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# Prescription Stimulant Use and Hospitalization for Psychosis or Mania

## A Population-Based Study

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**Abstract:** Small studies suggest that prescription stimulants can precipitate psychosis and mania. We conducted a population-based case-crossover study to examine whether hospitalization for psychosis or mania was associated with initiation of stimulant therapy. Between October 1, 1999 and March 31, 2013, we studied 12,856 young people who received a stimulant prescription and were subsequently hospitalized for psychosis or mania. Of these, 183 commenced treatment during 1 of 2 prespecified 60-day intervals (defined as the “risk interval” and “control interval,” respectively) prior to admission. We found that stimulant initiation was associated with an increased risk of hospitalization for psychosis or mania in the subsequent 60 days (odds ratio, 1.86; 95% confidence interval, 1.39–2.56). The risk was marginally higher in patients treated with antipsychotic drugs (odds ratio, 2.06; 95% confidence interval, 1.38–3.28), but remained in patients with no such history (odds ratio, 1.66; 95% confidence interval, 1.09–2.66). One third of subjects received another stimulant prescription after hospital discharge. Of these, 45% were readmitted with psychosis or mania shortly thereafter. We conclude that initiation of prescription stimulants is associated with an increased risk of hospitalization for psychosis or mania. Resumption of therapy is common, which may reflect a lack of awareness of the potential causative role of these drugs.

**Key Words:** attention deficit hyperactivity disorder, drug safety, stimulants, psychosis, mania

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The prescribing of stimulants for the symptoms of attention deficit hyperactivity disorder has increased dramatically over the past 2 decades in many parts of the world, including North America and Europe.<sup>1–4</sup> Recent estimates suggest that approximately 1 of every

9 young people has been assigned the diagnosis,<sup>3</sup> and more than 48 million prescriptions for stimulant medications were dispensed in the United States in 2011.<sup>4</sup> Stimulants potentiate the release of norepinephrine and dopamine, inhibit their neuronal reuptake, and are thought to provide short-term benefit for the core symptoms of attention deficit hyperactivity disorder, including hyperactivity, inattention, and impulsivity.<sup>5</sup> Despite their widespread use, data regarding their long-term effectiveness and safety are limited, and their effects on academic and social function are unclear.<sup>6–8</sup>

As might be expected from their pharmacology, small trials and case reports suggest an association between these drugs and new-onset mental illness, including psychosis and mania in particular.<sup>9–15</sup> As expected clinically, these episodes tend to occur early in the course of therapy.<sup>9,15</sup> After a review of available post-marketing surveillance data, the Food and Drug Administration issued alerts mandating safety updates to prescribing information.<sup>9,15</sup> However, no large-scale studies have explored whether prescription stimulants are associated with the development of psychosis or mania in clinical practice. Accordingly, we sought to characterize the risk of psychosis or mania after initiation of stimulant therapy in a large population of children and young adults.

## MATERIALS AND METHODS

### Ethics

This project was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. The Institute for Clinical Evaluative Sciences (ICES) is named as a prescribed entity under section 45 of the Personal Health Information Protection Act (Ontario Regulation 329/04, Section 18). Under this designation, ICES can receive and use health information without consent for the purposes of analysis and compiling statistical information about the health care system of Ontario.

### Setting and Design

We conducted a population-based case-crossover study<sup>16</sup> among Ontario social assistance recipients aged 25 years or younger between October 1, 1999 and March 31, 2013. These patients had universal access to hospital care, physicians' services, and prescription drugs. The case-crossover design is an exclusively within-patient analysis. When an exposure (such as a drug) is a risk factor for an adverse event, exposures will be more common immediately before the event (the risk interval) than during an earlier period (the control interval). The case-crossover design is increasingly used in observational studies,<sup>17,18</sup> including studies of drug safety.<sup>19–21</sup> Unlike case-control and cohort study designs, the within-patient analysis controls implicitly for fixed patient characteristics, including those that are unmeasurable.

