Exposure to Second-Generation Antipsychotics and Risk of Type 2 Diabetes Mellitus in Adolescents and Young Adults: A Nationwide Study in Taiwan

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ABSTRACT

Background: The association between second-generation antipsychotics (SGAs) and type 2 diabetes mellitus (T2DM) has been well investigated in adults. However, T2DM risk has been less examined among adolescents with SGA exposure, and the risk remains uncertain in this population.

Methods: A total of 91,185 adolescents and young adults within the Taiwan National Health Insurance system who were exposed to SGAs were enrolled into this study between 2000 and 2011. The patients were divided into 4 subgroups on the basis of cumulative defined daily doses (cDDDs) of SGAs taken by them in the study period: < 30 cDDDs, 30–179 cDDDs, 180–364 cDDDs, and ≥ 365 cDDDs. Those who developed T2DM *(ICD-9-CM)* during follow-up, which was the period from enrollment to the end of 2011, were identified.

Results: Compared with those in the < 30 cDDD group, adolescents and young adults in the 30–179, 180–364, and ≥ 365 cDDD groups exhibited a high risk of T2DM in later life that increased dose dependently (hazard ratio [HR] = 1.15, 95% CI, 0.98–1.34; HR = 1.54, 95% CI, 1.28–1.84; HR = 1.91, 95% CI, 1.67–2.18, respectively) after adjustment for demographic data, medical comorbidities, and psychiatric disorders.

Discussion: Our study results showed a significant relationship between SGA exposure and T2DM risk among adolescents and young adults. These results raise further concern about the use of SGAs in pediatric populations, and on the basis of these results, clinicians should monitor the metabolic condition of their patients.

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The use of second-generation antipsychotics (SGAs) among youths has increased during the past decades.[1–3] In Taiwan, the 1-year prevalence of SGA use in youths increased from 0.00% in 1997 to 0.09% in 2005.[4] SGAs are more commonly used than first-generation antipsychotics for treating psychiatric disorders in pediatric patients. SGAs are commonly used to treat schizophrenia spectrum disorders, major affective disorders, and autism spectrum disorders[4–6] and for many off-label indications, including impulsivity, emotional dysregulation, aggression, and disruptive behavior.[7,8] Because of the increasing prescription of SGAs in the child and adolescent psychiatry field, compiling data on the safety and adverse effects of SGAs is vital.[9,10]

SGAs have fewer neuromotor side effects than first-generation antipsychotics, but they cause more cardiometabolic consequences, such as weight gain, dyslipidemia, cardiovascular events, and type 2 diabetes mellitus (T2DM).[11,12] Children and young adults are more susceptible than adults to SGA-related metabolic effects, and the consequences appear faster.[13] However, limited information is available on the link between SGA use and impaired glucose tolerance, insulin resistance, and risk of T2DM in youths.[14,15] Several studies[13,14] have elucidated the associations of SGA use with T2DM and have shown an increased risk of T2DM in youths.

Considering the geographical diversity in SGA prescription and the risk of subsequent T2DM,[16] we conducted a nationwide longitudinal study to determine SGA effects. In this large cohort, longitudinal follow-up study, we used the Taiwan National Health Insurance Research Database (NHIRD) to assess the risk of subsequent T2DM in adolescents and young adults with SGA exposure. We hypothesized that SGA exposure increases the risk of T2DM during follow-up.

METHODS

Data Source

The Taiwan National Health Insurance (NHI) system was implemented in 1995 and offers comprehensive medical coverage for all residents of Taiwan. The National Health Research Institute (NHRI) is in charge of the entire insurance claims database, namely, the National Health Insurance Research Database (NHIRD), which consists of health care data from > 99% of the Taiwan population. The NHRI audits and releases the NHIRD for use in health service studies.

Clinical Points

- Adolescents and young adults with second-generation antipsychotic (SGA) exposure are at high risk of developing type 2 diabetes mellitus (T2DM) later in life that increases with cumulative dose.
- Among those with major affective disorders lies the highest risk of T2DM after SGA exposure.
- Clinicians should monitor the metabolic condition of youths who are exposed to SGAs.

