Here we present a new initiative of our journal, which aims to stimulate discussion about topics of current interest in Clinical Psychiatry. Authors interested are able to send a letter to the editor from now on aiming to become the focus of new discussions. If accepted, the Journal will invite other specialists in the area to provide their expert opinion, thus promoting debate.

In this issue, we started a debate based on the letter from Andrade-Nascimento et al., which presents different aspects on the comorbidity between Bipolar Disorder (BD) and Generalized Anxiety Disorder (GAD). We here emphasize the importance of a broad discussion involving nationally and internationally recognized colleagues, reinforcing the relevance of the topic and integrated aspects in the diagnosis of these disorders. Even though the prevalence of anxiety symptoms is frequently associated with the diagnosis of both BD and GAD, the current classification (DSM-IV) has several limitations and challenges to be overcome. These aspects are here critically addressed. This forum provides discussion on potential advances that may arise with the advent of DSM-5, which may give answers on the diagnosis and treatment of this common comorbid condition in our clinical practice.

Rodrigo Machado-Vieira
Editor-assistente

Comorbid generalized anxiety disorder in bipolar disorder: a possible diagnosis?

Transtorno bipolar em comorbidade com transtorno de ansiedade generalizada: um diagnóstico possível?

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Andrade-Nascimento M, et al. / Rev Psiq Clín. 2012;39(4):149-52

Dear Editor,

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR, 2000) we cannot diagnose Generalized Anxiety Disorder (GAD) in bipolar patients, when it occurs exclusively during a Mood Disorder regardless of illness phase. In fact, Issler *et al.* (2004)[1] have reported that some researchers criticize DSM diagnosis criteria for distinguishing these disorders, because in GAD there are criteria that overlap with those of bipolar disorder (BD). Recently, Goodwin and Jamison in their Comorbidity Chapter of second edition Maniac Depressive Illness Book (2007)[2] did not describe anything about GAD when they reviewed the comorbidity of bipolar and anxiety disorders. However, despite these milestones that transform diagnosing of anxiety disorder in bipolar patients to a difficult task, several studies have reported the feasibility of diagnosing the presence of GAD in BD[3,4]. In fact, several studies have found a higher prevalence of GAD in bipolar patients than in the general population[3-5]. Albert *et al.* (2008) have evaluated anxiety comorbidity in euthymic bipolar patients and shown that the current and lifetime prevalence of GAD in euthymic patients is 15.2% and 16.2%, respectively[5]. So, the question is: If the diagnosis of GAD in bipolar patients is not possible to be made, how can we explain the prevalence of GAD in euthymic patients through the SCID-I? Besides that, if the presence of GAD in 15.2% of euthymic patients was detected, what is the true significance of this rate? Do patients in a euthymic phase actually have GAD as a comorbid condition or is this in fact just a subthreshold presentation of BD? We would appreciate hearing your opinion about the presented issues regarding the role of GAD in each BD phase and the reliability and feasibility of performing a comorbid diagnosis in bipolar individuals. Finally, it would be interesting to study not only the overlapping characteristic but also the boundaries between GAD and BD in order to determine whether distinguishing anxious symptoms from GAD in bipolar patients in feasible and clinically relevant.

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COMMENTARY ON THE LETTER

Re: Comorbid generalized anxiety disorder in bipolar disorder: a possible diagnosis?

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Wherever possible, classifications of medical conditions should be based on etiological aspects (etiological paradigm) or at least on pathophysiological aspects (pathophysiological paradigm). However, in view of scarce information on both pathophysiology and etiology of most psychiatric conditions, the phenomenological paradigm is still hegemonic in widely adopted international classifications such as American Psychiatric Association DSM-IV and World Health Organization ICD-10. Both ICD and DSM schemes are largely based on kraepelinian classifications of mental disorders, relying on observed symptomatology, course of illness, and outcome. Reliability of psychiatric diagnosis has significantly increased with introduction of operational diagnostic criteria in current classifications. However, diagnostic validity has not improved at all. Therefore, at least for clinical purposes, it is critical that phenomenologically-oriented classifications have practical implications, especially for instructing clinicians about most appropriate treatments for a given condition.

