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The Impact of Psychopharmacotherapy on Body Mass Index (BMI) of Children and Adolescents with Bipolar Disorder

by

Ayush V. Patel, MS

A dissertation submitted in partial fulfillment of

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The Impact of Psychopharmacotherapy on Body Mass Index (BMI) of Children and Adolescents with Bipolar Disorder

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Dedicated to my family and friends

Abstract

Objectives: To assess the impact of psychopharmacotherapy on BMI among bipolar children and adolescents with bipolar disorders, and to assesses the change of BMI after the treatment discontinuation.

Methods: This retrospective cohort study used General Electric electronic medical records to identify children and adolescents with bipolar diagnosis (18 years or younger) and prescribed atypical antipsychotics (AT), mood stabilizers (MS) or antidepressants (AD). A minimum of 6 months of baseline period was applied prior to the first bipolar diagnosis defined as the index diagnosis date. After excluding individuals who had bipolar diagnosis or psychotropic prescription during the baseline period, and without body mass index (BMI) measures in the pre-index or follow-up period; the individuals in the study cohort were followed up to 3, 6, 9 and 12 months to determine the effect of treatment regimens on Body Mass Index (BMI). Those who discontinued the treatment within the 12 month post index period were continuously followed for an additional 3, 6, 9, and 12 months to observe whether the BMI patients gained during the treatment could return to the baseline. The repeated measures mixed models were applied to account for the nesting effect of multiple BMI measures available to each individual, and estimate the effect of treatment and subsequent discontinuation on BMI after adjusting for the baseline BMI, socio-demographics, comorbidities and psychotherapy.

Results: The cohort consisted of 2,299 individuals in the treatment and 1,265 individuals in the discontinuation phase of the study. MS monotherapy regimen was associated with a steady increase in BMI over time (3 months: 0.11 kg/m^2, 6 months: 0.09 kg/m^2, 9 months: 0.09 kg/m^2 and 12 months: 0.089 kg/m^2. As compared to children and

adolescents who were on MS monotherapy, those who were on AD monotherapy, AT+MS, AT+AD or MS+AD had similar pattern of change of BMI. AT monotherapy was the only regimen associated with more BMI gain (3 months: 0.244 kg/m^2, 6 months: 0.10 kg/m^2, 9 months: 0.07 kg/m^2, 12 months: 0.05 kg/m^2) at all time points than MS monotherapy. After the treatment discontinuation, most patients' BMI stayed on the level during the treatment and did not return to the baseline level. The proportion of children and adolescents who were overweight/obese (≥85 percentile), 12 months after treatment discontinuation, was significantly higher (53.49%) than that at the start of the treatment (51.03%). The change in BMI after the treatment discontinuation was neither associated with the type of treatment the individuals received in the treatment phase nor was it associated with time elapsed from the treatment discontinuation. Being older and having lower BMI at the end of the treatment was associated with relative more reduction of BMI after the treatment discontinuation at all follow-up periods.

Conclusion: Significant increase in BMI among children was observed in all children and adolescent who were on all psychotropic regimens. The magnitude of BMI increase was positively associated with the duration of the exposure. Atypical antipsychotics was the treatment associated with the most significantly increase in BMI. BMI gained during treatment is, on average, not reversible after discontinuation of treatment. Extra effort is needed to minimize the weight gain during the treatment to prevent the long term cardiovascular consequence of being overweight and obese.

Table of Contents

Effect of Psychopharmacotherapy Treatment on Body Mass Index (BMI) Among Bipolar Children and Adolescents

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Dissertation Manuscript I

Abstract

Objective: To assess the differential impact of all treatment options for bipolar disorders on BMI and explore factors protecting patient from the increase in BMI.

Methods: A retrospective cohort study was conducted using the General Electric electronic medical records (GE-EMR) database from 1995 to 2010 to identify bipolar children and adolescents (18 years or younger) who were prescribed atypical antipsychotics (AT), mood stabilizers (MS) and antidepressants (AD). The first bipolar diagnosis was defined as the index diagnosis date. After excluding patients with bipolar diagnosis or medication prescription within 6 months pre-index date and without at least one BMI measure pre-index and post-index, the individuals were followed for up to 3, 6, 9 and 12 months to estimate the effect of treatment regimens on BMI. Primary independent variable was treatment regimens, classified as AT monotherapy, MS monotherapy, AD monotherapy, AT+MS, AT+AD and MS+AD. The repeated measures mixed models were applied to account for the nesting effect of multiple BMI measures available to each individual, and estimate the effect of treatment on BMI after adjusting for the baseline BMI, socio-demographics, comorbidities and psychotherapy. Logistic regression model was employed to further explore the factors associated with worsening of adverse events among those children and adolescents who increase BMI.

Results: Cohort consisted of 2,299 individuals (mean age: 13.51±3.87 years). MS monotherapy regimen was associated with a steady increase in BMI over time (3 months: 0.11 kg/m^2, 6 months: 0.09 kg/m^2, 9 months: 0.09 kg/m^2 and 12 months: 0.089 kg/m^2. As compared to children and adolescents who were on MS monotherapy, those who were on AD monotherapy, AT+MS, AT+AD or MS+AD had similar pattern of change of BMI. AT monotherapy was the only regimen associated with more BMI gain (3 months: 0.244

kg/m^2, 6 months: 0.10 kg/m^2, 9 months: 0.07 kg/m^2, 12 months: 0.05 kg/m^2) at all time points than MS monotherapy. Overweight/Obese children at baseline or younger individuals were associated with less increase in BMI at all time points.

Conclusion: Atypical antipsychotics are significantly associated with increase in BMI as compared to mood stabilizers with baseline BMI and time of atypical antipsychotic as significant determinants of BMI increase among bipolar atypical antipsychotic using children and adolescents.

Introduction

Affecting about 1% of all adolescence (Pfeifer et al. 2010), bipolar disorder is a severe recurrent mood disorder defined by a pattern of mania, hypomania or mixed episodes of mania or hypomania and depression (Bebbington, Ramana 1995). It is a chronic mental disease related to relapse of symptoms (Lin, et al. 2006) that leads to abnormal shifts in mood, energy and activity level and is characterized by the experience of unusually intense emotional states that occur in distinct periods called "mood episodes". The first line medications commonly used in youth with bipolar disorder are mood stabilizing medications such as lithium, divalproex and carbamazepine as well as atypical antipsychotics such as aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone (Kowatch, et al. 2005).

Both categories of drugs, atypical antipsychotics and mood stabilizers have been associated with weight gain in children and adolescents (Corell, Carlson 2006, Fedorowicz, Fombonne 2005). Previous studies report 40.8% of "at-risk for overweight" and 22.1% of "overweight" bipolar children and adolescents (Goldstein, et al. 2008) as compared to about 35.5% and 18% among United States youth (Ogden, et al. 2006). In 2013 alone, 42 million children under the age of 5 were overweight or obese (World Health Organization, 2014). Childhood obesity has both immediate as well as long-term health effects (CDC, Accessed 2015). Moreover obese children and adolescents are at a greater risk of having prediabetes (Li C, et.al. 2009, CDC 2011) bone and joint problems, sleep apnea, and social and psychological problems including low self-esteem and stigmatization (Daniels SR, et.al. 2005, DHHS 2010, Dietz, et.al. 2004). Long-term effects include likelihood of future adult obesity (Guo SS, et.al. 1999, Freedman DS,

et.al. 2009, Freedman DS, et.al. 2005, Freedman DS, et.al. 2001) increasing the risks for heart diseases, diabetes, stroke, several types of cancer and osteoarthritis (DHHS 2010).

A systematic review of nineteen studies, involving data collected from 24 individual medication trials (open label or randomized controlled trials) by Correll et.al on 684 children and adolescents (mean age: 12.3 years) with bipolar disorder showed significant increase in weight associated with the use of mood stabilizers and atypical antipsychotic. The polytherapy of mood stabilizers and atypical antipsychotics caused more weight gain as compared to mood stabilizer monotherapy but not different from atypical antipsychotic monotherapy users (Correll 2007). There are also limited observational studies comparing the differential risk of weight gain associated with SGAs and mood stabilizers in the adolescent population (Ghate et.al. 2012, Patel et. al, 2007, Kompoliti et.al 2010, Castro-Fornieles et.al. 2008, Macmillan et.al. 2008, Chengappa et.al 2002). The findings are generally consistent with the conclusion of the systematic review, although most of these studies are not limited to bipolar children and adolescents.

Despite the existing evidence, there are still unanswered questions regarding the risk of weight gain associated with the treatment for bipolar disorders in children. Bipolar disorder is a chronic disorder that often requires lifelong treatment. The existing studies, regarding trials or observational studies, all have short duration of follow-up (with mean duration of 15.4±12.7 (ranging from 4 to 48) weeks for clinical trials (Correll 2007) and 4 to 12 weeks for observational studies) which is not enough to inform the longer term impact of the mood stabilizing medications, especially the long term impact of psychotropic polytherapy. Also, medication utilization and management for bipolar disorder is complex in real world practice. Many patients went through a process for

which drugs are titrated, augmented or switched. These patients are often censored in clinical trials and excluded in most observational studies. The findings of these studies may not fully reflect the risk faced by patients who are undergoing treatment for bipolar disorder. Moreover, medications used in the treatment of bipolar disorder include not only atypical antipsychotics and mood stabilizers, but also antidepressants (American Psychiatric 2002, Ng, et al. 2009). Some antidepressants have also been associated with weight gain in adults, the existing literature that examined the medication associated weigh change in pediatric bipolar disorder, however, has focused solely on atypical antipsychotics and mood stabilizers. The head-to-head comparison of potential weight modification effect of all available treatment regimens in children and adolescents in real world setting has not yet been explored. Lastly, despite weight gain is a common side effect among treated bipolar cases, it is known that at least a fraction of patients are not affected (Torrent, et al. 2008). It remains unexplored whether patients with certain characteristics or non-pharmacotherapy concurrently used with psychotropic medication could prevent or attenuate the adverse effect of psychotropic medications.

Therefore, the objectives of our study were to assess the differential impact of all treatment options for bipolar disorders on BMI and explore factors protecting patient from the increase in BMI.

Methods

Data Source:

This study was conducted using the General Electric (GE) Centricity electronic medical record (EMR) research database. The data includes longitudinal ambulatory

health records from 1995 through 2010 for 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. For each patient visit, the specialty of physician who attended patient and the practice type is also documented. The database is de-identified in accordance with the Health Insurance Portability and Accountability Act and has been used widely in published literature (Ghate, et al. 2013, LaFleur, et al. 2011, McAdam-Marx, et al. 2011).

Sample Population:

The individuals eligible for inclusion were - (i) under 18 years of age; (ii) receiving a diagnosis of bipolar disorder (ICD-9-CM code: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8) after a minimum of 180-day period (also known as the baseline/washout period) free of either bipolar diagnosis or prescription (defined as index bipolar diagnosis); (iii) receiving at least 3 months of prescription medication for bipolar disorder after the index bipolar diagnosis; and (iv) with BMI measures taken at the baseline and during the follow-up. Index prescription date was defined as the date on which the patient received first bipolar related medication, namely atypical antipsychotics (AT) or mood stabilizers (MS) or antidepressants (AD), after the Index Bipolar diagnosis. The baseline BMI was defined as a BMI measure taken within 30 days prior to or on the index prescription date, while the follow-up BMI was defined as the ones that were reported during the 12 months post the index prescription period.

Study Design:

This study used a retrospective cohort design for which every patient was followed for one year from the first medication prescription, defined as index prescription date, to compare the impact of different medication regimens for the treatment of bipolar disorders on BMI.

Exposure: This study includes 5 mutually exclusive drug regimens. These regimens were AT monotherapy, MS monotherapy, AD monotherapy, AT+MS polytherapy, AT+AD polytherapy and MS+AD polytherapy. Although AD monotherapy has been associated with manic switch, we still observed that some patients in our cohort received the regimen briefly during the follow-up period. The drug exposure of each individual during the 12 month follow-up period was ascertained by the prescriptions written by physicians. As GE data does not have days of supply of medication, it was assumed that each prescription was for 30 days after consulting with psychiatrists.

