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Research paper

Anxiety disorders anticipate the diagnosis of bipolar disorder in comorbid patients: Findings from an Italian tertiary clinic

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ABSTRACT

Background: Studies indicate bipolar disorder (BD) syndromal symptoms are commonly preceded by sub-syndromal BD symptoms, dysregulated sleep, irritability, and anxiety. We aimed to evaluate prevalence and clinical correlates of anxiety disorders (ADs) at BD onset in outpatients with versus without at least one AD at BD onset.
Methods: 246 bipolar spectrum outpatients, according to the text revision of the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM- IV-TR), attending Sacco University Hospital in Milan, were recruited and their onset and clinical features assessed retrospectively. Patients were stratified into those with versus without an AD at BD onset (w/A and wo/A), according to a semi-structured clinical interview to provide diagnoses according to (DSM- IV-TR).
Results: 29% of patients reported being w/A, among whom Panic Disorder (PD, in 55.6%) was the most frequent AD, and first AD occurred approximately 4 years before BD diagnosis.

Patients w/A versus wo/A had higher ($p < 0.05$) rates of BDII and first mood episode being depression versus elevation (mania/hypomania), and lifetime rates of separation anxiety disorder, substance poly-abuse and benzodiazepine abuse. In contrast, patients wo/A had higher lifetime rates of alcohol and illicit drug use.
Conclusion: In this naturalistic sample, ADs, in particular PD, preceded BD in almost 1/3 of BD outpatients, and had distinctive clinical correlates. Further investigation into relationships between BD and AD at onset may enhance early BD diagnosis and treatment.

Introduction

Bipolar disorder (BD) is a highly disabling condition affecting about 1.5% of the general population globally (Kendall et al., 2014) and responsible for 1.3% of total years lived with disability and 0.4% of total disability-adjusted life years worldwide (Ferrari et al., 2016). BD is characterized by different and complex clinical features over its longitudinal course, including recurrent mood episodes, comorbid psychiatric and medical problems, progressive social and cognitive impairment and, ultimately, much higher suicide/suicide attempt risks, compared to the general population (Cremaschi et al., 2017; Simon et al., 2007)

Indeed, BD is frequently associated with other psychiatric comorbid conditions, in particular anxiety disorders (ADs) (Nabavi et al., 2015) and substance use disorders (Gold et al., 2018). Epidemiologic and clinical studies report lifetime rates of development of at least one AD over the longitudinal course of BD ranging between 39% and 55% (Vázquez et al., 2014). Comorbidity with ADs determines several negative implications (Shah et al., 2017), including more depressive episodes, increased frequency of BD episode relapses, more frequent suicidal ideation and behaviours (Goldstein et al., 2012; Simon et al., 2007), and comorbid substance and alcohol use disorders (Simon et al.,

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Table 1
Socio-demographic and clinical features of the total sample and related subgroups with and without comorbid AD at onset.

