Bipolar Disorder with Co-Occurring Eating Disorders:
Prevalence and Pharmacotherapeutic Implications

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Abstract: Bipolar disorder and eating disorders co-occur more often than expected by chance alone, yet little is known about the recognition and treatment of these disorders when they co-occur. This article briefly reviews studies examining the co-occurrence of these disorders, compares studies of their treatment, and presents preliminary suggestions for the management of the patient with bipolar disorder with an eating disorder. The objective was to provide an update on the scientific evidence examining the comorbidity among bipolar disorder and eating disorders and potential treatments for patients with both disorders. The authors updated two earlier reviews of all published English language studies addressing the occurrence of anorexia nervosa, bulimia nervosa, and binge eating disorder in patients with bipolar disorder and studies of comorbidity of bipolar disorder in patients with eating disorders. In addition, the authors discuss treatment implications for the patient with comorbid conditions from reviewed studies of pharmacotherapy and psychotherapy strategies used in both conditions. Community and clinical population studies of the lifetime prevalence rates of eating disorders in patients with bipolar disorder and of bipolar disorder in patients with eating disorders indicate high rates of comorbidity among these illnesses, particularly when subthreshold and spectrum manifestations of these disorders are included. Pharmacological treatment approaches to patients with bipolar disorder and a co-occurring eating disorder require examination of the possible adverse effects of treatment of one syndrome on the other and attempts to manage both syndromes with agents that might be beneficial to both.

An increasing number of studies published over the past 20 years have indicated that anxiety and substance use disorders occur at elevated rates in individuals with bipolar disorder (1–4). Likewise, anxiety, substance use, and depressive disorders have been found to occur more frequently than expected by chance in persons with eating disorders (5–10). In contrast, the comorbidity among eating disorders—anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED)—and bipolar disorder has not received similar systematic attention (11–14).

There are a number of important reasons to examine the comorbidity of eating disorders with bipolar disorder. First, if the prevalence of eating disorders is higher than expected in patients with bipolar disorder, then eating disorders need to be assessed when evaluating patients with bipolar dis-

Author Information and CME Disclosure

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Consultant or Scientific Advisory Board: Alkermes, Eli Lilly, Shire. *Principal or Co-investigator on research sponsored by:* AHRQ, Alkermes, AstraZeneca, Bristol-Myers Squibb, Cepahlon, Eli Lilly, Forest Labs, GlaxoSmithKline, Jazz Pharmaceuticals, Marriott foundation, NIMH, Orexigen Therapeutics, Pfizer, Shire, Takeda. *Inventor US Patent 6,323,236 B2,* use of sulfamate Derivatives for Treating Impulse Control Disorders and also with the patent's assignee U Cincinnati, has received payments from Johnson & Johnson which has exclusive rights under the patent.

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order. Conversely, symptoms of bipolar disorder need to be evaluated in patients presenting with an eating disorder. Second, although treatment guidelines for both bipolar disorder and for eating disorders are generally silent on the treatment of these conditions when they co-occur, the patient with bipolar disorder with an eating disorder often requires specific treatment considerations (13, 14). For example, pharmacological or psychotherapeutic interventions that might parsimoniously address both syndromes would be important to consider. When such interventions are not available, treatment choices that are therapeutic for one syndrome but do not have an adverse impact on the other would be important to consider. Third, if these syndromes are indeed more frequently comorbid than anticipated by their independent occurrence rates, then an understanding of this association has important implications regarding the pathophysiology of these disorders, especially in light of the increasingly important roles affective instability and impulsivity are thought to play in both conditions.

Methods

We reviewed all studies published since our two earlier reviews (13, 14) of the co-occurrence of bipolar disorder and eating disorders. As in our earlier article, we included studies that examined individuals with traditionally defined syndromes, e.g., bipolar I disorder, AN, or BN, as well as studies that included individuals with bipolar II disorder and other bipolar spectrum syndromes, BED, and subsyndromal forms of disordered eating behavior, e.g., binge eating that may not have met the criteria for BED. We cast this broad net based on evidence that subthreshold or spectrum presentations closely resemble threshold illnesses and are often more prevalent, providing insights into comorbidity relationships that might not be as evident by limiting comparisons to narrowly defined syndromes (3, 13–19). Indeed, the proposed DSM-5 criteria for both bipolar and eating disorders are generally broader than those for DSM-IV (20). We also reviewed studies of medications and psychotherapies used to treat bipolar disorder (4, 21, 22) in eating disorder populations (23, 24), focusing on randomized, controlled trials. We conclude by discussing pharmacological treatment considerations in patients with comorbid bipolar and eating disorders, and the possibility that the two conditions may share an underlying dysregulation in mood, eating behavior, and impulse control. Of note, because the only medication presently approved by the U.S. Food and Drug Administration for the treatment of an eating disorder is fluoxetine for BN, any discussion of other medications for use in eating disorders will represent unlabeled or investigational uses of these medications.

