WITHIN-SUBJECT COMPARISON AS A TOOL TO EXPLORE EFFECTIVENESS IN REGISTER STUDIES

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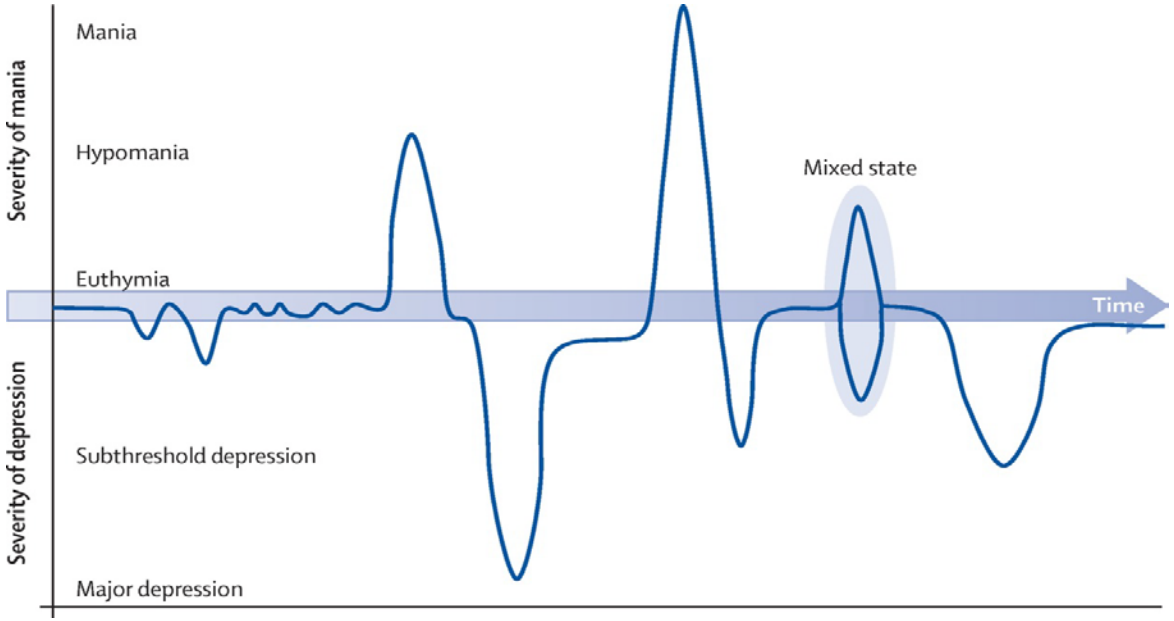
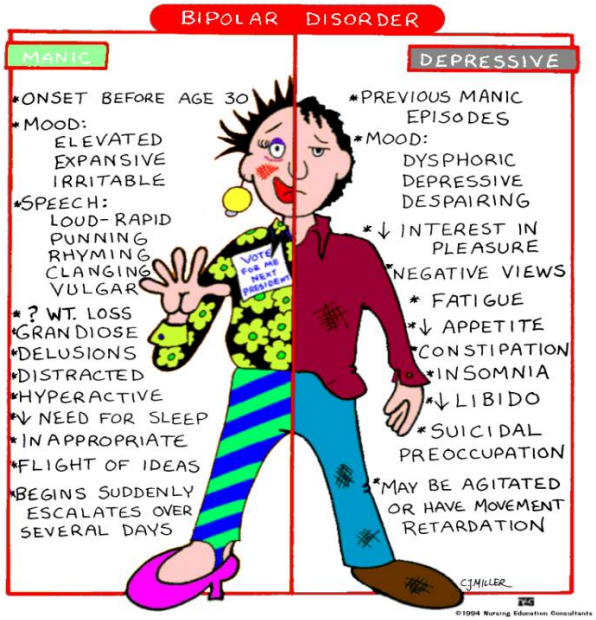
Disclosures

- Over the past 36 months:
  - lecture honoraria from Lundbeck pharmaceuticals and AstraZeneca Sweden
  - served as scientific consultant for EPID Research Oy.
  - No other equity ownership, profit-sharing agreements, royalties, or patent.

Bipolar disorder / Manic depressive illness

- *Recurrent episodes* of extreme mood (mania and depression)





Life chart of bipolar disorder (*Grande I et. al., 2016)*

Three important clinical questions

1. Which mood stabilizing treatment is the most effective?
2. Do mood stabilizers decrease the risk for suicide attempts?
3. Can antidepressants or central stimulants be given to bipolar disorder patients without triggering manic episodes?

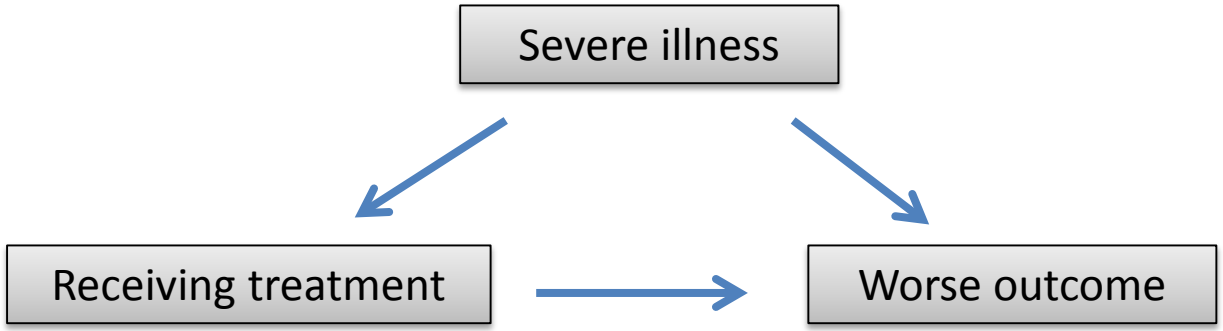
Observational studies

- Draw inferences from a sample or population but do not control the independent variable
  - Case-control studies
  - Longitudinal studies
- *Pro*
  - Provide information on ’real-world’ effectivness
  - Generalisable and can inform clinical practise

Observational studies - *Contra*

Observational studies are hampered by **indication bias**

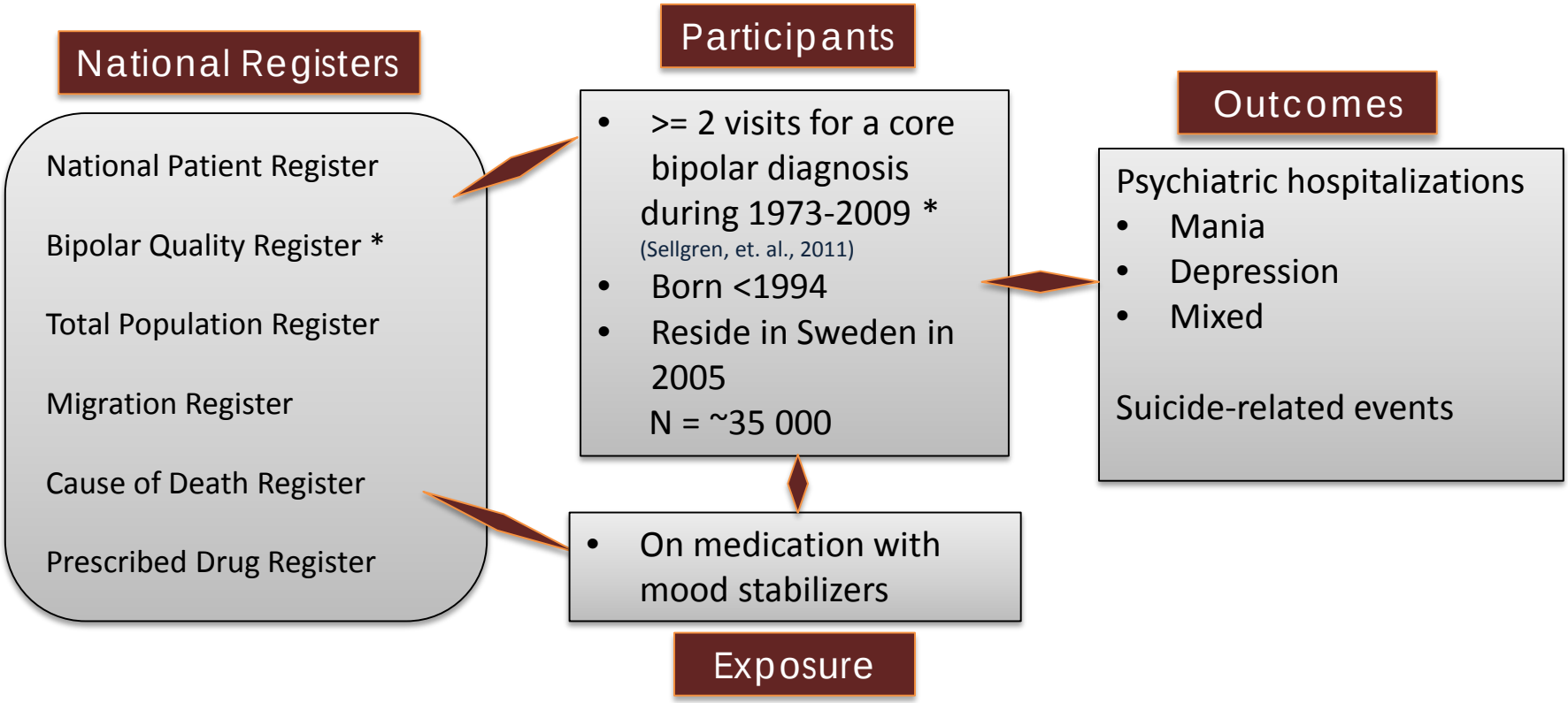
- Treatment is not given randomly in the population
- The outcome is associated with why the drug was given



