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BIPOLAR DISORDER WITH SEASONAL PATTERN: CLINICAL CHARACTERISTICS AND GENDER INFLUENCES

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ABSTRACT

Bipolar disorder (BD) has a multifactorial etiology with heterogeneous clinical presentations. Around 25% of BD patients may present with a depressive seasonal pattern (SP). However, there is limited scientific data on the prevalence of SP, its clinical manifestations and any gender influence. Four hundred and fifty-two BD I and II cases (62% female), recruited from three French university-affiliated psychiatric departments, were assessed for SP. Clinical, treatments and socio-demographic variables were obtained from structured interviews. One hundred and two (23%) cases met DSM-IV criteria for SP, with similar frequency according to gender. Multivariate analysis showed a significant association between SP and BD II (OR=1.99, p=0.01), lifetime history of rapid cycling (OR=2.05, p=0.02), eating disorders (OR=2.94, p=0.003) and total number of depressive episodes (OR=1.13, p=0.002). 71% of cases were correctly classified by this analysis. However, when stratifying the analyses by gender, SP was associated with BD II subtype (OR=2.89, p=0.017) and total number of depressive episodes (OR=1.21, p=0.0018) in males but with rapid cycling (OR=3.02, p=0.0027) and eating disorders (OR=2.60, p=0.016) in females. This is the first study to identify different associations between SP and clinical characteristics of BD according to gender. We suggest that SP represents a potentially important specifier of BD. Our findings indicate that seasonality may reflect increased severity or complexity of disorder.

KEYWORDS: bipolar disorder, seasonality, season, gender, rapid cycling, eating disorder.

INTRODUCTION

Bipolar disorder (BD) is a severe psychiatric disorder characterized by alternating periods of elevated mood (manic or hypomanic episodes) and depression, interspaced with periods of euthymia. BD affects 1

(Colom & Vieta, 2009), these findings warrant replication. Furthermore, there are obvious gaps in research surrounding issues specific to gender differences in BD and their implications for management (Kawa et al., 2005). To date, sub-group analyses according to gender have not been performed, usually because sample sizes had inadequate statistical power to explore any statistically significant differential associations. However, this is an important issue, especially given findings of the potentially different influences of seasons between genders on mood disorders (Morken et al., 2002).

We suggest that, if SP is to be considered as a possible specifier, it is necessary to demonstrate that (1) SP is frequent amongst BD patients, (2) SP is robustly associated with clinical characteristics of BD and (3) to clarify if these associations are sensitive to gender. Our aims are to (1) identifying the frequency of SP in a larger well-characterized clinical sample of BD cases, (2) comparing those individuals with and without SP for demographic and clinical features, and then (3) exploring whether there are any gender effects on the presentation of SP.

MATERIALS AND METHODS

a. Sample

Caucasian individuals who met DSM-IV criteria (A.P.A., 1994) for BD I or BD II were recruited from three university-affiliated psychiatric departments in France (Paris, Bordeaux, Nancy). The experimental protocol is conform to international ethical standards (Portaluppi et al., 2010). With Institutional review board ethics approval, participants who gave written informed consent were assessed by a psychiatrist or psychologist trained in the use of the French version of the Diagnostic Interview for Genetic Studies (DIGS). The DIGS is a structured interview schedule that provides a retrospective lifetime diagnosis of BD, treatments and other axis I disorders meeting DSM IV criteria (Nurnberger et al., 1994). Both

familial and sporadic cases could be included in the study. Patients had to be in symptomatic remission for at least three months and with MADRS and YMRS scores lower than 5 at inclusion.

b. Measures and procedures

Seasonal pattern was defined according to DSM-IV criteria: (A) Regular temporal relationship between the onset of major depressive episodes and a particular time of the year (unrelated to obvious season-related psychosocial stressors), (B) Full remissions (or a change from depression to mania or hypomania) also occur at a characteristic time of the year, (C) Two major depressive episodes meeting criteria A and B in the past two years and no non-seasonal episodes in the same period, (D) Seasonal major depressive episodes substantially outnumber the non-

non-normal distributions. Univariate two-sided analyses were performed on the total sample of 452 subjects followed by backward stepwise logistic regression (LR) for variables showing statistically significant associations.

