

Stimulant Medication and Psychotic Symptoms in Offspring of Parents With Mental Illness

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abstract

BACKGROUND: Stimulants, such as methylphenidate, are among the most commonly used medications in children and adolescents. Psychotic symptoms have been reported as rare adverse reactions to stimulants but have not been systematically inquired about in most previous studies. Family history of mental illness may increase the vulnerability to drug-induced psychotic symptoms. We examined the association between stimulant use and psychotic symptoms in sons and daughters of parents with major mood and psychotic disorders.

METHODS: We assessed psychotic symptoms, psychotic-like experiences, and basic symptoms in 141 children and youth (mean \pm SD age: 11.8 \pm 4.0 years; range: 6–21 years), who had 1 or both parents with major depressive disorder, bipolar disorder, or schizophrenia, and of whom 24 (17.0%) had taken stimulant medication.

RESULTS: Psychotic symptoms were present in 62.5% of youth who had taken stimulants compared with 27.4% of participants who had never taken stimulants. The association between stimulant use and psychotic experiences remained significant after adjustment for potential confounders (odds ratio: 4.41; 95% confidence interval: 1.82–10.69; $P = .001$) and was driven by hallucinations occurring during the use of stimulant medication. A temporal relationship between use of stimulants and psychotic symptoms was supported by an association between current stimulant use and current psychotic symptoms and co-occurrence in cases that were assessed on and off stimulants.

CONCLUSIONS: Psychotic symptoms should be monitored during the use of stimulants in children and adolescents. Family history of mood and psychotic disorders may need to be taken into account when considering the prescription of stimulants.



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Ms MacKenzie conceived the study, contributed to the design of the study and the assessment schedule, carried out participant assessments, contributed to statistical analyses, interpreted results, and drafted the manuscript; Dr Abidi conceived the study, contributed to participant assessments, interpreted results, and reviewed and revised the manuscript; Dr Fisher contributed to the study design, trained the team in assessing psychotic symptoms, curated psychotic-like experiences ratings, contributed to the interpretation of results, and reviewed and revised the manuscript; Drs Propper, Bagnell contributed to study design and participant assessments, interpreted results, and reviewed and revised the manuscript; Ms Morash-Conway and Ms Glover contributed to the study design and assessment schedule, carried out participant

WHAT'S KNOWN ON THIS SUBJECT: Stimulants, commonly used in children to treat attention-deficit/hyperactivity disorder, are known to cause psychotic symptoms, but these are considered to be rare adverse effects.

WHAT THIS STUDY ADDS: This study finds that in children at familial risk of mental illness, stimulant medication is associated with high risk of hallucinations. Children with a family history of mental illness should be monitored for psychotic symptoms during treatment with stimulants.

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood mental disorders, affecting 5% to 10% of school-aged children.¹ Stimulant medications such as methylphenidate and dexamphetamine effectively decrease the core symptoms of hyperactivity, inattention, and impulsivity²⁻⁴ and are the first-line treatments for ADHD.⁵ The prescription of stimulant medication in children is common and increasing.⁶⁻⁸ When making decisions about whether to prescribe stimulant medication, family practitioners, pediatricians, and psychiatrists weigh the risk of adverse effects against the benefits of such pharmacotherapy.

The common adverse effects of stimulants are appetite reduction, sleep problems, and growth suppression. As dopamine agonists, stimulants also have the potential to induce psychotic symptoms, including hallucinations, delusions, and disorganized behavior in children and adults.⁹⁻¹¹ On the basis of data from regulatory randomized controlled trials, psychotic symptoms have been estimated to be a rare adverse reaction, affecting 0.25% to 1.5% of children treated with stimulants.^{8,12} But these may be underestimates, because regulatory trials preferentially enroll participants with few psychiatric comorbidities and a high probability of success. In addition, psychotic symptoms are usually not systematically assessed in these trials. Two recent reports suggest that the risk of psychotic symptoms may be higher in clinical settings: a chart review found psychotic symptoms in 9 of 98 (9%) youth newly treated with stimulant medication¹³ and a group of community child and adolescent psychiatrists reported 4 cases (20%) of psychotic symptoms among 20 consecutive prescriptions of stimulants.¹⁴ These reports suggest the need to further examine

psychotic adverse reactions to stimulants and their moderators.