	Total sample	Patients w/A	Patients wo/A
N	246	72 (29%)	174 (71%)
Age (years)	55.16 ± 12.67	51.57 ± 12.57	56.67 ± 12.67
Female	156 (63.4%)	49 (68.1%)	107 (61.5%)
College degree	134 (54.5%)	43 (59.7%)	91 (52.3%)
Psychiatric family history	139 (56.5%)	47 (65.3%)	92 (52.9%)
BD family history	34 (13.8%)	10 (13.9%)	24 (13.8%)
Age at onset of anxiety (years)		**31.46 ± 12.78****	
Age at onset of BD (years)	35.5 ± 11.98	**35.97 ± 12.47**	35.29 ± 10.74
DIAGNOSIS			
BD I	73 (29.7%)	11 (15.3%)	**62 (35.6%)****
BD II	118 (48%)	**42 (58.3%)***	76 (43.7%)
Cyclothymia	11 (4.5%)	2 (2.8%)	9 (5.2%)
BD NOS	44 (17.8%)	17 (23.6%)	27 (15.5%)
COMORBID ANXIETY DISORDER AT ONSET			
Panic Disorder	40 (16.3%)	40 (55.6%)	
GAD	31 (12.6%)	31 (43%)	
IAD	1 (0.4%)	1 (1.4%)	
Any	72 (29%)	72 (100%)	
OTHER CLINICAL FEATURES			
History of Separation Anxiety	60 (24.4%)	**38 (52.8%)****	22 (12.6%)
Rapid Cycling (lifetime)	5 (2%)	1 (1.4%)	4 (2.3%)
Psychotic Features (lifetime)	3 (1.2%)	0	3 (1.7%)
ONSET POLARITY			
DO	200 (81.3%)	64 (88.9%)	136 (78.2%)
FIRST CYCLE			
Depression to Hypo/Mania	178 (73.2%)	**61 (84.7%)****	117 (67.2%)
Hypo/Mania to Depression	32 (13%)	3 (4.2%)	**29 (16.7%)****
Other (no cycling/missing data)[a]	34 (13.8%)		
PSYCHOTROPIC DRUGS			
Antidepressant	189 (76.8%)	59 (81.9%)	130 (74.7%)
Mood Stabilizer/Atypical Antipsychotic	180 (73.2%)	128 (73.6%)	52 (72.2%)
PREVIOUS HOSPITALIZATION			
DH	68 (27.6%)	20 (27.8%)	48 (27.6%)
Inpatients	47 (19.1%)	7 (9.7%)	**40 (23%)****
Any Hospitalization (DH + InPts)	115 (46.7%)	27 (37.5%)	88 (50.6%)
COMORBID SUBSTANCE USE DISORDER (lifetime)			
Alcohol	26 (11.4%)	3 (4.2%)	**24 (13.8%)***
Illicit Drugs	28 (10.6%)	2 (2.8%)	**25 (14.4%)***
BDZ abuse	10 (4.1%)	**6 (8.3%)***	4 (2.3%)
Poly-abuse	33 (13.4%)	**15 (20.8%)***	18 (10.3%)
Any	97 (39.4%)	26 (36.1%)	71 (40.8%)

* $p < 0,05$;

** $p < 0,01$; BD I: Bipolar Disorder I; BD II: Bipolar Disorder II; BD NOS: Bipolar Disorder Not Otherwise Specified; GAD: General Anxiety Disorder; IAD: Illness Anxiety Disorder; DH: Day Hospital; BDZ: Benzodiazepine;

[a] missing data/no cycling: 13.8%

5.38% are excluded from the statistical analysis due to lack in clinical and demographical features.

2004b). As a consequence, long-term prognoses of BD patients with comorbid anxiety is generally poorer (Sala et al., 2012; Shah et al., 2017), especially when specific and proper treatment indications are lacking (Mitchell, 2015). In fact, selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) represent first-line treatments for ADs: in patients with BD, however, these drugs can be ineffective or induce rapid cycling or mood elevation (hyomania/mania) episodes (Yatham et al., 2018).

With respect to the lifetime comorbidity of ADs in BD patients, panic disorder (PD) was reported to be the most prevalent (15.3–23.4%) in community and clinical samples, followed by social phobia (SP) (15.0–24.8%), generalized anxiety disorder (GAD) (14.7–26.2%), agoraphobia (7.8%−15.6) and obsessive compulsive disorder (OCD) (7.9–12.6%)(Du et al., 2017). However, comorbidity between BD and ADs is frequently underdiagnosed and potentially confounding, particularly when ADs occur as the first clinical manifestation of BD, prior to any mood episode (Baldessarini et al., 2014; Duffy et al., 2010).

Hence, although a consistent amount of evidence is currently available about lifetime and cross-sectional anxiety comorbidity in BD, little is known about the differential characteristics of bipolar patients presenting with versus without an AD at the onset.

In this perspective, the main aim of the present study was to assess the prevalence of ADs at the onset in a sample of BD patients. In addition, we aimed at comparing BD patients with versus without an AD at the onset in terms of socio-demographic and clinical characteristics. In particular, we hypothesized that BD patients with versus without AD at onset could exhibit distinctive and overall more pernicious clinical characteristics.

Methods

The study sample consisted of 260 BD outpatients, all Caucasian, who sought evaluation and treatment at the Center for Treatment of Depressive Disorders (CTDD), of the University Department of Mental Health at the Hospital “L. Sacco” in Milan, Italy. All subjects provided written informed consent to have their clinical charts and medical records used for research purpose.

This study was conducted through a retrospective review of patients’ medical records, referred and treated at the CTDD between January 2008 and December 2015.

Participants were assessed by psychiatrists or residents in psychiatry with specific training in mood disorders management, through a semi-structured interview, in order to ascertain psychiatric diagnoses and comorbidities, according to the criteria of the Diagnostic and Statistical

Manual for Mental Disorders, 4th Edition – text revision (DSM-IV-TR).

