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Original article

Association Between Second-Generation Antipsychotics and Changes in Body Mass Index in Adolescents

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A B S T R A C T

Purpose: To assess the association of second generation antipsychotics (SGAs) with changes in body mass index (BMI) among adolescents compared with a matched untreated comparison group.
Methods: A retrospective cohort study was conducted using an electronic medical record database between January 2004 and July 2009. Adolescents (12–19 years old), newly initiated on SGAs formed the exposure group and untreated adolescents formed the comparison group matched (3:1) to the antipsychotic group based on age, gender, and month of index SGA. Both the exposure and comparison groups were followed for slightly more than a year (395 days). Baseline and follow up BMI were evaluated for both groups and percentage change from baseline BMI to follow up BMI was calculated. Multivariate linear regression was conducted to assess the impact of SGAs on percent change in follow up BMI from baseline controlling for demographic characteristics, baseline medications, comorbidities, and other covariates.
Results: The mean percentage increase in follow up BMI from baseline for antipsychotic group was significantly higher than the comparison group ($p < .01$). After adjusting for covariates, adolescents on olanzapine had the highest percentage increase in follow up BMI from baseline (5.84%, 95% confidence interval [CI], 4.07–7.61) followed by aripiprazole (4.36%; 95% CI, 3.08–5.64), risperidone (3.65%; 95% CI, 2.61–4.68), and quetiapine (1.53%; 95% CI, .53–2.52) compared with the comparison group.
Conclusion: This study further validates a growing concern of increased BMI in adolescents on SGA therapy.

IMPLICATIONS AND CONTRIBUTION

Second generation antipsychotic treatment in adolescents is associated with significant increase in body mass index relative to a matched untreated comparison group in a predominantly primary care setting. This study provides estimates of differential impact of individual antipsychotics on change in body mass index accounting for age and gender related differences.

Second generation antipsychotics (SGAs), also known as atypical antipsychotics, are prescribed to adolescents in the United States as first line treatment for a variety of psychiatric and mood disorders [1–4]. The Food and Drug Administration granted pediatric exclusivity for SGAs such as olanzapine, aripiprazole, and risperidone in 2007, whereas quetiapine was approved for pediatric use in 2009. Ziprasidone, another SGA, although without pediatric exclusivity, is used off label in the pediatric population [5]. Although SGAs are associated with relatively lower side effects they have been noted for their potential of causing metabolic disturbances including obesity, dyslipidemia, and diabetes, leading to metabolic syndrome. Published clinical trials have reported an increased risk of

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weight gain among both preadolescent and adolescent pop ulations as a result of SGAs [6–9]. Recently, a meta analysis of randomized clinical trials conducted in children on SGAs revealed that the mean weight gain compared with placebo was highest for olanzapine (3.74 kg) followed by risperidone (1.72 kg), quetiapine (1.41 kg), and aripiprazole (.85 kg) [10]. Increased weight elevates the risk of adverse health outcomes both during childhood and growing into adulthood [11,12]. Although clinical trials have addressed the issue of weight gain resulting from antipsychotic treatment, none has compared the individual SGAs to assess the differential impact of weight gain among adolescents.

A naturalistic cohort study compared difference in metabolic changes associated with SGA treatment among children and adolescents with bipolar disorder and psychotic and nonpsy chotic disorders. The authors reported that 71% of patients had significant increases in weight and in body mass index (BMI) z scores [13]. A recent prospective cohort study conducted in 203 youths ages 4 to 19 years with 1 week or less of lifetime anti psychotic treatment reported that weight increased by 8.5 kg with olanzapine, by 6.1 kg with quetiapine, by 5.3 kg with ris peridone, and by 4.4 kg with aripiprazole compared with minimal weight change of .2 kg in the untreated comparison group [14]. Another retrospective cohort study evaluated Medicaid medical and pharmacy claims in children and adoles cents treated with antipsychotics found that antipsychotic treatment was associated with 2.13 times increased likelihood of obesity (odds ratio [OR], 2.13), compared with the untreated cohort [15].

There are limited retrospective studies comparing the differ ential risk of weight gain associated with SGAs in the adolescent population. The observational studies that have been conducted so far have either used short duration of treatment, used small comparison group, did not account for the gender related differences in BMI, or conducted studies that cannot be gener alizable to the national population. A real world retrospective study that assesses the differential impact of SGAs on weight gain in adolescent population is warranted. The goal of the current study is to compare the change in BMI among adolescents within 1 year of initiating antipsychotic treatment to the change in BMI among an age and gender matched, randomly selected, untreated comparison group.

