Supplementary Data

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Appendix 1. Risk of mania following methylphenidate medication based on mania diagnoses and new prescriptions of antipsychotics

Results from an analysis counting diagnoses of mania and new dispensations antipsychotics towards elevated mood, but not new dispensations of lithium or valproate semisodium.

ST 1. Risk of mania following methylphenidate medication based on mania diagnoses and new prescriptions of antipsychotics*

Group	Number	Period	Hazard Ratio	P-value	95% Confidence Interval	Number of mania events (rate****)
No stabilizer**	718	0-3 months	6.67	0.002	1.98 - 22.4	47 (0.07)
		3-6 months	5.00	0.011	1.45 - 17.3	
Stabilizer***	1103	0-3 months	0.59	0.019	0.38 - 0.92	173 (0.16)
		3-6 months	1.09	0.768	0.61 - 1.95	

* 486 individuals presented with uncertain mood stabilizer status and was excluded from the analysis. If no dispensation of an antipsychotic (aripiprazole, olanzapine, quetiapine, haloperidol, and risperidone) was observed in the nine months prior methylphenidate medication (period A in Figure 1), a dispensation after the methylphenidate medication (period C in Figure 1) was considered an indication of elevated mood. This definition was applied to both groups, and doses of aripiprazole, olanzapine, and quetiapine below 5mg, 5mg, and 100mg respectively were not considered.

** Cannot have any type of of stabilizer medication during the 6 months prior the dispensation of methylphenidate (period B in Figure 1), nor at the date of dispensation of methylphenidate. This includes lithium, valproic acid, lamotrigine, olanzapine, quetiapine, aripiprazolam, risperidone, haloperidol, and carbamazepine.

*** Must have at least two dispensations of stabilizing drugs (lithium, valproic acid, olanzapine, quetiapine, or aripiprazolam) within the 9 months prior methylphenidate dispensation (period A in Figure 1). At least one dispensation of a stabilizing drug has to be within 6 months prior methylphenidate treatment (period B in figure 1).

**** Rate denotes number of identified mania events divided by total number of subjects in the group.

Appendix 2. Analyses counting a schizophrenia diagnosis after methylphenidate treatment as mania

A patient suffering a psychotic manic episode may have received a schizophrenia diagnosis from a treating clinician unfamiliar with the patient's bipolar disorder history. To test the effect of such potential misclassification, we conducted supplemental analyses counting a schizophrenia diagnosis after methylphenidate treatment as mania, instead of censoring follow up at this time.

Only two patients had received a schizophrenia diagnosis after methylphenidate treatment. As is shown in the Tables ST 2 and ST 3, counting these diagnoses as mania had only minor effects on the results.

ST 2. Risk of mania following methylphenidate medication based on mania diagnoses, new schizophrenia diagnoses, and new prescriptions of typical and atypical antipsychotics, lithium and valproate semisodium*

Group	Number	Period	Hazard Ratio	P-value	95% Confidence Interval	Number of mania events (rate****)
No stabilizer	718	0-3 months	6.67	0.002	1.98 - 22.4	61 (0.08)
		3-6 months	9.67	<0.001	2.94 - 31.7	
Stabilizer	1103	0-3 months	0.57	0.014	0.37- 0.89	197 (0.18)
		3-6 months	0.96	0.879	0.53 - 1.74	

* A diagnosis of schizophrenia after methylphenidate treatment (N=2) did not lead to censoring but was counted towards mania

ST 3. Risk of mania following methylphenidate medication based on mania diagnoses and new schizophrenia diagnoses

Group	Number	Period	Hazard Ratio	P-value	95% Confidence Interval	Number of mania events (rate****)
No stabilizer	718	0-3 months	3.33	0.067	0.92 - 12.11	24 (0.03)
		3-6 months	1.00	1.000	0.20 - 4.95	
Stabilizer	1103	0-3 months	0.50	0.003	0.32 - 0.79	146 (0.13)
		3-6 months	0.91	0.758	0.50 - 1.67	

* A diagnosis of schizophrenia after methylphenidate treatment (N=2) did not lead to censoring but was counted towards mania

Appendix 3. All types of mood stabilizing medications and antipsychotics dispensed in the stabilized group

ST 4. All types of mood stabilizing medications and antipsychotics dispensed in the mood-stabilizer group*

		Females (N=660)		Males (N=443)		Total (N=1,103)	
Name	**ATC**	**Number**	**Percent****	**Number**	**Percent****	**Number**	**Percent****
Quetiapine	N05AH04	475	72.0	283	63.9	758	68.7
Lamotrigine***	N03AX09	467	70.8	275	62.1	742	67.3
Lithium	N05AN01	458	69.4	298	67.3	756	68.5
Olanzapine	N05AH03	325	49.2	263	59.4	588	55.3
Valproate semisodium	N03AG01	297	45.0	233	52.6	530	48.1
Aripiprazole	N05AX12	228	34.6	120	27.1	348	31.6
Risperidone***	N05AX08	125	18.9	87	19.6	212	19.2
Carbamazepine***	N03AF01	66	10.0	42	9.5	108	9.8
Haloperidol***	N05AD01	43	6.5	43	9.7	86	7.8

* The number and percentage of study subjects with at least one dispensation of the specifed medications during the nine-month period prior methylphenidate treatment initiation. Subjects can be treated with several types of medication during the period.

