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Utilization and Predictors of Adjuvant Metformin for Children and Adolescents on Mixed Receptor Antagonists (Second-Generation Antipsychotics)

Hua Chen, MD, PhD,
University of Houston, College of Pharmacy, Houston, Texas.

Ning Lyu, MS,
University of Houston, College of Pharmacy, Houston, Texas.

Wenyaw Chan, PhD,
University of Texas Health Science Center at Houston, School of Public Health, Houston, Texas.

Austin De La Cruz, PharmD, BCPP,
University of Houston, College of Pharmacy, Houston, Texas.

Chadi Calarge, MD
Baylor College of Medicine, Houston, Texas.

Abstract

Objective: To examine utilization and predictors of adjuvant metformin among pediatric recipients of second-generation antipsychotics (SGAs) (mixed receptor antagonist).

Method: This study used 2016-2021 data of a national electronic medical record database. Eligible participants were children aged 6 to 17 with a new SGA prescription for at least 90 days. Predictors of prescribing adjuvant metformin in general and to nonobese pediatric SGA recipients

Correspondence to Hua Chen, MD, PhD, College of Pharmacy, University of Houston, Health Building 2 – Office 4049, 4349 Martin Luther King Boulevard, Houston, TX 77204; hchen25@central.uh.edu.

Author Contributions

Conceptualization: Chen, Lyu, Chan, De La Cruz, Calarge
Data curation: Chen, Lyu
Formal analysis: Chen, Lyu
Funding acquisition: Chen
Investigation: Chen
Methodology: Chen, Lyu, Chan, Calarge
Project administration: Chen
Resources: Chen
Software: Chen, Lyu
Supervision: Chen, Chan, De La Cruz, Calarge
Validation: Chen, Lyu
Visualization: Chen, Lyu
Writing – original draft: Chen
Writing – review and editing: Chen, Lyu, Chan, De La Cruz, Calarge

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in particular were assessed using conditional logistic regression and logistic regression analyses, respectively.

Results: Of 30,009 pediatric SGA recipients identified, 2.3% (n = 785) received adjuvant metformin. Among 597 participants with a body mass index *z* score documented during the 6-month period before metformin initiation, 83% were obese, and 34% had either hyperglycemia or diabetes. Significant predictors for metformin prescribing were high baseline body mass index *z* score (odds ratio [OR] 3.5, 95% CI 2.8-4.5, $p < .0001$), having hyperglycemia or diabetes (OR 5.3, 95% CI 3.4-8.3, $p < .0001$), and undergoing a switch from a higher metabolic risk SGA to a lower risk one (OR 9.9, 95% CI 3.5-27.5, $p = .0025$) or a switch in the opposite direction (OR 4.1, 95% CI 2.1-7.9, $p = .0051$) compared with no switch. Nonobese metformin users were more likely to have a positive body mass index *z* score velocity before metformin initiation than their obese counterparts. Receiving the index SGA prescribed by a mental health specialist was associated with higher likelihood of receiving adjuvant metformin and receiving metformin before the development of obesity.

Conclusion: Utilization of adjuvant metformin among pediatric SGA recipients is uncommon, and early introduction of the medication among nonobese children is rare.

Keywords

adjuvant metformin; antipsychotic-induced weight gain

Population-based studies estimate that 0.3% to 4.5% of children in the United States are prescribed second-generation antipsychotics (SGAs), also referred to as mixed receptor antagonists in neuroscience-based nomenclature.[1-3] Weight gain is one of the most troublesome side effects of SGAs in children,[4,5] with up to 80% of children showing significant weight gain.[6] An electronic medical record (EMR)–based study that included more than 2,000 pediatric psychotropic recipients as well as many small-scale, short-term pediatric trials found that most of the weight gain associated with exposure to antipsychotics in children occurs during the first 12 weeks of treatment.[7,8] Another EMR-based study further demonstrated that antipsychotic-induced weight gain (AIWG) may not be reversible in children and adolescents, which further highlights the importance of early intervention for AIWG.[9]

The effect of metformin in reducing AIWG among children was demonstrated in 4 randomized controlled trials, including the most recent IMPACT trial.[10-13] A meta-analysis of adult trials indicated that early introduction of metformin during SGA treatment is beneficial. Patients who started metformin and SGA concurrently showed a much larger difference in mean body weight reduction (−5.94 kg [95% CI −6.75 to −5.12 kg]) than trials of chronic patients (−2.06 kg [95% CI −2.71 to −1.41 kg]).[7-9] However, the preventive effect of metformin has not been confirmed in children on SGAs.