Various epidemiological studies have demonstrated that some of the most common comorbid disorders among individuals with bipolar disorder are the anxiety disorders, including generalized anxiety disorder (lifetime prevalence of about 16%), especially among those with earlier onset of bipolar disorder[1,2]. In addition, different studies have suggested that this finding has important clinical implications, since the presence of comorbid anxiety disorders negatively affects course, outcome, and treatment response in bipolar disorder[3,4]. Furthermore, different studies have suggested that comorbid anxiety is associated with poorer psychosocial functioning and lower overall quality of life[1,2]. Finally, different clinical trials have suggested that specific drugs such as divalproex and quetiapina are preferentially indicated when comorbid anxiety is present in bipolar disorder[5].

In conclusion, although current mental disorders classifications are highly reliable, diagnostic validity is clearly unsatisfactory. Since disorder boundaries are not well established, it appears to be inappropriate *a priori* exclusion of generalized anxiety disorder as a possible comorbidity in bipolar disorder. This view is reinforced by empirical data from clinical studies suggesting that diagnosis of comorbid anxiety in BD has practical implications in clinical practice, including choice of treatment interventions.

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Clinical and psychiatric comorbidities are frequently present in bipolar patients. The STEP-BD data showed that 58.8% of the subjects evaluated presented clinical comorbidities and also that a lifetime diagnosis of anxiety disorders and substance abuse disorder increased the risk for clinical illnesses[1]. So not making a diagnosis of anxiety disorder and not treating the symptoms related to it in bipolar patients could worsen their health across the lifespan.

Many patients have anxiety disorders previous to the development of bipolar symptoms but many others could develop anxiety, panic, obssessive compulsive, eating disorders symptoms after receiving a bipolar disorder (BD) diagnosis, not even mentioning a more complicated association between trauma, PTSD and BD.

The association of so many symptoms in the same individual makes it very complex to give a right diagnosis and to propose an adequate treatment. The DSM-V will propose more categories, with obssessive compulsive spectrum and trauma related disorders apart from the anxiety disorders chapter[2], what can unfortunately increase the difficult to categorize patients with symptoms related to different nosological disorders.

Patients that receive a manualized diagnosis of BD could not receive a diagnosis of generalized anxiety disorder (GAD) as a comorbidity, although it seems to be inadequate since it is well known that they can have symptoms for both diagnosis, it can avoid prescribing antidepressants, that are the first line of treatment for GAD. Giving antidepressants to the majority of BD patients is not beneficial, it can even be harmfull leading to rapid cycling or mood swings[3].

Treating first the BD and reaching stability could be sufficient to diminish anxiety symptoms, nevertheless for the patients that still have anxiety symptoms after being stabilized it will be necessary to individualize the pharmacological approach.

Some patients could benefit from antidepressants but always associated with mood stabilizers, others will not receive this recomendation because of a hystory of rapid cycling or bipolarity more prone to manic episodes[4].

Treating BD patients with comorbidities is a challenge and a rationale has to be created for each case. More studies are necessary to increase our knowledge on how to benefit a bigger number of individuals whith such complex comorbidities.

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The authors discuss critically a present and pertinent topic that affects a large range of bipolar disorder's patients. The high levels of incidence of generalized anxiety disorder (GAD) in bipolar patients suggest that GAD is a commonly observed comorbid entity. If we imagine a rat trained to press a lever to avoid a mild shock, the anticipation of mastery might activate pleasurable dopamine release to the frontal cortex. If the lever is disconnected, however, so that pressing it no longer prevents shocks, the rat will frantically press the lever repeatedly, attempting to gain control. This is the essence of anxiety, characterized mainly by adrenaline and norepinephrine secretion and to a lesser extent by cortisol production. As the shocks continue and the rat finds its attempts at coping useless, a transition occurs where cortisol dominates and key neurotransmitters are depleted. In my opinion, GAD is a subsyndromal comorbid feature and it seems to be a feature associated with bipolar disorder as a consequence of a general dysfunction in specific mechanisms associated with neurotransmitters. In this sense, GAD approach in bipolar disorder's patients should raise an integrated and global treatment.

