CME

Obsessive-Compulsive–Bipolar Comorbidity: A Systematic Exploration of Clinical Features and Treatment Outcome

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Background: Notwithstanding the emerging literature on comorbidity between obsessive-compulsive disorder (OCD) and bipolar disorder, relatively few systematic data exist on the clinical characteristics of this interface and its treatment. The aim of the present study is to address this challenge as it appears in a setting of routine clinical practice.

Method: The sample comprised 68 patients with comorbid DSM-IV diagnoses of OCD and major depressive episode admitted and treated at the day-hospital in the Department of Psychiatry at the University of Pisa (Pisa, Italy) during a 3-year period (January 1995–December 1998). Thirty-eight patients (55.8%) showed lifetime comorbid bipolar disorder (12 [31.6%] bipolar I and 26 [68.4%] bipolar II). Diagnoses and clinical features were collected by means of structured (Structured Clinical Interview for DSM-IV) and semistructured interviews (OCD-Interview). Assessments of drug treatments, clinical outcome, and adverse effects were made prospectively as part of routine clinical care throughout the course of their day-hospitalization.

Results: In contrast with non-bipolar OCD patients, OCD-bipolar patients showed a more episodic course with a greater number of concurrent major depressive episodes. They reported a significantly higher rate of sexual obsessions and significantly lower rate of ordering rituals. Furthermore, they reported more frequent current comorbidity with panic disorder-agoraphobia and abuse of different substances (alcohol, sedatives, nicotine, and coffee). Drug treatment with clomipramine and, to a lesser extent, with selective serotonin reuptake inhibitors was associated with hypomanic switches in OCD-bipolar patients, especially in those not concomitantly treated with mood stabilizers. A combination of multiple mood stabilizers was necessary in 16 OCD-bipolar patients (42.1%) and a combination of mood stabilizers with atypical antipsychotics was required in 4 cases (10.5%). OCD-bipolar patients tended to show a less positive outcome for mood symptomatology and general functioning. Three patients required hospitalization for severe mixed episode.

Conclusion: In a tertiary care center, comorbidity between OCD and bipolar disorder is a significant clinical problem affecting a large number of patients and has a substantial impact on the clinical characteristics and treatment outcome of both disorders.

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Major depression has been considered the most common complication of obsessive-compulsive disorder (OCD), ranging from 13% to 75%.[1–5] Less attention has been devoted to the comorbidity between OCD and bipolar disorder, despite numerous reports based on a nonsystematic search for such an association.[6,7] The development of mania or hypomania in response to treatment with tricyclic antidepressants or selective serotonin reuptake inhibitors (SRRIs) has been described widely in OCD case series and reports.[6–14] Lifetime comorbidity between OCD, panic disorder, and social phobia on the one hand, and mood disorder on the other, has been systematically investigated by means of standardized assessment in a recent Pisa-San Diego collaborative study.[15] Major depression was the most common comorbid disorder, and the rate of comorbid major depression was significantly higher in the social phobia (52.1%) and OCD (38%) groups than in the panic disorder (29.4%) group. Even bipolar II disorder was more frequently associated with social phobia (21.1%) and OCD (17.7%) than with panic disorder (5.0%). These findings contradict a common perception that the relationship between anxiety and mood disorders is largely limited to unipolar depression and dysthymia. Epidemiologic studies in the community support the significant relationship between bipolar disorder and OCD,[16–18] suggesting that such comorbidity is not simply a result of clinical center bias.