The use of adjuvant metformin in real-world practice has not been examined. It remains unknown whether metformin has been prescribed to nonobese SGA recipients to prevent the development of obesity or was more commonly used in obese SGA recipients or SGA recipients with hyperglycemia for weight management and blood glucose control. Therefore,

the aims of our study were to assess the utilization of adjuvant metformin among overall, obese, and nonobese pediatric recipients of SGAs and to examine patient and provider factors associated with prescribing adjuvant metformin using a national EMR database.

METHOD

This study was approved by the University of Houston Institutional Review Board.

Data

The IQVIA Ambulatory EMR-US database is a deidentified, Health Insurance Portability and Accountability Act–compliant research database with 345 million patient records collected from 82 million patients seen by more than 100,000 providers.[14] The patient information recorded in the database includes demographics, diagnoses, procedural information, vital signs, and laboratory test results. Additionally, the database includes provider information such as their identification number and specialty. Medication list entries included in the database are dose, route of administration, start and stop dates, and the reason for discontinuation.

Sample

This analysis comprised children and adolescents 6 to 17 years of age initiating a new SGA treatment and receiving a minimum of 90 days of continuous SGA prescriptions during the years 2016 to 2021. A new SGA treatment is defined as a new prescription order (index SGA) after a 6- month preceding period without an SGA prescription order.

Design

As presented in Figure 1, a nested case-control design was applied to compare the differences in patient and provider characteristics between matched adjuvant metformin users and nonusers. A retrospective cohort design was subsequently applied to identify the factors associated with prescribing adjuvant metformin to nonobese vs obese SGA recipients.

Study Variable Construction

Adjuvant Metformin Users.—Adjuvant metformin users were defined as patients who received a metformin prescription after the initiation of an SGA with at least a 1-week overlap between the SGA and metformin prescriptions. The date of metformin initiation is defined as the index date.

Adjuvant Metformin Nonusers.—Each metformin user was matched with 2 participants who continued SGA treatment but had not initiated metformin up to the user’s metformin initiation date (nonusers). The matching is necessary because the chance of patients receiving adjuvant metformin is dependent on the duration of SGA exposure. Patients who had early SGA discontinuation were less likely to receive adjuvant metformin than the longer-term SGA users (immortal time bias). To preclude this bias associated with immortal person-time, which is common in studies comparing treatments against a nonuser comparator group, it is necessary to identify a specific time point among nonuse episodes to

mark their study index date.[15,16] The 1:2 matching ratio was selected for the main analysis because it is a matching ratio that can be satisfied for all adjuvant metformin recipients. A sensitivity analysis was conducted by increasing the matching ratio to 1:3 and 1:4 to test the robustness of the findings from the main analysis.

Obese and Nonobese Metformin Users.—The use of adjuvant metformin was further categorized based on its role in AIWG management as the use in nonobese and obese SGA recipients. Being obese was defined as a BMI *z* score >1.64, corresponding to a BMI *z* score above the 95th percentile.[17,18] We did not differentiate metformin use as prevention vs treatment for AIWG, as that has been defined in clinical trials. Preventive use was defined in trials as starting SGA and metformin simultaneously, while the trials that focused on the treatment of AIWG usually included children who were stabilized on SGAs. However, the duration between SGA initiation and metformin initiation in real-world patients is a continuous distribution (Figure S1, available online). Therefore, instead of imposing a cutoff on the duration between SGA initiation and metformin initiation to differentiate the role of adjuvant metformin, we categorized the metformin recipients by their BMI *z* score last taken within the 6-month period before the adjuvant metformin initiation.

Potential Predictors for Prescribing Adjuvant Metformin.—The potential predictors for prescribing adjuvant metformin were collected during the 6-month period before the index date. These predictors were identified based on the conceptual framework of Eisenberg's model of decision making by clinicians.[19] According to Eisenberg's framework models, clinical decisions (eg, prescribing adjuvant metformin) are determined by 4 dynamics: patient characteristics, physician or prescriber characteristics, the physician's relationship with the patient, and the physician's interaction with their profession and the health system. Because a direct measure for sharing decision style is not available in the data, our analysis focused on the other 3 predictor categories.

