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Preliminary Findings regarding Overweight and Obesity in Pediatric Bipolar Disorder

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Abstract

Objective—Overweight (OW) and obesity (OB) is highly prevalent among adults with bipolar disorder (BP), and has been associated with illness severity. Little is known regarding OW/OB among youth with BP.

Methods—Subjects were 348 youth ages 7 to 17 years old, with BP-I, BP-II, or study-operationalized criteria for BP-NOS enrolled in the Course and Outcome of Bipolar Youth study. Ageand sex-adjusted body mass index (BMI) was computed according to International Obesity Task Force cut points, based on self- and parent-reported height and weight, to determine OW/OB.

Results—OW/OB was prevalent among 42% of subjects. The most robust predictors of OW/OB in a logistic regression model were younger age, non-Caucasian race, lifetime physical abuse, substance use disorders, psychiatric hospitalizations, and exposure to ≥2 medication classes associated with weight-gain.

Conclusions—The prevalence of OW/OB among youth with BP may be modestly greater than the general population. Moreover, similar to adults, OW/OB among youth with BP may be associated with increased psychiatric burden. These preliminary findings underscore the importance of early identification of OW/OB among youth with BP. Future studies are needed to clarify the direction of the associations between OW/OB and the identified predictors, and to compare the prevalence of OW/OB among youth with BP versus other psychiatric disorders.

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DISCLOSURE

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Keywords

bipolar disorder; child; adolescent; pediatric; overweight; obesity

INTRODUCTION

Bipolar disorder (BP) is a serious, recurrent illness associated with high rates of medical and psychiatric comorbidity[1], and increased mortality[2,3]. In addition to the burden of psychiatric symptoms, BP is associated with increased mortality due to medical causes, most notably cardiovascular disease[2,3]. Cardiovascular disease and diabetes mellitus (DM) are among the most common medical conditions in BP, and the onset of these conditions may occur earlier than among individuals without BP[4]. Recent findings from large-scale clinical studies of BP indicate that the majority of adults with BP are overweight or obese (OW/OB)[5,6]. Canadian epidemiologic data suggest that the prevalence of OW/OB among adults with BP is significantly higher than among the general population[7]. Data from the National Comorbidity Survey Replication indicate that OB is associated with an approximately 25% increase in odds of mood and anxiety disorders in general, and approximately 50% increase in odds of BP specifically[8]. In addition to adverse medical outcomes associated with OW/OB, including hypertension, diabetes mellitus, osteoarthritis[6], and the metabolic syndrome[9], studies have demonstrated that OW/OB in BP is associated with markers of BP illness severity[5,6,9-11]. BP subjects with a history of suicidality have been found to have greater BMI as compared to those with no such history[5], and BP subjects with OB[9] or extreme OB[6] are more likely than those without OB to have made a suicide attempt. Fagiolini and colleagues[10] reported a 68% prevalence of OW/OB among BP patients; followed prospectively, the majority of weight gain occurred early in treatment and amount of BMI increase was positively associated with the severity of depressive symptoms and negatively associated with baseline BMI. This group also reported that OB was associated with greater depressive severity, increased rate of depressive recurrence, and short time to recurrence[11].

Taken together, these findings indicate that adults with BP may be at increased risk of OW/OB, and that OW/OB may be associated with a more severe course of illness. However, no previous study has specifically examined OW/OB among children and adolescents with BP. Given the findings from adults with BP, in addition to evidence that obesity among youth has profound psycho-social, medical, and economic consequences[12], a study of OW/OB among youth with BP is indicated. This report describes the prevalence and correlates of OW/OB among participants in the multi-center, NIMH-funded, Course and Outcome of Bipolar Youth (COBY) study.

METHODS

Participants

The COBY study enrolled 446 subjects, ages 7-17 years. However, present analyses are restricted to 348 (78%) subjects for whom data regarding height and weight were available. Prior to data collection, subject assent and parental informed consent was provided for participation in the COBY study. Subjects were primarily recruited through clinical referrals within three academic medical centers (University of Pittsburgh, Brown, UCLA); community referrals and print advertisements were also utilized to recruit subjects. Institutional Review Board approval was obtained at each site prior to subject enrollment. Demographic and clinical characteristics are reported in Table 1.

