Journal of Affective Disorders 243 (2019) 322–326

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

# Seasonality in bipolar disorder: Effect of sex and age

Matthäus Fellinger[a], Thomas Waldhoer[b,*], Daniel König[a], Barbara Hinterbuchinger[a], Nathalie Pruckner[a], Josef Baumgartner[a], Sandra Vyssoki[a], Benjamin Vyssoki[a]

[a] Clinical Division of Social Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria
[b] Centre for Public Health, Department of Epidemiology, Medical University of Vienna, Kinderspitalgasse 15, Vienna 1090, Austria

ARTICLE INFO

*Keywords:*
Bipolar disorder
Seasonal variation
Seasons
Sex characteristics
Age
Hospitalization

ABSTRACT

*Background:* Mood episodes in bipolar disorder (BD) are reported to exhibit a seasonal pattern (SP). However, it is unclear whether this pattern is influenced by a patient's sex and age.
*Methods:* In this nationwide registry study, we examined all inpatient treatments due to a manic (F31.0–2), depressive (F31.3–5) or mixed (F31.6) BD-episode in Austria for 2001–2014. Calculations were based on directly age-standardized rates and seasonality was analyzed on a monthly basis.
*Results:* The database comprised 60,607 admissions (35.8% men). SP were shown for women during manic (summer–autumn), depressive (winter) and mixed (summer) episodes, for men only during manic (summer) episodes. However, no significant sex differences (manic $p = 0.101$, depressive $p = 0.295$, mixed $p = 0.622$ episode) were found. Women at young age (15–35 years) seemed to be more vulnerable to a SP in manic and mixed episodes.
*Limitations:* Only aggregated patient data of inpatient treatments and no single case histories were available.
*Conclusions:* In this nationwide registry study, a distinct SP could be shown for manic episodes in men and women, as well as a SP for depressive and mixed episodes in women. As no significant difference in any BD-subgroup could be observed, the effect of sex on the SP seems to be small, if existing at all. However, when taking age into account, we observed a higher likelihood for a SP in young women. Single case studies with information on possible further influencing factors (e.g. medication use) might help to clarify the impact of sex and age on SP in more detail.

## Introduction

Mood episodes in bipolar disorder (BD) are found to exhibit a seasonal pattern (SP), with peaks for manic episodes in spring-summer and peaks for depressive episodes in early winter (Geoffroy et al., 2014; Lee et al., 2007; Volpe et al., 2010; Medici et al., 2016; Parker et al., 2017). Mixed episodes are most often described to peak in early spring and summer (Cassidy and Carroll, 2002; Lee et al., 2007; Whitney et al., 1999; Yang et al., 2013). These patterns have been observed in countries of the northern as well as the southern hemisphere, however, rarely in equatorial regions (Medici et al., 2016).

The causes for SP are still poorly understood. However, various factors have been discussed to possibly influence the occurrence of SP, including sleep deprivation and variations in circadian genes; with the most compelling evidence for an effect of climatic factors. While the intensity of sunshine (Carney et al., 1988; Sayer et al., 1991; Suhail and Cochrane, 1998; Lee et al., 2002; Volpe and Del Porto, 2006; Medici et al., 2016) and the number of daylight hours (Carney et al., 1988; Cassidy and Carroll, 2002; Sayer et al., 1991) have been found to increase the frequency of manic episodes, studies examining the influence of rainfall, snow, humidity, evaporation and temperature on triggering manic episodes reported mixed results (Carney et al., 1988; Sayer et al., 1991; Volpe and Del Porto, 2006; Volpe et al., 2010; Geoffroy et al., 2014; Medici et al., 2016; Parker et al., 2017; Bullock et al., 2017). Furthermore, increased time of sunshine as well as higher temperature were associated with decreased rates of depressive episodes (Lee et al., 2007; Shapira et al., 2004). No influence of climate change was reported in recent studies (Medici et al., 2016; Parker et al., 2017). To further understand the pathophysiological mechanisms of seasonality in BD recent research suggests the investigation of markers like plasma melatonin, sleep-wake rhythms and genetic or epigenetic variants within the melatonin synthesis pathway (Maruani et al., 2018).

On an individual level, seasonality was shown to influence the clinical course of mood episodes, affecting up to one fourth of patients with BD profoundly (Magnusson, 2000; Geoffroy et al., 2013, 2014). This patient group shows an increased risk for a more severe course of

* Corresponding author.
*E-mail address:* thomas.waldhoer@muv.ac.at (T. Waldhoer).

https://doi.org/10.1016/j.jad.2018.09.073
Received 28 June 2018; Received in revised form 30 August 2018; Accepted 19 September 2018
Available online 20 September 2018

illness with higher rates of rapid cycling, BD II subtype, comorbid eating disorders and younger age of onset (Geoffroy et al., 2013).

Numerous studies investigated differences in the clinical course of bipolar disorders between men and women, as well as the influence of age on frequency and severity of mood episodes (Diflorio and Jones, 2010; Joslyn et al., 2016). Only a few studies have hitherto explored whether sex and age are also relevant regarding seasonality – with conflicting results. Sex differences in SP are hypothesized to be due to higher rates of antidepressant use and increased rates of hypothyroidism in woman as well as sex-specific hormone effects (e.g. menstrual cycle, premenstrual symptom) (Kim et al., 2011; Leibenluft, 1996; Morken et al., 2002). While some studies identified women to be more susceptible to seasonal variations (Kerr-Corrêa et al., 1998; Morken et al., 2002; Murray et al., 2011; Suhail and Cochrane, 1998), recent studies found no sex difference regarding SP (Medici et al., 2016) or described a stronger SP in male bipolar patients (Hochman et al., 2016; Rajkumar and Sarkar, 2015). Regarding age, Morken et al. (2002) found younger patients (under 25 years) to be especially vulnerable for SP, while Rajkumar and Sarkar (2015) observed an association with age greater than 25 years. Medici et al. did not find a SP when taking admission status in manic episodes, first or following admission, as proxy-parameter for age (Medici et al., 2016).