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## Data Sources

We identified prescription records using the Ontario Drug Benefit Database, which contains comprehensive records of prescription drugs dispensed to Ontarians aged 65 years and older, as well as younger patients who receive social assistance. This database is of high validity<sup>22</sup> and has been used extensively to examine questions related to drug safety.<sup>23–28</sup> We obtained hospitalization data from the Canadian Institute for Health Information, Discharge Abstract Database and the Ontario Mental Health Reporting System, which contain detailed clinical information regarding all hospital admissions. Emergency department visits were obtained from the National Ambulatory Care Reporting System. Basic demographic information was obtained from the Registered Persons Database, a registry of all residents eligible to receive insured health services in the province, and the Ontario Health Insurance Plan was used to identify physician service claims. These databases were linked in an anonymous fashion using unique encrypted Ontario health card numbers and are routinely used to study drug safety.<sup>23–28</sup>

## Study Population

We studied young patients who were hospitalized for psychosis or mania between October 1, 1999 and March 31, 2013 using the *International Classification of Diseases, 9th and 10th Revision* codes (see Supplementary Table S1, Supplemental Digital Content 1, <http://links.lww.com/JCP/A326>). Only the first such hospitalization was considered for patients with multiple episodes. The date of hospitalization served as the index date for all analyses. For each case, we identified a number of comorbid conditions and preexisting medications that might influence risk of psychosis or mania (see Supplementary Table S2, Supplemental Digital Content 2, <http://links.lww.com/JCP/A327>).

## Assessment of Drug Exposure

Because we anticipated that individual susceptibility to the psychotomimetic effects of stimulants would cause psychosis or mania to manifest early in the course of treatment, we limited our analysis to subjects whose first prescription for a stimulant occurred in the 180 days preceding hospitalization for psychosis or mania. The analysis was informed exclusively by patients whose first prescription occurred in either the 60 days immediately preceding admission (risk interval) or a corresponding period spanning 121 to 180 days preceding admission (control interval) (see Fig. 1). We incorporated a 60-day washout interval between the risk and control intervals to avoid contamination between the two, excluding subjects whose first stimulant prescription was dispensed in this period. We selected a 60-day risk interval because most reported psychosis or manic episodes occur shortly after therapy is begun. This is also clinically intuitive because

susceptible individuals are generally more likely to experience an adverse drug reaction at the outset of therapy.<sup>9,15</sup>

## Statistical Analysis

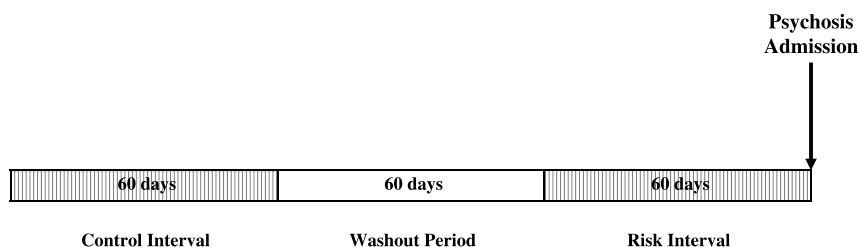
The analysis examines whether initiation of a prescription stimulant just before admission (the risk interval) is more likely than initiation during an earlier period (the control interval). Under the case-crossover design, the odds ratio is given by the quotient of the number of individuals newly exposed during the risk interval divided by the control interval (Fig. 1). We calculated Wald 95% confidence intervals for binomial proportions. Because stimulants may be particularly likely to precipitate psychosis or mania in patients with preexisting psychotic conditions, we conducted a secondary analysis stratified according to whether or not patients had received a prescription for an antipsychotic drug. Because the case-crossover design yields an estimate of relative risk rather than absolute risk, we performed a supplementary analysis to estimate the absolute risk of psychosis or mania in the first 60 days of therapy. To do this, we identified all individuals hospitalized for psychosis or mania within 60 days of their first stimulant prescription and divided this by the total number of young people who commenced stimulant therapy during the study period. All analyses used a 2-sided type I error rate of 0.05 as the threshold for statistical significance and were performed using SAS version 9.3 (SAS Institute, Cary, NC).

## RESULTS

Over the 14-year study period, we identified 12,856 young people who received a stimulant prescription and were subsequently hospitalized for psychosis or mania. Of these, we identified 183 patients who informed our analysis by virtue of commencing treatment either in the risk period or the control period (Table 1). The median age was 21 years, 60% were male, and methylphenidate was the most commonly prescribed stimulant. Preexisting comorbidities and psychiatric medication use were common antecedents of stimulant therapy.

