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Reversibility of psychotropic medication induced weight gain among children and adolescents with bipolar disorders

Navneet Upadhyay[a], Ayush Patel[a], Wenyaw Chan[b], Rajender R. Aparasu[a], Melissa Ochoa-Perez[c], Jeff T. Sherer[d], Swarnava Sanyal[a], Hua Chen[a,*]

[a] Department of Pharmaceutical Health Outcomes and Policy, University of Houston College of Pharmacy, Health and Biomedical Sciences Building 2, Room 4049, 4849 Calhoun, Houston, TX 77204-5000, United States
[b] Department of Biostatistics, School of Public Health, The University of Texas Health Science Center, Houston, TX, United States
[c] Legacy Community Health, Houston, TX, United States
[d] Department of Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, TX, United States

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ABSTRACT

Objective: To assess the reversibility of weight gain associated with psychotropic medications in children.
Methods: A retrospective cohort study was conducted using an ambulatory electronic medical records database. Individuals under 18 years of age were identified if they were initiating a new course of second generation/atypical antipsychotics (SGA) or mood stabilizers (MS) following a bipolar disorder diagnosis and subsequently discontinued treatment within 24 months of treatment initiation.
Results: Of the 297 children who had experienced positive BMI percentile increase (mean ± SD: 8.71 ± 11.94) during the treatment of SGA and/or MS, treatment discontinuation led to an average of 1.88 (± 13.41) unit decrease in BMI percentile during a 12-month period since the treatment discontinuation. Repeated measure mixed model analysis showed that the reduction of BMI percentile after treatment discontinuation was neither associated with the treatment regimens patients previously received, nor associated with time since the treatment discontinuation. The three statistically significant predictors were baseline BMI percentile, BMI percentile gained during the treatment, and comorbid substance abuse disorder.
Conclusion: Children with bipolar disorder were able to lose a fraction of weight gained during pharmacotherapy after the treatment discontinuation, however, their BMI percentile may not return to the prior treatment level within a year post-medication discontinuation.

1. Introduction

Bipolar disorder is a severe chronic mood disorder affecting 1–1.5% of the pediatric population (Bebbington and Ramana, 1995; Kleinman et al., 2003; Pfeifer et al., 2010). It is associated with frequent recurrences that require long term medication management (Lin et al., 2006). During the study period (1995–2010), the commonly used first line treatment for pediatric bipolar disorders were mood stabilizing medications (MS) such as lithium, divalproex and carbamazepine as well as second generation/atypical antipsychotics (SGA) such as risperidone, quetiapine, olanzapine and aripiprazole (Kowatch et al., 2005).

Our previous study examined the weight change associated with psychopharmacotherapy in children with bipolar disorder using the 1995–2010 General Electric (GE) Centricity® electronic medical record (GE EMR) research database (Patel et al., 2017). In this study, we observed a 12-month weight change trajectory among 2299 children and adolescents aged 6–17 years who had received at least 3 months of prescription medication indicated for bipolar disorder following a bipolar disorder diagnosis. The findings indicated that there was an additional BMI increase in children and adolescents using SGA beyond the normal BMI change due to growth and development. The majority of the weight gain associated with SGA exposure in children occurred during the acute treatment phase and it diminished over time and became stabilized beyond 6 months of the treatment. Our findings add to the previous pediatric literature on weight change associated with psychopharmacotherapy (Almandil et al., 2013; Castro-Fornieles et al., 2008; Citromea and Vreelandb, 2009; Correll, 2007; Correll and

* Corresponding author.
E-mail addresses: Wenyaw.Chan@uth.tmc.edu (W. Chan), rraparasu@uh.edu (R.R. Aparasu), mochoa-perez@legacycommunityhealth.org (M. Ochoa-Perez), JTSherer@uh.edu (J.T. Sherer), ssanyal@uh.edu (S. Sanyal), hchen20@uh.edu (H. Chen).

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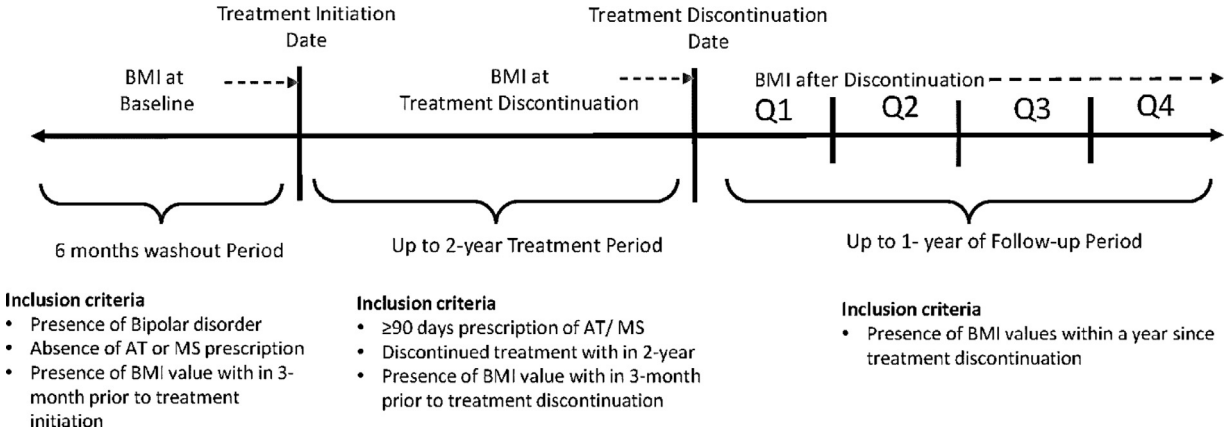

Fig. 1. Schematic of design and BMI measures.

