

Anxiety disorders comorbidity in bipolar disorder

Comorbidade com transtornos de ansiedade em transtorno bipolar

Cilly Klüger Issler,^a Marcia Kauer Sant'Anna,^b Flavio Kapczinski^b and Beny Lafer^a

^aPROMAN – Assistance and Research Project on Bipolar Disorder of the Institute of Psychiatry of the Clinical Hospital of the Medical School of the University of São Paulo.

^bLaboratory of Experimental Psychiatry, Psychiatric Service of the Clinical Hospital of Porto Alegre

Abstract

High comorbidity between bipolar and anxiety disorders is frequently described in epidemiological and clinical studies. This association has important implications for diagnoses, clinical outcome, therapeutic intervention and prognoses of bipolar disorder that are presented in this review.

Keywords: Bipolar disorder; Anxiety disorders; Diagnosis, dual/Psychiatry

Resumo

Comorbidade elevada de transtornos de ansiedade em bipolares é freqüentemente relatada em estudos epidemiológicos e clínicos. A associação tem implicações importantes no diagnóstico, evolução clínica, tratamento e prognóstico do transtorno bipolar, que são apresentadas nesta revisão.

Descritores: Transtorno bipolar; Transtornos da ansiedade; Diagnóstico duplo/Psiquiatria

Introduction

Reports dated from 460-337 BC have already described psychopathological conditions such as 'irritated-disphoric mania' and 'agitated depression', highlighting the importance of restlessness and irritability present in conditions with mood disturbance.¹ Kraepelin,² in 1921, described anxiety as a symptom that can be present either in manic or depressive episodes. In his reports of mixed states he described episodes of what he called 'Depressive or anxious mania' in which anxious symptoms were prominent, described as a 'desperately anxious mood'.² He also described anxious aspects on depression, calling it 'excited depression', with great restlessness, anxious and irritable mood. Despite that, up to some years ago, only comorbidity of unipolar depression with anxiety disorders (AnxD) was valued. More recent studies showed that, besides disorders due to the use of psychoactive substances, anxiety disorders have high prevalence in bipolar subjects, with odds ratio for bipolar disorder (BD) higher than for unipolar depression (2.38 vs. 0.50).³

Clinical research found that 24.0% to 79.2% of bipolar subjects present at least one AnxD during their lifetime,³⁻⁵ of these, 47% receive the diagnoses of two or more disorders.⁵ Among psychotic patients, including bipolar, depressed and schizoaffective ones, the frequency of comorbidity with AnxD found was 33.8% for one single disorder and 14.3% for two or more.⁶ Despite conflicting results in the prevalence rates and frequency order, most common AnxD in BD are OCD, PD and SP.^{3-4,7-8}

Goldberg 1996⁹ contested the high prevalence of comorbidity between mood and anxiety disorders, claiming that the association is probably not a measure of the frequency in which two independent morbid conditions coexist, but rather a result of an artifact of the categorical classification employed in psychiatry which divides the psychopathological symptoms of patients in separate classes, instead of aggregating them as should be done. Freeman et al¹ reviewed the literature, verified the high co-occurrence of AnxD and BD, and suggested three hypotheses to

explain the association observed, which partially agree with Goldberg hypothesis. They may be two distinct entities that overlap by chance considering the high prevalence of these two disorders. These disorders may co-occur because, although being different entities, their pathophysiology partially overlaps. Or lastly, this association may be due to the fact that both disorders have the same fundamental pathophysiology of deregulation of affection, being different manifestations of the same underlying abnormality. Further studies are needed to elucidate the mechanisms involved.

Most studies^{1,3-4,7-8} assess the comorbidity with AnxD by means of the diagnostic criteria of the DSM-IV or DSM-III-R.¹⁰ The main criticisms directed to the studies which demonstrate the association of BD with AnxD regard the diagnostic criteria employed. In generalized anxiety disorder (GAD), as well as in post-traumatic stress disorder (PTSD), there are criteria which prevail over those of BD.¹¹ Insomnia, distractibility, excitability and irritability aspects may meet criteria for both mood and anxiety disorders in a less strict assessment. Similarly, the scales used to assess symptoms presence and improvement over time, such as Hamilton anxiety and Hamilton Depression, overlap, especially on items related to insomnia and somatic symptoms. Other diagnostic difficulty associated with anxious symptoms in BD, especially the mildest ones, is the similarity of their clinical presentation with characteristics of borderline personality disorder. Although controversial, many authors believe that behaviors initially assigned to personality alterations may stem from a severe deregulation of affection, in which mood lability and interpersonal sensitivity play a central role.¹²