Inclusion Criteria

Subjects met the following criteria: 1) DSM-IV bipolar I disorder (BPI), bipolar II disorder (BPII), or study-operationalized criteria for bipolar disorder not otherwise specified (BP NOS); 2) determined to have a primary bipolar disorder (not induced by substance use, medications, or a medical condition); and 3) intellectual functioning within normal limits. Details regarding the study-operationalized diagnosis of BP-NOS have been previously reported, and COBY data on clinical course and outcome provide preliminary validation for these operationalized BP NOS criteria[13,14].

Procedures

Procedures for the COBY study have been previously reported [13,14], and are presented here in summarized format. All of the information described below was ascertained at the intake assessment.

Diagnosis

All COBY diagnosticians have a bachelor's, master's or Ph.D. degree in a mental health field, and attended K-SADS training sessions. Parents were interviewed about their children, and children were directly interviewed. Mood symptoms were assessed by the mood disorder sections of the K-SADS-P (Present Episode, fourth revision[15]) plus additional items from the K-SADS-MRS [16]. Non-mood disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime version (K-SADS-PL)[17]. K-SADS symptom ratings and diagnoses were based on consensus ratings incorporating all available data; in the event of conflicting information, summary ratings were guided by clinical judgment. Diagnoses were confirmed by a consensus conference with a child psychiatrist or psychologist following the interview. To maintain reliability, bimonthly conference calls between sites addressed assessment questions and concerns. Based on ratings of 13 study interviews (4-7 raters per case), inter-rater reliabilities for mood disorders were ≥ 0.75 (kappa); kappas for non-mood disorders were ≥ 0.80. The intraclass coefficient (ICC) for the K-SADS-MRS (12 cases) was 0.96, and the K-SADS-P depression section (12 cases) was 0.98.

Other Demographic and Clinical Information—Basic demographic information was obtained at intake. Socio-economic status (SES) was ascertained using the 4-factor Hollingshead Scale[18]. Information regarding subjects' comorbid diagnoses (e.g., anxiety disorders, conduct disorder) and clinical characteristics (e.g., psychosis, physical abuse, sexual abuse) were discerned from summary scores from the K-SADS interview with the child and the parent. The age of onset for a subject's BP illness was considered to be when the subject first met DSMIV criteria for a manic, mixed, hypomanic, or major depressive episode, or when he/she first met COBY criteria for BP NOS. Given that the validity of DSM-IV diagnostic criteria for preschool-aged children has not been established, the minimum age of onset for BP-spectrum illness was set at 4 years.

Subjects were considered to have a lifetime substance use disorder (SUD) if they met DSM-IV criteria via the K-SADS for abuse or dependence of alcohol or any drug other than nicotine. Suicide attempt was defined by self-injurious behavior that met one of the following criteria: a seriousness or lethality score of 3 on the K-SADS-P depression section (0-6 scale); a seriousness or lethality score of 2 on the K-SADS-PL depressive disorders section (0-3 scale); a lifetime suicide attempt rated as clinically significant on the K-SADS summary lifetime diagnostic checklist. These scores reflect behaviors that were deemed to have suicidal intent of at least "definite but ambivalent" seriousness.

Height and weight were determined by parent-report or self-report (participants ≥12 years of age) at intake. Age- and sex-adjusted body mass index (BMI) cutoffs for OW/OB were determined in accordance with International Obesity Task Force (IOTF) recommendations in order to provide continuity with the recommended adult cutoff of BMI≥25 kg/mg^2 and 30kg/m^2 , for OW and OB respectively [19,20]. These recommendations were based on data from the United States National Health and Nutrition Examination Survey (NHANES).[19] The IOTF method was endorsed in a recent supplement on the assessment of child and adolescent OW/OB published by the American Academy of Pediatrics[21]. For analyses, subjects categorized as OW/OB were compared with non-OW/OB subjects. Although indirect ascertainment of height and weight may yield suboptimal correlation with measured height and weight in certain populations[22], the reliability of this method *for categorizing OW/OB* among youth ranges from excellent (94-96%)[23,24] to good (69-70%)[25]. The available evidence suggests that this method has excellent specificity (95%-99%) and fair-good sensitivity (52%-69%)[23-28]. The reliability of the categorization of OW/OB was also examined using data from 35 consecutive clinical patients with BP ascertained at the Pittsburgh site. Patients (≥12 years old; N=23) and parents (children <12 years old; N=12) provided self-report in identical fashion to the COBY protocol prior to direct measurement of height and weight. OW/OB determined by self-reported height and weight was strongly correlated with OW/OB determined by direct measurement (Pearson r=0.78, p<0.01). There was good-to-excellent sensitivity (94%), specificity (83%), positive predictive value (84%) and negative predictive value (94%).