If patients had another comorbid psychiatric disorder, BD had to be the condition primarily affecting their everyday functioning, help seeking and quality of life.

Data were gathered from patients, their relatives, and available clinical records.

In case of missing data (with the exception of the polarity first mood episopde with a <15% rate of missing data), subjects were excluded from the analysis: i,e., 14 out of 260 patients (5.4%) were excluded from the statistical analysis due to this reason.

Socio-demographic variables included: age, gender and educational level. Clinical variables included: diagnosis, age at AD onset, age at BD onset, family history for BD, BD subtype, family history of psychiatric disorders, comorbid AD at BD onset, and lifetime history of separation anxiety disorder, panic disorder (PD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), agoraphobia, psychiatric hospitalization (day hospital or inpatient unit), psychotic features, rapid cycling ($\geq$ 4 mood episodes in 1 year), alcohol /benzodiazepine abuse or illicit substance use, as well as onset polarity and type of first cycle (depressed to elevated or elevated to depressed), . Pharmacological treatment data were collected, focusing in particular on use of antidepressants (SSRIs, SNRIs, noradrenergic and specific serotonergic antidepressants [NaSSAs], serotonin and dopamine reuptake inhibitors [SDRIs], tricyclic antidepressants [TCAs]), mood stabilizers (Lithium, Valproic Acid, Lamotrigine, Carbamazepine) and atypical antipsychotics (Quetiapine, Olanzapine, Paliperidone, Risperidone and Aripiprazole) at onset.

Depending on the presence of AD at onset, the total sample was dichotomized into patients with (w/A) versus without (wo/A) at least one AD.

For categorical variables, patients with (w/A) versus without AD (wo/A) were compared using Chi-square tests ($\chi 2$). A two-tailed significance threshold was set at $p < 0.05$, with no correction for multiple comparisons. For continuous variables, patients w/A versus wo/A were compared using Student's t-Test. A two-tailed significance threshold was set at $p < 0.05$, with no correction for multiple comparisons. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 19.

Results

Table 1 shows patients' socio-demographic and clinical data of the entire sample and related subgroups.

The analysed sample (n = 246) consisted of 156 females and 90 males. Thus, 73 patients were diagnosed with BD I (29.7%), 118 with BD II (48%), 11 with Cyclothymia (4.5%) and 44 with BD not otherwise specified (17.8%).

On the basis of AD onset, more than one fourth (n = 72, 29%,) of our sample had an AD at BD onset.

We found that PD was the most represented diagnosis among bipolar patients with AD at the onset, with a lifetime prevalence of 55.6%, followed by Generalized Anxiety Disorder (GAD) with a lifetime prevalence of 43%.

Rates of family history for psychiatric conditions among first-degree relatives were high within the overall sample (56.5%), and tended to be even higher among patients w/A versus wo/A (65.3 versus 52.9), but not to a statistically significant level. Instead, no difference was found in bipolar family history in the two subgroups.

A comparison between patients w/A versus wo/A did not show any significant difference in terms of age of BD onset (36.0 ± 12.5 years for w/A, 35.3 ± 10.7 years for wo/A).

In the w/A subgroup, the AD diagnosis occurred significantly earlier compared to the onset of BD (31.5 ± 12.8 versus 36.0 ± 12.5 years, $p < 0.001$).

Fig. 1 shows socio-demographic and clinical features with statistically significant differences in BD patients w/A versus wo/A at onset.

With respect to clinical variables, patients w/A versus wo/A had significantly higher rates of BD II (58.3% versus 43.7%, $\chi 2 = 4.4$, df = 2, $p < 0.05$) as well as more frequent depressive onset (88.9% versus 78.2%, $\chi 2 = 3.4$, df = 2, $p = 0.07$) and first cycle with depression to mania/hypomania (84.7% versus 67.2%, $\chi 2 = 7.0$, df = 2, $p < 0.01$,). However, antidepressant or mood stabilizer/atypical antipsychotic use at onset showed no significant difference between the two groups.

Patients w/A versus wo/A showed a significantly higher lifetime comorbidity rate of separation anxiety disorder (SAD) (52.8% versus 12.3%, %, $\chi 2 = 44.5$, df = 2, $p < 0.01$).