Methods

Data source

The General Electric (GE) Centricity electronic medical record (EMR) database was used for this study. The GE EMR database includes approximately 10 million patients and comprises data collected during routine use of the EMR by more than 70 consortium member institutions located in more than 40 states. Several practice types are represented ranging from solo practi tioners to community clinics, academic medical centers, and large integrated delivery networks. The resulting research data base provides information reflective of the clinical data, medi cation lists (patient reported prescription and over the counter drug use), laboratory orders and results, and biometric readings. The EMR database is de identified, Health Insurance Portability and Accountability Act–compliant and has been used in previous health outcomes studies [16–18].

Study population

A retrospective cohort study design was used for this study. The study population consisted of adolescents on SGAs classified as the exposure group and untreated adolescents classified as the comparison group. Patients in the exposure or antipsychotic group were eligible for inclusion in this study if they (1) were 12–19 years old and, (2) had at least one prescription for any SGA between January 2004 and July 2009; (3) had at least one documented physician visit ≥540 days before the index date (defined later) and at least one documented physician visit ≥395 days after the index date; and (4) had no prescription for any antipsychotic agent during the 540 days before the index date (Figure 1). Patients in the exposure group were assigned an index date that was the date of their first prescription for anti psychotic medication. Patients in this group were categorized as exposed to individual SGAs depending on the type of antipsy chotic prescribed on index date. We limited the analysis to antipsychotic naive patients (i.e., no prescription during the pre index period of 540 days) to increase the chances of identifying fresh starts on antipsychotic treatment. Patients who received a prescription for an antipsychotic during the follow up period (defined later) that was different from the index antipsychotic agent were excluded. Specifically, a patient must have received the same antipsychotic agent as the index agent throughout the follow up period. However, this criterion does allow for the possibility of more than one prescription of the same agent in the follow up period as the index agent. We therefore defined these patients as being on "monotherapy." Only a relatively small proportion of exposed patients (10%) switched antipsychotic medications or was prescribed more than one antipsychotic other than the index antipsychotic during the follow up period and were thus excluded from this study.

The comparison group was identified based on presence of an activity (medical visit or prescription) in the GE EMR database and no prescriptions for any SGA. Patients in the comparison group were eligible for inclusion in this study if they (1) were12–19 years old; (2) had no prescription for any antipsy chotic agent between January 2004 and July 2009; and (3) had at least one documented physician visit ≥540 days before the index date and at least one documented physician visit ≥395 days after the index date. The index date in comparison group was defined as the date of first physician visit after a pre index period of 540 days.

Both the exposure and comparison group were followed for a period of 395 days from the index date, defined as the follow up period. A follow up period of 395 days was used to account for any gaps in therapy and to allow 30 days follow up period for antipsychotic prescriptions prescribed closest to the 365th day. We restricted analysis to patients with a documented physician visit at least 540 days before index date and at least one docu mented physician visit 395 days after index date. This was done to ensure that patients were active participants in the health care system and were regularly visiting the physician during this period. This methodology has been applied in previous publi cations based on the GE database [16–18]. The final comparison group population consisted of individuals who were matched (3:1) to the antipsychotic group through a stratified, random sampling procedure based on age, gender, and month of activity. A matching ratio of 3:1 is considered optimal in observational studies and it is generally known that little power is gained with matching in excess of 3:1.

