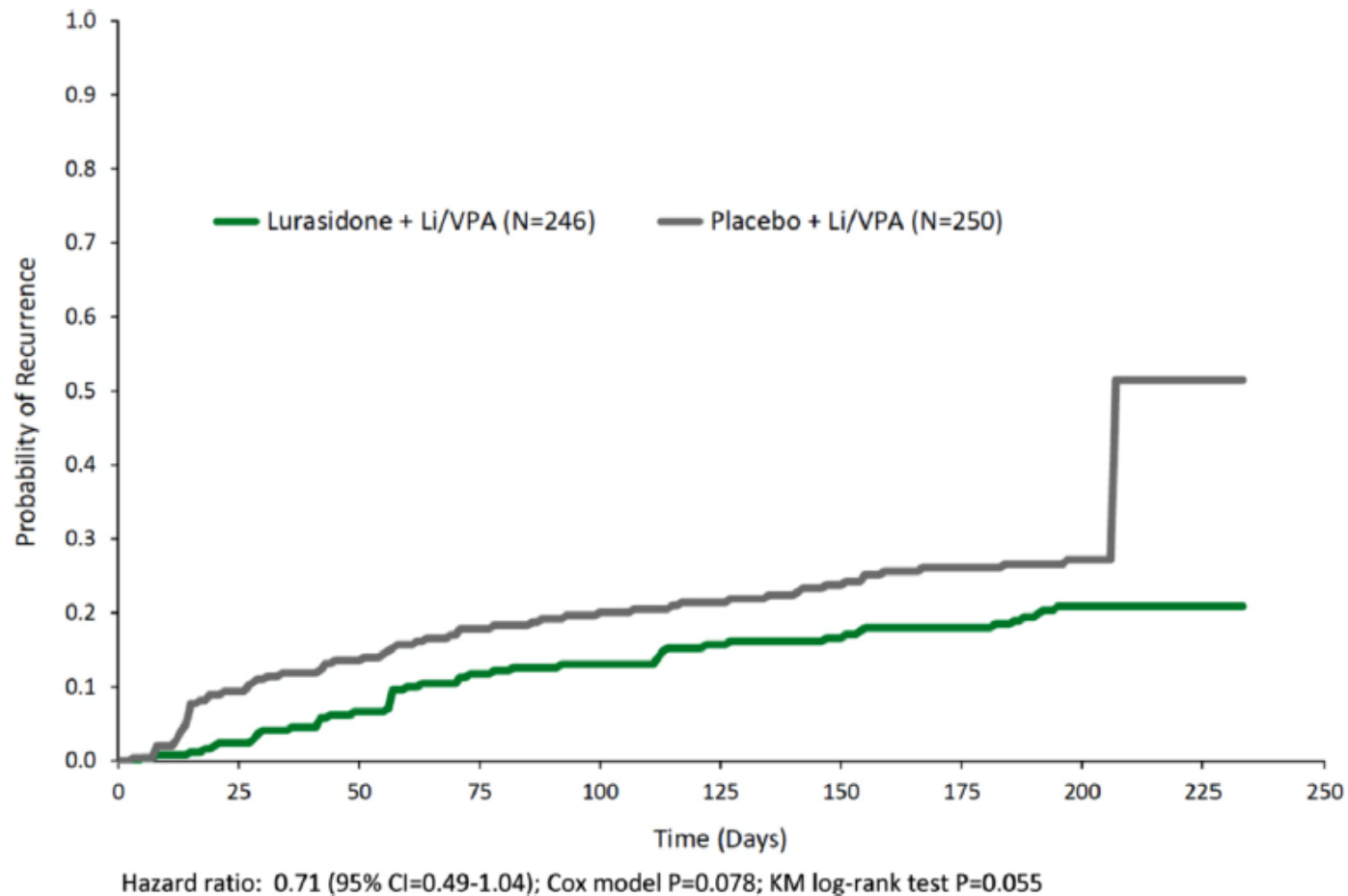
