**Diplomarbeit**

# The Role of Sex in Clinical Characteristics and Pharmacological Treatment of Bipolar Disorder


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Graz, 29. Oktober 2025 Erik Putz, m.p.

# Zusammenfassung

Einleitung: In den letzten Jahren hat der Fokus auf Geschlechtsunterschiede bei der bipolaren Störung zugenommen, dennoch bleibt vieles über deren Einfluss auf klinische Merkmale und Behandlungsansätze offen. Ziel dieser Studie ist es, Geschlechtsunterschiede zu identifizieren, die Diagnose- und Behandlungsstrategien beeinflussen könnten und dadurch möglicherweise die Therapietreue sowie die Behandlungsergebnisse verbessern.

Methoden: Diese retrospektive Studie analysierte Daten aus Interviews mit 340 Teilnehmenden (171 Männer, 169 Frauen; Alter zwischen 18 und 82 Jahren) aus der BIPFAT/BIPLONG-Studie am Spezialambulatorium für bipolare Störungen der Medizinischen Universität Graz, Österreich. Wir untersuchten Geschlechtsunterschiede in klinischen Merkmalen und medikamentöser Therapie vorwiegend mit logistischen und linearen Regressionsmodellen. Ergänzend wurden Chi-Quadrat-Tests und Mann-Whitney-U-Tests für Subgruppenvergleiche herangezogen.

Ergebnisse: Unsere Ergebnisse zeigten, dass das Erkrankungsalter bei Frauen früher lag (B = -3.05, 95% KI = [-5.08, -1.02], p = .003). Frauen berichteten ihre ersten affektiven Symptome im Durchschnitt im Alter von 22,7 Jahren (SD = 9,9), verglichen mit 26,4 Jahren (SD = 12,1) bei Männern. Komorbide Zwangsstörungen traten bei Frauen signifikant häufiger auf (OR = 2.24, 95% KI = [2.12, 41.33], p = .003). Männer hingegen zeigten häufiger manische Episoden pro Jahr (B = -.32, 95% KI = [-.59, -.05], p = .019). Unterschiede in der Behandlung zeigten sich nur innerhalb bestimmter Altersgruppen, nicht jedoch in der Gesamtstichprobe.

Schlussfolgerungen: Insgesamt fanden wir weniger Unterschiede als erwartet, was darauf hindeutet, dass andere Faktoren als das Geschlecht eine größere Rolle im Verlauf der bipolaren Störung spielen. Unsere Analyse weist darauf hin, dass mehr Frauen unter einer Zwangsstörung als Komorbidität leiden als Männer, ein Thema, das bisher noch wenig untersucht wurde. Während frühere Studien überwiegend ein früheres Erkrankungsalter bei Männern zeigen, fanden wir in unserer Stichprobe das Gegenteil. Ein weiterer bemerkenswerter Unterschied im Krankheitsverlauf war, dass Männer mehr manische Episoden pro Jahr erlebten. Weitere Forschung ist notwendig, um unsere Ergebnisse zu bestätigen, idealerweise mit einem spezifischen Fokus auf Zwangsstörungen bei bipolar erkrankten Männern und Frauen, da Geschlechtsunterschiede bei dieser Komorbidität bislang kaum erforscht sind.

# Abstract

Introduction: There has been an increasing focus on sex differences in bipolar disorder in recent years, yet much remains to be understood about their impact on clinical characteristics and treatment approaches. The aim of this study is to identify sex differences that could alter diagnosis and treatment strategies, potentially improving patient compliance and outcomes.

Methods: This retrospective study analysed data from interviews with 340 participants (171 men, 169 women; ages ranging from 18 to 82 years) from the BIPFAT/BIPLONG study at the specialised outpatient centre for bipolar disorder at the Medical University of Graz, Austria. We examined sex differences in clinical characteristics and drug therapy primarily using logistic and linear regression models, with chi-square tests and Mann–Whitney U tests applied as supplementary analyses for subgroup comparisons.

Results: Our findings revealed that the age of onset for bipolar disorder was earlier in women (B = -3.05, 95% CI = [-5.08, -1.02], p = .003), with women reporting their first affective symptoms at an average age of 22.7 (SD = 9.9) compared to 26.4 (SD = 12.1) in men. Comorbid obsessive-compulsive disorder was significantly more prevalent in women (OR = 2.24, 95% CI = [2.12, 41.33], p = .003). In comparison, men were shown to experience manic episodes per year more frequently (B = -.32, 95% CI = [-.59, -.05], p = .019). Differences in treatment emerged only within specific age subgroups rather than the overall study sample.

Conclusions: Overall, we found fewer differences than expected, which suggests that factors other than sex play a greater role in the course of bipolar disorder. Our analysis indicates that more women are suffering from OCD as comorbidity than men, a topic that has not yet been extensively researched. While previous studies mostly show that men have an earlier onset of symptoms, we found the opposite in our sample. Another notable difference in illness course was that men experienced more manic episodes per year. Further research in this area is needed to verify our findings, ideally focusing specifically on OCD in bipolar men and women, as sex differences in this comorbidity remain underexplored.

# Veröffentlichungen

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**The Role of Sex in Clinical Characteristics and Pharmacological Treatment of Bipolar Disorder**

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**ABSTRACT**

**Introduction:** There has been an increasing focus on sex differences in bipolar disorder in recent years, yet much remains to be understood about their impact on clinical characteristics and treatment approaches. The aim of this study is to identify sex differences that could alter diagnosis and treatment strategies, potentially improving patient compliance and outcomes.

**Methods:** This retrospective study analysed data from interviews with 340 participants (171 men, 169 women; ages ranging from 18 to 82 years) from the BIPFAT/BIPLONG study at the specialised outpatient centre for bipolar disorder at the Medical University of Graz, Austria. We examined sex differences in clinical characteristics and drug therapy primarily using logistic and linear regression models, with chi-square tests and Mann–Whitney U tests applied as supplementary analyses for subgroup comparisons.

**Results:** Our findings revealed that the age of onset for bipolar disorder was earlier in women *(B = -3.05, 95% CI = [-5.08, -1.02], p = .003)*, with women reporting their first affective symptoms at an average age of 22.7 (SD = 9.9) compared to 26.4 (SD = 12.1) in men. Comorbid obsessive-compulsive disorder was significantly more prevalent in women *(OR = 2.24, 95% CI = [2.12, 41.33], p = .003)*. In comparison, men were shown to experience manic episodes per year more frequently *(B = -.32, 95% CI = [-.59, -.05], p = .019)*. Differences in treatment emerged only within specific age subgroups rather than the overall study sample.

**Conclusions:** Overall, we found fewer differences than expected, which suggests that factors other than sex play a greater role in the course of bipolar disorder. Our analysis indicates that more women are suffering from OCD as comorbidity than men, a topic that has not yet been extensively researched. While previous studies mostly show that men have an earlier onset of symptoms, we found the opposite in our sample. Another notable difference in illness course was that men experienced more manic episodes per year. Further research in this area is needed to verify our findings, ideally focusing specifically on OCD in bipolar men and women, as sex differences in this comorbidity remain underexplored.