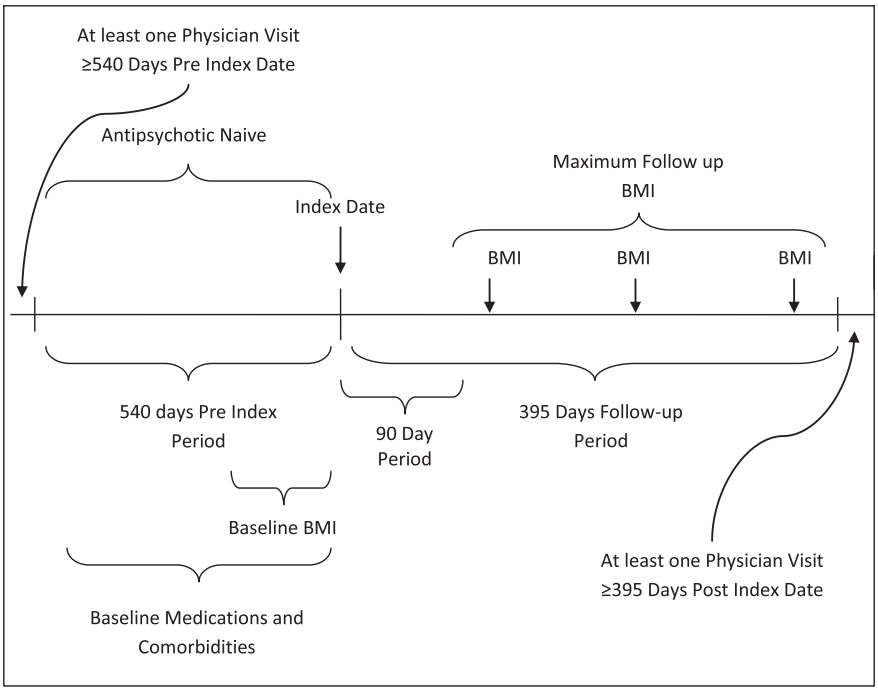

Figure 1. Schematic of study design.

The National Heart Lung and Blood Institute Adult Treatment Panel (ATP) III guidelines [19] and the International Diabetes Federation [20] use waist circumference as a measure of central or abdominal obesity. However, waist circumference is rarely available in clinical data. Several published studies have sug gested that BMI and waist circumference are highly correlated to each other [21–24]. Therefore, BMI calculated from a patient's height and weight data was used in this study as a proxy because waist circumference was not available in the GE EMR database. The EMR was examined for the presence of baseline and follow up BMI measurements. Baseline BMI measurements were defined as those that occurred in the 30 days before the index date. BMI measurements that occurred 90 days post index date through the end of follow up period were categorized as follow up measurements. Only those patients with baseline and at least one follow up BMI measurement were included in the analysis. An average of baseline values was taken if more than one existed during the 30 day pre index period. Follow up BMI measure ments were categorized to each month depending on the date of BMI measurement and number of days from index date. An average of BMI values was taken if more than one BMI measurement was present in a particular month. The maximum BMI value during the follow up period was identified and the mean difference and percentage change in baseline to maximum follow up BMI was calculated. Excess weight for children and adolescents is defined based on the year 2000 Centers for Disease Control and Prevention gender specific BMI for age growth charts [25]. Children and adolescents with BMI <5th percentile are considered underweight, 5th to 85th percentile are normal weight, 85th to 95th percentile are considered overweight and those at and beyond the 95th percentile are considered obese [26]. Gender specific growth charts were used to categorize patients as underweight, normal weight, overweight, or obese at baseline and at follow up.

Demographic characteristics such as age and gender, region, insurance type, medications, and comorbid conditions were identified during the pre index period. Insurance type and geographic region (Northeast, Southeast, Midwest, and West) were identified to examine the baseline differences by insurance type and regional variation. Medications other than SGAs that may influence BMI such as beta blockers, antiobesity drugs, anorexiants, oral antidiabetic agents that cause weight gain (such as human insulin, sulphonylureas, and thiazolidinediones) or weight loss (such as incretin mimetic agents and biguanides), antidepressants, anticonvulsants, and corticosteroids were iden tified among all patients using prescription orders during the pre index period. Comorbid conditions that may influence BMI such as dyslipidemia, hypertension, obesity, hypothyroidism, and type 2 diabetes; psychiatric conditions such as schizophrenia, depression, bipolar disorder, and other mental illness; and miscellaneous diagnosis were identified using ICD 9 codes during the pre index period.

Analysis

Test of proportions was used to evaluate the differences in baseline demographics, baseline medications, and baseline comorbidities between the exposed and comparison groups. Student's t test with unequal variances was used to evaluate the differences in age, baseline BMI, maximum follow up BMI, mean difference, and percentage change in baseline to follow up BMI between the exposed and comparison groups. Test of propor tions was used to evaluate the differences in proportion of underweight, normal weight, overweight, and obese at baseline and follow up. Finally, multivariate linear regression analysis was conducted to assess the impact of SGA exposure on percentage change in maximum follow up BMI from baseline BMI controlling for demographic characteristics, baseline BMI,

baseline medications, baseline comorbid conditions, number of follow up BMI measurements, number of months to maximum follow up BMI, and year of index prescription. Analyses were performed using STATA Version 10.0 (StataCorp, Stata Statistical Software: Release 10. College Station, TX). This study was approved by the institutional review board at the University of Utah on September 24, 2010.