Results

Studies of the Comorbidity of Eating Disorders and Bipolar Disorders in Community Populations

Seven studies have examined the co-occurrence of bipolar disorder and eating disorders in community populations (9, 10, 15, 25–31) (Table 1). These studies differed in their inclusion of threshold versus subthreshold disorders and subject demographics.

Three community surveys included only adults (10, 15, 25). Fogarty et al. (25) evaluated 3,258 residents of Edmonton, Alberta, Canada, aged 18 years and older using the Diagnostic Interview Schedule and DSM-III criteria and found no overlap between the 22 (0.6%) persons with lifetime bipolar I disorder and the 4 persons (0.1%) with lifetime AN (25). There was also no diagnostic overlap between persons with major depressive disorder and those with AN (32). Other types of bipolar and eating disorders, including subthreshold forms, were not assessed.

Angst (15)evaluated 4,547 adult residents of Zurich, Switzerland, for the co-occurrence of binge eating (defined as $\geq$4 binge eating attacks/year) with hypomania (defined according to several thresholds) (15). Compared with individuals with depression and healthy control subjects, individuals with hypomania, regardless of threshold definition, had higher rates of binge eating. Thus, for individuals with hypomania according to DSM-IV criteria, the rate of binge eating was 13%; for individuals with brief ($<$4 days) recurrent hypomania, the binge eating rate was 22%; for individuals with sporadic brief hypomania, it was 15%; and for individuals with mania, it was 14%, compared with 11% for individuals with depression and 5% for healthy control subjects. There was a trend for binge eating to be more common in people with hypomania than in those with depression ($p=0.06$).

In the third study, 2,980 respondents aged 18 years and older from the National Comorbidity Survey Replication were evaluated with the Composite International Diagnostic Interview (CIDI) by Hudson et al. (9). Bipolar disorder (defined as DSM-IV bipolar I and II disorder) was significantly

more common in adults with BN (odds ratio 4.7, 95% confidence interval 2.1–10.8), BED (3.6, 2.1–6.3), and any binge eating (defined as binge eating episodes occurring twice a week for at least 3 months) (3.5, 2.0–6.1) but not in adults with AN (0.8, 0.2–3.7) or in subthreshold BED (3.0, 0.9–9.8). Specifically, bipolar disorder was present in 17.7% of those with BN, 12.5% of those with BED, and 12% of those with any binge eating compared with 3% of those with AN and 10.5% of those with subthreshold BED.

Of note, CIDI questions closely paralleled DSM-IV BED criteria, except that DSM-IV requires a minimum duration of 6 months of regular binge eating episodes and the CIDI asks whether the individual experienced symptoms for 3 months. However, proposed BED criteria for DSM-5 include binge eating episodes for 3 months rather than 6 months (20). Overlap of eating disorders with subthreshold forms of bipolar disorder was not assessed.

The other four surveys of community populations included pediatric or young adult samples (10, 26–31). Evaluating 2,548 individuals aged 14–24 years using DSM-IV criteria, Wittchen et al. (26) reported that 9% of individuals with hypomania or major depressive disorder and 8% of individuals with mania had a lifetime history of an eating disorder. The odds of having an eating disorder were significantly higher than those in the general sample for the individuals with hypomania (1.8) or major depressive disorder (2.7) but not mania (2.1). Specific types of bipolar disorder and eating disorders were not provided.

Lewinsohn et al. (27–30) assessed 1,710 randomly selected high school seniors in Oregon aged 14–18 years for DSM-III-R bipolar and eating disorders using the Schedule for Affective Disorders and Schizophrenia for School-Age Children. There was no significant overlap between bipolar and eating disorders when full DSM-III-R threshold criteria were used to define syndromes (27). However, subthreshold bipolar disorder was significantly associated with subthreshold and threshold eating disorders (30). The authors followed a subset of 810 female subjects for 1 year and 534 subjects until their 24th year of age, separating the group according to three eating disorder categories: subjects with full syndrome eating disorders (N=19, 7 with AN), subjects with partial syndrome eating disorders (N=23, 9 with AN), and subjects with no eating disorder (N=768) (29). As in the overall sample, there were no significant differences in the rates of syndromal bipolar disorder between the groups with full (0%) or partial syndrome (4%) eating disorders and the group with no eating disorders (5%). However, when subthreshold bipolar disorders were included, significantly higher co-occurrence rates were found in the full syndrome (26%) and partial syndrome (22%) eating disorder groups compared with the no eating disorder (4%) group.

Lewinsohn et al. (29) introduced two other female comparison groups at the 24 years of age evaluation based on psychopathology identified at age 18 years: individuals with depression (N=207) and those without a mood disorder (N=83). At age 24 years, the full syndrome and partial syndrome eating disorder groups had significantly higher period prevalence rates of bipolar disorder (11% and 8%, respectively) compared with the depressed (0.5%) and no disorder (0%) groups.