**INTRODUCTION**

The field of psychiatry has made significant strides in overcoming sex stereotypes over the last century, allowing for a more nuanced understanding of differences between men and women in mental health [1]. Historically, psychiatric research often failed to distinguish between subjective perceptions and scientifically validated differences between sexes, but recent decades have seen a shift towards more evidence-based approaches. Notably, the prevalence of mental disorders differs by sex, with women more likely to experience internalising disorders such as depression and anxiety disorders, whereas men tend to suffer more from externalising disorders like substance use disorders or attention-deficit/hyperactivity disorder (ADHD) [2, 3, 4, 5].

In the context of bipolar disorder (BD), sex differences have become a focal point of research, reflecting this broader shift towards personalised medicine. In recent years, several studies have examined different aspects and differences concerning the role of sex in BD, such as age of onset, comorbidity patterns and diagnostic prevalence. For instance, a large American retrospective cohort study that utilised insurance claims data from over 97 million people found that women are more frequently diagnosed with BD [6], although other studies report similar prevalence rates across sexes [7, 8, 9]. Bipolar II disorder, characterised by hypomanic episodes, appears to be more common in women, while bipolar I disorder

shows no significant sex disparity [10, 11, 12]. These findings suggest either a potential underdiagnosis of bipolar II disorder in men or distinct biological underpinnings.

The age of onset for BD seems to be another area of conflicting evidence. While some studies report no significant sex differences [13,14], others suggest that men experience an earlier onset of symptoms [10, 15, 16]. Sex differences extend to episode polarity as well; women are more likely to experience depressive and mixed episodes [10, 16, 17, 18, 19], with depression frequently marking the first episode of the disorder [16, 19, 20]. In line with this, men have been shown to be more likely to experience manic episodes and to have mania as the polarity of onset [19]. Psychiatric comorbidities also vary by sex, with women more commonly presenting with eating, anxiety and post-traumatic stress disorders [10, 12, 16, 18, 21] while men more frequently suffer from substance use and alcohol use disorders [16, 17, 20, 21, 22]. Furthermore, while women with BD attempt suicide more frequently, men have a higher suicide mortality rate [23].

Sex-related differences have also been observed in the psychopharmacological treatment of bipolar disorder, although the data in this area remains relatively sparse. A 2015 Swedish study found that women were more likely than men to receive psychiatric treatment, including antidepressants [24]. However, there is insufficient data to clearly delineate sex-specific differences in treatment response [10, 13, 25]. Therapeutic approaches vary globally. Many current guidelines for the management of BD primarily focus on pharmacological interventions [26]. Long-term drug therapy is often based on mood stabilisers, namely lithium or anticonvulsants such as valproate, lamotrigine, carbamazepine and topiramate, which can reduce the number and severity of episodes [26]. Options for the acute treatment of hypomanic, manic or mixed episodes include lithium, valproate, atypical antipsychotics such as quetiapine, olanzapine, risperidone or aripiprazole and typical antipsychotics such as haloperidol [26]. Both monotherapy and combination therapy are possible and the short-term administration of benzodiazepines may also be considered. Bipolar depression can be treated with lithium, quetiapine or lamotrigine as monotherapy or in combination with antidepressants. As there is a risk of antidepressant-induced manic/hypomanic switch, monotherapy with antidepressants without a mood stabiliser is contraindicated [26, 27]. Considerations for sex in these guidelines apply only to valproate as it is potentially teratogenic and should therefore be avoided when treating women of childbearing age [27]. A 2024 study also suggests an increased risk of neurodevelopmental problems in children conceived while the father was receiving valproate therapy and for three months after stopping treatment [28]. Further sex differences in drug therapy may be related to the clinical characteristics mentioned above, as treatment depends on the polarity and severity of the episode. Women would therefore receive antidepressants more often than men due to their higher likelihood of experiencing bipolar depression. In terms of psychotherapy, men are less likely to seek this type of help, despite evidence that it is equally beneficial for them [29, 30].

In summary, the existing evidence underscores the need for further research into sex differences in the characteristics and treatment of BD. A deeper understanding of these differences is crucial for improving diagnostic accuracy, tailoring treatment plans, reducing side effects and ultimately enhancing patient outcomes. This study aims to contribute to this body of knowledge by examining both established and novel variables related to sex differences in the clinical presentation and treatment of BD.

Based on these insights from prior research, we formulated several hypotheses to be tested in this study: We hypothesise that (1) men experience an earlier onset of affective symptoms, (2) men receive an earlier diagnosis of bipolar disorder, (3) bipolar II disorder is more prevalent among women, (4) women are more likely to suffer from depressive episodes, (5) men are more likely to experience manic episodes, (6) anxiety disorder is primarily found in women, (7) comorbid substance and alcohol use disorders are more common in men and (8) women are more likely to be prescribed antidepressants than men.

## METHODS

*Participants*

The study sample consists of participants in the ongoing BIPFAT/BIPLONG (The Bipolar Disorder in the Longitudinal Course) study at the specialised outpatient centre for BD at the Medical University of Graz, Austria. The BIPLONG study, which has been running since 2012, has collected a wide range of information

about individuals with BD, including clinical, psychological and demographic data. Inclusion criteria require adulthood and the absence of dementia, schizophrenia and severe somatic illness such as cancer, Parkinson's disease or multiple sclerosis. Written informed consent was obtained before participation and the study was approved by the Ethics Review Committee of the Medical University of Graz in accordance with the Declaration of Helsinki (EC-Number: 24-123 ex 11/12) [31].

*Procedure*

For the purpose of this analysis, only data from the first measurement time was used. The diagnosis of BD was determined using the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID) [32]. For the remaining variables a demographic questionnaire was utilised. Patients were euthymic at the time of inclusion of the study. Nevertheless, due to the nature of the disorder not all patients remained stable over time.

The examined clinical characteristics were age of onset, age of diagnosis and diagnostic delay, prevalence of bipolar I and II disorders, polarity of onset, number of manic and depressive episodes, number of episodes per year, number of suicide attempts, alcohol use disorder, other substance use disorder, psychosis history, anxiety disorder, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD). The selected comorbidities were assessed by questionnaire and were not diagnosed at the time of testing. Additionally, medical records from the patients were analysed from both the hospital and the local medical record system, which covers regional inpatient medical records.
Medications at time of testing were categorised as antidepressants in general, selective serotonergic antidepressants, tricyclic antidepressants, other antidepressants, lithium, anticonvulsants in general, valproate separately, typical and atypical antipsychotics and benzodiazepines. The tests did not consider dosage or duration of use. Further testing was performed regarding combination therapy of two or more psychotropic medications, monotherapy with only one drug class and polytherapy with three or more drug classes.

*Statistical Methods*

Logistic regression analyses were conducted to examine sex differences in nominal clinical characteristics and medication variables [33, 34]. In each model, sex (female = 2; male = 1) served as the primary predictor and age was included as a covariate to control for potential confounding. For each model, odds ratios (*OR*) and 95% confidence intervals (*CI*) were reported for sex (female). Continuous clinical variables (e.g. age of onset, number of episodes) were assessed using multiple linear regression with sex and age entered as independent variables [33, 34].

