Anxiety and bipolar disorders: epidemiological and clinical aspects

Disturbi bipolari e d'ansia: aspetti epidemiologici e clinici

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Summary

Objectives

While the worldwide prevalence of bipolar disorder is approximately 2%, it increases to 6% if the broad bipolar spectrum subtypes are also considered. Among other psychiatric conditions, anxiety disorders are most frequently observed in bipolar patients. Anxiety can be a symptom of bipolar disorder, and was first recognized by Kraepelin in 1921 who described "anxious mania" and also "excited depression", which included a "great restlessness". He specifically named anxiety as one of the components of this illness, but at present "anxiety" is not generally considered as a symptom of bipolar disorder, but rather as a comorbid condition. However, comorbid anxiety disorders have a significant impact on clinical presentation and prognosis of bipolar disorder in at least one-half of cases of bipolar disorder beyond the acute phase (in the euthymic phases). The aim of this study was to explore the correlation between anxiety and bipolar disorder through a critical review of the recent literature.

Methods

A search in MEDLINE and PUBMED was performed using the following keywords: bipolar disorder, anxiety disorders, bipolar spectrum subtypes and comorbidity. We selected both epidemiological and clinical studies written in English and published in international journals. Moreover, only publications with appropriate sample size, standardized experimental procedures and validated assessment scales were considered.

Results

From a clinical point of view, the presence of comorbid anxiety in bipolar patients is related to more severe acute episodes (increased duration and severity), poorer course (rapid cycling) and increased risky behaviour such as substance abuse and suicide attempts. Moreover, bipolar patients with comorbid anxiety show a decreased response to pharmacological treatment and deterioration in both quality of life and social-work functioning.

Conclusions

There are two ways of looking at anxiety in bipolar disorders: as a symptom of the illness, or as a separate condition that requires a distinct treatment. Given the high rate of occurrence and significant clinical impact on quality of life of anxiety disorders in bipolar patients, we hypothesize that the anxiety symptoms are an integral part of clinical presentation: they do not identify a distinct disorder (comorbidity of bipolar disorder), and should therefore be considered an epiphenomenon of bipolar disorder itself.

Key words

Anxiety disorder • Bipolar disorder • Comorbidity

Riassunto

Obiettivi

La prevalenza del disturbo bipolare nella popolazione generale è del 2% circa, e sale fino a 6% se vengono considerati anche i sottotipi di bipolarità appartenenti allo spettro bipolare allargato. Il disturbo bipolare è tra le malattie psichiatriche con più alto tasso di comorbidità con altri disturbi mentali, in particolare con i disturbi d'ansia.

L'ansia, peraltro, può essere un sintomo del disturbo bipolare stesso, come già rilevato da Kraepelin nel 1921. Egli descrisse infatti la "mania ansiosa" e la "depressione eccitata", che erano caratterizzate da grande irrequietezza, e identificò l'ansia come una delle componenti di questa malattia. Ad oggi però l'ansia non è generalmente considerata un sintomo del disturbo bipolare, bensì una condizione di "comorbidità".

In ogni caso, la presenza di disturbi d'ansia complica il quadro clinico del disturbo bipolare aggravandone la prognosi e condizionando il trattamento. La premessa al problema clinico è la dimensione epidemiologica del fenomeno: i disturbi d'ansia complicano il disturbo bipolare in almeno la metà dei casi e spesso anche oltre la remissione degli episodi acuti, ovvero negli intervalli liberi da malattia (fasi eutimiche).

Lo scopo di questo articolo è di fare il punto sul problema clinico della comorbidità tra disturbo bipolare e disturbi d'ansia attraverso un'accurata revisione critica della letteratura sull'argomento.

Metodi

È stata effettuata una ricerca su MEDLINE e PUBMED utilizzando parole chiave quali ad esempio disturbo bipolare, disturbi d'ansia, spettro bipolare allargato, comorbidità. Sono stati selezionati articoli sia epidemiologici che clinici, scritti in lingua inglese e pubblicati su riviste internazionali con impact factor. Inoltre nella scelta degli studi sono stati considerati anche altri criteri quali la presenza di ampi campioni di pazienti e l'utilizzo

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sia di procedure sperimentali standardizzate sia di scale di valutazione validate.