Clinical data regarding the comorbidity between bipolar disorder and OCD have also been reported in both

mood disorders and OCD patients. Kruger et al.[19] assessed 149 inpatients with affective disorders and found that 13 (35%) of 37 patients with bipolar disorder suffered from comorbid OCD; the prevalence of OCD was similar among patients with unipolar depression and bipolar disorder. In a more recent report, the same group[20] evaluated 143 inpatients with bipolar I and II disorder, observing current comorbid OCD in 10 patients (7%). All bipolar subjects with OCD were bipolar II, were male, and had been diagnosed with dysthymia. A similar lifetime prevalence of 10% has been reported by McElroy et al.[21] in a large multinational sample (N = 288) of bipolar I and II patients. In a clinical study of 345 outpatients with OCD conducted by our group,[22] lifetime comorbidity with bipolar disorder (primarily bipolar II) was 16%. Most patients (13.6%) suffered from bipolar II disorder. Unlike OCD patients without bipolar disorder, those with bipolar disorder reported a more episodic course of OCD symptoms, a greater frequency of concurrent major depressive episodes, higher rates of sexual and religious obsessions, and a lower rate of checking rituals. In addition, panic disorder and substance abuse were more common among OCD patients with comorbid bipolar disorder. Recently, a survey conducted among the French Association of OCD patients (N = 453) showed a high prevalence of comorbid bipolarity, especially when this disorder was dimensionally explored by using self-rated questionnaires for hypomania and cyclothymia.[23] In this national survey, 30% of the OCD group presented lifetime comorbid hypomanic episodes (score ≥ 10 on Angst's Checklist) and almost 50% presented cyclothymic traits (score ≥ 10 on a cyclothymia questionnaire).

The aim of the present study is to describe the clinical characteristics and treatment outcome of bipolar versus non-bipolar OCD patients with current concomitant major depression in a setting of routine clinical practice.

METHOD

The sample comprised 68 patients with comorbidity between OCD and major depressive episode, admitted and treated at the day-hospital of the Department of Psychiatry at the University of Pisa (Pisa, Italy) during a 3-year period (January 1995–December 1998). Thirty-eight patients (55.9%) showed lifetime comorbid bipolar disorder (12 [31.6%], bipolar I; 26 [68.4%], bipolar II). The subjects came from a variety of sources, almost equally divided between self-referrals; those from general practitioners, various medical specialists, and psychiatrists; and, finally, those referred by former patients. All patients gave their informed consent to participate in the present study.

The inclusion criterion for participation was fulfillment of the DSM-IV criteria for OCD and major depressive episode. Patients were excluded if they had a lifetime history of schizophrenia or related psychotic disorders, organic mental syndrome, or uncontrolled or serious medical conditions.

Diagnostic and Symptomatological Evaluation

A systematic face-to-face interview that consisted of structured and semistructured components was used to collect data. Diagnostic evaluation and comorbidity with mood and other anxiety disorders were recorded by means of the Structured Clinical Interview for DSM-IV.[24] Demographic and illness characteristics, as well as family history, were obtained by means of a specific interview for OCD; this instrument, adapted for our Italian clinic population, has been extensively described elsewhere.[25]

The interview and all the ratings were completed by psychiatrists with at least 4 years' experience in anxiety and mood disorders. Each interviewer underwent a training program in the use of the interview instruments, which included direct observation of experienced interviewers, direct supervision of interviews, and interrater reliability. High reliability and diagnostic concordance have been documented in previous reports.[25–27] Reliable assessment of familial, developmental, and psychopathologic antecedents at the Pisa Center is considerably aided by the fact that access to past records is readily made available by patients and their physicians and, in particular, by the availability of numerous family members to corroborate personal history data obtained from patients. Clinical data were reviewed by the interviewer team for the purpose of consensus. When questions arose, patients were recontacted for further clarification, patients' medical records were reviewed, and information was obtained from family members and previous physicians.