Backward stepwise logistic regression analysis (to classify cases as SP+ or SP-) was performed on 407 cases (90% total sample) with data available on all variables. Covariates included in the analysis were: gender; presence or absence of: BD II, rapid cycling or eating disorders; total number of depressive episodes, duration of BD, and age of onset. The analysis showed statistically significant OR for SP+ status and: BD II subtype (OR=1.99; 95% ci 1.15 to 3.42; p=0.014), presence of rapid cycling (OR=2.05; 95% ci 1.14 to 3.69; p=0.017), lifetime history of eating disorders (OR=2.94 [1.43 - 6.02], p=0.0032) and total number of depressive episodes (OR=1.13; 95% ci 1.05 to 1.21; p=0.0015). 71% of cases were correctly classified by LR analysis (see Table 2). However, when the LR analysis was repeated with stratification by gender (males=157; females=250), significant differences emerged. In males, the analysis showed significant associations between SP+ status and BD II subtype (OR=2.89; 95% ci 1.21 to 6.68; p=0.017) and total number of depressive episodes (OR=1.21; 95% ci 1.07 to 1.36; p=0.0018); and 69% of males were correctly classified using these two variables. In females, analysis showed significant associations between SP+ status and presence of rapid cycling (OR=3.02; 95% ci 1.47 to 6.2; p=0.0027) and lifetime history of eating disorders (OR=2.60 [1.19 - 5.64], p=0.016); these two variables correctly classified about 51% of female patients (see Table 2).

TABLE 2 ABOUT HERE

DISCUSSION

The aim of this study was to examine the prevalence of SP in a sample of BD cases recruited from three university-affiliated general adult psychiatry clinics, to clarify if any specific clinical features of BD are associated with this pattern and to examine whether SP shows any significant gender differences

First, we replicated the high rates of SP in a bipolar sample: 23% cases in our study as compared to 23% and 26% in previous studies using the same DSM-IV criteria (Goikolea et al., 2007; Schaffer et al., 2003). This one in four prevalence in BD is noteworthy since it exceeds the 10-20% prevalence found in populations of depressed out-patients who have been screened for seasonal variations (Magnusson, 2000). Only one community-based survey of seasonality in patients with BD exists which suggested that individuals with BD report significantly greater seasonal fluctuation in mood and behaviour than individuals with unipolar depression or healthy controls (Shin et al., 2005). These findings highlight that amongst mood disorders, BD may be a subtype more prone to SP.

Second, we confirm the findings of the multivariate analysis reported by Goikolea et al. (2007) who showed that SP cases have a significantly higher number of major depressive episodes and were more likely to meet criteria for BD II subtype. A previous study in a community sample in the province of Ontario also noted an association with Bipolar II subtype and SP (Schaffer et al., 2003). Our findings thus reinforce the links between seasonality and BD II. As in previous research, we failed to find any association between SP and onset polarity, predominant polarity or psychotic symptoms (Goikolea et al., 2007). However, our superior sample size gave greater statistical power than previous studies, and we were able to demonstrate other important associations such as a two-fold increase in rates of rapid cycling and eating disorders in SP. However, the most important revelation is that there are significant gender differences in the clinical characteristics associated with SP.

To our knowledge this is the first study of BD to demonstrate that each gender displays distinct clinical associations with some of the characteristics associated with SP. We suggest

that not only is it highly relevant in clinical practice to identify bipolar patients at risk for SP, but also to bear in mind that there may be different factors associated with SP according to gender. About seventy percent of male SP+ cases had BD II subtype and a higher number of depressive episodes (69%). In females, the classification rate was lower (51%), but SP+ status was associated with rapid cycling and a lifetime history of eating disorders. The different expressions of seasonal pattern between men and women may reflect to some extent the differences in the seasonal variation in admissions for depression observed between genders (Morken et al., 2002), but the specific findings are not entirely predictable (eg BD II is more commonly associated with female rather than male gender).

Rapid cycling has been repeatedly associated with female gender (Burt & Rasgon, 2004; McElroy, 2004) and several hypotheses have been proposed for this observation including higher rates of hypothyroidism, greater use of antidepressants, and gonadal steroid effects (Leibenluft, 1996). Further research is needed to consolidate the findings on the gender-specific aspects of rapid cycling and SP status as these may have particular treatment implications for women (Burt & Rasgon, 2004). Likewise, the prevalence of eating disorders (ED) in BD is 5-14% and of course is strongly associated with female gender (Seixas et al., 2012; McElroy et al., 2011). In our study, lifetime comorbidity of ED with SP+ was over twice as frequent as ED with SP- cases (19% versus 9%). Our findings support the notion that ED is closely associated with BD in females and particularly when SP is present. Earlier studies suggesting a relationship between BD and ED, specifically bulimia nervosa and BD II, have failed to examine whether the association was linked with a third factor such as SP (Lunde et al., 2009). So, we provide here evidence for some variables clustering within BD females: seasonal pattern, rapid cycling and eating disorders, which opens up new avenues for research into the putative underlying mechanisms driving these associations.