Among cases, 119 (65.0%) received a new prescription for a stimulant during the risk interval compared with 64 (35.0%) during the control interval, corresponding to a 86% increase in the risk of hospitalization for psychosis or mania in the first 60 days of therapy (odds ratio, 1.86; 95% confidence interval, 1.39–2.56). In a stratified analysis, the risk was marginally higher among patients with a history of antipsychotic drug treatment (odds ratio, 2.06; 95% confidence interval, 1.38–3.28) and marginally lower but persistent in patients with no such treatment (odds ratio, 1.66; 95% confidence interval, 1.09–2.66) (Table 2).

We speculated that the potential causative role of stimulants in cases of psychosis or mania might not be appreciated and that these medications might therefore be resumed after discharge. Of 183 cases discharged from hospital, 62 (34%) received another



**FIGURE 1.** Study design. All cases were hospitalized with psychosis or mania on the index date and commenced treatment with a stimulant in either the risk interval or control interval. Each study subject served as his or her own control. The case-crossover odds ratio is given by the quotient of the number of patients exposed in the risk and control intervals.

stimulant prescription within 100 days of discharge. Of these, 28 (45%) were readmitted for psychosis or mania at a median of 18 days after the subsequent stimulant prescription, consistent with a potential contributing role of the drug.

We conducted a supplementary analysis to approximate the absolute risk of psychosis after stimulant initiation. Among 65,835 young patients who began treatment with a stimulant during our study period, 177 were hospitalized for psychosis within 60 days of initiating treatment. This corresponds to an estimated

**TABLE 1.** Characteristics of Cases

Variable	Cases (n = 183)
Baseline characteristics	
Age at index date, median (IQR)	21 (18–24)
Male, n (%)	110 (60.1)
Income quintile, n (%)	
1 (lowest)	61 (33.3)
2	41 (22.4)
3	30 (16.4)
4	30 (16.4)
5 (Highest)	20 (10.9)
Missing	≤5
Rural residence, n (%)	16 (8.7)
Healthcare utilization, in preceding year, median (IQR)	
Hospital admissions	0 (0–1)
Days in hospital	0 (0–2)
Emergency department visits	2 (1–5)
Primary care visits	4 (2–10)
Specialist physician visits	5 (1–13)
ADHD treatment factors in prior 180 days, n (%)*	
Amphetamine	55 (30.1)
Atomoxetine	≤5
Methylphenidate	137 (74.9)
Comorbidities, n (%)	
Johns Hopkins ACG	
0–4	≤5
5–9	26 (14.2)
10–14	88 (48.1)
15–19	51 (27.9)
20+	14 (7.7)
Affective disorders	87 (47.5)
Anxiety and sleep disorders	34 (18.6)
Other mental health disorders	65 (35.5)
Diabetes mellitus	≤5
Miscellaneous illness associated with psychosis	≤5
Drugs in preceding year, n (%)	
No. drugs, median (IQR)	4 (2–9)
Corticosteroids, n (%)	22 (12.0)
Insulin	≤5
Oseltamivir	≤5
Anticonvulsants	11 (6.0)
Antidepressants	79 (43.2)
Antipsychotics	98 (53.6)
Benzodiazepines	56 (30.6)
Opioids	25 (13.7)

\*Some patients had more than 1 stimulant in their exposure interval. ACG indicates Aggregated Clinical Groups; IQR, interquartile range.

**TABLE 2.** Risk of Psychosis or Mania and Recent Stimulant Use

	Exposure in Risk Interval	Exposure in Control Interval	Odds Ratio (95% Confidence Interval)
Primary analysis			
Cases (n = 183)	119	64	1.86 (1.39–2.56)
Secondary analysis			
No antipsychotic drug history (n = 85)	53	32	1.66 (1.09–2.66)
Antipsychotic drug history (n = 98)	66	32	2.06 (1.38–3.28)

absolute risk of approximately 0.3%, or approximately one such admission for every 372 young people started on a stimulant.

