Diagnosing and Treating Comorbid (Complicated) Bipolar Disorder

Susan L. McElroy, M.D.

Comorbidity is the rule, not the exception, in bipolar disorder. The most common mental disorders that co-occur with bipolar disorder in community studies include anxiety, substance use, and conduct disorders. Disorders of eating, sexual behavior, attention-deficit/hyperactivity, and impulse control, as well as autism spectrum disorders and Tourette's disorder, co-occur with bipolar disorder in clinical samples. The most common general medical comorbidities are migraine, thyroid illness, obesity, type II diabetes, and cardiovascular disease. Bipolarity is a marker for comorbidity, and comorbid disorders, especially multiple conditions occurring when a patient is young, may be a marker for bipolarity. Relatively few controlled clinical studies have examined the treatment of bipolar disorder in the context of comorbid conditions (i.e., complicated or comorbid bipolar disorder). However, the first step in treating any type of complicated bipolar disorder—stabilizing a patient's mood—may be associated with improving the comorbid disorder. Standard mood stabilizers, atypical antipsychotics, and non-antimanic antiepileptic agents are emerging as potentially useful treatments for several of the disorders that frequently co-occur with bipolar disorder, and therefore may be useful treatments for comorbid bipolar disorder. *(J Clin Psychiatry 2004;65[suppl 15]:35–44)*

Comorbidity—broadly defined as the co-occurrence of lifetime diseases or disorders[1]—is common in individuals with psychiatric disorders. Epidemiologic studies have shown that one quarter to one half of people in the community with 1 mental disorder have 1 or more other mental disorders.[1–7] Emerging epidemiologic studies have also shown a link between some mental disorders and certain general medical illnesses.[6,8–13] These findings are particularly true for persons with bipolar disorder, in whom psychiatric[2–6,14–22] and general medical[8,12,13,23] comorbidities are especially common.

PREVALENCE OF COMORBIDITY IN BIPOLAR DISORDER

The Epidemiologic Catchment Area study (ECA) evaluated about 18,000 adults aged 18 years and older from the community with the Diagnostic Interview Schedule. The ECA found that among individuals with bipolar I and II disorder (N = 168), 46% had alcohol abuse or dependence, 41% had drug abuse or dependence, 21% had panic disorder, and 21% had obsessive-compulsive disorder (OCD), compared with 13%, 6%, 0.8%, and 2.7% of the general population, respectively.[14–16] Persons with bipolar I disorder were more than 3 times as likely to have alcohol abuse or dependence and about 7 times more likely to have drug abuse or dependence than those in the general population.[14] In another analysis, persons with bipolar I and II disorder were 26 times more likely to have panic disorder and 8 times more likely to have OCD than those in the general population without mood disorder.[15,16]

The National Comorbidity Survey (NCS) evaluated the prevalence of comorbid psychiatric disorders with the Composite International Diagnostic Interview (CIDI) among nearly 8100 respondents and found that 48% had a lifetime history of 1 or more comorbid disorders. In a clinical reappraisal study of the 59 subjects who initially met CIDI criteria for bipolar I disorder, 29 subjects had mania that was more narrowly defined by euphoria, grandiosity, and the ability to maintain energy without sleep. All of these subjects met criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) for 1 other disorder, and 95.5% met criteria for 3 or more disorders. Anxiety, substance use, and conduct disorders were the most common comorbidities, occurring in 92.9%, 71.0 %, and 59.4 %, respectively, of individuals with mania. Of note, the study did not evaluate the prevalence of other conditions that commonly occur in patients with bipolar disorder, such as OCD, attention-

From the University of Cincinnati College of Medicine, Ohio.

Based in part on a presentation at the National Summit Meeting of the Bipolar Care OPTIONS initiative, which was held September 4–6, 2003, in Washington, D.C., and supported by an unrestricted educational grant from Janssen Medical Affairs, L.L.C.

Corresponding author and reprints: Susan L. McElroy, M.D., Department of Psychiatry, University of Cincinnati College of Medicine, 231 Albert Sabin Way, ML559, Cincinnati, OH 45267 (e-mail: susan.mcelroy@uc.edu).

deficit/hyperactivity disorder, and eating disorders, nor did it evaluate hypomania or "soft spectrum" bipolar disorders (e.g., bipolar II disorder).[17]

Comorbidity with other mental disorders has also been found to be elevated in persons from the community with hypomania and soft spectrum bipolar disorders.[18,19] In the Zurich cohort study, a 15-year prospective study of 4547 young adults, Angst[18] found that persons with hypomania defined by both DSM-IV and broader criteria (e.g., recurrent and sporadic brief periods of hypomanic symptoms of 1 to 3 days) had elevated lifetime rates of anxiety disorders, alcohol abuse, tobacco dependence, and binge eating. For example, individuals with DSM-IV hypomania and those with recurrent brief hypomania each had higher lifetime prevalence rates of any anxiety disorder (48.8% and 77.8%, respectively), panic disorder (12.2% and 22.2%), OCD (5.1% and 5.6%), alcohol abuse (23.1% and 22.7%), and binge eating (12.8% and 22.2%) compared with controls (21.6%, 1.2%, 1.2%, 7.6%, and 4.6%, respectively).

Of further note, many (although not all) epidemiologic studies have found that persons with bipolar disorder have higher rates of comorbid substance use and anxiety disorders than those with depressive disorders, even though substance use and anxiety disorders are elevated in depressive disorders compared with the general population. This was true in the ECA, NCS, and Zurich cohort studies. In the ECA study, 56.1% of persons with bipolar disorder had a substance use disorder compared with 27.2% of those with unipolar major depression.[14] The odds ratio of a person with bipolar disorder having a substance use disorder (6.6) was more than 3 times the odds ratio for a person with depression (1.9). Similarly, the lifetime prevalence rates of panic disorder and OCD in persons with bipolar disorder were both 21%, compared with 10% and 12.2% in persons with unipolar depression, even though the prevalence of panic disorder and OCD in persons with unipolar depression were 12.5 and 4.7 times that of comparison subjects. The differences between the bipolar disorder and unipolar depression groups were each highly statistically significant ($p < .0001$).[15,16]

In the NCS, 58% of the group with major depressive disorder had a comorbid anxiety disorder, 38.6% had a substance use disorder, and 16.2% had a conduct disorder compared with 92.9%, 71.0%, and 59.4% of the bipolar disorder group.[20] Similarly, in the Zurich cohort study, both DSM-IV and broader definitions of hypomania were associated with higher lifetime rates of many DSM-III anxiety disorders, alcohol abuse, tobacco dependence, and binge eating, even though these conditions were more common in persons with depression than in controls.[18]

