



Real World Impact of Second-generation Antipsychotics on Weight Gain in an Adolescent Population

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ABSTRACT

Purpose: Second-generation antipsychotics (SGAs) are associated with weight gain in adolescent populations. Body Mass Index (BMI) has been studied in clinical trials with limited comparison between drugs. Using a national electronic medical record (EMR) database, the real-world impact of SGAs on BMI in adolescents taking antipsychotics was evaluated.

Methods: This was a retrospective database analysis employing data from a consortium of 5,000 physicians using GE Healthcare CPO EMR to document care for five million patients. Naive monotherapy patients (12-19 years) receiving an antipsychotic prescription between February 2001 and March 2006 were identified; patients on clozapine or depot antipsychotic were excluded. Baseline BMI recorded within less than 180 days prior to first prescription and closest to index date was compared with maximum BMI obtained within 365 days after first antipsychotic prescription. Regression analysis was used to estimate adjusted mean differences between baseline and post-prescription BMI for each SGA compared with all first generation antipsychotics (FGAs), controlling for age, gender, psychiatric diagnosis, baseline BMI, medications thought to promote weight gain or weight loss, and geographic region of residence. Logistic regression was used to determine predictors of increased BMI (5% or more), using aripiprazole as the reference drug group and controlling for covariates.

Results: A total of 679 eligible patients were identified; mean age was 15.7 years and 55.2% were female. The sample contained 36.5% patients on any FGA (mean baseline BMI [MBB], 25.8), 6.6% on aripiprazole (MBB, 25.1), 17.5% on olanzapine (MBB, 25.3), 17.7% on quetiapine (MBB, 25.1), 20.0% on risperidone (MBB, 24.3), and 1.6% on ziprasidone (MBB, 30.6). Compared with FGAs, patients on olanzapine had a statistically significant mean increase in BMI of 5 kg/m² (95% confidence interval [CI], 0.15-1.94). Aripiprazole (CI, -1.90-0.42), quetiapine (CI, -1.00-0.62), and risperidone (CI, -0.42-1.18) did not show any significant increase in BMI. When BMI increase was categorized as 5% or more vs less than 5%, logistic regression results showed a similar trend. Patients on olanzapine were 2.32 (CI, 1.08-5.01, *P*<0.03) times more likely to have a post-index BMI of 5% or more compared to aripiprazole.

Conclusions: Antipsychotics differ in propensity to cause weight gain in adolescents. Antipsychotics without weight gain potential should be considered especially in adolescents who are overweight or at risk for overweight.

Educational Objective: This work provides a foundation for the understanding of how second generation antipsychotics impact weight gain in adolescent patients treated in a real-world environment as opposed to a clinical trial. This information is useful in initiating SGA therapy in patients where weight gain may have a negative impact on patient outcomes.

BACKGROUND

- Second-generation antipsychotics (SGAs) are associated with weight gain in adolescent populations^{1,2}
- Body Mass Index (BMI) has been studied in clinical trials in adolescents with limited head-to-head comparison between drugs
- We hypothesized that patients treated with SGAs would have differential risk of weight gain

OBJECTIVES

- To evaluate the real-world impact of antipsychotics on weight gain in adolescents
- To evaluate the impact of individual SGAs, relative to first-generation antipsychotics (FGAs) on adolescent weight

METHODS

Study Population

- The primary data source used for this project was the GE Centricity research database
- Centricity is an electronic medical record (EMR) system

METHODS (continued)

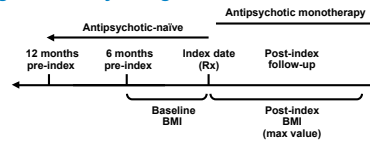
that enables ambulatory care physicians and clinical staff to document patient encounters, streamline clinical workflow, and securely exchange clinical data with other providers, patients, and information systems

- Centricity EMR (Logician, Version 4.6, Hillsboro, Oregon, MedicalLogic/Medscape, Inc., 1994) is used by over 20,000 clinicians to manage about 30 million patient records in 49 states, making it a widely used ambulatory care EMR
- A subset of over 5,000 physicians and other providers using Centricity contribute to the medical quality improvement consortium (MQIC) to create a research database

Study Design

- Naive monotherapy adolescent patients (12-19 years) receiving an antipsychotic prescription between February 2001 and March 2006 were identified
- Date of this prescription was called the index date
- Patients were followed only if they were on monotherapy post-index date
- Baseline BMI was recorded within less than 180 days prior to first prescription and closest to index date
- Post-index date BMI was recorded as the maximum BMI obtained in the monotherapy follow-up period post-index date (Figure 1)
- Patients on clozapine or depot antipsychotic were excluded

