Supplementary Materials for *Suicidal Behavior During Lithium and Valproate Medication: A Within-individual Eight Year Prospective Study of 50,000 Patients With Bipolar Disorder*

Supplementary Methods

We defined the following drugs with Anatomical Therapeutic Chemical (ATC) classification codes: lamotrigine (N03AX09), antipsychotics (N05A) excluding lithium, antidepressants (N06A), anticonvulsants (N03A) excluding lamotrigine and valproate, benzodiazepines (N05BA) and thyroid hormones and antithyroid drug (H03).

In the sensitivity analysis we used a subgroup of BD without a lifetime diagnosis of comorbid psychiatric conditions, including personality disorders, substance use disorders, attention-deficit/hyperactivity disorder (ADHD), acute stress, adjustment disorders and posttraumatic stress disorders, and conduct disorders. The ICD codes are in supplementary Table S1.

Swedish Bipolar Quality Register

Patients with bipolar I and bipolar II disorder were derived from BipoläR, the Swedish national quality register for bipolar disorder. This register was described in detail elsewhere (1). In brief, the register was established in 2004 with annual updates of follow-ups. It records individualized data for patients diagnosed with bipolar I disorder, bipolar II disorder, schizoaffective disorder of bipolar type and not otherwise specified. The diagnoses were based on systematically collected data and best-estimate according to the DSM-IV-TR and ICD-10 assigned by trained treating psychiatrists. Since the psychiatrists volunteered in the register have access to all clinical data including available longitudinal perspectives of patients' course of illness, the specificity of diagnosis of bipolar disorder in BipoläR is likely to be high. The register covers both basic clinical epidemiology data and longitudinal data on the natural history and clinical course of the illness. It includes patients with severe forms of bipolar disorder which require hospitalization as well as those treated in psychiatric outpatient healthcare units. When we extracted data in December 2013, 12,837 patients with bipolar disorder were registered in BipoläR during 2004-2013 with annual follow-up. Among those patients, we identified those with a most recent diagnosis of bipolar I disorder (N= 5981) and bipolar II disorder (N=5868).

Propensity Score Estimation

Based on a recent method review (2), we constructed the propensity scores (PS) following the steps below. First, we identified all factors available by linking Swedish national registers that were decided a priori and were likely to affect clinician's prescribing choice according to existing studies (3). These variables included sex, age, history symptoms or diagnosis of cardiovascular disease, hypertension, chronic kidney disease, hypothyroidism/hyperthyroidism, liver disease, type 2 diabetes mellitus, epilepsy, alcohol use, illicit drug use, anxiety and depression, history of hospitalization length due to psychiatric disorders, and history of previous suicide. For demographic and health-related covariates, the entire medical record before baseline was reviewed. It was not possible to adjust for ethnicity, smoking status and body mass index. Second, to balance between variables' effects on bias and efficiency, we checked the associations between these variables and outcomes as well as between variables and treatments (2). Finally, we developed the PS based on variables of sex, age, history symptoms or diagnosis of alcohol/drug use, epilepsy, anxiety and depression, and history of hospitalization length due to psychiatric disorders.

To be able to use PS, we modified our designs according to a recently published paper (3). Instead of defining medication status as time-varying variables, we did not allow individuals to reenter the cohort once they had switch treatment status (i.e., only keep the first observation period for each individual). Only ordinary Cox regression was used for PS analyses (i.e., between-individuals comparisons). The rates of suicide-related events were compared between groups in: 1) Valproate monotherapy vs. no medication (not treated with lithium, valproate, lamotrigine, antipsychotic, antidepressant and anticonvulsants); 2) Lithium monotherapy vs. no medication; 3) Lithium monotherapy vs. valproate monotherapy.

We used three models to perform analyses: adjusted analysis, PS adjustment analysis and 1:1 PS matching analysis. The PS was calculated by logistic regression using the covariates described above as independent variables and drug treatment as the dependent variable. In PS adjustment analysis, the PS was used as a linear term in the Cox regression. In 1:1 PS-matched analysis, patient pairs were matched with calipers of 0.02 standard deviations of the propensity score, dropping all other patients from the analysis. PS adjustment and PS matching analyses have different strengths: The adjusted analysis may be more generalizable. The matched analysis only included patients with similar observed characteristics and may provide a more valid estimate of drug effect.