Patient characteristics available in our data are patient demographics (age, sex, race/ethnicity), family history of diabetes, potential indications for receipt of metformin (eg, hyperglycemia, diabetes), SGA regimen measured as the index SGA and the history of SGA switch, and weight status measured as BMI *z* score (included only for the comparison between metformin users and nonusers) and BMI *z* score velocity. Comorbidities and comedications that could potentially affect patients' weight status were also included. BMI *z* score velocity was calculated as the difference between the earliest and the latest BMI *z* scores obtained during the 6-month preindex period and divided by the time interval between these 2 BMI *z* scores.[20,21] BMI *z* score velocity was further categorized as weight increase (>0) vs weight neutral or decrease (≤0). Family history of diabetes was identified by *ICD-9* (V18.0) and *ICD-10* (Z83.3) codes.[22,23] Index SGA was defined as the specific SGA patients received on the date of metformin initiation. The history of SGA switch was defined as changing SGA during the 6-month preindex period. The SGA switch was further categorized as switching SGAs from lower risk to higher risk, within the same risk, and switching from higher risk to lower risk according to the propensity of metabolic adverse effects associated with individual SGAs. Low-risk SGAs include aripiprazole, asenapine, ziprasidone, lurasidone, and cariprazine; moderate-risk SGAs are risperidone, quetiapine,

paliperidone, and iloperidone; and high-risk SGAs include clozapine and olanzapine.[6] The physician characteristic available in our data that may influence the prescribing decision is the specialty. Geographic region was also included as a proxy measure of the physician's interaction with the health care system, given the known geographic variations in medical practice.

Statistical Analysis

The Student *t* test was used for comparisons between continuous variables, and the χ^2 test was used for comparisons between categorical variables. A conditional logistic regression analysis, the logistic regression model for matched data, was performed for the comparison between matched adjuvant metformin users and nonusers (dependent variable 1), and a logistic regression analysis was performed for the comparison between obese and nonobese adjuvant metformin users (dependent variable 2) to identify potential predictors associated with the prescribing of metformin (independent variables).

RESULTS

Utilization of Adjuvant Metformin in Children Exposed to SGA

During 2016 to 2021, 30,009 children and adolescents aged 6 to 17 who received an SGA prescription for at least 90 days were identified from the IQVIA database. Of these children, 42.2% (n = 12,682) were obese, 12.5% (n = 3,775) were overweight, and 24.2% (n = 7,285) had more than a 0.5 unit increase in BMI *z* score during the SGA treatment.

Of the pediatric patients with long-term use of SGAs, 2.3% (n = 785) received a metformin prescription after the initiation of SGA and had at least a 1-week overlap between the SGA and the metformin prescription. The mean (SD) duration of metformin use was 365 (365) days, and the median (interquartile range) was 230 (98-493) days. The mean duration from SGA initiation to metformin initiation was 401 (462) days, and the median was 223 (32-635) days. The mean overlap between SGA and metformin prescriptions was 309 (335) days, and the median was 189 (86-418) days. Of the 785 adjuvant metformin users identified, 86.2% (n = 677) had 30 days or longer overlap, and 75% (n = 591) had 60 days or longer overlap between SGA and metformin prescriptions.

The index SGA was most prescribed by primary care providers (38.8%), followed by mental health specialists (22.3%), and other specialists (13.7%). Half (50.4%) of the adjuvant metformin users received their metformin prescription from the same prescriber of their index SGA prescription.

Descriptive Statistics of Matched Metformin Users vs Nonusers

To examine the differences between adjuvant metformin users and nonusers, 597 adjuvant metformin users with BMI *z* scores available during the 6-month period before metformin initiation were successfully matched with 1,194 nonusers with a comparable duration of SGA exposure. Among the 597 adjuvant metformin users, 83.4% (n = 498) were obese, and 16.6% (n = 99) were either normal or overweight before the initiation of adjuvant

metformin. The sample attrition during the matching process is presented in Figure S2, available online.

As presented in Table 1, the adjuvant metformin users included more adolescents than matched nonusers and relatively more females (50% vs 32%). A higher proportion of adjuvant metformin users were prescribed olanzapine as the index SGA (11% vs 5%) and had their index SGA prescribed by a psychiatrist (22.5% vs 14.7%). SGA switch was more common among adjuvant metformin users than nonusers during the 6-month period before metformin initiation (20% vs 4%). Of these, only 5.5% of metformin users and 0.7% of nonusers switched to an SGA with a lower propensity of metabolic side effects, while the majority switched to a relatively higher-risk SGA. The baseline BMI *z* score was nearly 2 times higher in adjuvant metformin users compared with the nonusers (mean [SD] = 2.03 [0.6] vs 1.03 [1.2]). Before metformin initiation, 34.3% of adjuvant metformin users and 6.5% of nonusers had abnormal blood glucose or a diagnosis of diabetes.