There are ways to to do better observational studies

- Sibling controls
- **Within-individual comparisons**
- … but no method is flawless

Identifying study subjects



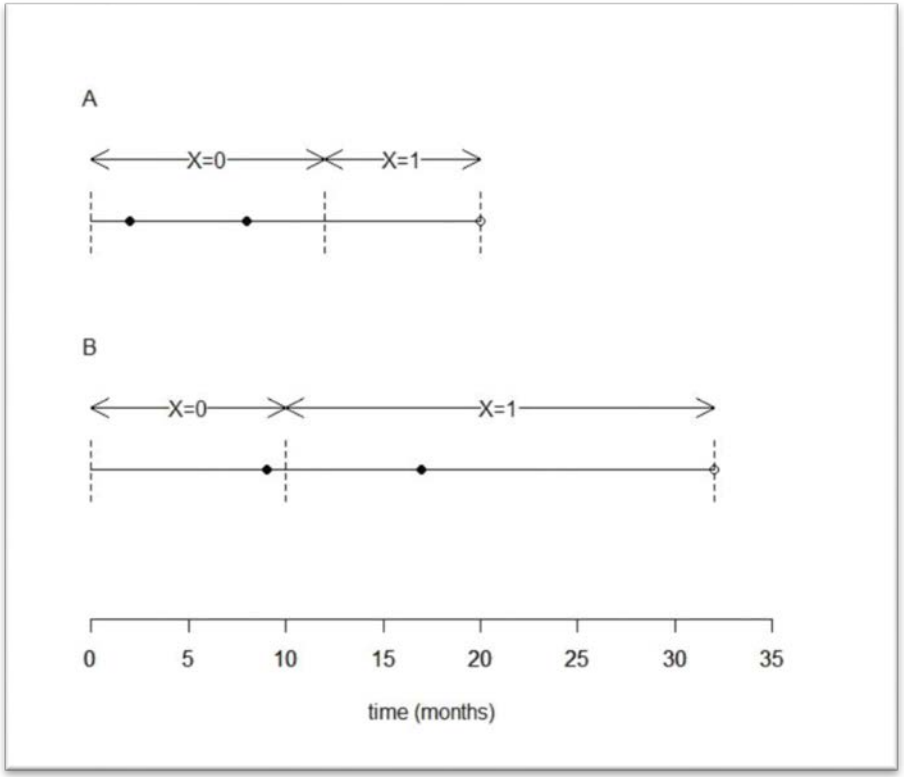
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Medication for Attention Deficit–Hyperactivity Disorder and Criminality

Paul Lichtenstein, Ph.D., Linda Halldner, M.D., Ph.D., Johan Zetterqvist, M.Ed., Arvid Sjölander, Ph.D., Eva Serlachius, M.D., Ph.D., Seena Fazel, M.B., Ch.B., M.D., Niklas Långström, M.D., Ph.D., and Henrik Larsson, M.D., Ph.D.

Lichtenstein et al. Medication for Attention Deficit–Hyperactivity Disorder and Criminality. N Engl J Med 2012; 367:2006-2014, supplement



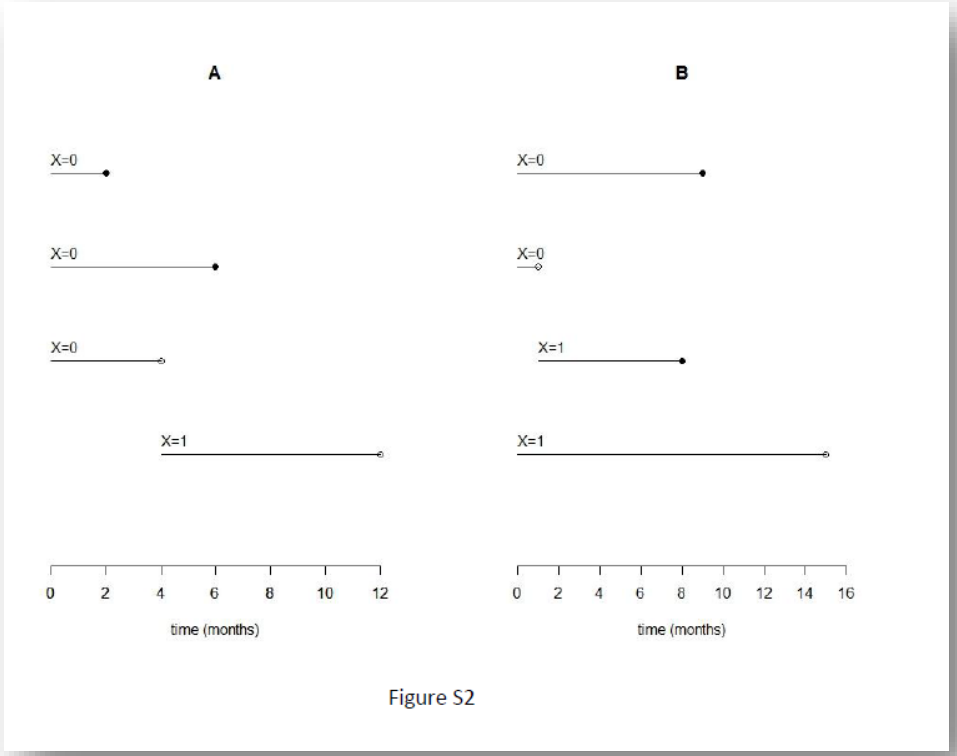


Figure S2

- Stratified Cox regression (stratified per individual)
- No confounding from factors that are constant: e.g., genetic makeup, childhood events (but do not control for time varying covariates)

Lichtenstein et al. Medication for Attention Deficit–Hyperactivity Disorder and Criminality. N Engl J Med 2012; 367:2006-2014, supplement

Erik Joas

BJPsych The British Journal of Psychiatry
1–6. doi: 10.1192/bjp.bp.116.187989

Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder

Erik Joas, Alina Karanti, Jie Song, Guy M. Goodwin, Paul Lichtenstein and Mikael Landén

Background
Clinical trials have examined the efficacy of drugs to prevent relapse in patients with bipolar disorder, however, their design often limits generalisation to routine clinical practice.

Aims
To estimate the effectiveness of drugs used for maintenance treatment in bipolar disorder.

Method
We used national registers to identify 35 022 individuals diagnosed with bipolar disorder and information on lithium, valproate, carbamazepine, lamotrigine, quetiapine and olanzapine treatment from 2006 to 2009. The main outcome was psychiatric hospital admissions. We used stratified cox regression to compare periods on and off medication within the same individual.

quetiapine and olanzapine. The effects of specific drugs depended on the polarity of the mood episode.

Conclusions
Our findings complement results from randomised controlled trails, but suggest that lithium is more effective than both quetiapine and olanzapine in routine clinical practice.

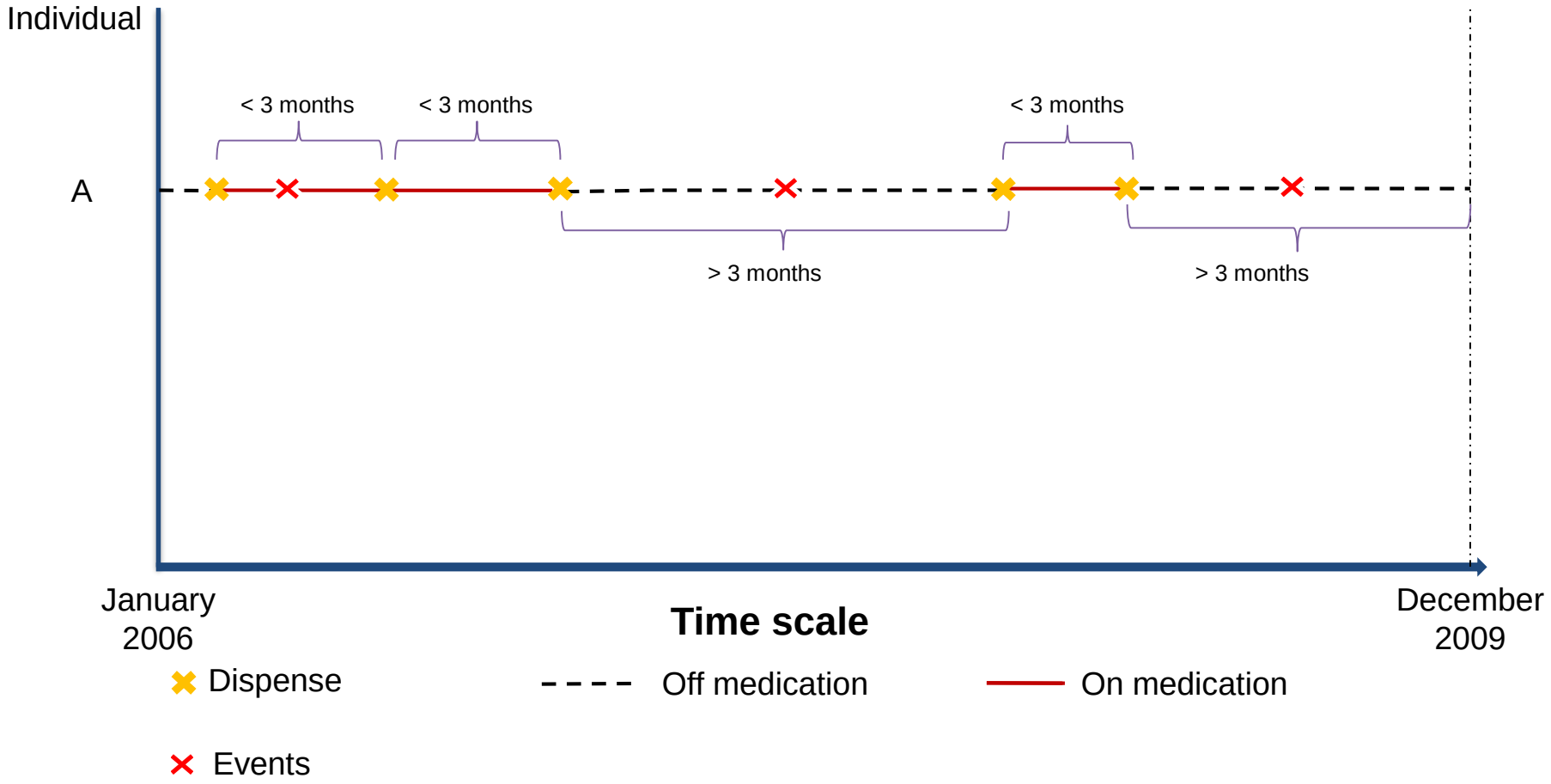
Declaration of interest
A.K. declares that, over the past 36 months, she has received lecture honoraria from Eli Lilly Sweden. M.L. declares that, over the past 36 months, he has received lecture honoraria from Biophausia Sweden, Servier Sweden, AstraZeneca. G.M.G. has held grants from Servier, received honoraria for speaking or chairing educational meetings from Abbvie, AZ, GSK, Lilly, Lundbeck, Medscape, Servier, and advised AZ, Cephalon/Teva, Lundbeck, Merck, Otsuka, P1vital, vital.