Outcome: Outcome measured in this study is 'change in BMI' during the treatment calculated as the difference between the measures taken during follow-up and the baseline measure. The BMI was measured monthly and the months without a BMI measure were coded as missing. If there were multiple BMI measures available for a particular month, an average of all BMI measures was considered for that monthly observation. Similarly, treatment regimens were mapped out for each month for each patient based on their prescriptions and number of refills prescribed by the physician. Considering the likelihood of patients switching treatment regimens, BMI measures for each month was attributed to the treatment regimen prescribed to the patient for that particular month. Figure 1 shows a schematic of patient's BMI measures and treatment

regimens as measured over the follow-up period. In order to examine both short term and long term treatment effects on BMI, individuals were followed up to 3, 6, 9, and 12 months according to their availability of BMI measure in each quarter of the year. For instance, a patient with BMI measures in month 4, 6 and 8 will be included in the 6 month and 9 month follow-up cohorts, but will not be eligible to the 3 month and 12 month follow-up cohort. In contrast, a patient with BMI measures only within 3 months of treatment initiation will be included only in the 3 month follow-up cohort.

Statistical Analysis:

Repeated measure mixed model was used to model treatment effect on change in BMI due to the presence of repeated medication exposure and outcome (BMI) measures for each individual. These observations nesting under each individual are correlated. Mixed models are a flexible approach to model correlated data. In addition, as likelihood of having measured BMI at all months for each individual is not possible, there were missing BMI measures. Given that vast majority of the pediatric bipolar patients received weight and BMI measures during each of the their follow-up visit, there is no reason to believe that the chance of having a BMI measure in a particular month is associated with the treatment regimen the patient received in the month. Therefore, we assume that the BMI measures were missing at random and it was non-differential across the treatment groups. To determine the nature of autocorrelation between the observations nested under a patient, we compared the Akaike Information Criterion (AIC) value of the models assuming different covariance matrixes. Autoregressive heterogeneous (ARH) variance-covariance structure was found to be the best fit.

The dependent variable was monthly change in BMI from baseline modeled at 3, 6, 9 and 12 months. The primary independent variable was type of treatment regimens patients received in each month. The treatment exposure was treated as time-varying which could change from month to month. The association between treatment regimen patients exposed at each month and the BMI measured in the same month was assessed in the model to compare the relative risk of increase in BMI across treatment regimens during various observation periods.

Covariates controlled in this study were demographics (age, gender, race, insurance type and region), clinical characteristics (baseline and concurrent psychosocial and behavioral intervention, baseline BMI and psychiatric comorbidities (anxiety disorder, attention deficit hyperactivity disorder, depression, learning disability, oppositional/conduct disorder and substance use disorder).

To further explore whether patients with certain characteristics or the utilization of medication concurrent psychosocial or behavioral interventions could prevent or attenuate the adverse effect of psychotropic medications, a logistic regression model was employed to explore the differences in demographic, clinical, baseline BMI and psychiatric comorbidities between children and adolescents whose BMI had increased during the treatment versus whose BMI stayed stable.

All analysis was carried out using Statistical Analysis Software 9.3 (SAS, Cary, NC, USA). This study was approved by the Institutional Review Board at the University of Houston.

Results

Cohort Characteristics

As presented in figure 2, a total of 17,779 children and adolescents were identified with bipolar disorder diagnosis. After excluding patients without any kind of medication treatment by the providers who were using the GE EMR system (N=10,419); those who were not prescribed any guideline recommended first line treatment for bipolar disorders (atypical antipsychotics or mood stabilizers) (N=897); those without a minimum of one BMI measures at baseline and one during the follow-up visits (N=1,793); those without 180days of treatment free period before the index date (N=2,371), the final cohort consisted of 2,299 treated children and adolescents with a new bipolar episode.

As presented in table 1, the majority of the cohort was whites (N=1,067; 46.41%) residing in the Midwest (N=870; 37.84%) region of US, and had commercial insurance (N=806; 35.06%). The mean age of the cohort was 13.51 (±3.87) years and had roughly equal proportions of males (48.42%) and females (51.28%).

Treatment Utilization Patterns

Table 1 also presents the treatments prescribed to the study cohort. 76.81% (N=1,766) of individuals in the cohort initiated treatment with monotherapies and 23.19% (N=533) with polytherapy. The most commonly prescribed psychotropic monotherapy was AT monotherapy (N=846), followed by MS monotherapy (N=715) and AD monotherapy (N=205). Of the 1,766 patients who were initially prescribed monotherapy, 966 (54.70%) received treatment augmentation during the one year follow up, and of those 533 patients who initiated treatment with polytherapy, 293 (55%)

switched to monotherapy regimen during the follow-up. In total, 54.76% (N=1,259) of all individuals were ever prescribed polytherapy during the one year follow-up period. The commonly prescribed combination regimens were AT and MS (ATMS) polytherapy (N=444), AT and AD (ATAD) polytherapy (N=440), and MS and AD (MSAD) polytherapy (N=375).

Absolute Change in BMI Associated with the Initial Psychotropic Regimens:

The unadjusted analysis found the maximum increase in BMI was observed among individuals who initiated their treatment with atypical antipsychotic monotherapy (1.20±2.26 kg/m2), followed by those initiated with ATMS combination (1.04±2.71 kg/m2) and ATMS combination (1.01±3.24 kg/m2), with mood stabilizers monotherapy (0.62±2.37 kg/m2), and those initiated with mood stabilizer-antidepressant combination (0.61±3.01 kg/m2).

Multivariate Analysis on the Association between Treatment Regimens and the correspondent change of BMI

Table 2 presents the estimated change in BMI associated with each treatment regimen during the 3, 6, 9 and 12 months follow up periods using repeated measure mixed model. In all comparison, MS monotherapy was used as the reference group and the effects of the treatments, the time and the interaction effect between the two were observed.

Treatment and Time Effect:

The time effect estimated in the model indicated that the longer the use of mood stabilizers (the reference group), the higher the increase of BMI. Each additional month exposure to mood stabilizer was associated 0.11 kg/m^2 increases in BMI within the 3

month follow-up cohort (p-value: 0.0436), 0.09 kg/m^2 increase within the 6 month follow-up cohort (p-value: 0.0004), 0.09 kg/m^2 within the 9 month follow-up cohort(p-value: <0.0001) and 0.089 kg/m^2 within the 12 months follow-up cohort (P <0.0001). The magnitude of the estimates suggested that the increase had been steady overtime.

As compared to MS monotherapy, the change in BMI associated with AT monotherapy was 0.244 kg/m^2 (3 months follow-up, P= 0.0006), 0.10 kg/m^2 (6 months follow-up, P= 0.0019), 0.07 kg/m^2 (9 months follow-up, P= 0.0021) and 0.05 kg/m^2 (12 months follow-up, p-value: P=0.0034) higher, indicating a steeper slope over time especially during the short term exposure. None of the regimen other than AT monotherapy showed any difference in change in BMI as compared to the MS monotherapy.

Baseline BMI:

Children and adolescents who were overweight or obese at baseline were less likely to have increased BMI during the psychotropic treatment. Every one unit higher BMI at baseline led to 0.038 kg/m^2, (p-value: <0.0001), 0.036 kg/m^2, (p-value: <0.0001), 0.029 kg/m^2, (p-value: <0.0001) and 0.028 kg/m^2, (p-value: <0.0001) less increase in BMI at 3, 6, 9 and 12 months of follow-up cohorts respectively.

Age:

Older age children and adolescents were subjected to more increase in BMI. Every one year older of age led to 0.38 kg/m^2, (p-value: <0.0001), 0.036 kg/m^2, (p-value: <0.0001), 0.031 kg/m^2, (p-value: <0.0001), 0.030 kg/m^2, (p-value: <0.0001) increase in BMI at 3, 6, 9 and 12 months of follow-up respectively.

Other covariates:

Gender, race, geographical region, type of insurance and comorbid conditions were not associated with change in BMI during the follow-up.

Predictors of 'Increase in BMI' among Atypical Antipsychotic Users

Given that atypical antipsychotics was found to be the regimen that associated with the most BMI gain and these drugs are also the most commonly used therapeutic category used among bipolar patients (N=1,385, 60%). An ad hoc analysis was conducted to explore, within the atypical antipsychotic users, the factors that protected patients from getting excessive BMI gain. Of the 1,385 atypical antipsychotic users, 65% (N=896) showed 'increase in BMI' at the end of follow-up. Baseline BMI, number of months on AT and region were found to be significant predictors for increase in BMI (Table 3.). With each kg/m^2 increase in baseline BMI, it is 4% less likely to increase BMI at the end of follow-up (OR: 0.963; C.I.: 0.946-0.980), while with each additional month exposure to AT, a patient is 1.095 (CI: 1.055-1.136) times more likely to have increased BMI. For region, those residing in the South region are 1.32 (C.I.: 1.199-1.401) times more likely to have increased BMI as compared to those that reside in the mid-west region.

Discussion

Consistent with the existing short term pediatric studies that examined the relative risks of weight gain associated with various psychotropic regimens (Almandil et.al. 2013, Fiedorowicz et. al. 2012, Maayan 2011, Correll, et al. 2010, Citrome& Vreeland, 2009, Correll 2007, Fleischhaker 2007, Martin 2000,), our analysis found that children treated with atypical antipsychotics are at the highest risk for weight gain. As compared to

patients on mood stabilizer monotherapy, those on atypical antipsychotic monotherapy had a greater increase in BMI in the 3, 6, 9 and 12 month follow up period, while the statistically significant differences were not observed in children on all other psychotropic regimens (AD monotherapy, AT+MS polytherapy, AT+AD polytherapy and MS+AD polytherapy).

More importantly, our analysis provided data that help clarify the association between the duration of exposure to psychotropic medications and the change in BMI. Our findings suggested that the longer the exposure to psychotropic medications, the more increase in BMI in children and adolescents with bipolar diagnosis. Within one year follow up period, the duration of exposure to psychotropic medications was associated with steady and continuous increase in BMI and the time effect was observed in patients on all psychotropic treatment regimens. The repeated measure mixed model showed that each additional month exposure to mood stabilizer monotherapy (the reference group) was associated with 0.09-0.11 kg/m^2 increases in BMI during the 3, 6, 9 and 12 month follow up periods. Similar (statistically indifferent) trends were observed in children on all other psychotropic regimens (AD monotherapy, AT+MS polytherapy, AT+AD polytherapy and MS+AD polytherapy) with the only exception observed in those on antipsychotic monotherapies.

Limited studies that have examined the association between duration of psychotropic treatment and weight gain were conducted in adults who were on atypical antipsychotics. In a retrospective analysis on long-term effect of olanzapine treatment on weight change among patients with schizophrenia, Kinon et al. (2001) reported a mean weight gain of 6.26 kgs which plateaued at 39 weeks of treatment. Another retrospective

report from the Pittsburg Study of maintenance Therapies in Bipolar Disorder that evaluated weight change during acute psychotropic treatment and the first year of maintenance psychotropic treatment among individuals age 18 or over, report that most of the weight gain occurs during the acute treatment phase rather than the maintenance treatment phase, which further indicates a leveling effect over longer periods of treatment time (Fagiolini 2002). In our study, a similar levering effect was observed in children and adolescents on antipsychotic monotherapy. However, the change of BMI was not reduced to 0 at the end of the one year follow-up; rather, it is leveling closer to the BMI trends associated with other psychotropic regimens.

Atypical antipsychotic and other psychotropic medications are known to alter resting metabolic rate, energy expenditure and activity levels along with increasing appetite and food intake and decreasing satiety (Maayan, Correll 2010). Lithium is known to directly stimulate appetite at the hypothalamus, causing fluid retention, and increase thirsty that might lead to consumption of high-calorie beverages (Torrent et.al. 2008; McKnight ey.al. 2012, Elmslie et.al. 2001). Valproic acid also increases appetite, but may also increase insulin secretion from pancreatic beta cells and reduce insulin clearance which leads to hyperinsulinemia and associated weight gain (Verrotti et.al. 2011). The exact mechanism of antipsychotic weight gain is still undetermined, but evidence points to the receptor affinities for histamine H1, serotonin 5-HT2 and dopamine D2 receptors (Wetterling et.al. 2001). These receptor activities, coupled with their influence on hypothalamic peptides and hormones, may affect energy homeostatsis causing increase in appetite and reducing satiety (Correll, Malhotra 2004).Additionally, increase in the level of ghrelin, a peptide hormone also known as “hunger hormone”,

which increases weight was observed in patients with long-term atypical antipsychotics (Jin et.al, 2008). Some psychotropics have also shown to increase carbohydrate cravings (Garland et.al., 1988). Based on animal studies, Hoebel et.al. (2009) has developed a behavioral circuit model, known as the sugar addiction model, that explains the long-term effect of carbohydrate craving. As per the model, sugar bingeing causes repeated release of excessive dopamine (DA) and opioid stimulation during abstinence from sugar, causing a feeling similar to opioid withdrawal, causing greater risks of relapsing. No matter what is the mechanism of action, mood stabilizers and antipsychotics are both known to increase appetite and reduce satiety, which may lead to long-term changes in diet which may be attributed to sugar bingeing. This may also explain our findings that older individuals are more likely to gain BMI, considering parent's role in controlling diet among younger individuals.