Despite some criticisms, several studies have reported the evident presence of anxious symptoms in BD,¹³⁻¹⁴ even if they do not meet criteria for a specific disorder. Subsyndromal symptoms have recently acquired more importance¹⁵ being highlighted in articles that deal with the bipolar spectrum.¹⁶ They emphasize the importance of mild or non classical' symptoms of bipolarity which may have repercussion in treatment and prognosis of

patients, mainly in cases in which anxiety and depression or impulsiveness coexist.¹⁶ The quality of life and the degree of functioning are among the main outcomes affected by uncontrolled symptoms.¹⁷ AnxD patients may also show higher mood subsyndromal oscillation than normal subjects,¹⁸ and the prevalence of BD in patients with PD and SP is also higher than among the general population.^{1,4,19}

Bipolar patients who have comorbid AnxD seem to show more severe clinical characteristics. Researches suggest that there is an association between the presence of anxiety symptoms with worse prognosis, higher rate of suicide attempts and different response to mood stabilizers.¹³⁻¹⁴ Young et al,¹³ in one study which included 81 BD patients, found that 24% of them showed high level of anxiety. This highly anxious group had more suicide attempts, more alcohol abuse and worse response to lithium. In other study,¹⁴ BD patients in manic, mixed or depressive episode, who presented current or past comorbid anxiety symptoms, took more time and needed higher number of medications to have their symptoms remitted. In one study with psychotic patients, including bipolar, depressed and schizoaffective ones, those with multiple diagnoses of associated AnxD showed higher intensity of symptoms and more stimulants abuse.⁶

However, the treatment of anxiety symptoms in BD is controversial and scarcely studied, as a result of the frequent exclusion of patients with comorbidities from controlled studies.

Obsessive-compulsive disorder

Epidemiological studies showed a prevalence from 14.6 to 21% of OCD in bipolar subjects, a rate up to 8.1 times higher than what was expected for the general population.^{8,20} Clinical studies diagnosed the association with OCD between 1.55%²¹ and 35.1%²² of bipolar subjects. Most studies find percentages above 10%²⁴⁻²⁷ and prevalences vary according the type of casuistic – outpatients or inpatients, euthymic, depressed or psychotic patients, originated from primary care settings or specialized clinics – and the diagnostic instruments employed. Clinical studies have not detected differences in the prevalence of OCD in BD I or II, however, the number of patients with BD II evaluated was low.^{4-5,22}

Family studies also revealed association between BD and OCD. Coryell et al²¹ diagnosed OCD in, 2.7% and 5.3% of relatives of BD II and BD I patients, respectively, compared to 0.8% among relatives of non-bipolar probands. Other study²⁸ found the same prevalence of mania, 2.3%, in relatives of probands with BD or OCD. However, NESTADT et al²⁸ found higher prevalence of all anxiety and mood disorders, except for BD, in family members of OCD patients than among family members of normal controls.

There are also clues of a triple association between BD, PD and OCD. In the Epidemiologic Catchment Area (ECA),⁸ the percentage of OCD in BD was 16.7% in the absence of PD and 37.1% with its presence. Among OCD patients, Perugi et al³⁰ found 37.0% of PD in patients with comorbid BD and 22.1% in patients with comorbid unipolar depression.

There is little information about the clinical course of BD in patients with OCD comorbidity. Some authors^{25,31} described that this association occurs mainly in bipolar subjects who experience mixed states, and Strakowsky et al²⁵ suggested that the co-occurrence of disorders reflects rather a variability in the expression of BD than comorbid OCD diagnosis per se. Krüger et al³² found OCD only in male cases, who had BD II and had been hospitalized to treat depression and had lower number of episodes although more suicide attempts than the others. Studies comparing OCD patients with comorbid BD or unipolar depression found, among bipolar subjects, earlier onset of obsessive-compulsive symptoms, more episodic course of OCD, higher comorbidity with alcohol,

psychostimulant and sedative abuse, and with PD-agoraphobia, as well as higher number of depressive episodes.³⁰

Issler et al³³ observed a higher number of depressive episodes and of chronic affective phases and residual symptoms among women with comorbidity of BD with OCD than among those without OCD. The group with the comorbidity BD-OCD showed more frequently the presence of some antidepressant-induced manic or hypomanic episode, higher association with anxiety disorders as a whole, bulimia or binge eating disorder, tics disorder, besides a higher number of comorbidities per patient, confirming the hypothesis of the authors who suggested that the existence of one comorbid disorder increases the risk of having two, three or more comorbidities.³⁴⁻³⁵