All analyses were performed with Stata 13.0 (4). For testing the balance of covariates between groups before and after PS matching, we used *pstest* command in Stata (5-7). Supplementary Tables S5-S7 showed the baseline participant characteristics before and after 1:1 PS matching.

Derivation of population attributable fraction (PAF)

The derivation of population attributable fraction (PAF) is the same as in previous publications (in eMethods in Supplementary Online Content for details) in our group (8).

The PAF is defined as

$$1 - \frac{p(Y_0 = 1)}{p(Y = 1)},$$

where $p(Y = 1)$ is the probability of the outcome (suicide attempt or completed suicide) in a short time interval (e.g. a month), and $p(Y_0 = 1)$ is the probability of the outcome had everybody been medicated. Assuming that the covariates that we adjust for in the within-individual analysis are sufficient for confounding control, the PAF can be algebraically rewritten as

$$p(X = 1|Y = 1)\left(1 - RR_{adj}^{-1}\right) = \left\{1 + RR^{-1}\frac{1 - p(X = 1)}{p(X = 1)}\right\}^{-1}\left(1 - RR_{adj}^{-1}\right), \quad (1)$$

where $p(X = 1)$ is the proportion of unmedicated months, $p(X = 1|Y = 1)$ is the proportion of unmedicated months among the months where an outcome occurs, RR is the unadjusted risk ratio, and RR_{adj} is the within-individual risk ratio; for these risk ratios the unmedicated enter into the numerator. For the stratified Cox regression analysis of lithium we used the right-hand side of (1), with $p(X = 1) = 1 - 17.9\% = 0.82$, $RR = 1/0.86 = 1.16$ (obtained from ordinary Cox regression) and $RR_{adj} = 1/0.86 = 1.16$ (obtained from stratified Cox regression). This gives an estimated PAF equal to 12%.

95% confidence intervals for the estimated PAFs were obtained by the bootstrap with 1000 resamples.

Supplementary Table S1. Definition of comorbid psychiatric conditions

Psychiatric disorder	ICD 8 (1969-1986)	ICD 9 (1987-1996)	ICD 10 (1997-)
Bipolar disorder [a]	296.0- 296.3, 296.8, 296.9	296A-296E, 296W, 296X	F30, F31
Personality disorders	301	301	F60-F62, F69
Substance use disorders	303, 304	303, 304, 305A, 305X	F10-F19 except x.5
ADHD	-	314	F90
Acute stress, adjustment disorders and posttraumatic stress disorders	-	308, 309	F43
Conduct disorders	-	312	F91

a. The definition of bipolar disorder requires at least two inpatient or outpatient admissions. Individuals with sole diagnoses of ICD-8 296.2 (manic-depressive psychosis, depressed type) and/or ICD-9 296B (unipolar affective psychosis, melancholic form) were excluded. Individuals with two or more inpatient or outpatient admissions of schizophrenia or schizoaffective disorder (ICD-8: 295; ICD-9: 295; ICD-10: F20, F25) were also excluded.(9)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ICD, International Classification of Disease

Supplementary Table S2. Risk of suicide-related events from 2005-10-01 to 2013-12-31 during medication periods compared to non-medication periods among patients with bipolar disorder in Sweden (**adjusted for concurrent medication**)

	Within-individual analysis		**Between-individual analysis**	
Analysis model[a]	**Stratified Cox regression**		**Cox regression**	
Estimates	**Hazard ratio**[b]	**95%CI**	**Hazard ratio**[b]	**95%CI**
Lithium	0.81	0.73-0.90	0.80	0.73-0.87
Valproate	0.97	0.85-1.10	1.01	0.90-1.13
Lamotrigine	0.94	0.86-1.03	1.01	0.95-1.09
Antipsychotics	1.10	1.02-1.18	1.17	1.10-1.24
Antidepressants	1.03	0.96-1.11	1.28	1.21-1.36
Anticonvulsants	1.16	1.06-1.27	1.29	1.20-1.40
Benzodiazepines	1.41	1.30-1.52	1.54	1.44-1.64
Test of difference between HRs for lithium and valproate	P = 0.030		P = 0.001	

a. Stratified Cox regression was applied with adjustment for time-varying covariates including categorical age and previous number of suicide attempts. Ordinary Cox regression was applied with adjustment for the same covariates as in the stratified Cox regression and, additionally, with adjustment for time-invariant covariates including sex, length of baseline hospitalization periods due to psychiatric admissions (a measure of illness severity), and history of suicide-related events before entering follow-up.

b. Hazard Ratio is the ratio of the hazard rates during medication periods compared with nonmedication periods, for each treatment, separately.

