Substance Use Disorders and Overweight/Obesity in Bipolar I Disorder: Preliminary Evidence for Competing Addictions

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Objective: This investigation was undertaken to explore the relationship between alcohol/illicit drug dependence and overweight/obesity in individuals with bipolar I disorder.

Method: The data for this analysis were procured from the Canadian Community Health Survey-Mental Health and Well-Being (CCHS) conducted by Statistics Canada in 2002. Bipolar I disorder was defined as persons screening positive for a lifetime manic episode using the World Mental Health 2000 version of the Composite International Diagnostic Interview (WMH-CIDI). Substance abuse and illicit drug dependence were determined using criteria commensurate with the DSM-IV-TR. Overweight and obesity were defined as a body mass index of 25.0 to 29.9 and greater than or equal to 30.0 kg/m^2, respectively.

Results: The total sample comprised 36,984 individuals (≥ 15 years old) screening positive for a lifetime manic episode. Subgroup analysis indicated that overweight/obese bipolar individuals had a significantly lower rate of substance dependence than the normal weight sample (13% vs. 21%, $p < .01$). Conversely, bipolar individuals who screened positive for substance dependence had a lower rate of overweight/obesity when compared with non–substance-dependant bipolar respondents (39% vs. 54%, $p < .01$). The inverse association between the presence of these 2 comorbid conditions in bipolar I disorder continued to be statistically significant in multivariate analysis (OR = 0.57, 95% CI = 0.34 to 0.95, $p < .05$).

Conclusions: An inverse relationship between the presence of comorbid overweight/obesity and substance use disorders was observed in bipolar I disorder. These results suggest that comorbid addictive disorders (i.e., substance use and compulsive overeating) may compete for the same brain reward systems.

(J Clin Psychiatry 2007;68:1352–1357)

Received Nov. 8, 2006; accepted Jan. 8, 2007. *From the Departments of Psychiatry (Drs. McIntyre, Castel, and Kennedy) and Pharmacology (Dr. McIntyre) and the Institute of Medical Science (Mr. Konarski and Dr. Kennedy), University of Toronto, Ontario, Canada; the Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Ontario, Canada (Drs. McIntyre, Bottas, and Kennedy and Ms. Soczynska); the Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio (Dr. McElroy); and the Health Statistics Division, Statistics Canada, Ottawa, Ontario, Canada (Ms. Wilkins).*

Financial disclosure appears at the end of this article.

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Substance use disorders, obesity, and bipolar disorder are major public health problems in North America and other industrialized nations.[1–3] Compelling evidence indicates that persons with bipolar disorder have an increased risk for substance use disorders and overweight/obesity.[2,4–8] Moreover, both conditions independently pose a serious hazard to the course and outcome of bipolar disorder (e.g., increased severity of symptoms and increased probability of nonrecovery, recurrence, depression, and suicidality).[1,2,6,9–11]

Several epidemiologic studies have reported that moderate alcohol consumption may convey a protective effect for cardiovascular disease and diabetes.[12–14] It is postulated that this effect may be partially mediated by the weight-reducing effects and improved insulin sensitivity associated with alcohol intake.[14] In keeping with this view, population-based studies have reported an inverse relationship between habitual moderate alcohol intake and body mass index (BMI).[15] However, high alcohol intake in the long term has been associated with more detrimental consequences (e.g., weight gain, hypertension).[13] Alcohol, when consumed without food, is also a risk factor for hypoglycemia. To our knowledge, no studies have primarily evaluated the relationship between substance use disorders and overweight/obesity in bipolar disorder.

A defining characteristic of addiction is the overpowering motivational strength and decreased ability to control the desire to obtain a substance despite economic,

social, and/or health-related consequences.[1,16] Obesity is increasingly viewed as a consequence of an addictive behavior; that is, foraging and ingestion habits persist and strengthen despite the threat of catastrophic consequences.[1,17,18] Moreover, it is conjectured that both obesity and substance use disorders are subserved by an overlapping, and aberrant, reward-motivation neural network (e.g., ventral tegmental-nucleus accumbens circuit).[5,16,17,19–23]

Herein, we explore the interrelationship between substance use disorders and overweight/obesity in a large population-based sample of persons with bipolar I disorder. The impetus for this endeavor was provided by the need to elucidate factors that predispose and portend comorbidity in bipolar disorder, and the putative pathoetiologic similarities between these 2 comorbidities.