Patients included in the NHIRD are anonymous to maintain individual privacy. Comprehensive information is included in the database, including patients' demographic data, dates of clinical visits, disease diagnoses, and medical procedures. The diagnostic codes used were based on the *International Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.[17–20]

Inclusion Criteria for Adolescents and Young Adults Exposed to SGAs

Adolescents aged between 12 and 17 years and young adults aged between 18 and 29 years who were identified as having any prescription of SGA, including clozapine, risperidone, olanzapine, quetiapine, ziprasidone, amisulpride, aripiprazole, or paliperidone, between January 1, 2000, and December 31, 2011, and who had no history of any diabetes mellitus (*ICD-9-CM* code: 250) before enrollment, were included as the SGA cohort. The time of first SGA prescription was defined as the enrollment time. Diagnosis of T2DM (*ICD-9-CM* code: 250.x0 and 250.x2, x = 0–9) given by board-certified physicians, pediatricians, internal medicine physicians, endocrinologists, and family medicine physicians based on laboratory examination was identified during the follow-up (from enrollment to December 31, 2011, or to death). Psychiatric disorders, including schizophrenia, major affective disorders, and autism spectrum disorder, given by board-certified psychiatrists were assessed in our study. T2DM-related medical comorbidities, including hypertension, dyslipidemia, and obesity, were assessed as the confounding factors in our study. On the basis of the cumulative use of SGAs in the study period, the SGA cohort was divided into 4 subgroups: users with < 30 cumulative defined daily doses (cDDDs) during the follow-up period, users with 30–179 cDDDs, users with 180–364 cDDDs, and users with ≥ 365 cDDDs. The defined daily dose (DDD) recommended by the World Health Organization (http://www.whocc.no/atc_ddd_index) is a unit for measuring a prescribed amount of drug; it is the assumed average dose per day of a drug consumed for its main indication. Independent of price, package size, currencies, and strength, DDDs give the researcher a fixed unit of measure to assess trends in drug consumption and to perform comparisons between population groups. Level of urbanization (levels 1 to 5, with level 1 the most urbanized region and level 5 the least) was also assessed in our study. This study was approved by Taipei Veterans General Hospital Institutional Review Board.

Table 1. Demographic Data of Adolescents and Young Adults Exposed to SGAs

Characteristic[a]	Adolescents and Young Adults With SGA Exposure (n = 91,185)
Age at enrollment, y	22.80 (4.71)
< 18 y	16,821 (18.4)
18–29 y	74,364 (81.6)
Sex	
Male	48,281 (52.9)
Female	42,903 (47.1)
SGA exposure	
< 30 cDDDs	34,505 (37.8)
30–179 cDDDs	19,214 (21.1)
180–364 cDDDs	7,311 (8.0)
≥ 365 cDDDs	30,155 (33.1)
SGA exposure by drug	
Risperidone	31,890 (35.0)
Olanzapine	15,576 (17.1)
Clozapine	7,536 (8.3)
Quetiapine	17,496 (19.2)
Ziprasidone	3,657 (4.0)
Amisulpride	11,052 (12.1)
Aripiprazole	10,861 (11.9)
Paliperidone	4,089 (4.5)
T2DM	2,654 (2.9)
Age at diagnosis, y	29.18 (4.88)
Psychiatric disorder	
Schizophrenia	45,338 (49.7)
Major affective disorders	30,811 (33.8)
Autism spectrum disorder	4,490 (4.9)
Medical disorder	
Hypertension	4,292 (4.7)
Dyslipidemia	6,087 (6.7)
Obesity	3,608 (4.0)
Level of urbanization	
1 (most urbanized)	20,720 (22.7)
2	29,206 (32.0)
3	12,436 (13.6)
4	9,998 (11.0)
5 (most rural)	18,825 (20.6)
Income-related insured amount per month[b]	
≤ NT$15,840	56,880 (62.4)
NT$15,841–NT$25,000	26,488 (29.0)
≥ NT$25,001	7,817 (8.6)

[a]All values are n (%) except for age, which is mean (SD).
[b]Multiply NT$ by 0.0324 for an approximate conversion to US dollars, eg, NT$15,841–NT$25,000 is approximately equivalent to $513–$810.
Abbreviations: cDDDs = cumulative defined daily doses, NT$ = New Taiwan Dollar, SGA = second-generation antipsychotic, T2DM = type 2 diabetes mellitus.