Logistic regression models were checked for linearity of the logit for continuous predictors, model fit (Hosmer–Lemeshow test) and multicollinearity. For typical and atypical antipsychotics, the assumption of linearity of the logit for age was violated. The models were re-estimated using a quadratic transformation of age (age and age$^2$) to account for non-linearity. The Hosmer–Lemeshow test for the valproate model was significant ($p$ = .02), indicating potential model misfit. In addition, the model explained only a small proportion of the variance (Nagelkerke $R^2$ = 0.010). Therefore, the results for valproate should be interpreted with caution.

For linear regression models, standard assumptions were tested and met, including linearity, normality and homoscedasticity of residuals and absence of multicollinearity. For the predictor age, a suspicious non-linear pattern was detected in relation to the variable suicide attempts. Therefore, a quadratic term (age$^2$) was added to the regression model to account for potential curvilinear effects.

As a supplementary analysis, participants were grouped into three age categories: <35 years ($n$=110), 35-50 years ($n$=117) and >50 years ($n$=113). Age ranges were chosen based on previous research in this field. For instance, a large US study of 2019 focusing on comorbidities in bipolar patients employed comparable age stratifications [35]. Furthermore, a prospective study conducted in 2024 defined the age range of 15 to 35 years for young individuals at risk of developing bipolar disorder (BD) [36]. BD occurring in individuals over

the age of 50 is classified as old age bipolar disorder (OABD) [37], which served as the basis for selecting this age cut-off.
A different statistical approach was implemented for the age group analyses, as age was no longer treated as a continuous covariate but instead used to define the strata. Within each age group, sex differences were then assessed using a chi-square-test ($\chi^2$-test) for all nominal variables including drug therapy and most clinical characteristics. For metric variables, namely age of onset and diagnosis, diagnostic delay, number of manic and depressive episodes and suicide attempts the Mann–Whitney U test was applied instead of the *t*-test due to smaller subgroup sample sizes and non-normal distribution of the data.

The level of significance was set at $p < .05$, all hypotheses were tested two-tailed and data analysis was conducted with IBM SPSS Statistics 29.

Significant sex differences in education were considered using the Mann-Whitney U test.

Missing values were considered MCAR (missing completely at random) and were not altered for calculations. Most of these were related to questions concerning polarity of onset (*n*=18), age of onset (*n*=6), age of diagnosis (*n*=12), number of depressive episodes (*n*=55) and number of manic episodes (*n*=53). This was mostly because people did not have a clear recollection of these events and were therefore unable to answer. Four individuals reported a mixed episode as polarity of onset, which was categorised as invalid for calculations, as we only compared depressive and (hypo)manic phases.

**RESULTS**
The sample consists of 340 participants (171 men, 169 women). For the current investigation, data from 349 participants were considered for the analyses. Due to missing data for relevant variables, nine individuals were excluded, yielding a final sample size of $N = 340$.

Table 1 presents the timeline and course of illness, polarity of onset and comorbidities of BD in the total sample. Compared to men, the age of onset was earlier in women *(B = -3.05, 95% CI = [-5.08, -1.02], p = .003)*. OCD was significantly more prevalent in women overall *(OR = 2.24, 95% CI = [2.12, 41.33], p = .003)*. Men experienced manic episodes per year more frequently than women *(B = -.32, 95% CI = [-.59, -.05], p = .019)*.

Table 2 depicts the number of male and female patients treated with each drug class and also compares combination therapy, monotherapy and polytherapy. No statistically significant sex differences were observed.

Tables 3-5 report the detailed statistical results of the regression analyses.

Tables 6-7 display the results of the supplementary analysis stratified by age group. Women aged 35–50 had an earlier age of onset *(U = 1221.50, Z = –2.31, p = .021)*, as did women over 50 *(U = 1090.50, Z = –2.65, p = .008)*. The age of diagnosis was only earlier in women over 50 *(U = 1036.50, Z = -2.85, p = .004)*. OCD was more prevalent in the age groups under 35 *($\chi2(1) = 6.67$, p = .010, $\phi = .25$)* and between 35 and 50 *($\chi2(1) = 5.18$, p = .023, $\phi = .21$)*. PTSD occurred more often in women between 35 and 50 *($\chi2(1) = 5.18$, p = .023, $\phi = .21$)*. In men over 50, the combination of 2 or more drug classes was more prevalent *($\chi2(1) = 5.43$, p = .020, $\phi = .22$)* and antidepressants in general were prescribed more frequently *($\chi2(1) = 4.93$, p = .026, $\phi = .21$)*. Women between 35 and 50 received typical antipsychotics more often *($\chi2(1) = 5.83$, p = .016, $\phi = .22$)*.

**DISCUSSION**
We analysed the sample in terms of clinical characteristics and drug therapy of BD to identify significant differences between male and female participants. We expected to find several sex differences, particularly regarding the course of illness and comorbidities in the former and mood stabilisers in the latter.

We found that the age of onset of BD was earlier in women, while the age of diagnosis was only earlier in women over 50. OCD was significantly more common in women. There was a higher prevalence of manic

episodes per year in men, however no statistically significant difference was found regarding depressive episodes or total number of episodes. In terms of medication, men over 50 were more likely to receive a combination of two or more psychiatric drugs, with antidepressants in general being more common. Women between 35 and 50 were treated with typical antipsychotics more frequently.

A 2020 study found the lifetime prevalence in the general population to be 1.0% in men and 1.5% in women [38]. In our sample of participants with BD we found a prevalence of around 1.2% in men and 10.1% in women, with one in six women under the age of 35 affected. The common co-occurrence of BD and OCD has already been established [39, 40], with one study suggesting that the symptoms of OCD are more likely to be secondary to BD, rather than representing a separate condition [41]. This conclusion can be drawn considering OCD in BD seems to exhibit an episodic course with symptoms worsening in depressive episodes and improving during manic or hypomanic episodes [41, 42]. However, the sex disparity in our findings calls for further exploration of sex-specific factors that may contribute to this comorbidity, particularly as it has important clinical implications. The elevated rates of OCD in women with BD may influence treatment strategies, as pharmacological treatments commonly used to manage OCD, particularly serotonergic drugs, can induce mood instability in individuals with BD [39, 40]. While our sample did not show an increased use of antidepressants, it is important to note that higher doses of SSRIs, which are often used to treat OCD, could have a different impact on mood regulation, particularly in patients with BD. Given that the dosage of SSRIs in OCD treatment is typically higher than in depression treatment, it is possible that even a non-significant increase in antidepressant use could exacerbate mood instability if higher doses were used. Future studies accounting for medication dosage may provide more insight into whether this comorbidity should be managed differently in women with BD, considering the increased risk of manic switches or hypomania associated with serotonergic treatments. Additionally, the findings have implications for psychotherapeutic interventions. Standard psychotherapeutic approaches for BD, such as psychoeducation, cognitive-behavioural therapy (CBT), and interpersonal and social rhythm therapy (IPSRT) [43], may need to be adjusted when OCD is present. Specifically, techniques focused on monitoring and managing prodromal symptoms of BD could potentially exacerbate obsessive-compulsive symptoms. Therefore, clinicians should consider integrating specific interventions targeting OCD symptoms into treatment plans for women with BD, ensuring that the approaches used do not inadvertently reinforce OC behaviours. A more nuanced, tailored approach to both pharmacological and psychotherapeutic interventions could improve outcomes for this population.