METHOD

The data for this analysis were procured from The Canadian Community Health Survey-Mental Health and Well-Being (82-617-XIE), a component of the Canadian Community Health Survey (CCHS) conducted by Statistics Canada (Ottawa, Ontario, Canada).[24] The survey employed the World Health Organization World Mental Health 2000 version of the Composite International Diagnostic Interview (WMH-CIDI).[25] Respondents were residents of private dwellings; a multistage stratified cluster design was used to sample dwellings. Most interviews (86%) were conducted in person, the remainder by telephone. The responding sample totaled 36,984 people aged 15 years or older; the participation rate was high (77%). The data were weighted to be representative of the household population of the 10 provinces of Canada in 2002.

On the basis of WMH-CIDI screening criteria, the survey collected information on lifetime and past 12-month prevalence of various mental disorders (i.e., major depressive episode, manic episode, panic disorder, agoraphobia, social phobia, alcohol and drug dependence, gambling, suicide, abnormal eating behavior), self-reported height and weight, and previously diagnosed medical disorders. Body mass index was calculated by dividing self-reported body weight (kg) by height (m^2). Overweight and obesity were defined as a BMI of 25.0 to 29.9 kg/m^2 and greater than or equal to 30.0 kg/m^2, respectively.[26] Small subsample size necessitated combining overweight and obese respondents into 1 category (i.e., overweight/obese).

Although smoking status and suicidality variables were not recorded, information was obtained on access to, and use of, mental health care services; hospitalizations; use of medications; disability associated with mental health; and factors (e.g., work and lifestyle) that influence, or are influenced by, mental health. The CCHS also collected information on determinants and correlates of mental health such as sociodemographic information, income, self-reported distress, level of leisure time physical activity, medication use, and social support.

Statistical analyses were calculated for respondents screening positive for a manic episode. Sociodemographic characteristics (sex, age group, marital status, level of education, and income) were examined in relation to the presence of a lifetime manic episode. Level of household income was dichotomized into 2 categories according to the number of people in the household; "low" income was defined as net annual income from all sources: i.e., less than $15,000 for 1 to 2 people in the household, less than $20,000 for 3 to 4 people, and less than $30,000 for 5 or more people. The remaining individuals were categorized as "high" income.

Alcohol dependence within the past year was determined using a series of questions measuring 7 different symptoms, corresponding to DSM-IV-TR criteria.[27] Questions on alcohol dependence were only applicable to respondents who reported having 5 or more drinks during an occasion at least once a month during the 12 months prior to the survey interview.

Illicit drug dependence within the past year was determined for respondents who reported that they used such drugs at least once a month. Respondents were asked about use of cannabis, cocaine, amphetamines, ecstasy, hallucinogens, heroin, and solvents. The criteria used to define dependence were commensurate with DSM-IV-TR criteria.[28]

Among the respondents screening positive for lifetime bipolar I disorder, the categories of alcohol and illicit drug dependence were combined together (herein referred to as substance dependent). The separate subgrouping of alcohol and illicit drug dependence did not provide sufficient power to conduct the analysis herein.

Multiple logistic regression modeling was used to control for the effects of income level, sex, age group, and physician-diagnosed chronic medical disorders (diabetes, heart disease, or hypertension); use in the past 12 months of mood stabilizers, antidepressants, antipsychotics, or sedatives; recent distress (a 40-point scale assessed by 10 questions and known as the K-10[29]), lifetime history of a major depressive episode; leisure time physical activity (inactive vs. moderately active or active); and the Eating Attitudes Test[30] score. A small percentage (14%) of interviews were conducted by telephone. As the potential for underreporting overweight/obesity and substance abuse is greater in telephone surveys, a variable for mode of interview (personal or telephone) was included in the regression models.