Statistical Analysis

Cox regression model was used to investigate the association between the level of SGA use (< 30 cDDDs [reference group], 30–179 cDDDs, 180–364 cDDDs, and ≥ 365 cDDDs) and the hazard ratio (HR) with a 95% CI of T2DM after adjusting for demographic data (age, sex, level of urbanization, and income), psychiatric comorbidities (schizophrenia , major affective disorders, autism spectrum disorder), and medical comorbidities (hypertension, dyslipidemia, obesity). We also performed the subanalyses of the risk of T2DM with SGA exposure stratified by sex,

Table 2. Risk of T2DM Among Adolescents and Young Adults Exposed to SGAs[a]

	T2DM Risk		
Variable	Model 1,[b] HR (95% CI)	Model 2,[c] HR (95% CI)	Model 3,[d] HR (95% CI)
SGA exposure			
< 30 cDDDs	1 (reference)	1 (reference)	1 (reference)
30–179 cDDDs	**1.26 (1.08–1.47)**	**1.18 (1.01–1.38)**	1.15 (0.98–1.34)
180–364 cDDDs	**1.87 (1.57–2.23)**	**1.63 (1.36–1.94)**	**1.54 (1.28–1.84)**
≥ 365 cDDDs	**2.70 (2.40–3.03)**	**2.07 (1.84–2.33)**	**1.91 (1.67–2.18)**
Medical comorbidities, presence vs absence			
Hypertension		**2.56 (2.33–2.82)**	**2.57 (2.33–2.83)**
Dyslipidemia		**4.32 (3.96–4.72)**	**4.32 (3.96–4.71)**
Obesity		**2.81 (2.55–3.11)**	**2.82 (2.55–3.12)**
Psychiatric comorbidities, presence vs absence			
Schizophrenia			1.16 (0.97–1.39)
Major affective disorders			1.01 (0.84–1.22)
Autism spectrum disorder			**1.30 (1.06–1.60)**

[a]Boldface represents significant at $P < .05$.
[b]Model 1 adjusting for demographic data.
[c]Model 2 adjusting for demographic data and medical comorbidities.
[d]Model 3 adjusting for demographic data, medical comorbidities, and psychiatric comorbidities.
Abbreviations: cDDDs = cumulative defined daily doses, CI = confidence interval, HR = hazard ratio, SGAs = second-generation antipsychotics, T2DM = type 2 diabetes mellitus.

Table 3. Risk of T2DM Among Adolescents and Young Adults Exposed to SGAs, Stratified by Sex or Age[a]

	T2DM Risk				
SGA Exposure	Males, HR (95% CI)	Females, HR (95% CI)	Adolescents, HR (95% CI)	Young Adults, HR (95% CI)	Total, HR (95% CI)
< 30 cDDDs (reference)	1	1	1	1	1
30–179 cDDDs	**1.24 (1.00–1.52)**	1.02 (0.81–1.29)	0.65 (0.37–1.16)	**1.20 (1.02–1.41)**	1.15 (0.98–1.34)
180–364 cDDDs	**1.59 (1.24–2.03)**	**1.48 (1.13–1.93)**	1.08 (0.56–2.10)	**1.59 (1.31–1.92)**	**1.54 (1.28–1.84)**
≥ 365 cDDDs	**1.86 (1.55–2.22)**	**1.97 (1.62–2.39)**	**1.77 (1.14–2.73)**	**1.93 (1.68–2.22)**	**1.91 (1.67–2.18)**

[a]Adjusting for demographic data, medical comorbidities, and psychiatric comorbidities. Boldface represents significant at $P < .05$.
Abbreviations: cDDDs = cumulative defined daily doses, CI = confidence interval, HR = hazard ratio, SGA = second-generation antipsychotic, T2DM = type 2 diabetes mellitus.