As presented in Table 2, the obese and nonobese adjuvant metformin users had similar distributions of demographics, comorbidities, and comedications. Prominent differences were observed in baseline BMI *z* score velocity and the index SGA prescriber specialty. More than one baseline BMI *z* score was obtained in 65% of children in both groups, which enabled the calculation of BMI *z* score velocity. Among the nonobese metformin users, 47% experienced positive weight gain during the baseline period, measured as a change of BMI *z* score velocity >0, while the rate was only 18% among obese users. The distribution of BMI z score velocity as a continuous measure is presented in Table S1, available online. The index SGA prescription was written by a mental health specialist in a significantly higher proportion of nonobese metformin users (41%) than obese users (19%).

Multivariable Analysis Assessing Factors Associated With Prescribing Adjuvant Metformin

As presented in Table 3, the conditional logistic regression analysis results revealed that the patient's likelihood of receiving adjuvant metformin increased 3.7 times with every 1 unit increase of the baseline BMI *z* score (odds ratio [OR] 3.5, 95% CI 2.8-4.5). Patients with either hyperglycemia or diabetes had 5 times the odds compared with patients without either condition (OR 5.3, 95% CI 3.4-8.3). Patients switching from an SGA with relatively higher metabolic risk to a lower risk SGA during the baseline period had a 9 times higher chance of receiving adjuvant metformin than patients who did not switch (OR 9.9, 95% CI 3.5-27.5). Having SGA switching in the opposite way was also associated with a 4 times higher chance of receiving adjuvant metformin (OR 4.1, 95% CI 2.1-7.9). Receiving olanzapine as the index SGA (OR 2.2, 95% CI 1.2-4.2) and receiving an index SGA prescribed by a mental health specialist (OR 3.5, 95% CI 2.2-5.6) were associated with higher odds of receiving adjuvant metformin. Additional factors associated with the use of adjuvant metformin were being female, having comorbid polycystic ovarian syndrome, having a family history of diabetes mellitus, and receiving a selective serotonin reuptake inhibitor as a comedication. The sensitivity analysis results on the cohorts using 1:3 and 1:4 matching were consistent with the main analysis (Tables S2 and S3, available online). Nearly all the risk factors identified in the main analysis were also found to be statistically

significant in the sensitivity analyses except for the family history of diabetes and receiving anxiolytics as a comedication.

Multivariable Analysis Assessing Factors Associated With Prescribing Adjuvant Metformin to Nonobese vs Obese SGA Recipients

As presented in Table 4, the logistic regression analysis results showed that compared with patients who were obese before the initiation of adjuvant metformin, their nonobese counterparts were 3.5 times more likely to have a positive baseline BMI *z* score velocity (OR 3.5, 95% CI 1.8-6.7); their odds of having hyperglycemia or diabetes before metformin initiation were 60% less (OR 0.4, 95% CI 0.2-0.9).

DISCUSSION

Although metformin is the most extensively studied intervention for AIWG in children, our findings suggest that the use of adjuvant metformin in pediatric recipients of SGAs is rare. Only 1.7% of all pediatric SGA recipients aged 6 to 17 and 2.9% of long-term users of SGAs were prescribed adjuvant metformin despite the fact that more than half of the study cohort were overweight or obese, and a quarter experienced significant weight gain during SGA treatment.

The limited use of adjuvant metformin in pediatric SGA recipients could be due to multiple reasons. Metformin does not carry a pediatric indication, and some prescribers, especially primary care providers, may be hesitant to use it off-label.[24] In addition, the use of a medication to address the adverse events associated with another medication is usually discouraged in medical practice due to concerns regarding polypharmacy and additional side effects. In fact, gastrointestinal side effects have been cited as the primary barrier to metformin use in qualitative interviews of providers and adult patients with type 2 diabetes.[25-27]

Our results showed that the current use of adjuvant metformin was mainly in children who developed metabolic syndrome associated with SGAs, even though the pattern of AIWG suggests that early intervention might be critical to attenuate it. Most adjuvant metformin users (83%) identified in our study were obese, and one-third had hyperglycemia or diabetes at metformin initiation.

We also found that 20% of adjuvant metformin users had a history of SGA switch. It was reported in the IMPACT study that switching to an SGA with a lower propensity for metabolic side effects is an effective intervention for AIWG.[13] Yet, switching an SGA may not always be feasible because the 2 most effective SGAs on the market, clozapine and olanzapine, also have the highest reported metabolic adverse effects.[28] Our study showed that there were more patients switching from SGAs with a lower propensity to higher propensity agents than vice versa before metformin initiation. SGA switch in either direction was associated with a higher chance of receiving adjuvant metformin. This finding implies that adjuvant metformin is often reserved when switching to an SGA with lower metabolic risk is either ineffective or not feasible.