Lifetime exposure to psychotropic medications was ascertained systematically in categorical fashion in the treatment history section of the K-SADS-PL and from a medical history questionnaire utilized in research protocols at the Western Psychiatric Institute and Clinic. Information regarding adherence, dosage, and duration of treatment was not ascertained at intake.

Statistical Analyses: Statistical analyses were performed using the Statistical Package or the Social Sciences Version 14 (SPSS). Potential risk factors were screened for their association with OW/OB using chi-square analyses for categorical measures and t-tests for continuous measures. Given the dearth of information on predictors of OW/OB in this population, these analyses were approached as hypothesis-generating and were not adjusted for multiple comparisons. Statistical significance was set at $\acute{\alpha} = 0.05$. Factors that were significantly associated with OW/OB in univariate analyses were entered into a logistic regression models in order to estimate the adjusted odds of OW/OB associated with each factor. In addition, BP-subtype was also included as a covariate because of a trend toward statistical significance. Finally, age was included as a covariate because this variable is significantly associated with multiple other variables in the model and thus is a potential confound.

RESULTS

The prevalence of OW/OB in this sample was 42% (145/348). Thirty-nine percent of OW/OB subjects, 16.5% of the overall sample, exceeded the threshold for OB (IOTF-adjusted BMI≥30 kg/m^2). Demographic and clinical characteristics of OW/OB and non-OW/OB subjects are presented in Table 1. As compared to non-OW/OB subjects, OW/OB subjects were significantly more likely to be of non-Caucasian race (p=0.03), and had a significantly earlier age of BP-onset (p=0.03). The lifetime prevalence of physical abuse (p<0.001), SUD (p=0.007), and psychiatric hospitalization (p=0.02) was significantly greater among OW/OB subjects as compared to non-OW/OB subjects. OW/OB subjects were significantly more likely to have been treated with medications from two or more classes with the propensity to cause weight gain. The only specific class of medications that was significantly associated

with OW/OB was atypical antipsychotics (p=0.008). There was a trend toward an association between OW/OB and lithium that did not reach statistical significance (p=0.07). There were no statistically significant between-group differences in sexual abuse, suicide attempts, psychosis, anxiety, or any of the other clinical or demographic characteristics examined (Table 1).

The following variables were included in a logistic regression model used to predict OW/OB status: age, BP subtype, race, lifetime psychiatric hospitalization, SUD, physical abuse, atypical antipsychotics, and multiple lifetime weight-promoting classes of medications taken. The most robust predictors of OW/OB were: younger age ($\chi 2=8.61$, df=1, p=0.003), non-Caucasian race (OR 1.91, 95% CI 1.06-3.43; p=0.03), lifetime SUD (OR 2.79, 95% CI 1.24-6.27; p=0.01), physical abuse (OR 2.74, 95% CI 1.37-5.50; p=0.004), and psychiatric hospitalization (OR 1.70, 95% CI 1.01-2.86; p=0.04), and lifetime exposure to medications in two or more classes with propensity for weight gain (OR 1.66, 95% CI 1.01-2.73; p=0.04).

For the purpose of comparison with the most recent data from the United States population, we additionally examined the prevalence of "at risk for overweight" and "overweight" as defined by NHANES BMI percentile thresholds of ≥ 85th percentile and ≥ 95th percentile. The prevalence of "at risk for overweight" and "overweight" (comparable to IOTF-defined OW and OB) was 40.8% and 22.1%, respectively, versus approximately 35.5% and 18% among United States youth[29]. The difference for OW/OB was nearly significant ($\chi 2=3.81$, p=0.05; odds ratio 1.25, 95% confidence interval 0.99-1.57). The analyses in this study were repeated using NHANES 85th percentile as a cutoff for OW/OB, and this yielded similar results. Thus, for simplicity, only the analyses using IOTF-defined OW/OB are presented.