Substance poly-abuse was identified in 13.4% of all subjects and more frequently observed in patients w/A versus wo/A (20.8% versus 10.3%, $\chi 2 = 4.8$, df = 2, $p < 0.05$). Moreover, patients w/A versus wo/A more frequently had benzodiazepine abuse (8.3% versus 2.3%, $\chi 2 = 4.7$, df = 2, $p < 0.01$). BD I was the most common diagnosis in patients wo/A versus w/A (35.6% versus 15.3%, $\chi 2 = 10.11$, df = 2, $p < 0.01$) as well as a first cycle with mania/hypomania to depression (16.7% versus 4.2%, $\chi 2 = 7.8$, df = 2, $p < 0.01$). Patients wo/A versus w/A also had higher comorbid rates of alcohol abuse (13.8% versus 4.2%,%, $\chi 2 = 5.2$, df = 2, $p < 0.05$) and illicit drug use (14.4% versus 2.8%,%, $\chi 2 = 6.5$, df = 2, $p < 0.05$). Nonetheless, the subgroup wo/A versus w/A had a significantly higher prevalence of inpatient hospitalization (23% versus 9.7%, $\chi 2 = 5.8$, df = 2, $p < 0.05$).

There were no other statistically significant differences between the two groups in terms of clinical features including rapid cycling, cyclothymia or psychotic symptoms.

Discussion

According to Authors' knowledge, the present study is one few reports specifically investigating the prevalence of AD at BD onset and related clinical features in a sample of BD patients. We found that the presence of AD at BD onset occurred in almost one out of three BD patients (29%), being significantly more represented in BD II (58.3%) versus BD I (15.3%) and BD NOS (23.6%) patients, even though BD II was the most prevalent diagnosis in the whole sample (48%), likely due to the recruitment setting (i.e., a tertiary mood disorders clinic).

Consistent with the literature, our results supported the hypothesis that ADs may be viewed as a core element of the phenotypic expression of BD (Baldessarini et al., 2014; Brückl et al., 2007; Duffy et al., 2007; Faedda et al., 2014; Homish et al., 2013; Johnson et al., 2000; Kinley et al., 2011).

Compared to our results, a previous study (Baldessarini et al., 2014) found lower rates of BD patients with a history of AD as first psychiatric manifestation (7.6%). However, as a possible explanation for this difference, the analysis in the aforementioned study was limited to BD I and BD II patients, while we included a broader spectrum of BD diagnoses.

We confirmed that BD patients with versus without AD at BD onset tended to have younger age at BD onset (in our sample 4 years earlier, on average) (Baldessarini et al., 2014), in line with the hypothesis that ADs may occur as a prodromal stage in a sub-group of BD patients (Duffy et al., 2007; Salvatore et al., 2014)

Among the subtypes of ADs taken into examination, PD was the most prevalent AD at onset in our sample (16.3% overall and 55.6% among patients with ADs). This is consistent with previous studies reporting PD as the most frequent comorbid AD in bipolar patients, being around 18–25% (Doughty et al., 2004; Saunders et al., 2012). For instance, in a recent meta-analysis by Eser and colleagues (2018), the lifetime prevalence of comorbid PD in BD patients was 18.1% (Yapici Eser et al., 2018). However, the chronological onset of BD and PD was not assessed in most of these studies, making it difficult to determine the proportion of bipolar patients whose PD represented the psychiatric onset. In our opinion, it is possible that in some BD patients, PD precedes the BD onset, remaining over its longitudinal course as a