Regarding other clinical characteristics, fewer differences were found than we had anticipated. In medicine, age of onset is considered a key factor, as it helps define the likelihood of a disease occurring within certain age ranges, aiding in screening and prevention efforts. Furthermore, this variable can provide insight into the underlying causes of illnesses, with early onset often suggesting a genetic component, which may vary in strength between sexes. As mentioned above, prior studies have reported mixed results on the age of onset [10, 13, 14, 15, 16], generally indicating an earlier onset in men. However, our results contrast with this trend, suggesting the opposite pattern. It is important to note that this information was based on reports of 'first affective symptoms', which could theoretically be caused by a variety of factors other than BD. This could also explain the discrepancy with older age groups reporting a later age of onset, as mental health awareness has increased in recent years [44]. It is likely that people's self-assessment of their emotional state will change as they become more sensitive to the issue, presumably leading them to regard affective symptoms as pathological earlier than before. Age of diagnosis and diagnostic delay show less significant differences, although it is interesting to observe a much lower diagnostic delay among younger people, suggesting a significant improvement in the speed with which people are being diagnosed. Even though polarity of onset shows a tendency towards results found in previous studies, with women having a depressive onset more frequently [16, 20], we did not find a statistically significant difference between sexes. Neither could we confirm that women are more often affected by bipolar II disorder which supports the above-mentioned assumption that bipolar II disorder is equally prevalent in both sexes and that the results of prior studies may be influenced by under-diagnosis of men [6, 7, 8, 9, 10, 11, 12]. One possible reason for this is that men are less likely to seek help for issues related to mental health [45]. A 2020 article on mental health stigma argues that mental illness is often overlooked in men and that they are more likely than women to engage in unhealthy behaviours such as substance use disorder [46]. In addition, bipolar II

disorder has less severe symptoms and an affected person might not even feel ill during hypomanic episodes. The perception of illness likely varies in men and women, driven by differences in societal standards and sex role stereotypes [47]. Friends and family members noticing the change in behaviour during a hypomanic episode might look at it more positively in men, less likely urging them to seek out help. While the total number of episodes and depressive episodes per year did not differ significantly between sexes, men experienced significantly more manic episodes per year, indicating subtle sex-specific variations in the course of illness. This outcome is in line with previous findings [19]. Nonetheless, the number of episodes is only one of many indicators of illness course and may be affected by recall bias, as it relies on self-reported data. The differences in comorbidities observed were consistent with previous studies [10, 12, 16, 17, 20, 21, 22], though none reached statistical significance.

Given the discrepancies between our findings and prior research, it is crucial to explore potential contributing factors. Geographical variations, including differences in genetic predisposition, environmental exposures, and socioeconomic factors, may play a role in shaping the onset and progression of illness [48, 49]. A 2021 study on health inequality in the EU revealed that significant differences exist even between neighbouring countries with comparable economic strength [50]. Additionally, disparities in healthcare systems could affect access to care, potentially leading to delays in diagnosis in certain populations, particularly when comparing European and American health care data [51]. The nature of the outpatient specialised setting in our study may have influenced participant selection, potentially capturing less severe cases. In contrast, many of the study populations referenced in our background research also included inpatients or focused exclusively on them [15, 16, 17, 21]. As a final point, the availability of specialised treatment and the utilisation of outpatient care may have contributed to symptom stabilisation, resulting in a more uniform illness course within our sample.

Medication was overall more similar between the sexes than initially expected, with only a few differences observed in specific subgroups. This could however be attributed to sample size limitations, as trends were generally moving in the direction of expected results. Contrary to findings in the background literature, women received antidepressants less frequently than men, with this finding reaching statistical significance only in those aged over 50. Non-TCA (tricyclic antidepressants)/non-SSRI (selective serotonin reuptake inhibitors) antidepressants like trazodone and mirtazapine had the biggest impact on this outcome. Conversely, a large Swedish study on sex differences in the treatment of bipolar patients, previously mentioned in the introduction, reported that women received antidepressants more often than men [24]. Apart from the difference in scale, this discrepancy may be attributed to differences in prescribing practices and clinical guidelines. The influence of such regional disparities has been documented before; a study on treatment patterns of antidepressants in children and adolescents across Scandinavia revealed significant variations between Sweden, Norway and Denmark regarding treatment [52]. Sweden, in particular, demonstrated the highest overall rate of antidepressant use. Although that study did not specifically examine sex differences, it underscores the importance of regional factors on pharmacological treatment practices.

Previous research has indicated that SSRIs may be less effective in older women due to hormonal interactions, particularly the effects of declining oestrogen levels on serotonin systems [53]. While our study did not show a significant reduction in SSRI prescriptions for women, this finding may suggest that SSRIs could be less efficacious in older women, which could warrant a shift in treatment approaches. However, this hypothesis remains speculative and would benefit from further investigation into medication effectiveness in this demographic. Although it is possible that bipolar disorder (BD) may become less severe with age, thus reducing the need for medication, existing literature suggests the opposite trend. In fact, BD symptoms often worsen with age, with increased somatic comorbidities adding complexity to the treatment regimen [54, 55]. This highlights the necessity for age-adjusted treatment strategies, as the evolving clinical picture of BD in older adults may require tailored therapeutic approaches to address both the progression of mood symptoms and age-related somatic health concerns.

## STRENGTHS & LIMITATIONS

### Strengths

This study investigates various aspects, including the differences in pharmacological treatment of bipolar patients, an area that has received limited attention in prior research. The sample is demographically diverse in terms of age, sex, and educational background, supporting a comprehensive analysis of the research issue. The selected region is underrepresented in the existing literature, providing an opportunity for new insights. The reliability of the interview was strengthened by incorporating real-world clinical data, including medical records from both the hospital and the local medical record system. Additionally, although regression was the primary analytical approach, including supplementary age group analyses using pre-defined categories enhances comparability with previous and future research in the field of bipolar disorder. Lastly, the variety of factors considered offers a helpful starting point for further research and the development of hypotheses.

**Limitations**

Despite its merits, the study is subject to several limitations. The size and diversity of the sample limit the strength of our conclusions and to some extent reduce their applicability on a global scale. Participants were outpatients, which may have influenced the urgency with which they were approached and also potentially represented cases of lesser severity. The sample itself consisted mainly of Austrians of Caucasian ethnicity, which leaves out other ethnic or cultural groups. Since we require the participants to put in time and effort during the interview, there is also selection bias to be considered regarding certain character traits which are supposedly more frequent in less ill patients, namely patience and agreeableness. Also, as there is a large pool of information gathered in the interview, every single variable is more likely to be prone to inaccuracies. The wide range of information collected also limited in-depth exploration of individual variables during the interviews. In addition, the classification of drugs is difficult because there is not yet a widely accepted norm, hence, for example, the rather vague subdivision into 'other antidepressants'. Furthermore, the dosage of medication and duration of use were not regarded, as this would have rendered analysis impossible.