Results

A total of 7,967 adolescents with at least one prescription for SGAs and 669,207 adolescents without SGAs were identified in the GE EMR database between January 2004 and July 2009 (Figure 2). The final exposed group consisted of 793 patients with at least one BMI recorded at 90 days or more following their index antipsychotic prescription, whereas the final comparison group consisted of 2,374 randomly selected patients matched to the antipsychotic group based on gender, age, and month of index antipsychotic prescription.

Demographics and comorbidities

Table 1 presents the demographics, medication use, and comorbidities among the exposed and comparison group. The antipsychotic group had significantly higher proportion of patients from the Northeast, Southeast, Medicare, and Medicaid insurance ($p < .01$). Also, the antipsychotic group had significantly higher proportion of patients with baseline medications, comor bidities, psychiatric conditions, and other conditions ($p < .05$).

Baseline and follow up BMI values in exposed and comparison group

Table 2 presents summary statistics for the baseline and follow up BMI values among the comparison group, antipsy chotic group, and antipsychotic group stratified by individual antipsychotic agents. Overall, the exposure group had signifi cantly higher mean baseline BMI, follow up BMI, mean differ ence, and percent change from baseline to follow up BMI. The

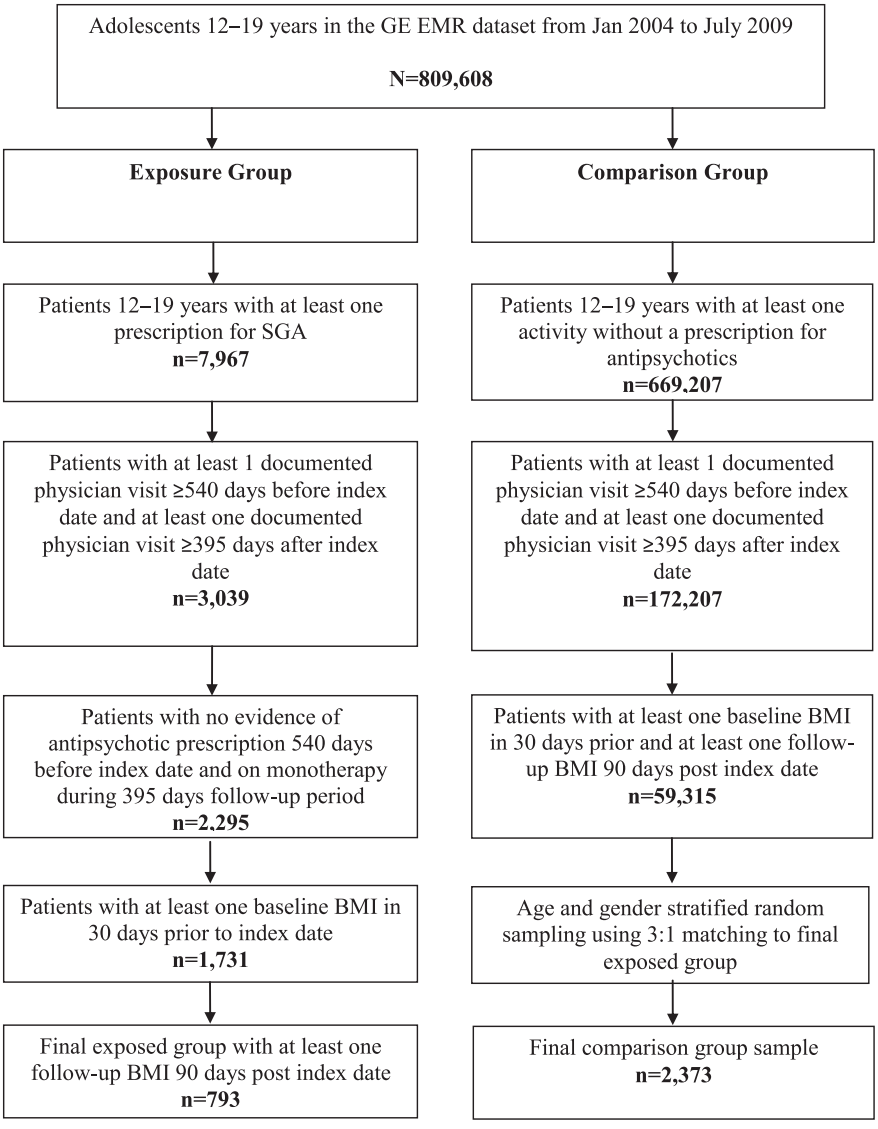

Figure 2. Flowchart of patient selection.

