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## The course of bipolar disorder as a function of the presence and sequence of onset of comorbid alcohol use disorders in outpatients attending the Fundamental Advanced Centres of Expertise

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1 **The course of bipolar disorder as a function of the presence and sequence of onset of**  
2 **comorbid alcohol use disorders in outpatients attending the Fundamental Advanced**  
3 **Centres of Expertise**

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43 **Abstract**

44 *Objectives:* The comorbidity of alcohol use disorder (AUD) and bipolar disorder (BD) has  
45 been repeatedly associated with poorer clinical outcomes than BD without AUD. We aimed  
46 to extend these findings by focusing on the characteristics associated with the sequence of  
47 onset of BD and AUD. *Methods:* 3,027 outpatients from the Fundamental Advanced Centres  
48 of Expertise were ascertained for BD-1, BD-2 and AUD diagnoses, including their respective  
49 ages at onset (AAOs, N =2,804). We selected the variables associated with both the presence  
50 and sequence of onset of comorbid AUD using bivariate analyses corrected for multiple  
51 testing to enter a binary regression model with the sequence of onset of BD and AUD as the  
52 dependent variable (AUD first - which also included 88 same-year onsets, vs. BD first).  
53 *Results:* BD patients with comorbid AUD showed more severe clinical profile than those  
54 without. Compared to BD-AUD (N =269), AUD-BD (N =276) was independently associated  
55 with a higher AAO of BD (OR =1.1,  $p < 0.001$ ), increased prevalence of comorbid cannabis use  
56 disorder (OR =2.8,  $p < 0.001$ ) a higher number of (hypo)manic/mixed BD episodes per year of  
57 bipolar illness (OR =3,  $p < 0.01$ ). *Limitations:* The transversal design prevents from drawing  
58 causal conclusions. *Conclusion:* Increased severity of BD with AUD compared to BD alone did  
59 not differ according to the sequence of onset. A few differences, though, could be used to  
60 better monitor the trajectory of patients showing either one of these disorders.

61

62 **Keywords:** bipolar disorder; alcohol use disorder; dual diagnosis; comorbidity; sequence of  
63 onset; clinical trajectory

64

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## 67        **1. Introduction**

68    Bipolar disorder (BD) is a chronic and debilitating mental illness that affects ~2% of the  
69    population worldwide (McIntyre et al., 2020). It is the 16<sup>th</sup> leading cause of disability (Ferrari  
70    et al., 2016) and is associated with ~10 years of life lost (Ferrari et al., 2016). Alcohol use  
71    disorders (AUDs) are the second most common addiction found in BD individuals after  
72    tobacco use disorders (Blanco et al., 2017). BD increases the incidence of AUD as soon as  
73    during adolescence (Birmaher et al., 2014), and individuals with AUD also show increased  
74    incidence of BD (Bukh et al., 2016). According to numerous studies on the comorbidity  
75    between BD and AUD, this condition is overall associated with poorer clinical outcomes than  
76    BD alone, especially related to a more severe course of bipolar illness. More precisely, the  
77    presence of comorbid AUD has been associated with increased risk of attempted and  
78    completed suicide (SA) (Østergaard et al., 2017), increased number of depressive episodes  
79    (Janiri et al., 2017), delayed remission from mood episodes (Farren et al., 2013) and  
80    increased affective lability (Lagerberg et al., 2017).

81    A common clinical assumption is that people with BD drink alcohol to self-medicate anxiety  
82    (Baigent, 2012), depressive symptoms (Meyer et al., 2012), irritability during mixed episodes  
83    (Maremmani et al., 2012) and promote sleep (Lorberg et al., 2010), but also to further  
84    increase mood during (hypo)manic (Meyer et al., 2012). The few longitudinal studies that  
85    have been conducted so far have confirmed that the recovery from mood episodes is slower  
86    in BD-AUD than in BD alone (Gold et al., 2018) and that AUD are preferentially associated  
87    with bipolar depressive episodes (Simhandl et al., 2015), but rather argue against the self-  
88    medication hypothesis in showing that increased alcohol use often precedes BD relapses  
89    (Baethge et al., 2008; Strakowski et al., 2005). Interestingly in the study from Strakowski et  
90    al., BD patients for whom AUD preceded BD had a quicker recovery from acute mood

91 episodes than both the BD-AUD and the no AUD groups, highlighting the importance of the  
92 sequence of onset of BD and AUD in BD-AUD. A larger transversal study of 1090 BD-type 1  
93 patients recruited after a manic episode (Azorin et al., 2017) reported that the group with  
94 AUD beginning before BD (AUD-BD) showed higher rates of comorbid non-psychiatric,  
95 anxiety and addictive disorders with a more frequent depressive polarity at onset than the  
96 group where BD occurred before AUD (BD-AUD). The AUD-BD group was further  
97 characterized by an irritable temperament.