## CONCLUSION

In summary, we found far fewer differences than we had expected based on previous research.
In our sample, women with BD had an earlier age of onset and were significantly more likely to experience OCD, while men were shown to experience manic episodes per year more frequently. In this context, OCD may present differently and can often be viewed more as a symptom of BD rather than a distinct, separate condition. The fact that men had an earlier onset of affective symptoms contradicted our expectations from previous studies, which found the opposite or no difference at all. This suggests that other factors may play a more important role when it comes to the data on the age of onset of BD. Further research in this area is needed to verify our findings, ideally focusing specifically on OCD in bipolar men and women, as sex differences in this comorbidity remain underexplored.

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## STATEMENT OF ETHICS

Written informed consent was obtained before participation and the study was approved by the Ethics Review Committee of the Medical University of Graz in accordance with the Declaration of Helsinki (EC-Number: 24-123 ex 11/12).

## CONFLICT OF INTEREST STATEMENT

Nina Dalkner and Eva Z. Reininghaus were members of the journal's Editorial Board at the time of submission. The authors have no conflicts of interest to declare.

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## AUTHOR CONTRIBUTIONS

Credit roles – Erik Putz: conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – original draft, and writing – review and editing; Elena Schönthaler, PhD: conceptualization, formal analysis, methodology, supervision, and writing – review and editing; Eva Reininghaus, MD: conceptualization, investigation, methodology, project administration, supervision, and writing – review and editing; Nina Dalkner, PhD; Frederike T. Fellendorf, MD; Adelina Tmava-Berisha, MD; Susanne A. Bengesser, MD; Melanie Lenger, PhD; Robert Queissner, MD; Alexander Maget, MD; Alfred Häussl, MSc; Tatjana Stross, MSc: investigation, project administration, and writing – review and editing; Alexander Finner, BSc; Julia Ilic: investigation

**DATA AVAILABILITY STATEMENT**

The data supporting the findings of this study are not publicly available due to containing information that could compromise the privacy of the research participants, but are available from the corresponding author Dr Elena Schönthaler (elena.schoenthaler@medunigraz.at) upon reasonable request.

**REFERENCES**

1. The Lancet Psychiatry. Sex and gender in psychiatry. The Lancet Psychiatry. 2016;3(11):999.

2. Boyd A, Van de Velde S, Vilagut G, et al. Gender differences in mental disorders and suicidality in Europe: results from a large cross-sectional population-based study. J Affect Disord. 2015;173:245-254.

3. European Institute for Gender Equality. Gender Equality Index 2021: Health. 2021. Accessed June 15, 2024. Available from: https://eige.europa.eu/publications-resources/toolkits-guides/gender-equality-index-2021-report/gender-differences-mental-disorders-begin-early-life

4. Jacobi F, Höfler M, Siegert J, et al. Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: the Mental Health Module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). Int J Methods Psychiatr Res. 2014;23(3):304-319.

5. Kramer MD, Krueger RF, Hicks BM. The role of internalizing and externalizing liability factors in accounting for gender differences in the prevalence of common psychopathological syndromes. Psychol Med. 2008;38(1):51-61.

6. Liu G, Kong L, Baweja R, Ba D, Saunders EFH. Gender disparity in bipolar disorder diagnosis in the United States: A retrospective analysis of the 2005-2017 MarketScan Commercial Claims database. Bipolar Disord. 2022;24(1):48-58.

7. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA. 1996;276(4):293-299.

8. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication [published correction appears in Arch Gen Psychiatry. 2007 Sep;64(9):1039]. Arch Gen Psychiatry. 2007;64(5):543-552.

9. Nierenberg AA, Akiskal HS, Angst J, et al. Bipolar disorder with frequent mood episodes in the national comorbidity survey replication (NCS-R). Mol Psychiatry. 2010;15(11):1075-1087.

10. Arnold LM. Gender differences in bipolar disorder. Psychiatr Clin North Am. 2003;26(3):595-620.

11. Baldassano CF, Marangell LB, Gyulai L, et al. Gender differences in bipolar disorder: retrospective data from the first 500 STEP-BD participants. Bipolar Disord. 2005;7(5):465-470.

12. Barnes C, Mitchell P. Considerations in the management of bipolar disorder in women. Aust N Z J Psychiatry. 2005;39(8):662-673.

13. Kawa I, Carter JD, Joyce PR, et al. Gender differences in bipolar disorder: age of onset, course, comorbidity, and symptom presentation. Bipolar Disord. 2005;7(2):119-125.

14. Hendrick V, Altshuler LL, Gitlin MJ, Delrahim S, Hammen C. Gender and bipolar illness. J Clin Psychiatry. 2000;61(5):393-397.

15. Kennedy N, Boydell J, Kalidindi S, et al. Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. Am J Psychiatry. 2005;162(2):257-262.

16. Azorin JM, Belzeaux R, Kaladjian A, et al. Risks associated with gender differences in bipolar I disorder. J Affect Disord. 2013;151(3):1033-1040.

17. Buoli M, Cesana BM, Dell'Osso B, et al. Gender-related differences in patients with bipolar disorder: a nationwide study. CNS Spectr. 2019;24(6):589-596.

18. Altshuler LL, Kupka RW, Hellemann G, et al. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. Am J Psychiatry. 2010;167(6):708-715.

19. Pillai M, Munoli RN, Praharaj SK, Bhat SM. Gender Differences in Clinical Characteristics and Comorbidities in Bipolar Disorder: a Study from South India. Psychiatr Q. 2021;92(2):693-702.

20. Nivoli AM, Pacchiarotti I, Rosa AR, et al. Gender differences in a cohort study of 604 bipolar patients: the role of predominant polarity. J Affect Disord. 2011;133(3):443-449.

21. Patel RS, Virani S, Saeed H, Nimmagadda S, Talukdar J, Youssef NA. Gender Differences and Comorbidities in U.S. Adults with Bipolar Disorder. Brain Sci. 2018;8(9):168.

22. Miquel L, Usall J, Reed C, et al. Gender differences in outcomes of acute mania: a 12-month follow-up study. Arch Womens Ment Health. 2011;14(2):107-113.

23. Hu FH, Jia YJ, Zhao DY, et al. Gender differences in suicide among patients with bipolar disorder: A systematic review and meta-analysis. J Affect Disord. 2023;339:601-614.

24. Karanti A, Bobeck C, Osterman M, et al. Gender differences in the treatment of patients with bipolar disorder: a study of 7354 patients. J Affect Disord. 2015;174:303-309.

25. Diflorio A, Jones I. Is sex important? Gender differences in bipolar disorder. Int Rev Psychiatry. 2010;22(5):437-452.