Prevalence estimates for lifetime bipolar I disorder in the general population, and for substance dependence and overweight/obesity within the bipolar population, were produced using weighted cross-tabulations. The odds of substance dependence in relation to overweight/obesity, and vice versa, were estimated using multiple logistic re-

Table 1. Prevalence of Lifetime Bipolar I Disorder by Sociodemographic Characteristics (household population aged 15 years or older, Canada, 2002)[a]

Characteristic	%
Total prevalence	2.4
Sex	
Male	2.4
Female	2.3
Age group, y	
15–29[b]	3.3
30–44	2.7
45+	1.6[d]
Marital status[c]	
Married/living with partner[b]	1.8
Never married/divorced/separated/widowed	5.0[d]
Level of education[c]	
Less than secondary diploma[b]	3.6
Secondary diploma	2.2[d]
Some postsecondary education	4.2
Postsecondary diploma or degree	2.3[d]
Level of household income[c]	
Low[b]	4.8
High	2.4[d]

[a]Data from reference 24.
[b]Reference group.
[c]Estimates shown for persons aged 25–64 years.
[d]Significantly different from value for reference group ($p < .05$).

gression analysis, controlling for the influence of the effect of the potentially confounding factors mentioned above.

All statistical analyses were performed using SAS statistical software, release 9.1 (SAS Institute, Cary, N.C.). Variables for analysis were selected a priori on the basis of previous research. To account for the complex sampling design of the CCHS, coefficients of variation on estimates and significance of differences between estimates were calculated using the bootstrap technique. The level of statistical significance was defined as $p < .05$.

RESULTS

A total of 36,984 respondents completed the CCHS survey. A positive screen for a manic episode (i.e., DSM-IV–defined bipolar I disorder) was reported in 938 of the respondents; when survey weights were applied, this number amounted to an estimated 2.4% of the Canadian population aged 15 years or older. Lifetime history of a manic episode was more frequent in younger respondents, in persons not married or living with a partner, and in persons in the lower income bracket (Table 1).

Respondents with bipolar I disorder had a significantly higher rate of substance dependence as compared with the general population (16.97% vs. 2.72%, $p < .01$). The age-adjusted rate of overweight/obesity in bipolar individuals was also significantly higher than that of the general population (55.4% vs. 47.6%, $p < .001$).

As compared with the normal weight bipolar sample, overweight/obese bipolar individuals had a significantly lower rate of substance dependence (13.0% vs. 21.4%, $p < .01$). The negative association between overweight/obesity and substance dependence persisted in a multivariate analysis that controlled for sex, age, socioeconomic status, psychotropic medication use, psychological distress, comorbid eating disorder and comorbid cardiovascular disease, diabetes mellitus, level of leisure time physical activity, and hypertension (OR = 0.57, 95% CI = 0.34 to 0.95, $p < .05$) (Table 2). (Note that the regression analyses were based on a subsample of 873 bipolar respondents for whom data were available on the variables included in the models.)

Table 2. Adjusted Odds Ratios for Substance Dependence in Past 12 Months in Relation to Overweight or Obesity in Persons With Lifetime Bipolar Disorder (household population aged 15 years or older, Canada, 2002)[a]

