# Comorbidity between panic-disorder and bipolar disorder

## *Comorbidità tra disturbo di panico e disturbo bipolare*

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## Summary

*The study of comorbidity between bipolar (BPD) and anxiety disorders (AD), and in particular panic/agoraphobic (PD) disorder provides an opportunity to address important clinical and research questions. Epidemiological and clinical studies have documented the high lifetime rates and risks related to BPD comorbidity in PD patients. This comorbidity is associated with several indices of severity such as early onset, mixed presentations, severity of symptoms, poor symptomatic and functional recovery, suicidal behaviour, diminished acute response to pharmacological treatment, decreased quality of life and an unfavourable course and outcome. The identification of the temporal sequence in comorbid BPD and AD may provide a refined view of the association between these comorbid syndromes. Coexisting conditions, whose onset often precedes BPD, may divert the clinicians' attention from the detection of mood instability, thus diminishing the possibility of early and timely intervention. The empirical basis for therapeutic decisions remains largely inadequate. No firm recommendations can be made as to which mood stabilizer is best for a BPD patient based on his/her particular co-morbid AD. Generally, the available data support the use of valproate as the mood stabilizer of choice for PD patients with comorbid BPD, especially in the presence of prominent anxiety symptoms, mixed features and/or rapid cycling. Antidepressants should be used with caution and in combination with mood stabilizers.*

### Key words

*Comorbidity • Bipolar disorder • Anxiety disorder • Panic/agoraphobic disorder*

Anxiety disorders (AD), and especially panic disorder (PD), have been subject to different interpretative paradigms. Until the end of the 20th century, all AD were conceived as part of the neurotic realm and the co-presence of anxiety with depression, phobic features and dependent personality disorders was widespread brought within the so-called general neurotic syndrome [1].

During the 1980s, the revaluation of the pharmacological dissection operated by D. Klein in the 1960s made PD out of the realm of neuroses, challenging a switch of the current paradigm [2]. Since that revolutionary breakthrough, PD was treated essentially with tricyclic antidepressants for about 20 years. The introduction of serotonin reuptake inhibitors (SSRIs) at the end of the 1980s, and evidence of their anxiolytic efficacy, made the treatment of AD more feasible, even in primary care settings. Widespread confidence with the use of SSRIs, at every level of care, has often led to underestimation of other psychopathological features associated with AD, especially those of the soft bipolar spectrum. Neglect of these latter manifestations may bring out several complications related to inadequate or incomplete treatment, from the risk of mood switch to the induction of mixed states (even if attenuated) or rapid cycling.

Epidemiological, clinical and familial studies provide compelling evidence that bipolar disorder (BPD) is frequently associated with AD [3]. Moreover, AD-BPD comorbidity is associated with intensification of symptoms, increased risk of alcohol and drug abuse, inadequate treatment response, pseudo-resistance, poor functional outcome and suicidality [4-7].

## Epidemiological and clinical data

The reliability of lay interviewers diagnosing AD in community-based samples is well established, while the reliability of identifying BPD cases with a predominantly mixed/dysphoric presentation is not ideal with the currently available diagnostic interviews [8 9]. Clinical studies indicate that AD comorbidity may be more prevalent in mixed and "softer" expressions of BPD (or bipolar spectrum) [10-12], suggesting that community-based epidemiological studies may underestimate the prevalence of BPD comorbidity in AD subpopulations.

In the National Comorbidity Survey (NCS) (13, 14), the estimated lifetime prevalence of any AD in BPD was 92.9% (odds ratio, OR = 31.2). Specific phobia was the most prevalent AD comorbidity (66.6%), while PD was the least prevalent (33.1%). The reported risk of comorbid PD is higher in BPD (OR = 11.0) compared to unipolar disorder (OR = 7.0). Two iterations of the NCS have shown

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that these data are reflective of the overall population in the US and potentially for most other countries across the world [15]. In a European sample, Angst et al. [16] reported higher rates of comorbidity with PD in subjects suffering from DSM-IV hypomania, recurrent brief hypomania and sporadic brief hypomania compared to population controls. More recently, in a European community sample, Carta et al. [17] confirmed the strong relationship between AD and soft expressions of BPD, quite often presenting as subclinical depressive-anxious syndromes.