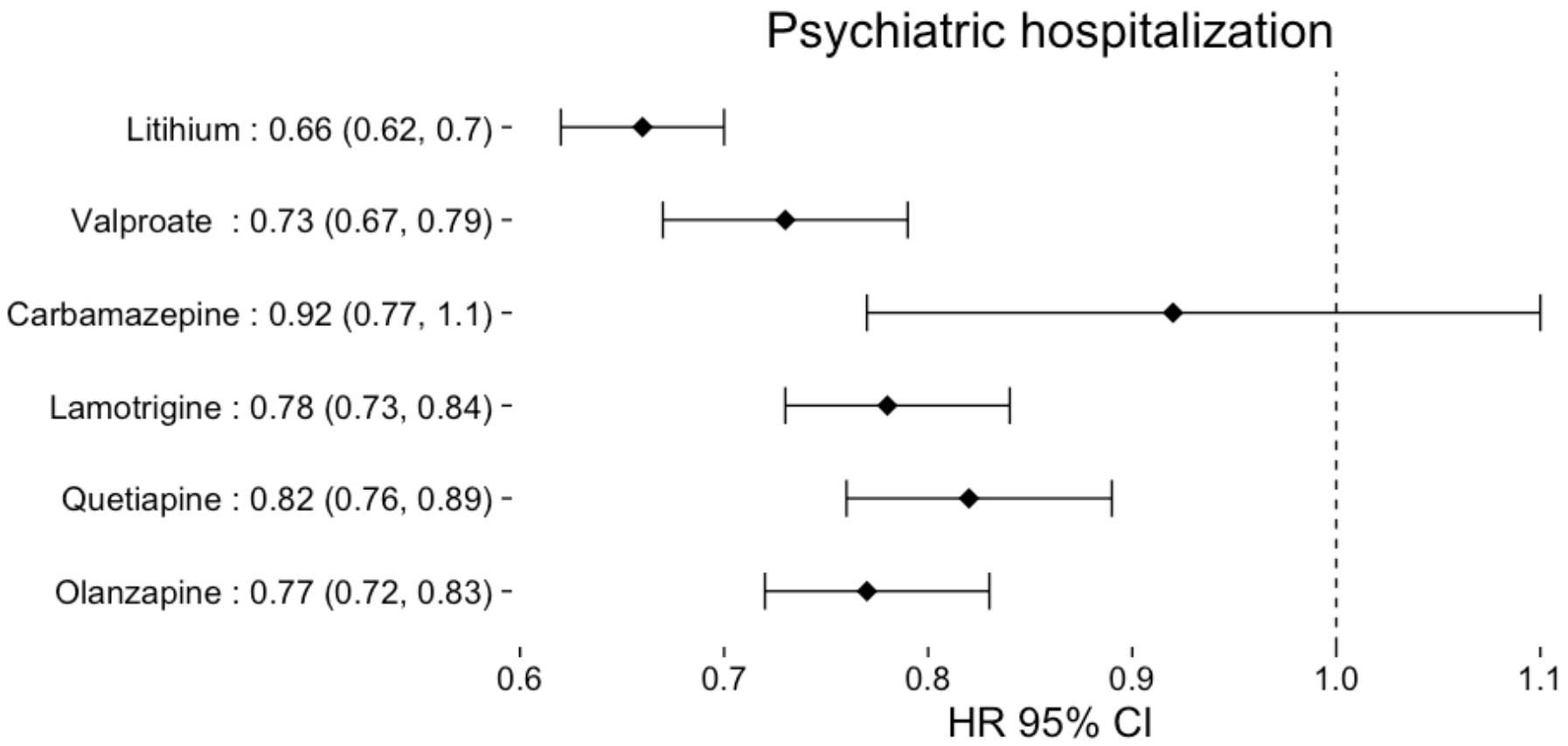
Table 2 Associations between different treatments and admission to psychiatric hospital estimated using within-individual models ($n = 35\,022$)[a]

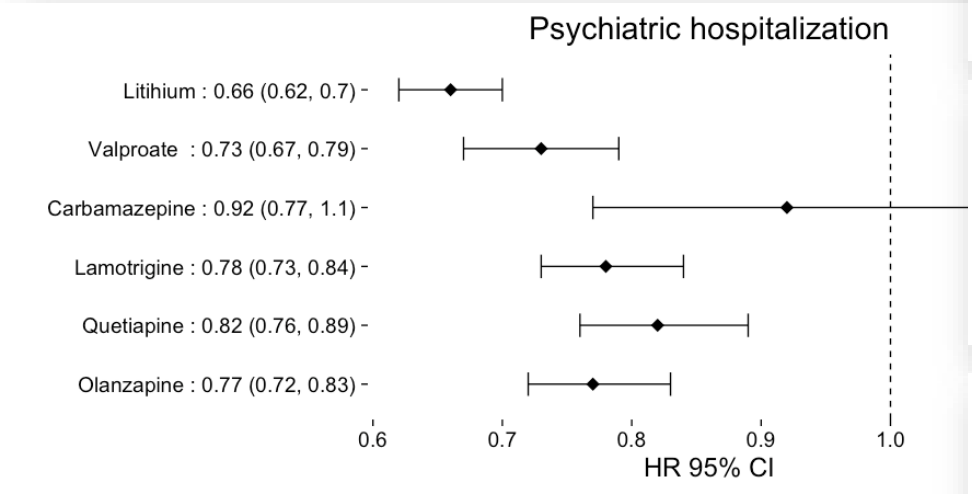
	Psychiatric hospital admissions			
	All	Manic episodes	Depressive episodes	Mixed episodes
Medication, hazard ratios (95% CI)				
Lithium	0.66 (0.62–0.70)	0.56 (0.48–0.65)	0.61 (0.53–0.69)	0.56 (0.39–0.79)
Valproate	0.73 (0.67–0.79)	0.64 (0.53–0.78)	0.73 (0.59–0.89)	0.66 (0.44–0.99)
Carbamazepine	0.92 (0.77–1.10)	0.50 (0.29–0.86)	0.98 (0.64–1.48)	1.65 (0.59–4.62)
Lamotrigine	0.78 (0.73–0.84)	1.00 (0.78–1.28)	0.73 (0.63–0.84)	0.82 (0.53–1.27)
Quetiapine	0.82 (0.76–0.89)	0.73 (0.58–0.93)	0.66 (0.54–0.81)	0.92 (0.62–1.39)
Olanzapine	0.77 (0.72–0.83)	0.56 (0.46–0.67)	0.80 (0.68–0.93)	0.78 (0.52–1.17)
Events, *n*	23 383	4363	6637	973