The especially low use of metformin in nonobese pediatric SGA recipients or recipients who have not developed hyperglycemia or diabetes could be due to the dearth of pediatric data supporting the preventive use of metformin for AIWG. Nearly all subjects included in current pediatric metformin trials for AIWG are SGA users who were either obese or had experienced significant weight gain.[10-13] However, such studies are available in adult populations.[28] Future studies are needed to understand the effectiveness of adjuvant metformin in real-world patients and to generate more evidence to inform the benefits and adverse effects associated with the preventive use of adjuvant metformin in pediatric SGA recipients.

Our study is the first to our knowledge to describe the utilization of metformin in SGA-treated children, using current national EMR data. The rich clinical details included in the data allow an in-depth examination of the use of adjuvant metformin in the management of SGA-induced metabolic side effects and the patient and prescriber characteristics associated with prescribing adjuvant metformin.

Despite many strengths, this study also has several limitations. The IQVIA Ambulatory EMR-US database is an ambulatory EMR for which inpatient medication use is not captured. Adjuvant metformin might have been used more frequently in institutionalized youth. The prescription orders from a provider whose practice is not included in the EMR data are unknown. Therefore, we are not able to exclude the possibility of misclassification that some nonusers might have received metformin prescriptions from such providers. Another limitation of EMR data is that it does not capture the socioeconomic status of the child's family, which prevents us from examining the potential impact of these factors on the provider's prescribing decision. Additionally, BMI *z* score before SGA initiation was not universally available to all patients included in the study, which prevents us from determining whether the participants were obese because of the SGA or were obese before its initiation.

In conclusion, adjuvant metformin is used in a small fraction of pediatric SGA recipients, and early introduction among SGA recipients who have yet to develop obesity or hyperglycemia is rare. Future studies should be conducted to assess the effectiveness and safety of preventive use of adjuvant metformin in children and explore barriers to using metformin more readily.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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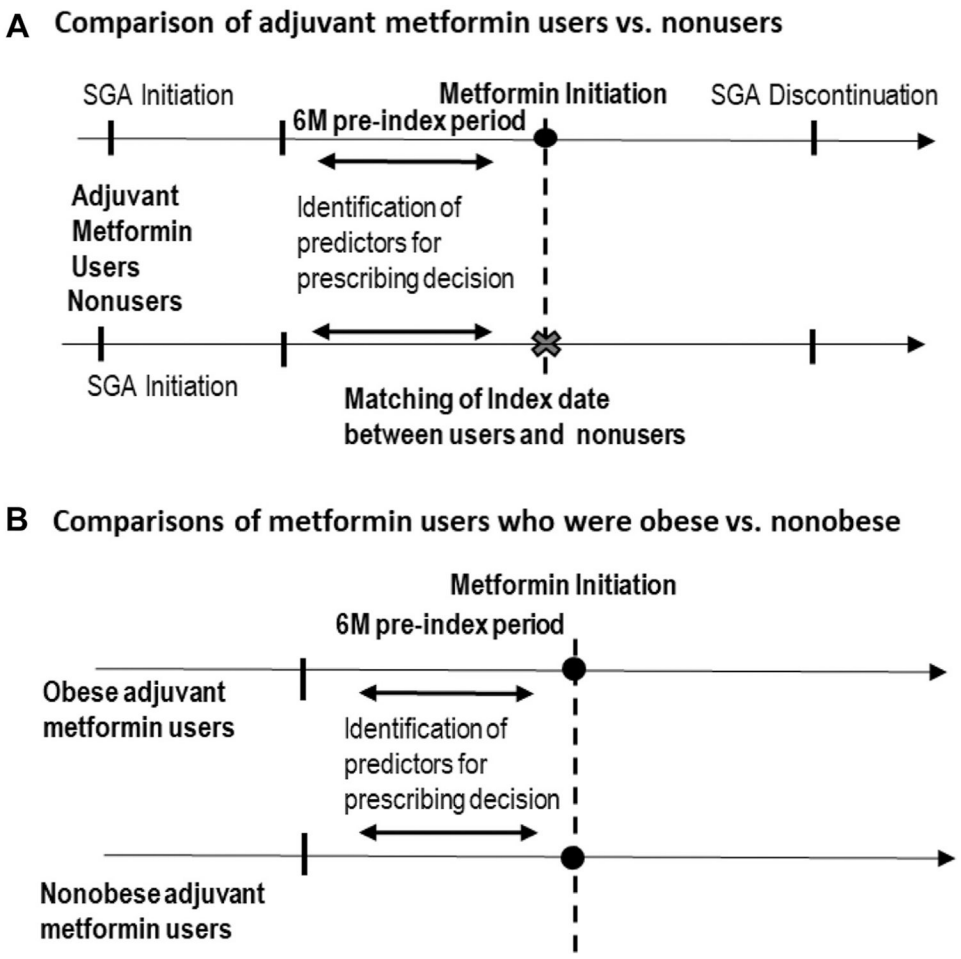

FIGURE 1. Study Design

Note: SGA = second-generation antipsychotic.