Variable	Odds Ratio	95% Confidence Interval
BMI		
Overweight or obese (BMI ≥ 25)	0.57[e]	0.34 to 0.95
Not overweight (BMI < 25)[b]	1.00	NA
Sociodemographic characteristic		
Male	3.01[e]	1.88 to 4.82
Female[b]	1.00	NA
Low income	1.72	0.92 to 3.24
Middle/high income[b]	1.00	NA
Age, y[c]	0.96[e]	0.94 to 0.99
Leisure time physical activity		
Inactive[b]	1.00	NA
Moderately active/active	0.98	0.59 to 1.63
Medication use in past 12 mo[d]		
Mood stabilizer	0.59	0.22 to 1.60
Antidepressant	1.32	0.72 to 2.42
Antipsychotic	0.58	0.04 to 8.19
Sedative	0.63	0.30 to 1.34
Comorbidity[d]		
Lifetime major depressive episode	2.10[e]	1.18 to 3.72
Psychological distress[c]	1.04[e]	1.01 to 1.08
Heart disease/diabetes/hypertension	0.83	0.43 to 1.61
Meets criteria for eating disorder	1.18	0.41 to 3.41
Interview mode		
Personal[b]	1.00	NA
Telephone	0.63	0.20 to 1.97

[a]Data from reference 24. Based on data for 873 respondents meeting the criteria for lifetime bipolar disorder and for whom data on the other variables included in the model were not missing. To maximize sample size, a variable for "missing" income was included; the odds ratios are not shown.
[b]Reference category, for which the odds ratio is always 1.00.
[c]Used as a continuous variable.
[d]Reference category is absence of characteristic.
[e]Significantly different from estimate for reference category ($p < .05$).
Abbreviations: BMI = body mass index, NA = not applicable.

Similarly, substance-dependent bipolar individuals displayed a lower rate of overweight/obesity as compared with non–substance-dependent bipolar respondents (39% vs. 54%, $p < .01$). The negative association between overweight/obesity and substance dependence among the bipolar respondents remained statistically significant in a multivariate analysis controlling for identical variables as in the converse analysis (OR = 0.58, 95% CI = 0.35 to 0.98, $p < .05$) (Table 3).

Substance dependence and overweight/obesity were also inversely correlated in nonbipolar respondents (i.e.,

Table 3. Adjusted Odds Ratios for Being Overweight/Obese in Relation to Substance Dependence in Persons With Lifetime Bipolar Disorder (household population aged 15 years or older, Canada, 2002)[a]

Variable	Odds Ratio	95% Confidence Interval
Substance dependence		
Dependent	0.58[e]	0.35 to 0.98
Not dependent[b]	1.00	NA
Sociodemographic characteristic		
Male	1.87[e]	1.22 to 2.87
Female[b]	1.00	NA
Low income	1.05	0.60 to 1.82
Middle/high income[b]	1.00	NA
Age, y[c]	1.04[e]	1.02 to 1.05
Leisure time physical activity		
Inactive[b]	1.00	NA
Moderately active/active	1.10	0.71 to 1.71
Medication use in past 12 mo[d]		
Mood stabilizer	0.85	0.42 to 1.73
Antidepressant	1.17	0.71 to 1.93
Antipsychotic	2.03	0.76 to 5.37
Sedative	1.01	0.61 to 1.68
Comorbidity[d]		
Lifetime major depressive episode	1.04	0.69 to 1.59
Psychological distress[c]	1.00	0.97 to 1.03
Heart disease/diabetes/hypertension	3.22[e]	1.76 to 5.92
Meets criteria for eating disorder	1.41	0.66 to 3.02
Interview mode		
Personal[b]	1.00	NA
Telephone	1.66	0.85 to 3.26

[a]Data from reference 24. Based on data for 873 respondents meeting the criteria for lifetime bipolar disorder and for whom data on the other variables included in the model were not missing. To maximize sample size, a variable for "missing" income was included; the odds ratios are not shown.
[b]Reference category, for which the odds ratio is always 1.00.
[c]Used as a continuous variable.
[d]Reference category is absence of characteristic.
[e]Significantly different from estimate for reference category ($p < .05$).
Abbreviation: NA = not applicable.

general population). In the fully controlled logistic regression model, the odds of being overweight or obese for those who were alcohol dependent or illicit drug dependent was 0.80 (95% CI = 0.66 to 0.97, $p < .05$).

DISCUSSION

This is the first community-based investigation to report a higher age-adjusted rate of overweight/obesity in bipolar disorder. We also found a higher rate of substance use disorders among individuals with bipolar I disorder. As in the general population, an inverse association between these 2 comorbidities was observed, remaining significant after controlling for the effects of possible confounders.