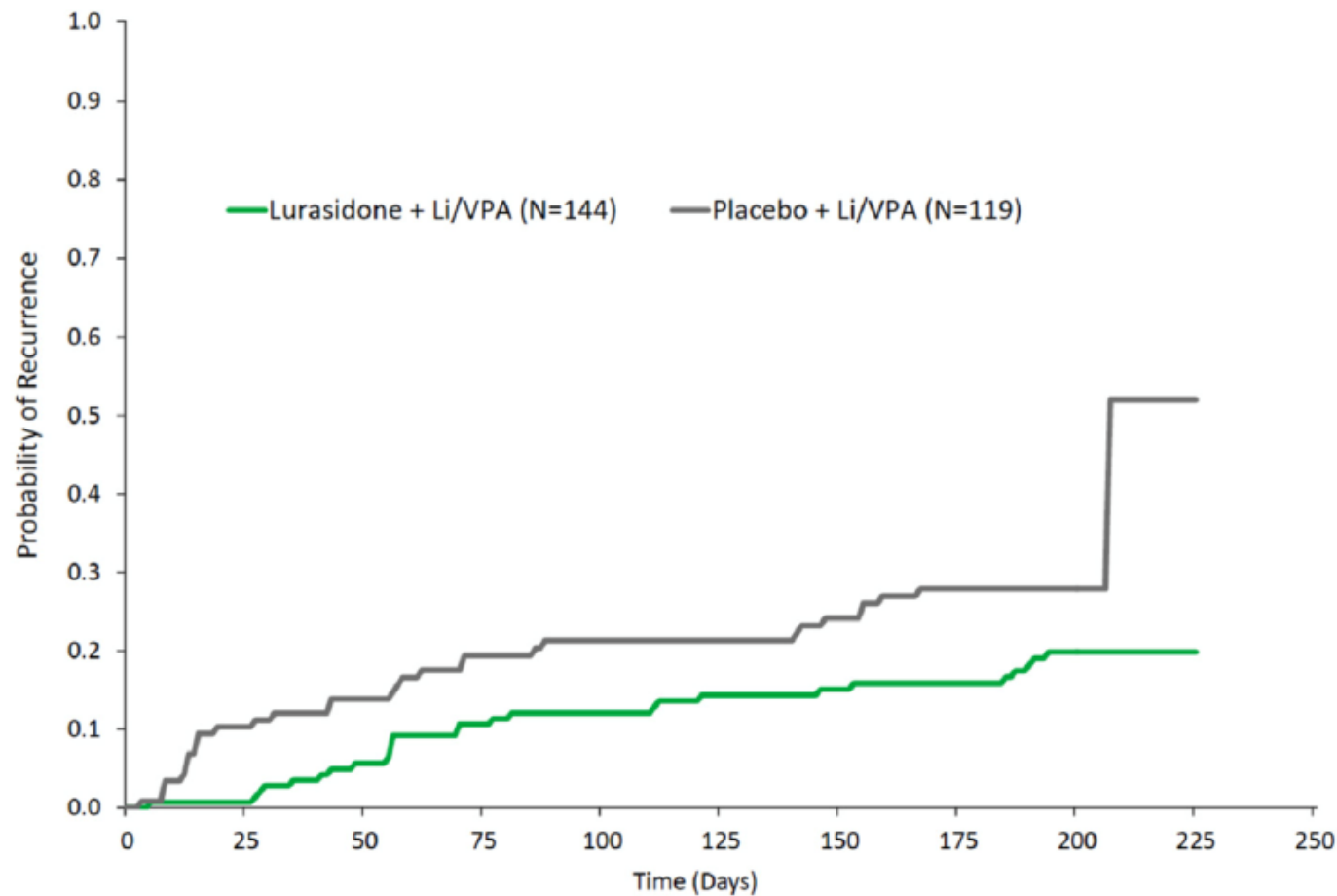