Risultati
Sul piano clinico, la presenza di disturbi d'ansia in pazienti affetti da disturbo bipolare si associa sia a più gravi episodi di scompenso acuto (maggiore durata e gravità) sia ad un decorso prognosticamente più sfavorevole (riduzione della durata della fase eutimica, decorso caratterizzato da rapida ciclicità). Inoltre i soggetti bipolari che presentano disturbi d'ansia sono maggiormente esposti all'assunzione di condotte a rischio gravi quali abuso/dipendenza da sostanze e tentativi anticonservativi. Infine, in tali soggetti, si manifesta anche una diminuita risposta clinica ai trattamenti farmacologici con stabilizzatori dell'umore e un peggioramento sia della qualità di vita che del funzionamento socio-lavorativo.

Conclusioni
Data l'elevata frequenza e il notevole impatto clinico e sulla qualità di vita dei disturbi d'ansia nei pazienti bipolari, si può ipotizzare che i sintomi ansiosi in questi pazienti non identifichino disturbi distinti (in comorbidità con il disturbo bipolare), ma costituiscano parte integrante del quadro clinico e debbano quindi essere considerati un epifenomeno del disturbo bipolare stesso.

Parole chiave

Disturbi d'ansia • Disturbo bipolare • Comorbidità • Clinica

Introduction

Kraepelin was the first to describe anxious symptomatology as an integral part of the clinical manifestations in patients with manic-depressive psychosis. In the first complete description of manic-depressive psychosis, he described not only alternating cycles of affective episodes, but also mixed states (concomitant euphoric and depressive states), in which he also included the so-called 'anxious-depressive mania'. Compared to patients with pure manic episodes, they were described as terribly anxious, anguished and agitated, and often showed severe complications such as suicide [1].

Today, it is well-known that the 'pure' forms of bipolar disorder, or those characterized only by alternating depressive and manic symptoms, are quite rare, and that bipolar disorder is more frequent in association with other psychic disturbances: most importantly anxiety, but also disturbances correlated with substance abuse [2], personality disturbances [3], eating disorders [4] and impulse control disorders [5].

In patients with bipolar disorder, symptoms and/or disturbances of anxiety have a primary role for several reasons. Firstly, they are very frequent (in particular, obsessive-compulsive disorder [OCD], panic disorder and social phobia). Secondly, they also have clinical relevance (e.g. can mask the characteristic cyclic expression and worsen the course of the disorder), and are important for planning therapy (lower response to treatment with mood stabilizers) [6-8].

Anxiety disturbances not only complicate episodes of acute compensation of bipolar disorder: they are very frequent during the euthymic phase, leading to negative consequences on functioning and the quality of life even in the absence of affective episodes [9]. According to the diagnostic criteria of the DMS-IV-TR (American Psychiatry Association 2000)[10], in the case of coexistence of symptoms of bipolar disorder and anxiety disturbance, both disturbances are diagnosed in comorbidity. In recent years, however, a good deal of evidence has emerged that the concept of bipolarity should be enlarged: according to experts, several symptomatological manifestations, including anxiety, should be considered as epiphenomena of bipolar disorder, and thus should not be diagnosed and treated separately [9 11 12].

The aim of the present review is to carry out a critical examination of the available literature on the relationship between bipolar disorder and anxiety disturbances from epidemiological and clinical standpoints.

Anxiety and bipolar disorder: epidemiology

Epidemiologic studies

From one of the most recent epidemiological studies, the National Comorbidity Survey Replication Study (NESARC), carried out on 9282 subjects, it emerged that 74.9% of patients affected by bipolar disorder also show an anxiety disturbance. Comorbidity with general anxiety disturbance is found, respectively, in 86.7% and 89.2% of patients with bipolar disorder type 1 and II, and in 63.1% of the "soft bipolar spectrum" forms [11]. Table I shows the prevalence of each comorbid anxiety disturbance: in particular, a higher frequency of OCD is seen in bipolar type I, and social phobia and panic disorder in bipolar type II [11]. Similar results were obtained in an Italian epidemiological study carried out at Sesto Fiorentino on 2500 subjects, conforming the high rates of comorbidity between bipolar disorders and anxiety in the clinically-evident forms (bipolar type I and II), and less in the subclinical forms [13].