One factor that may influence the risk of psychotic symptoms during treatment with stimulants is familial disposition to mental illness. Data from adults indicate that genetic liability to stimulant-induced psychosis overlaps with genetic liability for schizophrenia¹⁵ and that stimulants may cause schizophrenia in individuals at familial risk.¹⁶ These findings suggest that the risk of psychotic adverse effects of stimulants may be higher in youth with a family history of mental illness. This contingency could be clinically important because ADHD is more common among offspring of parents with severe mental illness¹⁷ and because psychotic symptoms induced by stimulants may signal long-lasting vulnerability to psychosis.^{16,18} To our knowledge, psychotic adverse effects of stimulant medication have not been studied in youth at familial risk for mental illness. Therefore, we systematically examined the association between stimulant use and psychotic symptoms in a sample of youth at familial risk of severe mental illness.

METHODS

Participants

We investigated the relationship between stimulant medication use and psychotic symptoms among 141 participants of Families Overcoming Risks and Building Opportunities for Wellbeing, a study of developmental psychopathology in offspring of parents with severe mental illness (major depressive disorder, bipolar disorder, schizophrenia).¹⁹ Parents were identified through inpatient and outpatient psychiatric services in Nova Scotia, Canada, that systematically inquired whether patients with psychotic and major mood disorders (schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder)

had children below the age of 21 years. The youth participants were ascertained through parents, and recruited irrespective of whether any psychopathology was present in the offspring. An inclusion criterion for the current study was age 6 to 21 years, because assessment of psychotic symptoms may be unreliable in children younger than 6 years. Exclusion criteria were brain injury or severe intellectual disability of a degree that would preclude assessments. There were no exclusion criteria based on offspring psychopathology.

The study protocol was approved by the Research Ethics Board of the Nova Scotia Health Authority. Participants with capacity provided written informed consent. For children who did not have capacity to make a fully informed decision, a substitute decision-maker (parent or guardian) provided a written informed consent and the child provided assent.

Parent Assessment

We established parent Diagnostic and Statistical Manual of Mental Disorders (DSM), Fourth Edition, and DSM, Fifth Edition, diagnoses with the Schedule for Affective Disorders and Schizophrenia²⁰ followed by clinical consensus with a psychiatrist blind to child psychopathology and with the *Structured Clinical Interview for DSM Disorders*.²¹

Offspring Assessments

Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version

We interviewed all youth and parents with the *Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version* (K-SADS),^{18,22} and established the diagnoses of ADHD and other disorders on the basis of DSM Fourth Edition criteria and all available information in a consensus meeting with a child- and adolescent psychiatrist blind

to information on parents. We used the K-SADS interview psychosis module and appendix to assess psychotic symptoms, which were also consensus rated by the child-and-adolescent psychiatrist blind to parent psychopathology. We considered only psychotic symptoms confirmed as “definite.”

The use of stimulant medication (methylphenidate, amphetamine, dextroamphetamine, lisdexamfetamine) was assessed by parent and child report as part of the K-SADS interview and checked against pharmacy records. The use of stimulant was dated and doses were recorded.

Structured Interview for Prodromal Syndromes

In participants aged ≥ 11 years, we also assessed psychotic symptoms with the *Structured Interview for Prodromal Syndrome* (SIPS),²³ which allows the derivation of attenuated psychotic symptoms and definition of at-risk mental state for psychosis.²³ We only considered SIPS ratings that met the threshold for at-risk mental state.

Funny Feelings

We assessed self-reported psychotic-like experiences (PLEs) with the “Funny Feelings”^{24–26} interview in which the psychotic character of initial self-reported answers to 7 questions is corroborated with probes and independent clinical curation.^{24–26} We recorded frequency, distress, impairment, and appraisal (internal/external, significant/not significant) for each symptom. We submitted the verbatim transcripts for independent clinical curation to establish a psychotic character of experience, rated as none, probable, or definite. Two independent curators reached high agreement in rating the psychotic character of PLEs ($\kappa = 0.85$; 95% CI: 0.79–0.88), and the few disagreements were resolved in consensus meetings. We

only considered PLEs curated as “definite” by consensus between the 2 independent raters.