Comorbidity with OCD implies difficulties in the clinical management of BD. Perugi et al³⁰ recommend that in these cases priority should be given to the control of mood rather than obsessive-compulsive symptoms. However, the persistence of obsessive-compulsive symptoms may contribute for the chronification of depressive episodes,³⁶ what worsens the course of BD. Most efficient medications for OCD, clomipramine and serotonin reuptake inhibitors, besides the potential of inducing mania and mixed states, may lead to rapid cycling.¹² There is no proof of efficacy of any mood stabilizer in the treatment of OCD. Open studies or case reports describe some efficacy of lithium,³⁷⁻³⁹ divalproate⁴⁰⁻⁴¹ and carbamazepine⁴²⁻⁴³ in the treatment of obsessive-compulsive symptoms. Curiously, Swartz & Shen⁴⁴ described four cases of OCD with acute onset and episodic course who did not respond to antidepressant treatment, but that even not having depressive symptoms, benefited from the use of lithium or ECT. After comparing the good therapeutic result obtained in this case reports to the reduced efficacy of these approaches in typical OCD, with gradual installation and chronic course, the authors suggested that OCD of episodic course may consist of an atypical expression of BD.⁴⁴⁻⁴⁵

Several studies on the treatment of refractory OCD deal with the association of antidepressants with atypical antipsychotics in order to increase their efficacy. A recent double-blind placebo-controlled study⁴⁶ administered olanzapine or placebo to a group of 26 patients who had not responded to SSRIs and obtained significant improvement in 46% of cases. There are open studies and case reports that show improvement of obsessive-compulsive symptoms with the association of other atypical antipsychotics, such as amisulpride,⁴⁷ quetiapine⁴⁸⁻⁴⁹ and risperidone.⁵⁰⁻⁵¹ Contradictorily, there are also descriptions of inducement of obsessive-compulsive symptoms among patients treated with atypical antipsychotics.⁵²

Due to what was exposed, the most appropriate therapeutic for patients with BD and OCD comorbidity seems to consist of the stabilization of mood through the combination of lithium, anticonvulsivants and, possibly, atypical antipsychotics, in association with cognitive-behavioral therapy, knowingly efficient for the treatment of obsessive-compulsive symptoms.⁵³⁻⁵⁴ If antidepressants should be used, preference must be given to those with low potential of inducing mania.¹²

Panic disorder

Epidemiological and clinical studies have demonstrated a clear relationship between BD and PD. Data reports show high prevalence of PD among patients with BD, varying from 33%,¹⁹ 25%,⁵⁵ to 10%.⁵⁶ depending on the population assessed, and may reach 36% among patients with bipolar depression.³ The prevalence of PD in BD is higher compared to the prevalence in unipolar depression or in the general population, as shown by the data of the ECA study,⁷ in which PD was diagnosed in 20.8%

of BD patients, whereas among depressed subjects and in the general population its rates were only 10% and 0.8%, respectively. Angst⁵⁷ found significant association with PD and social phobia (SP), among hypomanic subjects, as defined according to the DSM-IV criteria, and among those who had recurrent brief hypomania (a recurrent condition which lasts between 1 and 3 days). On the other hand, patients with panic disorder have also high rates of BD, from 5.8%³⁹ up to 23.1%, when including cyclothymic patients.⁵⁸

The link between BD and PD have also been demonstrated by genetic studies.⁵⁹⁻⁶⁰ In 2002 MacKinnon et al⁶¹ studied 203 families of probands with BD and demonstrated that family history of BD is a risk factor of PD. This hypothesis was also reinforced by Doughty et al⁶² who assessed 109 families of bipolar probands and confirmed data that PD is primarily associated with affective disorder in families with BD history. This clinical finding is corroborated by neurochemical studies, which found the association of PD comorbidity with markers in the long arm of the chromosome 18 of BD patients.²² Rotondo et al⁶³ found a significant difference in the polymorphisms of enzymes related to neurotransmitters, especially serotonin, between bipolar subjects with comorbid PD and the BD group without PD.

Therefore, it is possible to think of a BD subtype associated with PD, which seems to have some differences in its clinical presentation. Patients with comorbid BD and PD have lower insight than patients with associated OCD and/or SP.⁶⁴ BD patients, in manic, depressed or mixed episode, who had current or past comorbid anxious symptoms, took more time to have their symptoms remitted, reported more severe side-effects and those who showed panic attacks did not reach full remission.¹⁴

The dilemma regarding the treatment of PD among bipolar patients is similar to that reported for OCD patients. The antipanic efficacy of antidepressant medications, such as tricyclic and SSRIs is similar. However, the latter are associated with a lower rate of manic inducement, being preferentially used when there is BD comorbidity.⁶⁵ Preliminary studies showed some efficacy of sodium divalproate.⁶⁶⁻⁶⁸ especially when there is rapid cycling;⁶⁵ and gabapentine⁶⁹⁻⁷⁰ in the control of panic symptoms, what may represent an alternative to the use of antidepressants in these cases. It is remarkable, in face of these difficulties, the importance of the association of cognitive-behavioral therapy for the treatment of these patients. Bowen & D'Arcy,⁷¹ after comparing PD patients with and without hypomanic symptoms, verified that the presence of these symptoms does not compromise the efficacy of treatment for PD.