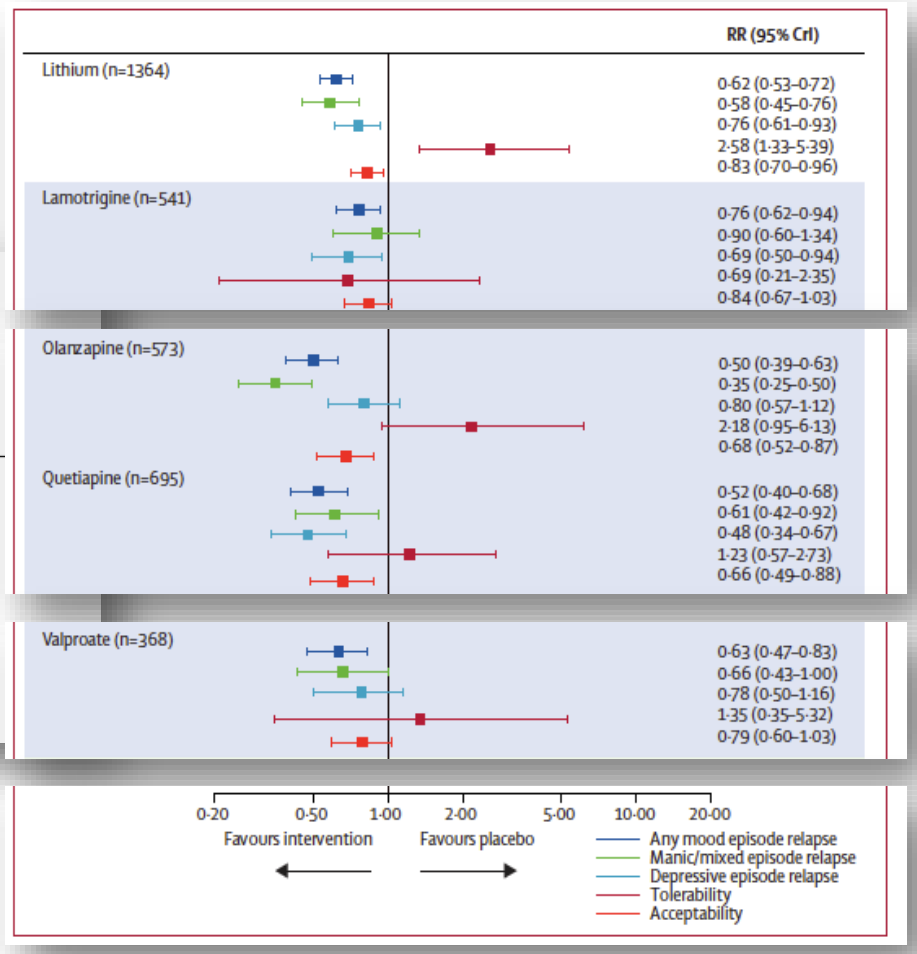
a. All models adjusted for previous time spent in psychiatric in-patient care and age.

Within-individual analysis

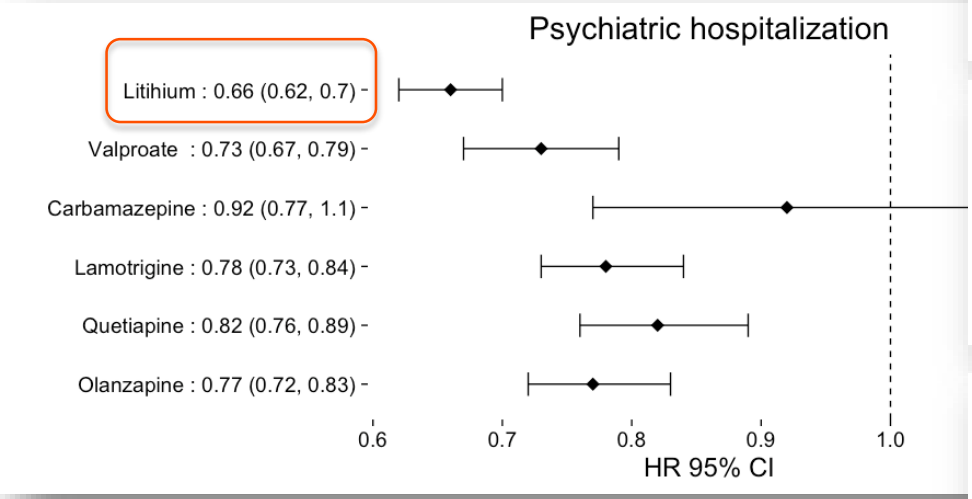


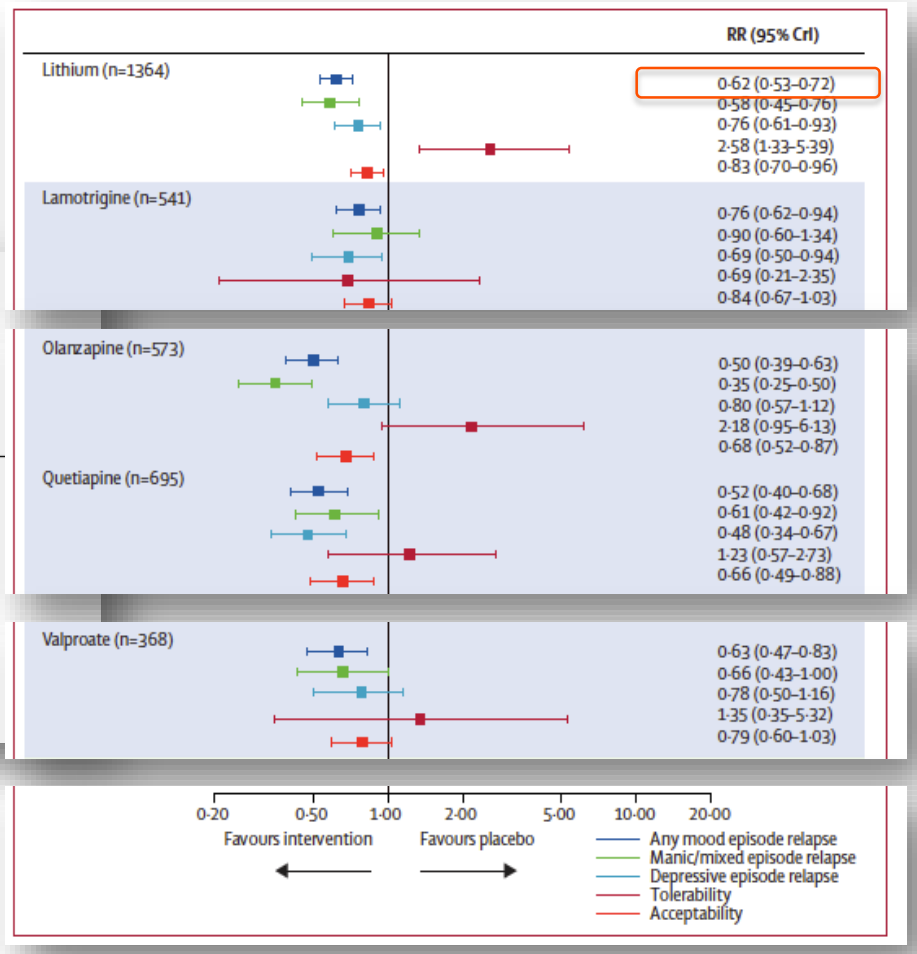

Psychiatric hospitalization
Litihium : 0.66 (0.62, 0.7)
Valproate : 0.73 (0.67, 0.79)
Carbamazepine : 0.92 (0.77, 1.1)
Lamotrigine : 0.78 (0.73, 0.84)
Quetiapine : 0.82 (0.76, 0.89)
Olanzapine : 0.77 (0.72, 0.83)
0.6
0.7
0.8
0.9
1.0
1.1
HR 95% CI





Miura, Tomofumi, et al. "Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis." The Lancet Psychiatry 1.5 (2014): 351-359.





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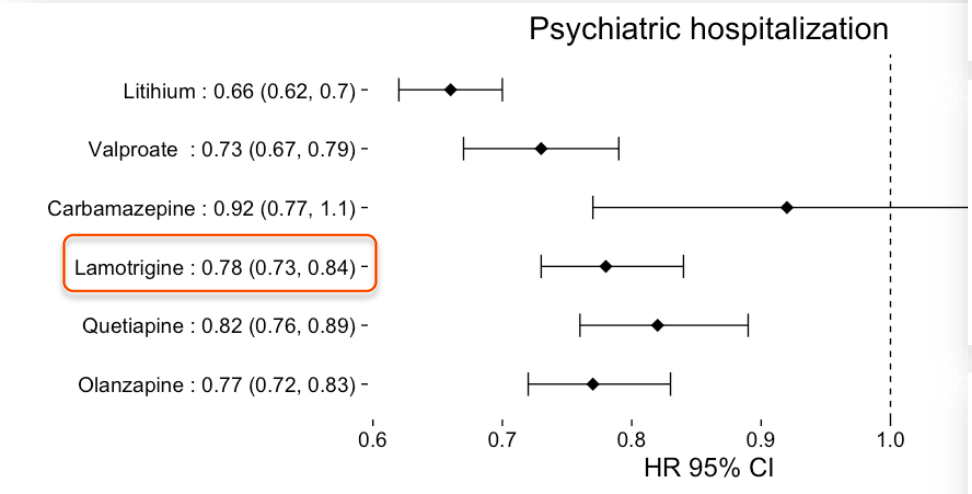