Carlson, 2006; Fiedorowicz et al., 2012; Ghate et al., 2013; Kompoliti et al., 2010; Maayan and Correll, 2010; Macmillan et al., 2008; Martin et al., 2004; McIntyre and Jerrell, 2008; Sikich et al., 2004) and provide evidence to support that prolonged exposure to SGA in children and adolescents is associated with a continuous increase in BMI.

Despite the strong evidence that associates psychopharamcotherapy to weigh gain, the reversibility of the side effect remains uncertain. Limited literature is available on the effect of psychotropic medication discontinuation on weight change in adults, with an even bigger gap in pediatric literature. The largest study that examined the weight change after discontinuation of antipsychotics was conducted by de Kuijper et al. (2013), among 99 adults with intellectual disability. The study reported an average of 3.5 kg absolute weight decrease and 1.4 kg/m^2 of reduction in BMI 12 weeks after discontinuing antipsychotic medications. One of the limitations of this study was that it didn't measure changes of weight and BMI during the treatment due to the incomplete baseline data and therefore fails to inform the reversibility of antipsychotics associated weight gain. Another study using an adult sample found that only 25% of 35 patients treated with atypical antipsychotics (who gained 20 or more pounds during the medication treatment) were able to lose more than 10 pounds after the treatment discontinuation (O'Keefe et al., 2003).

There were only two pediatric studies that have examined the reversibility of antipsychotics related weight gain. The study by Lindsay et al. (2004) assessed the weight changes during risperidone treatment and further effect due to risperidone discontinuation in 14 children diagnosed with disruptive behavior disorders. The study concluded that for 11 children, the weight gain was reversible at 9 to 12 months after discontinuation. In another observational study conducted by Calarge et al. (2014), 18 out of 101 pediatric participants (7-17-year-old) discontinued the treatment with risperidone during a 1.6 to 2.5 year follow up period. The BMI in the antipsychotic discontinuation group did not significantly change between study entry (6 months after the initiation of SGA) and follow-up, taking age-appropriate growth into account, the unchanged BMI translated into a reversal of the age-sex specific BMI z scores in the SGA discontinuation group to the pre-risperidone level.

These pediatric studies, though provided valuable information, have limited sample sizes and did not limit the study to patients who experienced positive weight gain during treatment. Although SGA has been identified as the therapeutic category that caused most weight gain, our prior study showed that 35% of children exposed to SGA did not experience weight increase during the up to one year period of treatment (Patel et al., 2017). Positive weight change has been also observed in children took mood stabilizers (Correll, 2007; Patel et al., 2017). During the long-term management of bipolar disorder, treatment augmentation using medications from other therapeutic category was often observed in “real world” disregard patient had initial treatment with SGA or MS. To address the gap, our study focused on a large cohort of children and adolescents with bipolar disorder who had experienced weight gain during the treatment. The objective was to assess the association of time since medication discontinuation and previous psychotropic medication regimen (SGA, mood stabilizer and their combination) with the weight change within a 12 months period after the treatment discontinuation.

2. Methods

2.1. Data source

This study was conducted using the General Electric (GE) Centricity® electronic medical record (EMR) research database. The GE EMR database includes longitudinal ambulatory health records from 1995 through 2010 of around 10 million patients and is represented by more than 70 consortium member institutions across 40 states of United States. The database records patient information such as detailed patient demographics, payment types, patient diagnosis and procedural information, vital signs, and laboratory test results. Medication list entries (both prescription and over the counter drug use) include the start and stop dates along with the reason for stopping the medication. Validation studies done of GE centricity data indicated that the age distribution of the population included in the data is similar to that in the US population, and the estimated prevalence of common chronic conditions (hypertension, hyperlipidemia, diabetes) using GE EMR were comparable to the estimates generated from the national health surveys (Crawford et al., 2010; Jones et al., 2012; Marrett et al., 2014). The database is de-identified in accordance with the Health Insurance Portability and Accountability Act and has been used widely in published literature (Brixner et al., 2006; Ghate et al., 2013; LaFleur et al., 2011; McAdam-Marx et al., 2011)