In the third study, an analysis of interview data from 2,363 people aged 14 years or older randomly selected from central Italy, subjects with subthreshold bipolar disorder (bipolar disorder that failed to fulfill DSM-IV criteria for bipolar I or II disorder, 4.7% of the population) had significantly greater comorbidity with AN (4.3%) than those with unipolar depression (0.7%) (31). Rates of AN did not differ significantly among subjects with bipolar disorder (4.0%) and those with unipolar depression, nor did they differ among subjects in the three different mood disorder groups for bulimia nervosa, in which rates were low, ranging from none for full-spectrum bipolar disorder to 1.3% for unipolar depression. Rates of eating disorders were not compared with those in the group without mood disorders.

In the final study, a nationally representative sample of 10,123 adolescents aged 13–18 years from the National Comorbidity Survey Replication Adolescent Supplement were evaluated with the CIDI by Swanson et al. (10). AN and BN were evaluated by DSM-IV criteria and BED by the proposed DSM-5 criteria (20). Bipolar disorder (defined as bipolar I and II disorder by DSM-IV criteria) was significantly more common in adolescents with BN (adjusted odds ratio 7.3, 95% confidence interval 3.1–17.2) and BED (3.0, 1.5–5.7), but not in adolescents with AN (0.7, 0.1–4.9), subthreshold AN (2.5, 0.7–8.2), or subthreshold BED (0.8, 0.5–1.5). Criteria for subthreshold AN included lowest body weight less than 90% of the adolescent's ideal body weight, intense fear of weight gain at the time of the lowest weight, and no history of another threshold-level eating disorder. Criteria for subthreshold BED included binge eating at least twice a week for several months, perceived loss of control, and no history of another threshold-level eating disorder or subthreshold AN.

Taken together, six of these seven community

Table 1. Community studies of overlap of bipolar and eating disorders

Study	Population	Interview, Criteria	Findings
Fogarty et al. (25)	3,258 adults from Edmonton, AB, Canada, aged ≥18 years	DIS; DSM-III	No overlap between AN and BP (or MDD)
Angst (15)	4,547 adults from Zurich, Switzerland, aged 22–35 years	SPIKE; DSM-IV, binge eating = ≥4 binge eating attacks/year	13% rate of binge eating for DSM-IV hypomania, 22% for recurrent brief hypomania, 15% for sporadic brief hypomania, 14% for manic symptoms, 11% for depression, and 5% for healthy control
Wittchen et al. (26)	2,548 adolescents and young adults aged 14–24 years	DSM-IV	People with hypomania (1.8) or MDD (2.7), but not mania (2.1), had significantly increased odds of having an ED
Lewinsohn et al. (27–30)	1,710 high school seniors in Oregon, U.S.	SADS; DSM-III-R	No overlap between BP and partial or full syndrome EDs; SBP significantly more common in adolescents with partial-syndrome (22%) and full-syndrome (26%) EDs than no ED (4%)
Faravelli et al. (31)	2,363 adolescents and adults from Sesto Fiorentino, Italy, aged ≥14 years	MINI; FPI; DSM-IV	AN significantly more common in people with SBP (4.3%) then in unipolar depression (0.7%); AN not significantly more common in people with BP (4.0%); BN not significantly more common in people with unipolar depression (1.3%) versus BP (0.0%) or versus SBP (1.1%)
Hudson et al. (9)	2,980 adults from United States, aged ≥18 years	CIDI; DSM-IV	BP (BP I and BP II) significantly associated with BN (OR=4.7, 95% CI 2.1–10.8), BED (3.6, 2.1–6.3), and any binge eating (3.5, 2.0–6.1), but not AN (0.8, 0.2–3.7) or SBED (3.0, 0.9–9.8); specifically, BP present in 17.7% of those with BN, 12.5% of those with BED, 12% of those with any binge eating, 3% of those with AN, and 10.5% of those with SBED
Swanson et al. (10)	10,123 adolescents from United States, aged 13–18 years	CIDI; DSM-IV	BP (BP I and BP II) significantly associated with BN (OR=7.3, 95% CI 3.1–17.2) and BED (3.0, 1.5–5.7), but not AN (0.7, 0.1–4.9), SAN (2.5, 0.7–8.2), or SBED (0.8, 0.5–1.5); specifically, BP present in 18.5% of those with BN, 9.0% of those with BED, 2.1% of those with AN, 8.1% of those with SAN, and 2.6% of those with SBED, compared with 2.8% of those with no ED; all ED diagnoses associated with MDD except for AN

BP, bipolar disorder; CI, confidence interval; DIS, Diagnostic Interview Schedule; ED, eating disorder; FPI, Florence Psychiatric Interview; MDD, major depressive disorder; MINI, Mini International Neuropsychiatric Interview; OR, odds ratio; SADS, Schedule for Affective Disorders and Schizophrenia for School-Age Children; SAN, subthreshold anorexia nervosa; SBED, subthreshold BED; SBP, subthreshold bipolar disorder.

surveys found that bipolar disorder and eating disorders significantly co-occurred in adolescents or adults, at least when subthreshold definitions of the disorders were considered (9, 10, 15, 26, 29–31). The pattern of comorbidity differed by age group. In the studies of adults only, bipolar disorder was associated with BN, BED, and binge eating, but not with AN (9). Studies including pediatric populations similarly found links between bipolar disorder and BN and BED (10). Associations that included AN were also found, but only when subthreshold definitions of bipolar disorder were used (29–31).