Treatment Assessment and Management

Assessment of pharmacologic treatments, clinical outcome, and adverse effects were carried out prospectively as a part of routine clinical care throughout the course of the patients' day-hospitalization. Clinicians involved in treatment decisions and management were independent from the interviewers. All patients received pharmacologic treatment according to the judgment of the individual physician. Although in fact no patients received formal psychotherapeutic treatment during the period of observation, pharmacotherapy was nevertheless managed in the context of an educational and supportive relationship. Patients were followed up for a mean ± SD period of 23.2 ± 24.3 weeks, ranging from 8 to 52 weeks. Response was defined as a final score on the Clinical Global Impressions-Improvement scale[28] of either 1 (marked improvement, virtual remission of symptoms, and return to normal functioning) or 2 (moderate improvement, significant reduction of symptoms, and clearly improved social or vocational functioning), associated with a DSM-IV Global Assessment of Functioning (GAF)[29] improvement,

compared with the baseline levels, expressed by a score > 60 lasting for at least 6 weeks. No patients met this criterion at the initial evaluation. We used this relatively conservative threshold to ensure that the response was not determined by the natural fluctuation of the mood and OCD symptoms and that the improvement was reflected in a significant change in global functioning. All those who had dropped out of treatment or had been hospitalized were considered to be nonresponders.

Data Analyses

Comparative analyses of continuous variables were carried out using the Student t test, and of categorical variables, using the chi-square analysis. Fisher exact test was used when cell sizes were sparse and chi-square analysis was unrealizable. Considering the large number of comparisons performed and the number of subjects in each group, our results are prone to both type I and type II errors. However, given the exploratory nature of our study, we decided to use a 2-tailed significance level of $p < .05$.

RESULTS

The mean ± SD age of our sample at the time of admission to the study was 34.2 ± 12.5 years (range = 18–73 years); 32 (47.1%) patients were males. Slightly over half of the subjects (N = 40; 58.8%) were married, 21 (30.9%) were single, and the remaining 7 (10.3%) were widowed or divorced. Most patients had attended school for 13 years (N = 38; 55.9%), and 17 (25.0%) for 8 years; 13 subjects (19.1%) had schooling at the university level. Most patients were white-collar workers (N = 29; 42.6%), 10 (14.7%) were blue-collar workers, 10 (14.7%) were students, and 8 subjects (11.7%) were managers; the remaining 11 subjects (16.2%) did not work. With regard to demographic characteristics, no statistically significant differences between bipolar and non-bipolar OCD patients were observed.

Mean ± SD age at onset was 21.5 ± 9.1 years for OCD and 24.1 ± 9.4 years for mood disorder. The global severity of the symptoms measured during the first visit by the mean ± SD DSM-IV GAF score was 47.7 ± 21.1. Thirty-eight patients (55.8%) showed lifetime comorbid bipolar disorder (12 [31.6%], bipolar I; 26 [68.4%], bipolar II). Forty-four patients (64.7%) met current DSM-IV criteria for at least 1 additional mental disorder: generalized anxiety disorder in 19 (27.9%), panic disorder-agoraphobia in 24 (35.3%), social phobia in 13 (19.1%), eating disorders in 7 (10.3%; 5 subjects with bulimia and 2 subjects with anorexia), drug and/or alcohol abuse in 25 (36.7%).

In contrast with non-bipolar OCD patients, OCD-bipolar patients showed a more episodic course with a greater number of major depressive episodes and suicide attempts; their OCD began more frequently in concomitance with the mood disorder (Table 1). They currently reported a significantly higher rate of sexual obsessions and a significantly lower rate of order rituals (Table 1). Compared with non-bipolar, OCD-bipolar patients reported more frequent current comorbidity with panic disorder-agoraphobia and with abuse of different substances (alcohol, sedatives, nicotine, and coffee) (Table 1).

Previously with OCD-bipolar patients, drug treatment with clomipramine (Table 2) and, to a lesser extent, SSRIs was associated with (hypo)manic switches. Pharmacologic (hypo)mania was more frequent in patients who were not concomitantly treated with a mood stabilizer (12/31, 38.7% vs. 3/34, 8.8%; $\chi^2 = 9.19$, $p = .002$). A combination of multiple mood stabilizers (lithium plus antiepileptics) was necessary in 12 OCD-bipolar patients (31.6%), and a combination of mood stabilizers with atypical antipsychotics (clozapine, olanzapine, risperidone) was required in 4 OCD-bipolar patients (10.5%). In 4 non-bipolar OCD patients (13.3%), antiepileptics were prescribed in order to alleviate agitation and/or antidepressant-resistant panic/anxious symptoms. Finally, OCD-bipolar patients tended to show less frequent remission of mood disorder symptoms, and 3 patients (7.9%) required hospitalization as inpatients for the appearance of severe mixed-manic episode.