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TABLE 1

Characteristics of Metformin Users and Matched Nonusers on Duration of Second-Generation Antipsychotic (SGA) Exposure

	Metformin users (n = 597)		Nonusers (n = 1,194)		
	Mean	**(SD)**	**Mean**	**(SD)**	***P***
BMI z score	2.03	(0.6)	1.03	(1.2)	< .0001[a]
	n	**(%)**	**n**	**(%)**	
BMI z score velocity					< .0001[a]
Positive	134	(22.5)	336	(28.1)	
Negative	21	(3.5)	264	(22.1)	
Zero	237	(39.7)	302	(25.3)	
Unknown	205	(34.3)	292	(24.5)	
Age at index date					
5-11	163	(27.3)	488	(40.8)	< .0001[a]
12-17	415	(69.5)	674	(56.4)	
18-19	19	(3.2)	32	(2.6)	
Sex					< .0001[a]
Male	299	(50.1)	811	(67.9)	
Female	298	(49.9)	382	(31.9)	
Unknown	0		1	(0.1)	
Race/ethnicity					.2166
Asian	4	(0.7)	12	(1.0)	
Hispanic	2	(0.3)	3	(0.3)	
Non-Hispanic Black	74	(12.4)	128	(10.7)	
Non-Hispanic White	392	(65.6)	837	(70.1)	
Others	19	(3.2)	47	(3.9)	
Unknown	106	(17.7)	167	(13.9)	
Region					.0015[a]
South	279	(46.7)	538	(45.1)	
Midwest	124	(20.8)	335	(28.1)	
Northeast	128	(21.4)	190	(15.9)	

	Metformin users (n = 597)		Nonusers (n = 1,194)		
West	66	(11.1)	130	(10.9)	
SGA prescriber specialty					.0003[a]
PCP	213	(35.7)	483	(40.5)	
Mental health specialists[b]	134	(22.5)	176	(14.7)	
Others	159	(26.6)	310	(25.9)	
Unknown	91	(15.2)	225	(18.8)	
Nonpsychiatric comorbidities					
Hyperglycemia	148	(24.8)	70	(5.9)	< .0001[a]
Type 2 diabetes	57	(9.6)	8	(0.7)	< .0001[a]
Polycystic ovarian syndrome	29	(4.8)	5	(0.4)	< .0001[a]
Psychiatric diagnoses					
ADHD	325	(54.4)	705	(59.1)	.0630
Mood disorder	352	(58.9)	574	(48.1)	< .0001[a]
Anxiety disorder	264	(44.2)	406	(34.0)	< .0001[a]
Autism disorder	194	(32.5)	324	(27.8)	.0194[a]
Conduct disorder	184	(30.8)	409	(34.2)	.1455
Substance use disorder	42	(7.0)	74	(6.2)	.4972
Schizophrenia-related[c]	46	(7.7)	27	(2.3)	< .0001[a]
Tic disorder	24	(4.0)	57	(4.7)	.4693
Comedications					
Antidepressants					
Selective serotonin reuptake inhibitors	225	(37.7)	292	(24.5)	< .0001[a]
Serotonin norepinephrine reuptake inhibitors	36	(6.0)	30	(2.5)	.0004[a]
Tricyclic antidepressants	15	(2.5)	14	(1.1)	.0342[a]
Atypical antidepressants	32	(5.4)	42	(3.5)	.0648
Alpha-2 antagonist antidepressants	7	(1.2)	33	(2.8)	.0317[a]
ADHD medications					
Stimulants	185	(30.9)	404	(33.8)	.2266