Social phobia

Epidemiological studies described comorbidity with SP in 5.9%⁷ to 47.1%¹⁹ of BD patients, with higher percentages among subjects with BD II⁷ or recurrent brief hypomanias.⁵⁷ Clinical studies found a lifetime prevalence of SP from 13.6%²⁷ to 33.3%³³ among bipolar patients.

There are studies suggesting the existence of SP subtypes according to the presence of mood alterations. Himmelhoch⁷² observed that 14 out of 18 social phobic subjects who responded well to the treatment with monoamino-oxidase inhibitors developed hypomanic episodes. The author discusses the possible association of the mechanism of desinhibition in mania and inhibition and anxiety in depression with the bases of SP, and suggests that one subgroup of phobic patients would belong to the bipolar spectrum, having higher probability of showing excessive desinhibition with the treatment, what seems to manifest only after the use of antidepressants.

This subgroup was also perceived by Perugi et al⁷³ who reported higher susceptibility of a percentage of phobic patients to the euphoric effects of alcohol.⁷³ In the sample assessed, 22% of patients with SP showed alcohol abuse and the diagnosis of BD II was exclusively found in these patients, as well as family history of bipolarity. The authors consider that alcohol abuse, in these cases, may be related to bipolar diathesis rather than to SP per se. They describe the observation that in social-phobic subjects without BD alcohol does not reduce social anxiety and that desinhibition and improvement in socialization shown by bipolar subjects with SP may be mediated by the increase in self-confidence due to alcohol-triggered hypomania. In the population of patients with alcohol abuse the prevalence of BD and anxiety disorders in general is also high.⁷⁴

In patients with SP comorbidity with BD II seems to have as its main consequences the severity and generalization of SP symptoms, multiple comorbidities, and association with alcohol abuse.⁷³ In most patients with SP observed in one retrospective study, anxiety disorders preceded the onset of BD. Besides, these patients had, more frequently, early onset, severe incapacitation due to generalized SP and avoidant personality.¹²

Post-traumatic stress disorder

In one epidemiological study it was found a lifetime prevalence of post-traumatic stress disorder (PTSD) of 38.8% among BD I subjects.⁵⁷ Clinical studies reported a prevalence of 7.0 to 21.0% of this comorbidity among bipolar subjects.^{4,25,33} PTSD subjects have also increased risk of having BD, besides other anxiety disorder comorbidities.⁷⁵

Mueser et al⁷⁶ assessed the prevalence of PTSD in 275 patients with BD and schizophrenia, and found a 43% prevalence of PTSD, highlighting the fact that 98% of them had history of traumatic event. Patients with history of trauma tend to have more severe symptoms, more use of psychoactive substances and higher number of hospitalizations.⁷⁷ Negative life events have been associated with the development of the first BD episode, and seem to favor relapses, although few studies have investigated this association.^{75,78} Subjects who showed severe negative life events, prospectively assessed, took three times more to obtain improvement of their symptoms.⁷⁸

For the treatment of comorbidity of BD with PTSD the guidelines described in the management of BD associated with the other AnxD apply. Open studies and case reports show efficacy of mood stabilizers, either lithium,⁷⁹⁻⁸⁰ divalproate,⁸⁰⁻⁸¹ or carbamazepine⁸²⁻⁸⁴ in the treatment of PTSD. In case the symptoms are not controlled with these medications, it is indicated the association with SRRIs⁸⁵. Benzodiazepines can be also acutely useful, as anxiolytics or associated with mood stabilizers to control hyperactivity and insomnia in manic episodes.⁸⁶

Final considerations

Comorbidity of BD with anxiety disorders have diagnostic, therapeutical and prognostic implications. The association of BD II with anxiety disorders may lead many times to the erroneous diagnosis of borderline personality disorder,²⁴ resulting in inefficacious therapeutical approaches. The presence of anxiety disorders among bipolar subjects determines a subgroup of patients with higher frequency of mixed states,³¹ increased severity and instability of symptoms, besides higher risk of association with disorders due to the use of psychoactive substances⁸⁶ and suicide attempts.⁴