Schizophrenia Proneness Instrument–Child and Youth Version

We interviewed participants aged 8 to 21 years with the *Schizophrenia Proneness Instrument–Child and Youth Version* (SPI-CY)^{27,28} to assess basic symptoms (BSs).^{27,28} BSs describe subjective deficits and abnormalities in multiple domains (perception, cognition, language, feelings) and often represent early manifestations of psychosis. BSs strongly and specifically predict the development of schizophrenia.^{29,30} In analyses, we only considered BSs fulfilling criteria for the high-risk profiles of cognitive disturbances or cognitive-perceptive BSs that predict psychosis with high specificity.³⁰

Data Analysis

The primary dependent variables were any psychotic symptoms defined as lifetime occurrence of ≥ 1 of the following: (1) definite clinically significant hallucinations or delusions on K-SADS; (2) positive symptoms on SIPS rated ≥ 3 , ie, reaching threshold for at-risk mental state; (3) self-reported PLEs confirmed as definite psychotic symptoms through independent curation; and (4) high-risk BS profiles of cognitive disturbances or cognitive-perceptive BSs on SPI-CY. We tested the relationship between lifetime use of stimulants and lifetime psychotic symptoms with logistic regression. We used SEs robust to clustering of individuals within families. In fully adjusted models, we included potential confounders that had a significant ($P < .05$) relationship with outcome in univariate analyses or were deemed significant on the basis of previous literature and substantive considerations (age, gender, family history). We also explored the role of the ADHD in addition to the above covariates. Effect sizes were

quantified as odds ratios (ORs) with 95% confidence intervals (CIs). Associations with P values $< .05$ were considered significant. Analyses were carried out in Stata 12.1 (Stata Corp LP, College Station, TX).³¹

RESULTS

Stimulant Medication and ADHD

Of the 141 eligible participants aged 6 to 21 years, 24 (17.0%) had taken stimulant medication (20 methylphenidate, 3 lisdexamfetamine, 1 dextroamphetamine). A diagnosis of ADHD was confirmed in 33 (23.4%) participants, of whom 17 received stimulants and 16 were unmedicated. Neither the diagnosis of ADHD nor the use of stimulants was associated with participant age, gender, or parent diagnosis (all $P > .05$). Table 1 provides details of the 141 eligible participants.

Psychotic and Related Symptoms

Forty-seven (33.3%) participants had confirmed psychotic and related symptoms (12 had definite psychotic symptoms on K-SADS, 3 fulfilled the at-risk mental state criteria on SIPS, 21 reported definite PLEs on Funny Feelings, and 25 had high-risk BS profiles on SPI-CY). Psychotic and related symptoms were associated with older age (OR: 1.14; 95% CI: 1.04–1.24 per year; $P = .004$), were present in 3 (37.5%) of 8 offspring of parents with schizophrenia, in 21 (34%) of 62 offspring of parents with bipolar disorder, and in 23 (32%) of 71 offspring of parents with major depressive disorder and showed no significant association between the type of family history and psychotic symptoms ($\chi^2 = 0.099$, degrees of freedom = 2, $P = .95$).

Association Between Stimulant Use and Psychotic Symptoms

Psychotic and related symptoms were found in 15 (62.5%) of the 24 participants who had taken

TABLE 1 Participant Characteristics

	Exposed to Stimulant Medication (<i>n</i> = 24)	Not Exposed to Stimulant Medication (<i>n</i> = 117)
Age, mean (SD), y	11.8 (4.0)	12.0 (3.4)
Male gender, <i>n</i> (%)	12 (50)	55 (47.0)
Parent diagnosis, <i>n</i> (%)		
Depression	13 (54.2)	58 (49.5)
Bipolar disorder	10 (41.7)	52 (44.4)
Schizophrenia	1 (4.2)	7 (6.0)
Child diagnosis, <i>n</i> (%)		
ADHD	17 (70.8)	16 (13.6)
ASD	3 (12.5)	3 (2.56)
Anxiety disorders	8 (33.3)	30 (25.6)
MDD	3 (12.5)	13 (11.1)
Psychotic symptoms, <i>n</i> (%)		
Hallucinations (K-SADS/SIPS)	9 (37.5)	9 (7.7)
Delusions (K-SADS/ SIPS)	3 (12.5)	5 (4.3)
PLEs (FF)	4 (16.6)	17 (14.5)
BSs (SPI-CY)	6 (25.0)	19 (16.2)
Any psychotic symptom	15 (62.5)	32 (27.4)