Figure 2 Kaplan-Meier curve: time to recurrence of any mood episode (primary efficacy analysis, total sample).

Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder ☆

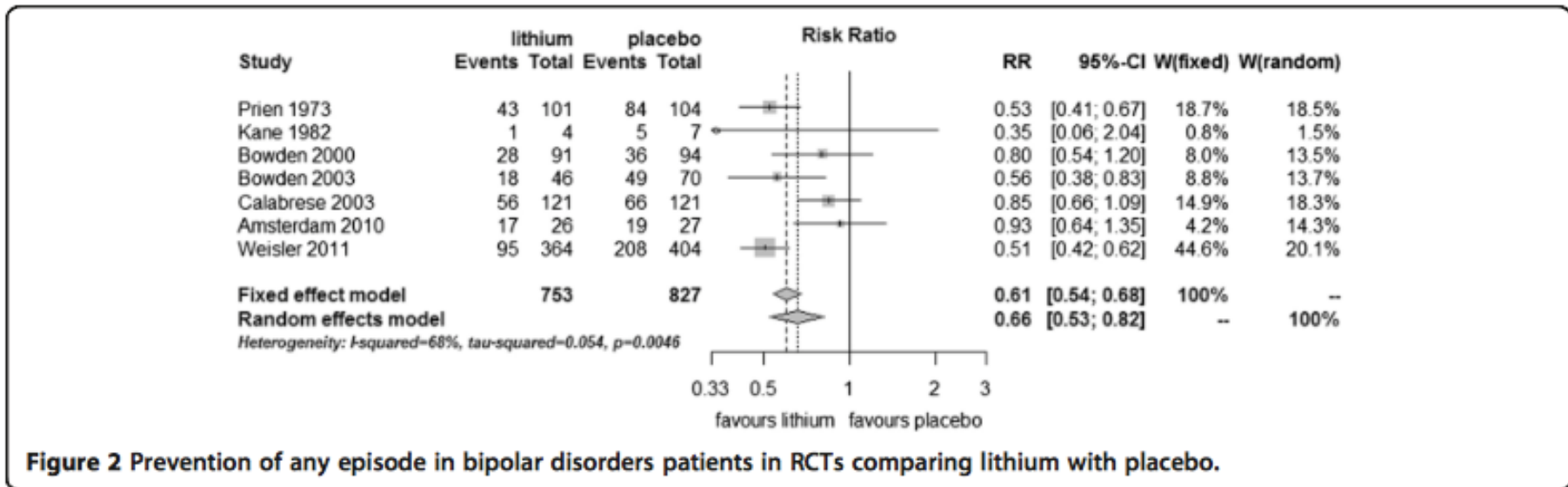


Hazard ratio: 0.57 (95% CI=0.34-0.97); Cox model P=0.039; KM log-rank test P=0.068

Figure 4 Kaplan-Meier curve: time to recurrence of any mood episode for patients with an index episode of depression.

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 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