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Important questions were raised referring to the letter about the association between bipolar disorder (BD) and generalized anxiety disorder (GAD). In fact, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 2000) excludes the possibility of a comorbid diagnosis, considering a relict of DSM-III, which remained in the subsequent editions[1].

Normally, epidemiological and clinical studies which aim to determine comorbidities between psychiatric disorders or syndromes disregard the diagnostic hierarchy and thus, generate prevalences as observed by the author of the letter. In the 5th edition of the DSM (DSM-V)[2], which will be launched in 2013, the number of associated symptoms will decrease from six to two and the minimum duration of current symptoms from six to three months; the diagnosis will center on excessive anxiety and worry in two or more spheres of life[1]. However, the diagnostic hierarchy will be retained, and GAD cannot be due to another mental disorder. Furthermore, as the DSM-V will include the specifier "with anxiety" for depressive disorders because of the impact of anxiety on morbidity and mortality rates of mood disorders in general, the diagnosis has to be distinguished from depressive disorders[3].

Goodwin and Jamison (2007)[4] did not mention GAD as a comorbidity of BD. They consider that subsyndromal anxiety symptoms were frequent and influence the course and progression of BD, being associated with an increased risk of suicide, substance abuse, and worse response to treatment, and thus, were part of the problem, not another diagnosis. One hundred years ago, Kraepelin already described, that in case of a good course the MDI [manic-depressive insanity] was free form symptoms of anxiety, and that patterns which are more difficult to treat, especially mixed episodes, often showed anxiety symptoms of significant intensity.

Swann *et al.* (2009)[5] showed that psychopathology changed when a depressive episode of BD was superimposed by at least one manic symptom (*e.g.*, racing thoughts) and a manic episode by at least two depressive symptoms, since anxiety emerged and symptoms worsened. Suicide attempts occurred in manias with at least three depressive symptoms and in depressions superimposed by at least two manic symptoms. This study was essential for the inclusion of the specifier "with mixed features" in all episodes of mood disorders in the DSM-V, whether bipolar or not. In addition to anxiety, which is predominant in relation to euphoric or depressive mood, dysphoria (defined by internal tension, irritability, aggressive behavior, and hostility) also emerged as a distinct phenomenology among bipolar inpatients that showed mania with at least three depressive symptoms or depression with at least one manic symptom[6]. Therefore, one could confuse GAD with a depressive mixed state, in which racing thoughts result in exaggerated worrying and anticipated suffering, irritability, and important anxiety, but does not configure a depressive episode. According to Goodwin and Jamison (2007, p. 78-79), "symptomatic presentations of mixed states range from a single opposite-state symptom found in the midst of an otherwise 'pure' manic or depressive syndrome (such as depressed mood during mania or racing thoughts during depression) to more complex mixes of mood, thought, and behavior".

BD has a fluctuating course with syndromic, subsyndromic and euthymic periods. As definitions of euthymia vary from one study to another and as a function of the threshold used for its determination, the results are inconsistent[7]. In the mentioned article, patients were considered euthymic if they had a HAM-D score of < 8 and a YMRS score of < 6 for at least two months, and thus, they were neither asymptomatic nor did they have only one or two mild symptoms[8]. The authors ignored the diagnostic hierarchy, but did not discuss the problem.