Table 1
Demographics, medication use, and comorbidities in exposed and comparison group adolescents, 2004 2009

	Comparison group		Exposure group		*p* value
	n 2,373		n 793		
	n	%	n	%	
Mean age (SD)	15.35 (2.27)		15.35 (2.28)		.928
Gender					
Males	1,248	52.59	418	52.71	.953
Females	1,125	47.41	375	47.29	.953
Region					
Northeast	436	18.37	197	24.84	<.001
Southeast	823	34.68	371	46.78	.006
Midwest	453	19.09	117	14.75	<.001
West	661	27.86	108	13.62	<.001
Insurance type					
Commercial	1,159	48.84	370	46.66	.287
Medicaid	119	5.01	145	18.28	<.001
Medicare	3	.13	10	1.26	<.001
Self-pay	46	1.94	12	1.51	.440
Other/unknown	1,046	44.08	256	32.28	<.001
Baseline medications					
Beta blockers	0	0.00	14	1.77	<.001
Oral antidiabetics	3	.13	15	1.89	<.001
Antidepressants	2	.08	30	3.78	<.001
Anticonvulsants	0	0	62	7.82	<.001
Corticosteroids	17	.72	59	7.44	<.001
Baseline comorbid conditions					
Dyslipidemia	25	1.05	13	1.64	.190
Hypertension	4	.17	6	.76	.011
Obesity	72	3.03	63	7.94	.011
Hypothyroidism	6	.25	8	1.01	<.001
Type 2 diabetes	7	.29	56	7.06	<.001
Psychiatric conditions					
Schizophrenia	0	0.00	4	.50	<.001
Bipolar disorder	9	.38	66	8.32	<.001
Depression	4	.17	31	3.91	<.001
Other mental illness[a]	167	7.04	379	47.79	.000
Miscellaneous diagnosis[b]	285	12.01	299	37.70	.000

[a] Mental illness was identified using ICD-9 codes 290 to 294 and 297 to 319.
[b] Miscellaneous diagnosis consists of ICD-9 codes 780 to 799.

time in months to maximum BMI value was significantly shorter, and the numbers of BMI measurements were greater in the exposed group compared with the group not prescribed SGAs.

Among the individual antipsychotic agents, the mean base line BMI among patients on olanzapine and risperidone was similar to the comparison group ($p > .05$). However, patients on ziprasidone, aripiprazole, and quetiapine had higher baseline BMI compared with the group not prescribed SGAs. Adolescents on individual antipsychotic agents had a significant percentage increase ($p < .01$) in follow up BMI from baseline except for patients prescribed ziprasidone where the percentage increase was not significant (p .211) compared with those not prescribed SGAs.

Linear regression results

Table 3 presents the adjusted linear regression results for percent change in BMI from baseline to follow up among adolescents on individual antipsychotic agents compared with the group not prescribed SGAs adjusting for demographic char acteristics, baseline medications, baseline comorbid conditions, year of index date, number of follow up BMI measurements, and time in months to maximum follow up BMI. Adolescents on olanzapine had the highest percentage increase in BMI during the 395 day follow up period (5.84%, 95% confidence interval [CI], 4.07–7.61). Patients on aripiprazole had a 4.36% (95% CI, 3.08–5.64) increase followed by risperidone (3.65%; 95% CI, 2.61–4.68) and quetiapine (1.53%; 95% CI, .53–2.52) compared with the comparison group. The small number of adolescents on ziprasidone did not show a statistically significant change in BMI.

Baseline BMI was significantly associated with percentage change in baseline to follow up BMI. Although not statistically significant, adolescents who were underweight had a 1.2% increase in baseline to follow up BMI compared with normal weight adolescents. However, adolescents who were normal weight gained more weight compared with overweight and obese adolescents. Normal weight adolescents had .96% increase in baseline to follow up compared with overweight and 1.42% increase in follow up BMI compared with obese adolescents.