2.2. Study design and study population

This study used a retrospective cohort design for which every treated pediatric bipolar case was followed from six months prior to the bipolar treatment initiation to one-year post the treatment discontinuation. Fig. 1 presents the study design and the inclusion criteria. Individuals were first identified if they were under 18 years of age and ever received a diagnosis of bipolar disorder (defined by ICD-9-CM code documented in EMR: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8). To observe the change of each individual's BMI prior to, during, and post the treatment, only patients initiating a new course of SGA or MS treatment following a bipolar disorder diagnosis and subsequently discontinued the treatment within 24 months of treatment initiation were incuded. A new course of treatment was defined as patients being active in the data for ≥6 months prior to the treatment initiation and

had not received an SGA or MS in that period. We excluded those patients who were exposed to medication briefly (<90 days), and those who continued the treatment beyond 24 months to ensure that patients had long enough exposure to medication treatment and also reserve a sufficient window (1 year) to observe the medication discontinuation effect. Medication discontinuation was determined primarily by the documented discontinuation date. In the absence of a documented discontinuation date, the date that last prescription was ordered plus 30 days' supply will be used as the discontinuation date assuming that patients often do not finish their last prescription. One BMI measure taken at the each of the following three observation periods were also required: within 3 months prior to the treatment initiation (to calculate baseline BMI), during the treatment (to measure changes in BMI on pharmacotherapy) and within 12 months post-medication discontinuation (to measure the BMI changes following medication discontinuation).

2.3. Outcome of interest

The primary outcome measure was the change in BMI percentile after the treatment discontinuation calculated as (BMI percentile after discontinuation–BMI percentile at discontinuation). As illustrated in the Fig. 1, BMI value recorded on the date of the treatment initiation or the closest BMI measure taken within 3 months prior to the treatment initiation was defined as "*Baseline BMI*". BMI measure taken at treatment discontinuation date or the nearest measure taken within 3 months before the treatment discontinuation, was defined a *"BMI at discontinuation"*. During the one-year follow-up period after treatment discontinuation, four BMI measures taken within each quarter of the year were considered in the analysis. If BMI value was absent in a given quarter, then it was considered as missing. In case of multiple BMI measures within a quarter, the BMI measure taken most recently was considered. The last measure taken during the one-year period of treatment discontinuation was defined as *"BMI after discontinuation"*.

To account for the impact of growth in childhood and adolescence, all BMI measures identified were converted to BMI percentile using the SAS® program for the 2000 CDC growth Charts (age 0 to <20 years) (CDC 2016; Kuczmarski, 2002). BMI percentiles express a child's BMI relative to children of same age and sex in the U.S. who participated in national representative surveys that were conducted during 1963–1994 (Kuczmarski, 2002).

2.4. Main independent variables

The main independent variables were the time since the treatment discontinuation, the psychopharmacotherapy patients received and treatment duration. The type of bipolar treatment patients received was categorized as (a) those who ever received AT and MS combination, (b) those who never received MS but received SGA monotherapy, and (c) those who never received SGA but received MS monotherapy.

2.5. Covariates

Other variables identified that could affect the weight change after treatment discontinuation were patient demographic characteristics (age, gender, region and type of insurance), comorbid psychiatric conditions and treatment (attention-deficit hyperactive disorder (ADHD), depression, anxiety disorder, substance use disorder, oppositional defiant disorder (ODD) or conduct disorder and learning disability), BMI percentile at baseline, BMI percentile gained during treatment, and psychosocial/behavioral intervention received during the baseline and concurrently with the pharmacotherapy.

2.6. Statistical analysis

Paired *t*-test was used to compare the reversibility of BMI percentile after the treatment discontinuation. Specifically, the BMI percentile gained during treatment (BMI percentile at discontinuation minus BMI percentile at baseline) and the BMI percentile change after the treatment discontinuation (BMI percentile after discontinuation minus BMI percentile at discontinuation) were compared to determine the reversibility of BMI percentile gained during psychopharmacotherapy within a year after the treatment discontinuation.

The repeated measures mixed model was used to model the change in BMI percentile during 3, 6, 9 and 12 months after treatment discontinuation. This model was selected to account for the correlations of multiple BMI measures taken at different time points nested within each individual and the presence of missing BMI measures at some time points during the follow up period (Blackwell et al., 2006). On comparing the Akaike Information Criterion (AIC) value of models with different covariance matrixes, Autoregressive heterogeneous (ARH) variance-covariance structure was found to be the best fit model and was used in this study. All analysis was carried out using SAS® 9.3, Cary, NC, USA. This study was approved by the Institutional Review Board at the University of Houston.

3. Results

3.1. Cohort characteristics

Fig. 2 presents the study sample attrition after imposing each inclusion criteria. 15,214 pediatric bipolar disorder cases were first identified from the data according to patients' age (<18 years of age) and diagnosis. Of these pediatric bipolar cases identified, 8,840 (58%) received their treatment (AT, MS) from providers within the 70 consortium member institutions of the GE centricity EMR database. Bipolar disorder is a chronic condition that requires long term pharmacotherapy. Of the 8,840 treated bipolar cases, we excluded 4,414 (49%) prevalent cases for whom the bipolar treatment initiation date was unknown and 1,188 who did not have BMI measures both at the baseline and during the treatment. Among the 3,279 newly treated cases left, we further excluded 824 who only received the treatment briefly (<90 days), 1,613 whose treatment discontinuation was not observe (continued the treatment >24 months), and 305 who did not have a BMI measure after the treatment discontinuation. The final cohort consisted of 537 children and adolescents who have met all inclusion criteria.