The finding of elevated comorbidity between eating disorders and subthreshold forms of bipolar disorder in female adolescents is particularly noteworthy, given the frequent presentation of eating disorders in this population, the early onset of bipolar disorder, and the increasing reorganization of subthreshold forms of bipolar disorder, including in pediatric populations (33–36). These data underscore the need to include the full spectra of bipolar and eating disorders in evaluating patients for the co-occurrence of these syndromes (13, 14).

Studies of the Comorbidity of Eating Disorders and Bipolar Disorders in Clinical Populations

In addition to the above-described community surveys, a number of studies examined the co-occurrence

of bipolar and eating disorders in clinical or treatment-seeking populations using structured interviews based on operationalized diagnostic criteria. As in our earlier papers (13, 14), we divided these studies between those assessing eating disorders in patients with bipolar disorder (Table 2) (2, 37–53) and those assessing bipolar disorder in patients with eating disorders (Table 3) (5, 6, 54–82).

Studies of eating disorders in patients with bipolar disorder. In studies that assessed lifetime prevalence rates of AN and BN in patients with bipolar disorder, all but one (45) found higher rates of these eating disorders compared with prevailing rates in the general adult population (Table 2) (9, 24, 83–86). Likewise, the lifetime prevalence rates of BED in patients with bipolar disorder (8%–18%) were higher than recently reported general population rates (1%–3%) (9, 24, 87, 88). Five studies assessed the prevalence of the full spectrum of eating disorders in patients with bipolar disorder (46–49, 51, 53). Although one study found AN to be the most common co-occurring eating disorder (53), the other four studies found BED to be the most common (46–49, 51).

Studies comparing patients with bipolar disorder with and without eating disorders generally found that patients with eating disorders were more likely to be symptomatic; have an earlier age of onset of bipolar disorder and more lifetime mood episodes; have lifetime suicide attempts, mixed states, or rapid cycling; and have greater psychiatric comorbidity (48–51). In a prospective study of recurrence in 858 recovered subjects with bipolar disorder, the presence of a lifetime eating disorder was significantly associated with depressive recurrence (89). In another study, however, patients with bipolar disorder with subsyndromal mood symptoms were significantly more likely to have had an eating disorder (28%) compared with syndromally ill (16%) and euthymic patients (5%) (46).

One study compared adult patients with bipolar disorder with a lifetime history of one of the three major eating disorders with one another (51). Lifetime AN in bipolar disorder was associated with normal weight and a lifetime anxiety disorder, lifetime BN was associated with overweight, and lifetime BED was associated with obesity and severe obesity. Another study assessing binge eating in patients with bipolar disorder with the Binge Eating Scale found that binge eating was associated with significantly higher body mass index (BMI), waist circumference, and fasting blood glucose but not with medication (90).

Studies of bipolar disorder in patients with eating disorders. A large number of studies have examined the lifetime prevalence rates of bipolar disorder in patients with eating disorders using structured clinical interviews based on operational diagnostic criteria (Table 3) (5, 6, 54–82). Every study reported elevated rates of lifetime mood disorders in patients with eating disorders, but the specific rates of bipolar disorder were highly variable, ranging from 0% (68, 69, 73, 79) to 64% (66). This wide range in prevalence rates of bipolar disorder is probably due to methodological differences in definitions of bipolar disorder, criteria used to exclude mood disorder diagnoses (e.g., some studies excluded a mood disorder diagnosis in patients with AN while they were underweight), assessment tools, and population characteristics (e.g., inpatient versus outpatient) (13, 14). The weighted mean rate of 8% of bipolar disorder among patients with eating disorders (Table 3) is nevertheless higher than rates of bipolar disorder in the general population, including the recently reported lifetime prevalence rate of 4.4% for bipolar spectrum disorder from the National Comorbidity Survey Replication, which includes subthreshold forms (3).

Relatively few studies explored the clinical correlates of bipolar disorder in patients with eating disorders. The study reporting the highest rate of bipolar disorder (64%) was in treatment-resistant inpatients with AN or BN (66), suggesting that treatment resistance of eating disorder symptoms may be associated with bipolar disorder. Several studies found suicidal or self-destructive behavior in patients with eating disorders was associated with bipolar disorder (91, 92).