ASD, autism spectrum disorder; MDD, major depressive disorder; FF, Funny Feelings.

stimulants compared with 32 (27.4%) of the 117 participants who had not taken stimulants. All 15 participants who had used stimulants and had experienced psychotic symptoms were sons or daughters of a parent with a major depressive disorder or bipolar disorder (Table 2). The association between stimulant medication use and psychotic symptoms was significant in univariate analysis (OR: 4.43; 95% CI: 1.76–11.12; $P = .002$) and remained unchanged after controlling for age, gender, and parent diagnosis in a model robust to clustering of participants within families (OR: 4.41; 95% CI: 1.82–10.69; $P = .001$).

Relative Roles of Stimulant Medication and ADHD

Because stimulant medication is typically used for the treatment of ADHD, it is possible that the association between stimulant use and psychotic symptoms may reflect an association between ADHD and psychotic symptoms rather than an effect of stimulant medication per se. Therefore, we explored the relative roles of stimulant medication and

ADHD. In univariate analysis, the diagnosis of ADHD was positively but nonsignificantly related to psychotic symptoms (OR: 1.98; 95% CI: 0.89–4.40; $P = .094$). Within the group of individuals with a confirmed diagnosis of ADHD, 11 (65%) of the 17 stimulant-treated individuals experienced psychotic symptoms compared with only 4 (25%) of the 16 who had not been treated with stimulants. When both stimulant use and ADHD were entered as predictors into a fully adjusted model, the effect of stimulant use on psychotic symptoms remained significant (OR: 4.51; 95% CI: 1.48–13.72; $P = .008$) and the effect of ADHD was small and nonsignificant (OR: 1.16; 95% CI: 0.41–3.28; $P = .781$), suggesting that the use of stimulant medication rather than the ADHD diagnosis increases the risk of psychotic symptoms.

Types of Psychotic Symptoms and Stimulant Use

We further explored which types of psychotic symptoms were associated with the use of stimulants (Table 3). Stimulant use was strongly associated with definite psychotic

symptoms on the K-SADS and SIPS interviews, less strongly associated with BSs, and the least strongly associated with the self-reported PLEs. Table 2 lists the psychotic symptoms observed in the individuals taking stimulant medication.

Temporal Relationship Between Stimulant Medication and Psychotic Symptoms

To establish if psychotic symptoms coincided with the use of stimulant medication, we carried out a sensitivity analysis, testing the association of current use of stimulants (defined as continuous use of stimulants over the past 12 months) with current psychotic symptoms (definite psychotic symptoms during the past 12 months; note that the rate of current psychotic symptoms is likely an underestimate, because we could not include symptoms that were reported but not dated and accurate dating was only available for the K-SADS and SIPS instruments; see Supplemental Table 4 for details). Of the 15 individuals with current stimulant use, 4 (27%) experienced current definite psychotic symptoms. Of the 126 individuals without current use of stimulants, 6 (5%) experienced current definite psychotic symptoms. Although the numbers of current stimulant users were small, the association between current use of stimulant medication and current psychotic symptoms was strong and significant (OR: 7.25; 95% CI: 1.76–29.92; $P = .006$). In addition, there were 3 participants for whom we were able to establish presence and absence of psychotic symptoms when they were on and off stimulant medication; in all 3 cases, the occurrence of psychotic symptoms coincided with the use of stimulants (see Supplemental Information for vignettes).