Clinical studies

From published clinical studies, the lifetime prevalence of anxiety disturbances in subjects with bipolar disorder varies from 11-79% [6 7 14-20], while 31.8% are comorbid for one or more concomitant anxiety disturbances [17]. No statistically significant differences were seen between bipolar types I and II (52.8% *vs.* 46.1%, respectively), even when considering the anxiety disturbances individually [7]. The reported rates of comorbidity generally vary greatly:

TABLE I.
Epidemiological study (NESARC; n = 9282) reporting rates of lifetime comorbidities of anxiety disorders in patients with a principal diagnosis of bipolar disorder (Merikangas et al.) [11]. *Studio epidemiologico NESARC (n = 9282): tassi di comorbidità lifetime dei disturbi d'ansia in pazienti con diagnosi principale di disturbo bipolare (Merikangas et al.) [11].*

Anxiety disorder	Bipolar	Bipolar I	Bipolar II	Subclinical bipolar
Agoraphobia without panic disorder	5.7%	5.6%	8.1%	4.6%
Panic disorder	20.1%	29.1%	27.2%	13.1%
Panic attacks	61.9%	63.9%	72.9%	56.0%
Post-traumatic stress disorder	24.2%	30.9%	34.3%	16.5%
Generalised anxiety disorder	29.6%	38.7%	37.0%	22.3%
Simple phobia	35.5%	47.1%	51.1%	23.3%
Social phobia	37.8%	51.6%	54.6%	24.1%
Obsessive compulsive disorder	13.6%	25.2%	20.8%	4.3%
Separation anxiety	35.4%	41.2%	42.8%	29.4%
At least one anxiety disorder	74.9%	86.7%	89.2%	63.1%

for social phobia between 2.4% and 31.1% [6-8 15-18 20-23], for generalised anxiety disorder from 2.8% to 31.6% [7 8 14-18 20 21 23 24] and for post-traumatic stress disorder from 4.8% to 29.5% [7 8 15-17 19-21 25].

Regarding panic disorder, in analyses of subjects with bipolar disorder, the expected prevalence is between 4% and 38.6% [6-8 14-23 26-29]. In many studies, the concomitant presence of panic disorder and bipolar disorder is so high that several authors have hypothesised that they have a common genetic origin [30 31]: since panic attacks and rapid mood swings are characterized by sudden fluctuations in the affective state, it is believed that the genetic component, or perhaps even a single gene involved in metabolism of catecholamines, is responsible for this phenotype [32]. One study, in particular, has investigated polymorphisms in genes that code for serotonin transporters, tryptophan hydroxylases, and catechol-o-methyltransferase (COMT) [33].

The reported rates of comorbidity for OCD and bipolar disorder are likewise somewhat variable, between 2.6% and 35% [6 7 14-21 23 25 27 34]. Moreover, a recent study investigating the correlation between affective temperaments and OCD reported that 19.2% of patients with a diagnosis of OCD present a dominant cyclothymic temperament, considered by most authors as a premorbid manifestation of bipolar disorder (soft bipolar spectrum) [35]. As already mentioned, considering the data from different clinical studies, large differences in the rates of comorbidities have been reported between anxiety disorders and bipolar disorder; this can be explained by a variety of factors such as the type of study, characteristics of the patient cohort and methods used for diagnostic evaluation.

Considering the type of study, it is known that retrospective investigations can lead to errors in reconstruction of episodes and symptoms over the course of a patient's lifetime. This bias is so strong that some authors have chosen to include only patients with an age less than 45 years so that the past can be more accurately reconstructed, and at the same time, to exclude symptoms and secondary disturbances such as vasculopathies or degenerative neurological pathologies [18 25]. Such stricter inclusion criteria, however, have the obvious consequence of revealing lower incidences since the mean age of the sample population is lower.

Even the characteristics of the sample can influence the results, and patient age has already been mentioned in this regard. The power of statistical analyses can be influenced by sample size since the results are more reliable if a greater number of subjects are recruited; even the structure in which the study takes place can affect the results of a study. In fact, subjects that are referred to a specialised psychiatric clinic will generally have more severe symptoms, and thus a higher probability of comorbid anxiety disorders with respect to those at a general hospital or in a general practitioner setting (Berkson's bias). The duration and type of therapy are also important factors that can mask symptoms and disturbances that are concomitant with bipolar disorder. It is important to distinguish between cohorts of patients with current affective episodes and those in partial or total remission. Lastly, cultural differences should be taken into consideration when interpreting data, in addition to the country where the study took place and the socioeconomic class. Moreover, it should be pointed out that some differences in the prevalence of anxiety disorders in patients with bipolar disorder are related to different criteria used for to define comorbidity: individual symptoms of anxiety (e.g. panic attacks) are undoubtedly more frequent in the actual

disorder (i.e. panic attack disorder). Lastly, the choice of the scale used for assessment is critical, in addition to the operator carrying out the interview and questionnaire: self-administered scales have a diagnostic precision and data collection that is quite different from tests administered by non-specialised personnel or specialised psychiatrists.