98 The observed impact of lifetime AUD and its sequence of onset with BD on suicidal risk may  
99 be related to factors modified by the comorbidity of AUD in BD (Hunt et al., 2016), such as  
100 gender, bipolar subtype, impulsiveness (Etain et al., 2013), affective lability (Ducasse et al.,  
101 2017), childhood trauma (Agnew-Blais and Danese, 2016), other comorbid addictions, or  
102 decreased adherence to medication (Belzeaux et al., 2015). Extending the findings regarding  
103 the relative onsets of BD and AUD using a large, representative and extensively  
104 characterized BD sample could further our understanding of comorbid patients' trajectories.  
105 This would pave the way to develop targeted prevention strategies aimed at individuals with  
106 either BD or AUD, who are at higher risk of developing the comorbid disorder.

107 In order to identify risk factors differentiating bipolar disorder with vs. without alcohol use  
108 disorder as a function of their sequence of onset, we analysed data from 2,804 outpatients  
109 enrolled in the French network Fondamental Advanced Centres of Expertise – Bipolar  
110 Disorders (FACE-BD). We hypothesized (i) that the presence of alcohol use disorder would be  
111 associated with more severe clinical profiles of bipolar disorder compared to bipolar  
112 disorder without alcohol use disorder but that (ii) several of these risk factors would depend  
113 on the sequence of onset between bipolar disorder and alcohol use disorder.

114

115

## 116 **2. Material and methods**

### 117 *2.1. Clinical sample*

118 De-identified patient-level data from the FACE-BD national network were used for the  
119 current study. The study was carried out in accordance with ethical principles for medical  
120 research involving humans (WMA, Declaration of Helsinki). The assessment protocol was  
121 approved by the relevant ethical review board (CPP-Ile de France IX, January 18th, 2010).  
122 Although the committee waived the requirement for written informed consent, the patients  
123 received a letter informing them of the study and asking whether they agreed to participate.  
124 Briefly, patients with difficult-to-treat or difficult-to-diagnose BD are referred to one of the  
125 12 centres of the network by general practitioners or psychiatrists. Once BD is ascertained,  
126 patients undergo a two-days evaluation of their sociodemographic and clinical history by  
127 trained nurses, psychologists and M.D.s in order to provide the treating physician and the  
128 patient with adequate feedback regarding personalized therapeutic/diagnostic guidance.  
129 The FACE-BD network procedures have been described in details elsewhere (Henry et al.,  
130 2011). For the current study, we analysed data from 3,027 outpatients with ascertained BD  
131 type 1 or 2; 2,804 of whom had available AUD diagnosis and AAOs of both BD and AUD,  
132 enrolled between 2009 and August 2020 (date of data extraction from the centralized data  
133 management system).

134 We focused on subsamples according to the presence and sequence of onset of BD and  
135 AUD: “no AUD”, “BD-AUD” or “AUD-BD”. The “no AUD” group was defined by the absence of  
136 lifetime AUD, the “BD-AUD” group by BD preceding AUD, the “AUD-BD” by AUD preceding  
137 BD and the “BAUD” group by both disorders occurring the same year.

### 138 *2.2. Assessments*

139 Throughout the manuscript, the term substance use disorder (SUD) will refer to the  
140 presence of abuse or dependence according to the *Diagnostic and Statistical Manual for*  
141 *Mental disorders - fourth edition, text revised (DSM-IV, TR)* criteria (American Psychiatric  
142 Association, 2000). Data regarding age, gender, educational attainment (years since  
143 elementary school) and current living arrangement (living with partner, yes/no) and  
144 employment status (currently employed >50%, yes/no) were selected for the current study.  
145 History of BD and psychiatric comorbidity, including SUDs, was collected by the *Structured*  
146 *Clinical Interview for DSM, axis I of the Diagnostic and Statistical Manual for Mental*  
147 *Disorders, fourth edition (SCID-IV)* (Kübler, 2013), which has shown fair to good reliability in  
148 SUD samples (Kranzler et al., 1996). Age at onset (AAO) of BD was defined as the age, at  
149 which participants reported having their first major mood episode, which was further used  
150 to compute BD duration (age at interview – AAO BD). AAO of AUD was considered the age,  
151 at which participants first fulfilled DSM-IV criteria for AUD. Polarity at onset referred to the  
152 same first BD episode, further dichotomized into “up” ((hypo)manic or mixed] vs. “down”  
153 (depressive) categories. The number of mood episodes was also collected, dichotomized on  
154 the same basis, and used as a rate per year (density of episodes). The presence of psychotic  
155 symptoms during any mood episode occurring during the course of BD (hereafter termed  
156 “history of psychosis”) was also collected.