Discussion

The purpose of the study was to assess the association of SGAs with changes in BMI among adolescents compared with a strat ified random age and gender matched untreated comparison group. Prescription of olanzapine was associated with significant changes in BMI after initiating antipsychotic treatment followed by aripiprazole, risperidone, and quetiapine compared with the untreated comparison group. Adolescents prescribed ziprasi done did not show significant changes in BMI compared with the untreated comparison group, probably because of the small sample size, but also consistent with other studies conducted in adults where ziprasidone had the lowest risk of weight gain [27,28]. Olanzapine was shown to have the greatest increase in BMI and these results are also consistent with previous studies. The results that aripiprazole was associated with significant increase in BMI second to olanzapine were surprising based on previous literature supporting a decreased effect of aripiprazole on BMI [14]. A possible rationale for these results is that the aripiprazole cohort had a higher proportion of obese (37%) patients at baseline and may thus have a tendency to gain weight, leading to channeling bias in prescribing. Antipsychotics with lowest risk of weight gain are often prescribed to prevent further increase in BMI among obese patients. We controlled for baseline BMI in the regression model; however, lifestyle factors including diet and exercise and other unmeasured confounding factors may also have played a role, resulting in an increased change in BMI among patients receiving aripiprazole. Patients prescribed quetiapine had the lowest percentage change in follow up BMI from baseline BMI compared with the comparison group and those on other antipsychotics.

The results indicate that adolescents on antipsychotics increased BMI in a shorter duration of time compared with the comparison group. Adolescents on antipsychotics increased 7% of baseline BMI in 8 months of initiating antipsychotic treatment, whereas those in comparison group increased 3% of baseline BMI in 9 months. As a confirmatory analysis, we further examined the mean changes in weight and height separately in the corre sponding time periods. Specifically, for the adolescents on anti psychotics weight increased by 8.93 pounds and height increased by .55 inches, whereas the comparison group gained 5.03 pounds in weight and .63 inches in height. These figures generally support our findings on BMI increase as reported previously. The results of this study were consistent with the previously discussed prospective cohort study where olanzapine,

Table 2
Summary statistics for baseline and follow up BMI values among exposed and comparison group adolescents, 2004 2009