26. Shah N, Grover S, Rao GP. Clinical Practice Guidelines for Management of Bipolar Disorder. Indian J Psychiatry. 2017 Jan;59(Suppl 1):S51-S66.

27. Hasler, G., Preisig, M., Müller, Th.J. et al.: Bipolare Störungen: Update 2019. Swiss Medical Forum. 2019;19(33-34):537-546.

28. Wise J. Valproate: Men are advised to use contraception owing to risk of neurodevelopmental disorders in children. BMJ. 2024;386:q1957.

29. Riffer, F., Knopp, M., Burghardt, J. et al. Geschlechtsspezifische Unterschiede in der psychotherapeutischen Versorgung. Psychotherapeut 66, 511–517 (2021).

30. Schneider D, Zobel I, Härter M, Kech S, Berger M, Schramm E. Wirkt die Interpersonelle Psychotherapie besser bei Frauen als bei Männern? Ergebnisse einer randomisierten, kontrollierten Studie. Psychotherapie – Psychosomatik – Medizinische Psychologie 2008; 58: 23–31.

31. National Library of Medicine. BIPLONG - The Bipolar Disorder in the Longitudinal Course (BIPLONG). 2021. Available from: https://www.clinicaltrials.gov/study/NCT05064995

32. Wittchen, H.-U., Wunderlich, U., Gruschwitz, S., & Zaudig, M. (1997). SKID I. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. Interviewheft und Beurteilungsheft. Eine deutschsprachige, erweiterte Bearb. d. amerikanischen Originalversion des SKID I. Göttingen: Hogrefe.

33. Field A. Discovering Statistics Using IBM SPSS Statistics. 4th ed. Sage Publications; 2013.

34. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression. 3rd ed. Wiley; 2013.

35. Hossain S, Mainali P, Bhimanadham NN, Imran S, Ahmad N, Patel RS. Medical and Psychiatric Comorbidities in Bipolar Disorder: Insights from National Inpatient Population-based Study. Cureus. 2019;11(9):e5636.

36. Martini J, Bröckel KL, Leopold K, et al. Young people at risk for developing bipolar disorder: Two-year findings from the multicenter prospective, naturalistic Early-BipoLife study. Eur Neuropsychopharmacol. 2024;78:43-53.

37. Beunders AJM, Orhan M, Dols A. Older age bipolar disorder. Curr Opin Psychiatry. 2023;36(5):397-404.

38. Fawcett EJ, Power H, Fawcett JM. Women Are at Greater Risk of OCD Than Men: A Meta-Analytic Review of OCD Prevalence Worldwide. J Clin Psychiatry. 2020;81(4):19r13085.

39. Amerio A, Odone A, Marchesi C, Ghaemi SN. Treatment of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review. J Affect Disord. 2014;166:258-263.

40. Amerio A, Maina G, Ghaemi SN. Updates in treating comorbid bipolar disorder and obsessive-compulsive disorder: A systematic review. J Affect Disord. 2019;256:433-440.

41. Amerio A, Odone A, Liapis CC, Ghaemi SN. Diagnostic validity of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review. Acta Psychiatr Scand. 2014;129(5):343-358.

42. de Filippis R, Aguglia A, Costanza A, et al. Obsessive-Compulsive Disorder as an Epiphenomenon of Comorbid Bipolar Disorder? An Updated Systematic Review. J Clin Med. 2024;13(5):1230.

43. Novick DM, Swartz HA. Evidence-Based Psychotherapies for Bipolar Disorder. Focus (Am Psychiatr Publ). 2019;17(3):238-248.

44. Foulkes L, Andrews JL. Are mental health awareness efforts contributing to the rise in reported mental health problems? A call to test the prevalence inflation hypothesis. New Ideas in Psychology. 2023. Available from https://www.sciencedirect.com/science/article/pii/S0732118X2300003X

45. Sagar-Ouriaghli I, Godfrey E, Bridge L, Meade L, Brown JSL. Improving Mental Health Service Utilization Among Men: A Systematic Review and Synthesis of Behavior Change Techniques Within Interventions Targeting Help-Seeking. Am J Mens Health. 2019 May-Jun;13(3):1557988319857009.

46. Chatmon BN. Males and Mental Health Stigma. Am J Mens Health. 2020;14(4):1557988320949322.

47. Montero HA. Bipolar symptoms in Men: 10 signs to look for (J. Kim, Ed.). 2022. Accessed August 9, 2024. Available from: https://www.healthcentral.com/condition/bipolar-disorder/bipolar-symptoms-in-men

48. Craddock N, Sklar P. Genetics of bipolar disorder. Lancet. 2013;381(9878):1654-1662.

49. Menculini G, Balducci PM, Attademo L, Bernardini F, Moretti P, Tortorella A. Environmental Risk Factors for Bipolar Disorders and High-Risk States in Adolescence: A Systematic Review. Medicina (Kaunas). 2020;56(12):689.

50. Mazeikaite G, O'Donoghue C, Sologon DM. What drives cross-country health inequality in the EU? Unpacking the role of socio-economic factors. Soc Indic Res. 2021;155(1):117-155.

51. Blumenthal D, Schneider EC, Tikkanen R, et al. Mirror, Mirror 2024: A Portrait of the Failing U.S. Health System - Comparing Performance in 10 Nations. The Commonwealth Fund; 2024.

52. Rasmussen L, Jensen PB, Reutfors J, et al. Treatment patterns of antidepressants in children and adolescents in Scandinavia. Eur Child Adolesc Psychiatry. 2025;34(1):159-167.

53. LeGates TA, Kvarta MD, Thompson SM. Sex differences in antidepressant efficacy. Neuropsychopharmacology. 2019;44(1):140-154.

54. Coryell W, Fiedorowicz J, Solomon D, Endicott J. Age transitions in the course of bipolar I disorder. Psychol Med. 2009;39(8):1247-1252.

55. Arnold I, Dehning J, Grunze A, Hausmann A. Old Age Bipolar Disorder-Epidemiology, Aetiology and Treatment. Medicina (Kaunas). 2021;57(6):587.