DISCUSSION

The comorbidity between OCD and bipolar disorder reported in this article is a major clinical problem affecting a large number of patients in our tertiary psychiatric care setting. As observed in previous clinical[27,30] and epidemiologic[16,17] studies, when OCD was associated with bipolar disorder, there was also an increased lifetime comorbidity with panic disorder-agoraphobia. Our bipolar-OCD patients also reported, more frequently than the non-bipolar OCD patients, abuse of alcohol, sedatives, nicotine, and caffeine, as well as the concomitant onset (usually during depressive phases) and episodic course of OCD. Several investigators[22,31,32] have observed that OCD symptoms may vary during the course of bipolar disorder. For example, cases have been reported in which OCD symptoms remitted during mania and then reappeared with the remission of the manic episode.[9–11] In addition, it has been noted that patients with mixed mania are more likely than patients with pure mania to have comorbid OCD[33] and lithium response in episodic OCD.[32] In a recent study,[27] we reported a rate of 27.4% of episodic course in 135 patients meeting DSM-III-R criteria for OCD with a personal history of at least 10 years of illness. Episodic course was correlated positively with family history for mood disorders, lifetime comorbidity for panic and bipolar II disorders, and late age at onset and correlated negatively with generalized anxiety disorder. The concurrence of episodic OCD with bipolar II disorder and

Table 1. Comparison of Demographic and Clinical Characteristics of 68 OCD Patients With Concomitant Bipolar or Non-Bipolar Major Depressive Episode

Characteristic	Bipolar (N = 38)	Non-Bipolar (N = 30)	t or χ^2 (df = 1)	p
Gender, male, N (%)	20 (52.6)	12 (40.0)	1.01	.30
Age, mean (SD), y	35.9 (12.2)	35.6 (12.6)	0.11	.91
Age at onset, mean (SD), y				
OCD	23.1 (8.1)	21.9 (9.4)	1.19	.23
Mood disorder	24.9 (8.4)	23.7 (9.7)	0.99	.33
No. depressive episodes, mean (SD)	3.4 (3.0)	2.4 (2.6)	2.43	.02
No. manic + hypomanic episodes, mean (SD)	2.7 (2.4)			
No. suicidal attempts, mean (SD)	0.8 (0.9)	.2 (0.6)	2.17	.03
No. hospitalizations, mean (SD)	0.9 (0.8)	.2 (0.4)	2.17	.03
Age at first consultation, mean (SD), y	24.3 (10.1)	24.0 (8.7)	0.67	.50
Onset of OCD vs mood disorder, N (%)				
Before	12 (31.6)	19 (63.3)		
Concomitant	20 (52.6)	10 (33.3)		
After	6 (15.8)	1 (3.3)	7.65[a]	.02
Episodic course of OCD, N (%)	20 (52.6)	5 (16.7)		.002
Lifetime comorbidity, N (%)				
Generalized anxiety	11 (28.9)	8 (26.7)	0.04	.83
Panic disorder-agoraphobia	20 (52.6)	4 (13.3)	11.34	.001
Social phobia	3 (7.9)	10 (33.3)	1.05	.30
Eating disorders				
Anorexia	1 (2.6)	1 (3.3)	0.03	.86
Bulimia	3 (7.9)	2 (6.7)	0.04	.85
Drug abuse[b]				
Alcohol	12 (31.6)	3 (10.0)	4.54	.03
Sedatives	10 (26.3)	1 (3.3)	6.53	.01
Opioids	2 (5.3)	0 (0)	1.63	.20
Stimulants	2 (5.3)	0 (0)	1.63	.20
Nicotine	12 (31.6)	3 (10.0)	4.54	.03
Coffee	10 (26.3)	2 (6.7)	4.45	.03
First-degree family history, N (%)				
Anxiety disorder	16 (42.1)	5 (16.7)	5.08	.02
OCD	4 (10.5)	6 (20.0)	1.20	.27
Mood disorders	16 (42.1)	9 (30.0)	1.06	.30
Alcohol abuse	3 (7.9)	2 (6.7)	0.04	.85
Schizophrenia	0 (0)	1 (3.3)	1.29	.26
Obsessions, N (%)				
Aggressive	20 (52.6)	12 (40.0)	1.07	.30
Contamination	11 (28.9)	15 (50.0)	3.15	.08
Sexual	21 (55.3)	8 (26.7)	5.61	.02
Religious	10 (26.3)	5 (16.7)	0.90	.34
Symmetry/Order	11 (28.9)	12 (40.0)	0.92	.34
Somatic	13 (34.2)	5 (16.7)	2.65	.10
Other	17 (44.7)	11 (36.7)	0.45	.50
Compulsions, N (%)				
Control	23 (60.5)	16 (53.3)	0.36	.55
Cleaning	17 (44.7)	16 (53.3)	0.50	.48
Order	7 (18.4)	15 (50.0)	7.64	.006
Numeric	11 (28.9)	8 (26.7)	0.04	.84
Other	16 (42.1)	9 (30.0)	1.06	.30