The comparison of current and lifetime prevalence of comorbidities among bipolar subjects in association with anxiety

disorders showed that the prevalence of the latter do not decrease along the treatment, such as occurs in alcohol and drug abuse.^{88,22} The persistence of anxiety disorders probably reflects the difficulty in the clinical management of these cases, as serotonin and monoamino-oxidase reuptake inhibitors, employed in the therapeutic of anxiety disorders, may induce manic, hypomanic or mixed state conditions. Therefore, the importance of the association of cognitive-behavioral therapy outstands in the treatment of anxiety symptoms. Patients with comorbid AnxD are generally excluded from controlled studies, what hampers a more objective treatment of these cases.

Lastly, comorbidity with AnxD is very important in the management of bipolar patients due to their high prevalence, impact on the disease's course and for representing a challenge in the planning of efficient therapeutical strategies. The complexity of clinical presentations and the association patterns between these disorders does not allow to identify an exclusive model to explain the phenomenon of comorbidity between mood and anxiety. The rising interest in research and clinical studies in this field is fundamental to elucidate the pathophysiology of deregulation of affect and consequently to provide a more specific treatment for BD and its comorbidities, having also more consistent evidence.

References

- Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology and treatment issues. *J Affect Disord.* 2002;68(1):1-23. Review.
- Kraepelin E. *Manic-depressive insanity and paranoia.* Edinburgh: Livingstone; 1921.
- Pini S, Cassano GB, Simonini E, Savino M, Russo A, Montgomery SA. Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. *J Affect Disord.* 1997;42(2-3):145-53.
- McElroy SL, Altshuler LL, Suppes T, Keck PE Jr, Frye MA, Denicoff KD, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry.* 2001;158(3):420-6.
- Henry C, van Den Bulke D, Bellivier F, Etain B, Rouillon F, Leboyer M. Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. *J Clin Psychiatry.* 2003;64(3):331-5.
- Cassano GB, Pini S, Sacttoni M, Dell'Osso L. Multiple anxiety disorder comorbidity in patients with mood spectrum disorders with psychotic features. *Am J Psychiatry.* 1999;156(3):474-6.
- Chen YW, Dilsaver SC. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. *Am J Psychiatry.* 1995;152(2):280-2.
- Chen YW, Dilsaver SC. Comorbidity for obsessive compulsive-disorder in bipolar and unipolar disorders. *Psychiatry Res.* 1995;59(1-2):57-64.
- Goldberg D. A dimensional model for common mental disorders. *Br J Psychiatry Suppl.* 1996;(30):44-9.
- Diagnostic and statistical manual of mental disorders: DSM-IV. 4^a ed. Washington: Apa; 1994.
- Parvin MM, Swartz CM. Mania or anxiety disorders linked to panic disorder. *Am J Psychiatry.* 2002;159(12):2115-6.
- Perugi G, Toni C, Akiskal HS. Anxious-bipolar comorbidity. Diagnostic and treatment challenges. *Psychiatr Clin North Am.* 1999;22(3):565-83, viii. Review.
- Young LT, Cooke RG, Robb JC, Levitt AJ, Joffe RT. Anxious and non-anxious bipolar disorder. *J Affect Disord.* 1993;29(1):49-52.
- Feske U, Frank E, Mallinger AG, Houck PR, Fagiolini A, Shear MK, et al. Anxiety as a correlate of response to the acute treatment of bipolar I disorder. *Am J Psychiatry.* 2000;157(6):956-62.
- McQueen GM, Marriott M, Begin H, Robb J, Joffe RT, Young LT. Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. *Bipolar Disord.* 2003;5(5):349-55.
- Katzow JJ, Hsu DJ, Nassir Ghaemi S. The bipolar spectrum: a clinical perspective. *Bipolar Disord.* 2003;5(6):436-42.