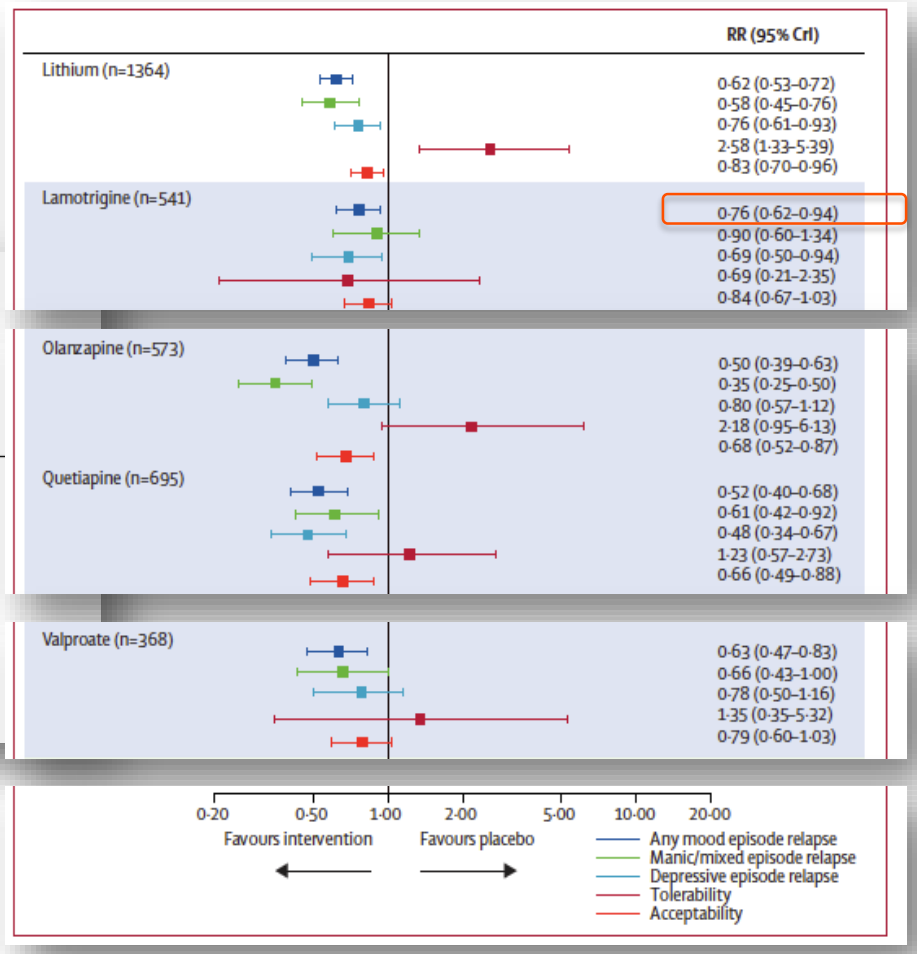

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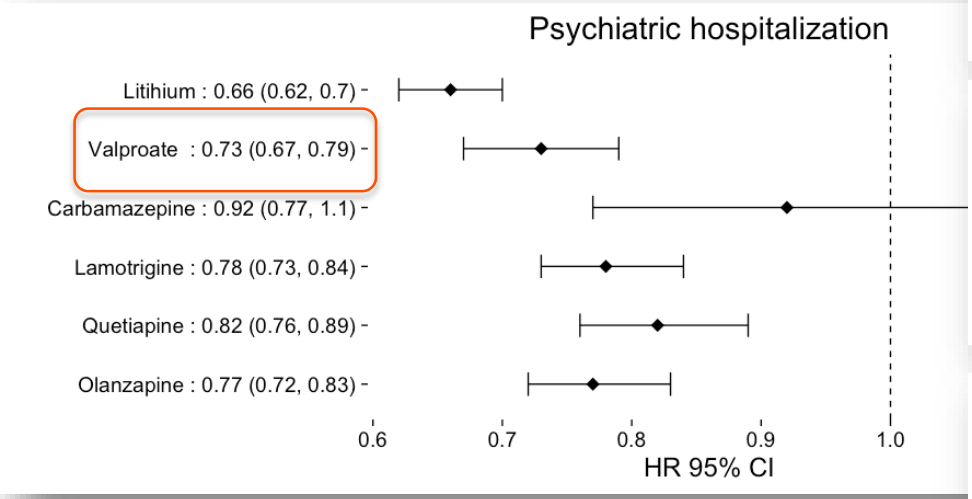

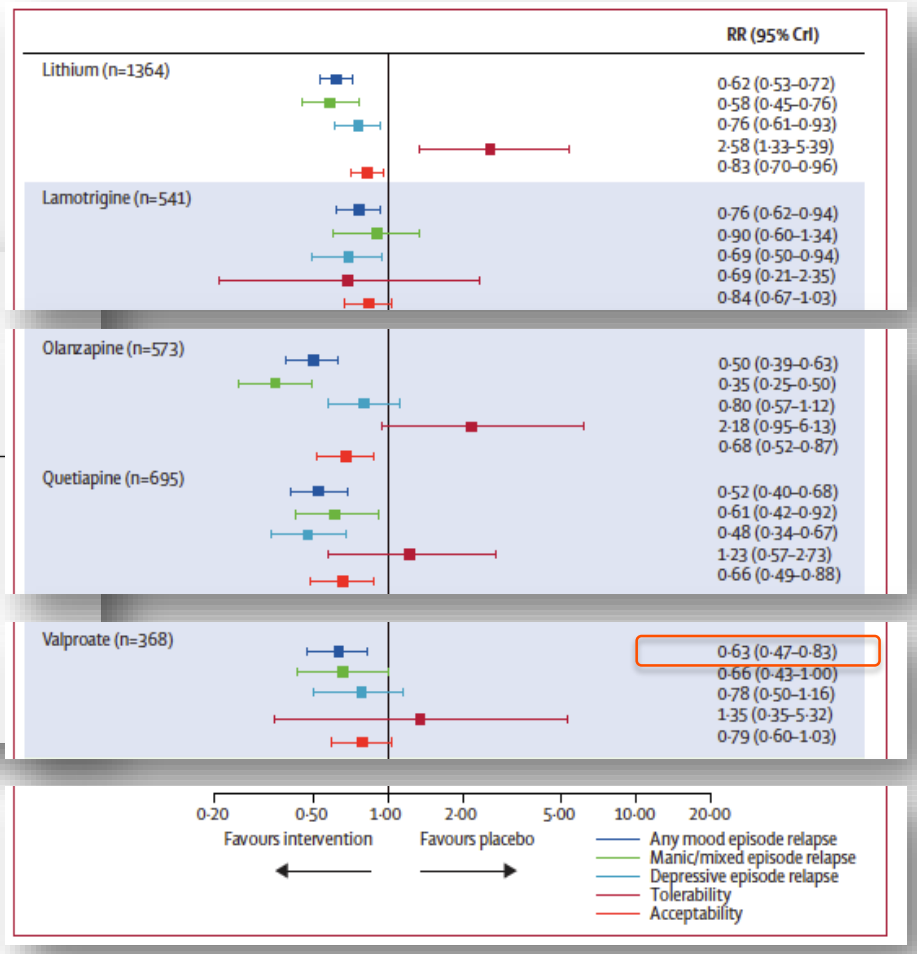

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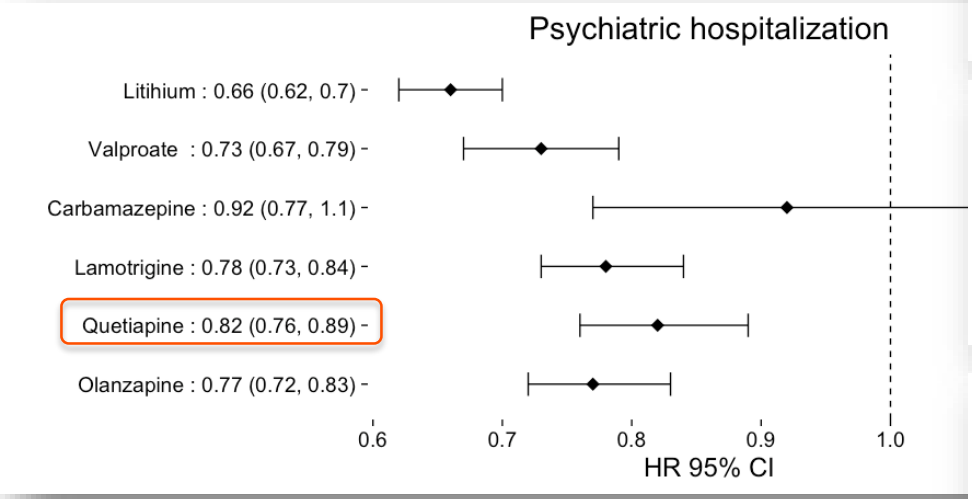