Figure 1. Study Design



Statistical Analysis

- Linear regression analysis was used to estimate the impact of antipsychotic therapy initiation on post-prescription BMI for each SGA compared with the FGA group
- In addition, logistic regression analysis was used to estimate the impact of antipsychotic therapy initiation on clinically significant weight gain for each SGA and the FGA group compared with aripiprazole
 - Clinically significant weight gain was defined as an increase of 5% or more in the value of post-index date BMI compared to baseline BMI (pre-index BMI) and was coded as 1 (<5% was coded as zero)
- Both multivariate analyses controlled for age, gender, psychiatric diagnosis, baseline BMI, medications thought to promote weight gain or weight loss, and geographic region of residence
 - Weight gain drugs included hormonal agents, cyclophosphamide, methotrexate, fluorouracil, antidepressants, antidiabetic agents, anticonvulsants, and corticosteroids; weight loss drugs included stimulants and anti-obesity agents

RESULTS

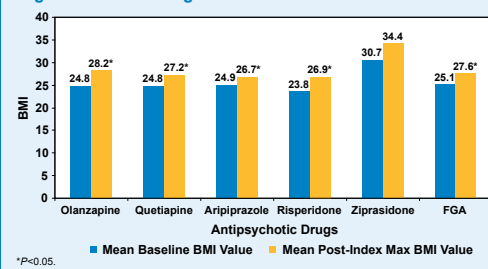
Summary Statistics

- Summary statistics are provided in Table 1 and Figures 2 and 3
- A total of 679 eligible patients were identified; mean age was 15.7 years and 55.2% were female; mean follow-up time after index date was 27 months
- The sample contained 36.5% patients on any FGA, 17.5% on olanzapine, 17.7% on quetiapine, 6.6% on aripiprazole, 20.0% on risperidone, and 1.6% on ziprasidone
- For all medication groups, mean post BMI was higher after initiation of therapy compared with baseline BMI
- Mean percent change between pre- and post-therapy BMI was smallest in the case of aripiprazole (7.4%) and largest in the case of olanzapine (13.7%)

Table 1. Summary Statistics

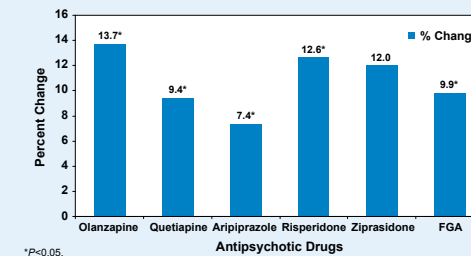
	Variables	N=679	% or Mean (SD)
	Max post-index BMI		27.80 (7.47)
	Baseline BMI		24.83 (6.70)
	Follow-up period on index medication (months)		27.39 (16.64)
Demographics	Age (12-19)		15.71 (2.34)
	Females	375	55.23%
Antipsychotic Drugs	FGA	248	36.52%
	Olanzapine	119	17.53%
	Quetiapine	120	17.67%
	Aripiprazole	45	6.63%
	Risperidone	136	20.03%
	Ziprasidone	11	1.62%
Concomitant Medications	Promoting weight gain	4	0.59%
	Promoting weight loss	11	1.62%
Psychiatric Diagnosis	Depression	253	35.17%
	Bipolar	130	19.15%
	Schizophrenia	11	1.62%
	Other	86	12.67%
Region	West	27	3.98%
	Northeast	226	33.28%
	Midwest	113	16.64%
	South	313	46.10%
Adverse Event	≥5% increase in BMI	433	63.77%

Figure 2. Mean Change Between Pre- and Post-BMI



RESULTS

Figure 3. Percent Change in Mean Pre- and Post-BMI



Linear Regression Analysis

- Linear regression results are presented in Table 2
- Compared with FGAs, patients on olanzapine had a statistically significant mean increase in BMI of 1.05 kg/m² (95% confidence interval [CI], 0.15-1.94)
- Aripiprazole (CI, -1.90-0.42), quetiapine (CI, -1.00-0.62), and ziprasidone (CI, -0.99-3.36) did not show a significant increase in BMI; risperidone (CI, -0.42-1.18) tended towards weight increase compared to FGAs
- Patients with a diagnosis of schizophrenia were significantly more likely to have increased BMI (CI, 1.05-5.27), compared to those without a diagnosis for schizophrenia

Table 2. Linear Regression Results (Dependent Variable: Maximum BMI Post-index Date)