[a]df = 2.
[b]Patients abused multiple drugs.
Abbreviation: OCD = obsessive-compulsive disorder.

the presence of a positive family history for mood disorders would suggest common pathogenetic mechanisms. Other studies indicate high rates of obsessive traits in the offspring of bipolar probands.[34] Coryell[35] reported an equal incidence (2.3%) of mania in the families of probands with OCD and in those families with a bipolar-disordered member. In a more theoretical vein, we would suggest that, in a substantial minority of cases, episodic OCD may be the phenotypic expression of an underlying affective genotype. Further prospective studies are necessary in order to define more accurately the relationship between OCD and mood disorder.

With regard to OCD symptoms in patients with comorbid bipolar disorder, in the present study there would appear to be fewer rituals, in particular those concerning ordering, and more sexual obsessions. These findings are consistent with previous reports from our group[27] and indicate that bipolar comorbidity has a clinically relevant influence on the symptomatological expression, other than course and complications, of OCD. Furthermore, in the French OCD Association survey, the group of "bipolar OCD" was characterized by a significantly higher rate of anger attacks and suicide attempts.[23] With regard to treatment management, in the present sample, OCD-bipolar comorbidity is associated with the need for more complex interventions (drug combinations, hospitalization) and produces a negative impact on treatment outcome, for mood symptoms and general functioning. Most controlled trials involving major depression or bipolar disorder have excluded patients with OCD and vice versa; as a result, the empirical bases for treating patients with comorbidity are almost exclusively founded on anecdotal reports and open clinical experiences. The present report has the advantage of being systematic and based on a very large sample. Bipolar OCD patients are among the most difficult to treat, and no mood stabilizer has been shown to exert any anti-OCD activity in controlled studies. In our patients, the administration of effective anti-OCD pharmacologic treatments (clomipramine and, to a lesser extent, SSRIs) demonstrated a high potential for inducing (hypo)manic switches. In fact, a switch from depression to mania or hypomania is not rare in bipolar patients and should not necessarily be regarded as a consequence of drug treatment. Nevertheless, according to DSM-IV criteria, substance-induced (hypo)mania—in this case, antidepressant-medication–induced—is defined as "an elevated, euphoric, or irritable mood due to the direct physiological effect of a substance"[29(p370)] and does not count toward the diagnosis of bipolar disorder. The existence of a temporal relationship between treatment with antidepressants and onset of (hypo)mania has relevant implications for the management of this complex comorbidity, in which high dosages of antidepressants are