**Table 1.**

*Timeline of Illness, Polarity of Onset, Course of Illness and Comorbidities of Bipolar Disorder in entire sample*

| Clinical Characteristics | All age groups (*n*=340) | |
|---|---|---|
| | m | f |
| | 171 | 169 |
| | Timeline of illness (in years) | |
| Age of onset[a] *M(SD)* | **26.4 (12.1)*** | **22.7 (9.9)*** |
| Age of diagnosis[a] *M(SD)* | 37.0 (13.7) | 34.2 (11.9) |
| Diagnostic delay[a] *M(SD)* | 10.6 (11.7) | 11.5 (10.6) |
| | Polarity of onset in % (*n*) of m/f | |
| Depressive first episode | 63.7 (109) | 73.4 (124) |
| Manic first episode | 26.3 (45) | 23.7 (40) |
| | Diagnosis in % (*n*) of m/f | |
| Bipolar I | 65.5 (112) | 62.1 (105) |
| Bipolar II | 32.7 (56) | 36.7 (62) |
| | Course of illness | |
| Depressive episodes in total[a] *Med* | 8.0 | 8.0 |
| Manic episodes in total[a] *Med* | 5.0 | 4.0 |
| Depressive episodes per illness year[a] *Med* | .50 | .48 |
| Manic episodes per illness year[a] *Med* | **.35*** | **.30*** |
| Total episodes per illness year[a] *Med* | .98 | .90 |
| Suicide attempts *M(SD)* | .42 (.97) | .49 (1.04) |
| | Comorbidities in % (*n*) of m/f | |
| Alcohol use disorder | 17.5 (30) | 11.8 (20) |
| Other SUD | 13.5 (23) | 8.3 (14) |
| Psychosis in past | 14.6 (25) | 19.5 (33) |
| Anxiety disorder | 16.4 (28) | 19.5 (33) |
| OCD | **1.2 (2)*** | **10.1 (17)*** |
| PTSD | 2.3 (4) | 4.7 (8) |

*Note.* m = male; f = female; *Med* = median; ; *M(SD)* = mean with standard deviation; SUD = substance use disorder; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress syndrome
*significant difference with $p < .05$
**significant difference with $p < .001$
[a]significant number of missing values (polarity of onset (*n*=18), age of onset (*n*=6), age of diagnosis (*n*=12), number of depressive episodes (*n*=55) and number of manic episodes (*n*=53))

**Table 2.**

*Drug class and Type of Drug Therapy in entire sample*

| Medication | All age groups (*n*=340) | | |
|---|---|---|---|
| | m% (*n*) | f% (*n*) | *n'* |
| | Drug class | | |
| ADs in general | 64.9 (111) | 58.0 (98) | 209 |
| SSRIs | 31.0 (53) | 25.4 (43) | 96 |
| TCAs | 4.1 (7) | 4.7 (8) | 15 |
| Other ADs[a] | 43.9 (75) | 36.1 (61) | 136 |
| Lithium | 35.7 (61) | 28.4 (48) | 109 |
| Anticonvulsants[b] | 28.1 (48) | 34.9 (59) | 107 |
| Valproate | 15.8 (27) | 13.0 (22) | 49 |
| Typical APs | 15.2 (26) | 23.1 (39) | 65 |
| Atypical APs | 59.1 (101) | 64.5 (109) | 210 |
| Benzodiazepines | 8.2 (14) | 10.1 (17) | 31 |
| | Type of drug therapy | | |
| Combination therapy | 83.0 (142) | 77.5 (131) | 273 |
| Monotherapy | 16.4 (28) | 21.3 (36) | 64 |
| Polytherapy | 39.8 (68) | 37.9 (64) | 132 |

*Note.* m% = percentage of male participants; f% = percentage of female participants; *n'* = total number of participants receiving treatment; ADs = antidepressants; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; APs = antipsychotics.
*significant difference with $p < .05$
**significant difference with $p < .001$
[a]including trazodone, venlafaxine, duloxetine, milnacipran, mirtazapine, reboxetine, agomelatine, tianeptine, bupropion
[b]including valproate, lamotrigine, pregabalin, oxcarbazepine, levetiracetam, carbamazepine

**Table 3.**

*Linear regression results of Clinical Characteristics with sex (female) as predictor in entire sample (n=340)*

| Outcome (yes/no) | *B* | *SE* | *t* | *p* | *95% CI* for *B* |
|---|---|---|---|---|---|
| Age of onset | **-3.05*** | **1.03*** | **-2.96*** | **.003*** | **[-5.08, -1.02]*** |
| Age of diagnosis | -1.59 | .92 | -1.73 | .086 | [-3.41, .22] |
| Diagnostic delay | 1.31 | 1.16 | 1.13 | .259 | [-.97, 3.59] |
| Depressive episodes in total | .36 | 1.89 | .19 | .850 | [-3.37, 4.08] |
| Manic episodes in total | -2.01 | 1.75 | -1.15 | .252 | [-5.45, 1.44] |
| Depressive episodes per illness year | -.24 | -.24 | -1.58 | .114 | [-.54, .06] |
| Manic episodes per illness year | **-.32*** | **.14*** | **-2.35*** | **.019*** | **[-.59, -.05]*** |
| Total episodes per illness year | -.46 | .25 | -1.85 | .065 | [-.96, .03] |
| Suicide attempts | .07 | .11 | .61 | .542 | [-.15, .29] |

*Note.* Linear regression models were adjusted for age. Only sex (female) was included as a predictor in this table. Sex coded as 1 = male, 2 = female. *B* = unstandardized regression coefficient; *SE* = standard error; *CI* = confidence interval.
*significant difference with $p < .05$
**significant difference with $p < .001$

**Table 4.**

*Logistic regression results of Clinical Characteristics with sex (female) as predictor in entire sample (n=340)*

| Outcome (yes/no) | *B (SE)* | *p* | *OR [95% CI]* |
|---|---|---|---|
| Depressive first episode[a] | -.25 (.25) | 0.333 | .78 [.48, 1.29] |
| Bipolar I[b] | .17 (.23) | 0.473 | 1.18 [.75, 1.17] |
| Alcohol use disorder | -.46 (.31) | 0.141 | .63 [.34, 3.71] |
| Other SUD | -.60 (.36) | 0.099 | .55 [.27, 1.12] |
| Psychosis in past | .36 (.29) | 0.215 | 1.44 [.81, 2.54] |
| Anxiety disorder | .19 (.29) | 0.505 | 1.21 [.69, 2.11] |
| OCD | **2.24 (.76)*** | **0.003*** | **9.36 [2.12, 41.33]*** |
| PTSD | .72 (.62) | 0.247 | 2.06 [.61, 6.97] |

*Note.* Logistic regression models were adjusted for age. Only sex (female) was included as a predictor in this table. *OR* = odds ratio; *CI* = confidence interval.
*significant difference with $p < .05$
**significant difference with $p < .001$
[a]other outcome being Manic first episode
[b]other outcome being Bipolar II

**Table 5.**

*Logistic regression results of Drug class and Type of Drug Therapy with sex (female) as predictor in entire sample (n=340)*

| Outcome (yes/no) | *B (SE)* | *p* | *OR [95% CI]* |
|---|---|---|---|
| ADs in general | -.31 (.22) | .174 | .74 [.48, 1.14] |
| SSRIs | -.31 (.24) | .211 | .74 [.46, 1.19] |
| TCAs | .26 (.54) | .631 | 1.30 [.45, 3.71] |
| Other ADs[a] | -.33 (.22) | .134 | .72 [.46, 1.11] |
| Lithium | -.33 (.23) | .156 | .72 [.45, 1.14] |
| Anticonvulsants[b] | .34 (.24) | .146 | 1.41 [.89, 2.2] |
| Valproate | -.20 (.31) | .524 | .82 [.45, 1.51] |
| Typical APs | .51 (.28) | .070 | 1.67 [.96, 2.90] |
| Atypical APs | .19 (.23) | .398 | 1.21 [.78, 1.88] |
| Benzodiazepines | .22 (.38) | .566 | 1.24 [.59, 2.61] |
| Combination therapy | -.36 (.28) | .192 | .70 [.41, 1.20] |
| Monotherapy | .34 (.28) | .223 | 1.41 [.81, 2.44] |
| Polytherapy | -.09 (.22) | .691 | .92 [.59, 1.42] |