by age group (adolescents 12–17 years and young adults 18–29 years), and by psychiatric disorders (schizophrenia, major affective disorders, and autism spectrum disorder). In addition, Cox regression analyses were performed to clarify each SGA exposure (≥ 30 cDDDs) with the risk of T2DM after adjusting for demographic data and psychiatric and medical comorbidities. A 2-tailed *P* value of less than .05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc., Chicago, Illinois) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Of 91,185 adolescents and young adults with SGA exposure, 37.8% were identified as the reference group (< 30 cDDDs), 21.1% as users with 30–179 cDDDs, 8.0% as users with 180–364 cDDDs, and 33.1% as users with ≥ 365 cDDDs (Table 1). Regarding psychiatric disorders, 49.7% had schizophrenia, 33.8% had major affective disorders, and 4.9% had autism spectrum disorder. During the follow-up period, 2,654 (2.9%) developed T2DM at the mean age of 29.18 ± 4.88 years. Regarding physical comorbidities, 4.7% had hypertension, 6.7% had dyslipidemia, and 4.0% had obesity (Table 1).

Cox regression analyses with the adjustment of demographic data, psychiatric disorders, and physical comorbidities showed a dose-dependent relationship between level of SGA exposure (30–179 cDDDs: HR = 1.15, 95% CI, 0.98–1.34; 180–364 cDDDs: HR = 1.54, 95% CI, 1.28–1.84; ≥ 365 cDDDs: HR = 1.91, 95% CI, 1.67–2.18) and the likelihood of developing T2DM during the follow-up compared with the reference group (Table 2). Subanalyses stratified by age and by sex revealed the consistent findings that males (HR = 1.24, 95% CI, 1.00–1.52; HR = 1.59, 95% CI, 1.24–2.03; HR = 1.86, 95% CI, 1.55–2.22), females (HR = 1.02, 95% CI, 0.81–1.29; HR = 1.48, 95% CI, 1.13–1.93; HR = 1.97, 95% CI, 1.62–2.39), and young adults (HR = 1.20, 95% CI, 1.02–1.41; HR = 1.59, 95% CI, 1.31–1.92; HR = 1.93, 95% CI, 1.68–2.22) with SGA exposure were associated with an increased risk of developing T2DM in later life in a dose-dependent manner (Table 3). In addition, adolescents who were exposed to ≥ 365 cDDDs of SGAs had an increased risk of subsequent T2DM (HR = 1.77, 95% CI, 1.14–2.73) (Table 3).

Table 4. Risk of T2DM Among Adolescents and Young Adults Exposed to SGAs, Stratified by Psychiatric Comorbidities[a]

	T2DM Risk		
SGA Exposure	Schizophrenia, HR (95% CI)	Major Affective Disorders, HR (95% CI)	Autism Spectrum Disorder, HR (95% CI)
< 30 cDDDs (reference)	1	1	1
30–179 cDDDs	1.13 (0.90–1.43)	1.09 (0.85–1.41)	0.75 (0.39–1.46)
180–364 cDDDs	**1.31 (1.02–1.68)**	**1.85 (1.36–2.51)**	1.05 (0.50–2.18)
≥ 365 cDDDs	**1.71 (1.42–2.06)**	**2.35 (1.87–2.96)**	0.97 (0.58–1.61)

[a]Adjusting for demographic data and medical comorbidities. Boldface represents significant at $P < .05$.
Abbreviations: cDDDs = cumulative defined daily doses, CI = confidence interval, HR = hazard ratio, SGA = second-generation antipsychotics, T2DM = type 2 diabetes mellitus.

Table 5. Risk of T2DM Among Adolescents and Young Adults Exposed to SGAs, Stratified by Each SGA[a]

SGA	T2DM Risk, HR (95% CI)
Risperidone	**1.19 (1.10–1.30)**
Olanzapine	**1.10 (1.01–1.20)**
Clozapine	**1.34 (1.22–1.48)**
Quetiapine	**1.23 (1.13–1.34)**
Ziprasidone	**1.40 (1.23–1.59)**
Amisulpride	**1.38 (1.26–1.51)**
Aripiprazole	**1.24 (1.12–1.37)**
Paliperidone	1.09 (0.94–1.27)

[a]Adjusting for demographic data, medical comorbidities, and psychiatric comorbidities. Boldface represents significant at $P < .05$.
Abbreviations: CI = confidence interval, HR = hazard ratio, SGA = second-generation antipsychotic, T2DM = type 2 diabetes mellitus.