3.2. Clinical characteristics

As presented in Table 1, the mean age of the cohort was 13.60 (± 3.13) years. Half of all individuals in the cohort were whites (*N* = 273, 50.84%) and females (*N* = 283, 52.7%). About one third of all individuals resided in the Midwest region of US (*N* = 169; 31.47%) and had commercial insurance (*N* = 201; 38.43%). Vast majority of the study cohort were prescribed one of the follow three treatment regimens: 45.25% (*N* = 243) only prescribed atypical antipsychotic monotherapy; 24.77% (*N* = 133) only prescribed mood stabilizer monotherapy; 29.98% (*N* = 161) were ever prescribed a combination of an atypical antipsychotic plus a mood stabilizer. 5.03% (*N* = 27) and 12.85% (*N* = 69) of the individuals received psychosocial and behavioral intervention prior to and during the treatment, respectively.

Of the 537 patients identified, 297 (55.30%) had experienced BMI percentile increase during the treatment. A half (*N* = 146) of these 297 patients received antipsychotic monotherapy as the initial treatment, followed by those who received AT and MS combination (*N* = 88) and MS monotherapy (*N* = 63). As compared to those whose BMI percentile remained stable during the treatment, these patients were slightly younger (mean age: 13.21 vs. 14.08 years), most were male (51.85% vs. 41.67%), more likely to receive antipsychotic monotherapy as the initial treatment (49.15% vs. 40.42%), and had a lower average BMI percentile at the baseline (72.30% vs. 79.18%).

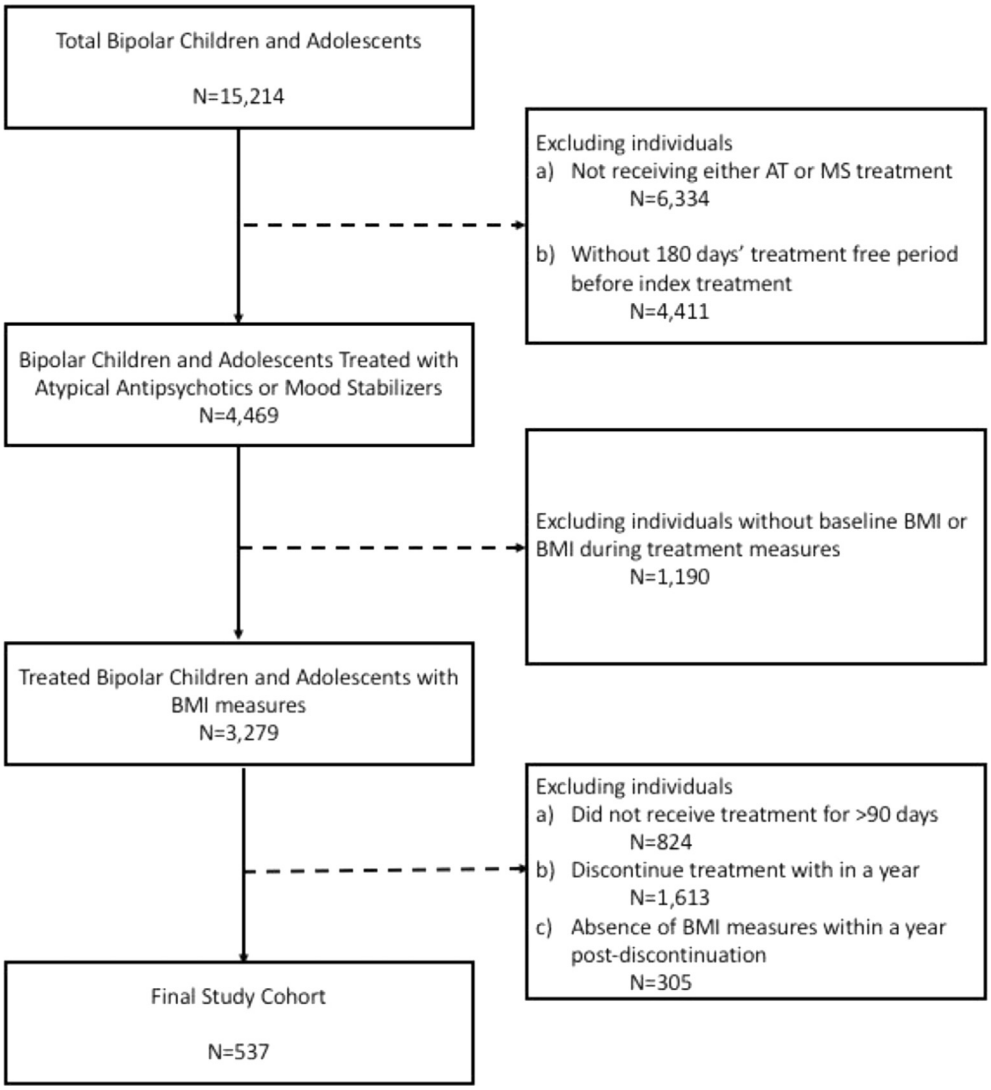

Fig. 2. Consort diagram of study population and attrition due to inclusion criteria.