Comorbidities during the euthymic phase

As already mentioned, uncompensated thymic episodes can influence the rates of comorbidity between bipolar and anxiety disorders: anxiety symptoms are particularly frequent during both depressive and mixed episodes (already hypothesised by Kraepelin), and thus can follow a clinical course that depends on bipolar disorder [20 36]. It is possible that the prevalence of anxiety disorders is overestimated if they evaluated in bipolar patients during acute affective episodes.

In recent years, an interesting line of study has emerged with the aim of evaluating comorbidities in bipolar patients without the potential influence of thymic decompensation, considering only subjects with bipolar disorder in the euthymic phase. Notwithstanding, several authors have reported elevated rates of comorbid anxiety disorders [9 12 37]: in particular, from the results of the study by Albert et al. carried out on 105 subjects with bipolar disorder (44 type I, 65 type II), the presence of at least one anxiety disorder was seen in 41% of patients [12]. Data on the spectrum of the anxiety disorders are similar to those already highlighted (Table II). The reported rates of comorbidity for anxiety disorders show little variation between subjects with either type I or type II bipolar disorder (40.9 *vs*. 41%, respectively); a higher rate of OCD is seen in bipolar type II (16.4%), and generalised anxiety disorder in bipolar type I (22.7%) [12].

Considering the above, the presence of anxiety disorders in patients with a principal diagnosis of bipolar disorder is highly relevant in both epidemiological and clinical studies in all phases that characterize the course of bipolar disorder (during both decompensation affective episodes and the euthymic phase), and in all the subtypes of bipolar disorder (types I, II and the 'soft' forms).

Anxiety and bipolar disorder: clinical aspects

The clinical relationship between bipolar disorder and anxiety is complex and has important consequences when considering presentation of symptoms and patient management. First, it should be stressed that not all patients with bipolar disorder have the same risk of developing an anxiety disorder. In particular, the age at onset seems to have a substantial predictive role: Golstein and Levitt reported that patients with bipolar disorder and an early age of onset have almost twice the lifetime risk (OR 1.92; CI 1.56-2.37) of developing any anxiety disorder compared to patients with a later age of onset. Moreover, considering anxiety disorders individually, it was shown that the subgroup with an early age of onset had a greater risk of developing generalised anxiety disorder (OR 2.99; CI 2.02-4.43) and panic disorder (OR 3.49; CI 2.28-5.35) [38]. According to literature data, female gender can be considered predictive of a comorbid anxiety disorder [18 39-43]: in particular, a recent study on 711 patients with bipolar disorder and subgrouped according to gender reported that 46% of women had at least one anxiety disorder compared to 29% of men [44].

In any case, the presence of an anxiety disorder can have a negative impact on psychopathological symptoms in both the short- and long-term: it worsens the course of disease, and is associated with poorer social/work functioning and quality of life. As a consequence, the concomitant presence of an anxiety disorder is associated with poorer prognosis of bipolar disorder. In some cases, symptoms of anxiety can even mask the cycling of phases that are characteristic of bipolar disorder, thus rendering it difficult for the clinician to detect mood swings.

Affective episodes

Several investigators have reported that patients with bipolar disorder and comorbid anxiety disorders have more severe depressive episodes, as confirmed by the HAM-D, MADRS and BDI scales, which show significantly less severity of symptoms in patients without comorbid anxiety [19]. Other authors have highlighted that the presence of anxiety disorders worsens symptoms during the expansive phase [15]. Most investigators agree that the presence of comorbid anxiety is associated with greater symptomology of both depressive and hypo(manic) episodes [7 17 42]. Zutshi et al., moreover, emphasized that comorbid anxiety disturbances are associated with a higher rate of psychotic symptoms during mood swings, and lead to greater severity (evaluated by the need for hospitalization) [18].

The greater severity of affective episodes in individuals with comorbid anxiety disorders is also reflected by the greater duration of affective episodes from a study on 80 patients [18] and from a prospective investigation on 187 patients with 12-month follow-up [8]. This latter study showed that patients with bipolar disorder and a comorbid anxiety disorder have depressive episodes that last longer and require a longer time to achieve complete remission of symptoms (HR: 0.661; CI 0.47-0.94). This has also been confirmed in a recent study by Goldstein and Levitt on 1411 patients with bipolar disorder [45].