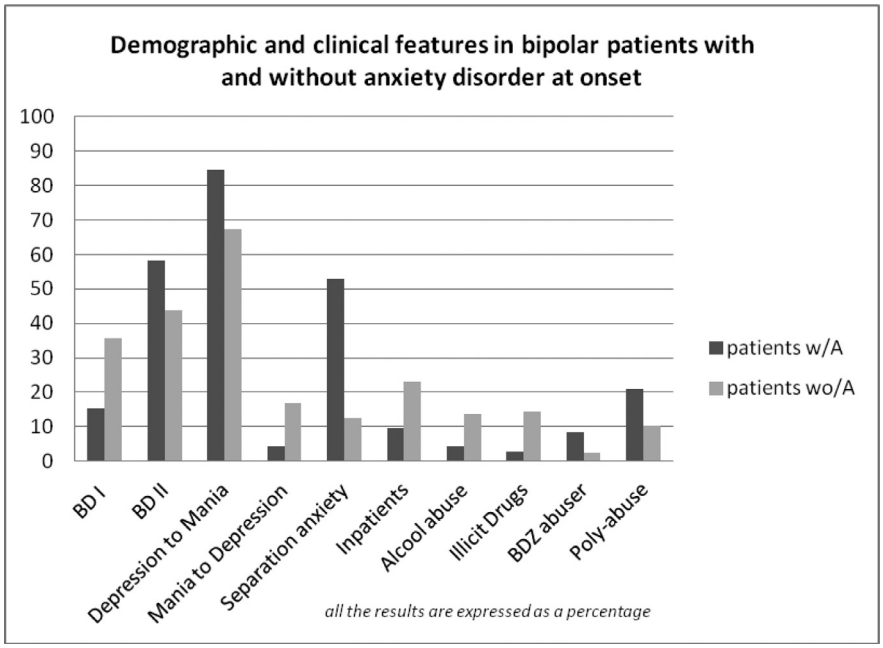

Fig. 1. Socio-demographic and clinical variables with statistically significant differences in bipolar patients with versus without comorbid AD at onset.

lifetime comorbid condition thereafter. In contrast, we found significantly lower lifetime rates of other ADs at onset – with the exception of GAD, compared to PD in BD patients. That is, other subtypes of ADs may follow the onset of BD, likely representing a subsequent manifestation rather than a prodromal stage of the disease (Duffy et al., 2014).

To our knowledge, no study to date has addressed how often ADs are secondary to BD (i.e., how often mood stabilization yields remission of AD symptoms.

It is important to note that our retrospective findings are consistent with previous prospective investigation on the early phases of BD, in which developmental pathways of illness from initial anxiety towards subsequent mood episodes were demonstrated (Duffy, 2018).

For instance, Aguglia and colleagues prospectively followed up for several years a small sample of outpatients diagnosed with ADs (Aguglia et al., 2017) showing that, after 10 years, 22% of patients developed BD, family history for BD and the presence of a substance use disorder being identified as potential predictors of BD onset. Accordingly, studies conducted on the offspring of bipolar patients showed preliminary evidence that ADs occurring in patients with a family history of BD may represent an early stage of BD (Duffy et al., 2010). In contrast with those findings, our results showed no significant difference between the presence of BD family history in the two subgroups (w/A 13.9% versus wo/A 13.8%): nonetheless a positive psychiatric family history was more frequently reported by w/A than wo/A patients (65.3% versus 52.9%).

In the present study, we also observed that history of hospitalization was comparable between patients w/A versus wo/A at onset. Indeed, in our sample, the wo/A subgroup had a significantly higher prevalence of inpatients (23% versus 9.7%). This could be explained by the higher prevalence of BD I in the wo/A group.

In regard to comorbidity between BD and separation anxiety disorder (SepAD), according to literature (Brückl et al., 2007; Tasdemir et al., 2016), in our sample, such a comorbidity pattern was frequently observed: almost one out of four patients in the total sample and half of the w/A subgroup had a history of SepAD. Moreover, according to literature (Selbes et al., 2018), SepAD could be a comorbid condition in patients with PD or it could significantly increase the risk of development of PD (Kossowsky et al., 2013). Since PD seems to precede BD, as shown in our sample, we could at least assume that SepAD could also be considered a prodromal condition in longitudinal course of BD. (Tasdemir et al., 2016). In this prospective, it could be useful to assess the presence of SepAD in those patients with an AD at onset, especially PD, in order to stratify the potential risk for BD.

Many recent studies underline the importance of onset polarity (OP) in the clinical history and evolution of illness in bipolar patients (Cremaschi et al., 2017; Tundo et al., 2015). In the present study, depressive onset (DO) was the most frequent onset considering the whole sample (81.3% of cases) and related subgroups (w/A 88.9% versus wo/A 78.9%). In line with a previous study (Cremaschi et al., 2017), BD patients w/A more frequently showed DO than elevated onset. Therefore, the above-mentioned study found that DO was more frequently associated with BD II and this diagnosis was, in turn, significantly associated with AD at BD onset in our sample. This result may show that there could be a specifically subtype of BD in which AD at BD onset might represent a different expression of illness with specific clinical peculiarities also in terms of first cycle (e.g., depression to mania/hypomania or vice-versa). Furthermore, our results showed a significantly higher rate of depression to mania/hypomania cycle in the w/A versus wo/A group. This finding may need further investigation to understand the clinical impact and role of the first cycle over the course of BD but, to date, literature offers limited evidence of studies considering the first complete cycle in mood disorders.