- Altshuler LL, Gitlin MJ, Mintz J, Leight KI, Frye MA. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. *J Clin Psychiatry.* 2002;63(9):807-11.
- Bowen R, Clark M, Baetz M. Mood swings in patients with anxiety disorders compared with normal controls. *J Affect Disord.* 2004;78(3):185-92.
- Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med.* 1997;27(5):1079-89.
- Fogarty F, RusseL JM, Newman SC, Bland RC. Epidemiologic of psychiatric disorders in Edmonton. Mania. *Acta Psychiatr Scand Suppl.* 1994;376:16-23.
- Coryell W, Endicott J, Andreasen N, Keller M. Bipolar I, bipolar II, and nonbipolar major depression among the relatives of affectively ill probands. *Am J Psychiatry.* 1985;142(7):817-21.
- Vieta E, Colom F, Corbella B, Martinez-Aran A, Reinares M, Benabarre A, Gasto C. Clinical correlates of psychiatric comorbidity in bipolar I patients. *Bipolar Disord.* 2001;3(5):253-8.
- Krüger S, Cooke RG, Hasey GM, Jorna T, Persad E. Comorbidity of obsessive compulsive disorder in bipolar disorder. *J Affect Disord.* 1995;34(2):117-20.
- Perugi G, Akiskal HS, Lattanzi L, Cecconi D, Mastrocinque C, Patronelli A, et al. The high prevalence of "soft" bipolar (II) features in atypical depression. *Compr Psychiatry.* 1998;39(2):63-71.
- Strakowski SM, Sax KW, McElroy SL, Keck PE Jr, Hawkins JM, West SA. Course of psychiatric and substance abuse syndromes co-occurring with bipolar disorder after a first psychiatric hospitalization. *J Clin Psychiatry.* 1998;59(9):465-71.
- Yerevanian BI, Koek RJ, Ramdev S. Anxiety disorders comorbidity in mood disorder subgroups: data from a mood disorders clinic. *J Affect Disord.* 2001;67(1-3):167-73.
- Pini S, Dell'Osso L, Mastrocinque C, Marcacci G, Papasogli A, Vignoli S, et al. Axis I comorbidity in bipolar disorder with psychotic features. *Br J Psychiatry.* 1999;175:467-71.
- Coryell W. Obsessive-compulsive disorder and primary unipolar depression. Comparisons of background, family history, course, and mortality. *J Nerv Ment Dis.* 1981;169(4):220-4.
- Nestadt G, Samuels J, Riddle M, Bienvenu OJ 3rd, Liang KY, LaBuda M, et al. A family study of obsessive-compulsive disorder. *Arch Gen Psychiatry.* 2000;57(4):358-63.
- Perugi G, Akiskal HS, Pfanner C, Presta S, Gemignani A, Milanfranchi A, et al. The clinical impact of bipolar and unipolar affective comorbidity on obsessive-compulsive disorder. *J Affect Disord.* 1997;46(1):15-23.
- McElroy SL, Strakowski SM, Keck PE Jr, Tugrul KL, West SA, Lonczak HS. Differences and similarities in mixed and pure mania. *Compr Psychiatry.* 1995;36(3):187-94.
- Krüger S, Braunig P, Cooke RG. Comorbidity of obsessive-compulsive disorder in recovered inpatients with bipolar disorder. *Bipolar Disord.* 2000;2(1):71-4.
- Issler CK, Amaral JAMS, Tamada RS, Schwartzmann AM, Shavitt RG, Miguel EC, et al. Obsessive-compulsive and bipolar disorder comorbidity: a controlled study. [Fifth International Conference on Bipolar Disorder Pittsburgh, PA, USA 12-14 June 2003: POSTER Bipolar Disord Supplement 2003;5(Supplement 1):55.
- Boyd JH, Burke JD Jr, Gruenberg E, Holzer CE 3rd, Rae DS, George LK, et al. Exclusion criteria of DSM-III. A study of co-occurrence of hierarchy-free syndromes. *Arch Gen Psychiatry.* 1984;41(10):983-9.
- Sturt E. Hierarchical patterns in the distribution of psychiatric symptoms. *Psychol Med.* 1981;11(4): 783-92.
- Zitterl W, Demal U, Aigner M, Lenz G, Urban C, Zapotoczky HG, Zitterl-Eglseer K. Naturalistic course of obsessive compulsive disorder and comorbid depression. Longitudinal results of a prospective follow-up study of 74 actively treated patients. *Psychopathology.* 2000;33(2):75-80.