Clinical studies have confirmed the frequent comorbidity of bipolar disorder with anxiety, substance use, and conduct disorders.[21–25] Clinical reports have also described the co-occurrence of bipolar disorder with a wide range of other psychiatric disorders (Table 1). These include eating disorders such as anorexia nervosa, bulimia nervosa, and binge-eating disorder,[23,26] attention-deficit/hyperactivity disorder,[27] sexual disorders such as paraphilias and nonparaphilic sexual addictions,[28] impulse-control disorders,[29] autism spectrum disorders,[30] and Tourette's disorder.[31]

Table 1. Psychiatric Disorders Commonly Comorbid With Bipolar Disorder

Substance use disorders[22,23]
Anxiety disorders[23]
Panic disorder
Generalized anxiety disorder
Obsessive-compulsive disorder
Social phobia
Posttraumatic stress disorder
Eating disorders[23,26]
Anorexia nervosa
Bulimia nervosa
Binge-eating disorder
Sexual disorders[28]
Paraphilias
Sexual addictions
Impulse-control disorders[29]
Intermittent explosive disorder
Kleptomania
Pathological gambling
Trichotillomania
Compulsive shopping
Psychogenic excoriation
Attention-deficit/hyperactivity disorder[27]
Autism spectrum disorders[30]
Conduct disorder[27]
Tourette's disorder[31]

General medical disorders that frequently co-occur with bipolar disorder include migraine,[32] thyroid disease,[12,33] obesity,[34–36] and type II diabetes.[37] Community studies have shown significant associations between bipolar disorder and migraine,[8] Tourette's disorder,[38] multiple sclerosis,[39] and obesity.[34] Indeed, bipolar disorder is associated with increased mortality from cardiovascular disease and some cancers.[40]

IS COMORBIDITY REAL?

Some mental health professionals have questioned whether the concept of comorbidity is meaningful or whether it is merely an artifact of our current diagnostic system. Andrews and colleagues recently evaluated a general population sample of adults in Australia to explore the relationship between psychiatric comorbidity and disability and service utilization. The 12 psychiatric disorders evaluated included 2 mood disorders (depression and dysthymia), 5 anxiety disorders (panic disorder/agoraphobia, social phobia, generalized anxiety disorder [GAD], OCD, and posttraumatic stress disorder [PTSD]); 2 substance use disorders (alcohol abuse/dependence and other drug abuse/dependence); and 3 personality disorder clusters. Bipolar disorder was not evaluated. Forty percent of the

subjects with 1 disorder met the diagnostic criteria for having at least 1 other concurrent disorder. Andrews et al. found positive associations between the number of current comorbid diagnoses and levels of distress, disability, neuroticism, and utilization of medical services. The authors concluded that degree of comorbidity was a clinically meaningful construct.[41]

IMPACT OF COMORBIDITIES ON THE PRESENTATION, COURSE, AND OUTCOME OF BIPOLAR DISORDER

Preliminary clinical data suggest that comorbid psychiatric and medical disorders have a significant impact on the presentation of bipolar disorder, as well as on its course and treatment. Substance use in particular, and comorbidity in general, may be associated with an earlier age at onset of affective symptoms.[23,42] Comorbid disorders also have been associated with a higher frequency of mixed states or rapid cycling, greater suicidality, and poorer outcome.[16,43–46] Other studies have demonstrated that comorbid disorders are associated with a less favorable response to lithium-based therapy (particularly in patients with co-occurring panic spectrum disorders and obesity)[24,36,46] and reduced levels of medication adherence (especially in patients with co-occurring substance abuse).[22]

Conversely, bipolar disorder can adversely affect the outcome of comorbid conditions. In one study, patients with OCD who had comorbid bipolar disorder had a significantly higher rate of sexual and religious obsessions, a more episodic course of OCD, and a greater number of concurrent depressive episodes compared with OCD patients without comorbid bipolar disorder.[47] In another study with 161 patients with OCD, patients with comorbid bipolar disorder (9% of the group) had an earlier age at onset of OCD. The median age at onset among OCD patients with bipolar disorder was 9.5 years, compared with 13.5 years of age in patients without comorbid bipolar disorder ($p = .003$).[48]

Comorbid disorders can occur in all phases of bipolar disorder. Preliminary clinical data suggest comorbid psychiatric disorders may more commonly manifest during depressive and mixed states, however, than during periods of pure mania or euthymia.[49] In some patients, bipolar disorder, especially soft spectrum forms, may be masked by comorbidities.

Pharmacotherapy for Comorbid (Complicated) Bipolar Disorder: Randomized Controlled Trials in Comorbid Bipolar Disorder and its Comorbid Conditions

Despite the prevalence and serious clinical implications of comorbid bipolar disorder, neither the pharmacologic nor psychologic treatment of the disorder has been well studied. Regarding clinical trials, only a few monotherapy studies and no combination treatment studies have been reported for comorbid bipolar disorder. Those studies that have been conducted generally have methodologic limitations. Moreover, medications with well-documented efficacy in the treatment of bipolar disorder have received relatively little systematic study in the treatment of conditions that frequently co-occur with bipolar disorder (e.g., anxiety, substance use, eating, attention-deficit/hyperactivity, and conduct disorders).

Randomized Controlled Trials in Comorbid (Complicated) Bipolar Disorder

We identified 4 randomized controlled trials[50–53] with mood-stabilizing agents in patients with bipolar disorder and at least 1 other comorbid disorder. In all trials, comorbid symptoms responded to mood-stabilizer therapy.

Geller et al. randomly assigned 25 adolescents with bipolar disorder ($N = 17$) or major depressive disorder ($N = 8$) and comorbid substance abuse (alcohol or marijuana) to 6 weeks of treatment with either lithium* or placebo. Compared with placebo, lithium was associated with a significant reduction in positive random drug screens and improvement in psychopathology.[50] Brady et al. conducted a randomized, placebo-controlled comparison of carbamazepine* for cocaine-dependent individuals. Fifty-seven of these subjects had mood disorders (only 2 had bipolar disorder); 82 subjects did not. Among those with mood disorders, carbamazepine was associated with fewer positive drug screens and a longer interval until consumption of cocaine. Carbamazepine had no impact on cocaine use in subjects without mood disorders.[51]

Frankenburg and Zanarini compared the efficacy of divalproex and placebo in 30 women with bipolar II disorder and comorbid borderline personality disorder in a 6-month trial. Subjects who received divalproex demonstrated reductions in measures of anger/hostility, interpersonal sensitivity, and aggression compared with those who received placebo. Reductions in measures of depression, however, were not significant.[52]

Hollander et al. studied the effects of lithium versus placebo for 6 weeks in 40 pathological gamblers with soft spectrum bipolar disorders. Lithium was more effective than placebo in reducing hypomanic symptoms and mean scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS) modified for pathological gambling.[53]