Pharmacological Treatment Implications of Comorbid Bipolar and Eating Disorders

No controlled pharmacological or psychological treatment studies of bipolar disorder co-occurring with an eating disorder have yet been published (93). Medications with well-documented efficacy in bipolar disorder (i.e., mood stabilizers and second-generation antipsychotics) have received relatively little systematic study in the treatment of eating disorders. Moreover, although antidepressants have been studied in both conditions, results have been inconsistent. We review below medications and psychotherapies evaluated in the treatment of bipolar disorder that have also been evaluated in the treatment of eating disorders, focusing on randomized controlled data. We also discuss the implications for the treatment of patients with bipolar disorder with co-occurring eating disorders.

Mood-stabilizing agents. The association of eating disorders with depressive and manic symptoms and positive case reports or open-label studies (13, 94–96) lead to small placebo-con-

Table 2. Studies of lifetime prevalence rates of eating disorders in patients with bipolar disorder

Study, Interview, Criteria	BP (*n*)	Female (%)	Eating Disorder (%)			
			ED	AN	BN	BED
Strakowski et al. (37) SCID, DSM-III-R	41 I, 1st manic	61	7	0	7	ND
Strakowski et al. (38) SCID, DSM-III-R	60 I, 1st manic	ND	7	0	7	ND
McElroy et al. (39) SCID, DSM-III-R	71 I, manic	55	9	ND	ND	ND
Kruger et al. (40) Semistructured clinical interview, DSM-IV	61 I and II	63	ND	ND	ND	13
Schuckit et al. (41) SAGA, DSM-III-R	14 I	100	7	0	7	ND
Cassano et al. (42) SCID, DSM-III-R	47 I, psychotic	ND	6	2	4	ND
Edmonds et al. (43) DIGS, DSM-IV	64 I and II	ND	7	ND	ND	ND
Pini et al. (44) SCID, DSM-III-R	125 I, psychotic	59	ND	2	4	ND
McElroy et al. (2) SCID, DSM-IV	288 I and II	56	6	2	3	ND
Vieta et al. (45) SCID, DSM-IV	129 I	59	2	ND	3	ND
MacQueen et al. (46) SCID, DSM-IV	139 I and II	68	15	3	7	9
Ramacciotti et al. (47) SCID, BEDCI, DSM-IV	51 I	43	27	0	10	18
Wildes et al. (48, 49) SCID, EDE, DSM-IV	81 I, II, and NOS	65	17	7	9	11
Brietzke et al. (50) SCID, DSM-IV	137 I	100	15	3	3	ND
McElroy et al. (51) SCID, DSM-IV	875 I and II	56	14	3	5	9
Schoofs et al. (52) Semistructured clinical interview, DSM-IV	52 I and II	100	29	ND	ND	29
Fornaro et al. (53) SCID, EDE-Q, DSM-IV	148 I, II, and Cyclo	100	31	23	21	8

AN, anorexia nervosa; BED, binge eating disorder; BEDCI, Binge Eating Disorder Clinical Interview; BN, bulimia nervosa; BP, bipolar disorder; Cyclo, Cyclothymia; DIGS, Diagnostic Interview for Genetic Studies; DSM, Diagnostic and Statistical Manual for Mental Disorders; ED, eating disorder; EDE, Eating Disorder Examination; ND, No data specifically provided, or not assessed; NOS, not otherwise specified; SAGA, Semistructured Assessment for the Genetics of Alcoholism; SCID, Structured Clinical Interview for DSM.

trolled trials of lithium in the treatment of AN (97) and BN (98). Gross et al. (97) randomly assigned 16 underweight patients with AN to lithium or placebo for 4 weeks and found that patients receiving lithium had significantly greater weight gain after 3 and 4 weeks of treatment compared with that of patients receiving placebo. Lithium-treated patients also showed significantly greater improvement on a measure of insight. In contrast, Hsu et al. (98) did not find significantly greater efficacy for lithium over placebo in reduction of binge eating episodes in patients with BN. Lithium treatment, however, was associated with a significant reduction in self-induced vomiting compared with placebo. The efficacy of lithium may have been limited by the relatively low mean therapeutic plasma concentration, 0.6 mEq/liter, achieved in this trial.

Among other mood-stabilizing agents, carbamazepine has been studied in a placebo-controlled manner in BN (99). In this small crossover trial involving six patients, carbamazepine was not superior to placebo. Lamotrigine was evaluated in a randomized, placebo-controlled trial in the treatment

of 51 patients with BED (82). Because lamotrigine and placebo had similarly high rates of reduction in the weekly frequency of binge eating episodes, the efficacy of lamotrigine in BED could not be determined. However, lamotrigine was associated with a numerically greater amount of weight loss (1.17 versus 0.15 kg) and statistically significant reductions in fasting levels of glucose, insulin, and triglycerides, consistent with findings that lamotrigine is associated with weight loss in healthy patients with obesity (100) and in patients with bipolar disorder who are obese (101). The therapeutic profile of lamotrigine in bipolar depression along with its beneficial metabolic effects make it a viable option for the depressed patient with bipolar disorder who is overweight or obese and has binge eating with or without purging (21, 22). If depressive but not eating disorder symptomatology responds to lamotrigine addition, other medications or psychotherapy could then be added, targeting specific residual eating disorder symptoms (see below).