One surprising finding of our study was that, the effect of any combination regimen on BMI did not differ from MS monotherapy. Bipolar being a chronic condition is frequently treated by complex combination regimens. Our study, reflecting the real world clinical practices in treating bipolar children and adolescents, takes into account all types of treatment regimens prescribed by physicians and shows that these combination regimens do not cause and significant additional weight gain over mood stabilizer monotherapy. Although we excluded all patients who were prescribed psychotropic medications within 6 months prior to the index bipolar disorder; individuals, especially those who initiated treatment with complex combination regimens, may have been exposed to simpler treatment regimens much before the controlled 6 months. Even though our study did not compare baseline BMI measures between different treatment

regimens, considering the long term eating habits and lifestyle changes as explained by the sugar addiction model, it may be possible that these individuals having been affected by their historical use of psychotropic medications are overweight or obese to begin with. With clear evidence of weight gaining properties of atypical antipsychotics, physicians may be inclined to treat overweight or obese individuals with other safer options, namely mood stabilizers, either alone or in combination with atypical antipsychotics to better manage the disorder and control high doses of atypical antipsychotics. Combination regimens may not significantly worsen the existing lifestyle changes and eating habits and so increase in BMI may not significantly differ from mood stabilizer regimens. Furthermore our findings also show that children and adolescents with greater BMI at baseline, are less likely to increase their BMI at follow-up further supporting our theory that physicians are more likely to be careful with their choice of treatment regimen and monitor their effects on an individuals' BMI and weight especially for those who have a greater BMI to begin with.

Our study focuses on bipolar children and adolescents on psychopharmacotherapy followed for a period of 12 months. Although, evidence from clinical trials are considered gold standard, they are bound by the controlled nature of the study do not represent the real world clinical practice. Additionally, systematic reviews of these clinical trials have short duration of follow-up (with mean duration of 15.4±12.7 weeks and a median duration of 8 weeks) and small sample sizes (less than 100 individuals), with some studies as small as 9 individuals (Correll 2010). These short follow-up periods are inadequate to inform the long term impact of the medications, especially psychotropic polytherapy on children's weight and BMI.

The result implicates that children and adolescent patients on long-term psychotropic drugs, especially atypical antipsychotics, are associated with significant cardiometabolic adverse effects. The effect could aggregate overtime, and has more threat to adolescents than children. At present obesity is a serious health concern among all adolescents Children and adolescents who are obese are more likely to become obese adults. A study published by Whitaker et al. found that approximately 80% of children who were overweight at age 10–15 years were obese adults at age 25 years (Whitaker et.al, 1977). In addition, childhood obesity is associated with adult cardiovascular adverse outcomes and impaired glucose tolerance (Baker et al. 2007, Bhargava et. al. 2004, Sinaiko et.al. 1999, Srinivasan et.al. 2002). It is also associated with long term health risks of obesity, type 2 diabetes, hyperlipidemia, and hypertension (Stigler et. al, 2004). Our results not only indicate that antipsychotic medications were associated with weight gain but that it is just associated with more weight gain than other therapeutic categories. If weight gain among adolescents on antipsychotics is not controlled, it may result in high burden and increased use limited health resources to treat obesity-related diseases in addition to mental health issues when these adolescents become adults. Also, obesity and mental illness may result in serious consequences on the quality of life of children and adolescents. The potential mechanism of change in lifestyle and eating habits associated with psychotropic medication use implies a need for appropriate monitoring of BMI in children and adolescents on psychotropic treatment along with providing nutritional and weight management counseling.

The primary strength of this study is that actual clinical measures such as BMI values in the GE EMR database were used to assess change in weight among children

and adolescents on pharmacotherapy. Previous observational studies have used current ICD-9 codes and not actual clinical measures to assess obesity/weight gain in adolescents on antipsychotics (McIntyre et. al. 2008) 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 30kg/m^2 which may not apply to adolescents where overweight and obesity is defined based on BMI percentiles compiled on growth charts from the Centers for Disease Control and Prevention (Kuczmarski et. al, 2002). Another strength of the study is that it looks at the main treatment effect, effect of time and the interaction effect of treatment with time (slope). The slope shows the trajectory of change in BMI for different treatment regimens overtime within different follow-up periods, making the results more intuitive. Lastly, unlike previous studies, in this study, switching between the treatment regimens has been accounted for. Most of the previous studies classify children and adolescents based on treatment initiation regimen, while bipolar children and adolescents experience constant changes in medication until they reach symptomatic stability.

As with any research study there are several limitations. One of the most important limitations of this study 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. However, as the study includes only those eligible individuals with at least 3 months of treatment, patients with multiple prescriptions are more likely to have filled their prescriptions. Additionally, as all individuals in the study have been diagnosed

with bipolar and have bipolar related follow-up visits, it is less likely to have prescriptions unfilled. Secondly, we have no evidence to suggest that the missing BMI measures are not missing at random. Nevertheless, these missing observations fail to give us a complete picture of changes in BMI at each time point in association with the treatment regimens. Finally, the database lacks information on socioeconomic status, diet, physical activity, or overall health of patient's parents. Although these unmeasured variables may play a significant role in impacting the weight of adolescents in the data, controlling baseline BMI partially addresses the effect of these missing variables.

Conclusion

Atypical antipsychotics are significantly associated with increase in BMI as compared to mood stabilizers. Augmenting mood stabilizer monotherapy regimen with an atypical antipsychotic does not affect BMI differently. Moreover, baseline BMI and time of atypical antipsychotic use are significant determinants of BMI increase among bipolar atypical antipsychotic using children and adolescents. Bipolar children and adolescents need to be monitored aggressively for height, weight and BMI during and after treatment and should be provided with nutritional and weight management counseling especially after treatment.

References

Almandil, N. B., Liu, Y., Murray, M. L., Besag, F. M., Aitchison, K. J., & Wong, I. C. (2013). Weight gain and other metabolic adverse effects associated with atypical antipsychotic treatment of children and adolescents: a systematic review and meta-analysis. Pediatric Drugs, 15(2), 139-150.

American Psychiatric A. American Psychiatric Association Practice Guidelines for the Treatment of Patients with Bipolar Disorder. Vol 159: Amer Psychiatric Pub Inc, 2002.

Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med. 2007;357(23):2329-37.

Bebbington P and Ramana R. The epidemiology of bipolar affective disorder. Social psychiatry and psychiatric epidemiology. 30:279-292, 1995.

Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med. 2004;350(9):865-75.

CDC. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011,Atlanta, GA: U.S. Department of Health and Human Services.

CDC. Childhood obesity facts. Retrieved August 23, 2015, from http://www.cdc.gov/healthyschools/obesity/facts.htm

Chengappa, KN Roy, L. Chalasani, Jaspreet S. Brar, H. Parepally, Patricia Houck, and Joseph Levine. "Changes in body weight and body mass index among psychiatric patients receiving lithium, valproate, or topiramate: an open-label, nonrandomized chart review." Clinical therapeutics 24, no. 10 (2002): 1576-1584.

Correll, C. U., E. M. Sheridan, et al. (2010). "Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo- controlled trials." Bipolar disorders 12(2): 116-141.

Correll CU. (2007) Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. Journal of the American Academy of Child and Adolescent Psychiatry. 46:687-700.

Corell CU and Carlson HE. (2006) Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. Journal of the American Academy of Child and Adolescent Psychiatry. 45:771-791.

Correll, C.U. and Malhotra, A.K., 2004. Pharmacogenetics of antipsychotic-induced weight gain. Psychopharmacology, 174(4), pp.477-489.

Daniels SR, Arnett DK, Eckel RH, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation 2005;111;1999–2002.

Department of Health and Human Services, Office of the Surgeon General. The Surgeon General's Vision for a Healthy and Fit Nation. Rockville, MD; 2010.

Dietz WH. Overweight in childhood and adolescence. New England Journal of Medicine2004;350:855-857.

Elmslie JL, Mann JI, Silverstone JT, Williams SM, Romans SE. Determinants of overweight and obesity in patients with bipolar disorder. J Clin Psychiatry. 2001;62(6):486-491.

Fagiolini, A., Frank, E., Houck, P.R., Mallinger, A.G., Swartz, H.A., Buysse, D.J., Ombao, H. and Kupfer, D.J., 2002. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. Journal of Clinical Psychiatry, 63(6), pp.528-533.

Fedorowicz VJ and Fombonne E. Metabolic side effects of atypical antipsychotics in children: a literature review. Journal of psychopharmacology (Oxford, England). 19:533, 2005.

Fiedorowicz, J. G., Miller, D. D., Bishop, J. R., Calarge, C. A., Ellingrod, V. L., & Haynes, W. G. (2012). Systematic review and meta-analysis of pharmacological interventions for weight gain from antipsychotics and mood stabilizers. Current psychiatry reviews, 8(1), 25.

Fleischhaker, Ch, et al. "Weight gain associated with clozapine, olanzapine and risperidone in children and adolescents." Journal of neural transmission114.2 (2007): 273-280.

Freedman DS, Kettel L, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: the Bogalusa Heart Study. Pediatrics2005;115:22–27.

Freedman D, Wang J, Thornton JC, et al. Classification of body fatness by body mass index-for-age categories among children. Archives of Pediatric and Adolescent Medicine 2009;163:801–811.

Freedman DS, Khan LK, Dietz WH, Srinivasan SA, Berenson GS. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. Pediatrics2001;108:712–718.

Garland, E. Jane, Ronald A. Remick, and Anastasios P. Zis. "Weight gain with antidepressants and lithium." Journal of clinical psychopharmacology 8, no. 5 (1988): 323-330.

Ghate SR, Porucznik CA, Said Q, Hashibe M, Joy E and Brixner DI. Association between second-generation antipsychotics and changes in body mass index in adolescents. Journal of Adolescent Health. 52:336-343, 2013.

Ghate, Sameer R., Christina A. Porucznik, Qayyim Said, Mia Hashibe, Elizabeth Joy, and Diana I. Brixner. "Association between second-generation antipsychotics and changes in body mass index in adolescents." Journal of Adolescent Health 52, no. 3 (2013): 336-343.

Goldstein BI, Birmaher B, Axelson DA, Goldstein TR, Esposito-Smythers C, Strober MA, Hunt J, Leonard H, Gill MK and Iyengar S. Preliminary findings regarding overweight and obesity in pediatric bipolar disorder. The Journal of clinical psychiatry. 69:1953, 2008.

Guo SS, Chumlea WC. Tracking of body mass index in children in relation to overweight in adulthood. American Journal of Clinical Nutrition 1999;70:S145–148.

Jin H, Meyer J.M, Mudaliar S, Jeste D.V. Impact of atypical antipsychotic therapy on leptin, ghrelin, and adiponecti. Schizophr Res. 2008;100(1-3):p70–85.

Kinon, B. J., Basson, B. R., Gilmore, J. A., & Tollefson, G. D. (2001). Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. The Journal of clinical psychiatry, 62(2), 92-100.

Kompoliti, Katie, Glenn T. Stebbins, Christopher G. Goetz, and Wenqing Fan. "Association between antipsychotics and body mass index when treating patients with tics." Journal of child and adolescent psychopharmacology 20, no. 4 (2010): 277-281.

Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL and Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 44:213-235, 2005.

Kuczmarski, Robert J., Cynthia L. Ogden, Shumei S. Guo, Laurence M. Grummer-Strawn, Katherine M. Flegal, Zuguo Mei, Rong Wei, Lester R. Curtin, Alex F. Roche, and Clifford L. Johnson. "2000 CDC Growth Charts for the United States: methods and development." Vital and health statistics. Series 11, Data from the national health survey 246 (2002): 1-190.

LaFleur J, McAdam-Marx C, Alder SS, Sheng X, Asche CV, Nebeker J, Brixner DI and Silverman SL. Clinical risk factors for fracture among postmenopausal patients at risk for fracture: a historical cohort study using electronic medical record data. Journal of bone and mineral metabolism. 29:193-200, 2011.

Li C, Ford ES, Zhao G, Mokdad AH. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among US adolescents: NHANES 2005–2006.Diabetes Care 2009;32:342–347.

Lin D, Mok H and Yatham LN. Polytherapy in bipolar disorder. CNS drugs. 20:29-42, 2006.