At least 3 open-label studies[54–56] have evaluated mood stabilizers for bipolar disorder with comorbid anxiety, substance abuse, or sexual disorders. Although limited, these studies suggest that anxiety symptoms and substance use, but not paraphilic symptoms, may be ameliorated with mood stabilizer treatment of comorbid bipolar affective symptoms. In a study by Calabrese and Delucchi, 55 patients who had rapid-cycling bipolar disorder plus comorbid panic attacks, generalized anxiety, and/or substance abuse were treated prospectively with valproate for

nearly 8 months. In addition to reductions in manic and depressive symptoms, the majority of subjects achieved decreases in or remission of comorbid anxiety and substance abuse symptoms.[54] Brady et al. evaluated the effectiveness of valproate in 9 patients with bipolar disorder complicated by substance abuse. During 16 weeks of follow-up, valproate therapy was associated with significant reductions in mania and depression, as well as a significant decrease in the number of days of alcohol and drug use and a reduction in the quantity of substances used.[55] By contrast, a retrospective review by Nelson et al. of the records of sex offenders with bipolar disorder concluded that valproate therapy was associated with significant improvements in manic symptoms, but not paraphilia symptoms in the subset of patients admitting those symptoms.[56]

STUDIES IN DISORDERS COMMONLY COMORBID WITH BIPOLAR DISORDER

Antimanic and mood-stabilizing agents have received some systematic study in the treatment of the conditions that commonly are comorbid with bipolar disorder when bipolar disorder is not present.

Lithium

Lithium has received surprisingly little systematic study in the treatment of anxiety disorders.[57] Indeed, we found no controlled studies of lithium in GAD, panic disorder, PTSD, or social phobia. However, 2 double-blind, controlled studies of lithium augmentation (one with lithium[58] and the other with a thyroid hormone[59]) in patients with OCD who were resistant to selective serotonin reuptake inhibitor (SSRI) therapy were negative.

Several small studies conducted in the 1970s and 1980s suggesting that lithium antagonized the effects of alcohol intoxication in normal subjects[60,61] and detoxified alcoholics[62] led to several small controlled studies (N = 30, 71, and 104)[63–65] of lithium in alcohol dependence. These studies suggested that lithium was superior to placebo in reducing alcohol consumption[63,64] or maintaining abstinence,[65] especially in patients with comorbid depression[63,64] and those who were compliant.[65] A study that compared the effects of lithium and diazepam on reducing or exacerbating the effects of alcohol found that lithium tended to antagonize the effects of alcohol on psychomotor skills except for coordination. Alcohol and diazepam were found to potentiate each other's harmful effects.[65]

However, other studies have concluded that the use of lithium does not attenuate the effects of alcohol. A study with 23 normal male subjects compared response to a standardized dose of 95% ethanol after 2 weeks of placebo and 2 weeks of lithium. Pretreatment with lithium did not prevent or reduce the effect of an alcohol-induced "high" in patients, but lithium did reduce an alcohol-related decline in cognitive efficiency.[60] In a larger study of 457 male veterans hospitalized for alcoholism, 171 of whom had a depressive disorder, no differences were found between lithium and placebo among all subjects who entered the study and completers.[66]

Controlled data suggest lithium may be helpful in conditions characterized by impulsive aggression. Two controlled studies found lithium to be superior to placebo in children and adolescents with conduct disorder.[67,68] Malone et al. conducted a randomized, placebo-controlled study in which either lithium or placebo was administered to 40 child and adolescent inpatients with conduct disorder characterized by severe and persistent aggression. Ratings on the Overt Aggression Scale decreased significantly ($p = .004$) for patients treated with lithium compared with those given a placebo. On the basis of results on the Global Clinical Judgements (Consensus) Scale, 16 of the 20 patients receiving lithium responded to therapy, a statistically ($p = .004$) significant difference compared with 6 of 20 patients in the placebo group.[67] Campbell et al. found lithium to be superior to placebo in a study with 50 children (mean age = 9.4 years) who were hospitalized for treatment-refractory severe aggressiveness and explosiveness and who had been diagnosed with conduct disorder. However, lithium was significantly ($p = .035$) more effective than placebo only in reducing aggression.[68] Another study found lithium to be superior to placebo in 66 male prisoners with chronic impulsive aggressive behavior as measured by a decrease in violent infractions.[69]

A small controlled study of 16 young women with anorexia nervosa found lithium to be superior to placebo for weight restoration when administered in conjunction with behavior therapy after 3 and 4 weeks of treatment.[70] In contrast, the results of an 8-week controlled study of 68 women with bulimia were difficult to interpret because both lithium and placebo were associated with a substantial decrease in bulimic episodes.[71]

Divalproex

Divalproex also has received relatively little empirical study in conditions commonly comorbid with bipolar disorder except for migraine, for which it has an indication for migraine prevention.[72,73] In a preliminary controlled crossover trial, 12 patients with panic disorder were randomly assigned to 6 weeks of therapy with divalproex followed by 6 weeks of receiving a placebo, or vice versa. Study results suggested that divalproex may decrease panic symptoms. Panic attacks and generalized anxiety improved significantly more with divalproex than placebo in the patients who received divalproex as their initial therapy compared with those who received placebo as their first treatment.[74]

Divalproex was shown to be superior to placebo in facilitating maintenance of abstinence from alcohol dependency (N = 29) in a 12-week, randomized, placebo-

controlled trial. A significantly smaller number of patients in the divalproex treatment group (N = 14) relapsed to heavy drinking compared with those in the placebo group (N = 15), although drinking decreased significantly in both treatment groups.[75] In an open-label pilot study with 16 patients, divalproex reduced the symptoms of alcohol withdrawal more rapidly and consistently than a benzodiazepine, a standard therapy for alcohol detoxification. A greater percentage of patients receiving divalproex versus a benzodiazepine were completely abstinent at 6-week follow-up. The investigators suggested that divalproex may be an alternative for outpatient detoxification because it does not have any abuse potential, pharmacologic synergy with alcohol, or substantial cognitive or psychomotor side effects.[76]

Divalproex may also be beneficial in conditions characterized by impulsive aggression. In a 12-week crossover study, Donovan et al. administered divalproex or a placebo for 6 weeks to 20 children and adolescents (aged 8 to 18 years) with disruptive behavior disorders and then the alternate treatment for the next 6 weeks. At the end of the first phase of the study, 8 of 10 subjects had responded to divalproex, whereas none had responded to placebo. Of the 15 subjects who completed both phases of the study, 12 had superior responses with divalproex.[77]

A recent randomized controlled study of 71 incarcerated male adolescents (aged 14 to 18 years) with conduct disorder found that the use of divalproex at doses between 500 and 1500 mg/day achieved statistically significant improvements on the Clinical Global Impressions-Severity of Illness scale (CGI-S; $p = .02$) and the CGI-Improvement scale (CGI-I; $p = .0008$) as compared to divalproex doses up to 250 mg/day. Higher doses of divalproex improved both self-reported impulse control and self-restraint, poor control of which predicts criminal recidivism.[78] Divalproex also was superior to placebo in a multicenter, randomized, double-blind, placebo-controlled study of the treatment of impulsive aggression (as assessed by verbal assault and assault against objects) and irritability in adult patients with cluster B personality disorders.[79] However, divalproex was not superior to placebo in the subset of patients of this study with intermittent explosive disorder.