3.2.1. Descriptive statistics of change in BMI

Table 2 presents the BMI measures taken at baseline, at treatment discontinuation and within 12 months after treatment discontinuation of all individuals who experienced BMI percentile increase during the treatment. The median number of BMI measures was 5 (IQR: 3–8) during the treatment and 2 (IQR:1–4) within a 12-month period after the treatment discontinuation. These 297 patients have gained an average of 7.69 (± 6.11) Kg and the BMI percentile has increased 8.71 (± 11.94) units during the treatment period. Treatment discontinuation led to an average of 2.64 (± 6.97) Kg absolute weight loss or 1.88 (± 13.41) unit decrease in BMI percentile. Paired bivariate analyses showed that, despite some weight loss, BMI percentile gained during treatment was only partially reversed within a year after the treatment discontinuation. As presented in Fig. 3, the downward slope for the change in mean BMI percentile after the treatment discontinuation is not as steep as the upward trend of mean BMI percentile increase during the treatment. These patients mean BMI percentile remained significantly higher 12-month after the treatment discontinuation than that at the baseline (79.13% vs. 72.30%; $p = < 0.001$). The proportion of children and adolescents who were overweight/obese (≥85 percentile) had increase from 47.81% at the baseline to 57.24% one year after the treatment discontinuation. The most absolute weight gain observed during the treatment period was 49.5 kg (from 48.60 kg to 98.10 kg); whereas the largest increased in BMI percentile during treatment period was 79.94 (from 18.49 percentile to 98.43 percentile). The highest number of bipolar related follow-up visits was 41 during the 254 days since treatment discontinuation.

Table 2 also presents the change of BMI percentile by initial treatment regimen for those who experienced BMI percentile increase during the treatment. Children and adolescents who initiated their treatment with AT or MS monotherapy had significantly lower baseline BMI percentile (71.42% ± 28.77%; 70.03% ± 26.92%) than patients initiated with ATMS combination treatment (75.18% ± 28.77%). During the treatment, the BMI percentiles of children on all psychotropic regimens had increased an average of 8–9 percentiles. The treatment discontinuation led to an average of 1–3 units drop of BMI percentile 12 months after the treatment discontinuation, with the smallest decrease observed in antipsychotic monotherapy group (1.01 ± 12.86), and the largest decrease in the AT-MS combination group (3.22 ± 16.02). The BMI percentiles 12 months after the treatment discontinuation remained higher than that at the baseline in all treatment groups.

3.3. Change of BMI after treatment discontinuation

Table 3 presents the results of the mixed model. It shows that the change of BMI after treatment discontinuation was neither associated with the treatment regimens patients previously received, nor

Table 1
Baseline demographics and clinical characteristics of the study cohort.

Characteristics		Treatment discontinuation $N = 537$ (100%)	Negative/No BMI PCT change $N = 240$ (100%)	Positive BMI PCT change $N = 297$ (100%)
Baseline BMI percentile	Mean (SD)	75.38 (26.48)	79.18 (23.23)	72.30 (28.36)
	Median (IQR)	85.74 (60.70–96.72)	89.01 (66.07- 97.72)	84.14 (57.41- 96.08)
Age at treatment (in years)	Mean (SD)	13.60 (3.13)	14.08 (2.90)	13.21 (3.25)
	Median (IQR)	15 (11 to 16)	15 (12 to 16)	14 (11 to 16)
Race	White	273 (50.84)	117 (48.75)	156 (52.53)
	Black	15 (2.79)	7 (2.92)	8 (2.69)
	Hispanic	6 (1.12)	2 (0.83)	4 (1.35)
	Others*	210 (39.11)	98 (40.83)	112 (37.71)
Gender	Female	283 (52.7)	140 (58.33)	143 (48.15)
	Male	254 (47.3)	100 (41.67)	154 (51.85)
Insurance**	Commercial	201 (38.43)	91 (38.72)	110 (38.19)
	Medicaid	106 (20.27)	44 (18.72)	62 (21.53)
	Medicare	1 (0.19)	1 (0.43)	0 (.)
	Self-pay	4 (0.76)	1 (0.43)	3 (1.04)
	Unknown	211 (40.34)	98 (41.7)	113 (39.24)
Region	Midwest	169 (31.47)	66 (27.5)	103 (34.68)
	Northeast	144 (26.82)	76 (31.67)	68 (22.9)
	South	129 (24.02)	53 (22.08)	76 (25.59)
	West	95 (17.69)	45 (18.75)	50 (16.84)
Psychotherapy	Baseline	27 (5.03)	8 (3.33)	19 (6.4)
	Concurrent	69 (12.85)	31 (12.92)	38 (12.79)
Comorbidities	ODCD/CD	54 (10.06)	26 (10.83)	28 (9.43)
	Depression	105 (19.55)	45 (18.75)	60 (20.2)
	ADHD	97 (18.06)	43 (17.92)	54 (18.18)
	Anxiety Disorder	75 (13.97)	37 (15.42)	38 (12.79)
	Substance Use Disorder	24 (4.47)	15 (6.25)	9 (3.03)
	Learning Disability	11 (2.05)	6 (2.5)	5 (1.68)
Treatment Groups	Combination	161 (29.98)	73 (30.42)	88 (29.63)
	Atypical Antipsychotics	243 (45.25)	97 (40.41)	146 (49.16)
	Mood Stabilizers	133 (24.77)	70 (29.17)	63 (21.21)