As noted, there are no controlled trials of mood stabilizers in the treatment of bipolar disorder with a concurrent eating disorder. Case reports, however, describe patients with AN and comorbid bipolar disorder responding to lithium alone or in combination with carbamazepine (102). Case reports have also found lithium (103, 104) and carbamazepine (99) to be effective in the treatment of BN with co-occurring bipolar disorder. Likewise, valproate was reported to be effective in ameliorating mood and bulimic symptoms in a patient with both bipolar disorder and BN (105). However, valproate has also been reported to exacerbate binge eating in patients with BED and comorbid bipolar disorder (106). This increased binge eating was associated with weight gain.

Antipsychotics. Second-generation antipsychotics have been reported to be effective for AN in open-label reports in children, adolescents, and treatment-resistant patients (23, 107, 108). Olanzapine, followed by quetiapine and aripiprazole, have been the most commonly used drugs. These agents have been observed to be helpful for weight restoration; for many of the core psychological symptoms of AN, such as fear of fatness, difficulty eating, distorted body image, and poor insight; and for many symptoms associated with ANs, including agitation, hyperactivity, delusionality, depression, anxiety, and mood instability (13, 14, 23).

To date, however, only two randomized, placebo-controlled short-term weight-restoration trials have been published with mixed results (109, 110). In the first, 30 female outpatients with AN by DSM-IV criteria received olanzapine, 2.5 mg/day for 1 month and then 5 mg/day for 2 months or placebo, in addition to cognitive behavior therapy (CBT) (109). BMI increased significantly but similarly in both groups. In addition, there were no differences between groups in improvements in measures of eating pathology or aggressiveness. Measures of depression, though, improved significantly more with olanzapine than with placebo. In the second study, 34 patients with AN receiving day treatment were randomly assigned to receive flexible-dose olanzapine or placebo for 10 weeks (110). Twenty-eight patients (14 in each group) completed the trial. The mean (SD) olanzapine dose over the 10-week treatment period for study completers was 6.6 (2.3) mg/day. Compared with placebo, olanzapine was associated with a significantly greater rate of increase in BMI, an earlier achievement of target BMI, and a greater rate of decrease in obsessive symptoms. Significantly more olanzapine recipients (88%) achieved weight restoration compared with placebo recipients (56%). Of note, no placebo-controlled weight maintenance studies of antipsychotics have yet been published, but there are reports of successful open-label use (23, 111).

There are no published controlled studies of antipsychotics in BN or BED. Second-generation antipsychotics have been reported to induce or exacerbate binge eating in patients with BN or BED (112–115). In addition, the presence of binge eating has been associated with higher BMI in patients receiving second-generation antipsychotics (114).

Antidepressants. Antidepressants are commonly used in the treatment of bipolar depression, often with mood stabilizers or second-generation antipsychotics, although with inconsistent results regarding their efficacy and the attendant risk of increasing the switch rate into hypomanic, manic, and mixed states and the induction of rapid cycling (21, 22, 116). Antidepressants may result in better outcomes in patients with bipolar II disorder, for which they have been used as monotherapy (117, 118).

Results for antidepressants are similarly mixed for the treatment of eating disorders. Antidepressants from nearly every class have demonstrated efficacy in the treatment of BN and BED in randomized, placebo-controlled trials, and fluoxetine is approved by the U.S. Food and Drug Administration for the treatment of BN (23, 119, 120). However, the occurrence of manic symptoms in response to antidepressant treatment in patients with BN with previously unmanifested bipolar disorder has been reported (121). These agents could therefore be used cautiously in patients with bipolar disorder and co-occurring BN or BED. Although antidepressant monotherapy might be effective for

Table 3. Studies of lifetime prevalence rates of bipolar disorders in patients with eating disorders