** The percent figure is rounded to one decimal.

*** Dispensations of carbamazepine, haloperidol, risperidone, or lamotrigine were not counted towards the required two dispensations to be included in the stabilized group, as these drugs were assumed to reflect an acute mood-stabilizing treatment rather than a continuous course of treatment. The occurrence of these drugs thus represent medication additionally added to patients also having at least two dispensations of the any of the others medications.

Appendix 4. Prevalence of antidepressant treatment before and after methylphenidate treatment initiation and effects on the association between methylphenidate treatment and elevated mood

The distribution of antidepressant treatment in each group before and after methylphenidate treatment is displayed in ST 5 below.

ST 5. Prevalence of antidepressant treatment in the non-stabilizer and stabilizer groups before and after treatment initiation with methylphenidate*

			Antidepressant medication*	
Group	**Number**	**Period**	**N**	**%**
No stabilizer	718	Prior methylphenidate	332	46.2
		After methylphenidate	331	46.1
Stabilizer	1103	Prior methylphenidate	612	55.5
		After methylphenidate	658	59.7

* At least one dispensation of an antidepressant (4-digit ATC code N06A), excluding tryptophan.

The original analysis uses a stratified Cox regression model with a three-way interaction between stabilizer use, split time spans (0-3 months, 3-6 months), and the methylphenidate untreated/treated periods within the same individual (1/0). Adding an additional factor (antidepressant y/n) creates a four-way interaction that reduces power considerably and does not produce informative results. To test a potential interaction of antidepressant treatment and mania following methylphenidate treatment, we therefore dropped the time span factor and replaced it with the antidepressant variable.

The table ST 6 below presents the original three-way interaction model (top), followed by a two-way interaction model where time span is dropped. We thereby compare the 6 months prior to methylphenidate treatment with 6 months after methylphenidate initiation. The bottom of the table displays a three-way interaction where antidepressant treatment has replaced the time span.

The results indicate that the finding of the current study is not likely to be driven by concomitant antidepressant treatment: the stabilized group is largely unaffected and the largest relative risk (HR) of mania in the non-stabilizer group is in fact observed among those not treated with an antidepressant. Yet, the non-stabilizer group maintains the increased risk of mania following methylphenidate.

ST 6. Risk of mania following methylphenidate medication based on mania diagnoses and new prescriptions of antipsychotics and stabilizers*

Group	Number	Period	Anti-depressant	Hazard Ratio	P-value	95% Confidence Interval
No stabilizer	718	0-3 months	NA	6.67	0.002	1.98 - 22.4
		3-6 months		9.67	<0.001	2.94 - 31.7
Stabilizer	1103	0-3 months	NA	0.56	0.010	0.36 - 0.87
		3-6 months		0.91	0.758	0.50 - 1.67
Time span factor removed						
No stabilizer	718	0-6 months	NA	8.17	<0.001	3.50 - 19.1
Stabilizer	1103	0-6 months	NA	0.66	0.021	0.46 - 0.94
Three-way interaction with antidepressant treatment instead of time span						
No stabilizer	718	0-6 months	No	12.6	0.001	2.95 - 53.6
			Yes	6.39	0.003	1.89 - 21.7
Stabilizer	1103	0-6 months	No	0.65	0.117	0.37 - 1.12
			Yes	0.67	0.132	0.40 - 1.13

Appendix 5. Risk of mania following methylphenidate medication based on mania diagnoses and new prescriptions of stabilizers in a lamotrigine-only subgroup

In the mood-stabilizer cohort, there were 323 patients with lamotrigine as the only stabilizer. These were not included in either group (stabilized or non-stabilized) but analyzed separately below (Table ST 7 and ST 8).

ST 7. Risk of mania following methylphenidate medication based on mania diagnoses and new prescriptions of stabilizers in a lamotrigine-only subgroup*

Group	Number	Period	Hazard Ratio	P-value	95% Confidence Interval	Number of mania events (rate***)
Lamotrigine**	323	0-3 months	0.75	0.706	0.17 - 3.35	14 (0.04)
		3-6 months	1.00	1.000	0.14 - 7.10	

* If no dispensation of an antipsychotic (aripiprazole, olanzapine, quetiapine, haloperidol, and risperidone) was observed in the nine months prior methylphenidate medication (period A in Figure 1), a dispensation after the methylphenidate medication (period C in Figure 1) was considered an indication of elevated mood. This definition was applied to both groups, and doses of aripiprazole, olanzapine, and quetiapine below 5mg, 5mg, and 100mg respectively were not considered.

** Must have at least two dispensations of lamotrigine within the 9 months prior methylphenidate dispensation (period A in Figure 1). At least one dispensation of lamotrigine has to be within 6 months prior methylphenidate treatment (period B in figure 1). Cannot have other stabilizing drugs.

*** Rate denotes number of identified mania events divided by total number of subjects in the group.

ST 8. Risk of mania following methylphenidate medication based on mania diagnoses only in a lamotrigine-only subgroup

Group	Number	Period	Hazard Ratio	P-value	95% Confidence Interval	Number of mania events (rate**)
Lamotrigine*	323	0-3 months	0.25	0.215	0.03 - 2.24	10 (0.03)
		3-6 months	0.50	0.571	0.05 - 5.51	

* Must have at least two dispensations of lamotrigine within the 9 months prior methylphenidate dispensation (period A in Figure 1). At least one dispensation of lamotrigine has to be within 6 months prior methylphenidate treatment (period B in figure 1). Cannot have other stabilizing drugs.

** Rate denotes number of identified mania events divided by total number of subjects in the group.