Lastly, it should be stressed that a comorbid anxiety disorder also has a negative impact on the possibility of achieving complete remission of affective symptoms; in fact, in a study on 138 patients with bipolar disorder in

TABLE II.
Rates of lifetime anxiety disorders in patients with a principal diagnosis of bipolar disorder in clinical studies. *Tassi di comorbidità lifetime dei disturbi d'ansia in pazienti con diagnosi principale di disturbo bipolare: studi clinici.*

Author	N	Anxiety disorder	N (%)
Pini et al., 1997 [14]	24	Generalised anxiety disorder Panic disorder Obsessive-compulsive disorder Simple phobia At least one anxiety disorder	8 (31.6%) 9 (36.8%) 5 (21.1%) 2 (5.3%) 19 (79.2%)
Strakowski et al., 1998 [25]	77	Post-traumatic stress disorder Obsessive-compulsive disorder	16 (20.8%) 12 (15.6%)
Pini et al., 1999 [26]	125	Panic disorder	39 (31.2%)
Feske et al., 2000 [15]	124	Panic disorder Post-traumatic stress disorder Simple phobia Obsessive-compulsive disorder Generalised anxiety disorder Social phobia At least one anxiety disorder	13 (10.5%) 6 (4.8%) 5 (4.0%) 4 (3.2%) 4 (3.2%) 3 (2.4%) 56 (45.2%)
McElroy et al., 2001 [16]	288 239 Bipolar I 49 Bipolar II	Panic disorder Post-traumatic stress disorder Obsessive-compulsive disorder Social phobia Generalised anxiety disorder Simple phobia At least one anxiety disorder	58 (20.1%) 19 (6.6%) 27 (9.4%) 47 (16.3%) 8 (2.8%) 30 (10.4%) 101 (35.1%)
Goodwin et al., 2002a [24]	100	Panic disorder	35 (35%)
Goodwin et al., 2002b [29]	33	Generalised anxiety disorder	5%
Henry et al., 2003 [6]	318 237 Bipolar I 81 Bipolar II	Phobia (including social phobia) Obsessive-compulsive disorder Panic disorder At least one anxiety disorder	35 (11%) 9 (3%) 75 (24%) 35 (11%)
MacKinnon et al., 2003 [28]	606	Panic disorder	107 (17.7%)
Simon et al., 2003 [21]	122	Post-traumatic stress disorder Generalised anxiety disorder Social phobia Simple phobia Panic disorder Obsessive-compulsive disorder	23 (19.2%) 33 (27.3%) 37 (31.1%) 23 (19.7%) 45 (37.8%) 16 (13.4%)
Dilsaver et al., 2003 [22]	44	Panic disorder Social phobia	17 (38.6%) 13 (29.5%)
Simon et al., 2004 [7]	475 360 Bipolar I 115 Bipolar II	Panic disorder Post-traumatic stress disorder Generalised anxiety disorder Social phobia Obsessive-compulsive disorder At least one anxiety disorder At least one anxiety disorder BPI At least one anxiety disorder BPII	82 (17.3%) 81 (17.2%) 87 (18.4%) 104 (22%) 47 (9.9%) 243 (51.2%) 190 (52.8%) 53 (46.1%)
Zutshi et al., 2006 [18]	80 65 Bipolar I 10 Bipolar II 5 Subclinical bipolar	Generalised anxiety disorder Panic disorder Social phobia Obsessive-compulsive disorder At least one anxiety disorder	20 (25%) 6 (7%) 24 (30%) 28 (35%) 49 (61%)

(continues)

Table II – continued.

Author	N	Anxiety disorder	N (%)
Otto et al., 2006 [8]	918	Generalised anxiety disorder Obsessive-compulsive disorder Post-traumatic stress disorder Panic disorder Social phobia At least one anxiety disorder	122 (13.3%) 62 (6.8%) 44 (4.8%) 78 (8.5%) 122 (13.3%) 293 (31.9%)
Maina et al., 2007 [9]	142 90 Bipolar I 52 Bipolar II	Generalised anxiety disorder Panic disorder Obsessive-compulsive disorder Social phobia At least one anxiety disorder	30 (21.1%) 20 (14.1%) 18 (12.7%) 8 (5.6%) 63 (44.4%)
Albert et al., 2008 [12]	105 44 Bipolar I 61 Bipolar II	Panic disorder Generalised anxiety disorder Social phobia Obsessive-compulsive disorder At least one anxiety disorder At least one anxiety disorder BPI At least one anxiety disorder BPII	11 (10.5%) 17 (16.2%) 7 (6.7%) 14 (13.3%) 43 (41%) 18 (40.9) 25 (41%)
Lee et al., 2008 [19]	44	Post-traumatic stress disorder Obsessive-compulsive disorder Panic disorder At least one anxiety disorder	13 (29.5%) 2 (4.5%) 14 (31.8%) 23 (52.3%)
Coryell et al., 2009 [23]	427	Obsessive-compulsive disorder Generalised anxiety disorder Panic disorder Simple phobia/Social phobia	11 (2.6%) 20 (4.7%) 17 (4.0%) 23 (5.4%)
Mantere et al., 2010 [20]	144	Panic disorder Social phobia Simple phobia Obsessive-compulsive disorder Post-traumatic stress disorder Generalised anxiety disorder At least one anxiety disorder	54 (37.5%) 44 (30.6%) 22 (15.3%) 11 (7.6%) 28 (19.4%) 18 (12.5%) 63 (43.8%)