Notes:
* Others category included races other than White, Blacks, Asian and unknown.
** Sum of all categories may not be equal to N due to missing value. BMI PCT, Body Mass Index Percentile based on the US Population at the age. ADHD, Attention-deficit/hyperactivity disorder; ODCD/CD, Oppositional defiant disorder/Conduct disorder.

associated with time from the treatment discontinuation. The three statistically significant predictors for the BMI change after treatment discontinuations were the baseline BMI percentile, the degree of BMI percentile increase during the treatment, and the comorbid substance abuse disorder. For every one-unit additional increase in BMI percentile during treatment, there was 0.51 unit more reduction in BMI percentile after the treatment discontinuation. Baseline BMI showed a similar but relatively smaller effect on BMI percentile reduction after the discontinuation. For every 1 unit higher BMI percentile at baseline, it is associated with 0.14 unit additional drop after the treatment discontinuation.

4. Discussion

The principle finding of our study is that, for the vast majority of those who experienced BMI percentile increase during the treatment, they were only able to lose a small fraction of BMI gained during the treatment and the measure did not return to the prior treatment level within a year after the treatment discontinuation. Since the duration from discontinuation is not associated with additional reduction in BMI percentile, it is likely that those children and adolescents who have gained significant weight during the treatment will stay overweight or obese.

Studies have shown that antipsychotic induced weight gain poses significant risk of treatment discontinuation. A survey on physicians and bipolar disorders patients reported that 58% of patients recognized weight gain as a major adverse effect of bipolar disorder treatment and reported it to be one of the most prominent cause of treatment non-adherence (Johnson et al., 2007). Non-adherence to bipolar treatment can have serious short-term and long-term consequences which include increased risk of relapse, hospitalization and suicide attempts (Hong et al., 2011).

Moreover, childhood obesity can cause detrimental effect on structure and function of vascular and cardiac system both at short-term and long-term. Children with obesity are at higher risk of cardiovascular related morbidly and mortality. A recent study conducted on 8,579 children and young adults found that children with BMI above 85 percentiles have increased risk of having high levels of LDL cholesterol and high blood pressure as compared to those within 75–85 percentile of BMI (Skinner et al., 2015). Another prospective study which followed 2.4 million adolescents between the ages of 16 and 19 years reported that cardiovascular mortality risk among obese subjects was two times higher at the 10-year follow-up period and the risk doubled after the follow-up period of 30–40 years (Twig et al., 2016).

Our finding adds to the prior literature and highlights the importance of both preventions prior to the treatment initiation and weight management during psychotropic medication treatment. To prevent medication induced weight gain, the first step is to identify those who are at risk. In our sample, nearly a half of children and adolescents using psychotropic medications experienced BMI percentile increase. Our previous study has found that being male, younger and having lower BMI at baseline make individual susceptible to higher drug induced weight gain (Patel et al., 2017). However, not everyone who received bipolar treatment experienced the weight gain. Significant variations in the drug induced weight gain may be partially attributable to genetic polymorphism (Goes, 2016; Roerig et al., 2011). More research is currently underway to identify these genes and their interaction with environmental factors (Goes, 2016).

Physicians treating adolescents who are at high risk of psychotropic induced weight gain need to be familiar with treatment guidelines and review the weight gain potential associated with psychotropic agents and regularly monitor children and adolescents to avoid the long-term

Table 2
BMI percentile changes during the different time period in the cohort with a positive change in BMI percentile in treatment period overall and by treatment type (N = 297).