## DISCUSSION

We found that initiation of stimulants in young people was associated with an increased risk of hospitalization for psychosis or mania. This accords with the pharmacology of these drugs and is particularly important because stimulants are prescribed to millions of youth worldwide, including approximately 3.5 million children in the United States annually.<sup>3</sup> While the causal role of stimulants in each instance cannot be known, many patients resumed therapy after hospital discharge, and more than 40% of these were readmitted with recurrent psychosis or mania. These findings suggest a lack of awareness of the potential causative role of these drugs.

Our findings correspond with data from small clinical trials and case reports, which suggest an association between stimulants and the development of psychosis and mania.<sup>9–15</sup> These episodes tend to occur early in the course of therapy, resolve with drug discontinuation, and can recur upon rechallenge, all suggestive of a causal role of these drugs. Although our study cannot prove causality, several elements of the Bradford-Hill criteria are satisfied, including temporality, strength of association, biological plausibility, analogy, and consistency.<sup>29</sup>

Psychiatric comorbidities and medications were common in our study population, consistent with previous findings in patients with attention deficit hyperactivity disorder.<sup>30–34</sup> It is possible that patients with greater psychiatric comorbidity are more susceptible to stimulant-mediated psychosis or mania due to underlying neurotransmitter dysregulation. Furthermore, stimulants can intensify symptoms of psychosis or mania in patients with schizophrenia by virtue of their effects on catecholaminergic neurotransmission.<sup>35,36</sup> Accordingly, drug monographs indicate that stimulants are contraindicated in patients with a history of psychotic disorders and that care should be taken when prescribing to patients with a previous history of a primary psychiatric disorder. Despite these recommendations, half of all cases in our study had a history of treatment with an antipsychotic medication, suggesting the presence of an underlying psychotic disorder. In addition, many patients displayed a history of other mental health conditions. These findings suggest a lack of awareness of relative contraindications to stimulant therapy.

It is possible that a subset of patients with attention deficit hyperactivity disorder but without a history of other psychiatric or mental health conditions may also be susceptible to stimulant-induced psychosis or mania. Previous studies suggest a link between childhood attention deficit hyperactivity disorder and the development of psychotic disorders in adulthood.<sup>37–40</sup> In many

cases of stimulant-induced psychosis or mania reported to the United States Food and Drug Administration, no preexisting psychiatric comorbidities or substance abuse history were identified.<sup>9,15</sup>

Our study has several notable strengths. We studied a large population of subjects and employed a self-matched design, in which each patient served as his or her own control. This approach controls implicitly for measured and unmeasured fixed patient characteristics, enhances statistical power, and eliminates several shortcomings of more conventional observational designs.<sup>16</sup> Finally, our findings are biologically plausible, and the argument for causation is strengthened by the observation of recurrent psychosis or mania upon rechallenge after hospital discharge in a large proportion of subjects.

Some limitations of our study warrant emphasis. Importantly, our conclusions derive from patients receiving social assistance, and whether the findings are generalizable to all patients is unclear. Further research should test this association in other populations. Drug-induced psychosis or mania occurring after more than 6 months of treatment would not be identified using our study design,<sup>9–15</sup> which therefore may underestimate the true risk during treatment. Although we had limited information regarding other risk factors for psychosis or mania, the self-matched nature of our design controls implicitly for fixed patient characteristics,<sup>16</sup> including social and hereditary factors that may influence risk. Misuse of prescription stimulants is common,<sup>2,41</sup> and we cannot be certain that patients took their stimulants as directed. Finally, although the validity of diagnostic codes for acute psychosis or mania is unknown, previous epidemiologic studies have used many of these codes to examine these outcomes in children and adolescents.<sup>42–44</sup>

In conclusion, we found that initiation of stimulants is associated with hospitalization for psychosis or mania in young people. Moreover, drug therapy was often resumed after hospital discharge, suggesting a lack of awareness of the potential causal role of these drugs. Our findings should encourage clinicians to carefully consider the use of stimulants, particularly in patients with overt psychosis or those in whom a preexisting psychiatric illness might predispose to harm.

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#### AUTHOR DISCLOSURE INFORMATION

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No endorsement by ICES or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred. A.H. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

During the past 3 years, M.M.M. has been on advisory boards and/or received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffman-La Roche, Novartis, Novo Nordisk, and Pfizer. The rest of the authors have no conflicts of interest.

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