remission, MacQueen et al. reported that the persistence of anxious subsyndromal symptoms is associated with incomplete recovery after the acute phase [46]. This has been confirmed in a recent investigation by Koyuncu et al. in 214 patients with bipolar disorder and OCD. In that study, it was concluded that compared to patients with bipolar disorder alone, a comorbid anxiety disorder have a greater tendency for a major depressive episode to become chronic (duration > 2 years) [47].

Complications

Disorders correlated with psychoactive substances

Abuse/dependence on alcohol and/or psychoactive substances is frequent in patients with bipolar disorder. The results of three epidemiological studies (Epidemiologic Catchment Area – ECA, National Comorbidity Survey – NCS, National Epidemiologic Survey on Alcohol and Related Conditions – NESARC) all demonstrate that substance abuse disorders are more frequent in subjects with bipolar disorder compared to either the general population or those with major unipolar depression. In particular, in the ECA study comorbidity between a substance abuse disorder (including alcohol) and bipolar disorder was seen in 60.7% of patients, which is three times higher than that observed in patients with unipolar depression. Considering the subgroups of bipolar disorder, epidemiological studies have reported that the prevalence of disorders correlated with substance abuse was seen in 46-60% of individuals with bipolar type I disorder, from 19-40% in those with bipolar type II and in about 35% of cases with soft bipolar spectrum [11 40 48 49].

The high rates of comorbidity between substance abuse and bipolar disorders have also been observed in clinical studies. In particular, patients with bipolar disorder have a lifetime prevalence that varies from 10% [50] and 40% [51]

for alcohol abuse, and from 5% [16] to 68% [52] for abuse of psychoactive substances.
The presence of anxiety disorders can influence the rates of substance abuse in patients with bipolar disorder. Along these lines, conflicting data has been reported: Henry et al. observed that in a cohort of 318 patients with bipolar disorder, anxiety disorders were not associated with a significant increase in the lifetime risk of substance abuse disorders [6]. However, in an analysis carried out on a larger number of patients with bipolar disorder (STEP-BD), it was seen that the presence of a lifetime anxiety disorder was associated with a risk of lifetime alcohol dependence that was about two times higher [7]. Notwithstanding, most authors agree that the presence of an anxiety disorder tends to exacerbate the risk of substance abuse/dependence [24 53-55].
Thus, comorbidity between substance abuse and bipolar disorder is frequent and of substantial clinical relevance as it also favours the presence of anxiety disorders. In patients with difficult to manage and severe symptoms, additional complications may occur such as mixed episodes, rapid cycling, increased recovery times from affective episodes and higher rates of suicide [54].

Suicide

Bipolar disorder is one of the psychiatric pathologies with the highest risk for suicide, and it has been estimated that 8-15% of patients with bipolar disorder will die of suicide [34 56 57]. In a recent meta-analysis of 23 studies, several risk factors for suicide were identified in patients with bipolar disorder, including family history for suicide, early age of onset, chronic depressive episodes and poorer course of bipolar disorder [58]. Moreover, from the point of view of comorbidity, several authors have reported that the presence of anxiety disorders is also associated with an increased risk of suicide [7 19 55 59-63]. For example, considering a cohort of 143 patients with bipolar disorder, Kruger et al. show that comorbidity with OCD is associated with a higher number of suicide attempts, especially in bipolar type I compared to type II [14 31 65 66]. Dilsaver et al. (2008), in a study on 187 patients with bipolar disorder, also concluded that the risk of suicide was increased by the number of comorbid anxiety disorders [63]. While the majority of authors believe that comorbid anxiety disorders increase the risk of suicide in bipolar patients [7 67], others have held that it may have either a protective role [68] or no association [69]. Lastly, in a recent study, Simon et al. highlight that due to the increased risk of suicidal ideation, the presence of an anxiety disorder is more important at the time of evaluation than a positive history for a lifetime anxiety disorder [70].
Therefore, even if acute anxiety symptoms are considered a risk factor for suicide in the short-term, it is still difficult to understand the role of lifetime comorbid anxiety disorders for an increased risk of suicide. This is not only due to the fact that such an association is very frequent, but also because two or more comorbid anxiety disorders are often found in the same individual. In addition, contradictory results have been reported, and these can be explained by the fact that there does not appear to be a direct relationship between anxiety symptoms and anticonservative tendencies in bipolar disorder, but rather with the typical depressive ruminations [70 71]. Moreover, many studies in this regard had very different study designs, selection criteria, observation and follow-up times, affective states of patients, therapies and methodologies for evaluation, which render comparison difficult.