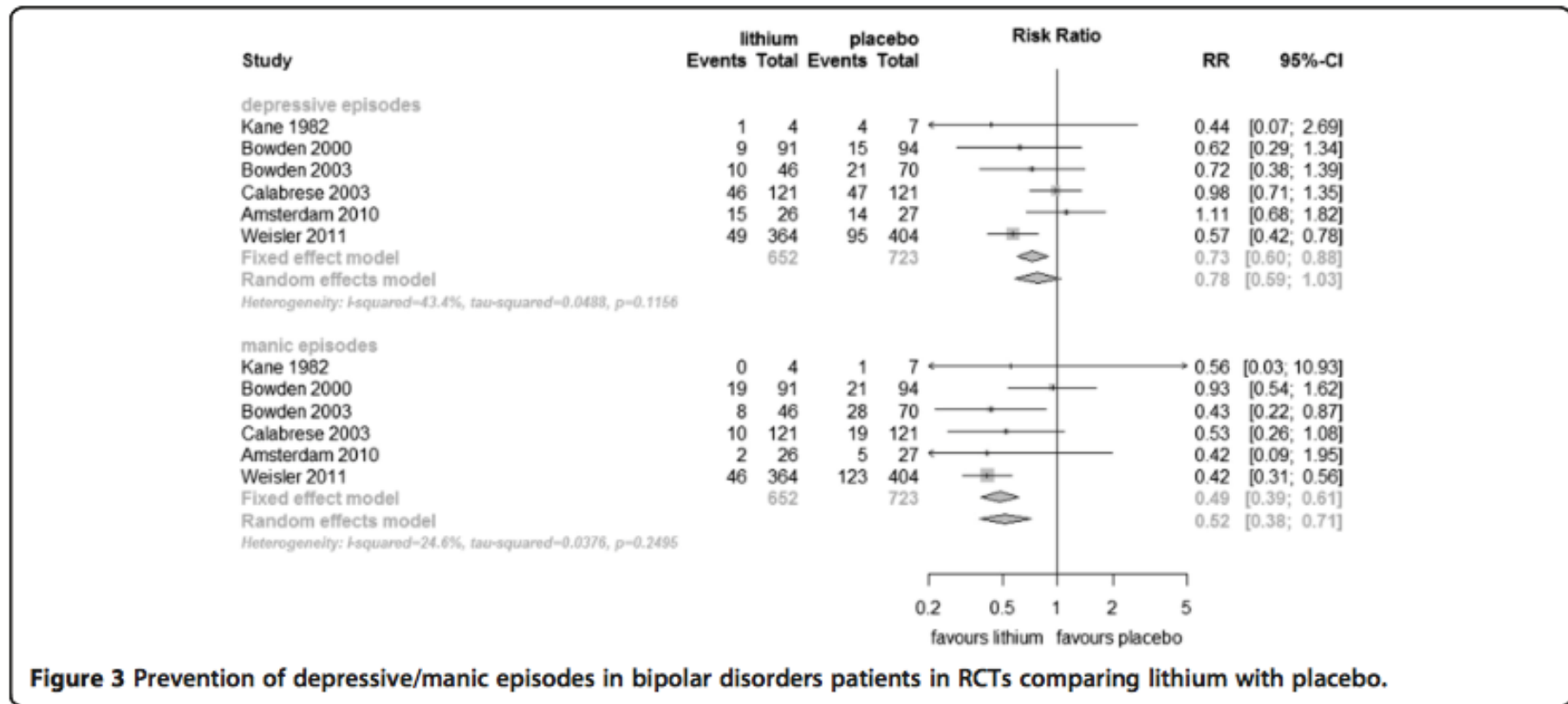
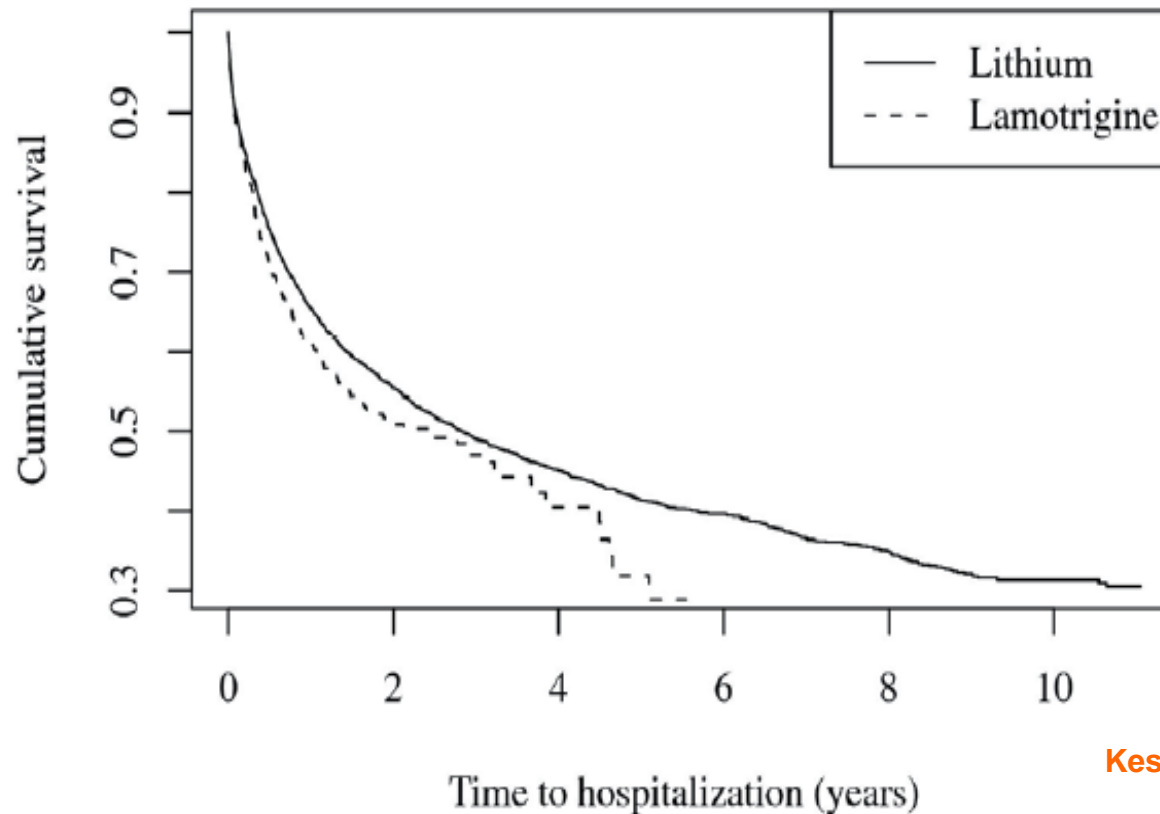