The results herein cohere with the findings of a cross-sectional survey that explored broad-based and illness-specific factors associated with obesity in a tertiary psychiatric population.[31] This smaller post hoc initiative (N = 560) also reported that alcohol abuse/dependence was significantly associated with a lower rate of categorical obesity (OR = 0.48, 95% CI = 0.24 to 0.91, p = .02).[31]

Our findings are not consistent with a study from the Stanley Foundation Bipolar Network that assessed the prevalence and clinical correlates of overweight, obesity, and extreme obesity in 644 patients.[4] A significant association was found between indices of excess weight and geographical site, gender, age, income level, lifetime and current comorbid binge-eating disorder, and coffee-drinking habits (i.e., > 3 cups of coffee per day).[4] No statistically significant association between alcohol or drug misuse and obesity was reported in this clinical sample. However, patients requiring special treatment for substance use disorders were excluded from participation.[4]

Several common and distinct mechanisms may mediate or moderate the observed interrelationship between substance use disorders and overweight/obesity in this bipolar sample. Intuitively, an individual with substance dependence may neglect somatic health issues (and hence sufficient caloric intake) in the context of craving, procuring, utilizing, and recovering from the effects of alcohol or illicit substances.[27] Additionally, substance use disorders may disrupt eating habits, nutrient absorption, and metabolism via associated medical morbidity (e.g., gastritis, hepatitis, pancreatitis).[32,33]

Several medications used in bipolar disorder could explain the increased rate of obesity in persons with bipolar I disorder and possibly mediate the observed inverse relationship between overweight/obesity and substance use disorders. For example, psychotropic medications may stimulate appetite, increase food intake, promote weight gain, and progressively disrupt the operating characteristics of the glucose homeostatic system.[4,34–37] Moreover, some bipolar treatments (e.g., valproic acid, atypical antipsychotics) are also capable of reducing alcohol and illicit substance craving and consumption.[38–43] The inverse association between overweight/obesity and substance use disorders in our study, however, remained significant after adjusting for the effects of psychotropic medication. Also, psychotropic medication would not explain the inverse association seen in the general population.

A testable hypothesis is that the inverse relationship between alcohol use and BMI may be a phenotypic expression of a competing brain reward system. A candidate neurotransmitter salient to this process may be dopamine.[17,44–48] For example, pharmacologic blockade of, or experimental damage to, forebrain dopaminergic circuits (e.g., the ventral tegmental-nucleus accumbens circuit) has been shown to attenuate free feeding and lever pressing for food reward, while suppressing the rewarding effects of cocaine, amphetamine, nicotine, and alcohol.[17,46,49,50]

Further evidence for the role of dopamine as a salient neurotransmitter in brain reward circuitry is provided by neuroimaging studies that report an inverse relationship

between BMI and the striatal density of dopamine D_2 receptors.[18] The reduction in dopamine D_2 receptors in the striatum in obese individuals is similar in magnitude to the reductions reported in persons with addictions to cocaine, alcohol, and opiates.[17,51–54] Several lines of evidence also implicate the dopaminergic system in the pathogenesis of manic and depressive episodes.[55]

Animal models indicate that the endogenous opioid system is also salient to feeding behavior via opioidergic modulation of mesolimbic dopamine neurotransmission. Central nervous system opioid concentration is highest in ventral striatum, lateral hypothalamus, nucleus accumbens, and central amygdala. Mu opioid receptors are localized on the inhibitory GABAergic neurons that project to dopamine systems; agonism of these receptors disinhibits dopamine release in the nucleus accumbens and other components of the brain reward circuit. Further evidence supporting the role of opioids is the observation that opioid receptor agonists exert an orexigenic effect, while the converse, an anorexigenic effect, is reported for opioid antagonists.[1]