	Comparison group N 2,373		Antipsychotic group N 793		Antipsychotic group N 793									
					Aripiprazole		Olanzapine		Risperidone		Quetiapine		Ziprasidone	
					N 158		N 74		N 255		N 286		N 20	
	N	N%	N	N%	N	N%	N	N%	N	N%	N	N%	N	N%
Mean baseline BMI (SD)	23.81 (5.23)		24.68 (6.41)*		26.09 (6.88)*		24.51 (6.15)		23.21 (5.80)		24.95 (6.35)*		29.08 (7.32)*	
Underweight[a]	40	1.69	29	3.66*	2	1.27	6	8.11*	11	4.31*	10	3.50**	0.0	.00
Normal weight[b]	1,473	62.07	429	54.1*	78	49.37*	40	54.05	150	58.82	154	53.85*	7	35.00**
Overweight[c]	407	17.15	123	15.51	18	11.39	11	14.86	44	17.25	48	16.78	2	10.00
Obese[d]	453	19.09	212	26.73*	60	37.97*	17	22.97	50	19.61	74	25.87*	11	55.00*
Mean follow-up BMI (SD)	24.57 (5.44)		26.25 (6.88)*		28.01 (7.29)*		26.60 (7.09)*		24.82 (6.13)		26.20 (6.95)*		29.93 (6.94)*	
Underweight	19	.8	14	1.77*	2	1.27	3	4.05*	1	.39	8	2.80*	0.0	.00
Normal weight	1,362	57.4	375	47.29*	61	38.61*	33	44.59**	135	52.94	141	49.30*	5	25.00*
Overweight	468	19.72	140	17.65	22	13.92	15	20.27	55	21.57	44	15.38	4	20.00
Obese	524	22.08	264	33.29*	73	46.20*	23	31.08	64	25.10	93	32.52	11	55.00*
Mean difference (baseline to max follow-up BMI) (SD)	.76 (1.72)		1.57 (2.26)*		1.93 (2.68)*		2.09 (2.42)*		1.61 (2.03)*		1.25 (2.04)*		.85 (2.95)	
Mean percentage increase (baseline to max follow-up BMI) (SD)	3.40 (6.95)		6.63 (9.07)*		7.88 (10.40)*		8.50 (9.57)*		7.34 (9.03)*		5.02 (7.69)*		3.97 (11.25)	
Mean Baseline Height in inches (SD)	65.18 (4.33)		64.41 (4.44)*		64.49 (4.20)		65.96 (4.44)		63.90 (4.79)*		64.39 (4.25)*		64.69 (3.27)	
Mean baseline weight in pounds (SD)	142.65 (39.31)		145.10 (45.97)		152.53 (48.98)*		154.17 (49.75)**		135.41 (44.96)*		146.17 (43.19)		160.93 (38.31)**	
Mean follow-up height in inches (SD)	65.81 (4.17)		64.96 (4.23)*		65.03 (4.01)**		66.21 (4.21)		64.63 (4.57)*		64.88 (4.06)*		65.21 (3.47)	
Mean follow-up weight in pounds (SD)	147.68 (39.36)		154.03 (47.70)*		162.22 (48.88)*		164.96 (53.49)*		144.96 (45.85)		153.24 (45.81)**		174.29 (44.46)*	
Mean baseline BMI z score	.65 (1.02)		.70 (1.21)		.98 (1.12)*		.46 (1.42)		.53 (1.17)*		.71 (1.20)		1.42 (1.08)*	
Mean follow-up BMI z score	.82 (.97)		.99 (1.11)*		1.29 (1.04)*		.86 (1.28)		.90 (1.02)		.91 (1.15)		1.56 (1.00)*	
Mean follow-up time to max BMI (months) (SD)	8.83 (2.39)		7.99 (2.92)*		7.99 (2.98)*		7.55 (3.04)*		8.17 (2.88)*		7.93 (2.85)*		8.00 (3.58)	
Mean number of BMI measurements after 90 days index Rx (SD)	2.08 (1.34)		2.70 (1.71)*		2.96 (1.87)*		2.35 (1.74)		2.47 (1.45)*		2.83 (1.77)*		3.00 (2.15)*	

Test of proportions were used to compare the individual antipsychotics to the comparison group.
BMI body mass index.
[a] Underweight: BMI <5th percentile.
[b] Normal weight: BMI ≥5th to <85th percentile.
[c] Overweight: BMI ≥85th to <95th percentile.
[d] Obese; BMI ≥95th percentile.
* $p < .01$.
** $p < .05$.

aripiprazole, risperidone, and quetiapine were associated with significant increases in weight among adolescents [14].

The public health implications of adolescent patients on anti psychotic drugs and its associated cardiometabolic adverse effects are substantial. At present obesity is a serious health concern among all adolescents. Weight gain is associated with long term health risks of obesity, type 2 diabetes, hyperlipidemia, and hypertension [29]. Children and adolescents who are obese are more likely to become obese adults. A study published by Whi taker et.al. found that approximately 80% of children who were overweight at age 10–15 years were obese adults at age 25 years [30]. In addition, childhood obesity is associated with adult cardiovascular adverse outcomes and impaired glucose tolerance [31–34]. If weight gain among adolescents on antipsychotics is not prevented or minimized, it may result in high burden and increased use of limited health resources to treat obesity related diseases in addition to mental health issues when these adoles cents become adults. Also, obesity and mental illness may result in serious consequences on the quality of life of adolescents.

Interestingly, normal weight adolescents on antipsychotics gained proportionally more during the follow up period compared with the overweight and obese adolescents. Physi cians may be more aggressively monitoring weight and taking steps to decrease weight gain in the overweight and obese adolescents on antipsychotics than their normal weight coun terparts. It is important to monitor BMI systematically in adolescents on antipsychotics. Adolescents experiencing signif icant weight gain after initiating antipsychotic treatment should be referred to weight management programs to prevent tran sitioning from normal weight to overweight or obese.

Strengths and limitations

The primary strength of this study is that actual clinical measures such as BMI values from an EMR database were used to assess change in weight among adolescents on antipsychotics. Previous studies have used current ICD 9 codes from adminis trative claims data and not actual clinical measures to assess obesity/weight gain in adolescents on antipsychotics [15], which may have resulted in reporting conservative estimates. ICD 9 codes for obesity are not frequently used, and patients who became obese after antipsychotic treatment may have been missed. Also, ICD 9 codes define obesity as BMI above 30 kg/m^2, which may not apply to adolescents in which overweight and obesity is defined based on BMI percentiles compiled on growth charts from the Centers for Disease Control and Prevention [25].