TABLE 2 Psychotic Symptoms in Participants Who Were Taking Stimulant Medication

Gender	Participant			Stimulant Medication				Psychotic Symptoms			
	Age at Assessment, y	Parent Diagnosis	Child Diagnoses	Compound (Preparation)	Age Stimulant Started, y	Dose, mg	Stimulant Use Current? ^{2a}	Concurrent Medication or Drug of Abuse	Symptom Type (Instrument)	Current	Notes
Female	7	Bipolar	ADHD combined	Methylphenidate (Ritalin)	6	20	No	Trazodone	Tactile and visual hallucinations (K-SADS)	No	—
Male	11	Bipolar	ADHD combined, Tourette's disorder, social anxiety disorder	Methylphenidate (Biphentin)	7	20	Yes	none	Persecutory delusion of being followed and spied on and that someone wants to kidnap him (K-SADS, SIPS, FF)	Yes	Fulfills criteria for at-risk mental state for psychosis (SIPS)
Female	11	Depression	ADHD combined, PDD	Lisdexamfetamine (Vyvanse)	9	40	Yes	Lorazepam	Auditory and visual hallucinations of voices and people (K-SADS, SIPS, FF)	Yes	—
Male	11	Depression	Fragile X, epilepsy, ADHD combined, Tourette's disorder	Methylphenidate (Ritalin SR)	10	40	Yes	Melatonin	Complex visual and auditory hallucinations, bizarre behavior (K-SADS); BSs: perceptual and cognitive disturbance (SPI-CY)	Yes	—
Male	11	Depression	ADHD combined, OCD	Methylphenidate (Concerta)	8	25	Yes	none	Visual hallucinations (K-SADS), derealization (SPI-CY)	Yes	Stimulant also caused vocal and motor tics
Female	12	Bipolar	ODD, ADHD combined	Methylphenidate (Concerta)	11	27	Yes	none	BSs: captivation of attention by details in visual field (meets COGDIS criteria)	Yes	—
Female	12	Bipolar	ADHD combined	Lisdexamfetamine (Vyvanse)	5	40	Yes	Melatonin	Auditory and visual hallucinations, including command hallucinations, persecutory delusions, bizarre behavior (K-SADS, SIPS, SPI-CY, FF)	Yes	—
Male	12	Bipolar	ADHD combined	Lisdexamfetamine (Vyvanse)	6	20	Yes	none	Visual hallucinations (ghosts), delusions (believes he possesses special powers) (FF, K-SADS)	Yes	—
Female	13	Depression	ODD	Methylphenidate (Biphentin)	6	60	Yes	Trazodone	PLEs: hears a voice, has seen a ghost (FF); BSs: acoustic echo, cognitive-perceptual disturbance (CPI-CY)	Yes	—

TABLE 2 Continued

Gender	Participant			Stimulant Medication				Psychotic Symptoms			
	Age at Assessment, y	Parent Diagnosis	Child Diagnoses	Compound (Preparation)	Age Stimulant Started, y	Dose, mg	Stimulant Use Current? ^a	Concurrent Medication or Drug of Abuse	Symptom Type (Instrument)	Current	Notes
Female	13	Bipolar	PDD, ADHD combined	Lisdexamfetamine (Vyvanse)	5	40	Yes	Melatonin	Auditory and visual hallucinations, including command hallucinations, persecutory delusions, bizarre behavior (K-SADS, SPI-CY, FF)	Yes	—
Female	14	Depression	ADHD combined, MDD	Methylphenidate (Biphentin)	6	60	Yes	none	BSS: acoustic echo, cognitive-perceptual disturbance (SPI-CY); PLEs: hears a voice, has seen a ghost (FF)	Yes	—
Female	16	Depression	ADHD combined, conduct disorder	Lisdexamfetamine (Vyvanse)	7	10	Yes	Cannabis, tobacco, alcohol	PLEs: hears a voice, sees a figure, feels strangers are talking about her (FF, K-SADS, SIPS)	Yes	Attempted suicide
Male	16	Bipolar	MDD	Lisdexamfetamine (Vyvanse)	13	unknown	Yes	none	PLEs: saw a ghost, floor was moving (FF, SPI-CY)	No	Attempted suicide
Male	17	Depression	None	Methylphenidate (Concerta)	7	25	No	none	Complex visual hallucinations (K-SADS) at age 7 when taking Concerta	No	Coincided with Concerta use
Male	17	Bipolar	Anxiety disorder NOS, alcohol abuse	Methylphenidate (Ritalin)	10	unknown	No	Fluoxetine, alcohol	BSS: cognitive-perceptual disturbance (SPI-CY)	Yes	Symptoms occur when sober

ASD, autism spectrum disorder; COGDIS, cognitive disturbances; MDD, major depressive disorder; K-SADS, *Kiddie Schedules for Affective Disorders and Schizophrenia*; SIPS, *Structured Interview for Prodromal Symptoms*; SPI-CY, *Schizophrenia Proneness Instrument—Child and Youth*; FF, *Funny Feelings*; OCD, obsessive-compulsive disorder; PDD, pervasive developmental disorder; NOS, not otherwise specified; Adderall (Shire Pharmaceuticals, Wayne, PA); Concerta (Janssen, Piscataway, NJ); Ritalin (Novartis, Basel Switzerland); Vyvanse (Shire Pharmaceuticals, Wayne, PA).