Furthermore, we investigated the levels of SGA exposure with the risk of subsequent T2DM among 3 psychiatric disorders and found a dose-dependent relationship between SGA exposure and T2DM risk in schizophrenia (30–179 cDDDs: HR = 1.13, 95% CI, 0.90–1.43; 180–364 cDDDs: HR = 1.31, 95% CI, 1.02–1.68; ≥ 365 cDDDs: HR = 1.71, 95% CI, 1.42–2.06) and major affective disorders (30–179 cDDDs: HR = 1.09, 95% CI, 0.85–1.41; 180–364 cDDDs: HR = 1.85, 95% CI, 1.36–2.51; ≥ 365 cDDDs: HR = 2.35, 95% CI, 1.87–2.96), but not in autism spectrum disorder (Table 4). Finally, we clarified each SGA exposure with the risk of T2DM and found that clozapine (HR = 1.34, 95% CI, 1.22–1.48), risperidone (HR = 1.19, 95% CI, 1.10–1.30), olanzapine (HR = 1.10, 95% CI, 1.01–1.20), quetiapine (HR = 1.23, 95% CI, 1.13–1.34), ziprasidone (HR = 1.40, 95% CI, 1.23–1.59), amisulpride (HR = 1.38, 95% CI, 1.26–1.51), and aripiprazole (HR = 1.24, 95% CI, 1.12–1.37), but not paliperidone (HR = 1.09, 95% CI, 0.94–1.27) were associated with an increased risk of subsequent T2DM (Table 5).

In addition, in the full adjustment model (Table 2), hypertension (HR = 2.57, 95% CI, 2.33–2.83), dyslipidemia (HR = 4.32, 95% CI, 3.96–4.71), obesity (HR = 2.82, 95% CI, 2.55–3.12), and autism spectrum disorder (HR = 1.30, 95% CI, 1.06–1.60) were independently related to the higher likelihood of T2DM risk.

DISCUSSION

Our study findings support the hypothesis that exposure to SGAs is associated with an increased risk of T2DM among adolescents and young adults after adjustment for demographic data, psychiatric disorders, and physical comorbidities. The results also demonstrate that a dose-dependent relationship exists between the cumulative dose of SGAs and T2DM risk.

Selecting an appropriate reference group is crucial for understanding the association between SGA use and T2DM because of potential confounding from indication and detection bias. Therefore, we carefully selected a group of adolescents and young adults whose cDDDs were less than 30 as the reference group; this group would be similar to SGA users in terms of mental health conditions and the potential for detection/diagnosis of T2DM. Previous studies[21–23] have used antidepressant users as the reference group but have provided inconclusive results for T2DM risk. By selecting users with < 30 cDDDs as the reference group in our study, we minimized the influence of confounding factors.

In our study, female subjects exposed to the highest cDDDs exhibited the highest risk of subsequent T2DM. This result is consistent with that of a prior study,[24] which showed that in the general pediatric population, T2DM is twice as common in female subjects as in male subjects. The increased risk was attributed to more prominent changes in insulin resistance during puberty because of estrogen elevation, relative body composition change, and glucose metabolism.[25,26]

Regarding the risk of T2DM between adolescents and young adults, our study showed that young adults exhibited the highest risk that increased dose dependently. Adolescents may have a superior pancreatic β-cell reserve, and young adults may have greater insulin resistance after pubertal development,[25] which increases the risk of T2DM in young adults compared with that in adolescents. In this study, we also examined the relationship between SGA exposure and the risk of T2DM across 3 major psychiatric disorders. The results consistently revealed a dose-dependent relationship with schizophrenia and major affective disorders, but not with autism spectrum disorder. Youths with affective disorders were at the highest risk of SGA-related T2DM than those with other psychiatric illness. Studies[27,28] have found that T2DM risk was 1.5- and 2-fold higher in psychiatrically ill youths exposed to SGAs than in healthy controls. The concomitant use of medications, such as antidepressants and mood stabilizers for depression and bipolar disorder, may increase the risk of adverse metabolic effects.[29] In

addition, neurovegetative symptoms and subclinical thyroid and cortisol dysfunction of affective disorder may be also related to the risk of weight gain.[30,31]