Variable	Mean	Std. Dev	Median	Lower quartile	Upper quartile
Positive change in BMI percentile (n = 297)					
BMI percentile mean					
Baseline	72.30	28.36	84.14	57.41	96.08
Treatment	81.00	23.28	90.53	74.94	97.63
Discontinuation	79.13	24.35	89.94	70.54	97.26
Changes in BMI measures during treatment period compared to baseline					
Average BMI percentile change	8.71	11.94	3.73	0.92	10.67
Average weight change	7.69	6.11	6.30	3.60	10.57
Change in BMI measure during treatment discontinuation compared with treatment period					
Average BMI percentile change	−1.88	13.41	−0.06	−4.97	2.74
Average weight change	2.64	6.97	2.25	−0.90	6.30
Paired t-test results					
					T test p value
BMI percentile gain during treatment period vs BMI percentile loss during follow-up period					7.62 < 0.01
Average BMI percentile at treatment discontinuation vs. Average BMI percentile at end of follow-up					2.41 0.02
Atypical antipsychotics (n = 146)					
BMI percentile mean					
Baseline	71.42	28.77	83.03	56.1	95.53
Treatment	80.33	23.89	90.42	76.1	97.19
Discontinuation	79.33	24.76	90.45	72.59	97.3
BMI measure change during treatment compared to baseline period					
Average BMI percentile change	8.91	11.44	5.45	1.13	10.71
Average weight change	7.85	6.27	6.71	3.6	10.8
BMI measure during treatment discontinuation compared with treatment period					
Average BMI percentile change	1.01	12.86	0.01	−3.12	5.07
Average weight change	−3.39	7.4	−3.15	−6.75	0.64
Mood stabilizers (n = 63)					
BMI percentile mean					
Baseline	70.3	26.92	80.18	53.74	91.65
Treatment	78.97	23.55	88.86	72.06	94.77
Discontinuation	76.94	22.77	86.37	61.69	95.47
BMI measure change during treatment compared to baseline period					
Average BMI percentile change	8.67	10.49	4.73	0.9	13.24
Average weight change	6.67	5.32	5.4	2.76	8.55
BMI measure change during treatment discontinuation compared with treatment period					
Average BMI percentile change	2.03	10.36	0	−3.05	6.8
Average weight change	−2.36	5.58	−1.8	−5.85	0.45
Dual therapy (n = 88)					
BMI Percentile Mean					
Baseline	75.18	28.77	88.7	62.46	97.07
Treatment	83.57	22.07	94.66	76.82	98.5
Discontinuation	80.36	24.92	91.2	69.06	97.71
BMI measure change during treatment compared to baseline					
Average BMI percentile change	8.39	13.72	2.26	0.77	7.53
Average weight change	8.17	6.35	6.3	3.5	10.91
BMI measure change during treatment discontinuation compared with treatment period					
Average BMI percentile change	3.22	16.02	0.26	−1.27	4.59
Average weight change	−1.6	7.06	−1.97	−6.19	2.25

Notes: BMI percentile, Body mass index percentile based on the US population at the age.

risks (Melkersson et al., 2004). However, for some extreme cases observed in our data, even with weekly weight monitoring and multiple adjustments on the treatment regimen, some individuals still gained more than 40 kg during the treatment. Weight loss treatments are often necessary for the subgroup of patients.

In addition to non-pharmacological treatment options that include weight gain psychotherapy (group or individual) and healthy lifestyle changes (Caemmerer et al., 2012), there are several pharmacological interventions available to control the hunger and glycemic level associated with psychotropic medications (Maayan and Correll, 2010). Pediatric trials have shown that metformin is significantly better than placebo in reducing antipsychotic induced weight gain (Klein et al., 2006; Shin et al., 2009). Observational studies are needed to further the understanding on how metformin and other pharmacological options have been used in practice, and to examine the effectiveness and unintended adverse effects of these pharmacological options.

Only a few factors positively associated with the magnitude of weight loss after the treatment discontinuation were identified from our analysis. One of these factors was BMI percentile patients gained during the treatment. Nearly all published studies examining antipsychotic induced weight gain have reported a positive association between weight increase during the treatment and better clinical improvements of patients' psychiatric symptoms (Basson et al., 2001; Czobor et al., 2002; Lane et al., 2003; Meltzer et al., 2003; Ascher-Svanumetal., 2005b; Bai et al., 1999; Hung et al., 2010; Hermes et al., 2011; Kemp et al., 2013). The greater weight loss after the treatment discontinuation observed among those who have gained relative more weight during the treatment might be explained by these patients' higher responsiveness to both beneficial and adverse effects of psychopharmacotherapy.

Another factor associated with weight loss after the treatment discontinuation was having a comorbid substance use disorder. The mechanisms behind the positive effect of substance use on weight loss are unclear but could be attributable to the brain appetite suppressing activity and changes in fat distribution due to controlled substances (Billing and Ersche, 2015). Several studies have noted the use of substances among adolescents as an unhealthy weight loss practice (Antin and Paschall, 2011; Eichen et al., 2012; Pisetsky et al., 2008; Vidot

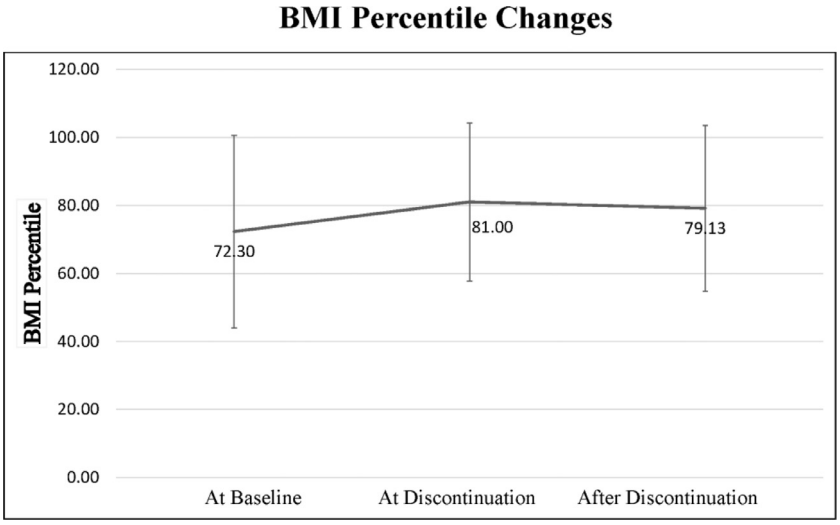

Fig. 3. Mean BMI prior, during and after the psychotropic treatment.