^a Current use was defined as continuous use of one or more stimulant medications for 12 mo period preceding the assessment.

TABLE 3 Associations Between Lifetime Exposure to Stimulant Medication and Psychotic Symptoms

	Unadjusted				Adjusted			
	95% CI				95% CI			
	OR	Lower	Upper	P	OR	Lower	Upper	P
Any psychotic symptom	4.43	1.76	11.12	.002	4.41	1.82	10.69	.001
Hallucinations	7.20	2.93	17.68	.001	7.27	3.14	16.86	.001
Delusions	3.20	0.90	11.32	.130	3.11	0.89	10.95	.137
PLEs	1.53	0.43	5.42	.507	1.25	0.40	3.91	.744
BSs	1.62	0.54	4.85	.393	1.89	0.73	4.89	.270

The adjusted model includes age, gender, and family history as covariates in addition to controlling for clustering of individuals within families.

DISCUSSION

We report an association between the use of stimulant medication and psychotic symptoms in children and adolescents at familial risk of mental illness. The association of current use of stimulants with current psychotic symptoms and the close temporal relationship between stimulant use and psychotic symptoms in youth who started and stopped stimulants indicated a potential causal relationship. The findings suggest that psychotic symptoms may be relatively common adverse effects of stimulants in youths with a family history of major psychiatric disorders.

The rate of psychotic and related symptoms among youth taking stimulants in the present sample was much higher than previously reported.^{8,12} This finding may be because we included participants with a family history of mood and psychotic disorders in first-degree relatives and because we actively inquired about all types of psychotic and related symptoms, using several detailed instruments. Psychotic symptoms have been found to be more common among children of parents with mood and psychotic disorders.^{25,32} However, to our knowledge, no previous study has examined the association between stimulant use and psychotic symptoms in a familial high-risk sample. Groups of experienced clinicians have expressed concerns about the prescription of stimulants to youth at familial risk of psychosis: the Eunethydis ADHD Guidelines

Group states that “evidence of vulnerability to psychosis in terms of a positive family history or prior psychotic episodes may increase the risk of psychotic symptoms with ADHD drugs.”³³ Our finding that all 15 children with stimulant-associated psychotic symptoms were sons and daughters of parents with depression or bipolar disorder suggest that this recommendation may be extended to a family history of major mood disorders.

A second factor that has likely contributed to the high rate of psychotic symptoms is the comprehensiveness of the assessments conducted. All previous reports relied on spontaneous reporting of psychotic symptoms.^{8,12,14} In contrast, we assessed psychotic symptoms with several detailed instruments.^{22–24,26,28} The use of these instruments has likely revealed symptoms that may not have been disclosed if not asked about explicitly.^{26,34} Yet, independent blind consensus with licensed child and adolescent psychiatrists confirmed the psychotic nature and clinical significance of these symptoms, and clinician-confirmed hallucinations and delusions were more strongly associated with the use of stimulant medication than self-reported symptoms. Therefore, the present findings suggest that psychotic symptoms associated with the use of stimulants may be clinically relevant. However, because the evidence presented here is indirect, the degree of clinical

relevance will need to be determined in further prospective studies.