Table 3
Adjusted linear regression coefficients for percentage change in baseline to maximum follow-up BMI in adolescents, 2004 2009

	Adjusted percentage change (%)[a]	95% CI		*p* value
Baseline BMI				
Normal weight (<85th percentile)	*ref*			
Underweight (<5th percentile)	1.20	−.57	2.96	.184
Overweight (≥85th to <95th percentile)	−.95	−1.65	−.24	.008
Obese (≥95th percentile)	−1.41	−2.07	−.74	<.001
Treatment				
Comparison group	*ref*			
Aripiprazole	4.36	3.08	5.64	<.001
Olanzapine	5.84	4.07	7.61	<.001
Risperidone	3.65	2.61	4.68	<.001
Quetiapine	1.53	.53	2.52	.003
Ziprasidone	.99	−2.32	4.30	.559
Gender				
Males	*ref*			
Females	−.25	−.78	.29	.364
Age in years	−.33	−.45	−.21	<.001
Region				
Northeast	*ref*			
Midwest	.16	−.56	.88	.664
South	−.29	−1.13	.55	.501
West	−.09	−.88	.71	.828
Insurance				
Commercial	*ref*			
Medicaid	−.65	−1.62	.33	.194
Medicare	−3.37	−7.42	.68	.103
Self-pay	−.37	−2.29	1.56	.710
Unknown	.18	−.39	.75	.535

BMI body mass index; ref reference.
[a] Adjusted for baseline medications, baseline comorbidities, psychiatric conditions, other conditions, number of follow-up BMI values, year of index prescription or activity, and number of months to maximum follow-up BMI.

Another strength of the study is the use of a national population and age and gender matched stratified random comparison group. Previous study has reported absolute change in BMI without adjusting for or matching the comparison group to the treatment group by gender and therefore did not account for gender related differences in BMI.

There are several limitations with this study. A key limitation is that prescriptions in an EMR database are tracked by prescription orders and medication lists and not by actual prescriptions filled at the pharmacy. We cannot be entirely sure if patients are filling and taking medications prescribed to them. Because of this limitation misclassification of exposure may occur. Patients with at least one prescription order for index SGA were considered to be on the drug during the follow up period. This may have resulted in misclassifying patients as antipsychotic users even if the drug was not taken throughout the follow up period and creating a bias toward no effect of the drug upon weight. Further, because of data limitations, it is unknown whether the adoles cents who were prescribed antipsychotic medication actually took them; therefore, it is possible that the magnitude of BMI increase in this group was underestimated. As a result, antipsy chotic medication may have an even greater impact on increasing the BMI trajectory in adolescents who take them.

Another limitation of the database is that it is predominantly a primary care physician network and, therefore, health care received outside of the primary care setting may not be captured in the database. We are probably studying antipsychotic users that are relatively less sick compared with those patients seeking care from psychiatrists. However, an increasing number of primary care physicians are prescribing antipsychotic drugs to children on the front line when it comes to diagnosing and treating mental disorders. Missing BMI values in the GE EMR database are another limitation for this study, but we have no evidence that inclusion of BMI values are associated with SGA prescription and assume that the bias is nondifferential. Infor mation on race is not widely available in the EMR database and was therefore not used in this study; this is a limitation of this study because higher proportion of those on SGAs was from the southern region of the United States, where a higher proportion of African American and Hispanics reside. Therefore, it is likely that the exposed group contained more adolescents from these two groups, which are known to have higher rates of overweight and obesity. However, we did adjust for region, coded as Northeast, Midwest, West, and South, in the regression model, which may have indirectly controlled for the varying proportion of racial groups by region. Although, we adjusted for ADHD diagnosis included in other mental illness, we may not have completely adjusted for the potent anorectic effects of individual stimulant medications on weight, which is a limitation of this study. Finally, the database lacks information on socioeconomic status, diet, physical activity, and overall health of patient's parents. These unmeasured variables may have played a role in impacting the weight of adolescents in the data.

SGA treatment in adolescents is associated with significant increase in BMI relative to a matched comparison group.

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