Table 3
Mixed linear regression model results for BMI percentile loss during treatment period by study predictors (N = 297).

Category	Estimates (95% LL to UL)	p value
Treatment Specific Predictors		
Treatment type		
Combination	Reference Category	
Atypical antipsychotics	−1.05 (−4.39 to 2.28)	0.54
Mood Stabilizers	0.10 (−4.11 to 4.31)	0.96
BMI percentile gain during treatment period	0.51 (0.36–0.66)	<0.01
BMI percentile at baseline	0.14 (0.08–0.21)	<0.01
Time since the discontinuation	0.00 (−0.02 to 0.01)	0.75
Duration of treatment	0.00 (−0.01 to 0.01)	0.68
Psychotherapy at baseline		
Presence vs. Absence	3.58 (−9.89 to 2.73)	0.27
Concurrent psychotherapy		
Presence vs. Absence	3.75 (−8.21 to 0.72)	0.10
Demographics		
Age at treatment	0.17 (−0.31 to 0.65)	0.48
Gender		
Female Vs. Male	0.28 (−2.82 to 3.38)	0.86
Region		
West	Reference category	
Midwest	2.39 (−2.22 to 6.99)	0.31
Northeast	3.46 (−1.13 to 8.05)	0.14
South	2.30 (−2.31 to 6.91)	0.33
Payment Type		
Commercial	Reference Category	
Medicaid	−1.55 (−5.75 to 2.65)	0.96
Others	−1.13 (−14.99 to 12.73)	0.49
Unknown	−0.09 (−3.36 to 3.18)	0.88
Comorbid conditions		
Substance use disorder		
Presence vs. Absence	10.32 (1.49–19.15)	0.02
Depression		
Presence vs. Absence	0.91 (2.84–4.67)	0.63
Learning disability		
Presence vs. Absence	0.48 (11.48–10.52)	0.93
ADHD		
Presence vs. Absence	2.64 (−1.21–6.49)	0.17
ODCD/CD		
Presence vs. Absence	0.95 (4.07–5.98)	0.71
Anxiety disorder		
Presence vs. Absence	1.24 (3.12–5.59)	0.58

Notes: BMI percentile, Body mass index percentile based on the US Population at the age. ADHD, Attention-deficit/hyperactivity disorder; ODCD/CD, Oppositional defiant disorder/Conduct disorder.

et al., 2016). Substance use may have replaced the eating habits of bipolar disorder patients.

To our knowledge, this is the first large EMR based observational study that examined the impact of psychopharmacotherapy (atypical antipsychotics, mood stabilizers) on BMI percentile increase and its reversibility after the treatment discontinuation in children and adolescent with bipolar disorders. Despite the richness in clinical details, EMR data does not include lifestyle related factors and neighborhood factors that may significantly contribute to weight gain as well as weight loss of patients. Patient data in the EMR are not 'linked' across providers, and the data in the EMR database during a patient's activity period represents care delivered by a single physician or practice. For our study, comedications (e.g. psychostimulants) that could affect weight and prescribed by another provider, were only captured if reported and documented in the EMR by the referring physician. To minimize the limitation, we controlled patients' comorbid conditions instead of co-medications. For instance, if a patient identified in our study was also receiving psychostimulants from a provider in a different practice, controlling the comorbid ADHD diagnosis can partially account for the likelihood that patients might have received a comedication relevant to the diagnosis.

Another limitation of the study is that a large number of patients were excluded by the inclusion criteria which might have limited the generalizability of study results. Studying medication discontinuation effect for the treatment of chronic disorders is challenging. It took an extended observation period to catch both the initiation and discontinuation of bipolar treatment within individual patients. Among patients whose medication initiation and discontinuation were both observed, many did not receive sufficient BMI monitoring needed for the study. Due to these limitations, only a few hundred children and adolescents were included in the analysis. Despite of the limitation, this study is still the largest pediatric study to date that examined the weight change associated with psychotropic medication discontinuation. The two existing studies examining similar research questions both had sample sizes of less than 20. The findings are significant given that it advances the understanding on the long-term impact of psychotropic medication induced weight gain and highlights the importance of weight management during psychotropic treatments.

5. Conclusion

More than a half of children and adolescent with bipolar disorder experienced significant BMI percentile increase during the treatment. Those who had experienced positive weight gain during the

pharmacotherapy were able to lose a fraction of weight gained after the treatment discontinuation, however, their BMI percentile may not return to the prior treatment level within a year post-medication discontinuation.

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