Concerning clinical studies, several investigations have reported on the prevalence of AD in patients with BPD. Rihmer et al. [18] described the prevalence of AD comorbidity in 2953 primary care patients with a diagnosable mood disorder. The estimated prevalence of any comorbid AD was lowest among persons with BPD-I and highest in the BPD-II patient group. The prevalence of comorbid AD for the major depressive disorder group was intermediate between the two BPD subgroups. This finding is consistent with the observation that softer expressions of BPD are often camouflaged as anxious depression in the primary care setting [19 20].

MacQueen et al. [21] reported that the prevalence of any AD comorbidity in BPD was higher in sub-syndromal (80.6%) than in the syndromal (54%) and euthymic (38.6%) phases. In contrast, Dilsaver and Chen [22] reported that social phobia (SoP) and PD presenting during a bipolar episode were highly associated with suicidality, particularly in depressive phases. Recent observations have shown that in subjects presenting with (unipolar) depressive or AD an adequate screening for lifetime (hypo)-manic features can not only help the recognition of actual BPD, but also the identification of a subgroup of patients with more severe symptomatology, more comorbid anxiety and alcohol dependence disorders and more suicidality [12].

In this respect, it should be highlighted that panic attacks, anxiety and varying degrees of phobic avoidance, up to extended agoraphobia, are frequently reported also by patients with cyclothymia [23]. Panic attacks can be triggered by separation events or under the influence of certain substances such as stimulants or cannabis. In some cases, panic attacks start on the acme of periods of hyperactivity or excitement, and sometimes mark the switch from an elated to a depressive phase [23]. These observations suggest that in some patients anxiety comorbidity is most pronounced at the extremes of affective excursions, while in others, anxiety may present primarily as an 'interepisodic' disturbance.

McElroy et al. [4] reported anxiety (n = 122, 42%) and substance use disorders (n = 122, 42%) as the most frequent lifetime comorbid disorders in BPD. There was no significant difference in AD comorbidity between patients with BPD-I and BPD-II. The reported lifetime and current prevalences of 'any AD' was 42% and 30%, respectively. Lifetime Axis I comorbidity was associated with early age of onset of BPD symptoms, progressive severity of illness and a family history of alcoholism and drug abuse. Current anxiety comorbidity was also associated with reduced occupational functioning, a history of rapid cycling and a shortening of well-being intervals.

The prevalence of AD and its correlates was investigated in the first 500 patients (BPDI n = 360, BPDII n = 115) enrolled in the Systematic Treatment Enhancement Program for BPD (STEP-BPD) [5]. The prevalence of any lifetime AD for the entire cohort was greater among patients with BPD-I (51.2%) *vs.* BPD-II (30.5%). The age at onset of BPD was significantly lower for patients with any lifetime AD than in patients without AD (15.6 vs. 19.4 years, respectively). Patients with a lifetime AD also had less education, shorter time of euthymia, lower rates of recovery and elevated rates of lifetime suicide attempts. It was also reported that BPD with comorbid ADs had a higher prevalence of alcohol and substance use disorders. The presence of multiple ADs was independently associated with added impairment in quality of life and functioning. AD comorbidity in BPD has recently attracted considerable attention and has been reported to be widely represented in BPD type II patients and predictive of a more severe clinical picture and worse prognosis [6 7 24 25].

The association between AD and alcohol and substance use disorders is an additional theme that is present in the BPD literature. Bauer et al. [26] examined the prevalence and the correlates of comorbid substance use disorders and AD in a sample of inpatients with BPD (n = 348). AD were associated with earlier age at onset, rapid cycling, higher probability of reporting depressive symptoms, higher rates of prior suicide attempts, greater number of prior-year episodes, higher severity of illness scores and lower quality of life. The negative effect of AD in BPD was particularly evident in patients with BPD who also had a comorbid substance abuse disorder. Goodwin et al. [27] reported the association between AD and substance use disorders in BPD. In particular, PD was associated with an increased prevalence of cocaine, sedative and stimulant use disorders.