*Note.* Logistic regression models were adjusted for age. Only sex (female) was included as a predictor in this table. *OR* = odds ratio; *CI* = confidence interval.
*significant difference with $p < .05$
**significant difference with $p < .001$
[a]including trazodone, venlafaxine, duloxetine, milnacipran, mirtazapine, reboxetine, agomelatine, tianeptine, bupropion
[b]including valproate, lamotrigine, pregabalin, oxcarbazepine, levetiracetam, carbamazepine

**Table 6.**

*Timeline of Illness, Polarity of Onset, Course of Illness and Comorbidities of Bipolar Disorder divided by age*

| Clinical Characteristics | Age under 35 (*n*=110) | | Age 35 to 50 (*n*=117) | | Age over 50 (*n*=113) | |
|---|---|---|---|---|---|---|
| | m | f | m | f | m | f |
| | 50 | 60 | 65 | 52 | 56 | 57 |
| | | | Timeline of illness in years | | | |
| Age of onset[a] *M(SD)* | 17.8 (5.6) | 18.1 (5.0) | **25.8* (9.4)** | **22.1* (9.0)** | **34.9* (13.5)** | **28.2* (11.8)** |
| Age of diagnosis[a] *M(SD)* | 23.8 (6.0) | 24.4 (4.9) | 36.7 (8.2) | 35.0 (8.8) | **49.2* (12.6)** | **44.0* (11.1)** |
| Diagnostic delay[a] *M(SD)* | 6.0 (5.9) | 6.3 (5.6) | 10.4 (9.9) | 13.2 (10.4) | 15.1 (15.4) | 15.5 (12.6) |
| | | | Polarity of onset in % of m/f of age group | | | |
| Depressive first episode | 64.0 | 78.3 | 61.5 | 69.2 | 66.1 | 71.9 |
| Manic first episode | 28.0 | 16.7 | 29.2 | 28.8 | 21.4 | 26.3 |
| | | | Diagnosis in % of m/f of age group | | | |
| Bipolar I | 58.0 | 65.0 | 69.2 | 61.5 | 67.9 | 59.6 |
| Bipolar II | 40.0 | 31.7 | 29.2 | 38.5 | 30.4 | 40.4 |
| | | | Course of illness | | | |
| Depressive episodes in total[a] *Med* | 5 | 5.5 | 10 | 7 | 9 | 10.5 |
| Manic episodes in total[a] *Med* | 4 | 3 | 5 | 4 | 7.5 | 5 |
| Depressive episodes per illness year[a] *Med* | .79 | .76 | .48 | .35 | .39 | .34 |
| Manic episodes per illness year[a] *Med* | .58 | .41 | .34 | .25 | .29 | .24 |
| Total episodes per illness year[a] *Med* | 1.29 | 1.24 | .90 | .56 | .84 | .61 |
| Suicide attempts *M(SD)* | .37 (.60) | .36 (.55) | .38 (.64) | .49 (.82) | .52 (1.46) | .63 (1.51) |
| | | | Comorbidities in % of age group; (*n*) for significant results | | | |
| Alcohol use disorder | 14.0 | 15.0 | 20.0 | 9.6 | 17.9 | 10.5 |
| Other SUD | 22.0 | 10.0 | 10.8 | 9.6 | 8.9 | 5.3 |
| Psychosis in past | 16.0 | 21.7 | 13.8 | 15.4 | 14.3 | 21.1 |
| Anxiety disorder | 12.0 | 26.7 | 20.0 | 21.2 | 16.1 | 10.5 |
| OCD | **2.0 (1)*** | **16.7 (10)*** | **0*** | **7.7 (4)*** | 1.8 | 5.3 |
| PTSD | 4.0 | 5.0 | **0*** | **7.7 (4)*** | 3.6 | 1.8 |

*Note.* m = male; f = female; *Med* = median; ; *M(SD)* = mean with standard deviation; SUD = substance use disorder; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress syndrome
*significant difference with $p < .05$
**significant difference with $p < .001$

**Table 7.**

*Drug class and Type of Drug Therapy divided by age groups*

| Medication | Age under 35 (*n*=110) | | | Age 35 to 50 (*n*=117) | | | Age over 50 (*n*=113) | | |
|---|---|---|---|---|---|---|---|---|---|
| | m% | f% | *n'* | m% | f% | *n'* | m% | f% | *n'* |
| | | | | Drug class | | | | | |
| ADs in general | 56.0 | 71.7 | 71 | 67.7 | 51.9 | 71 | **69.6*** | **49.1*** | 67 |
| SSRIs | 34.0 | 31.7 | 36 | 33.8 | 21.2 | 33 | 25.0 | 22.8 | 27 |
| TCAs | 2.0 | 1.7 | 2 | 3.1 | 5.8 | 5 | 7.1 | 7.0 | 8 |
| Other ADs[a] | 38.0 | 46.7 | 47 | 46.2 | 30.8 | 46 | 46.4 | 29.8 | 43 |
| Lithium | 34.0 | 23.3 | 31 | 40.0 | 30.8 | 42 | 32.1 | 31.6 | 36 |
| Anticonvulsants[b] | 24.0 | 36.7 | 34 | 21.5 | 36.5 | 33 | 39.3 | 31.6 | 40 |
| Valproate | 18.0 | 8.3 | 14 | 12.3 | 13.5 | 15 | 17.9 | 17.5 | 20 |
| Typical Aps | 18.0 | 10.0 | 15 | **16.9*** | **36.5*** | 30 | 10.7 | 24.6 | 20 |
| Atypical APs | 58.0 | 68.3 | 70 | 64.6 | 65.4 | 76 | 53.6 | 59.6 | 64 |
| Benzodiazepines | 8.0 | 10.0 | 10 | 9.2 | 11.5 | 12 | 7.1 | 8.8 | 9 |
| | | | | Type of drug therapy | | | | | |
| Combination therapy | 80.0 | 80.0 | 88 | 80.0 | 80.8 | 94 | **89.3*** | **71.9*** | 91 |
| Monotherapy | 16.0 | 18.3 | 19 | 18.5 | 19.2 | 22 | 14.3 | 26.3 | 23 |
| Polytherapy | 34.0 | 40.0 | 41 | 47.7 | 46.2 | 55 | 35.7 | 28.1 | 36 |

*Note.* m% = percentage of male participants within age group; f% = percentage of female participants within age group; *n'* = total number of participants receiving treatment within age group; ADs = antidepressants; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; APs = antipsychotics.
*significant difference with $p < .05$
**significant difference with $p < .001$
[a]including trazodone, venlafaxine, duloxetine, milnacipran, mirtazapine, reboxetine, agomelatine, tianeptine, bupropion
[b]including valproate, lamotrigine, pregabalin, oxcarbazepine, levetiracetam, carbamazepine