	Eating Disorder (*n*)			Bipolar Disorder (%)			
Study, Interview, Criteria	**AN**	**BN**	**BED**	**BP**	**BP I**	**BP II**	**BPNOS**
Hudson et al. (54) DIS, DSM-III	15	49	0	14	12	0	2
Gershon et al. (55) SADS, DSM-III, RDC	24	0	0	8	0	4	4
Stern et al. (56) Semistructured Interview, RDC	0	47	0	19	ND	ND	ND
Piran et al. (57) SADS, DSM-III	14	33	0	6	0	0	6
Walsh et al. (58) SADS, DSM-III	9	41	0	10	0	8	2
Powers et al. (59) SCID, DSM-III-R	0	30	0	7	4	0	3
Hudson et al. (60, 61) DIS, DSM-III	0	70	0	15	15	0	0
Hudson et al. (62) DIS, SADS, DSM-III	0	70	0	11	11	0	0
Toner et al. (63) DIS, DSM-III	47	0	0	6	6	0	0
Keck et al. (64) SCID, DSM-III-R	0	67	0	6	6	0	0
Halmi et al. (5) DIS, DSM-III-R	62	0	0	16	8	8	0
Herzog et al. (65) SADS, DSM-III-R	41	98	0	5	1	1	3
Simpson et al. (66) SADS, DSM-III-R	7	15	0	64	5	59	0
Yanovski et al. (67) SCID, DSM-III-R	0	0	13	2	2	0	0
Bushnell et al. (68) DIS, DSM-III	0	25	0	0	0	0	0
Braun et al. (6) SCID, DSM-III-R	56	49	0	8	8	0	0
Specker et al. (69) SCID, DSM-IV	0	0	43	0	0	0	0
Brewerton et al. (70) SCID, DSM-IV	0	59	0	3	0	0	3
Grilo et al. (71) SADS and SCID, DSM-IV	11	9	11	7	7	0	0
Lilenfeld et al. (72) SADS, DSM-III-R	0	47	0	2	2	0	0
Lilenfeld et al. (73) SADS, DSM-III-R	26	47	0	0	0	0	0
Telch and Stice (74) SCID, DSM-III-R	0	0	31	2	2	0	ND
Iwasaki et al. (75) SCID, DSM-III-R	98	73	0	4	0	3	1
Ivarsson et al. (76) SCID, DSM-III-R	51	0	0	6	6	0	ND
Eddy et al. (77)	136	0	0	4	ND	ND	ND
McElroy et al. (78) SCID, DSM-IV	0	0	61	10	ND	ND	ND
Fontenelle et al. (79) SCID, DSM-IV	0	0	33	0	0	0	ND
Joyce et al. (80) SCID, DSM-III-R	0	134	0	18	0	17	1
Javaras et al. (81) SCID, DSM-IV	0	0	285	11	ND	ND	ND
Guerdjikova et al. (82) SCID, DSM-IV	0	0	51	8	ND	ND	ND
Weighted mean	2,223				179 (8%)		

AN, anorexia nervosa; BED, binge eating disorder; BN, bulimia nervosa; BP, bipolar disorder; BP-NOS, bipolar disorder, not otherwise specified; DIS, Diagnostic and Interview Schedule; ND, no data specifically provided, or not assessed; RDC, Research Diagnostic Criteria; SADS, Schedule for Affective Disorders and Schizophrenia; SCID, Structured Clinical Interview for DSM.

some patients with bipolar II disorder and comorbid BN or BED (117, 118), antidepressants should probably be used in combination with mood-stabilizing agents or second-generation antipsychotics in patients with bipolar I disorder (21, 22, 116).

In contrast with the positive results of antidepressant trials in the treatment of BN and BED, randomized, placebo-controlled studies of antidepressants in the treatment of AN have been almost uniformly negative, especially for weight restoration (122) but also for weight maintenance (23, 123). The single exception was a placebo-controlled study in weight-restored patients with AN without binge eating who successfully maintained their weight with fluoxetine compared with patients receiving placebo (124).

Topiramate and zonisamide. The thymoleptic properties of two antiepileptic agents, topiramate and zonisamide, in the treatment of bipolar disorder have not been fully elucidated. Topiramate was not superior to placebo in the treatment of acute bipolar mania in several randomized, controlled trials (125, 126). Its efficacy in treating bipolar depression has been supported by only one small single-blind, comparator trial with bupropion, each used as adjunctive treatment with a mood stabilizer (127). There are no published randomized, controlled trials of zonisamide in the treatment of any phase of bipolar disorder, although data from several open-label studies suggest that this agent may have beneficial thymoleptic effects (128–130). In these studies, both topiramate and zonisamide displayed weight loss effects in patients with bipolar disorder (125–128).

Topiramate has demonstrated efficacy in the treatment of BN (131–133) and BED (78, 134–136), as well as obesity and psychotropic-related weight gain (137–140). Zonisamide has shown efficacy in the treatment of BED (141) and obesity (142). In addition, topiramate has been reported to improve eating disorder symptoms in patients with bipolar disorder with BN or BED (106, 143–145). These agents thus offer promise as adjunctive treatments with mood-stabilizing or second-generation antipsychotic agents for patients with bipolar disorder and comorbid BN or BED, especially when associated with overweight, obesity, or psychotropic drug -related weight gain.

There are no controlled studies of topiramate or zonisamide in AN. Although topiramate was reported to improve the concurrent AN of a patient with bipolar disorder (146), it may have "triggered" a recurrent episode of AN in a woman with a complex psychiatric history receiving the drug for epilepsy (147). Patients with eating disorders, including those with bipolar disorder, have misused topiramate to lose weight (148, 149).