On the other hand, if one separates subjects of the depressive and the bipolar spectrum from normal controls, comorbidity with GAD becomes questionable. In a study about the use of antidepressants (ADs) among an Italian general population sample with subsyndromal depression (SSD), use of ADs was only found in subjects with SSD who were considered bipolar by the Bipolar Mood Disorder Questionnaire (MDQ), but was due to the comorbidity with panic syndrome (PS) or GAD, as the diagnosis of PS and GAD were strictly associated with positive MDQ[9]. A Brazilian epidemiological study, in which the diagnostic hierarchy was disregarded, bipolar spectrum (BS) was compared with non-affective controls (which could present other disorders in a pure form). Lifetime prevalence of GAD in BS ranged from 5.6% to 35.6%, but was only 0.5% among non-affective controls[10]. A latent class analysis of all affective symptoms among the same sample showed that GAD was the only anxiety disorder with zero prevalence in the class labeled as "euthymics"[11].

Studies which clearly distinguish between GAD and BD are still limited, especially because research about the distinctive phenomenology of mixed states are recent and few, replicating the work of Kraepelin and Weygandt. The importance of the presence of anxiety symptoms results from the poor prognosis and chronicity of BD, but it is possible that mixed symptoms mediate the onset of anxiety and the associated risk of suicide. Future studies will determine whether the proposed new definition of GAD in the DSM-V facilitates the distinction, improving the knowledge about the clinical significance of comorbidity with BD.

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Through the last 20 years the interest concerning research integrating anxiety disorder and mood disorder comorbidities has been increased. Although, the amount of publications production are still bellow ideal to elucidate the doubts we have to deal with, regarding not only the diagnosis limitations but also the biological bases end it's treatments issues[1].

Many studies proves how it is important to achieve the anxious comorbidity diagnoses in patients suffering of bipolar disorders for the negative impact that such a combination perform in both treatment and prognosis[2-5].

The high comorbidity prevalence between GAD and BD found in the literature may at least partially attributed to a common neurobiological pathway present in both disorders or maybe caused by a current categorical psychiatry diagnoses effect that could sometimes share mutual symptoms in different class disorders blurring the clear definitions of the psychiatry disorders classification[6].

As quoted by Provencher *et al.*, a peper pending on DSM-5 could try to distinguish more accurately the psychiatry disorders, as has been done at the DSM-III and DSM-III-R time referring precisely to the classification of the anxious disorders in the 80's when distinct subtypes had been proposed.

The DSM-5, preliminarily, defines the anxious disorders as a specifier to describe mood episodes in bipolar disorder. Considering this change it will be possible to specify the bipolar disorder episode with mild or severe anxiety. Such a especifier could not be a new diagnosis category, but it could guide us on how far the bipolar disorder reaches the diagnosis frontiers in anxious disorder, especially GAD[1].

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The authors raise a broader and controversial question about the interface between anxiety disorders (AD) and bipolar disorder (BD), whose relationship is complex and requires several considerations. First, there is a high rate of comorbidity with AD in BD, as found by Andrade-Nascimento. Second, the higher prevalence rates of AD (including generalized anxiety disorder – GAD) found in offspring of individuals with BD (36%) compared with offspring of psychiatrically healthy controls (14%)[1,2] suggest that AD can be an alternative pathway for the development of BD[3]. Third, the fact that the diagnostic of GAD remains the most provisional diagnostic among anxiety disorders because of diagnostic difficulty regarding to the definition of excessive and unreal worrying, which is affected by the influence of social class, culture, personality, values about what constitutes a real concern, and the symptoms themselves, which are overlapping with underlying symptoms of GAD and with symptoms of chronic insomnia like fatigue and irritability, which form part of the diagnosis and in turn are also symptoms of BD. Other aspects include the fact that the diagnosis of GAD based on the DSM-III-R has changed, allowing now diagnostic comorbidities, and thus, a high rate of comorbidities had to be identified (in some studies over 90% of patients with GAD showed one or more comorbidities)[4]. Against this background, I agree with Brown's statement (1994)[5] that GAD would be better conceptualized as a trait or factor of vulnerability or even as a final common pathway for many psychiatric disorders, including BD. However, in clinical practice, the coexistence of more than one psychiatric disorder in an individual with BD influences the diagnostic process, the response to treatment, course and prognosis and requires better scientific evidence.

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