Due to the partially contradicting results of previous studies, as described above, it remains unclear whether an influence of sex or age on the seasonality of BD exists. Thus, the aim of this study was to further examine this question by analyzing a large national dataset on inpatient treatment episodes for BD over a 14-year time period.

## 2. Patients and methods

### 2.1. . Design

We conducted a nationwide registry-based study in Austria for the time period 2001–2014. Data was provided by Statistics Austria, the national statistics agency, in anonymized form. Statistics Austria collects data annually from the Austrian health system and provides data access for scientific research.

### 2.2. . Sample

For the current investigation, we examined data of all patients hospitalized with a diagnosis of bipolar disorder (F31.0–F31.9) as primary reason for inpatient treatment between 2001 and 2014 in Austria. Age-groups were given as 5-year intervals for 15 to <75 and one group ≥ 75.

The dataset contained the following variables: BD sub-diagnosis (F31.0–F31.9), sex, week of discharge and the length of hospital stay in days. For further calculations, BD sub-diagnoses were grouped, according to the subtype, in manic (F31.0–F31.2), depressive (F31.3–F31.5) and mixed (F31.6) episodes. ICD-10-diagnosis F31.7–9 (F 31.7 BD, currently in remission, F31.8 other BD, F31.9 BD, unspecified) were excluded from analysis due to lack of specificity, as well as patients with inpatient treatment longer than 1 year.

### 2.3. . Statistical methods

Data management and analysis were done in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The SP was calculated on a monthly basis and differences in SP between BD-subtypes and sex measured by a chi-square test. Directly age-standardized rates (Rothman et al., 2008) and 95% confidence intervals were calculated based on the European standard population and by means of SAS procedure “proc stdrate” in order to adjust for a possible shift in the age distribution. Comparisons of standardized rates by sex were done by rate ratios. To describe the influence of age we decided to use descriptive methods only to avoid inflation of alpha errors by large number of statistical tests. Age-groups were created as similar as possible according to Yang et al. (2013) 15 to <35, 35 to <55 and ≥55 years. Monthly age group-specific rates were divided by yearly rate in order to show seasonal patterns. The significance level was set to 5%. Levels of significance were not adjusted for multiple comparisons (Rothman et al., 2008), so *p*-values have to be interpreted exploratory only.

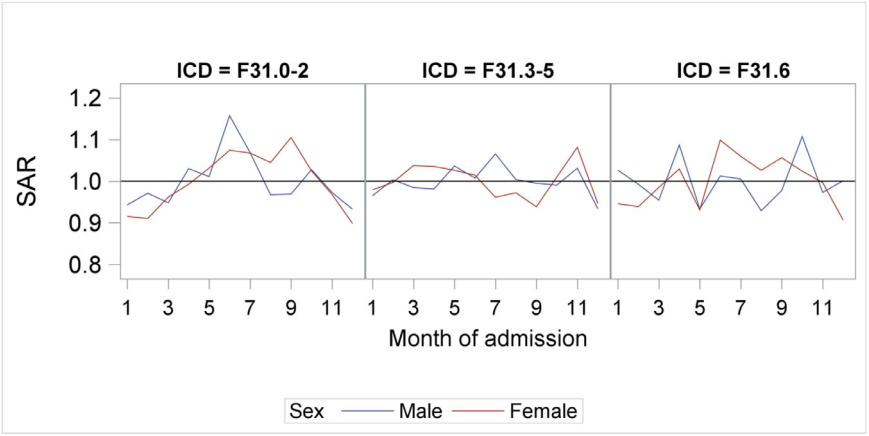
## 3. Results

The database included 60,607 admissions ($n$ = 23,198 for manic, $n$ = 28,311 for depressive and $n$ = 9098 for mixed episodes) after exclusion of 7798 admissions (F31.7–9 [$n$ = 7660] and inpatient stay > 1 year [$n$ = 38]). In total, 35.8% ($n$ = 21,711) of the admissions were men (manic: 39.6%, depressive: 34.4%, mixed: 30.5% episodes). Patients had a mean age of 47.56 years (SD 14.42) at admission, 46.71 years (SD 13.89) in men and 48.03 years (SD 14.69) in women.

### 3.1. . Seasonality and sex

SP for manic episodes was found in men ($p$ < 0.001 [maximum: June]), and women ($p$ < 0.001 [maximum: September]). These patterns did not differ between men and women ($p$ = 0.101) (see Graphic 1a).

While a SP in hospital admissions due to depression was found in women ($p$ = 0.001 [maximum: November]), no such pattern could be shown for male patients ($p$ = 0.469). However, no significant




**Graphics 1.** a–c: Seasonal variations of bipolar disorder subgroups according to ICD-10 (1a: manic F31.0–2; 1b: depressive F31.3–5, 1c: mixed F31.6 episodes) shown as standardized admission rate (SAR) in male and female.