Abbreviations: CI, confidence interval

Supplementary Table S3. Risk of suicide-related events from 2005-10-01 to 2013-12-31 during medication periods compared to non-medication periods among patients with bipolar disorder in Sweden (**considering combination therapy of lithium and valproate**)

	Within-individual analysis		**Between-individual analysis**	
Analysis model[a]	**Stratified Cox regression**		**Cox regression**	
Estimates	**Hazard ratio**	**95%CI**	**Hazard ratio**	**95%CI**
Periods without lithium and valproate (Reference)	1	-	1	-
Lithium	0.85	0.77-0.94	0.85	0.77-0.93
Valproate	1.00	0.87-1.15	1.08	0.95-1.22
Lithium and valproate	0.93	0.70-1.22	1.09	0.89-1.33

a. Stratified Cox regression was applied with adjustment for time-varying covariates including categorical age and previous number of suicide attempts. Ordinary Cox regression was applied with adjustment for the same covariates as in the stratified Cox regression and, additionally, with adjustment for time-invariant covariates including sex, length of baseline hospitalization periods due to psychiatric admissions (a measure of illness severity), and history of suicide-related events before entering follow-up.

Abbreviations: CI, confidence interval

Supplementary Table S4. Risk of suicide-related events during lithium and valproate monotherapy among patients with bipolar disorder in Sweden (**Periods with time-invariant medication**)

Medication status	**Adjustment analysis**		**Propensity Score adjustment** [a]		**1:1 Propensity Score matching** [a]	
	Hazard ratio	95%CI	Hazard ratio	95%CI[c]	Hazard ratio	95%CI[c]
Valproate monotherapy vs. no medication[b]	0.76	0.45-1.28	0.76	0.45-1.26	0.93	0.50-1.73
Lithium monotherapy vs. no medication[b]	0.47	0.32-0.69	0.47	0.32-0.68	0.45	0.29-0.68
Lithium monotherapy vs. **valproate** monotherapy	0.62	0.33-1.17	0.62	0.33-1.18	0.46	0.20-1.10

a. The propensity scores were constructed by including variables of sex, age at the start of treatment with the study drug, history of epilepsy, history of alcohol use, history of drug abuse, anxiety symptoms or diagnosis before baseline, depressive symptoms or diagnosis before baseline, history of hospitalization length due to psychiatric disorders. Adjustment analyses were performed by adjusting for these variables.

b. No medication refers to period without lithium, valproate, lamotrigine, antipsychotic, antidepressant and anticonvulsants.

c. Standard errors for calculation of confidence interval do not take into account that the propensity score is estimated.

Supplementary Table S5.1 Bias in the unmatched and matched covariates with treated group as **valproate** monotherapy and control group without medication (N=1,679 pair after PS matching)

Variable		Group	Mean		Standardized Bias (%)	Reduction in absolute bias (%)	T-test		V(T)/ V(C)
			Treated	Control			t	P	
Sex		Unmatched	1.545	1.6273	-16.8		-6.82	0.000	1.06
		Matched	1.545	1.5473	-0.5	97.1	-0.14	0.890	1.00
Age		Unmatched	44.512	46.076	-9.0		-3.47	0.001	0.82*
		Matched	44.512	44.179	1.9	78.7	0.59	0.558	0.99
Length in hospital due to psychiatric Symptoms (year)	<0.25	Unmatched	0.38118	0.37434	1.4		0.57	0.99	.
		Matched	0.38118	0.39428	-2.7	-91.5	-0.78	0.436	.
	0.25-0.5	Unmatched	0.07683	0.08361	-2.5		-0.98	0.325	.
		Matched	0.07683	0.06968	2.6	-5.4	0.79	0.427	.
	0.5-1	Unmatched	0.05837	0.05489	1.5		0.61	0.540	.
		Matched	0.05837	0.0542	1.8	-19.8	0.52	0.600	.
	≥1	Unmatched	0.05599	0.04681	4.2		1.74	0.083	.
		Matched	0.05599	0.05301	1.3	67.5	0.38	0.704	.
Alcohol use		Unmatched	0.16319	0.15186	3.1		1.27	0.206	.
		Matched	0.16319	0.17332	-2.8	10.6	-0.78	0.433	.
Drug abuse		Unmatched	0.11257	0.11643	-1.2		-0.48	0.629	.
		Matched	0.11257	0.11197	0.2	84.6	0.05	0.956	.
Depression		Unmatched	0.40739	0.43329	-5.2		-2.1	0.036	.
		Matched	0.40739	0.40024	1.4	72.4	0.42	0.673	.
Anxiety		Unmatched	0.24538	0.25714	-2.7		-1.08	0.280	.
		Matched	0.24538	0.243	0.5	79.7	0.16	0.872	.
Epilepsy		Unmatched	0.04467	0.01656	16.4		8.56	0.000	.
		Matched	0.04467	0.04288	1.0	93.6	0.25	0.800	.