DISCUSSION

To our knowledge, this preliminary study is the first to examine OW/OB in pediatric BP specifically. A substantial proportion of subjects, 42%, were OW/OB. Lifetime history of physical abuse and SUD were each independently associated with a nearly three-fold increased prevalence of OW/OB. Younger age, non-Caucasian race, history of psychiatric hospitalization, and treatment with medications from ≥2 classes associated with weight gain were independently associated with OW/OB. Lifetime treatment with atypical antipsychotics was significantly associated with OW/OB in univariate but not regression analyses.

The prevalence of OW/OB among youth continues to increase, and recent national data indicate that approximately 34% of youth are OW/OB[29]. The prevalence OW/OB among subjects in this study was approximately 15% greater than the national prevalence, and the prevalence of OB was approximately 20% greater[29]. The difference in OW/OB approached significance (p=0.05). Similarly, recent epidemiologic data indicate that adults with BP have approximately 16% greater prevalence of OW/OB compared to those without BP[7]. Therefore, although confirmatory controlled studies are needed to confirm this, present findings suggest that the association between BP and OW/OB may be of comparable magnitude among youth and adults.

Previous findings from adults with BP indicate that at least half and as many as two-thirds are OW/OB[5,6,9,10]. Several classes of mood-stabilizing medications are associated with obesity among adults with BP[5], and with weight gain among youth with BP[30]. Moreover, the impact of these medications on weight gain and other metabolic parameters may be greater among youth as compared to adults[31]. Indeed, a recent study of hospitalized children and adolescents exposed to atypical antipsychotics, half of whom carried a diagnosis of BP,

reported a 53% prevalence of OW[32]. Present findings provide further support for these associations among youth with BP despite that limited details regarding medication exposure were available (as described below).

In addition to the impact of medications, however, other putative explanations for the high prevalence of OW/OB among adults with BP have previously been described, and these may apply to youth as well. Previous studies have implicated excessive carbohydrate consumption, low rate and intensity of exercise, substance misuse, and maladaptive efforts at self-modulation of mood by over-eating[33-37]. There may be a medication-independent propensity toward binge-eating that is inherent in BP, and which may result in OW/OB[38]. Shared genetic factors and neurotransmitter abnormalities may underlie both of these conditions[35]. Clearly, more research is needed to parse medication-related from illness-related contribution to OW/OB, consumptive behavior, and exercise in BP. Another factor that may be contributory is a relative paucity of physician advice and counseling. A recent study of adults with BP, schizophrenia, or neither, found that BP subjects were the least likely to report discussing dietary intake or physical activity with their physician[33]. Although it is not known whether this is also true of youth with BP, strategies for incorporating such discussions in the treatment of BP youth are clearly indicated.

The association of non-Caucasian race with greater prevalence of OW/OB in the present study is consistent with epidemiologic data[28]. Age was significantly associated with OW/OB in multivariate, but not univariate, analyses. This could be because age is significantly associated with other variables such as SUD, medications, and psychiatric hospitalizations. Age accounted for a significant proportion of the variance in OW/OB once the contribution of the other variables was controlled for. The significant association of younger age with OW/OB suggests the possibility that children with BP may be particularly susceptible to OW/OB; however this finding requires replication. Kilbourne and colleagues also found that African-American race and younger age are each associated with lower likelihood of a physician discussing dietary intake and physical activity with adult patients with BP and schizophrenia[33]. It is possible that these demographic variables also contribute to differences in weight-related counseling among youth with BP.

The finding of an association of obesity with physical abuse has been previously identified[37]. A recent retrospective population-based study examined the association between multiple types of early adversity with weight and obesity. Physical abuse during childhood was the strongest predictor of obesity (BMI > 30 kg/m^2) in adulthood, accounting for a 39% increase in obesity after controlling for potential confounding variables[38]. A recent prospective study examined the association between childhood sexual abuse and obesity among young adult females[40]. Females with history of childhood sexual abuse were significantly more likely to be obese in young adulthood, however between-group differences were not significant during childhood or adolescence. The association between sexual abuse and OW/OB in the present sample may strengthen as the subjects are followed into young adulthood; however this remains to be determined. Nemeroff has hypothesized that significant early-life stress leads to greater stress responsiveness later in life, particularly via alterations in the corticotrophin-releasing factor (CRF) system[41]. This system is involved, directly and indirectly, in multiple metabolic processes that could contribute to OW/OB, such as insulin resistance, inflammation, and autonomic regulation.