Several longitudinal studies have suggested that childhood psychotic symptoms may predict psychotic disorders in adulthood,^{26,35,36} whereas other studies suggest a relatively good prognosis of psychotic symptoms in children.^{37–39} It should be noted that most stimulant-associated psychotic symptoms were hallucinations and there is lack of consensus about the predictive value of hallucinations in children. Some authors suggest that hallucinations in children have a relatively good prognosis^{37–40} unless they are accompanied by delusions.^{41,42} On the other hand, PLEs that were overwhelmingly hallucinations predicted psychotic symptoms and disorders in adulthood in several large cohorts.^{26,35,36,43} Although more data are needed on the long-term prognosis of hallucinations in childhood, recent reviews lean toward considering hallucinations in childhood as indicators of increased risk of adult psychiatric disorders.^{44,45} At present, it is unclear if psychotic symptoms provoked by stimulant medication carry prognostic implications. In adults, it was found that psychosis induced by stimulants or cannabis abuse often persists or recurs in the absence of continued drug use.^{18,46} It has also been shown that methamphetamine abuse in individuals at familial risk causes schizophrenia that persists regardless of whether the drug abuse continues.¹⁶ An extrapolation of these findings

suggests that stimulant-induced psychotic symptoms in children and adolescents may increase the long-term risk of psychotic disorders. A longitudinal follow-up of the current sample and other cohorts will be needed to establish whether this is the case.

The present results have to be interpreted with regard to several limitations. First, the inference that psychotic symptoms during treatment with stimulants may be more common in children with a family history of mental illness is based on comparison with previous studies. Because of the absence of a comparison group of stimulant-treated youth without a family history of mental illness, we were unable to explicitly test the hypothesis that family history moderates the risk of psychotic symptoms during treatment with stimulants. A comprehensive examination of psychotic symptoms in stimulant-treated youth in the general population is warranted to establish to what extent the reported association generalizes to youth without a family history of mental illness. Second, although the association between the use of stimulants and psychotic symptoms was supported by the temporal association between the use of stimulants and psychotic symptoms,

this finding does not prove causality. A systematic investigation of data from randomized placebo-controlled trials suggests that the association is likely causal.⁸ Assessment of psychotic symptoms with dedicated instruments in future double-blind, randomized, controlled trials is needed to confirm causality for the full range of psychotic symptoms. Third, the predominant stimulant medication in our sample was methylphenidate; therefore, more research is needed to establish to what extent the results generalize to other stimulants. Last, the present sample included too few offspring of parents with schizophrenia to allow meaningful comparison between offspring of parents with psychosis versus mood disorders. Therefore, further study of stimulant medication effects on youth at familial risk of schizophrenia is needed to complete the picture.

Many authors have noted the paucity of data concerning psychotic side effects of stimulant medication in children and adolescents.^{12,14,33,47} Others have argued that the lack of published data concerning psychotic adverse reactions may have led to an underrepresentation of the frequency of this phenomenon.⁴⁸ The majority of results have been presented as case reports. We add a systematic study of psychotic

symptoms and their association with stimulant medication in youth at familial high risk of severe mental illness. Prospective cohort studies are needed to determine the persistence and prognostic relevance of these side effects. In the meantime, we suggest that psychotic symptoms should not be assumed to be rare adverse reactions and should be systematically monitored in children and adolescents who are taking stimulant medication. In addition, a family history of mood and psychotic disorders should be assessed and considered as a factor in the choice of treatment.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
BS: basic symptom
CI: confidence interval
DSM: Diagnostic and Statistical Manual
K-SADS: *Kiddie Schedule for Affective Disorders and Schizophrenia*
OR: odds ratio
PLE: psychotic-like experience
SIPS: *Structured Interview for Prodromal Syndromes*
SPI-CY: *Schizophrenia Proneness Instrument-Child and Youth Version*

assessments, interpreted results, and reviewed and revised the manuscript and approved the final manuscript as submitted; Ms Cumby contributed to the study design and organization, enrolled participants, assessed the parents of the participants, interpreted results, and reviewed and revised the manuscript; Dr Hajek contributed to study conception, and statistical analysis and interpretation and reviewed and revised the manuscript; Dr Schultze-Lutter contributed to the study design and interpretation of results, trained the assessors in the assessment of basic symptoms, supervised the rating of basic symptoms, and reviewed and revised the manuscript; Dr Pajer contributed to the study design, interpreted results, and reviewed and revised the manuscript; Dr Alda contributed to study conception and design, interpreted results, and reviewed and revised the manuscript; Dr Uher conceived and designed the study, contributed to participant enrollment and assessment, carried out statistical analyses, interpreted results, drafted the manuscript jointly with Ms MacKenzie, designed the assessment schedule, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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