Carbamazepine

The antiepileptic carbamazepine has been investigated in randomized, placebo-controlled trials for several comorbid disorders, including panic disorder, alcohol withdrawal, bulimia nervosa, and borderline personality disorder.

Carbamazepine was not effective in a study of 14 patients with panic disorder. Carbamazepine was associated with reduced frequency of panic attacks in 40% of patients, but it had no effect in 10% of patients and was associated with an increase in panic attacks in 50% of patients.[80] Only 1 of 14 patients receiving carbamazepine had a marked and sustained clinical improvement in frequency of panic attacks. The drug produced a statistically significant decrease in generalized anxiety symptoms.

Substantial preliminary data suggest that carbamazepine may be helpful in alcohol withdrawal. In a double-blind, multicenter study with 100 male outpatients, carbamazepine was shown to be more effective than placebo in reducing the symptoms of alcohol withdrawal, including sleep disturbance. Also, patients' ability to work improved significantly faster with carbamazepine treatment.[81] In a double-blind, controlled, 7-day trial for severe alcohol withdrawal in 86 alcoholic men, carbamazepine was found to be as effective as oxazepam. In addition, patients receiving carbamazepine exhibited a decrease in global psychological distress from days 3 to 7, whereas patients receiving oxazepam had an increase in distress.[82] Mueller et al. provided further evidence of the efficacy of carbamazepine in treating alcohol dependence in a double-blind, placebo-controlled 12-month study of 29 adults with alcohol abuse or dependence. Despite the small sample size and a sizeable dropout rate, univariate analyses demonstrated that treatment with carbamazepine decreased the number of drinks per drinking day and number of consecutive heavy drinking days. A survival analysis found a significant ($p = .04$) delay in time to first episode of heavy drinking.[83]

In the only controlled study of carbamazepine in an eating disorder, 1 of 6 patients with bulimia who received carbamazepine in a double-blind, placebo-controlled, crossover trial had a favorable response. That patient had a history suggestive of bipolar disorder.[84]

Finally, carbamazepine was shown to be effective in a crossover trial with 16 female outpatients with borderline personality disorder and prominent behavioral dyscontrol who received placebo and 3 other medications—alprazolam, trifluoperazine, and tranylcypromine—for 6 weeks each. The trial with carbamazepine had one of the highest completion rates. Patients receiving carbamazepine had a marked decrease in the severity of behavioral dyscontrol and were rated as significantly improved by treating physicians.[85]

Atypical Antipsychotics

Atypical antipsychotics have received preliminary empirical attention in several anxiety disorders, conduct disorder, borderline personality disorder, Tourette's disorder, and autism. For example, both olanzapine and risperidone have been studied in PTSD with promising results. In a study of 19 patients with combat-related PTSD minimally responsive to 12 weeks of SSRI treatment, olanzapine augmentation was superior to placebo in specific measures of PTSD symptoms. Olanzapine addition was associated with significant improvements in Clinician Administered PTSD Scale (CAPS) scores (–14.80 vs. –2.67, $p < .05$), sleep disorder symptoms ($p < .01$), and depressive symp-

toms ($p < .03$). As measured by the CGI, response rates to the olanzapine augmentation were relatively low (30%) and not statistically superior to placebo (11%).[86] Olanzapine also did not produce a better treatment response than placebo in a randomized, double-blind, 10-week study in 15 patients with PTSD. However, the sample size was small, improvements in both the olanzapine-treated patients (N = 10) and the placebo group (N = 5) were comparable, and a high placebo response rate was seen.[87]

In a study of 73 patients with chronic, combat-related PTSD, risperidone or placebo was added to stable psychotropic medication. Risperidone-treated patients who completed the study (N = 48) had significantly greater reductions in their CAPS ($p = .024$) and CAPS-D (arousal) scores ($p = .004$) compared with placebo, as well as statistically greater improvements on scales measuring anxiety ($p = .002$) and psychotic symptoms ($p = .009$). Risperidone did not produce statistically significant improvements in depressive symptoms.[88] In a study of 38 patients with chronic PTSD, risperidone treatment led to a significant ($p < .05$) reduction in global psychosis, hallucinations, and delusions compared with placebo.[89] In a study of 15 patients with combat-related PTSD, risperidone adjunctive treatment (N = 7) produced a significantly greater reduction ($p < .05$) in irritability compared with placebo (N = 8).[90]

Preliminary evidence suggests that atypical antipsychotics may benefit SSRI-resistant OCD as well. In one study, risperidone (N = 20) or placebo (N = 16) was given to patients with OCD who were refractory to 12 weeks of therapy with an SSRI. Among patients who completed the study, 9 (50%) of the patients in the risperidone group responded compared with none of the patients in the placebo group ($p < .005$). Response was defined as a 35% or greater improvement on the YBOCS and a final YBOCS score ≤ 16; a final CGI rating of "very much improved" or "much improved"; and a consensus of the treating clinician and 2 of the primary investigators that the patient's condition was improved.[91]

Adjunctive therapy with the atypical antipsychotic quetiapine* was similarly effective in an 8-week, double-blind study for OCD that was resistant to treatment with at least 2 SSRIs. The 20 patients receiving quetiapine had significantly ($p = .001$) greater improvements in YBOCS scores compared with the placebo group (N = 20), as well as a higher percentage of responders, 55% versus 10%.[92]

Both olanzapine and risperidone have also demonstrated preliminary efficacy as adjunctive anxiolytic therapy for treatment-resistant GAD. Olanzapine was investigated as add-on therapy in a 6-week trial in 14 patients with GAD who had failed 6 weeks of fluoxetine therapy. Adjunctive olanzapine led to large effect sizes on the Hamilton Rating Scale for Depression and moderate effect sizes on the Hamilton Rating Scale for Anxiety (HAM-A).[93] In a 5-week, double-blind, placebo-controlled study with 49 patients who had failed at least 4 weeks of anxiolytic monotherapy, addition of risperidone achieved a statistically significant reduction (–9.8, $p = .034$) in HAM-A scores compared with placebo (–6.2).[94]

Preliminary controlled data indicate that atypical antipsychotics also have therapeutic effects in conditions characterized by impulsive aggression. Thus, risperidone was superior to placebo in a 10-week trial with 20 youths with conduct disorder in reducing aggression on several measures.[95]