With respect to substance abuse, in our sample, the w/A subgroup showed high rate of benzodiazepines abuse, likely used to control initial anxiety symptoms but potentially leading to more difficult clinical management and poorer outcome (Maina et al., 2011; Martins and Gorelick, 2011). Polyabuse (more than one substance of abuse including benzodiazepines, illicit drugs and alcohol) was also more frequent in w/A patients, consistently with the available literature (Bakken et al., 2005).

On the other hand, the wo/A subgroup had higher rate of illicit drug use. This result may be partially explained because substance use disorders (SUDs) are more frequent in mood disorders than in ADs, according to literature, even if both AD and BD showed higher rates of comorbid SUD than in the general population (Martins and Gorelick, 2011).

In contrast to our data, a previous investigation showed that the lifetime prevalence of AD in BD patients was associated with a risk of lifetime alcohol dependence that was about twice higher than in BD patients wo/A (Simon et al., 2004a). Notwithstanding, most authors

agree that the presence of an AD tends to exacerbate the risk of substance abuse/dependence (Cremaschi et al., 2017; Dunner, 2004; Krishnan, 2005).

Among limitations, recall bias due to the retrospective nature of the study may have limited the quality of assessment, although missing information was completed through direct patient or relative interviews. In addition, our sample was mainly constituted of female subjects and this may potentially limit the generalizability of our results, because there is some evidence that comorbid AD may be more prevalent among women than men suffering from BD (Vázquez et al., 2014). Besides, pharmacological prescriptions at onset were only reported as macro-categories (not specific compounds) and we were unable to assess prescription setting (e.g., primary care, secondary or tertiary psychiatric service) for all patients. Finally, another limitation is that our sample was recruited by a tertiary psychiatric service and this may explain the lower rate of BD I versus BD II patients that could have affected our results. Finally, we did not correct for multiple comparisons, which may limit interpretation of some findings, particularly those with p-values between 0.05 and 0.01.

In conclusion, we believe that the progression from ADs to BD may represent a continuous process in which, in some cases, AD could represent a prodromic phase within the BD course, according to literature (Du et al., 2017; Duffy et al., 2017) and to the results of this study, in which a large proportion of our BD patients showed an AD at BD onset. In our opinion, these findings emphasize the importance of a careful and detailed diagnostic assessment, especially at first psychiatric evaluations of patients with anxiety symptoms. Indeed, considering the longitudinal course of the disease, an early and adequate intervention in BD with or without AD is crucial for the subsequent course of both disorders.

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CRediT authorship contribution statement

Valentina Caricasole: Investigation, Writing - review & editing, Data curation. **Ilaria Di Bernardo:** Investigation, Writing - review & editing. **Alberto Varinelli:** Investigation, Writing - review & editing. **Cesare Galimberti:** Investigation, Writing - review & editing, Data curation. **Riccardo Zanello:** Investigation, Writing - review & editing. **Monica Bosi:** Investigation, Writing - review & editing. **Terence A. Ketter:** Writing - original draft. **Caterina A. Viganò:** Investigation, Writing - review & editing. **Bernardo Dell'Osso:** Writing - review & editing, Writing - original draft.

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Conflict of interest

Dr. Ketter has the following financial interests/arrangements or affiliations that could be perceived as real or apparent conflicts of interest: Grant/Research Support from the Astra Zeneca Pharmaceuticals LP, Cephalon Inc., Eli Lilly and Company, Pfizer Inc., and Sunovion Pharmaceuticals; Consultant Fees from Allergan, Inc., Avanir Pharmaceuticals, Bristol-Myers Squibb Company, Cephalon Inc., Forest Pharmaceuticals, Janssen Pharmaceutica Products, LP, Merck & Co.,Inc., Sunovion Pharmaceuticals, Teva Pharmaceuticals; Lecture Honoraria from Abbott Laboratories, Inc., AstraZeneca PharmaceuticalsLP, Glaxo Smith Kline, and Otsuka Pharmaceuticals; and Publication Royalties from American Psychiatric Publishing, Inc. In addition, Dr.Ketter's spouse is an employee of and holds stock in Janssen Pharmaceuticals.

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