More recently, data drawn from a controlled clinical trial of acamprosate for subjects with BPD and alcohol dependence showed that comorbid anxiety was prospectively associated with increased depressive symptoms and alcohol use [28]. Recent clinical studies on BPD confirmed previous observations as far as earlier age at onset, higher number of episodes, suicidality, more severe illness course and impairment are concerned in patients also suffering from AD [29 30]. Moreover, comorbid AD in a sample of BPD type II patients was associated with greater cognitive impairment than in BPD subjects without anxiety comorbidity, in terms of verbal, non-verbal, working memory, psychomotor speed and executive function scores [31].

Relatively fewer studies have reported the prevalence of BPD in AD populations. AD are often a phenomenological antecedent to overt BPD; this calls for careful screening for BPD in children and adolescents reporting to healthcare providers with prominent anxiety symptoms [32]. A history of manic or hypomanic episodes has been observed in patients with PD-agoraphobia [33]. The development of mania or hypomania in response to treatment with SSRIs has also been widely described in obsessive compulsive disorder (OCD) case series and reports [34 35]. In a clinical study of 345 outpatients with OCD [36], lifetime co-morbidity with BPD (primarily bipolar II) was 16%. More recently, Timpano et al. [37] found an overlapping percentage of BPD comorbidity (13%) in a sample of 605 OCD patients. Finally, patients with SoP have been found to have high rates of BPD [38].

In a collaborative study between Pisa and San Diego [39], major depression was the most common comorbid disorder in a large sample of patients with AD; however, bipolar II disorder was widely associated with SoP, OCD and PD. The relative neglect in clinical and epidemiological research for the BPD spectrum disorders and AD is especially due to under-diagnosis of bipolar II disorders (often misdiagnosed as unipolar or personality disorders) in patients with AD. It has been documented that current official diagnostic systems grossly underestimate bipolar II and related disorders, and that clinicians specifically trained in bipolar II outperformed routine interviewers in structured interviews such as the SADS or SCID [40]. Although this point goes against current literature on structured interviewing, it is consistent in suggesting that the proper identification of BPD type II requires a more sophisticated approach in diagnosis.

## Clinical presentation of comorbidity

The co-occurrence of PD and BPD seems to be more complex than a simple add-on effect. Multiple comorbidity and consequent symptomatological instability appear as the most relevant outcome [11]. Because of this, many of these patients receive diagnoses of borderline, narcissistic or histrionic personality disorders that in some cases prevent them from receiving adequate pharmacological treatment [7 41]. Increased risk of mixed states, suicidal behaviour and alcohol and drug abuse are other important prognostic implications.

AD are associated with multiple indices of poor outcome in BPD. Patients with BPD-AD are more likely to report severe depression, a chronic course of illness with greater long-term depressive morbidity and negative treatment outcomes [6 42 29]. Likewise, an earlier age at onset, higher frequency of rapid cycling, greater usage of benzodiazepine treatment and lower response to anticonvulsants has been reported [43 44]. Moreover, BPD patients with comorbid AD had significantly higher rates of substance abuse or dependence, illness severity and chronicity, and a lower mean global assessment of functioning (GAF) score [44 45].

Different temporal relationships seem to characterize the occurrence of hypomania in individual AD subtypes [46]. Usually, SoP chronologically precedes hypomanic episodes and disappears when the latter episodes supervene. In contrast, PD and OCD symptomatology, even when preceding hypomanic episodes, often persist during such episodes. Interestingly, a relevant proportion of all onsets of panic attacks, in patients with comorbid PD and BPD, may be during (hypo)mania [46]. These findings are consistent with the hypothesis that, at least in some patients, SoP, and to some extent OCD, seems to lie on a broad affective continuum of inhibitory restraint vs. disinhibited hypomania. However, PD, in the context of a (hypo)manic episode, might be interpreted as a dysphoric or mixed evolution of symptomatology. To confirm these observations, further investigations should focus on prospective assessment of patients with concomitant AD and BPD. Indeed, the retrospective methodology utilized in most clinical studies makes it difficult to ascertain the extent to which antidepressants, the most common treatment for severe AD, could justify anxiety-bipolar comorbidity.