Despite contradictory findings, previous studies suggest that there is a higher prevalence of manic episodes in the spring and summer months (Proudfoot et al., 2011) and/or that psychiatric admissions for mania peak in early spring (Lee et al., 2007; Cassidy & Carroll, 2002). However, we did not find an association between SP and predominant polarity (p= 0.47) and the association between total number of mania/hypomanic episodes and SP showed only trends towards significance (p= 0.08 and 0.10 respectively). In order to clarify these relationships further, we suggest that the diagnosis of SP in BD should not be confined to depressive episodes only and that the possible existence of manic SP needs further exploration.

Although this is the largest study of SP in BD undertaken, some limitations of this study require comment. It is not possible to exclude selection bias, retrospective recall biases nor to retrospectively disentangle any potential confounding effects of medication, so we cannot definitively exclude the possibility that medications may have altered the reported seasonal course in some cases (Westrin & Lam, 2007). Indeed, we could hypothesize that the association between SP and rapid cycling would be linked to a greater exposure to antidepressants. However we think that this is unlikely in our sample since no differences of lifetime treatments were observed between groups, especially regarding antidepressants.

Given the low frequency of eating disorders among males, we cannot definitively assert that the association between SP and this variable is specific to females.

The categorical approach to defining seasonality as derived from the DSM criteria is restricted to depressive SP, which does not allow investigation of correlations between specific phases of the illness and specific seasons of the year. Also, we did not use any adjunctive dimensional tools, such as the SPAQ, which potentially allow the more sensitive

measurement of the severity of any seasonality effects that are observed (Goikolea et al., 2007).

Having made the observations regarding associations of clinical features and SP, it is important to consider the interpretations of our findings. There is increasing interest in the circadian physiopathology of BD (Etain et al., 2011; Milhiet et al., 2011). Environmental stimuli, such as exposure to light, may influence the course of the disorder, as shown by the fact that seasonality is much more frequent in northern European countries (Friedman et al., 2006). The influence of latitude and seasonality pattern in BD remains controversial, but there is emerging evidence that seasonal effects may vary by latitude and BD polarity (Bauer et al., 2009; Magnusson & Partonen, 2005). An analysis of data from the multi-centre STEP-BD study found a significant higher prevalence rate of depression in the northern sites with possible higher vulnerability in BD II (Friedman et al., 2006).

Murray and coworkers (Murray & Harvey, 2010) propose that seasonal variation supports the role of light and biological rhythms in BD etiology. A recent study about euthymic patients highlighted that *'sleep, light and seasonality seem to be three interconnected features that lie at the basis of chronobiology that, when altered, have an important effect both on the psychopathology and on the treatment of mood disorders'* (Brambilla et al., 2012). Theoretically, seasonal depression in BD might be treatable by manipulating the circadian system using chronobiotic drugs (eg agomelatine or melatonin) (Calabrese et al., 2007; Livianos et al., 2012) and chronotherapeutics (eg bright light therapy or sleep deprivation) (Wu et al., 2009; Benedetti et al., 2005). In addition, since about 25% of patients have SP, clinicians should encouraged to closely monitor mood during winter

months, and consider the role of seasons in individualized early warning signs plans and other prevention strategies.

In conclusion, the high prevalence of SP in BD, its associated clinical characteristics and the observed differences between genders, suggest that SP represents a potentially important specifier of BD. Further studies are required and the possible extension of SP to include manic episodes should be considered in future nosographical classifications (Colom & Vieta, 2009). Large-scale studies are also needed in order to establish the differential influences of gender on the associations between BD and SP and especially to develop a better understanding of clinical characteristics that cluster amongst female patients such as rapid cycling and eating disorders. Our findings also imply that seasonality is associated to a more severe or complex disorder and thus might be discussed for inclusion in forthcoming treatment algorithms.

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CONFLICT OF INTEREST

Authors have no actual or potential conflicts of interest that could influence, or be perceived to influence, this work.