Figure 3 Prevention of depressive/manic episodes in bipolar disorders patients in RCTs comparing lithium with placebo.

An observational nationwide register based cohort study on lamotrigine versus lithium in bipolar disorder

Kaplan-Meier curves of time to psychiatric hospitalization in patients with bipolar disorder treated with lamotrigine versus lithium

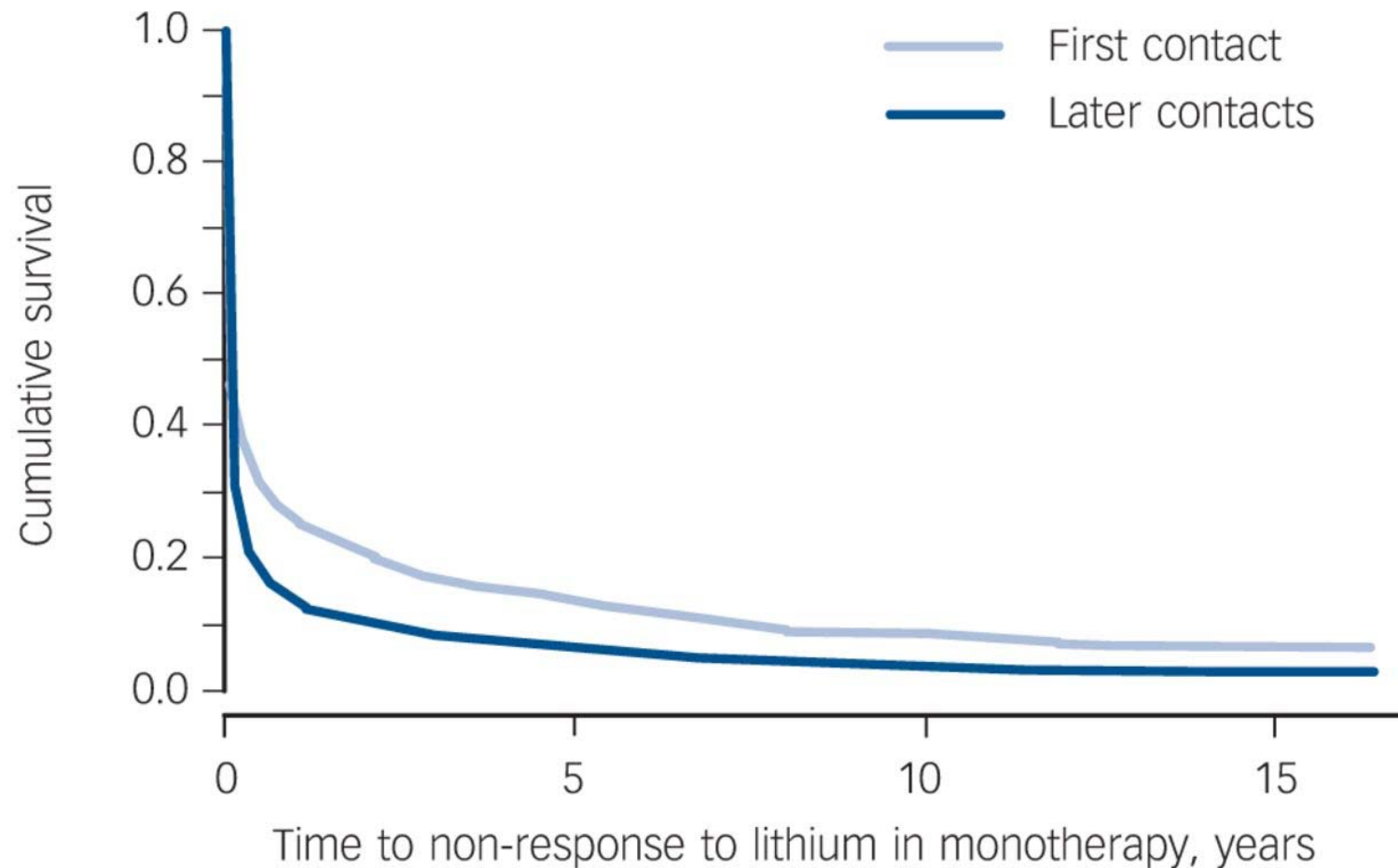


Kessing et al, 2012

Starting lithium prophylaxis early *v.* late in bipolar disorder

Lars Vedel Kessing, Eleni Vradi, Per Kragh Andersen

The British Journal of Psychiatry Sep 2014, 205 (3) 214-220



LITHIUM– TUBULE FUNCTION

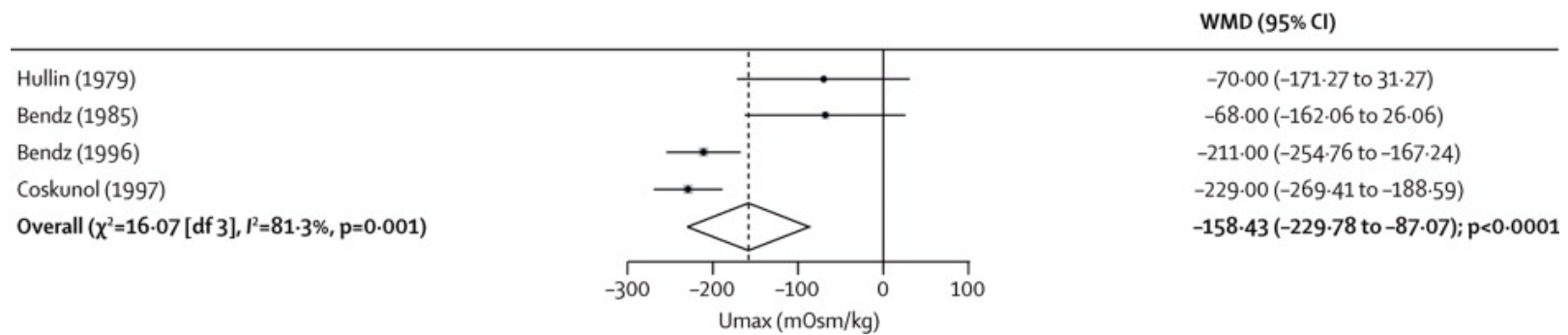
Impaired ability to concentrate urine, manifested as polyuria
Most common renal effect of lithium
Prevalence of lithium induced NDI 20-87%

Develops within months, though more common with chronic treatment. May become irreversible with prolonged treatment.

Due to lithium inhibition of G-protein coupled pathways activated by ADH (aquaporin channel expression in the collecting ducts)

DDAVP in principal unlikely to be effective.
Amiloride has some supportive evidence