	Metformin users (n = 597)		Nonusers (n = 1,194)		
Nonstimulants	111	(18.6)	188	(15.8)	.1277
Anxiolytics	92	(15.4)	167	(13.9)	.4193
Topiramate	31	(5.2)	25	(2.1)	.00041[a]
Weight loss medications[d]	10	(1.7)	9	(0.7)	.0728
Dietitian counseling	4	(0.7)	17	(1.4)	.1624
SGA switch	118	(19.8)	49	(4.1)	< .0001[a]
Lower risk to higher risk	68	(11.4)	31	(2.6)	< .0001[a]
Higher risk to lower risk	33	(5.5)	9	(0.5)	< .0001[a]
Same risk	36	(6.0)	11	(0.9)	< .0001[a]
Family history of diabetes mellitus	111	(18.5)	133	(11.2)	< .0001[a]
Index SGA					
Aripiprazole	236	(39.5)	387	(32.4)	.0029[a]
Risperidone	134	(22.5)	500	(41.8)	< .0001[a]
Quetiapine	56	(9.4)	178	(14.9)	.0011[a]
Olanzapine	66	(11.1)	57	(4.8)	< .0001[a]
Lurasidone	44	(7.4)	30	(2.5)	< .0001[a]
Ziprasidone	41	(6.8)	32	(2.7)	< .0001[a]
Paliperidone	9	(1.5)	8	(0.7)	.0849
Clozapine	3	(0.5)	1	(0.1)	.0768

Note: p values obtained via χ^2 test. ADHD = attention-deficit/hyperactivity disorder; BMI = body-mass index; PCP = primary care provider.

[a] Indication of statistical significance at .05 level.

[b] Mental health specialty includes child psychiatry, psychiatry, and psychology according to the code book of the IQVIA database.

[c] Schizophrenia-related diagnoses include schizophrenia, schizoaffective disorder, and psychosis.

[d] Weight loss medications include naltrexone-bupropion, liraglutide, orlistat, and phentermine-topiramate.

TABLE 2

Characteristics of Obese and Nonobese Metformin Users

	Obese users (n = 498)		Nonobese users (n = 99)		
	Mean	**(SD)**	**Mean**	**(SD)**	***P***
BMI z score	2.22	(0.3)	1.06	(0.6)	< .0001[a]
	n	**(%)**	**n**	**(%)**	
BMI z score velocity					< .0001[a]
Positive	88	(17.7)	46	(46.5)	
Negative	9	(1.8)	12	(12.1)	
Zero	229	(46.0)	8	(8.1)	
Unknown	172	(34.5)	33	(33.3)	
Age at index date					
5-11	131	(26.3)	32	(32.3)	.4703
12-17	351	(70.5)	64	(64.6)	
18-19	16	(3.2)	3	(3.0)	
Sex					.4520
Male	246	(49.4)	53	(53.5)	
Female	252	(50.6)	46	(46.5)	
Race/ethnicity					.6112
Asian	4	(0.8)	0		
Hispanic	2	(0.4)	0		
Non-Hispanic Black	65	(13.1)	9	(9.1)	
Non-Hispanic White	327	(65.7)	65	(65.7)	
Others	16	(3.2)	3	(3.0)	
Unknown	84	(16.8)	22	(22.2)	
Region					.5891
South	239	(47.9)	40	(40.4)	
Midwest	101	(20.3)	23	(23.2)	
Northeast	104	(20.9)	24	(24.2)	
West	54	(10.8)	12	(12.1)	

	Obese users (n = 498)		Nonobese users (n = 99)		
SGA prescriber specialty					.0003[a]
PCP	174	(34.9)	39	(39.4)	
Mental health specialists[b]	93	(18.7)	41	(41.4)	
Others	154	(30.9)	5	(5.1)	
Unknown	77	(15.4)	14	(14.1)	
Nonpsychiatric comorbidities					
Hyperglycemia	133	(26.7)	15	(15.2)	.0015[a]
Type 2 diabetes	55	(11.0)	2	(2.0)	.0053[a]
Polycystic ovarian syndrome	29	(5.8)	0		.0138[a]
Psychiatric diagnoses					
Mood disorder	286	(57.4)	66	(66.7)	.0879
ADHD	260	(52.2)	65	(65.7)	.0141[a]
Anxiety disorder	214	(42.9)	50	(50.5)	.1681
Autism disorder	160	(32.1)	34	(34.3)	.6674
Conduct disorder	150	(30.1)	34	(34.3)	.4059
Substance use disorder	34	(6.8)	8	(8.08)	.6560
Schizophrenia-related[c]	36	(7.2)	10	(10.1)	.3277
Tic disorder	18	(3.6)	6	(6.1)	.2578
Comedications					
Antidepressants					
Selective serotonin reuptake inhibitors	190	(38.2)	35	(35.4)	.5997
Serotonin norepinephrine reuptake inhibitors	31	(6.2)	5	(5.1)	.6539
Tricyclic antidepressants	11	(2.2)	4	(4.0)	.2876
Atypical antidepressants	29	(5.8)	3	(3.0)	.2598
Alpha-2 antagonist antidepressants	6	(1.2)	1	(1.0)	.8694
ADHD medications					
Stimulants	149	(29.9)	36	(36.4)	.2054
Nonstimulants	91	(18.3)	20	(20.2)	.6523
Anxiolytics	80	(16.1)	12	(12.1)	.3210
Topiramate	25	(5.0)	6	(6.1)	.6700