Aberrant regulation of consumptive behaviors may underlie both OW/OB and SUD, and this could account for the significant association between SUD and OW/OB in the present study. There may be shared functional neuroanatomical disturbances including reductions in striatal dopamine D2 receptors[42] as well as altered serotonergic dynamics[43]. However, recent findings from an epidemiologic study of adults with BP indicate that SUD and OW/

OB may be inversely related[7]. Further studies are needed to determine whether these discrepant findings are associated with developmental differences between youth and adults, differences between clinical and epidemiologic samples, or other factors as yet unknown.

Finally, the nature of the association between OW/OB and psychiatric hospitalizations merits further prospective investigation. This association could be explained by greater illness severity among OW/OB subjects precipitating hospitalizations. However the direction of this association is uncertain. Hospitalized youth are often exposed to highly caloric food options, have significant restrictions on physical activity and energy expenditure, and may be exposed to higher medication dosages. This study did not ascertain, and could not statistically examine, these factors.

Several limitations to the present study should be noted. First, this cross-sectional, observational study was not designed to examine medications in detail. Although categorical data were collected regarding current and lifetime exposure to a broad spectrum of medications, information regarding dosage, duration of treatment, and adherence was not ascertained at intake. Therefore, this study was not able to ascertain medication-related weight gain. Similarly, metabolic data were not collected. Since COBY is a prospective longitudinal study, in the future this sample will be able to provide more detailed data regarding medications and their propensity to cause weight-gain and OW/OB in this population. Second, as in several previous studies[5,6,27], height and weight (and therefore OW/OB) were indirectly ascertained. However, the reliability of self-reported height and weight in determining the OW/OB versus non-OW/OB dichotomy in a clinical sample at the Pittsburgh site was good-to-excellent. In addition, as detailed above, previous studies report that this method has good-to-excellent reliability, excellent specificity, and fair-good sensitivity[23-27]. In the future, COBY subjects will all be measured directly such that future reports will not be constrained by this limitation. Third, the direction of the associations found in this study cannot be determined definitively. For example, it is unclear whether SUD preceded the development of OW/OB or whether the reverse is true, and the same applies for physical abuse, medication exposure, and psychiatric hospitalization. Fourth, data were not available regarding binge eating other than in the context of bulimia nervosa, or regarding exercise, nutrition, and metabolic indices. Such information could inform the understanding of the mechanism/s for OW/OB in BP. Similarly, data were not available regarding these youths' dieting behaviors or perception of whether or not they were OW/OB, such that it remains to be determined how biases in weight perception among BP youth compare with those of non-BP youth and whether these biases are associated with dieting.[44] Fifth, this study also did not consider the impact of family history of OW/OB or psychiatric disorders on OW/OB among probands. Finally, this study did not include healthy controls or psychiatric controls. Therefore, the high prevalence of OW/OB in the present study may not be specific to BP. Indeed, depressed mood has been associated with a two-fold increased incidence of obesity among adolescents[45], and depressive disorders and ODD may be more common among chronically obese youth[46]. Future controlled studies are needed in order to directly compare the prevalence of OW/OB among youth with BP versus healthy controls and/or youth with other psychiatric conditions.

CONCLUSION

Despite the above limitations, this is the first study to our knowledge that examines OW/OB in pediatric BP and as such addresses a gap in the literature. These preliminary results suggest that scope of the problem of OW/OB may be modestly increased among youth with BP and that OW/OB among youth with BP may be associated with increased psychiatric burden, and as such converge with data from adults with BP. These findings underscore the importance of attempting to prevent OW/OB through healthy lifestyle strategies (e.g.,

balanced diet, regular exercise) and pharmacologic strategies (e.g., using medications with lesser propensity for weight gain)[30]. This study identifies several potential risk factors for OW/OB among youth with BP, and future studies from the COBY sample will examine whether these and other variables predict incident OW/OB and/or weight gain. Future controlled studies are needed to examine the prevalence of OW/OB among youth with different psychiatric conditions in order to determine the relative burden of OW/OB across these diagnostic groups, and to determine the impact of pharmacologic treatments on these differences. Future longitudinal studies from the COBY sample will examine in detail the impact of medications, polarity and severity of week-to-week symptoms, and comorbidity on OW/OB. Studies specifically addressing psychosocial and pharmacologic interventions and preventive efforts that target OW/OB among youth with BP are urgently needed.