Maayan, Lawrence, and Christoph U. Correll. "Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents." Journal of child and adolescent psychopharmacology 21.6 (2011): 517-535.
Maayan, Lawrence, and Christoph U. Correll. "Management of antipsychotic-related weight gain." (2010): 1175-1200.
Martin, A., Landau, J., Leebens, P., Ulizio, K., Cicchetti, D., Scahill, L., & Leckman, J. F. (2000). Risperidone-associated weight gain in children and adolescents: a retrospective chart review. Journal of child and adolescent psychopharmacology, 10(4), 259-268.
McAdam-Marx C, Bouchard J, Aagren M, Conner C and Brixner DI. Concurrent control of blood glucose, body mass, and blood pressure in patients with type 2 diabetes: an analysis of data from electronic medical records. Clinical therapeutics. 33:110-120, 2011.
McIntyre, Roger S., and Jeanette M. Jerrell. "Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents." Archives of pediatrics & adolescent medicine 162.10 (2008): 929-935.
McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 2012;379(9817):721-728
Ng F, Mammen OK, Wilting I, Sachs GS, Ferrier IN, Cassidy F, Beaulieu S, Yatham LN and Berk M. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar disorders. 11:559-595, 2009.
Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ and Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. Jama. 295:1549-1555, 2006.
Patel, Nick C., Monica Hariparsad, Mary Matias-Akthar, Michael T. Sorter, Drew H. Barzman, John A. Morrison, Kevin E. Stanford, Stephen M. Strakowski, and Melissa P. DelBello. "Body mass indexes and lipid profiles in hospitalized children and adolescents exposed to atypical antipsychotics."Journal of child and adolescent psychopharmacology 17, no. 3 (2007): 303-311.
Pfeifer JC, Kowatch RA and DelBello MP. Pharmacotherapy of Bipolar Disorder in Children and Adolescents: Recent Progress. CNS drugs. 24:575-593, 2010.
Sinaiko AR, Donahue RP, Jacobs DR, Jr., Prineas RJ. Relation of weight and rate of increase in weight during childhood and adolescence to body size, blood pressure, fasting insulin, and lipids in young adults. The Minneapolis Children's Blood Pressure Study. Circulation. 1999;99(11):1471-6.
Stigler KA, Potenza MN, Posey DJ, McDougle CJ. Weight gain associated with atypical antipsychotic use in children and adolescents: prevalence, clinical relevance, and management. Paediatr Drugs. 2004;6(1):33-44.
Torrent C, Amann B, Sánchez- Moreno J, Colom F, Reinares M, Comes M, Rosa AR, Scott J and Vieta E. Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. Acta Psychiatrica Scandinavica. 118:4-18, 2008.
Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F. Weight gain following treatment with valproic acid: pathogenic mechanisms and clinical implications. Obes Rev. 2011;12(5):e-32-43.
Wetterling, T., 2001. Bodyweight Gain with Atypical Antipsychotic. Drug Safety, 24(1), pp.59-73.
Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med. 1997;337(13):869-73.
World Health Organization: Obesity and overweight. Fact sheet N° 311. Available via http://www.who.int/mediacentre/factsheets/fs311/en/index.html. Accessed 25 Nov 2014.

Figures and Tables

Figure 1. Schematic of a Patient's BMI and Treatment measure.

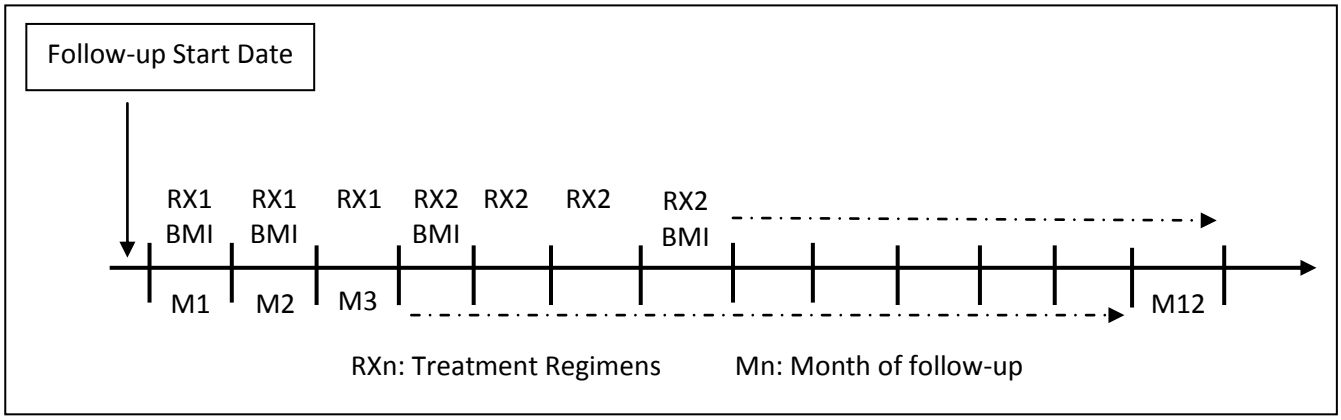

Figure 2. Schematic Representation of Cohort Selection

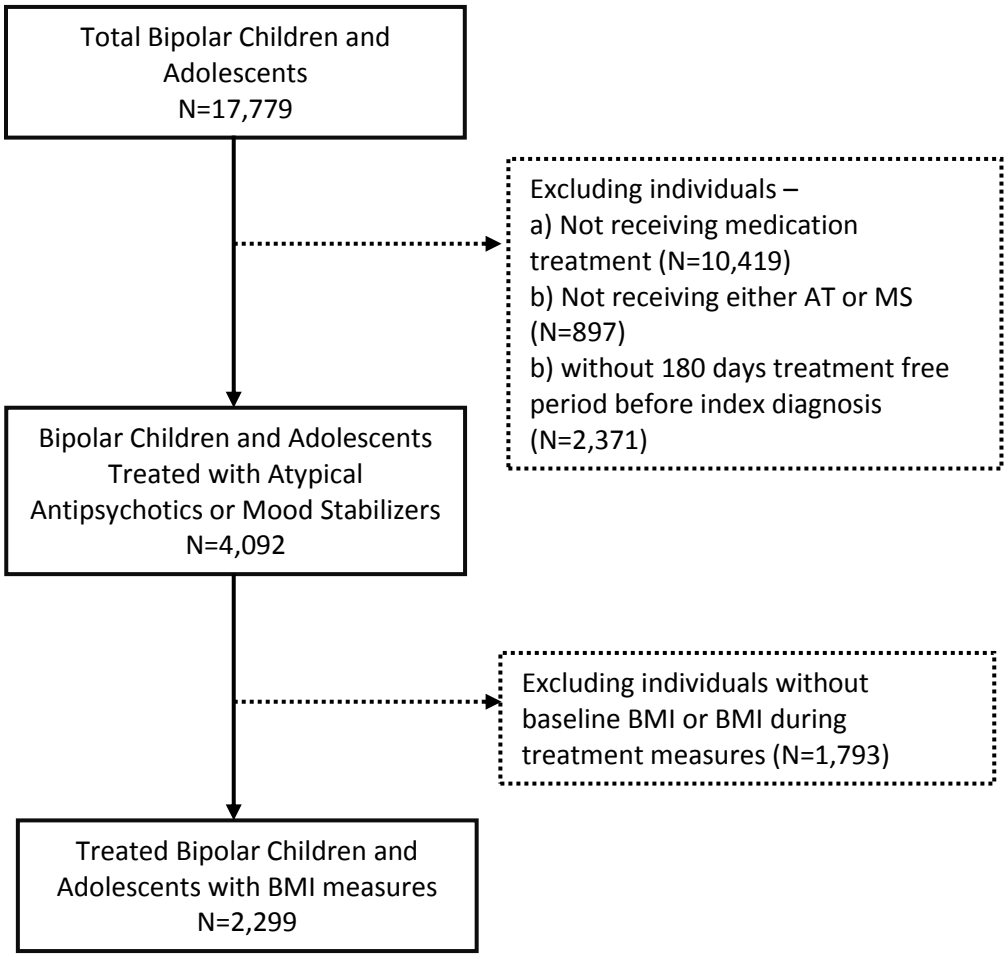

Table 1. Demographic Characteristics

Characteristics		Treatment (N=2,299 (100%))
Age (years)	Mean (SD)	13.51 (3.87)
	Median (IQR)	14 (11-17)
Race	White	1,067 (46.41%)
	Black	64 (2.78%)
	Hispanic	14 (0.61%)
	Other	1,154 (50.20%)
Gender	Male	1,120 (48.72%)
	Female	1,179 (51.28%)
Insurance	Commercial	806 (35.06%)
	Medicaid	558 (24.27%)
	Self-pay	65 (2.83%)
	Unknown	870 (37.84%)
Region	Midwest	870 (37.84%)
	Northeast	458 (19.92%)
	South	559 (24.31%)
	West	412 (17.92%)
Physician Type	Primary Care	1,534 (66.72%)
	Specialist	210 (9.13%)
	Unknown	555 (24.14%)
Psychosocial and Behavioral Interventions	Baseline	46 (2.00%)
	Concurrent	59 (2.57%)
Comorbidities	ODCD	235 (10.22%)
	Depression	327 (14.22%)
	ADHD	614 (26.71%)
	Anxiety Disorder	225 (9.79%)
	Substance Use Disorder	145 (6.31%)
	Learning Disability	41 (1.78%)
Treatment Ever Received During Follow-Up	Atypical Antipsychotics Monotherapy (AT)	1,067 (46.41 %)
	Mood Stabilizers Monotherapy (MS)	862 (37.49%)
	Antidepressants Monotherapy (AD)	290 (12.61%)
	AT+MS	444 (19.31%)
	AT+AD	440 (19.14%)
	MS+AD	375 (16.31%)

Table 2. Effect on Change in BMI (Reference: Mood Stabilizers)

Characteristics	Up to 3 months		Up to 6 months		Up to 9 months		Up to 12 months	
	Estimate (95% C.I.)	P-Value	Estimate (95% C.I.)	P-Value	Estimate (95% C.I.)	P-Value	Estimate (95% C.I.)	P-Value
Treatment (Ref: MS)								
AT	-0.24 (-0.424 - -0.057)	0.0106	-0.164 (-0.301 - -0.028)	0.0181	-0.155 (-0.272 - -0.039)	0.0091	-0.145 (-0.257 - -0.034)	0.0106
AD	-0.26 (-0.343 - 0.174)	0.476	-0.271 (-0.321 - 0.112)	0.164	-0.326 (-0.473 - 0.0101)	0.0943	-0.0224 (-0.354 - 0.290)	0.1551
ATMS	-0.16 (-0.417 - 0.096)	0.2195	-0.096 (-0.283 - 0.092)	0.3175	-0.106 (-0.265 - 0.053)	0.1909	-0.098 (-0.248 - 0.053)	0.2028
ATAD	-0.05 (-0.316 - 0.217)	0.7131	-0.051 (-0.249 - 0.148)	0.6156	-0.056 (-0.226 - 0.114)	0.5207	-0.04 (-0.202 - 0.122)	0.6253
MSAD	-0.102 (-0.385 - 0.182)	0.4797	-0.167 (-0.376 - 0.043)	0.119	-0.124 (-0.3 - 0.052)	0.1662	-0.095 (-0.26 - 0.07)	0.2598
Time (continuous)	0.108 (0.003 - 0.214)	0.0436	0.093 (0.042 - 0.145)	0.0004	0.094 (0.058 - 0.131)	<.0001	0.089 (0.06 - 0.118)	<.0001
Time*Treatment (Ref: MS)								
AT	0.244 (0.105 - 0.382)	0.0006	0.103 (0.038 - 0.169)	0.0019	0.071 (0.026 - 0.117)	0.0021	0.053 (0.017 - 0.088)	0.0034
AD	-0.054 (-0.2 - 0.092)	0.4668	0.04 (-0.03 - 0.11)	0.2614	0.016 (-0.032 - 0.064)	0.5127	0.002 (-0.036 - 0.04)	0.9139
ATMS	0.172 (-0.004 - 0.347)	0.0549	0.06 (-0.02 - 0.141)	0.1408	0.049 (-0.004 - 0.102)	0.0716	0.042 (-0.001 - 0.083)	0.0538
ATAD	0.085 (-0.094 - 0.263)	0.3516	0.06 (-0.023 - 0.144)	0.1558	0.049 (-0.009 - 0.107)	0.1006	0.028 (-0.019 - 0.074)	0.2444
MSAD	-0.017 (-0.2 - 0.166)	0.8581	0.05 (-0.038 - 0.138)	0.2678	0.027 (-0.033 - 0.086)	0.3771	0.003 (-0.043 - 0.049)	0.889
Baseline BMI	-0.038 (-0.044 - -0.031)	<.0001	-0.036 (-0.042 - -0.029)	<.0001	-0.029 (-0.035 - -0.023)	<.0001	-0.028 (-0.034 - -0.022)	<.0001
Age	0.038 (0.025 - 0.052)	<.0001	0.036 (0.022 - 0.049)	<.0001	0.031 (0.018 - 0.043)	<.0001	0.03 (0.018 - 0.043)	<.0001
Gender (Ref: Male)								
Female	-0.014 (-0.133 - 0.105)	0.7788	-0.032 (-0.15 - 0.087)	0.521	-0.045 (-0.159 - 0.068)	0.3497	-0.045 (-0.156 - 0.067)	0.3513
Race (Ref: White)								
Black	0.001 (-1.764 - 1.765)	0.9958	-0.014 (-0.611 - 0.583)	0.9275	-0.061 (-0.486 - 0.364)	0.6785	-0.081 (-0.502 - 0.34)	0.5839
Hispanic	0.052 (-3.361 - 3.465)	0.8789	-0.001 (-1.147 - 1.145)	0.9974	-0.082 (-0.887 - 0.723)	0.7675	-0.113 (-0.91 - 0.683)	0.6815
Others	-0.062 (-0.643 - 0.52)	0.4067	-0.056 (-0.252 - 0.14)	0.3425	-0.053 (-0.192 - 0.085)	0.3069	-0.053 (-0.19 - 0.083)	0.3013
Region (Ref: Midwest)								
Northeast	0.054 (-0.12 - 0.229)	0.4366	0.077 (-0.083 - 0.237)	0.2729	0.093 (-0.047 - 0.234)	0.1596	0.099 (-0.04 - 0.237)	0.1357
South	0.013 (-0.152 - 0.178)	0.8395	0.021 (-0.132 - 0.173)	0.7404	0.053 (-0.081 - 0.187)	0.3768	0.06 (-0.073 - 0.192)	0.3204
West	-0.106 (-0.294 - 0.081)	0.1896	-0.111 (-0.284 - 0.061)	0.1586	-0.086 (-0.238 - 0.066)	0.2237	-0.07 (-0.221 - 0.08)	0.3044