Previous studies[32–34] have shown that insulin resistance, the inhibition of insulin release, and the disturbance of glucose utilization may result from the antagonism of serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors caused by SGA use. SGAs also affect α_2-adrenergic receptors, which may influence pancreatic cell function.[32–34] Comparing each SGA, we found that an increased risk of subsequent T2DM was associated with the use of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, amisulpride, and aripiprazole, but not with the use of paliperidone. In smaller clinical samples, newer SGAs (ziprasidone and aripiprazole) might produce fewer adverse metabolic effects, particularly less weight gain, than other SGA medications.[35,36] By contrast, our study elucidated that newer SGAs were associated with higher T2DM risk. This finding is attributed to the preference of clinicians, who are more likely to prescribe these lower-risk SGAs to higher-risk patients, and it may be confounded by indication and overestimation of the risk.[37] Additionally, those with adverse cardiometabolic effects because of other SGAs might have switched to these 3 drugs and had longer exposure to antipsychotics, which may have led to weight gain, thereby elevating the risk of T2DM for reasons other than the prescribed drug.[38,39] Thus, the findings may be subject to channeling bias.

Our study indicated that hypertension, dyslipidemia, obesity, and autism spectrum disorder were independently related to higher T2DM risk in the fully adjusted model. Medical comorbidities were assessed as confounding factors in our study, and we adjusted for them carefully. Nevertheless, unobserved confounders, such as personal lifestyle, body mass index (BMI), or family history of metabolic diseases, may exist. Although the confounders may be associated with T2DM, it is improbable that the magnitude of the difference in prevalence between exposure and reference groups will nullify our results.

This study has several strengths. In addition to the long follow-up time, our investigation included a nationwide sample that represented a large, heterogeneous group of adolescents and young adults with SGA exposure for different periods. In addition to the large national sample, we used psychiatrically ill patients as the reference group and adjusted for potential confounders through multivariate regression analyses. Finally, T2DM was diagnosed by board-certified physicians, pediatricians, internal and family medicine physicians, and endocrinologists on the basis of laboratory examinations that validated the diagnoses and diminished the underestimation of the risk of T2DM. Bobo and colleagues' study[14] showed that children and youths aged between 6 and 24 years who were exposed to SGAs had an increased risk of T2DM that increased with cumulative dose, but the study excluded patients who previously received a diagnosis of schizophrenia. Our study further expanded the result by examining and comparing different psychiatric disorders. We found a dose-dependent association between SGA exposure and likelihood of T2DM in schizophrenia and major affective disorders, and results further suggested that youths with major affective disorders exposed to long-term SGAs had the highest risk of developing T2DM during the follow-up period. In addition, our study provided greater generalizability because the Taiwan NHI had approximately 99.6% coverage of the national population, which may reduce the effect of selection bias.

Despite these strengths, several limitations are inevitable. A registry study is not random, allowing for potential systemic biases between the exposed and unexposed groups. Unmeasured disparities between the groups in terms of the severity of illness, premorbid obesity, and personal lifestyle affected the results. Furthermore, because of the intention-to-treat design, we did not survey adherence to assigned treatment and did not measure nonadherence to treatment in the exposure and reference groups. Thus, the risk of sustained treatment of SGAs may be underestimated. Finally, this cohort study included patients from the Taiwan NHIRD, which limited the generalizability of the findings to countries with different health and social welfare systems, dissimilar economic and social factors, or distinct BMI distributions and metabolic profiles among youths.

In conclusion, this nationwide longitudinal study indicated that adolescents and young adults with SGA exposure were at a high risk of T2DM in later life that increased dose dependently after adjustment for demographic data, medical comorbidities, and psychiatric disorders. The results raise concerns about the use of SGAs in pediatric populations, and on the basis of these results, clinicians should monitor the metabolic condition of patients. Further research should be conducted on the individualization of SGA use based on a patient's risk-benefit profile. Additional studies should explore the pathophysiology underlying the association between SGA exposure and T2DM and should identify an intervention to reduce the risk of T2DM after SGA exposure.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.