157 Comorbid anxiety disorders, tobacco smoking status (never, former and current smokers)  
158 and SUDs were considered on a lifetime basis. Disorders related to cocaine and other  
159 stimulants were pooled into a “Stimulant use disorder” (StimUD) variable if any was present.  
160 Current functioning was assessed by the *Functional Assessment Short Test (FAST)* (Rosa et  
161 al., 2007) that was shown to reliably assess daily impairment in BD individuals. It consists of  
162 a composite measure of six specific areas of functioning, of which we retained the total

163 score and the cognitive functioning subscale, due to the well-established links between AUD  
164 and cognitive impairment in the general population (Koch et al., 2019). Higher scores  
165 indicate poorer functioning. Current depressive symptoms were assessed with the  
166 *Montgomery-Asberg Depression Rating Scale* (MADRS) (Montgomery and Asberg, 1979) and  
167 current manic symptoms were measured with the *Young Mania Rating Scale* (YMRS) (Young  
168 et al., 1978). Non-psychiatric medical history was collected as free text completed by  
169 standardized questions about the main categories of diseases. For the current study, we  
170 used dummy variables “any vs. none” non-psychiatric conditions from the following  
171 categories: any, cardiovascular (hypertension, infarction, coronary disease, arrhythmia,  
172 other), digestive (liver cirrhosis, gastric ulcer, drug hepatitis) conditions and dyslipidemia.  
173 Body mass index (BMI) was calculated as weight (kg) / height (M<sup>2</sup>) and waist circumference  
174 was measured in centimeters as a marker of abdominal obesity, following a standard  
175 procedure (“WHO | Waist circumference and waist–hip ratio,” 2011). Both were actually  
176 measured at the baseline visit. Trait impulsiveness was measured using the *Baratt*  
177 *Impulsiveness Scale - 10th version, BIS10* and affective lability by the *Affective lability scale,*  
178 *ALS* (Baylé et al., 2000). Childhood trauma was assessed by the *Childhood Trauma*  
179 *Questionnaire – short form, CTQ* (Bernstein et al., 2003), using only the total score in order  
180 to limit multiple testing and since CTQ was not the main focus of the study. These tools have  
181 been validated in French (Baylé et al., 2000; Henry et al., 2008; Paquette et al., 2004) and  
182 have been widely used in BD (Daruy-Filho et al., 2011; Etain et al., 2013; Lagerberg et al.,  
183 2017).

184 Internal consistency was fair to good for the measurement scales, with standardized  
185 Cronbach’s  $\alpha$  =0.68 for MADRS, 0.72 for YMRS, 0.63 for BIS10, 0.61 for the FAST, 0.68 for the  
186 CTQ and 0.57 for ALS.



187        2.3.        *Statistical analyses*

188        Continuous variables are described by medians (interquartile range), given that most had  
189        non-gaussian distributions (Shapiro-Wilk test  $p$ -value  $<0.05$ ). Categorical data are described  
190        by counts (frequency). Firstly, bivariate analyses were used to investigate associations  
191        between the collected variables and the presence of lifetime AUD, using Mann-Whitney  $U$   
192        for continuous data or  $\text{Chi}^2$  for categorical data. This was used to select the variables to test  
193        with the sequence of onset of BD and AUD using bivariate analyses. Secondly, we  
194        investigated associations of the collected variables and the sequences of onset of BD and  
195        AUD, *i.e.*, BD first vs. AUD first. We used Mann-Withney for continuous data or  $\text{Chi}^2$  for  
196        categorical data. Finally, a binary logistic regression model was ran with the variables  
197        associated with the BD and AUD onset variable showing significance in both the bivariate  
198        analyses. The regression model included a random term accounting for centre of inclusion  
199        (12 sites). As a sensitivity analysis aimed at checking whether BD and AUD occurring the same  
200        year better explained the results than our binary sequence variable, we also ran a  
201        multinomial regression comparing BD first vs. AUD first vs. same year onsets with the  
202        predictors identified in bivariate analysis. For bivariate analyses, statistical significance was  
203        set at (i)  $p < 0.05/36 = 0.001389$  (BD with vs. without AUD) and (ii)  $p < 0.05/\text{number of}$   
204        variables associated with the presence of AUD/2. Raw  $p$ -values are shown in all the tables,  
205        with significace after Bonferroni correction indicated by\*. Multicollinearity was assessed by  
206        computing the variance inflation factor (VIF) of each independent variable. A VIF above the  
207        “balanced” threshold of 2.5 is problematic and, in that case, the model was run again  
208        without the variable, until all VIF values became satisfactory. R version 4.0.2 (R Core Team,  
209        2020) through R studio version 1.3.1093 were used to compute statistics under Mac OS  
210        X.14.6 system. The R session summary is available as a supplementary online file.