Insurance (Ref: Commercial)								
Medicaid	0.02 (-0.248 - 0.288)	0.7754	0.019 (-0.179 - 0.216)	0.7809	-0.002 (-0.166 - 0.162)	0.9758	0.003 (-0.16 - 0.165)	0.9669
Self-pay	-0.556 (-1.157 - 0.045)	0.0576	-0.476 (-0.915 - -0.037)	0.041	-0.383 (-0.75 - -0.016)	0.0443	-0.366 (-0.728 - -0.003)	0.0488
Unknown	0.02 (-0.203 - 0.244)	0.7319	0.003 (-0.162 - 0.168)	0.955	-0.013 (-0.15 - 0.125)	0.8077	-0.018 (-0.154 - 0.118)	0.7327
Baseline Psychosocial and Behavioral Intervention (Ref: No)								
Yes	-0.225 (-0.585 - 0.135)	0.2206	-0.341 (-0.7 - 0.018)	0.0628	-0.396 (-0.74 - -0.052)	0.024	-0.407 (-0.746 - -0.067)	0.019
Current Psychosocial and Behavioral Intervention (Ref: No)								
Yes	0.236 (-0.07 - 0.542)	0.1311	0.308 (0.004 - 0.613)	0.0473	0.382 (0.093 - 0.672)	0.0097	0.398 (0.113 - 0.683)	0.0062
Oppositional/Conduct Disorder (Ref: No)								
Yes	0.029 (-0.949 - 1.007)	0.7718	0.006 (-0.966 - 0.977)	0.9539	0.021 (-0.905 - 0.947)	0.8212	0.03 (-0.884 - 0.944)	0.7461
Depression (Ref: No)								
Yes	0.006 (-0.767 - 0.778)	0.9422	0.019 (-0.174 - 0.211)	0.7784	0.011 (-0.148 - 0.171)	0.852	0.004 (-0.153 - 0.162)	0.9425
ADHD (Ref :No)								
Yes	-0.052 (-0.227 - 0.122)	0.4115	-0.042 (-0.216 - 0.131)	0.4946	-0.056 (-0.2 - 0.088)	0.3388	-0.059 (-0.201 - 0.084)	0.3164
Learning Disability (Ref: No)								
Yes	-0.009 (-2.109 - 2.091)	0.9651	-0.015 (-2.082 - 2.053)	0.9426	0.011 (-1.951 - 1.972)	0.9564	0.024 (-1.91 - 1.958)	0.9009

Table 3:. Predictors of 'Increase in BMI' among Atypical Antipsychotic Users

Effect	OddsRatioEst	LowerCL	UpperCL	p-Value
Baseline BMI	0.963	0.946	0.98	<.0001
Months on AT	1.095	1.055	1.136	<.0001
Age	1.015	0.98	1.052	0.4019
Gender (Ref: Male)				
Female	1.02	0.804	1.293	0.8723
Race (Ref: White)				
Black	1.479	0.722	3.031	0.2847
Hispanic	5.896	0.716	48.551	0.0991
Others	1.086	0.858	1.374	0.4909
Region (Ref: Midwest)				
Northeast	0.751	0.552	1.022	0.0683
South	1.321	1.199	1.401	0.033
West	0.851	0.589	1.229	0.3898
Insurance (Ref: Commercial)				
Medicaid	0.873	0.638	1.195	0.3969
Self-pay	1.366	0.576	3.237	0.4788
Unknown	0.953	0.724	1.256	0.7339
Baseline Psychosocial and Behavioral Intervention (Ref: No)	1.335	0.513	3.474	0.5539
Current Psychosocial and Behavioral Intervention (Ref: No)	1.314	0.548	3.146	0.5405
Oppositional/Conduct Disorder (Ref: No)	1.293	0.89	1.878	0.1769
Depression (Ref: No)	0.864	0.611	1.223	0.4102
ADHD (Ref :No)	0.93	0.719	1.203	0.5819
Substance Use Disorder (Ref: No)	0.758	0.449	1.279	0.2992

Effect of Psychopharmacotherapy Discontinuation on Body Mass Index (BMI) Among Bipolar Children and Adolescents

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Dissertation Manuscript II

Abstract

Objective: To conduct a one year comparative effectiveness study that assesses the effect of psychotropic medication discontinuation on BMI among bipolar children and adolescents.

Methods: A retrospective cohort study was conducted using the General Electric electronic medical records (GE-EMR) database from 1995 to 2010 to identify bipolar children and adolescents (18 years or younger) treated with atypical antipsychotics (AT), mood stabilizers (MS) or antidepressants (AD) and further discontinued the treatment. Date of treatment discontinuation was defined as index discontinuation date. After excluding those without at least one body mass index (BMI) measure; pre-treatment, at treatment discontinuation and post-discontinuation, patients were followed for up to 3, 6, 9 and 12 months after treatment discontinuation to observe whether the BMI patients gained during the treatment could return to the baseline. The repeated measures mixed models were applied to account for the nesting effect of multiple BMI measures available to each individual, and estimate the effect of treatment discontinuation on BMI after adjusting for the baseline BMI, socio-demographics, comorbidities and psychotherapy.

Results: Cohort consisted of 1,265 individuals (mean age: 13.67±3.83 years). After the treatment discontinuation, most patients' BMI stayed on the level during the treatment and did not return to the baseline level. The proportion of children and adolescents who were overweight/obese (≥85 percentile), 12 months after treatment discontinuation, was significantly higher (53.49%) than that at the start of the treatment (51.03%). The change in BMI after the treatment discontinuation was neither associated with the type of treatment the individuals received in the treatment phase nor was it associated with time

elapsed from the treatment discontinuation. Being older and having lower BMI at the end of the treatment was associated with relative more reduction of BMI after the treatment discontinuation at all follow-up periods.

Conclusion: There is no significant difference between effects of treatment regimen on BMI after treatment discontinuation. BMI gained during treatment is not completely reversible after discontinuation of treatment. Bipolar children and adolescents need to be monitored aggressively for height, weight and BMI during and after treatment and should be provided with nutritional and weight management counseling especially after treatment.

Introduction

Bipolar is a severe recurrent and chronic mood disorder affecting 1-1.5% of the pediatric population (Pfeifer, Kowatch et.al, 2010, Bebbington and Ramana 1995, Kleinman et.sl, 2003). It is associated with frequent recurrences that require long term medication management (Lin et.al, 2006). Medications commonly used in youth as the first line treatment are mood stabilizing medications such as lithium, divalproex and carbamazepine as well as atypical antipsychotics such as risperidone, quetiapine, olanzapine and aripiprazole. Published clinical trials and observational studies in both adults and pediatrics have reported weight and BMI gain among children and adolescents with psychiatric disorders on mood stabilizers and atypical antipsychotic medications (Ghate et.al. 2012, De Hert. et.al, 2011, Kompoliti et.al 2010, Castro-Fornieles et.al. 2008, Macmillan et.al. 2008, Correll 2007, Patel et. al 2007, Corell and Carlson 2006, Fedorowicz and Fombonne 2005, McIntyre and Konarski 2005; Newcomer 2005, Martin et. al 2004, Sikich et.al 2004, Chengappa et.al 2002, Shaw et.al. 2001, Allison, Mentore et al. 1999). Other psychotropic medications often used in the treatments for bipolar disorders, such as antidepressant, had controversial reports regarding its effect on weight, with tricyclics and monoamine oxidase inhibitors cause weight gain by increasing appetite and selective serotonin reuptake inhibitors (SSRIs) reduce weight by decreasing appetite and increasing basal metabolic rate (Torrent et.al. 2008).

Moreover, polypharmacy are frequently used in bipolar treatment. With increase in number of concurrent psychotropic medications, there increases risks of weight gain. Significantly greater weight gain associated with both short term as well as long term

psychotropic polypharmacy compared to monotherapies were observed in both children and adults (Centorrino et.al. 2008, Jerrell et.al. 2008) .

Despite the strong evidence that associates psychopharamcotherapy to weigh gain, the reversibility of the side effect remains uncertain. There is scarcity of data on the change of weight or BMI after treatment discontinuation. The largest study that examined the weight change after discontinuation of antipsychotics was conducted by Kuijper et.al, among 99 adults with intellectual disability. The study reported an average of 3.5 kgs absolute weight decrease and about 1.4 kg/m^2 of reduction in BMI 12 weeks after discontinuing antipsychotic medications. One of the drawbacks of this study was missing the baseline weight and BMI measures before the treatment initiation. The study fail to inform the change of weight and BMI during the treatment and answer whether the weight gain associated with antipsychotics was completely reversible because more than 80% of the participants used antipsychotics for more than 10 years and had incomplete records at the baseline. (Kuijper et al. 2013). Another study using an adult patient sample treated with atypical antipsychotics found that only 25% of 35 patients (who gained 20 or more pounds during the medication treatment) were able to lose more than 10 pounds after the treatment discontinuation (Lindsay et.al. 2004, o' Keefe et.al, 2001).

Not much literature is present on the effect of pharmacotherapy discontinuation on weight gain in adults, with even bigger gap in literature for children. The only relevant pediatric study was conducted by Lindsay et al. (2004) which assessed the weight changes due to risperidone and further effect due to discontinuation in 14 children diagnosed with disruptive behavior disorders (oppositional defiant disorder and conduct disorder) . The authors conclude that for 11 children, the weight gain was reversible at 9

to 12 months after discontinuation, but further admitted the need of more data from larger cohorts to make a definitive conclusion (Lindsay et.al, 2004).

The objective of our study was to conduct a one year comparative effectiveness study that assesses the effect of psychotropic medication discontinuation on BMI among bipolar children and adolescents.

Methods

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 for 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. For each patient visit, the specialty of physician who attended patient and the practice type is also documented. The database is de-identified in accordance with the Health Insurance Portability and Accountability Act and has been used widely in published literature. (Ghate et. al. 2013, LaFleur et.al. 2011, McAdam-Marx et.al. 2011, Brixner at.al. 2006,).