Psychological Treatments in Bipolar Disorder and Eating Disorders

Several psychological treatments, including CBT, have been shown to be effective in controlled studies for binge eating and associated eating disorder psychopathology in patients with BN and BED (24, 150). Although no one psychotherapeutic treatment modality has proven effective for adults with AN, family therapy practiced according to the Maudsley method may be effective for adolescents with the condition (24, 150–152). Similar psychological treatments, including CBT and family therapy, have also been shown to be effective, in combination with pharmacotherapy, in the treatment of bipolar disorder (22, 153, 154). Although we found no reports on the use of a psychological treatment in the management of bipolar disorder co-occurring with an eating disorder, in our experience, pharmacotherapy in combination with CBT or family therapy-based approaches is likely to be particularly helpful in such patients.

Co-occurrence, Psychopharmacology, and Pathogenesis

The data reviewed in this article indicate that bipolar disorder and eating disorders are frequently comorbid and may have some similar pharmacotherapy responses. Community studies indicate that bipolar disorder and eating disorders overlap significantly more often than their independent occurrence rates, especially when subthreshold or spectrum presentations are considered. Clinical studies indicate that patients with bipolar disorder have elevated rates of eating disorders compared with rates in the general population, whereas patients with eating disorders have elevated rates of bipolar disorder. Similar pharmacotherapy responses include response of mania and possibly AN to lithium and second-generation antipsychotics, response of BN, BED, and possibly bipolar depression to antidepressants, and lack of response of mania and AN to antidepressants, as well as reports of the emergence of hypomania or mania with antidepressant monotherapy in patients with both bipolar disorder and eating disorders.

In earlier articles, we discussed how these observations, along with others, such as similarly elevated comorbidity with anxiety and substance use disorders, suggest that bipolar disorder and eating disorders may be related by sharing a fundamental dysregulation of mood, eating behavior, and im-

pulse control (13, 14). Indeed, several authorities have hypothesized that impulsive behaviors, including overeating, may have mood-stabilizing effects (155). Thus, just as persons with addictions may "self-medicate" with drugs of abuse and those with eating disorders may engage in eating disorder behaviors to reduce uncomfortable affect, some patients with bipolar disorder might self-medicate their affective instability with eating disorder symptoms such as binge eating, purging, or excessive exercise. Providing preliminary support for common biological underpinnings linking both conditions, investigators have found abnormalities in brain-derived neurotrophic factor, which is involved in the regulation of mood and appetite, in persons with bipolar disorder and those with eating disorders (156–158). Likewise, variants of the neurotrophic tyrosine kinase receptor 3 gene (*NTRK3*) have been associated with early onset bipolar disorder and with eating disorders (159, 160).

There are several therapeutic goals of the pharmacological treatment of patients with bipolar disorder and a co-occurring eating disorder. First, ideally the most parsimonious treatment would be with an agent effective in treating both syndromes. For example, a second-generation antipsychotic drug might be considered in a patient with bipolar disorder and AN. Second, consideration of agents for the treatment of one illness needs to be done in light of the potential for that agent to at least not exacerbate the other, either by therapeutic action or side effects. Thus, as comorbid BED or BN may be important correlates of obesity in bipolar disorder and certain mood-stabilizing and second-generation antipsychotic agents may be more likely than others to worsen binge eating, the exacerbation of unrecognized binge eating by such agents could be a cause of weight gain in some patients with bipolar disorder. Likewise, unrecognized bipolar disorder in patients with eating disorders could lead to treatment nonresponse and/or to manic symptoms if antidepressant monotherapy was being used to manage the eating disorder.

Third, the types of co-occurring bipolar disorder and eating disorders may differentially affect treatment options. Whereas a patient with bipolar I disorder and AN might respond optimally to a second-generation antipsychotic, a patient with bipolar II disorder and BED might do well with a serotonin reuptake inhibitor given alone or in combination with lithium, lamotrigine, or even topiramate. Last, and most significant, there are no randomized, controlled trials of any pharmacological agent specifically in the treatment of patients with bipolar disorder and a co-occurring eating disorder. Moreover, although a growing number of clinical trials have established the efficacy of a range of agents in the treatment of bipolar disorder, there are relatively few options for the psychopharmacological treatment of eating disorders. Thus, a familiarity with the growing field of eating disorder pharmacotherapy would be helpful for managing the patient with bipolar disorder with an eating disorder.

Conclusions

Recognition of comorbid eating disorders in patients with bipolar disorder has important implications for treatment. Selection of agents that might parsimoniously address both syndromes, or, at least, address one illness without exacerbating the co-occurring illness, would be ideal. Stabilization of affective symptoms in patients with bipolar disorder and a co-occurring eating disorder with a mood-stabilizing agent with a low risk of exacerbating the eating disorder is often an important first step. However, polytherapy, usually with adjunctive psychotherapy, will often be required for optional outcome.

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