Olanzapine was shown to be superior to placebo in 2 small studies of borderline personality disorder. In the first study, 19 female patients with borderline personality disorder responded better to olanzapine than placebo on self-report measures of anxiety, paranoia, anger/hostility, and interpersonal sensitivity, but not depression, in a 6-month controlled study. Olanzapine was associated with a significantly ($p < .05$) greater rate of improvement over time than placebo in all of the symptoms except depression.[96] In the second study, olanzapine was significantly ($p < .05$) superior to placebo, with separation occurring as early as 4 weeks, on the CGI modified for borderline personality disorder in a placebo-controlled, 12-week trial with 40 men and women. However, weight gain was significantly ($p = .027$) greater in patients treated with olanzapine than in those receiving placebo.[97]

Preliminary controlled data also suggest that atypical antipsychotics may be beneficial in tic and developmental disorders. One small controlled study found that risperidone was superior to placebo in reducing severity of tics and improving global functioning in 48 patients with Tourette's disorder.[98] Risperidone has also been shown to be comparable to pimozide[99] and clonidine[100] in reducing tics in patients with Tourette's disorder. In a 52-week, double-blind, comparative crossover trial in 4 adults with severe Tourette's disorder, olanzapine (5 and 10 mg/day) was superior to low-dose pimozide (2 and 4 mg/day).[101] Similarly, ziprasidone was superior to placebo in a pilot study of 28 children and adolescents with Tourette's disorder.[102] Finally, risperidone (median dose of 2.5 mg/day) was superior to placebo for repetitive behavior, aggression, anxiety, depression, and irritability in 31 adults with autistic disorder or pervasive developmental disorder.[103]

Non–Antimanic Antiepileptics

Some conditions that co-occur with bipolar disorder have been shown to respond to non–antimanic antiepileptic agents in double-blind, placebo-controlled trials, including gabapentin,* topiramate,* zonisamide,* and lamotrigine. Gabapentin has been found to be effective in the treatment of social anxiety and panic disorders,[104,105] and topiramate has been shown to be effective in alcohol dependence,[106] bulimia nervosa,[107] binge-eating disorder,[108] migraine,[109] and obesity.[110] Zonisamide has

been demonstrated to be superior to placebo for weight loss in obesity.[111] In 1997, a relatively large (N = 110) double-blind, placebo-controlled study found that lamotrigine was no more effective than placebo in preventing migraine with and without aura.[112] However, in 2 subsequent relatively small trials (N = 15 and N = 24), lamotrigine was shown to be effective in preventing and reducing the duration of migraine with aura.[113,114]

Antidepressants

The treatment of bipolar disorder with antidepressants is controversial because of inadequate data about their short- and long-term efficacy in bipolar depression[115,116] and inconsistencies in available data about their ability to induce hypomania, mania, mixed states, and rapid cycling.[117,118] Nonetheless, clinical studies suggest that some patients with bipolar I and II disorders require acute and maintenance treatment with antidepressants (usually in combination with mood stabilizers) for optimal response,[119] whereas others destabilize upon antidepressant exposure.[117,120]

The use of antidepressants in complicated bipolar disorder is of further importance because these agents are frequently used in the treatment of many of the disorders that co-occur with bipolar disorder. Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors, and SSRIs have been shown to be effective in the treatment of many of the anxiety disorders[121] and some eating disorders.[122] Indeed, several SSRIs and venlafaxine are approved for the treatment of panic disorder, GAD, social phobia, and/or PTSD, and fluoxetine is approved for the treatment of bulimia nervosa.

By contrast, studies of antidepressants have yielded mixed results in substance abuse, eating, and impulse-control disorders,[122,123] as well as in migraine and obesity.[124,125] For example, SSRIs may help reduce alcohol consumption in some forms of alcohol misuse (heavy drinking and alcohol dependence with comorbid depression) but not in others (type B or early onset, in which SSRIs may be counterproductive).[126] Antidepressants have been shown to be superior to placebo in reducing binge eating in bulimia nervosa and binge-eating disorder, but not in restoring weight in anorexia nervosa.[122,127,128] SSRIs have been reported to be both effective and ineffective in various impulse-control disorders, particularly trichotillomania.[129] Regarding obesity, TCAs and MAOIs are associated with weight gain, SSRIs with short-term weight loss followed by regain of weight, and bupropion with long-term maintenance of weight loss.[125] Although virtually all controlled studies of these antidepressants in these disorders excluded patients with bipolar disorder, it is tempting to speculate that comorbid occult bipolarity may have contributed in part to their disparate results.

Benzodiazepines

Although benzodiazepines have not been shown to have acute antimanic or long-term mood-stabilizing properties, they are helpful for managing agitation, anxiety, insomnia, and catatonic symptoms associated with bipolar disorder.[24] Benzodiazepines are effective in panic disorder and GAD, but there have been no controlled studies of the use of these agents in bipolar disorder complicated by panic disorder or GAD. Moreover, benzodiazepines must be used cautiously in bipolar patients with comorbid substance use disorders because of their potential for abuse.

APPROACHES TO TREATING BIPOLAR DISORDER AND COMORBID DISORDERS

In managing patients with comorbid bipolar disorder, treatment of bipolar disorder and the comorbid condition ideally should proceed concurrently. Mood stabilization is critical. When utilizing pharmacotherapy for comorbid conditions, agents that are mood stabilizing or mood neutral should be employed before those that are mood destabilizing. Clinicians should therefore consider using mood stabilizers that might also be effective for co-occurring disorders.

As patients with bipolar disorder in general often require multiple medications for optimal response, patients with comorbid bipolar disorder are similarly likely to require combination pharmacotherapy. Various combinations of mood stabilizers (e.g., lithium and valproate), mood stabilizers and atypical antipsychotics, or mood stabilizers and/or atypical antipsychotics with non–antimanic antiepileptics, antidepressants, or benzodiazepines may be needed for optimal individualized response.[130]

Psychoeducational and cognitive-behavioral therapies have been shown to be important adjuncts to pharmacotherapy in controlled trials with patients with bipolar disorder in general.[131–133] These therapies have also been shown to be effective in the treatment of substance use, anxiety, eating, and impulse-control disorders when not complicated by bipolar disorder.[108,121]An open pilot study suggested that bipolar patients with substance dependence (N = 45) benefited from integrated group therapy employing a behavioral relapse-prevention model.[134] These treatments are likely to be especially important in the treatment of patients with comorbid bipolar disorder.

CONCLUSION

In summary, clinicians should assume that bipolar disorder is more likely than not to occur with other psychiatric disorders and possibly certain general medical disorders. Conversely, other psychiatric disorders, especially when they occur together at an early age, may be a marker for bipolarity. Moreover, comorbidity appears to adversely

affect the course and outcome of bipolar disorder. Treatment of comorbid bipolar disorder should always attempt mood stabilization. Given the complexity of treating comorbid bipolar disorder, combination pharmacotherapy with mood stabilizers, atypical antipsychotics, antiepileptics, antidepressants, and/or benzodiazepines is often needed. Pharmacotherapy in combination with psychotherapy will most likely be an essential aspect of treatment as well.