Study Population:

Bipolar disorder is a neuropsychiatric disorder with childhood onset. The individuals eligible for inclusion in this phase of the study if they were (i) under 18 years

of age; (ii) ever received a diagnosed with Bipolar (ICD-9-CM code: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8) after a minimum of 180-day period (also known as the baseline/washout period) free of bipolar diagnosis or prescription to increase the likelihood that the treatment identified represents a new treatment episode; (iii) received atypical antipsychotics or mood stabilizers; (iv) discontinue treatment within 12 months of treatment initiation; (v) and had at least three BMI measures, that were taken within 3 month prior to the treatment initiation, during the treatment and within 12 months after the treatment discontinuation.

Study Design:

This study used a retrospective cohort design for which every treated bipolar case was followed for up to one year since the date of treatment discontinuation. Treatment discontinuation date was defined as date on which all medications were stopped indicated as a noted removal by the physician in the data or the date of last prescription of bipolar medication plus 30 days. Individuals were followed quarterly, that is, up to 3 months, 6 months, 9 months and 12 months, from the date of treatment discontinuation.

Outcome: All weight and BMI measures taken between 3 month prior to the treatment initiation and 12 month post the treatment discontinuation were identified. As illustrated in the Figure 1, the weight and BMI measures taken during 3 month prior to or on the date of the treatment initiation was defined as “baseline weight” and “baseline BMI”; The BMI measure taken within 3 months before treatment discontinuation, was defined a “BMI at discontinuation”; The measures taken after the treatment discontinuation were defined as “weight after discontinuation” and “BMI after discontinuation”.

The primary outcome measure of our study was change in BMI after discontinuation calculated as: BMI after discontinuation – BMI at discontinuation. The difference was taken to see the change in BMI after treatment discontinuation. According to the availability of the BMI measure, these outcomes measured quarterly after the treatment discontinuation (up to 3, 6, 9 and 12 months) so as to examine short term and long term treatment discontinuation effects.

Statistical Analysis

Descriptive statistics (Means ±SD) were computed for BMI measures at different time points. T-test was used to compare the difference between weight and BMI measures at 3, 6, 9 after treatment discontinuation and the measures at the baseline (before the treatment initiation) to determine if the weight/BMI change is reversible.

Repeated measure mixed model was used to model the factors that affect the change of BMI during 3, 6, 9 and 12 months after treatment discontinuation. Due to the presence of multiple BMI measured for each individual (BMI measures at multiple time points), these observations nesting under each individual are correlated, and hence cannot be considered independent from each other. In addition, as no individuals have BMI measured at all follow-up months, the presence of missing BMI measures limits analysis techniques that can be used to model the data. Mixed models are a flexible approach to model correlated data, by taking into consideration the type of correlation, and observations with missing BMI values by excluding those observations from the analysis.

Independent Variables: To explore the factors associated with change in BMI after treatment discontinuation, the independent variables included in the repeated measure mix models were prior treatment regimen (categorized as (i) Those who ever

received AT plus MS combination, (ii) Those who never received MS but ever received AT monotherapy, (iii) Those who never received AT but received MS monotherapy), duration of prior treatment, BMI at treatment discontinuation, demographic characteristics (age, gender, race, region and type of insurance), baseline and concurrent psychosocial and behavioral intervention and comorbid conditions (attention-deficit hyperactive disorder, depression, anxiety disorder, substance use disorder, oppositional or conduct disorder and learning disability).

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 and was considered for this study.

All analysis was carried out using Statistical Analysis Software 9.3 (SAS, Cary, NC, USA). This study was approved by the Institutional Review Board at the University of Houston.

Results

Cohort Characteristics

Figure 2 shows a schematic flow chart depicting cohort formation. 17,779 children and adolescents (age 18 years or younger) were identified with bipolar disorder diagnosis (ICD-9-CM code: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8). Of which, 23.02% (N=4,092) were observed prescribed atypical antipsychotics, mood stabilizers following the index diagnosis in the database. After excluding those without baseline BMI or BMI during the treatment (N=1,793), and those who did not discontinue treatment within 12 months of treatment initiation and without post discontinuation BMI

measures (N=1,034), the final cohort consisted of 1,265 treated children and adolescent with bipolar diagnosis.

Clinical Characteristics

As presented in table 1, the mean age of the cohort was 13.67 (±3.83) years. A half of individuals in the cohort were whites (N=626, 49.49%), females (N=658, 52.02%) approximate one third resided in the Midwest region of US (N=493; 38.97%) and had commercial insurance (N=434; 34.31%). ADHD was found to be the most commonly diagnosed comorbid condition (N=292, 23.48%).

Vast majority of the study cohort received one of the follow three treatment regimens: 49% (N=614) were ever prescribed atypical antipsychotics but never received mood stabilizers; 33% (N=422) were ever prescribed mood stabilizers but never received atypical antipsychotics; 18% (N=229) were ever prescribed combination treatments of atypical antipsychotics plus mood stabilizer. Median (IQR) time to discontinuation of treatment was 7 (4-9) months with mean (±SD) of about 6.74(±2.82) months. Only about 3% (N=37) and 1.9% (N=24) of the individuals ever received treatment concurrent or prior treatment psychosocial and behavioral intervention respectively.

Descriptive statistics of change in BMI:

The average number of BMI measures within a 12 months period after the treatment discontinuation was 3.3(±2.27) with the median (IQR) of 3(1-4). Mean weight and BMI of the study cohort was 139.19 (±56.45) lbs and 24.03 (±8.58) kg/m2 at the baseline, 144.68 (±58.45) lbs and 25.53 (±8.32) kg/m2 at the treatment discontinuation and 152.41 (±59.55) lbs and 25.87 (±8.02) kg/m2 12 months after the treatment discontinuation. Mean BMI of the study cohort at the end of 12 month follow-up period was significantly

higher (p= <0.001) than BMI measured at the baseline. As shown in figure 3, there had been an upward trend of BMI during the treatment and after the treatment discontinuation. The proportion of children and adolescents who were overweight/obese (≥85 percentile) one year after the treatment discontinuations (53.49 %) were higher that at the start of the treatments (51.03%).

Table 2 presents the BMI measures of all individuals at baseline, at treatment discontinuation and within 3, 6, 9 and 12 months after treatment discontinuation by treatment groups. Children who initiated their treatment with atypical antipsychotics had significantly lower baseline BMIs (23.56±7.28) than patients initiated with mood stabilizer monotherapy (25.08±6.87) or ATMS combination (25.27±7.11). During the treatment, the BMIs of children on all psychotropic regimens had increased significantly. After the treatment discontinuation, the BMIs remained higher than the baseline BMI at all time points for those atypical antipsychotic monotherapy users; higher at 3, 6 and 9 months after treatment discontinuation for those mood stabilizer users; and higher at 3 and 6 months for those ATMS combination recipients. When compared with the last BMI taken during the treatment (at the treatment discontinuation), the previous atypical antipsychotic users' BMIs were still higher at 9 and 12 months after the treatment discontinuation indicating continuous increase of BMI after the treatment discontinuation. Children and adolescents who had been on mood stabilizer monotherapy or ATMS combination also showed a positive trend of increase in BMI as compared to the last BMI taken during the treatment. However, the differences were not statistically significant.

Factors associated with change of BMI after treatment discontinuation

Table3 presents the mixed effect model results which show factors associated with change in BMI after the treatment discontinuation. The change of BMI after treatment discontinuation was neither associated with the treatment regimens patients previously received, nor associated with time from the treatment discontinuation. The only two statistically significant predictors for the BMI change after treatment discontinuations were age and BMI lastly measured during the treatment (at treatment discontinuation). The increase in age was associated with more reduction of BMI after the treatment discontinuation, while the BMI at discontinuation had an opposite effect. Every one year older in age was associated with less increase of BMI by 0.083 kg/m2, 0.12 kg/m2, 0.14 kg/m2 and 0.15 kg/m2 at 3, 6, 9 and 12 months after the treatment discontinuation respectively. In contrast, for every one kg/m2 higher BMI lastly taken during the treatment, the BMI after treatment discontinuation was 0.10 kg/m2, 0.11 kg/m2, 0.12 kg/m2 and 0.119 kg/m2 higher at 3, 6, 9 and 12 months follow-ups respectively.

Discussion

Our findings suggest that, for most children who were on atypical antipsychotics, mood stabilizers (lithium, anticonvulsants), and the combination of these medications with atypical antipsychotics, their BMI stayed on the level at the end of the treatment and did not return to the baseline (prior treatment) level 12 months after the treatment discontinuation.

Limited research has examined the mechanisms of weight gain associated with the use of psychotropic medications and even less has explored the weight change and its

potential mechanisms after the treatment discontinuation Psychotropic medications could induce weight gain by increasing appetite for sweet and fatty food, known as "Food Craving" and by decreasing the resting metabolic rate (Fernstrom et.al, 1985). The continuous increase in BMI even after treatment discontinuation observed in our study could be explained by the behavioral circuit model, also known as *sugar addiction model;* developed by Hoebel et.al. (2009) from laboratory rat studies. As per the theory, sugar bingeing causes repeated release of excessive dopamine (DA) and opioid stimulation during abstinence from sugar. This causes a feeling similar to opioid withdrawal and leads to "sugar craving" leading to likelihood to have more sugary foods. This may indicate that the change in lifestyle and eating habits that persists for a long period of time, even after discontinuation of the treatment.

Multivariate analysis showed that the younger the age, the less likely the BMI will return to the level before the initiation of the psychotropic treatments. Children are constantly growing and developing resulting in increase in BMI and weight over time. This may explain our findings that younger aged children are less likely to reverse their BMI as compared to older children and adolescents, considering their growth and BMI starts to stabilize as they age. Interestingly, our findings show no difference between children and adolescents on psychotropic treatment discontinuation across different treatment regimens, implying the effect of treatment discontinuation is equal on all children and adolescents across different treatment regimens.

Another finding of the multivariate analysis was that the higher the BMI at treatment discontinuation, the less likely is the BMI to return to the level before treatment initiation. This finding is consistent with what has been reported in the previous research

conducted in adult population. O' Keefe et. al.'s clinician survey (2001) reported only 23% (12 out of 53) of all antipsychotics treated patients, who gained more than 20 pounds of weight, were able to lose 10 or more pounds of weight after discontinuation. Moreover, intellectual disability diagnosed adults who discontinued antipsychotic treatment was able to lose 3.5kg weight and 1.4 kg/m2 BMI among those who discontinued treatment. This study is limited by lack of original weight and BMI measures before treatment initiation making it impossible to establish complete reversibility of weight and BMI gain (Kuijper, 2013).

These results imply a need for strict BMI and weight monitoring during the treatment period and additional aggressive nutritional and weight counseling during and after discontinuation of the treatment. Furthermore there is need for development of effective interventions for children and adolescents to lose weight, especially after treatment discontinuation. The American Diabetes Association (ADA)/ American Psychiatric Association (APA) guidelines, published in February 2004, recommend monitoring of metabolic parameters such as weight and body mass index (BMI), blood pressure, fasting plasma glucose, and fasting lipid profile for all patients receiving antipsychotic treatment. Physicians treating adolescents with antipsychotics need to be familiar with treatment guidelines and review the weight gain potential associated with antipsychotic agents and regularly monitor children and adolescents to avoid the long term risks (Clark et. al. 2004).

The primary strength of this study is that actual clinical measures such as BMI values in the GE EMR database were used to assess change in weight among children and adolescents on pharmacotherapy. Previous studies have used current ICD-9 codes

and not actual clinical measures to assess obesity/weight gain in adolescents on antipsychotics (McIntyre et. al. 2008) 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 30kg/m2 which may not apply to adolescents where overweight and obesity is defined based on BMI percentiles compiled on growth charts from the Centers for Disease Control and Prevention (Kuczmarski et. al. 2002). Another strength of the study is that to our knowledge, this is the first observational study that studies the impact of pharmacotherapy (atypical antipsychotics, mood stabilizers and antidepressant) in bipolar children and adolescents on BMI increase and further impact of treatment after discontinuation making the results unique.

As with any research study there are several limitations. One of the most important limitations of this study 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. Secondly, the data has lot of missing BMI values but we have no evidence that inclusion of BMI values are associated with SGA prescription and assume that the bias is non-differential, and that the BMI measures are missing at random. Finally, the database lacks information on socioeconomic status, diet, physical activity, or overall health of patient's parents. These unmeasured variables, among other variables, play a significant role in impacting the weight of adolescents in the data.

The goal of the current study is to answer these questions and thereby assisting clinicians, psychiatrists and parents to make an informed decision on bipolar treatment in children and adolescents and thereby prevent premature discontinuation of treatment. Specifically,

Conclusion

In long-term, there is no significant difference between effects of treatment regimen on BMI after treatment discontinuation. BMI does not return back to baseline after discontinuation of treatment. Bipolar children and adolescents need to be monitored aggressively for height, weight and BMI during and after treatment and should be provided with nutritional and weight management counseling especially after treatment.