Several ingestive neuropeptides may also mediate food intake and alcohol-seeking behavior. For example, the adipokine leptin acts at the level of the hypothalamus regulating energy expenditure, temperature, appetite, and reproductive hormonal function.[56,57] Plasma leptin levels increase linearly with BMI; the increase in leptin levels is reported to suppress appetite and food intake. Preliminary evidence indicates that increasing leptin levels are also accompanied by an increase in self-rated cravings for alcohol.[23,58]

Several factors limit the interpretations and inferences that can be drawn from this analysis. For example, the diagnoses of substance use disorders and bipolar disorder were inferred from responses to the WMH-CIDI and not confirmed with a structured clinical interview. Although this methodology has been tested and established as valid, our rate of substance use disorders in persons with and without bipolar disorder was lower than rates reported in other investigations employing similar methodology.[2] We were therefore unable to examine the effects of alcohol and illicit drug dependence separately due to small subgroup size, and as such, we combined them together. Moreover, inquiry related to substance use disorders was limited to the past year, introducing the possibility that alterations in weight might have occurred prior to alcohol and substance usage. Specific information regarding the types of illicit drugs used would have been helpful, as they have multiple and differential effects on appetite, food intake, and metabolism. In addition, we did not have a sufficient sample size to evaluate overweight and obesity status separately.

Another limitation is that the determination of overweight/obesity in the CCHS was based on self-report with no direct measurement of anthropometric variables.[59] Self-report has been shown to underestimate rates of overweight/obesity. In addition, data are unavailable on whether persons with bipolar disorder are more, or less, likely to underreport their weight or height. Although the CCHS is a comprehensive, cross-national, population-based epidemiologic survey, data were not available for some variables, which may affect the substance use disorder–overweight/obesity interrelationship (e.g., smoking status).[60,61] As in all cross-sectional studies, the direction of causality between variables of interest cannot be established. Other possible confounders relate to the fact that the comparison group included persons without a mental disorder and persons with a mental disorder other than bipolar disorder, which was not separately controlled for. Nevertheless, the large sample size and community-based setting are strengths of this investigation.

In summary, this study showed that rates of both substance use disorders and overweight/obesity were higher, but inversely related, in persons with bipolar I disorder. Increasingly viewed as a food addiction, obesity may pathoetiologically overlap with substance dependence. Research endeavors that aim to parse out shared neurobiology between overweight/obesity and substance use disorders may help refine models of disease pathophysiology in bipolar disorder.

Financial disclosure: Dr. McIntyre has received grant/research support or honoraria from Wyeth, GlaxoSmithKline, Servier, and AstraZeneca and has served as a consultant for or on the speakers boards of AstraZeneca, Eli Lilly, Janssen-Ortho, Organon, Wyeth, Lundbeck, GlaxoSmithKline, Oryx, Biovail, Pfizer, and Prestwick. Dr. McElroy has served as a consultant for Abbott, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Ortho-McNeil, and Wyeth; has received grant/research support from Abbott, American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, Esai, Eli Lilly, Forest, GlaxoSmithKline, Janssen, National Institute of Mental Health, Ortho-McNeil, Pfizer, Sanofi-Synthelabo, Somaxon, and Stanley Medical Research Institute; and is an inventor on U.S. patent no. 6,323,236B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders. Dr. McElroy and the patent's assignee, University of Cincinnati (Cincinnati, Ohio), receive payments from Johnson & Johnson Pharmaceutical Research & Development, L.L.C., which has exclusive rights under the patent. Mr. Konarski has served as a consultant for Wyeth and has received grant/research support from Eli Lilly. Ms. Soczynska has received travel honoraria from Organon and Janssen. Dr. Bottas has received honoraria from or has served on the speakers or advisory boards of Eli Lilly Canada, Janssen Ortho, and AstraZeneca. Dr. Castel has received grant/research support from Canadian Institute of Health Research and has served on the speakers or advisory boards of Eli Lilly Canada. Ms. Wilkins and Dr. Kennedy report no financial relationship relevant to the subject of this article.

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