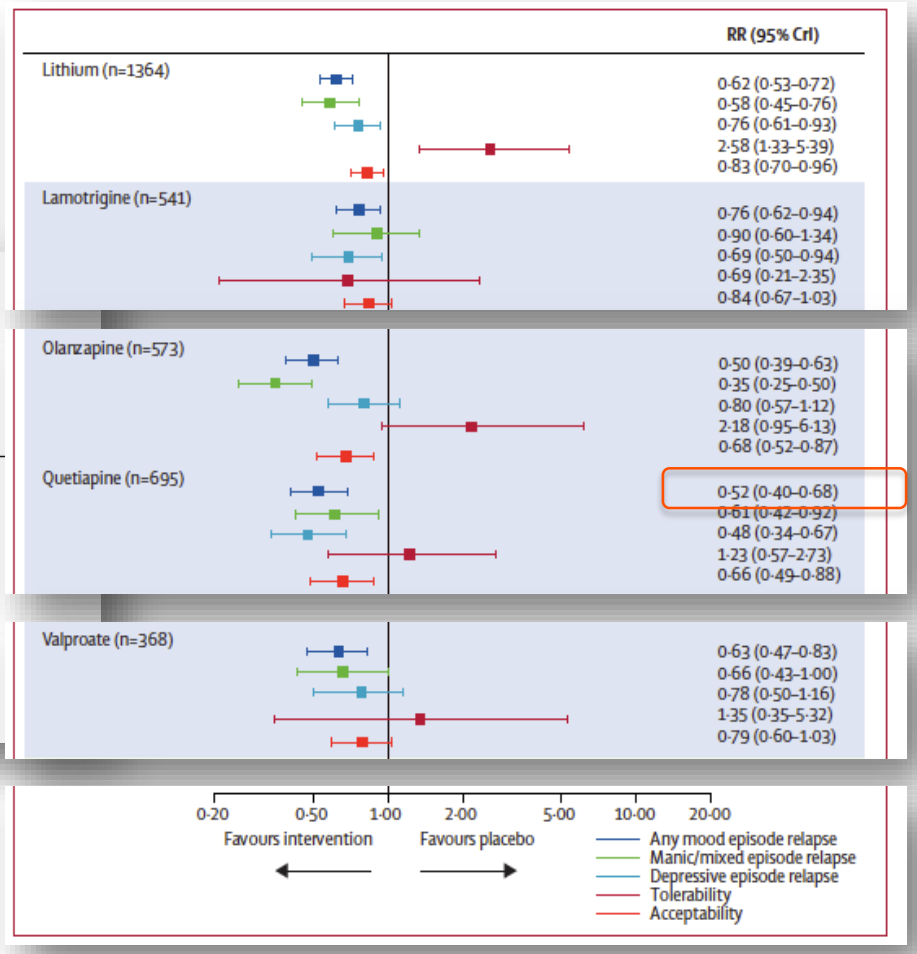

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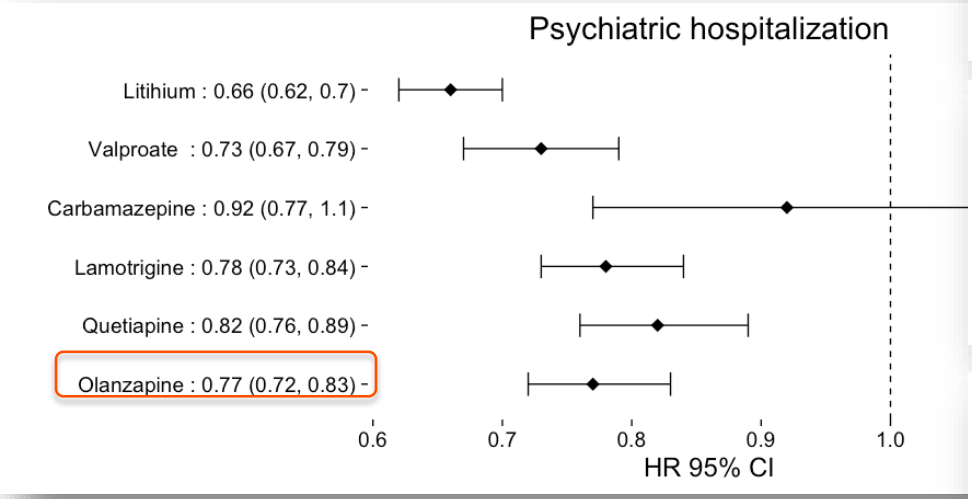

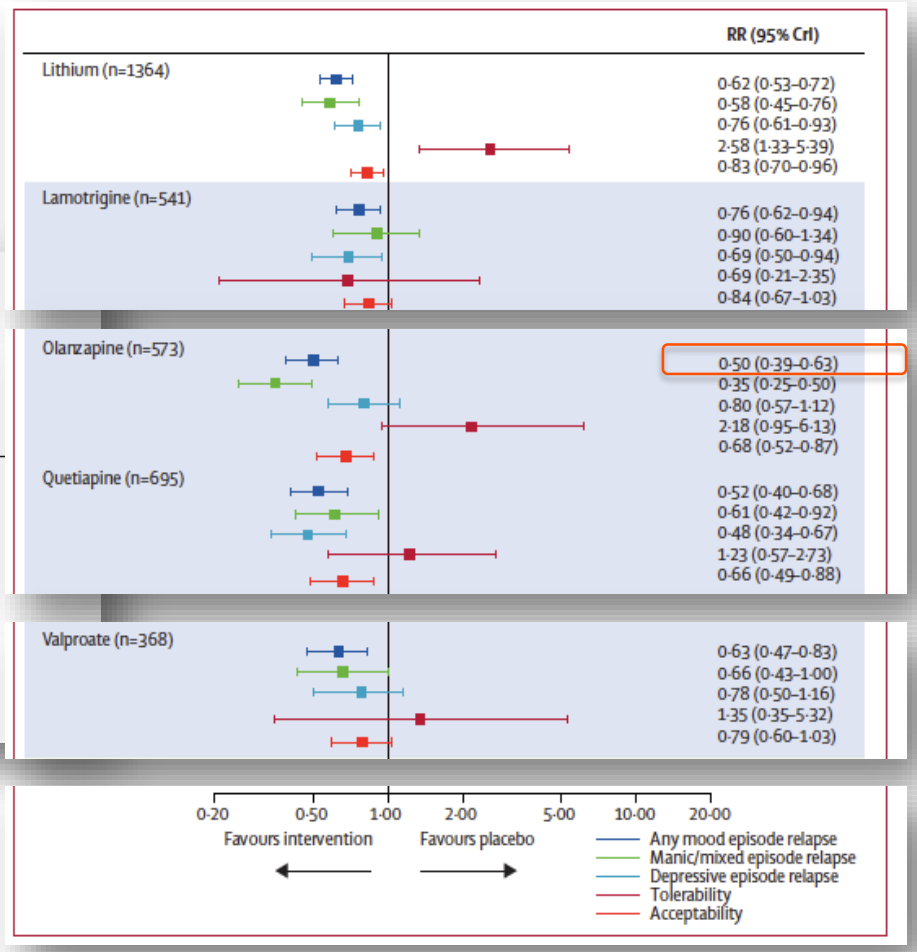

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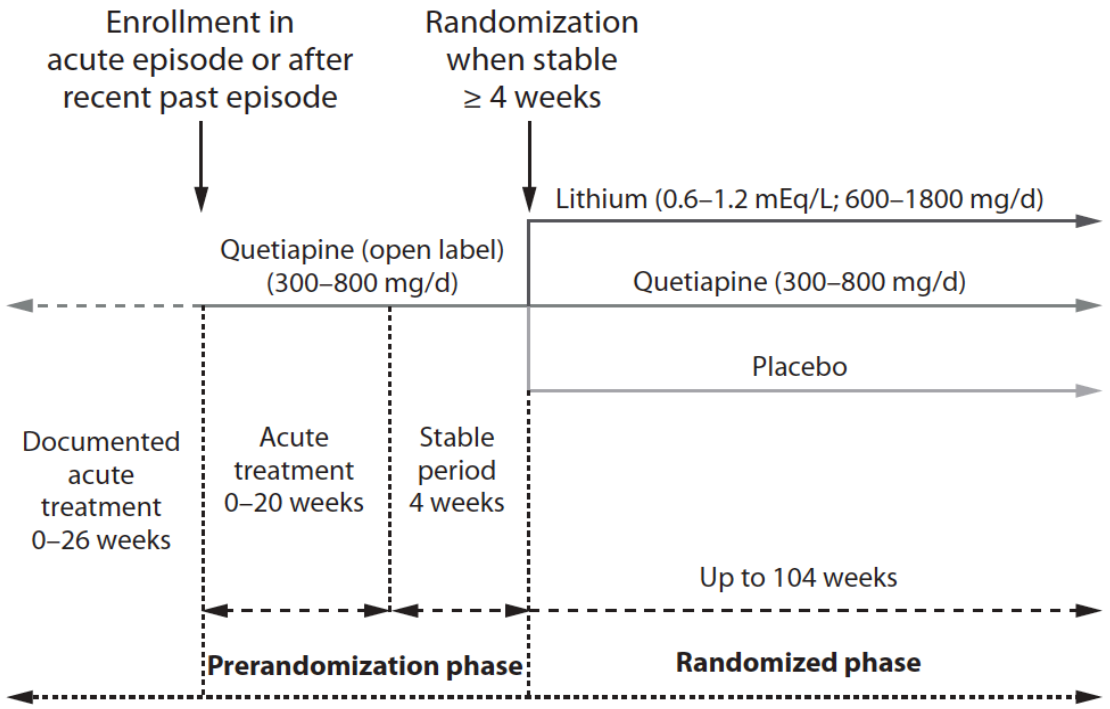
Enriched design favours study drug

Figure 1. Study Flow



Weisler, Richard H., et al. "Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study)." The Journal of clinical psychiatry 72.11 (2011): 1-478.