Clinical course

From the available data, it is clear that the concomitant presence of an anxiety disorder and bipolar disorder has substantial impact on the course of the latter; in fact, these patients are characterized by a poorer clinical picture and a reduction in the symptom-free interval [18]. The consequence of the latter is that subjects often manifest a clinical progression during the course of the disease from a condition of alternating cycles of affective episodes and long intervals of complete recovery to a period of rapid cycling (defined as at least 4 episodes per year), with a consequent decrease in the so-called intercritical phase (euthymic) [43 55 72].
In the STEP-BD study, it was demonstrated that the presence of at least an anxiety disorder, whether current or lifetime, is associated with a decrease in the duration of the intercritical phase in bipolar disorder, from a mean symptom-free interval of 262 days to 113 days [7]. Moreover, Boylan et al., in a study on 138 patients with bipolar disorder, showed that the presence of at least one anxiety disorder favours more frequent depressive recurrences, which was also confirmed by Gaudiano and Miller [17 42]. A similar result has also been reported by Zutshi et al. who found that individuals with bipolar disorder and at least one comorbid anxiety disorder have a greater risk of recurrence of mixed episodes [18].
Boylan et al. asked the question of whether worsening of disease was correlated with an increased number of comorbid anxiety disorders, and if patients with two or more anxiety disorders had a poorer outcome compared to those with only one anxiety disorder, although negative results were seen in both cases. What was seen, however, was that some anxiety disorders had a greater clinical impact, and in particular social phobia and generalised anxiety disorder [17]. Otto et al. confirmed these results in a prospective study assessing a relatively small cohort of 399 patients with 12-month follow-up. In particular, subjects with comorbid anxiety disorders were more frequently

affected by recurrent affective episodes compared to patients with bipolar disorder alone, with an increased risk especially for social phobia (OR 2.07; CI 1.36-3.15) and post-traumatic stress disorder (OR 2.45; CI 1.20-4.99) [8].
Lastly, Perlis et al., in an investigation in 644 patients with a follow-up of two years, identified the following factors to be predictive of recurrence in bipolar disorder: male gender, persistence of residual depressive or manic symptoms, rapid cycling, and especially the presence of an anxiety disorder during the last year of disease [73].

Quality of life

The presence of an anxiety disorder during clinical presentation has a negative impact on the quality of life of patients with bipolar disorder. The quality of life of bipolar patients with comorbid anxiety disorders was initially examined in two studies. The first found that the presence of an anxiety disorder in bipolar patients was associated with a general decrease in the quality of life and functioning[7]. The second study reported that patients with bipolar disorder and comorbid anxiety disorders showed a mean reduction the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), not only in the items that evaluate mental health, but also in those that assess perception of physical health [74].
In a later investigation, Otto et al. evaluated the number of days well. In this study, it was observed that in subjects with bipolar disorder presenting with comorbid anxiety disorder, having multiple anxiety disorders had an additive influence on the loss of days well, with a loss of 27.6 days for a single anxiety disorder, 43.5 days for two current anxiety disorders and 56.9 days for three or more current anxiety disorders. Analysis of individual anxiety disorder showed that there was a loss of, 29-30 days for panic disorder and generalised anxiety disorder, which increased to 34-44 days for social phobia, OCD and post-traumatic stress disorder. In addition, the authors evaluated the impact of anxiety disorders on the quality of life with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), which showed a significant reduction in the average score by 5.6 points in patients who had at least one anxiety disorder, and in particular social phobia and post-traumatic stress disorder. Lastly, patient functioning was assessed using the Longitudinal Interval Follow-up Evaluation – Range of Impaired Functioning Tool (LIFE-RIFT); even in this case, a reduction in functioning was seen for the co-presence of social phobia, post-traumatic stress disorder, or two or more comorbid anxiety disorders [8].
The above studies, however, have some limitations, and one of the most prominent is that the quality of life of patients has often been evaluated during uncompensated thymic episodes, during which symptoms and disturbances can be amplified or disappear in euthymia. Several authors have recently attempted to eliminate this confounding factor by evaluating the quality of life only in bipolar patients recruited during the euthymic phase.
From these studies, several interesting aspects have emerged. Firstly, the quality of life in patients with bipolar disorder is compromised even during the euthymic phase compared to both the healthy population and patients with recurrent major depressive disorder (also in an euthymic phase). Moreover, among patients with bipolar disorder, those with type II show an even greater impact on the quality of life during the euthymic phase compared to those with type I. This can be explained by the fact that bipolar type II disorder is characterized by frequent comorbid disorders and residual symptoms than type I, and that it has a euthymic phase that is less well defined with more psychopathological symptoms [9].
Albert et al., in addition, analyzed the impact of anxiety disorders on the quality of life in bipolar patients in the euthymic phase. It was found that this situation leads to further worsening of the perception of both mental and physical health, which was more evident in patients with bipolar type I compared to type II. This is likely related to the fact that, as already mentioned, the euthymic phase in bipolar type II is characterized by more symptoms and disorders than type I [12].