*These agents have not been approved by the U.S. Food and Drug Administration for the treatment of the comorbidities of bipolar disorder.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), clonidine (Catapres and others), diazepam (Diastat, Valium, and others), divalproex (Depakote), fluoxetine (Prozac and others), fluphenazine (Permitil, Prolixin, and others), gabapentin (Neurontin and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), oxazepam (Serax and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), tranylcypromine (Parnate), trifluoperazine (Stelazine and others), venlafaxine (Effexor), ziprasidone (Geodon), zonisamide (Zonegran).

REFERENCES

1. Maser JD, Cloninger CR, eds. Comorbidity of Mood and Anxiety Disorders. Washington, DC: American Psychiatric Press; 1990
2. Boyd JH, Burke JD Jr, Gruenberg E, et al. Exclusion criteria of DSM-III: a study of co-occurrence of hierarchy-free syndromes. Arch Gen Psychiatry 1984;41:983–989
3. Robins LN, Regier DA, eds. Psychiatric Disorders in America. New York, NY: Free Press; 1991
4. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
5. Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998; 33:587–595
6. Tohen M, ed. Comorbidity in Affective Disorders. New York, NY: Marcel Dekker; 1999
7. Kringlen E, Torgersen S, Cramer V. A Norwegian psychiatric epidemiological study. Am J Psychiatry 2001;158:1091–1098
8. Merikangas KR, Angst J, Isler H. Migraine and psychopathology: results of the Zurich cohort study of young adults. Arch Gen Psychiatry 1990;47:849–853
9. Eaton WW, Armenian H, Gallo J, et al. Depression and risk for onset of type II diabetes: a prospective population-based study. Diabetes Care 1996;19:1097–1102
10. Newport DJ, Nemeroff CB. Depression in the medically ill. In: Tohen M, ed. Comorbidity in Affective Disorders. New York, NY: Marcel Dekker; 1999:57–104
11. Penninx BW, Beekman AT, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry 2001;58:221–227
12. Calabrese JR, Hirschfeld RM, Reed M, et al. Impact of bipolar disorder on a US community sample. J Clin Psychiatry 2003;64:425–432
13. Keck PE Jr, Buse JB, Dagogo-Jack S, et al. Managing metabolic concerns in patients with severe mental illness: Expert Consensus Guidelines series. Postgrad Med Spec Report; 2004
14. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990;264:2511–2518
15. Chen YW, Dilsaver SC. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. Am J Psychiatry 1995;152:280–282
16. Chen YW, Dilsaver SC. Comorbidity for obsessive-compulsive disorder in bipolar and unipolar disorders. Psychiatry Res 1995;59:57–64
17. Kessler RC, Rubinow DR, Holmes C, et al. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997;27:1079–1089
18. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–151
19. Angst J, Gamma A, Benazzi F, et al. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003;73:133–146
20. Kessler RC. Comorbidity of unipolar and bipolar depression with other psychiatric disorders in a general population survey. In: Tohen M, ed. Comorbidity in Affective Disorders. New York, NY: Marcel Dekker; 1999:1–25
21. Perugi G, Toni C, Akiskal HS. Anxious-bipolar comorbidity. Diagnostic and treatment challenges. Psychiatr Clin North Am 1999;22:565–583
22. Sherwood Brown E, Suppes T, Adinoff B, et al. Drug abuse and bipolar disorder: comorbidity or misdiagnosis? J Affect Disord 2001;65:105–115
23. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420–426
24. Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. J Affect Disord 2002;68:1-23
25. Vieta E, Colom F, Corbella B, et al. Clinical correlates of psychiatric comorbidity in bipolar I patients. Bipolar Disord 2001;3:253–258
26. Kruger S, Shugar G, Cooke RG. Comorbidity of binge eating disorder and the partial binge eating syndrome with bipolar disorder. Int J Eat Disord 1996;19:45–52
27. Biederman J, Mick E, Faraone SV, et al. Pediatric mania: a developmental subtype of bipolar disorder? Biol Psychiatry 2000;48:458–466
28. McElroy SL, Soutullo CA, Taylor P Jr, et al. Psychiatric features of 36 men convicted of sexual offenses. J Clin Psychiatry 1999;60:414–420
29. McElroy SL, Pope HG Jr, Keck PE Jr, et al. Are impulse-control disorders related to bipolar disorder? Compr Psychiatry 1996;37:229–240
30. Frazier JA, Doyle R, Chiu S, et al. Treating a child with Asperger's disorder and comorbid bipolar disorder. Am J Psychiatry 2002;159:13–21
31. Comings BG, Comings DE. A controlled study of Tourette syndrome, V: depression and mania. Am J Hum Genet 1987;41:804–821
32. Breslau N, Merikangas K, Bowden CL. Comorbidity of migraine and major affective disorders. Neurology 1994;44(suppl 7):S17–S22
33. Kupka RW, Nolen WA, Post RM, et al. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. Biol Psychiatry 2002;51:305–311
34. Elmslie JL, Silverstone JT, Mann JI, et al. Prevalence of overweight and obesity in bipolar patients. J Clin Psychiatry 2000;61:179–184
35. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002;63: 207–213
36. Fagiolini A, Kupfer DJ, Houck PR, et al. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry 2003; 160:112–117
37. Sax KW, Strakowski SM. The co-occurrence of bipolar disorder with medical illness. In: Tohen M, ed. Comorbidity in Affective Disorders. New York, NY: Marcel Dekker; 1999:213–227
38. Kerbeshian J, Burd L, Klug MG. Comorbid Tourette's disorder and bipolar disorder: an etiologic perspective. Am J Psychiatry 1995; 152:1646–1651
39. Schiffer RB, Wineman NM, Weitkamp LR. Association between bipolar affective disorder and multiple sclerosis. Am J Psychiatry 1986;143: 94–95
40. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844–850
41. Andrews G, Slade T, Issakidis C. Deconstructing current comorbidity: data from the Australian National Survey of Mental Health and Well-Being. Br J Psychiatry 2002;181:306–314
42. Bellivier F, Golmard JL, Henry C, et al. Admixture analysis of age of onset in bipolar I affective disorder. Arch Gen Psychiatry 2001;58:510–512
43. Coryell W, Solomon D, Turvey C, et al. The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry 2003;60:914–920
44. McElroy SL, Arnold LM. Impulse-control disorders. In: Gabbard GO, ed. Treatments of Psychiatric Disorders. 3rd ed, vol 2. Washington, DC: American Psychiatric Press; 2001:2435–2471

45. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients using survival analysis. Arch Gen Psychiatry 1990;47:1106–1111
46. Frank E, Cyranowski JM, Rucci P, et al. Clinical significance of lifetime panic spectrum symptoms in the treatment of patients with bipolar I disorder. Arch Gen Psychiatry 2002;59:905–911
47. Perugi G, Akiskal HS, Pfanner C, et al. The clinical impact of bipolar and unipolar affective comorbidity on obsessive-compulsive disorder. J Affect Disord 1997;46:15–23
48. Diniz JB, Rosario-Campos MC, Shavitt RG, et al. Impact of age at onset and duration of illness on the expression of comorbidities in obsessive-compulsive disorder. J Clin Psychiatry 2004;65:22–27
49. Dilsaver SC, Chen YW, Swann AC, et al. Suicidality, panic disorder and psychosis in bipolar depression, depressive-mania and pure-mania. Psychiatry Res 1997;73:47–56
50. Geller B, Cooper TB, Sun K, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry 1998;37:171–178
51. Brady KT, Sonne SC, Malcolm RJ, et al. Carbamazepine in the treatment of cocaine dependence: subtyping by affective disorder. Exp Clin Psychopharmacol 2002;10:276–285
52. Frankenburg FR, Zanarini MC. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. J Clin Psychiatry 2002;63:442–446
53. Hollander E, Pallanti S, Baldini Rossi N, et al. Sustained-release lithium/placebo treatment response in bipolar spectrum pathological gamblers. Am J Psychiatry. In press
54. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 1990;147:431–434
55. Brady KT, Sonne SC, Anton R, et al. Valproate in the treatment of acute bipolar affective episodes complicated by substance abuse: a pilot study. J Clin Psychiatry 1995;56:118–121
56. Nelson E, Brusman L, Holcomb J, et al. Divalproex sodium in sex offenders with bipolar disorders and comorbid paraphilias: an open retrospective study. J Affect Disord 2001;64:249–255
57. Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. J Affect Disord 2002;68:1–23
58. McDougle CJ, Price LH, Goodman WK, et al. A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder: lack of efficacy. J Clin Psychopharmacol 1991;11:175–184
59. Pigott TA, Pato MT, L'Heureux F, et al. A controlled comparison of adjuvant lithium carbonate or thyroid hormone in clomipramine-treated patients with obsessive-compulsive disorder. J Clin Psychopharmacol 1991;11:242–248
60. Judd LL, Hubbard RB, Huey LY, et al. Lithium carbonate and ethanol induced "highs" in normal subjects. Arch Gen Psychiatry 1977;34: 463–467
61. Linnoila M, Saario I, Maki M. Effect of treatment with diazepam or lithium and alcohol on psychomotor skills related to driving. Eur J Clin Pharmacol 1974;7:337–342
62. Judd LL, Huey LY. Lithium antagonizes ethanol intoxication in alcoholics. Am J Psychiatry 1984;141:1517–1521
63. Kline NS, Wren JC, Cooper TB, et al. Evaluation of lithium therapy in chronic and periodic alcoholism. Am J Med Sci 1974;268:15–22
64. Merry J, Reynolds CM, Bailey J, et al. Prophylactic treatment of alcoholism by lithium carbonate: a controlled study. Lancet 1976;1: 481–482
65. Fawcett J, Clark DC, Aagesen CA, et al. A double-blind, placebo-controlled trial of lithium carbonate therapy for alcoholism. Arch Gen Psychiatry 1987;44:248–256
66. Dorus W, Ostrow DG, Anton R, et al. Lithium treatment of depressed and nondepressed alcoholics. JAMA 1989;262:1646–1652
67. Malone RP, Delaney MA, Luebbert JF, et al. A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. Arch Gen Psychiatry 2000;57:649–654
68. Campbell M, Adams PB, Small AM, et al. Lithium in hospitalized aggressive children with conduct disorder: a double-blind and placebo-controlled study. J Am Acad Child Adolesc Psychiatry 1995;34:445–453
69. Sheard MH, Marini JL, Bridges CI, et al. The effect of lithium on impulsive aggressive behavior in man. Am J Psychiatry 1976;133: 1409–1413
70. Gross HA, Ebert MH, Faden VB, et al. A double-blind controlled trial of lithium carbonate in primary anorexia nervosa. J Clin Psychopharmacol 1981;1:376–381
71. Hsu LK, Clement L, Santhouse R, et al. Treatment of bulimia nervosa with lithium carbonate: a controlled study. J Nerv Ment Dis 1991;179: 351–355
72. Mathew NT, Saper JR, Silberstein SD, et al. Migraine prophylaxis and divalproex. Arch Neurol 1995;52:281–286
73. Silberstein SD, Saper JR, Freitag FG. Migraine: diagnosis and treatment. In: Wolff HG, Lipton RB, Dalessio DJ, eds. Wolff's Headache and Other Head Pain. 7th ed. New York, NY: Oxford University Press; 2001: 121–237
74. Lum M, Fontaine R, Elie R, et al. Probable interaction of sodium divalproex with benzodiazepines. Prog Neuropsychopharmacol Biol Psychiatry 1991;15:269–273
75. Brady KT, Myrick H, Henderson S, et al. The use of divalproex in alcohol relapse prevention: a pilot study. Drug Alcohol Depend 2002; 67:323–330
76. Longo LP, Campbell T, Hubatch S. Divalproex sodium (Depakote) for alcohol withdrawal and relapse prevention. J Addict Dis 2002;21:55–64
77. Donovan SJ, Stewart JW, Nunes EV, et al. Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design. Am J Psychiatry 2000;157:818–820
78. Steiner H, Petersen ML, Saxena K, et al. Divalproex sodium for the treatment of conduct disorder: a randomized controlled clinical trial. J Clin Psychiatry 2003;64:1183–1191
79. Hollander E, Tracy KA, Swann AC, et al. Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. Neuropsychopharmacology 2003;28:1186–1197
80. Uhde TW, Stein MB, Post RM. Lack of efficacy of carbamazepine in the treatment of panic disorder. Am J Psychiatry 1988;145:1104–1109
81. Bjorkqvist SE, Isohanni M, Makela R, et al. Ambulant treatment of alcohol withdrawal symptoms with carbamazepine: a formal multicentre double-blind comparison with placebo. Acta Psychiatr Scand 1976;53: 333–342
82. Malcolm R, Ballenger JC, Sturgis ET, et al. Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. Am J Psychiatry 1989;146:617–621
83. Mueller TI, Stout RL, Rudden S, et al. A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. Alcohol Clin Exp Res 1997;21:86–92
84. Kaplan AS, Garfinkel PE, Darby PL, et al. Carbamazepine in the treatment of bulimia. Am J Psychiatry 1983;140:1225–1226
85. Cowdry RW, Gardner DL. Pharmacotherapy of borderline personality disorder: alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. Arch Gen Psychiatry 1988;45:111–119
86. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry 2002;159:1777–1779
87. Butterfield MI, Becker ME, Connor KM, et al. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. Int Clin Psychopharmacol 2001;16:197–203
88. Bartzokis G, Freeman T, Roca V. Risperidone in the treatment of chronic combat-related post traumatic stress disorder. Int J Neuropsychopharmacol 2002;5(suppl 1):130
89. Hamner MB, Faldowski RA, Ulmer HG, et al. Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. Int Clin Psychopharmacol 2003;18:1–8
90. Monnelly EP, Ciraulo DA, Knapp C, et al. Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. J Clin Psychopharmacol 2003;23:193–196
91. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 2000;57:794–801
92. Denys D, Van Megen H, Westernberg H. A double-blind, placebo-controlled study of quetiapine addition in treatment refractory patients with OCD. In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif. Abstract NR 770:288
93. Kinrys G, Nicolau DC, Simon NM, et al. Adjunctive olanzapine for treatment of refractory generalized anxiety disorder: an interim analysis.