Indication bias in between-individual analysis

Rates of hospitalizations for MANIA on different medications of mood stabilizing medication compared with non-medication

	Within-individual analysis
Carbamazepine	0.52
	[0.30; 0.89]
Olanzapine	0.57
	[0.47; 0.69]
Lithium	0.60
	[0.51; 0.69]
Valproate	0.62
	[0.51; 0.75]
Quetiapine	0.66
	[0.52; 0.85]
Lamotrigine	0.94
	[0.74; 1.19]

Indication bias in between-individual analysis

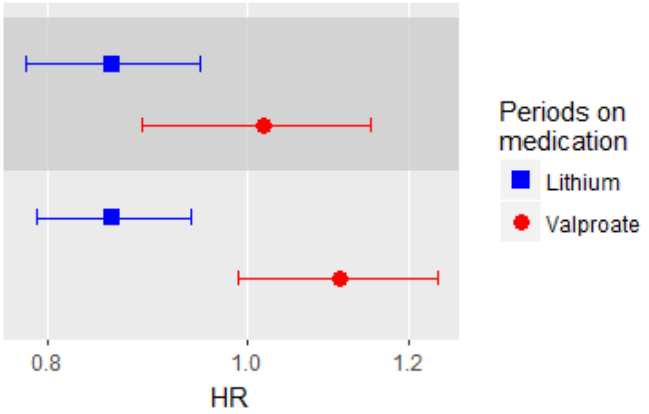
Rates of hospitalizations for MANIA on different medications of mood stabilizing medication compared with non-medication

	Within-individual analysis	Between-individual
Carbamazepine	0.52	0.55
	[0.30; 0.89]	[0.38; 0.79]
Olanzapine	0.57	0.91
	[0.47; 0.69]	[0.80; 1.03]
Lithium	0.60	0.61
	[0.51; 0.69]	[0.55; 0.69]
Valproate	0.62	0.77
	[0.51; 0.75]	[0.66; 0.90]
Quetiapine	0.66	1.58
	[0.52; 0.85]	[1.32; 1.88]
Lamotrigine	0.94	0.56
	[0.74; 1.19]	[0.47; 0.67]

Suicide-related events on lithium and valproate

Hazard ratio for suicide-related events (95% CI)

Within-individual comparison	Lithium: 0.86 (0.78 – 0.95) Valproate: 1.02 (0.89 – 1.15)	P=0.038
Between-individual comparison	Lithium: 0.86 (0.79 – 0.94) Valproate: 1.11 (0.99 – 1.24)	P=0.001



Jie Song

Rate of suicide-related event was reduced by 14% during on vs. off lithium medication periods

Song et al, Am J Psych, 2017 Aug 1;174(8):795-802.

Two questions:

- Is there an increased risk for mania when a patient with bipolar disorder take an antidepressant or a central stimulant?
- If so, can this be prevented by mood stabilizing treatment?

The Risk of Treatment-Emergent Mania With Methylphenidate in Bipolar Disorder

Alexander Viktorin, Ph.D., Eleonore Rydén, M.D., Ph.D., Michael E. Thase, M.D., Zheng Chang, Ph.D., Cecilia Lundholm, M.Sc., Brian M. D'Onofrio, Ph.D., Catarina Almqvist, M.D., Ph.D., Patrik K.E. Magnusson, Ph.D., Paul Lichtenstein, Ph.D., Henrik Larsson, Ph.D., Mikael Landén, M.D., Ph.D.

Objective: The authors sought to determine the risk of treatment-emergent mania associated with methylphenidate, used in monotherapy or with a concomitant mood-stabilizing medication, in patients with bipolar disorder.

Method: Using linked Swedish national registries, the authors identified 2,307 adults with bipolar disorder who initiated therapy with methylphenidate between 2006 and 2014. The cohort was divided into two groups: those with and those without concomitant mood-stabilizing treatment. To adjust for individual-specific confounders, including disorder severity, genetic makeup, and early environmental factors, Cox regression analyses were used, conditioning on individual to compare the rate of mania (defined as hospitalization for mania or a new dispensation of stabilizing medication) 0–3 months and 3–6 months after medication start following nontreated periods.

Results: Patients on methylphenidate monotherapy displayed an increased rate of manic episodes within 3 months of medication initiation (hazard ratio=6.7, 95% CI=2.0–22.4), with similar results for th
for patients taking moo
lower after starting met
CI=0.4–0.9). Comparab
hospitalizations for ma

Conclusions: No evide
ciation between methyl
mania among patient
concomitantly receivi
This is clinically import
with bipolar disorder s
the markedly increase
methylphenidate initia
mood stabilizers, care
disorder is indicated b
psychostimulants.

Am J Psychiatry 2017; 174:34

Article

The Risk of Switch to Mania in Patients With Bipolar Disorder During Treatment With an Antidepressant Alone and in Combination With a Mood Stabilizer

Alexander Viktorin, M.Sc.

Paul Lichtenstein, Ph.D.

Michael E. Thase, M.D.

Henrik Larsson, Ph.D.

Cecilia Lundholm, M.Sc.

Patrik K.E. Magnusson, Ph.D.

Mikael Landén, M.D., Ph.D.

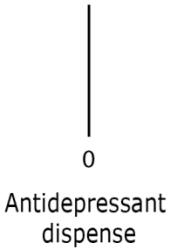
Objective: This study examined the risk of antidepressant-induced manic switch in patients with bipolar disorder treated either with antidepressant monotherapy or with an antidepressant in conjunction with a mood stabilizer.

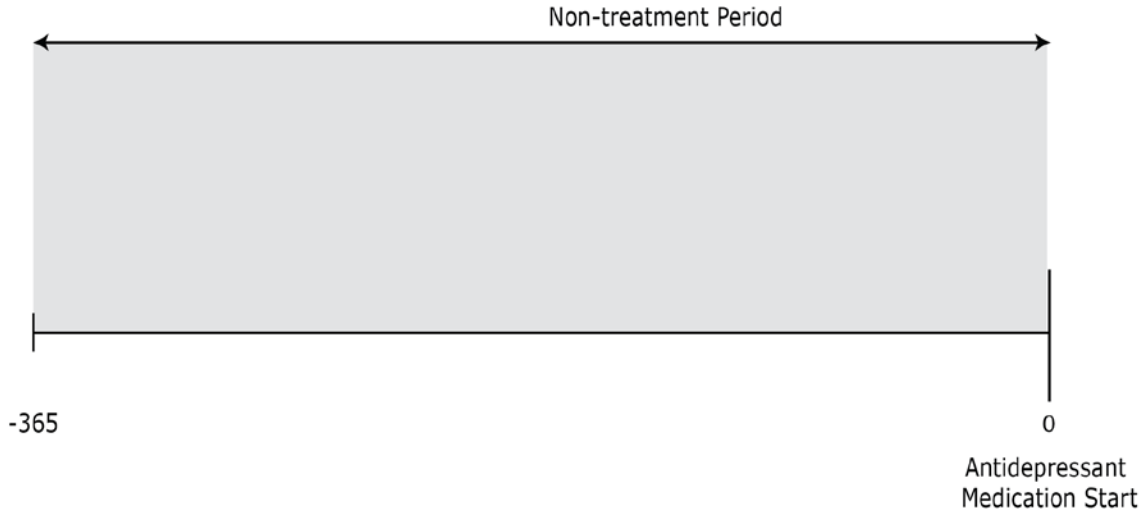
Method: Using Swedish national registries, the authors identified 3,240 patients with bipolar disorder who started treatment with an antidepressant and had no antidepressant treatment during the previous year. Patients were categorized into those receiving antidepressant monotherapy and those receiving an antidepressant plus a mood stabilizer. A within-individual design was used to control for confounding by disorder severity, genetic makeup, and early environmental factors. Cox regression analyses conditioned on individual were used to compare the rate of mania 0–3 months and 3–9 months after the start of antidepressant treatment with a preceding non-treatment period.

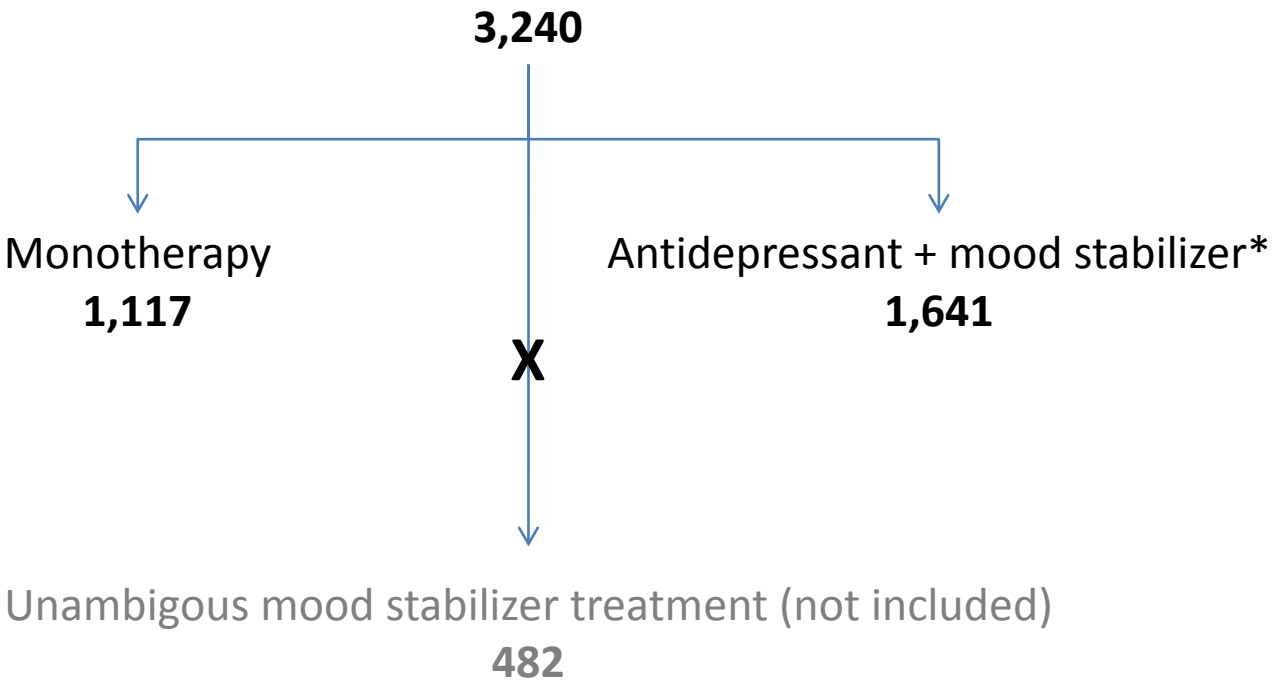
Results: Nearly 35% of the patients were treated with antidepressant monotherapy. The increased risk of treatment-emergent mania was confined to patients on antidepressant monotherapy (hazard ratio=2.83, 95% CI=1.12, 7.19). Among patients treated with a concurrent mood stabilizer, no acute change in risk of mania was observed during the 3 months after the start of antidepressant treatment (hazard ratio=0.79, 95% CI=0.54, 1.15), and a decreased risk was observed during the period 3–9 months after treatment initiation (hazard ratio=0.63, 95% CI=0.42, 0.93).