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Table 1

Comparison of Overweight/Obese and Non-Overweight/Obese Children and Adolescents with Bipolar Disorders

	Overweight/Obese (N=145)	Non-Overweight/Obese (N=203)	Statistic	p
Demographic characteristics				
	M+/-SD	M+/-SD		
Age	12.9±3.1	13.3±3.0	t=1.22	0.22
SES[1]	3.4±1.2	3.6±1.1	t=1.61	0.11
	%	%		
Sex (% Male)	53	53	$\chi 2$=0.00	0.99
Caucasian	77	86	$\chi 2$=4.79	0.03
Intact family	43	46	$\chi 2$=0.32	0.57
Clinical characteristics				
	M+/-SD	M+/-SD		
BP onset age	9.2±3.8	10.1±3.9	t=-2.15	0.03
BP duration (years)	4.8±3.2	4.2±2.9	t=1.83	0.07
Current depression severity[2]	16.1±10.9	14.3±10.0	t=1.58	0.11
Current manic severity[3]	20.7±11.9	23.2±12.1	t=-1.92	0.06
Current CGAS[4]	55.4±12.7	54.1±12.1	t=-1.00	0.32
	%	%		
BP diagnosis			$\chi 2$=5.34	0.07
BP-I	64	52		
BP-II	7	10		
BP-NOS	29	38		
Psychosis	30	23	$\chi 2$=1.87	0.17
Mixed episodes	30	25	$\chi 2$=1.16	0.28
Suicide attempt	33	30	$\chi 2$=0.37	0.55
Hospitalization	60	47	$\chi 2$=5.82	0.02
Physical abuse	21	8	$\chi 2$=13.19	<0.001
Sexual abuse	11	11	$\chi 2$=0.01	0.93
Comorbidity				
Any anxiety	43	38	$\chi 2$=1.07	0.30
ADHD	58	59	$\chi 2$=0.02	0.90
Oppositional defiant disorder	39	37	$\chi 2$=0.10	0.75
Conduct disorder	16	12	$\chi 2$=0.89	0.34
Substance use disorder	15	6	$\chi 2$=7.19	0.007
Bulimia nervosa	1	2	$\chi 2$=0.98	0.32
Anorexia nervosa	0	1	$\chi 2$=0.72	0.40
Lifetime Medications [5]				
Atypical antipsychotic	61	46	$\chi 2$=7.02	0.008
Antimanic anticonvulsant[6]	55	48	$\chi 2$=1.52	0.22
Lithium	41	32	$\chi 2$=3.22	0.07

	Overweight/Obese (N=145)	Non-Overweight/Obese (N=203)	Statistic	p
Weight-promoting medication[7]				
Total number:	1.6±1.0	1.3±1.0	t=2.91	0.004
≥2 classes	54	38	$\chi 2$=8.62	0.003
SSRI	55	52	$\chi 2$=0.17	0.68
Other antidepressant	36	34	$\chi 2$=0.13	0.72
Stimulant	54	54	$\chi 2$=0.01	0.94

[1] Socio-economic status ascertained using the 4-factor Hollingshead (1975) Scale.

[2] Current K-SADS-P depression section total score; valid N=344. Scores range from 0-63, and scores ≥13 are considered clinically significant.

[3] Current K-SADS-MRS total score; valid N=348. Scores range from 0-64, and scores ≥12 are considered clinically significant.

[4] Current CGAS; valid N=344

[5] Medications included if reported for ≥25% of overall sample

[6] Divalproex or carbamazepine

[7] Total number of classes from: lithium, atypical antipsychotic, typical antipsychotic, divalproex or carbamazepine (maximum = 4)