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Table 1. Clinical characteristics of patients with (SP+) and without seasonal pattern (SP-)

Variables	N (452)	SP+ (n=102, 22.6%)	SP- (n=350, 77.4%)	W/Chi^2	*P value*
		mean (SD) or n (%)[a]			
Demographic and social characteristics					
Gender					
Female [b]	452	65 (63.7)	216 (61.7)	0.13	0.71
Male [c]		37 (36.3)	134 (38.3)		
Age	452	44.70 (13.28)	44.50 (13.19)	18132.5	0.81
Family history of affective disorder					
Not	422	22 (23.2)	92 (28.1)	0.92	0.34
Yes		73 (76.8)	235 (71.9)		
Categorical variables					
Subtype					
Bipolar I	452	60 (58.8)	255 (72.9)	7.36	**0.0067**
Bipolar II		42 (41.2)	95 (27.1)		
Polarity at Onset					
Mania	447	23 (23.5)	97 (27.8)	0.73	0.39
Depression		75 (76.5)	252 (72.2)		
Predominant Polarity					
Manic	212	16 (30.8)	45 (28.1)	0.14	0.71
Depressive		36 (69.2)	115 (71.9)		
Rapid Cycling*					
No	445	59 (61.5)	286 (81.9)	18.14	**<0.0001**
Yes		37 (38.5)	63 (18.1)		
Psychotic Symptoms*					
No	451	56 (54.9)	170 (48.7)	1.21	0.27
Yes		46 (45.1)	179 (51.3)		
Attempted Suicide*					
No	447	58 (57.4)	177 (51.2)	1.23	0.27
Yes		43 (42.6)	169 (48.8)		
Anxiety Disorders*					
No	352	43 (48.3)	126 (47.9)	0.004	0.95
Yes		46 (51.7)	137 (52.1)		
Eating Disorder*					
Not	439	80 (80.8)	310 (91.2)	8.31	**0.0039**
Yes		19** (19.2)	30*** (8.8)		
Alcohol Misuse *					
Not	442	75 (75.8)	281 (81.9)	1.86	0.17
Yes		24 (24.2)	62 (18.1)		
THC Misuse *					
Not	448	26 (26.3)	114 (32.7)	1.47	0.23
Yes		73 (73.7)	235 (67.3)		
Continuous variables					
Age of Onset	450	23.13 (8.52)	26.39 (11.58)	20147.5	**0.028**
Age 1st Hospitalization	436	29.47 (14.11)	32.96 (14.50)	17757.5	0.05
Years of evolution	448	21.60 (12.84)	18.55 (11.06)	15358.5	0.06
Total Number of Episodes	415	8.40 (4.95)	6.64 (3.99)	10696.5	**0.00047**
Number of Depressive Episodes	426	6.08 (3.75)	4.52 (2.86)	10316.5	**<0.0001**
Number of Manic Episodes (BD1)	315	3.53 (3.65)	2.58 (2.20)	5795.5	0.08
Number of Hypomanic Episodes	137	6.5 (5.08)	4.5 (4.47)	439	0.10

*Lifetime history; ** 17 women (89.5%), 2 men (10.5%), ***28 women (93.3%), 2 men (6.7%).
[a]% of columns
[b]Female: 22% presented with SP (65/216)
[c]Male: 23% presented with SP (37/134)

Table 2. Logistic regression showing significant gender differences in the clinical characteristics that best classify cases into those with or without a seasonal pattern[a]

	Odds Ratio [95% CI]	*B(SD)*	*p*	*Odds Ratio* [95% CI]	*B(SD)*	*p*	*Odds Ratio* [95% CI]	*B(SD)*	*p*
Variables	**TOTAL SAMPLE (n=407)**			**MALES (n=157)**			**FEMALES (n=250)**		
Bipolar II Disorder	**1.99** [1.15 - 3.42]	0.69 (0.28)	**0.014**	**2.84** [1.21 - 6.68]	0.69 (0.28)	**0.017**	NS		
Rapid cycling*	**2.05** [1.14 - 3.69]	0.72 (0.30)	**0.017**	NS			**3.02** [1.47 - 6.2]	1.10 (0.37)	**0.0027**
Eating disorder*	**2.94** [1.43 - 6.02]	1.08 (0.37)	**0.0032**	NS			**2.60** [1.19 - 5.64]	0.95 (0.40)	**0.016**
Number of depressive episodes	**1.13** [1.05 - 1.21]	0.12 (0.037)	**0.0015**	**1.21** [1.07 - 1.36]	0.19 (0.06)	**0.0018**	NS		

*Lifetime history
[a]using the following covariates : age of onset, gender and duration of illness
NS : not significant.