LITHIUM- TUBULE FUNCTION

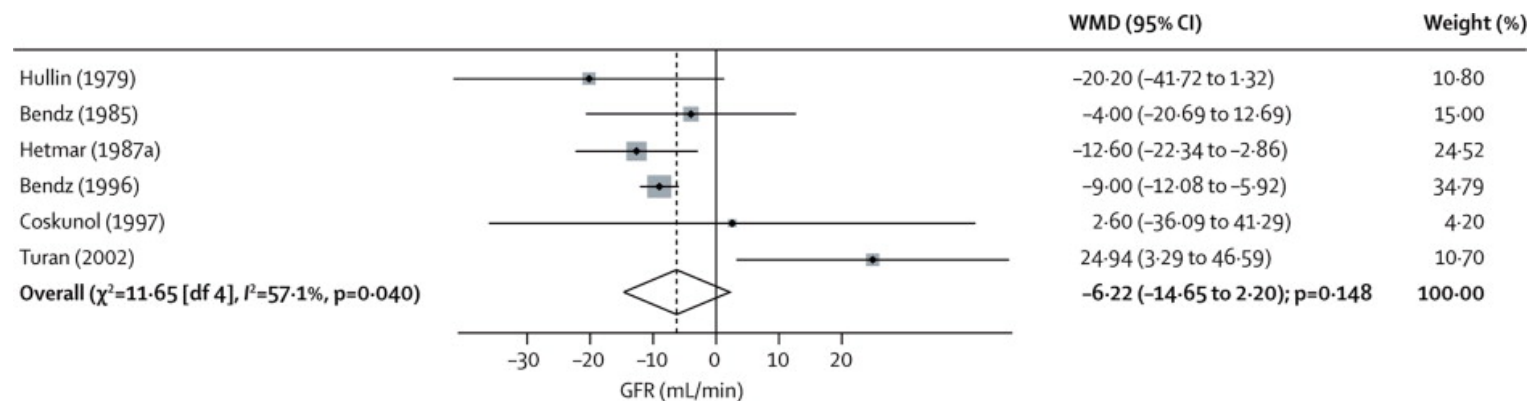


Rebecca F McKnight, Marc Adida, Katie Budge, Sarah Stockton, Guy M Goodwin, John R Geddes

Lithium toxicity profile: a systematic review and meta-analysis

LITHIUM- RENAL GFR

Increased creatinine occurs with lithium treatment
GFR impaired by lithium (0-5 ml/min; mean study 1 year)



Rebecca F McKnight, Marc Adida, Katie Budge, Sarah Stockton, Guy M Goodwin, John R Geddes

Lithium toxicity profile: a systematic review and meta-analysis