	Obese users (n = 498)		Nonobese users (n = 99)		
Weight loss medications[d]	8	(1.6)	2	(2.0)	.7695
Dietitian counseling	3	(0.6)	1	(1.0)	.6497
SGA switch	91	(18.3)	27	(27.3)	.0400[a]
Lower risk to higher risk	52	(10.4)	16	(16.1)	.1018
Higher risk to lower risk	23	(4.6)	10	(10.1)	.0292
Same risk	27	(5.4)	9	(9.1)	.1613
Family history of diabetes mellitus	92	(18.5)	19	(19.2)	.8668
Index SGA					
Aripiprazole	198	(39.7)	34	(34.3)	.3127
Risperidone	107	(21.5)	32	(32.3)	.0198[a]
Olanzapine	57	(11.5)	16	(16.2)	.1908
Quetiapine	57	(11.5)	15	(15.2)	.3011
Ziprasidone	44	(8.8)	8	(8.1)	.8079
Lurasidone	47	(9.4)	11	(11.1)	.6076
Paliperidone	8	(1.6)	2	(2.0)	.7695
Clozapine	5	(1.0)	2	(2.0)	.3910

Note: p values obtained via χ^2 test. ADHD = attention-deficit/hyperactivity disorder; BMI = body-mass index; PCP = primary care provider; SGA = second-generation antipsychotic.

[a]Indication of statistical significance at .05 level.

[b]Mental health specialty includes child psychiatry, psychiatry, and psychology according to the code book of the IQVIA database.

[c]Schizophrenia-related diagnoses include schizophrenia, schizoaffective disorder, and psychosis.

[d]Weight loss medications include naltrexone-bupropion, liraglutide, orlistat, and phentermine-topiramate.

TABLE 3

Predictors Associated With Prescribing Adjuvant Metformin to Pediatric Second-Generation Antipsychotic (SGA) Recipients

	Odds Ratio Estimates	
Effect	**Point Estimate**	**95% CI**
BMI z score	3.5	2.8-4.5
Sex		
Male vs female	0.5	0.4-0.7
Region		
Midwest vs West	0.4	0.2-0.7
Prescriber specialty		
Mental health specialist vs PCP	3.5	2.2-5.6
Family history of diabetes mellitus		
Yes vs no	1.5	1.1-2.4
SGA switch		
High-risk SGA to low-risk SGA vs no switch	9.9	3.5-27.5
Low-risk SGA to high-risk SGA vs no switch	4.1	2.1-7.9
Comorbidities		
Polycystic ovarian syndrome: yes vs no	6.2	1.7-22.5
Hyperglycemia/diabetes: yes vs no	5.3	3.4-8.3
Comedications		
SSRIs: yes vs no	1.6	1.1-2.2
Anxiolytics: yes vs no	0.5	0.3-0.7
Topiramate: yes vs no	2.7	1.1-7.0
Index SGA		
Olanzapine: yes vs no	2.2	1.2-4.2
Risperidone: yes vs no	0.5	0.4-0.8

Note: Factors included in this analysis were BMI z score, age, race, region, prescriber specialty, polycystic ovarian syndrome, hyperglycemia/diabetes, family history of diabetes, dietitian counseling, SSRIs, stimulants, anxiolytics, topiramate, weight loss medications, SGA switch, olanzapine, and risperidone. Only the statistically significant factors are included in the table. BMI = body mass index; PCP = primary care provider; SSRI, selective serotonin reuptake inhibitor.

TABLE 4

Predictors Associated With Prescribing Adjuvant Metformin to Nonobese vs Obese Pediatric Second-Generation Antipsychotic (SGA) Recipients

	Odds Ratio Estimates	
Effect	**Point Estimate**	**95% CI**
BMI z score velocity		
Positive vs negative/zero	3.5	1.8-6.7
Comorbidities		
Hyperglycemia/diabetes: yes vs no	0.4	0.2-0.9

Note: Factors included in this analysis were BMI z score velocity, age, race, region, prescriber specialty, polycystic ovarian syndrome, hyperglycemia/diabetes, family history of diabetes, dietitian counseling, selective serotonin reuptake inhibitors, stimulants, anxiolytics, topiramate, weight loss medications, SGA switch, olanzapine, and risperidone. Only the statistically significant factors are included in the table. BMI = body mass index.