Anxiety disorders comorbidity in bipolar disorder
Comorbidade com transtornos de ansiedade em transtorno bipolar

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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 frequentemente 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

Goldberg1996 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 categorial 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 studies3,4,7,8 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. \textsuperscript{16} The quality of life and the degree of functioning are among the main outcomes affected by uncontrolled symptoms. \textsuperscript{17} AnxD patients may also show higher mood subsyndromal oscillation than normal subjects, \textsuperscript{18} and the prevalence of BD in patients with PD and SP is also higher than among the general population. \textsuperscript{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. \textsuperscript{13,14} Young et al. \textsuperscript{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, \textsuperscript{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. \textsuperscript{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. \textsuperscript{8,20} Clinical studies diagnosed the association with BD at 1.55\%\textsuperscript{21} and 35.1\%\textsuperscript{22} of bipolar subjects. Most studies find percentages above 10\%\textsuperscript{24-27} and prevalences vary according to 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. \textsuperscript{4,22}

Family studies also revealed association between BD and OCD. Coryell et al\textsuperscript{21} 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 study\textsuperscript{28} found the same prevalence of mania, 2.3\%, in relatives of probands with BD or OCD. However, NESTADT et al\textsuperscript{28} 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),\textsuperscript{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 al\textsuperscript{30} 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\textsuperscript{29,31} described that this association occurs mainly in bipolar subjects who experience mixed states, and Strakowsky et al\textsuperscript{33} suggested that the co-occurrence of disorders reflects rather a variability in the expression of BD than comorbid OCD diagnosis per se. Krüger et al\textsuperscript{30} 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. \textsuperscript{30}

Issler et al\textsuperscript{33} 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. \textsuperscript{34,35}

Comorbidity with OCD implies difficulties in the clinical management of BD. Perugi et al\textsuperscript{33} 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 chronicification of depressive episodes,\textsuperscript{38} 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. \textsuperscript{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,\textsuperscript{39,39} divalproate\textsuperscript{40-41} and carbamazepine\textsuperscript{42-43} in the treatment of obsessive-compulsive symptoms. Curiously, Swartz & Shen\textsuperscript{44} 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.\textsuperscript{54,55}

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 study\textsuperscript{46} 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,\textsuperscript{17} quetiapine\textsuperscript{48-49} and risperidone.\textsuperscript{50-51}

Contradictorily, there are also descriptions of inducement of obsessive-compulsive symptoms among patients treated with atypical antipsychotics.\textsuperscript{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.\textsuperscript{53,54} If antidepressants should be used, preference must be given to those with low potential of inducing mania.\textsuperscript{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\%\textsuperscript{19} to 10\%,\textsuperscript{16} depending on the population assessed, and may reach 36\% among patients with bipolar depression.\textsuperscript{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,\textsuperscript{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. Angst\textsuperscript{27} 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\textsuperscript{.39} up to 23.1\textsuperscript{.21}, when including cyclotimic patients.\textsuperscript{58}

The link between BD and PD have also been demonstrated by genetic studies.\textsuperscript{70-72} In 2002 MacKinnon et al\textsuperscript{71} 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 Dougherty et al\textsuperscript{62} 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 biochemical studies, which found the association of PD comorbidity with markers in the long arm of the chromosome 18 of BD patients.\textsuperscript{25} Rotondo et al\textsuperscript{63} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{65} Preliminary studies showed some efficacy of sodium divalproate,\textsuperscript{66,68} especially when there is rapid cycling,\textsuperscript{65} and gabapentine\textsuperscript{69,70} 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,\textsuperscript{12} 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\textsuperscript{.7} to 47.1\textsuperscript{.19} of BD patients, with higher percentages among subjects with BD II or recurrent brief hypomania.\textsuperscript{53} Clinical studies found a lifetime prevalence of SP from 13.6\textsuperscript{.67} to 33.3\textsuperscript{.33} among bipolar patients.

There are studies suggesting the existence of SP subtypes according to the presence of mood alterations. Himmelhoch\textsuperscript{72} 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 al\textsuperscript{73} who reported higher susceptibility of a percentage of phobic patients to the euphoric effects of alcohol.\textsuperscript{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.\textsuperscript{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.\textsuperscript{75} 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.\textsuperscript{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\textsuperscript{57}. Clinical studies reported a prevalence of 7.0 to 21.0% of this comorbidity among bipolar subjects.\textsuperscript{4,25,33} PTSD subjects have also increased risk of having BD, besides other anxiety disorder comorbidities.\textsuperscript{75}

Mueser et al\textsuperscript{76} 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.\textsuperscript{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.\textsuperscript{75,78} Subjects who showed severe negative life events, prospectively assessed, took three times more to obtain improvement of their symptoms.\textsuperscript{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,\textsuperscript{79,81} divalproate,\textsuperscript{80,81} or carbamazepine,\textsuperscript{82,83} in the treatment of PTSD. In case the symptoms are not controlled with these medications, it is indicated the association with SRRIs.\textsuperscript{26} Benzodiazepines can be also acutely useful, as anxiolytics or associated with mood stabilizers to control hyperactivity and insomnia in manic episodes.\textsuperscript{86}

**Final considerations**

Comorbidity of BD with anxiety disorders have diagnostic, therapeutic and prognostic implications. The association of BD II with anxiety disorders may lead many times to the erroneous diagnosis of borderline personality disorder,\textsuperscript{14} resulting in inefficacious therapeutic approaches. The presence of anxiety disorders among bipolar subjects determines a subgroup of patients with higher frequency of mixed states,\textsuperscript{31} increased severity and instability of symptoms, besides higher risk of association with disorders due to the use of psychoactive substances and suicide attempts.\textsuperscript{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. The persistence of anxiety disorders probably reflects the difficulty in the clinical management of these cases, as serotonin and monoamine-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


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