37. Golden RN, Morris JE, Sack DA. Combined lithium-tricyclic treatment of obsessive-compulsive disorder. *Biol Psychiatry*. 1988;23(2):181-5.
38. Stern TA, Jenike MA. Treatment of obsessive-compulsive disorder with lithium carbonate. *Psychosomatics*. 1983;24(7):671-3.
39. Rasmussen SA. Lithium and tryptophan augmentation in clomipramine-resistant obsessive-compulsive disorder. *Am J Psychiatry*. 1984;141(10):1283-5.
40. Deltito JA. Valproate pretreatment for the difficult-to-treat patient with OCD. *J Clin Psychiatry*. 1994;55(11):500.
41. Cora-Locatelli G, Greenberg BD, Martin JD, Murphy DL. Valproate monotherapy in an SRI-intolerant OCD patient. *J Clin Psychiatry*. 1998;59(2):82.
42. Koopowitz LF, Berk M. Response of obsessive compulsive disorder to carbamazepine in two patients with comorbid epilepsy. *Ann Clin Psychiatry*. 1997;9(3):171-3.
43. Joffe RT, Swinson RP. Carbamazepine in obsessive-compulsive disorder. *Biol Psychiatry*. 1987;22(9):1169-71.
44. Swartz CM, Shen WW. Is episodic obsessive compulsive disorder bipolar? A report of four cases. *J Affect Disord*. 1999;56(1):61-6.
45. McDougle CJ. Update on pharmacologic management of OCD: agents and augmentation. *J Clin Psychiatry*. 1997;58(Suppl 12): 11-7. Review.
46. Bystritsky A, Ackerman DL, Rosen RM, Vapnik T, Gorbis E, Maidment KM, Saxena S. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry*. 2004;65(4):565-8.
47. Metin O, Yazici K, Tot S, Yazici AE. Amisulpiride augmentation in treatment resistant obsessive-compulsive disorder: an open trial. *Hum Psychopharmacol*. 2003;18(6):463-7.
48. Denys D, van Meegen H, Westenberg H. Quetiapine addition to serotonin reuptake inhibitor treatment in patients with treatment-refractory obsessive-compulsive disorder: an open-label study. *J Clin Psychiatry*. 2002;63(8):700-3.
49. Atmaca M, Kuloglu M, Tezcan E, Gecici O. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2002;17(3):115-9.
50. Pfanner C, Marazziti D, Dell'Osso L, Presta S, Gemignani A, Milanfranchi A, Cassano GB. Risperidone augmentation in refractory obsessive-compulsive disorder: an open-label study. *Int Clin Psychopharmacol*. 2000;15(5):297-301.
51. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. *J Clin Psychiatry*. 1995;56(9):423-9.
52. Lykouras L, Alevizos B, Michalopoulou P, Rabavilas A. Obsessive-compulsive symptoms induced by atypical antipsychotics. A review of the reported cases. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(3):333-46. Review.
53. Marks IM. Review of behavioral psychotherapy, I: Obsessive-compulsive disorders. *Am J Psychiatry*. 1981;138(5):584-92. Review.
54. van Balkom AJ, de Haan E, van Oppen P, Spinhoven P, Hoogduin KA, van Dyck R. Cognitive and behavioral therapies alone versus in combination with fluvoxamine in the treatment of obsessive compulsive disorder. *J Nerv Ment Dis*. 1998;186(8):492-9.
55. Cassano GB, Pini S, Saettoni M, Rucci P, Dell'Osso L. Occurrence and clinical correlates of psychiatric comorbidity in patients with psychotic disorders. *J Clin Psychiatry*. 1998;59(2):60-8.
56. Szadoczky E, Papp Z, Vitrai J, Rihmer Z, Furedi J. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. *J Affect Disord*. 1998;50(2-3):153-62.
57. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord*. 1998;50(2-3):143-51.
58. Bowen R, Clark M, Baetz M. Mood swings in patients with anxiety disorders compared with normal controls. *J Affective Disord*. 2004;78(3):185-92.
59. MacKinnon DF, McMahon FJ, Simpson SG, McInnis MG, DePaulo JR. Panic disorder with familial bipolar disorder. *Biol Psychiatry*. 1997;42(2):90-5.
60. MacKinnon DF, Xu J, McMahon FJ, Simpson SG, Stine OC, McInnis MG, DePaulo JR. Bipolar disorder and panic disorder in families: an analysis of chromosome 18 data. *Am J Psychiatry*. 1998;155(6):829-31.
61. MacKinnon DF, Zandi PP, Cooper J, Potash JB, Simpson SG, Gershon E, et al. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. *Am J Psychiatry*. 2002;159(1):30-5.
62. Doughty CJ, Elisabeth Wells J, Joyce PR, Olds RJ, Walsh AE. Bipolar-panic comorbidity within bipolar disorder families: a study of siblings. *Bipolar Disorder*. 2004;6(3):245-52.