Table 2. Drug Treatments and Treatment Responses of 68 OCD Patients With Concomitant Bipolar or Non-Bipolar Major Depressive Episode

Response and Treatment	Bipolar (N = 38)	Non-Bipolar (N = 30)	χ^2 (df = 1)	p
Past pharmacologic hypomania, N/N (%)				
Clomipramine	9/23 (39.1)	1/21 (4.8)	7.38	.007
SSRIs	5/36 (13.9)	0/30 (0)	4.51	.04
Mood switch during day-hospitalization, N (%)	4 (10.5)	0 (0)	3.35	.07
Last evaluation, N (%)				
CGI-Improvement 1 or 2 (OCD)	20 (52.6)	14 (46.7)	0.24	.62
CGI-Improvement 1 or 2 (mood disorder)	19 (50.0)	24 (80.0)	6.49	.01
GAF score > 60	16 (42.1)	20 (66.7)	4.06	.04
Hospitalization	3 (7.9)	0 (0)	2.48	.11
Concomitant medications and ECT, N (%)				
Lithium	10 (26.3)	2 (6.7)		
Antiepileptics	8 (21.1)	4 (13.3)		
Lithium plus antiepileptics	12 (31.6)	0 (0)		
2 or more antiepileptics	4 (10.5)	0 (0)		
Mood stabilizers plus atypical antipsychotics	4 (10.5)	0 (0)		
ECT	1 (2.6)	1 (3.3)		

Abbreviations: CGI = Clinical Global Impressions scale, ECT = electroconvulsive therapy, GAF = Global Assessment of Functioning, OCD = obsessive-compulsive disorder, SSRIs = selective serotonin reuptake inhibitors.

often required for the treatment of obsessive-compulsive symptoms. In our patients, previous administration of clomipramine was associated with a history of pharmacologically induced (hypo)mania in nearly 40% of the cases. This is consistent with the high incidence of switch into mania associated with clomipramine observed in a previous study.[36] The combination of different mood stabilizers (lithium plus antiepileptics) was often necessary, and many of our patients presented residual affective and OCD symptoms. Despite concomitant mood stabilizers, 3 patients reported severe manic or mixed episode (aggressive, hostile mood), which required hospitalization. In some cases, combination with atypical antipsychotics was necessary. Although atypical antipsychotics have been reported to exacerbate OCD symptoms,[37] in some patients these drugs seem to display anti-OCD and anti-aggressive activity, which provides an effective treatment of OCD symptoms.[38,39]

In conclusion, the correct identification of OCD-bipolar comorbidity has relevant clinical implications as far as other concomitant disorders, symptomatological features, course, complications, and treatment management and outcome are concerned. Symptomatological instability, multiple comorbidity, a high level of impulsivity, suicidal behavior, alcohol and substance abuse, more complex treatment management, and a less positive outcome for mood symptomatology and general functioning appear to be the most relevant consequences of OCD-bipolar coexistence. Our findings would seem to indicate that, in treating comorbid OCD-bipolar patients, the response of both disorders must be carefully monitored and it is preferable to begin the treatment with a mood stabilizer. If antidepressants are necessary, adequate mood stabilization should be achieved first of all, and antidepressants should then be added cautiously, while patients are monitored carefully for emerging symptoms of hypomania, mania, or mixed states. Clomipramine and, to a lesser extent, SSRIs may worsen the course of bipolar disorder, especially if their use has begun before treatment with a mood stabilizer. SSRIs should be preferred because of the lower risk of mood switching compared with clomipramine.

Drug names: clomipramine (Anafranil and others), clozapine (Clozaril and others), olanzapine (Zyprexa), risperidone (Risperdal).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, clozapine and risperidone are not approved by the U.S. Food and Drug Administration for the treatment of mixed-states mania.

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