Conclusions: In this national registry study, antidepressant monotherapy was associated with an increased risk of mania. However, no risk of mania was seen in patients receiving an antidepressant while treated with a mood stabilizer. The results highlight the importance of avoiding antidepressant monotherapy in the treatment of bipolar disorder.

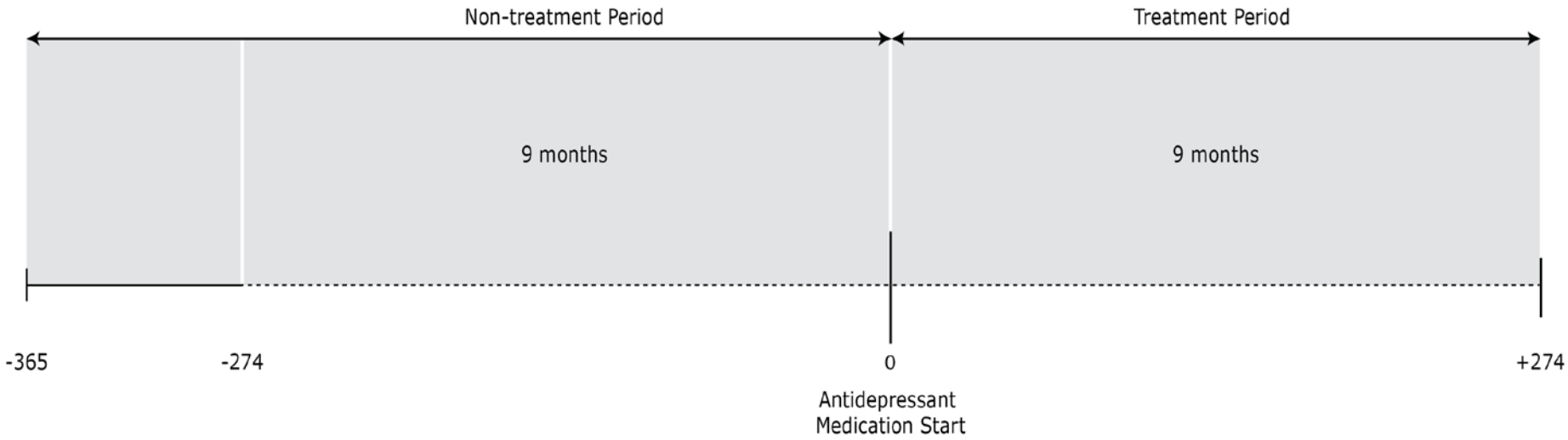
(Am J Psychiatry 2014; 171:1067–1073)

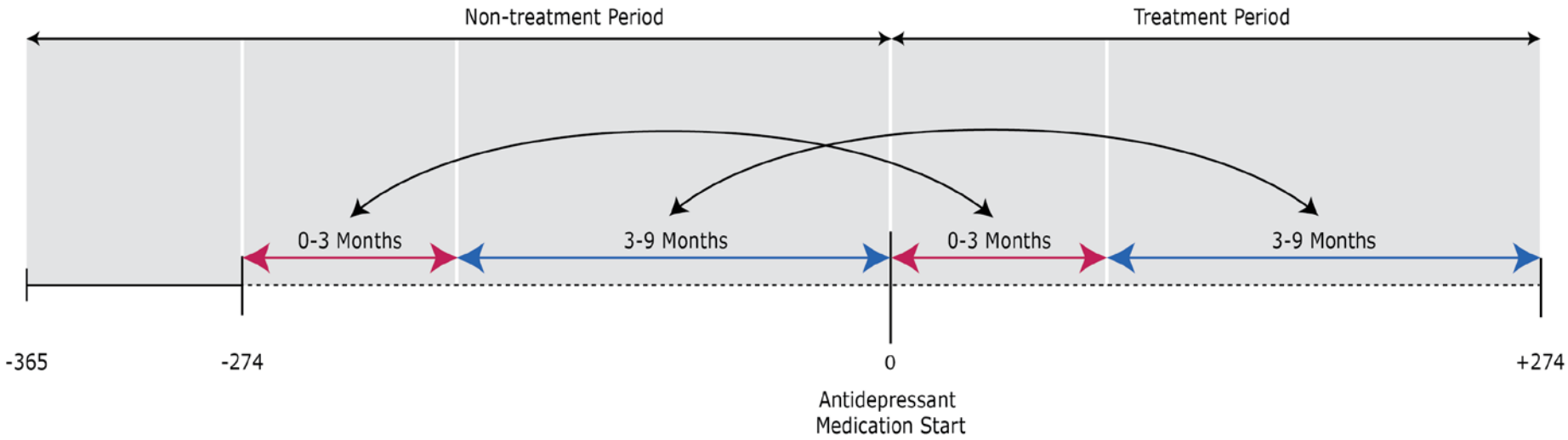

0
Antidepressant
dispense


Non-treatment Period
-365
0
Antidepressant
Medication Start



*Lithium, Valproic acid, or Lamotrigine


Non-treatment Period
Treatment Period
9 months
9 months
-365
-274
0
+274
Antidepressant
Medication Start


Non-treatment Period
Treatment Period
0-3 Months
3-9 Months
0-3 Months
3-9 Months
-365
-274
0
+274
Antidepressant
Medication Start

Antidepressant monotherapy			(N=1,117)
	Hazard ratio	**95% CI**	**P**
0-3 months	2.83	(1.12-7.19)	0.028
3-9 months	0.71	(0.23-2.26)	0.567

Viktorin et al, Am J Psych, 2014

Antidepressant monotherapy			(N=1,117)
	Hazard ratio	**95% CI**	**P**
0-3 months	2.83	(1.12-7.19)	0.028
3-9 months	0.71	(0.23-2.26)	0.567
Concurrent mood stabilizer treatment			(N=1,641)
	Hazard ratio	**95% CI**	**P**
0-3 months	0.79	(0.54-1.15)	0.214
3-9 months	0.63	(0.42-0.93)	0.020

Viktorin et al, Am J Psych, 2014

TABLE 2. Risk of Mania in Patients With Comorbid Bipolar Disorder and ADHD Following Methylphenidate Treatment, Based on Mania Diagnoses and New Prescriptions for Antipsychotics and Mood Stabilizers[a]

Group	Hazard Ratio	p	95% CI	Mania Events (12-Month Follow-Up) N	Mania Events (12-Month Follow-Up) Rate[b]
No mood-stabilizing medication[c] (N=718)				61	0.08
0–3 months	6.67	0.002	1.98–22.4		
3–6 months	9.67	<0.001	2.94–31.7		
Mood-stabilizing medication[d] (N=1,103)				195	0.18
0–3 months	0.56	0.010	0.36–0.87		
3–6 months	0.91	0.758	0.50–1.67		

[a] Patients whose mood stabilizer status was uncertain (N=486) were excluded from the analysis. If no dispensation of lithium, valproate, or an antipsychotic (aripiprazole, olanzapine, quetiapine, haloperidol, or risperidone) was observed in the 9 months before methylphenidate treatment (period A in Figure 1), a dispensation after the start of methylphenidate treatment (period C in Figure 1) was considered an indication of elevated mood. This definition was applied to both groups, and dosages of aripiprazole, olanzapine, and quetiapine below 5 mg/day, 5 mg/day, and 100 mg/day, respectively, were not considered.

[b] Rate denotes the number of identified mania events divided by the total number of patients in the group.

[c] Patients in this group received no type of mood-stabilizing medication during the 6 months before the dispensation of methylphenidate (period B in Figure 1) or at the date of dispensation of methylphenidate. This includes lithium, valproate, lamotrigine, olanzapine, quetiapine, aripiprazole, risperidone, haloperidol, and carbamazepine.

[d] Patients in this group had at least two dispensations of mood-stabilizing medication (lithium, valproate, olanzapine, quetiapine, or aripiprazole) within the 9 months before methylphenidate dispensation (period A in Figure 1). At least one dispensation of a mood-stabilizing medication had to be within 6 months before methylphenidate treatment (period B in Figure 1).

Limitations and hurdles

- Withdrawal / carry-over effects
  - Sensitivity analysis where time periods are added
- Reversed causality
  - What if criminal behaviour triggers discontinuation of ADHD-medication?
  - Hypomania → antipsychotics → not sufficient → hospitalization
  - The method suits chronic better than acute treatment

Limitations and hurdles

- Does the sequence of treatment matter?
  - 1st line treatment likely to be favoured since 2nd attempt is enriched with non responders
  - But this is a greater problem in RCTs where lithium responders (1st line) are unlikely to be included.

Conclusions

- Observational register studies are important complements to randomized clinical trials but beware of indication bias.
- Within-indivdual comparisons is a method that circumvents indication bias and controls for time-stationary confounders
- But there is still a risk for reversed causality