211

212 **3. Results**

213 The sample was composed of 3,027 outpatients with bipolar disorder. Comorbid AUD was  
214 diagnosed in 768 (25%) patient. Mean age of the sample was 41 years (SD =13). There were  
215 1,727 (62%) women and 1,351 (48%) patients with BD2 subtype. Other lifetime SUDs were  
216 distributed as follows: 600 cannabis use disorders (CUD, 19%), 141 sedative use disorder  
217 (SedUD, 5%) and 171 StimUD (6%). There were 545 patients with reliable data on BD and  
218 AUD AAOs, including 269 (49%) with bipolar disorder first and AUD in second, 276 (51%)  
219 with AUD first and bipolar in second (of which 88 developed BD and AUD the same year),  
220 leaving a total sample for the sequence of onset study of 2,804 patients.

221 *3.1. Risk factors of comorbid AUD compared to BD without AUD, regardless of*  
222 *their sequence of onset (Table 1)*

223 BD+AUD participants were more likely to be men (48% vs. 36%,  $p < 0.001$ ), with earlier AAO  
224 of BD (median =20 vs. 21,  $p < 0.001$ ), higher prevalence of lifetime SA (48% vs. 35%,  $p < 0.001$ )  
225 and of past-year mood episode (84% vs. 78%,  $p < 0.001$ ) but lower prevalence of psychosis  
226 history (32% vs. 40%,  $p < 0.001$ ). They also showed increased current mood symptoms  
227 according to both the MADRS (median =10 vs. 7) and the YMRS (median = 1 vs. 0) (both  $p$   
228  $< 0.001$ ), with poorer functioning according to FAST total (median =23 vs. 18,  $p < 0.001$ ) and  
229 cognition (mean =4.1 vs. 3.7,  $p = 0.004$ ) scores. They also had a larger waist circumference  
230 (median =93 vs. 91,  $p < 0.001$ ) despite similar BMI ( $p = 0.511$ ). They scored higher regarding  
231 BIS10 (median =71 vs. 65), ALS (mean =1.5 vs. 1.2) and CTQ (median =20 vs. 21) total scores  
232 (all  $p < 0.001$ ). Finally, they exhibited higher rates of comorbid anxiety disorders (53% vs.  
233 41%,  $p < 0.001$ ) and lifetime SUDs (all  $p < 0.001$ ): tobacco smoking (66% vs. 40%), sedUD (12%  
234 vs. 2%), CUD (41% vs. 13%) and stimUD (16% vs. 2%).

235

236

**Table 1 about here**

237

238       3.2.       *Factors associated with the sequence of onset of BD and AUD in comorbid*  
239                   *patients (Table 2)*

240 There were 21 significant associations with the presence of comorbid AUD. Thus, the  
241 threshold for significance in the “sequence” analysis was  $0.05/24 = 0.00208$ . When  
242 compared to the BD-AUD group, AUD-BD patients in the had a higher AAO of BD (21 vs. 18,  $p$   
243  $<0.0001$ ) but lower AAO of AUD (18 vs. 27,  $p <0.0001$ ) and lower ALS score (1 vs. 2,  $p$   
244  $<0.0001$ ). They also reported a higher rate of “up” episodes per year of bipolar illness (0.45  
245 vs. 0.32,  $p <0.0001$ ) and increased prevalence of CUD (49% vs. 34%,  $p <0.0001$ ).