Consensus advice is lacking

Mechanism poorly understood

- chronic interstitial GN not reliably linked to lithium
- numerous confounds (CVS, DM, age, medications)

Effects of 10 to 30 years of lithium treatment on kidney function

Harald Aiff¹, Per-Ola Attman², Mattias Aurell², Hans Bendz³, Bernd Ramsauer⁴, Staffan Schön⁵ and Jan Svedlund¹

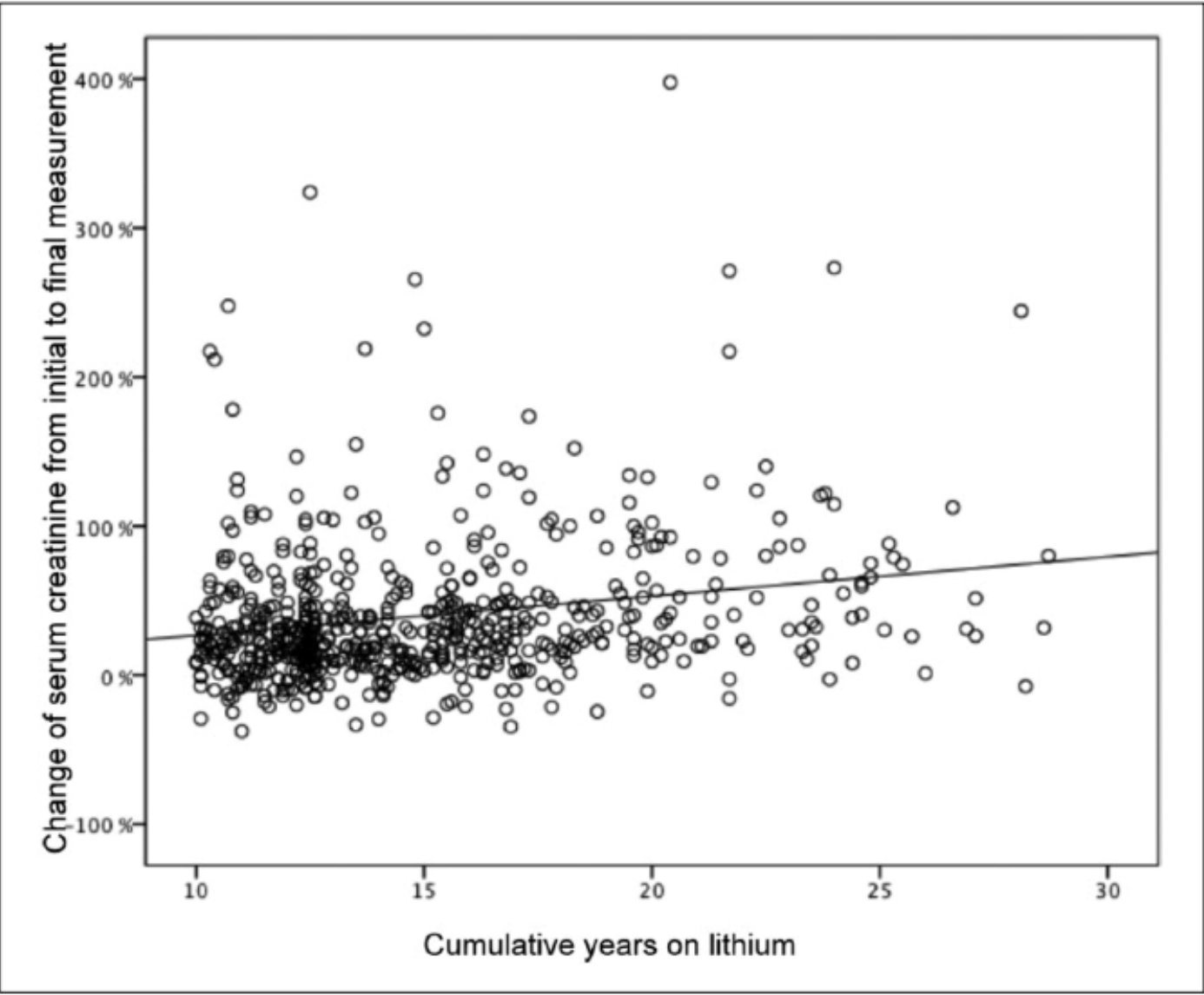
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Table 3. CKD stage at final serum creatinine level based on eGFR.