Poster III-26 abstract available at: http://www.nimh.nih.gov/ncdeu/abstracts2002/ncdeu3026.cfm
94. Brawman-Mintzer O. Adjunctive risperidone for treatment resistant general anxiety disorder patients: facing unmet needs: atypical antipsychotics for mood and anxiety. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
95. Findling RL, McNamara NK, Branicky LA, et al. A double-blind pilot study of risperidone in the treatment of conduct disorder. J Am Acad Child Adolesc Psychiatry 2000;39:509–516
96. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: a double-blind, placebo-controlled pilot study. J Clin Psychiatry 2001;62:849–854
97. Bogenschutz MP, Nurnberg HG. Olanzapine versus placebo in the treatment of borderline personality disorder. J Clin Psychiatry 2004;65:104–109
98. Dion Y, Annable L, Sandor P, et al. Risperidone in the treatment of Tourette syndrome: a double-blind, placebo-controlled trial. J Clin Psychopharmacol 2002;22:31–39
99. Bruggeman R, van der Linden C, Buitelaar JK, et al. Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. J Clin Psychiatry 2001;62:50–56
100. Gaffney GR, Perry PJ, Lund BC, et al. Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 2002;41:330–336
101. Onofrj M, Paci C, D'Andreamatteo G, et al. Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs low-dose pimozide. J Neurol 2000;247:443–446
102. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. J Am Acad Child Adolesc Psychiatry 2000;39:292–299
103. McDougle CJ, Holmes JP, Carlson DC, et al. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. Arch Gen Psychiatry 1998;55:633–641
104. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol 1999;19:341–348
105. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacol 2000;20:467–471
106. Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised, controlled trial. Lancet 2003;361:1677–1685
107. Hoopes SP, Reimherr FW, Hedges DW, et al. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, pt 1: improvement in binge and purge measures. J Clin Psychiatry 2003;64:1335–1341
108. McElroy SL, Arnold LM, Shapira NA, et al. Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. Am J Psychiatry 2003;160:255–261
109. Storey JR, Calder CS, Hart DE, et al. Topiramate in migraine prevention: a double-blind, placebo-controlled study. Headache 2001;41:968–975
110. Bray GA, Hollander P, Klein S, et al. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. Obes Res 2003;11:722–733
111. Gadde KM, Franciscy DM, Wagner HR, et al. Zonisamide for weight loss in obese adults: a randomized controlled trial. JAMA 2003;289: 1820–1825
112. Steiner TJ, Findley LJ, Yuen AW. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia 1997;17:109–112
113. Lampl C, Buzath A, Klinger D, et al. Lamotrigine in the prophylactic treatment of migraine: a pilot study. Cephalalgia 1999;19:58–63
114. D'Andrea G, Granella F, Cadaldini M, et al. Effectiveness of lamotrigine in the prophylaxis of migraine with aura: an open pilot study. Cephalalgia 1999;19:64–66
115. Keck PE Jr, Nelson EB, McElroy SL. Advances in the pharmacologic treatment of bipolar depression. Biol Psychiatry 2003;53:671–679
116. Thase ME, Sachs GS. Bipolar depression: pharmacotherapy and related therapeutic strategies. Biol Psychiatry 2000;48:558–572
117. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced manic and cyclic acceleration: a controversy revisited. Am J Psychiatry 1995;152:1130–1138
118. Coryell W, Solomon D, Turvey C, et al. The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry 2003;60:914–920
119. Altshuler L, Suppes T, Black D, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am J Psychiatry 2003;160: 1252–1262
120. Wehr TA. Can antidepressants induce rapid cycling? Arch Gen Psychiatry 1993;50:495–496
121. Stein DJ, Hollander E, eds. Textbook of Anxiety Disorders. Washington, DC: American Psychiatric Publishing, Inc; 2002
122. Zhu AJ, Walsh BT. Pharmacologic treatment of eating disorders. Can J Psychiatry 2002;47:227–234
123. McElroy SL, Pope HG Jr, Keck PE Jr, et al. Are impulse-control disorders related to bipolar disorder? Compr Psychiatry 1996;37: 229–240
124. Silberstein SD. Migraine: preventive treatment. Curr Med Res Opin 2001;17(suppl 1):S87–93
125. McElroy SL, Kotwal R, Malhotra S, et al. Are mood disorders and obesity related? a review for the mental health professional [CME]. J Clin Psychiatry 2004;65:634–651
126. Pettinati HM. The use of selective serotonin reuptake inhibitors in treating alcoholic subtypes. J Clin Psychiatry 2001;62(suppl 20):26–31
127. Attia E, Haiman C, Walsh BT, et al. Does fluoxetine augment the inpatient treatment of anorexia nervosa? Am J Psychiatry 1998;155:548–551
128. Carter JC, Olmsted MP, Kaplan AS, et al. Self-help for bulimia nervosa: a randomized controlled trial. Am J Psychiatry 2003;160:973–978
129. McElroy SL, Arnold LM. Impulse control disorders. In: Grabbard GD, ed. Treatment of Psychiatric Disorders. 3rd ed. Washington, DC: American Psychiatric Association Press; 2001:2435–2471
130. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2002; 159(suppl 4):1–50
131. Otto MW, Reilly-Harrington N, Sachs GS. Psychoeducational and cognitive-behavioral strategies in the management of bipolar disorder. J Affect Disord 2003;73:171–181
132. Miklowitz DJ, George EL, Richards JA, et al. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 2003;60:904–912
133. Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 2003;60:402–407
134. Weiss RD, Griffin ML, Greenfield SF, et al. Group therapy for patients with bipolar disorder and substance dependence: results of a pilot study. J Clin Psychiatry 2000;61:361–367