Treatment

The co-presence of bipolar disorder and anxiety is critical when considering treatment. First of all, many studies have shown that patients with bipolar disorder and anxiety have a decreased response to stabilizing therapies, both in terms of an increased time to remission from both the current episode and a greater risk of recurrence [15 75 76]. Moreover, the presence of an anxiety disorder can worsen compliance to pharmacological treatment, which is already sub-optimal in bipolar patients [77].
Lastly, the administration of selective serotonin reuptake inhibitors (SSRI) for anxiety disorders is questionable in bipolar patients due to the potential risk of worsening the course of bipolar itself (induction of mixed states, rapid cycling, switching in mania) [78 79]. Even benzodiazepines, frequently used for control of anxiety in patients with bipolar disorder, have limitations for long-term use due to the risk of abuse or dependence [75].
Some preliminary data, however, seems to point towards new treatment possibilities for these patients through an approach that favours mood stabilizers, rather than specific therapies based on serotoninergic agents for secondary symptoms such as anxiety. For example, two studies conducted on large cohorts of bipolar patients in the thymic decompensation phase demonstrated the clinical efficacy of second-generation antipsychotics in reducing anxiety symptoms. From the placebo-controlled, double-blind

study by Hirschfield et al. in 539 bipolar patients with a major depressive episode and non-specific anxiety symptoms, variable dose quetiapine (300-600 mg/day) was effective in reducing the mean HAM-A score compared to placebo (-10.4 *vs*. -5.1, respectively; $p < 0.001$) [80]. Another recent placebo-controlled, double-blind study by Tohen et al. on 833 patients showed that variable dose olanzapine (5-20 mg in monotherapy or in combination: olanzapine/fluoxetine at variable dosages (6/25, 6/50, 12/50 mg) reduced mean HAM-A scores by at least 50%, compared to placebo within 8 weeks (olanzapine, -15; olanzapine/fluoxetine, -16.6; placebo, -11; $p < 0.002$) [81]. Concerning treatment of anxiety symptoms in the euthymic phase using an approach that favours mood stabilizers, a recent study assessed the addition of a second mood stabilizer (olanzapine or lamotrigine) in patients with bipolar and anxiety symptoms on therapy with lithium. It was found that even if the number of patients was limited, this strategy reduced anxiety symptoms and led to recovery of psycho-social functioning without worsening the course of bipolar disorder [82].

Conclusions

From a critical literature review, it is apparent that there is a strict association between bipolar disorder and anxiety symptoms/disorders. Anxiety symptoms are seen in all subtypes of bipolar disorder (types I, II and other forms of the soft bipolar spectrum), and anxiety disorders have a negative impact on bipolar disorder. The majority of bipolar patients with anxiety, in fact, in addition to manifesting more severe acute episodes and a longitudinal course of disease (decrease in the symptom-free interval and increased risk of rapid cycling), is more prone to substance abuse disorders and suicidal ideation. The poorer course of disease and prognosis for bipolar disorder in the presence of comorbid anxiety disorders, as already shown, is due to the high risk of treatment failure. As a result, the presence of anxiety disorders in bipolar patients is associated with a poorer quality of life [9 83 84] during both acute affective episodes [7 74] and the euthymic phase [12]. Comorbid anxiety disorders present unique clinical and therapeutic challenges, and the question also arises as to whether anxiety disorders should be considered comorbid or as an epiphenomenon of bipolar disorder itself. Indeed, the latter possibility is supported by genetic data, the frequency of presentation of anxiety symptoms in bipolar disorder and the favourable response of anxiety symptoms to treatment with mood stabilizers.

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