Investigations on differential patterns of comorbidity may provide important information in distinguishing more homogeneous clinical subtypes of affective disorders from biological, genetic and therapeutic points of view. Preliminary evidence supports the hypothesis that differential risk for PD comorbidity is a promising tool to discern heterogeneous genetic subtypes of BPD. MacKinnon et al. [47] evaluated 528 members of 57 families ascertained for a genetic linkage study of BPD. Ten of these 57 bipolar probands had comorbid PD; in their relatives, PD co-segregated with BPD (in particular bipolar II and cyclothymia) at a significantly higher rate than would be expected by chance, suggesting that comorbid PD might be a specific marker for a familial subtype of BPD.

More recently, MacKinnon et al. [48 49] have carried out a series of clinical and family studies on BPD subjects with rapid mood switches, which are similar in many ways to those affected by cyclothymia. The presence of rapid mood fluctuations was associated with a high familial load for mood and AD, early onset, marked suicidal risk and comorbidity with PD.

These findings are consistent with the results of studies on the characteristics of BPD in children and adolescents, where high familial loading, comorbidity with multiple AD and rapid circadian switches have been reported [32]. Comorbidity with PD and rapid switches seem to define a particular familial subtype of BPD characterized by early onset and cyclothymic instability [32 50].

## Treatment implications of PD-BPD comorbidity

The lack of information about the anxiety-bipolar relationship may have a negative impact on choice of treatment and management. Most controlled trials on BPD have excluded patients with comorbid AD and vice-versa; as a consequence, the empirical basis for treating patients with anxiety-bipolar comorbidity are almost exclusively founded on anecdotal reports and open clinical experiences.

Overall, lithium has not been studied in AD. Some useful suggestions can however be derived from clinical experience with mood stabilizers and anti-AD agents. Bipolar patients with high anxiety ratings are less likely to respond to lithium [51].

The association of anxiety with suicidality and less favourable treatment responses in BPD patients has been consistently reported [5 6 52]. Feske et al. [52] examined the correlates of acute treatment response in 124 BPD-I patients. Anxiety symptomatology was associated with a longer time to remission in both depression and mania. Moreover, non-remitting patients were more likely to report a history of panic attacks, current or past anxiety, more severe depression and a greater number of previous affective episodes. Patients reporting a history of panic attacks also required a higher mean number of medications to achieve symptomatic remission.

Controlled data suggest that valproate may be more effective than lithium in mania associated with depressive features, even when depressive features are mild [53]. Since anxiety symptoms are often seen in mixed states and may even be related to depression in mania, future studies should evaluate anxiety features as possible predictors of response of mania to valproate (and other antimanic agents). Regarding AD, valproate has been used successfully in the treatment of PD [54]. In addition, in an open-label study, Calabrese and Delucchi [55] noted that rapid-cycling BPD patients with comorbid panic attacks described reduction in their panic symptoms with valproate treatment. Additionally, one open-label study [56] and one case report [57] have suggested that valproate may be helpful in the treatment of some patients with OCD, especially those with associated bipolar or epileptiform features. So far, the majority of studies focusing on the treatment of comorbid AD or nonspecific anxiety occurring during bipolar mood episodes indicate valproate as the mood stabilizer of choice [58].

Regarding the use of carbamazepine in AD, Uhde et al. [59] did not find carbamazepine to be an efficacious treatment for PD in a double-blind, placebo-controlled study of 14 patients. In OCD, Koopowitz and Berk [60] reported beneficial results with the use of carbamazepine in two patients, while Swinson and Joffe [61] found carbamazepine was ineffective in an open-label study.

Gabapentin has shown preliminary evidence of efficacy in the treatment of anxiety, but not BPD. In AD, gabapentin has been shown to be superior to placebo in a small controlled study on SoP [62], and in another controlled study on severe PD [63]. Predictors of response to gabapentin as adjunctive treatment have been evaluated in 43 patients with BPD who were resistant to standard mood stabilizers [50]. Gabapentin was administered as an adjunctive treatment for an 8-week period in combination with other mood stabilizers, benzodiazepines, antidepressants and neuroleptics. Eighteen (41.9%) of 43 patients who began treatment were considered responders; in particular, gabapentin showed antidepressant and anxiolytic properties. Comorbid PD and alcohol abuse were the best predictors of response. This finding may have clinical implications on treatment of anxiety-bipolar comorbidity, but should be confirmed in controlled clinical trials.