63. Rotondo A, Mazzanti C, Dell'Osso L, Rucci P, Sullivan P, Bouanani S, et al. Catechol o-methyltransferase, serotonin transporter, and tryptophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. *Am J Psychiatry*. 2002;159(1):23-9.
64. Pini S, Dell'Osso L, Amador XF, Mastrocinque C, Saettoni M, Cassano GB. Awareness of illness in patients with bipolar I disorder with or without comorbid anxiety disorders. *Aust N Z J Psychiatry*. 2003;37(3):355-61.
65. Sasson Y, Chopra M, Harrari E, Amitai K, Zohar J. Bipolar comorbidity: from diagnostic dilemmas to therapeutic challenge. *Int J Neuropsychopharmacol*. 2003;6(2):139-44.
66. Primeau F, Fontaine R, Beauclair L. Valproic acid and panic disorder. *Can J Psychiatry*. 1990;35(3):248-50.
67. Woodman CL, Noyes R Jr. Panic disorder: treatment with valproate. *J Clin Psychiatry*. 1994;55(4):134-6.
68. Baetz M, Bowen RC. Efficacy of divalproex sodium in patients with panic disorder and mood instability who have not responded to conventional therapy. *Can J Psychiatry*. 1998;43(1):73-7.
69. Pollack MH, Matthews J, Scott EL. Gabapentin as a potential treatment for anxiety disorders. *Am J Psychiatry*. 1998; 155(7):992-3.
70. Pande AC, Pollack MH, Crockatt J, Greiner M, Chouinard G, Lydiard RB, et al. Placebo-controlled study of gabapentin treatment of panic disorder. *J Clin Psychopharmacol*. 2000;20(4):467-71.
71. Bowen RC, D'Arcy C. Response of patients with panic disorder and symptoms of hypomania to cognitive behavior therapy for panic. *Bipolar Disord*. 2003;5(2):144-9.
72. Himmelhoch JM. Social anxiety, hypomania and the bipolar spectrum: data, theory and clinical issues. *J Affect Disord*. 1998;50(2-3):203-13.
73. Perugi G, Frare F, Madaro D, Maremmani I, Akiskal HS. Alcohol abuse in social phobic patients: is there a bipolar connection? *J Affect Disord*. 2002;68(1):33-9.
74. Schuckit MA, Tipp JE, Bucholz KK, Nurnberger Jr, Hesselbrock VM, Crowe RR, Kramer J. The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls. *Addiction*. 1997;92(10):1289-304.
75. Vieira RM, Gauer GJ. Transtorno de estresse pós-traumático e transtorno de humor bipolar. *Rev Bras Psiquiatr*. 2003;25(Suppl 1):55-61.
76. Mueser KT, Goodman LB, Trumbetta SL, Rosenberg SD, Osher C, Vidaver R, et al. Trauma and posttraumatic stress disorder in severe mental illness. *J Consult Clin Psychol*. 1998;66(3):493-9.
77. Briere J, Woo R, McRae B, Foltz J, Sitzman R. Lifetime victimization history, demographics, and clinical status in female psychiatric emergency room patients. *J Nerv Ment Dis*. 1997;185(2):95-101.
78. Johnson SL, Miller I. Negative life events and time to recovery from episodes of bipolar disorder. *J Abnorm Psychol*. 1997;106(3):449-57.
79. van der Kolk BA. Psychopharmacology. Psychopharmacological issues in posttraumatic stress disorder. *Hosp Community Psychiatry*. 1983;34(8):683-4, 691. Review.
80. Forster PL, Schoenfeld FB, Marmar CR, Lang AJ. Lithium for irritability in post-traumatic stress disorder. *J Trauma Stress*. 1995;8(1):143-9.
81. Fesler FA. Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry*. 1991;52(9):361-4.
82. Brodsky L, Doerman AL, Palmer LS, Slade GF, Munasifi FA. Post traumatic stress disorder: an eclectic approach. *Int J Psychosom*. 1990;37(1-4):89-95.
83. Lipper S. PTSD and carbamazepine. *Am J Psychiatry*. 1988;145(10):1322-3.
84. Stewart JT, Bartucci RJ. Posttraumatic stress disorder and partial complex seizures. *Am J Psychiatry*. 1986;143(1):113-4.
85. Davidson JR. Biological therapies for posttraumatic stress disorder: an overview. *J Clin Psychiatry*. 1997;58(Suppl 9):29-32. Review.
86. Ashton H. Guidelines for the rational use of benzodiazepines. When and what to use. *Drugs*. 1994;48(1):25-40. Review.
87. Goodwin RD, Stayner DA, Chinman MJ, Wu P, Tebes JK, Davidson L. The relationship between anxiety and substance use disorders among

individuals with severe affective disorders. Compr Psychiatry. 2002;43(4):245-52.
88. Sharma V, Mazmanian D, Persad E, Kueneman K. A comparison of comorbid patterns in treatment-resistant unipolar and bipolar depression. *Can J Psychiatry. 1995; 40(5):270-4.*

Correspondence

Cilly Klüger Issler
Rua Gandavo, 462
04023-001 São Paulo, SP, Brasil
E-mail: cillykissler@yahoo.com.br