References

Allison, D. B., J. L. Mentore, et al. (1999). "Antipsychotic-induced weight gain: a comprehensive research synthesis." American Journal of Psychiatry 156(11): 1686-1696.

American Diabetes Association (2004), Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 65:267-272

American Psychiatric Association, and Kernberg. American Psychiatric Association practice guideline for the treatment of patients with bipolar disorder. American Psychiatric Pub, 2002.

Bebbington, P. and R. Ramana (1995). "The epidemiology of bipolar affective disorder." Social psychiatry and psychiatric epidemiology 30(6): 279-292.

Brixner, Diana I., Qayyim Said, Patricia K. Corey-Lisle, A. Vickie Tuomari, J. L. Gilbert, William Stockdale, and Gary M. Oderda. "Naturalistic impact of second-generation antipsychotics on weight gain." Annals of Pharmacotherapy 40, no. 4 (2006): 626-632.

Castro-Fornieles, Josefina, Mara Parellada, César A. Soutullo, Immaculada Baeza, Ana Gonzalez-Pinto, Montserrat Graell, Beatriz Paya, Dolores Moreno, Elena de la Serna, and Celso Arango. "Antipsychotic treatment in child and adolescent first-episode psychosis: a longitudinal naturalistic approach." Journal of child and adolescent psychopharmacology 18, no. 4 (2008): 327-336.

Centorrino F, Cincotta SL, Talamo A, Fogarty KV, Guzzetta F, Saadeh MG, Salvatore P, Baldessarini RJ. Hospital use of antipsychotic drugs: polytherapy. Compr Psychiatry. 2008 Jan-Feb; 49(1):65-9.

Chengappa, KN Roy, L. Chalasani, Jaspreet S. Brar, H. Parepally, Patricia Houck, and Joseph Levine. "Changes in body weight and body mass index among psychiatric patients receiving lithium, valproate, or topiramate: an open-label, nonrandomized chart review." Clinical therapeutics 24, no. 10 (2002): 1576-1584.

Clark, N.G., 2004. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes care, 27(2), p.596.

Correll CU. Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. Journal of the American Academy of Child and Adolescent Psychiatry. 46:687-700, 2007.

Corell, C. U. and H. E. Carlson (2006). "Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents." Journal of the American Academy of Child and Adolescent Psychiatry 45(7): 771-791.

De Hert, Marc, M. Dobbelaere, E. M. Sheridan, D. Cohen, and C. U. Correll. "Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice."European Psychiatry 26, no. 3 (2011): 144-158.

De Kuijper, Gerda, Hans Mulder, Heleen Evenhuis, Frank Visser, and Pieter J. Hoekstra. "Effects of controlled discontinuation of long-term used antipsychotics on weight and metabolic parameters in individuals with intellectual disability." Journal of clinical psychopharmacology 33, no. 4 (2013): 520-524.

Fedorowicz, V. J. and E. Fombonne (2005). "Metabolic side effects of atypical antipsychotics in children: a literature review." Journal of psychopharmacology (Oxford, England) 19(5): 533.

Fernstrom MH, Epstein LH, Spiker DG and Kupfer DJ. Resting metabolic rate is reduced in patients treated with antidepressants. Biological psychiatry. 20:692-695, 1985.

Ghate, Sameer R., Christina A. Porucznik, Qayyim Said, Mia Hashibe, Elizabeth Joy, and Diana I. Brixner. "Association between second-generation antipsychotics and changes in body mass index in adolescents." Journal of Adolescent Health 52, no. 3 (2013): 336-343.

Jerrell JM, McIntyre RS. Adverse events in children and adolescents treated with antipsychotic medications. Hum Psychopharmacol. 2008 Jun; 23(4):283-90.

Kleinman LS, Lowin A, Flood E, Gandhi G, Edgell E and Revicki DA. Costs of bipolar disorder. Pharmacoeconomics. 21:601-622, 2003.

Kompoliti, Katie, Glenn T. Stebbins, Christopher G. Goetz, and Wenqing Fan. "Association between antipsychotics and body mass index when treating patients with tics." Journal of child and adolescent psychopharmacology 20, no. 4 (2010): 277-281.

Kuczmarski, Robert J., Cynthia L. Ogden, Shumei S. Guo, Laurence M. Grummer-Strawn, Katherine M. Flegal, Zuguo Mei, Rong Wei, Lester R. Curtin, Alex F. Roche, and Clifford L. Johnson. "2000 CDC Growth Charts for the United States: methods and development." Vital and health statistics. Series 11, Data from the national health survey 246 (2002): 1-190.

LaFleur, Joanne, Carrie McAdam-Marx, Stephen S. Alder, Xiaoming Sheng, Carl V. Asche, Jonathan Nebeker, Diana I. Brixner, and Stuart L. Silverman. "Clinical risk factors for fracture among postmenopausal patients at risk for fracture: a historical cohort study using electronic medical record data."Journal of bone and mineral metabolism 29, no. 2 (2011): 193-200.

Lin, D., H. Mok, et al. (2006). "Polytherapy in bipolar disorder." CNS drugs 20(1): 29-42.

Lindsay RL, Leone S, Aman MG. Discontinuation of risperidone and reversibility of weight gain in children with disruptive behavior disorders. Clinical pediatrics 2004;43:437-44.

Macmillan CM, Withney JE, KorndÖRfer SR, Tilley CA, Mrakotsky C and Gonzalez-Heydrich JM. Comparative clinical responses to risperidone and divalproex in patients with pediatric bipolar disorder. Journal of Psychiatric Practice. 14:160-169, 2008.

Martin, Andrés, Lawrence Scahill, George M. Anderson, Michael Aman, L. Eugene Arnold, James McCracken, Christopher J. McDougle, Elaine Tierney, Shirley Chuang, and Benedetto Vitiello. "Weight and leptin changes among risperidone-treated youths with autism: 6-month prospective data."American Journal of Psychiatry 161, no. 6 (2004): 1125-1127.

McAdam-Marx C, Bouchard J, Aagren M, Conner C, Brixner DI. Concurrent control of blood glucose, body mass, and blood pressure in patients with type 2 diabetes: an analysis of data from electronic medical records. Clinical therapeutics 2011;33:110-20.

McIntyre, Roger S., and Jeanette M. Jerrell. "Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents." Archives of pediatrics & adolescent medicine 162.10 (2008): 929-935.

McIntyre, R. S. and J. Z. Konarski (2005). "Tolerability profiles of atypical antipsychotics in the treatment of bipolar disorder." J Clin Psychiatry 66(Suppl 3): 28-36.

Newcomer, J. W. (2005). "Second-generation atypical antipsychotics and metabolic effects. A comprehensive literature review." CNS drugs 19(Suppl 1): 1-93.

O'Keefe C, Noordsky D, Liss T, Weiss H. Reversal of Weight Gain Associated with Antipsychotic Treatment. Phoenix, AZ: New Clinical Drug Evaluation Unit Program (NCDEU); 2001. Available at: www.nimh.nih.gov/ncdeu/abstracts2001/ncdeul006.cfm

Patel, Nick C., Monica Hariparsad, Mary Matias-Akthar, Michael T. Sorter, Drew H. Barzman, John A. Morrison, Kevin E. Stanford, Stephen M. Strakowski, and Melissa P. DelBello. "Body mass indexes and lipid profiles in hospitalized children and adolescents exposed to atypical antipsychotics."Journal of child and adolescent psychopharmacology 17, no. 3 (2007): 303-311.

Pfeifer JC, Kowatch RA and DelBello MP. Pharmacotherapy of Bipolar Disorder in Children and Adolescents: Recent Progress. CNS drugs. 24:575-593, 2010.

Torrent C, Amann B, Sánchez-Moreno J, Colom F, Reinares M, Comes M, Rosa AR, Scott J and Vieta E. Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. Acta Psychiatrica Scandinavica. 118:4-18, 2008.

Shaw, Jon A., John E. Lewis, Shlomo Pascal, Rakesh K. Sharma, Rosemarie A. Rodriguez, Ramiro Guillen, and Marilyn Pupo-Guillen. "A study of quetiapine: efficacy and tolerability in psychotic adolescents." Journal of child and adolescent psychopharmacology 11, no. 4 (2001): 415-424.

Sikich, Linmarie, Robert M. Hamer, Robert A. Bashford, Brian B. Sheitman, and Jeffrey A. Lieberman. "A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial."Neuropsychopharmacology 29, no. 1 (2004): 133-145.