CKD stage	eGFR level mL/min per 1.73 m ²	Male	%	Female	%	Total	%
1	≥90	23	10.1	50	12.4	73	11.6
2	60–89	131	57.5	222	55.2	353	56.0
3	30–59	64	28.1	111	27.6	175	27.8
4	15–29	8	3.5	19	4.7	27	4.3
5	<15	2	0.9	0	0.0	2	0.3
Total		228	100	402	100	630	100

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.



Continuation of lithium after a diagnosis of chronic kidney disease

Kessing LV, Feldt-Rasmussen B, Andersen PK, Gerds TA, Licht RW.
Continuation of lithium after a diagnosis of chronic kidney disease.

Objective: To investigate whether continued lithium or anticonvulsant treatment after a first diagnosis of chronic kidney disease (CKD) was associated with progression to irreversible end-stage kidney disease.

Methods: Nationwide cohort study including all individuals in Denmark in a period from 1995 to 2012 with a diagnosis of CKD and (i) a history of lithium treatment ($N = 754$, among whom 238 patients had a diagnosis of bipolar disorder) or (ii) a history of anticonvulsant treatment ($N = 5.004$, among whom 199 patients had a diagnosis of bipolar disorder). End-stage CKD was defined as chronic dialysis or renal transplantation.

Results: Continuing lithium (HR = 0.58 (95% CI: 0.37–0.90) and continuing anticonvulsants (HR = 0.53 (95% CI: 0.44–0.64) were associated with decreased rates of end-stage CKD. In the subcohorts of patients with a diagnosis of bipolar disorder, continuing lithium was associated with decreased end-stage CKD (HR = 0.40 (95% CI: 0.17–0.98), whereas continuing anticonvulsants was not (HR = 0.70 (95% CI: 0.21–2.37). There were no interactions of continuing lithium and anticonvulsants.

Conclusion: After an initial diagnosis of CKD, patients who are selected by their physicians to continue lithium treatment may not necessarily have an increased risk of developing end-stage CKD. Shifting to an anticonvulsant per se may not be associated with an advantage; however, this requires further investigation.

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Key words: bipolar disorder; chronic kidney disease; lithium; anticonvulsants

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Response TO LITHIUM NETWORK



PRIMARY GOALS

Bipolar disorder (BD) is a highly prevalent mental disorder and a leading cause of suicide. Lithium is the key treatment for prevention of BD relapse and suicide.