Included variables were sex, age at the start of treatment with the study drug, history of epilepsy, history of alcohol use, history of drug abuse, anxiety symptoms or diagnosis before baseline, depressive symptoms or diagnosis before baseline, history of hospitalization length due to psychiatric disorders. V(T)/ V(C): Variance ratio (for continuous covariates) of treated group vs. control group, * if variance ratio outside [0.91; 1.10]

Supplementary Table S5.2 Summary of mean and standardized difference for all covariates with treated group as **valproate** monotherapy and control group without medication (N=1,679 pair after PS matching)

Sample	Pseudo R^2	LR χ^2	p> χ^2	Mean Bias	Median Bias	Pseudo B	Pseudo R	%Var
Unmatched	0.009	130.44	0.000	5.8	3.1	27.4*	1.48	50
Matched	0.001	2.81	0.993	1.5	1.4	5.8	1.03	0

*If B > 25%, R outside [0.5; 2]; Pseudo B: the absolute standardized difference of the means of the linear index of the propensity score in the treated and (matched) non-treated group; Pseudo R: the ratio of treated to (matched) non-treated variances of the propensity score index (5).

Supplementary Table S6.1 Bias in the unmatched and matched covariates for treated group with **lithium monotherapy** and control group without medication (N=5,404 pair after PS matching)

Variable		Group	Mean		Standardized Bias (%)	Reduction in absolute bias (%)	T-test		V(T)/ V(C)
			Treated	Control			t	P	
Sex		Unmatched	1.5814	1.6273	-9.4		-6.52	0.000	1.04
		Matched	1.5814	1.5855	-0.8	91.1	-0.43	0.668	1.00
Age		Unmatched	48.325	46.076	12.9		8.61	0.000	0.85*
		Matched	48.325	48.396	-0.4	96.9	-0.22	0.828	0.99
Length in hospital due to psychiatric Symptoms (year)	<0.25	Unmatched	0.42598	0.37434	10.6		7.34	0.000	.
		Matched	0.42598	0.4319	-1.2	88.5	-0.62	0.534	.
	0.25-0.5	Unmatched	0.10492	0.08361	7.3		5.24	0.000	.
		Matched	0.10492	0.10289	0.7	90.4	0.35	0.729	.
	0.5-1	Unmatched	0.06884	0.05489	5.8		4.16	0.000	.
		Matched	0.06884	0.06255	2.6	54.9	1.32	0.187	.
	≥1	Unmatched	0.04034	0.04681	-3.2		-2.13	0.033	.
		Matched	0.04034	0.03793	1.2	62.8	0.64	0.519	.
Alcohol use		Unmatched	0.11547	0.15186	-10.7		-7.08	0.000	.
		Matched	0.11547	0.1114	1.2	88.8	0.67	0.505	.
Drug abuse		Unmatched	0.07457	0.11643	-14.3		-9.18	0.000	.
		Matched	0.07457	0.07087	1.3	91.2	0.74	0.459	.
Depression		Unmatched	0.401	0.43329	-6.6		-4.5	0.000	.
		Matched	0.401	0.39859	0.5	92.5	0.26	0.799	.
Anxiety		Unmatched	0.18042	0.25714	-18.6		-12.27	0.000	.
		Matched	0.18042	0.18301	-0.6	96.6	-0.35	0.727	.
Epilepsy		Unmatched	0.01203	0.01656	-3.8		-2.49	0.013	.
		Matched	0.01203	0.00777	3.6	6.1	2.23	0.025	.