	Variables	Adjusted Coefficients	P value	95% CI
Antipsychotic Drugs	FGA	1.0 (ref)		
	Olanzapine	1.05*	0.02	0.15 1.94
	Quetiapine	-0.19	0.65	-1.00 0.62
	Aripiprazole	-0.74	0.21	-1.90 0.42
	Risperidone	0.38	0.35	-0.42 1.18
	Ziprasidone	1.19	0.28	-0.99 3.36
	Demographics	Females	1.0 (ref)	
	Males	-0.34	0.26	-0.92 0.24
	Age	-0.09	0.16	-0.22 0.04
	Baseline BMI	0.98**	<0.001	0.93 1.02
Psychiatric Diagnosis	Depression	0.39	0.19	-0.19 0.98
	Bipolar	-0.65	0.08	-1.38 0.09
	Schizophrenia	3.16**	0.003	1.05 5.27
	Other	0.24	0.56	-0.58 1.06
Concomitant Medications	Promoting Weight Gain	-0.75	0.67	-4.21 2.71
	Promoting Weight Loss	0.23	0.84	-1.91 2.36
Region	West	1.0 (ref)		
	Northeast	-0.33	0.42	-1.13 0.47
	Midwest	-0.17	0.59	-0.80 0.46
	South	-0.81	0.26	-2.21 0.59

P*<0.01; *P*<0.05.

Logistic Regression Analysis

- Logistic regression results are presented in Table 3
- Patients on olanzapine were 2.32 (CI, 1.08-5.01) times more likely to have a post-index BMI of 5% or more compared to baseline BMI using aripiprazole as the referent group (*P*=0.03)
- Patients on risperidone were 1.52 (CI, 0.75-3.11) times more likely to have a post-index BMI of 5% or more compared to baseline BMI using aripiprazole as the referent group; this result was not statistically significant.
- Patients with a diagnosis of bipolar disorder were trending towards significance in both models as being associated with a decrease in BMI compared to other diagnoses

Table 3. Logistic Regression Results (Dependent Variable: ≥5% Change in BMI Post-index Date)

	Variables	Odds Ratio	P value	95% CI
Antipsychotic Drugs	Aripiprazole	1.0 (ref)		
	Olanzapine	2.32*	0.03	1.08 5.01
	Quetiapine	0.93	0.85	0.45 1.92
	Risperidone	1.52	0.25	0.75 3.11
	Ziprasidone	0.35	0.17	0.08 1.58
	FGA	1.24	0.54	0.62 2.49
Demographics	Females	1.0 (ref)		
	Males	0.85	0.39	0.60 1.22
	Age	0.96	0.35	0.89 1.04
	Baseline BMI	0.95**	<0.001	0.93 0.98
Psychiatric Diagnosis	Depression	1.4	0.07	0.98 2.03
	Bipolar	0.64	0.06	0.41 1.01
	Schizophrenia	1.88	0.41	0.42 8.36
	Other	1.56	0.10	0.91 2.67
Concomitant Medications	Promoting Weight Gain	2.44	0.46	0.23 26.24
	Promoting Weight Loss	0.61	0.45	0.17 2.22
Region	West	1.0 (ref)		
	Northeast	0.75	0.26	0.46 1.23
	Midwest	0.94	0.77	0.64 1.39
	South	0.90	0.80	0.38 2.11

P*<0.05; *P*<0.001.

LIMITATIONS

- Prescriptions in an EMR database are tracked by prescription orders and medication lists and not by actual prescriptions filled at the pharmacy
- In addition, patients enter the database via a primary care physician network and, therefore, healthcare received outside of the primary care setting may not be captured in the database
- This analysis did not control for growth using Z-scores, as is commonly done in a pediatric or adolescent population
- FGAs may not be appropriate as a reference group since they also can cause weight gain as noted by the differing results in the linear regression and logistic regression (where aripiprazole was the referent group)
- Schizophrenia patients may not have shown a significantly increased risk of BMI increase in the logistic regression due to sample size (n=11)
- It is also important to note that sample size on ziprasidone was very small (n=11), therefore results may not be a true reflection of adolescents on ziprasidone
- To maintain sample sizes, drug categories were not broken down by dose
 - BMI variance may be dose related in some products

CONCLUSIONS

- This work provides a foundation for the understanding of how second generation antipsychotics impact weight gain in adolescent patients treated in a real-world environment as opposed to a clinical trial
- Olanzapine is associated with a significantly increased risk of weight gain (BMI of 5% or more) in adolescents compared to aripiprazole; risperidone is associated with a non-significant increased risk compared with aripiprazole
- Antipsychotics without weight gain potential should be considered especially in adolescents who are overweight or at risk for overweight, such as those with schizophrenia

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