Concerning anti-anxiety agents, benzodiazepines are relatively safe and well tolerated when used in combination with mood stabilizers. However, long-term benzodiazepine use may be problematic in most patients, due to development of tolerance, physical dependence and withdrawal phenomena.

Antidepressants are often used in the treatment of AD and bipolar depression. However, these agents may worsen the course of the mood disorder by precipitating mania, mixed states or rapid cycling [64]. Antidepressant-induced (hypo)manic symptoms have been reported to occur specifically in the course of treatment of virtually all AD, including OCD, PD and SoP [38 65 66]. Prophylactic treatment with mood stabilizers may prevent, at least in part, antidepressant-induced switching [65 67]. When treating comorbid BPD and AD, it is imperative to begin treatment with a mood stabilizer. Indeed, initiating an antidepressant before adequate mood stabilization has been achieved could worsen anxiety symptoms by exacerbating BD.

The efficacy of typical and atypical antipsychotics in the treatment of primary or comorbid AD or anxiety symptoms in major depressive or BD was recently reviewed [68]. Six trials in primary generalized anxiety disorder (GAD), 15 in refractory OCD, 8 in posttraumatic stress disorder (PTSD), 6 in neurosis evaluated by means of the HAM-A, 1 in SoP and 2 in anxiety symptoms in bipolar depression were identified. Gao et al. [68] concluded that, except for trifluoperazine, there is no large, well-designed study of antipsychotics in the treatment of primary or comorbid anxiety symptoms or disorders. Most of the less well-designed studies showed that other typical antipsychotics might be superior to placebo or as effective as benzodiazepines in the treatment of GAD and other anxiety conditions. In most studies, risperidone, olanzapine and quetiapine augmentation to antidepressants was superior to placebo in treating refractory OCD and PTSD. Both olanzapine and quetiapine significantly reduced anxiety compared to placebo in

studies of bipolar depression. An increasing number of randomized controlled studies have shown promising results in 27-71% of patients with primary or comorbid AD treated with monotherapy atypical antipsychotics or augmentation therapy [69]. However, the efficacy of these agents in various anxiety conditions needs to be further investigated with large, well-designed comparative studies.

## Conclusion

The use of the term comorbidity in psychiatry is questionable and raises fundamental questions regarding the validity of diagnostic criteria and classification systems. The study of comorbidity, however, provides an opportunity to address important clinical and research questions. Epidemiological and clinical studies have documented the high lifetime rates and risks related to BPD comorbidity in PD patients. This comorbidity is associated with several indices of severity such as earlier age at onset, mixed presentations, severity of symptoms, poor symptomatic and functional recovery, suicidal behaviour, diminished acute response to pharmacological treatment, decreased quality of life and an unfavourable course and outcome.
The identification of the temporal sequence in comorbid BPD and AD may provide a better understanding of the association between these comorbid syndromes. Coexisting conditions, whose onset often precedes BPD, may divert the clinicians' attention from detection of mood instability, thus diminishing the possibility of early and timely intervention.
No firm recommendations can be made as to which mood stabilizer would be best for which BPD patient based on his/her particular comorbid AD. Nonetheless, several suggestions can be deduced from the available literature. Generally, current data support the use of valproate as the mood stabilizer of choice for patients with comorbid PD, especially if associated with prominent anxiety symptoms, mixed features and/or rapid cycling. SSRIs antidepressants should be preferred over TCA and should be utilized in association with mood stabilizers.
Despite intensified efforts to clinically characterize BPD comorbidity in AD, the empirical basis for therapeutic decisions remains largely inadequate as a consequence of the routine exclusion of patients with this comorbidity from the largest randomized clinical trials.

*Conflicts of Interest*

Giulio Perugi in the last 3 years received grants from Astra Zeneca, Eli Lilly and Lundbeck; honoraria for talks from Astra Zeneca, Janssen Cilag, Eli Lilly, Sanofi Aventis, Lundbeck, BMS Otsuka, Stroder and Servier; honoraria for advisory boards for Sanofi-Aventis, Astra Zeneca, Janssen Cilag, Lundbeck, BMS Otsuka and Eli Lilly.
Cristina Toni has not conflicts of interest to declare.

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