Included variables were sex, age at the start of treatment with the study drug, history of epilepsy, history of alcohol use, history of drug abuse, anxiety symptoms or diagnosis before baseline, depressive symptoms or diagnosis before baseline, history of hospitalization length due to psychiatric disorders. V(T)/ V(C): Variance ratio (for continuous covariates) of treated group vs. control group, * if variance ratio outside [0.95; 1.05]

Supplementary Table S6.2 Summary of mean and standardized difference for all covariates with treated group as **valproate** monotherapy and control group without medication (N=5,404 pair after PS matching)

Sample	Pseudo R^2	LR χ^2	p> χ^2	Mean Bias	Median Bias	Pseudo B	Pseudo R	%Var
Unmatched	0.014	448.47	0.000	9.4	9.4	31.3*	0.82	50
Matched	0.001	9.01	0.621	1.3	1.2	5.8	1.38	0

*If B > 25%, R outside [0.5; 2]; Pseudo B: the absolute standardized difference of the means of the linear index of the propensity score in the treated and (matched) non-treated group; Pseudo R: the ratio of treated to (matched) non-treated variances of the propensity score index.

Supplementary Table S7.1 Bias in the unmatched and matched covariates for group with **valproate monotherapy** and group with **lithium monotherapy** (N=1,659 pair after PS matching)

Variable		Group	Mean		Standardized Bias (%)	Reduction in absolute bias (%)	T-test		V(T)/ V(C)
			Treated	Control			t	P	
Sex		Unmatched	1.545	1.5814	-7.4		-2.64	0.008	1.02
		Matched	1.5461	1.5497	-0.7	90.1	-0.21	0.834	1.00
Age		Unmatched	44.512	48.325	-22.9		-8.17	0.000	0.96
		Matched	44.582	44.028	3.3	85.5	0.98	0.327	1.05
Length in hospital due to psychiatric Symptoms (year)	<0.25	Unmatched	0.38118	0.42598	-9.1		-3.26	0.001	-
		Matched	0.38095	0.36347	3.6	61.0	1.04	0.298	-
	0.25-0.5	Unmatched	0.07683	0.10492	-9.8		-3.38	0.001	-
		Matched	0.07776	0.05485	8	18.5	2.65	0.008	-
	0.5-1	Unmatched	0.05837	0.06884	-4.3		-1.51	0.132	-
		Matched	0.05726	0.05726	0.0	100.0	0.00	1.000	-
	≥1	Unmatched	0.05599	0.04034	7.3		2.73	0.006	-
		Matched	0.05485	0.05606	-0.6	92.3	-0.15	0.879	-
Alcohol use		Unmatched	0.16319	0.11547	13.8		5.14	0.000	-
		Matched	0.16034	0.13261	8.0	41.9	2.26	0.024	-
Drug abuse		Unmatched	0.11257	0.07457	13.1		4.92	0.000	-
		Matched	0.1085	0.09343	5.2	60.3	1.44	0.150	-
Depression		Unmatched	0.40739	0.401	1.3		0.47	0.641	-
		Matched	0.40567	0.40205	0.7	43.4	0.21	0.832	-
Anxiety		Unmatched	0.24538	0.18042	15.9		5.87	0.000	-
		Matched	0.24111	0.24111	0.0	100.0	0.00	1.000	-
Epilepsy		Unmatched	0.04467	0.01203	19.8		8.43	0.000	-
		Matched	0.03376	0.02893	2.9	85.2	0.80	0.426	-

Included variables were sex, age at the start of treatment with the study drug, history of epilepsy, history of alcohol use, history of drug abuse, anxiety symptoms or diagnosis before baseline, depressive symptoms or diagnosis before baseline, history of hospitalization length due to psychiatric disorders. V(T)/ V(C): Variance ratio (for continuous covariates) of treated group vs. control group, * if variance ratio outside [0.91; 1.10]

Supplementary Table S7.2 Summary of mean and standardized difference for all covariates for group with **valproate monotherapy** and group with **lithium monotherapy** (N=1,659 pair after PS matching)

Sample	Pseudo R^2	LR χ^2	p> χ^2	Mean Bias	Median Bias	Pseudo B	Pseudo R	%Var
Unmatched	0.027	211.05	0.000	11.3	9.8	40.1*	1.39	0
Matched	0.003	14.45	0.209	3.0	2.9	13.2	1.22	0

*If B > 25%, R outside [0.5; 2]; Pseudo B: the absolute standardized difference of the means of the linear index of the propensity score in the treated and (matched) non-treated group; Pseudo R: the ratio of treated to (matched) non-treated variances of the propensity score index.

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