Tables and Figures

Figure1. Schematic of Patients' BMI Measures

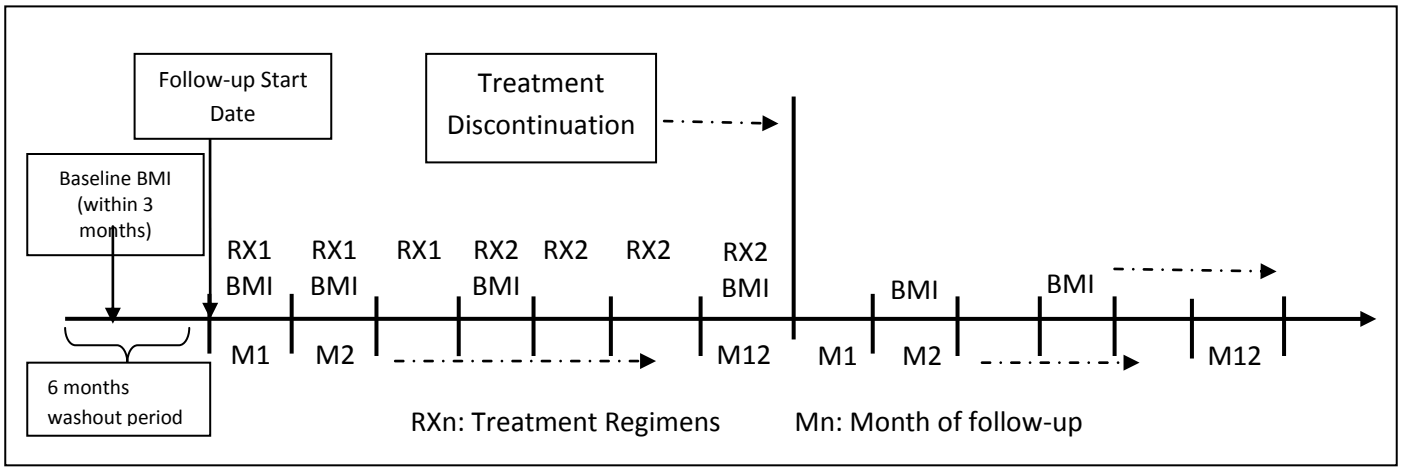

Figure 2. Schematic Representation of Cohort Selection

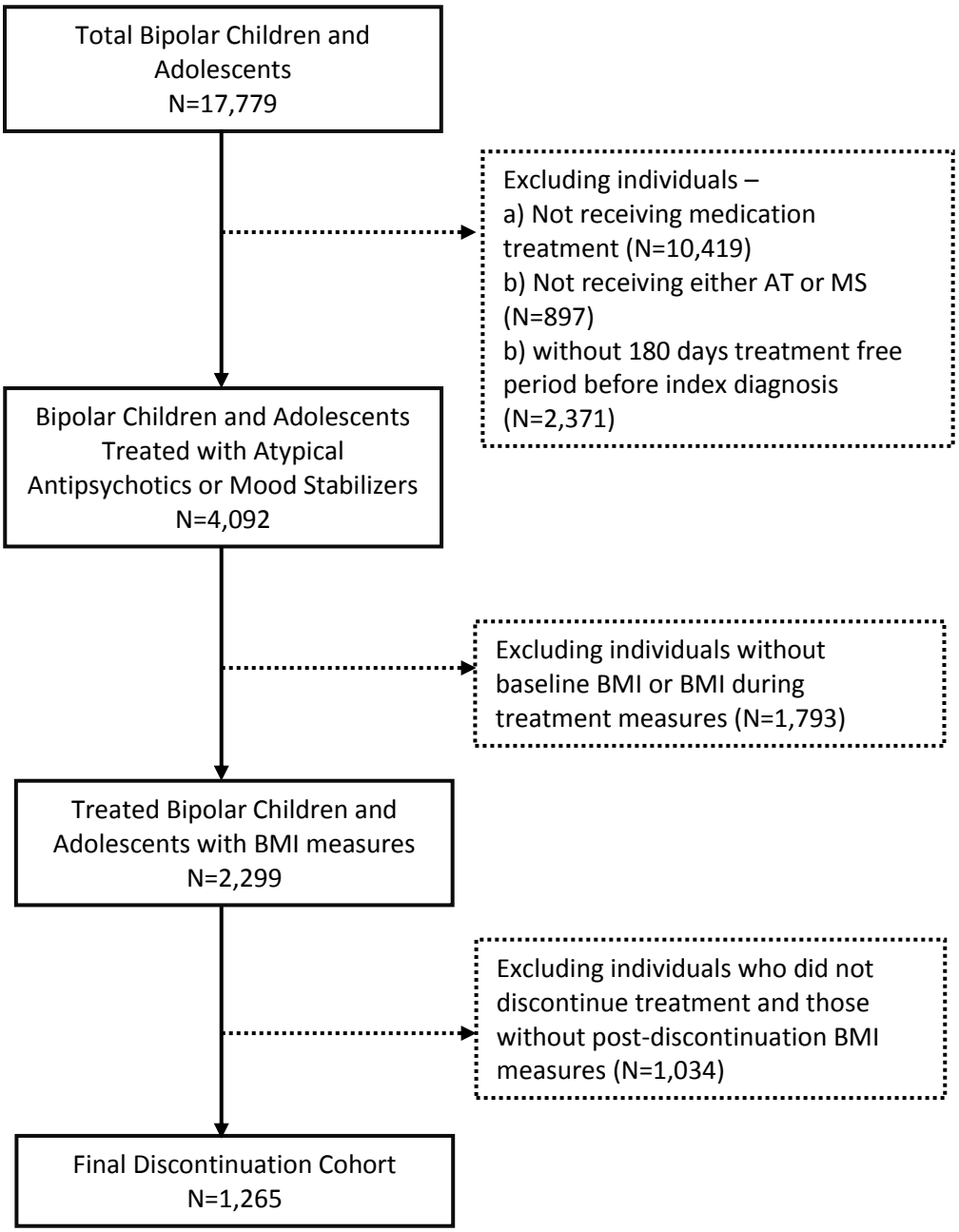

Table 1: Demographics and Clinical Characteristics

Characteristics		Treatment Discontinuation (N=1,265 (100%))
Age (years)	Mean (SD)	13.67 (3.83)
	Median (IQR)	15 (11-17)
Race	White	626 (49.49%)
	Black	38 (3.00%)
	Hispanic	11 (0.87%)
	Other	590 (46.64%)
Gender	Male	607 (47.98%)
	Female	658 (52.02%)
Insurance	Commercial	434 (34.31%)
	Medicaid	327 (25.85%)
	Self-pay	36 (2.85%)
	Unknown	468 (37.00%)
Region	Midwest	493 (38.97%)
	Northeast	286 (22.61%)
	South	275 (21.74%)
	West	211 (16.68%)
Psychosocial and Behavioral Interventions	Baseline	24 (1.90%)
	Concurrent	37 (2.92%)
Comorbidities	ODCD	128 (10.12%)
	Depression	172 (13.60%)
	ADHD	297 (23.48%)
	Anxiety Disorder	137 (10.83%)
	Substance Use Disorder	72 (5.69%)
	Learning Disability	23 (1.82%)
Treatment Groups	Atypical Antipsychotics plus Mood Stabilizers	229 (18.10%)
	Atypical Antipsychotics (AT)	614 (48.54%)
	Mood Stabilizers (MS)	422 (33.36%)

Figure 3: Mean BMI prior, during and after the psychotropic treatment

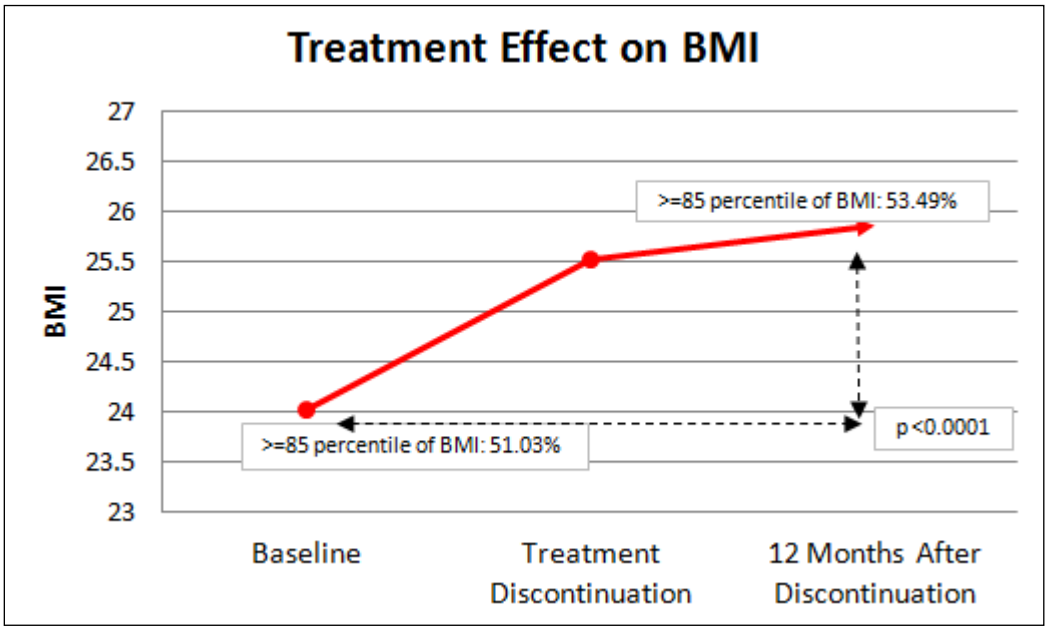

Table 2: BMI Measures

Measure	Atypical Antipsychotics plus Mood Stabilizers Mean(SD)	Atypical Antipsychotics Mean(SD)	Mood Stabilizers Mean(SD)
Baseline BMI	25.274 (7.114)	23.559 (7.277)	25.075 (6.867)
BMI at Discontinuation	26.107 (7.126)	24.637 (7.35)	25.878 (7.155)
Month 3 after Discontinuation	26.41 (7.439)*	24.64 (7.628)*	26.361 (7.695)*
Month 6 after Discontinuation	26.531 (7.898)*	24.901 (7.563)*	26.014 (7.712)*
Month 9 after Discontinuation	25.785 (7.248)	25.368 (7.502)*$	26.344 (7.811)*
Month 12 after Discontinuation	26.331 (7.004)	25.779 (7.554)*$	25.926 (8.191)
* - Statistical significant difference from baseline BMI ($p<0.05$) $ - Statistical significant difference from BMI at Discontinuation ($p<0.05$)			

Table 3. Effect on Change in BMI after Treatment Discontinuation								
Characteristics	**Up to 3 Months**		**Up to 6 Months**		**Up to 9 Months**		**Up to 12 Months**	
	Estimate (95% C.I.)	**P-Value**	**Estimate (95% C.I.)**	**P-Value**	**Estimate (95% C.I.)**	**P-Value**	**Estimate (95% C.I.)**	**P-Value**
Treatment (Ref: MS)								
ATMS	-0.102 (-0.641 - 0.437)	0.7104	-0.268 (-0.736 - 0.2)	0.2619	-0.384 (-0.823 - 0.055)	0.0865	-0.378 (-0.795 - 0.039)	0.0752
AT	0.074 (-0.354 - 0.501)	0.7354	0.216 (-0.157 - 0.589)	0.2555	0.232 (-0.114 - 0.579)	0.1878	0.225 (-0.102 - 0.553)	0.1777
Time (continuous)	0.017 (-0.059 - 0.093)	0.6628	0.017 (-0.052 - 0.085)	0.6336	0.001 (-0.063 - 0.065)	0.981	0.004 (-0.057 - 0.065)	0.9069
Months on Treatment	0.067 (-0.007 - 0.141)	0.0746	0.071 (-0.004 - 0.138)	0.0568	0.047 (-0.017 - 0.11)	0.1476	0.042 (-0.018 - 0.103)	0.1673
BMI at Discontinuation	0.103 (0.076 - 0.129)	<.0001	0.114 (0.091 - 0.138)	<.0001	0.121 (0.099 - 0.143)	<.0001	0.119 (0.097 - 0.14)	<.0001
Age	-0.083 (-0.138 - -0.028)	0.0033	-0.12 (-0.168 - -0.071)	<.0001	-0.139 (-0.185 - -0.093)	<.0001	-0.145 (-0.188 - -0.101)	<.0001
Gender (Ref: Male)								
Female	0.26 (-0.126 - 0.646)	0.1857	0.214 (-0.121 - 0.548)	0.2101	0.155 (-0.156 - 0.467)	0.327	0.21 (-0.085 - 0.505)	0.1623
Race (Ref: White)								
Black	0.39 (-0.747 - 1.526)	0.5009	0.361 (-0.6 - 1.321)	0.4613	0.448 (-0.45 - 1.346)	0.3277	0.446 (-0.405 - 1.297)	0.3042
Hispanic	2.369 (0.044 - 4.693)	0.0458	1.322 (-0.406 - 3.05)	0.1336	0.972 (-0.732 - 2.677)	0.2634	1.099 (-0.518 - 2.716)	0.1825
Others	0.137 (-0.235 - 0.509)	0.4697	0.235 (-0.09 - 0.56)	0.1556	0.34 (0.036 - 0.643)	0.0283	0.308 (0.02 - 0.596)	0.0364
Region (Ref: Midwest)								
Northeast	0.023 (-0.485 - 0.532)	0.928	-0.04 (-0.482 - 0.401)	0.8587	-0.033 (-0.445 - 0.38)	0.8761	-0.063 (-0.456 - 0.329)	0.751
South	0.042 (-0.457 - 0.54)	0.8696	-0.155 (-0.591 - 0.281)	0.4859	-0.081 (-0.49 - 0.329)	0.6985	-0.126 (-0.515 - 0.262)	0.5229
West	-0.345 (-0.938 - 0.249)	0.255	-0.277 (-0.795 - 0.241)	0.2944	-0.04 (-0.516 - 0.437)	0.8705	-0.179 (-0.628 - 0.269)	0.4332
Insurance (Ref: Commercial)								
Medicaid	0.037 (-0.463 - 0.537)	0.884	-0.047 (-0.481 - 0.387)	0.8313	0.038 (-0.37 - 0.447)	0.8537	0.025 (-0.362 - 0.413)	0.8981
Self-pay	-1.087 (-2.247 - 0.073)	0.0662	-0.547 (-1.585 - 0.491)	0.3013	-0.253 (-1.201 - 0.695)	0.6008	-0.08 (-0.981 - 0.821)	0.8616
Unknown	-0.019 (-0.463 - 0.426)	0.9344	0.089 (-0.297 - 0.475)	0.6498	0.15 (-0.206 - 0.507)	0.408	0.208 (-0.13 - 0.547)	0.2277
Baseline Psychosocial and Behavioral Intervention (Ref: No)								
Yes	-1.372 (-2.8 - 0.055)	0.0595	-0.829 (-2.19 - 0.532)	0.2322	-0.686 (-1.974 - 0.603)	0.2968	-0.362 (-1.581 - 0.857)	0.5604
Current Psychosocial and Behavioral Intervention (Ref:								

No) Yes	-0.589 (-1.87 - 0.691)	0.3665	-0.536 (-1.697 - 0.625)	0.365	-0.202 (-1.297 - 0.893)	0.7177	-0.825 (-1.852 - 0.201)	0.115
Oppositional/Conduct Disorder (Ref: No) Yes	-0.064 (-0.682 - 0.554)	0.8392	0.049 (-0.487 - 0.584)	0.8586	0.073 (-0.417 - 0.563)	0.77	0.075 (-0.394 - 0.543)	0.7543
Depression (Ref: No) Yes	0.35 (-0.207 - 0.908)	0.2179	0.431 (-0.053 - 0.915)	0.0806	0.517 (0.081 - 0.953)	0.0202	0.443 (0.028 - 0.859)	0.0367
ADHD (Ref :No) Yes	-0.093 (-0.54 - 0.354)	0.6835	0.007 (-0.381 - 0.395)	0.9721	0.087 (-0.276 - 0.449)	0.6386	0.1 (-0.245 - 0.445)	0.5691
Learning Disability (Ref: No) Yes	-0.056 (-1.328 - 1.217)	0.9315	0.595 (-0.507 - 1.696)	0.2897	0.745 (-0.323 - 1.813)	0.1714	0.753 (-0.258 - 1.765)	0.1442