246

247

**Table 2 about here**

248

249       3.3.       *Binary logistic regression with the BD-AUD vs. AUD-BD groups as the*  
250                   *dependent variable (Figure 1)*

251 In the fully adjusted regression model, the sequence of onset of BD and AUD remained  
252 independently associated with AAO of BD, which was lower in BD-AUD vs. AUD-BD patients  
253 (OR =0.92, 95% CI =0.91-0.96 ,  $p =0.00002$ ), with the number of “up” BD episodes per year  
254 of bipolar illness, which were less frequent in BD-AUD vs. AUD-BD (OR =0.3, 95% CI =0.22-  
255 0.8,  $p =0.01614$ ), with increased prevalence of past-year mood episode (OR =2,  $p =0.04$ ) and  
256 with the presence of CUD, which was less frequent in BD-AUD vs. AUD-BD patients (OR  
257 =0.39, 95% CI =0.23-0.62,  $p =0.00024$ ). The model was performed with 301 cases, yielding

258 area under curve (AUC) =0.73 (receiver operator curves are available by request from the  
259 authors). There was no evidence of multicollinearity (maximum VIF =1.1 for CUD).

260 3.4. *Sensitivity analysis by multinomial regression with the sequence of onset of BD*  
261 *and AUD in BD patients with a separate group for those, who began BD and AUD*  
262 *during the same year (Supplementary Table 1 & Supplementary Figure 1)*

263 In the multinomial regression model, the significant results from the binary regression  
264 remained overall similar as regards the comparison between BD-AUD and AUD-BD patients,  
265 except that ALS score was lower in the AUD-BD group and that the rate of (hypo)manic  
266 episodes/year of BD in patients, who developed BD and AUD during the same year,  
267 appeared preferentially higher than in the BD first group (noticing that the difference with  
268 the AUD-BD group yielded a  $p$ -value =0.06).

269

270 **Figure 1 about here**

271

#### 272 **4. Discussion**

273 Using extensive data obtained through the comprehensive assessment of a large sample of  
274 patients enrolled in the French national FACE-BD network, we first confirmed prior findings  
275 that the comorbidity of BD with AUD was associated with a wide range of factors indicating  
276 increased BD severity when compared to BD alone. A closer look at the sequence of onset  
277 between BD and AUD did not alter this global impression of increased severity. However,  
278 having AUD onset prior to BD onset in patients with BD+AUD comorbidity was  
279 independently associated with a later AAO of BD, higher rate of “up” episodes per year of  
280 bipolar illness and a increased prevalence of cannabis use disorder, as compared to having

281 BD onset prior to AUD onset. To our knowledge, this is the largest published study to date  
282 assessing the risk factors of the relative onset of BD and AUD. We relied on standardized and  
283 extensive assessment to eventually perform a fully-adjusted regression model. In particular,  
284 BD and AUD diagnoses were properly ascertained and we could estimate the effects of key  
285 clinical variables, including non-psychiatric comorbidity. The regression model had strong  
286 prediction ability power (AUC =0.73) and confidence intervals for odds ratios were overall  
287 narrow, indicating good reliability.

288 The first - and probably most expected - main finding was that patients with comorbid BD  
289 and AUD had a more severe clinical profile across most of the majors areas known to impact  
290 daily functioning and prognosis in BD, namely: current symptoms load, comorbid anxiety  
291 disorders and SUD, impulsiveness and affective lability, childhood trauma. This extends on  
292 prior literature emphasizing the poor clinical outcomes of individuals with BD and comorbid  
293 AUD (Simhandl et al., 2015) and further highlights the need to design targeted and more  
294 intensive care for patients with comorbid BD and AUD (Jones et al., 2019).

295 In the current study, we further aimed to characterize these patterns as a function of the  
296 sequence of onset of BD and AUD in order to identify more clinically meaningful trajectories  
297 that the sole increased severity of the comorbid condition. Firstly, compared to AUD-BD, BD-  
298 AUD remained independently associated with an earlier AAO of BD. Individuals with  
299 prodromal stages of BD likely drink alcohol prior to AUD diagnosis, attempting to self-  
300 regulate prodromal mood symptoms but thereby increasing their risk for first depressive  
301 episode (Turner et al., 2018). Since this episode will represent the index episode for dating  
302 the beginning of BD, this could lead to both an earlier AAO of BD and increased incidence of  
303 later AUD, the latter being associated with increased risk of conversion from unipolar  
304 depression to BD (Musliner and Østergaard, 2018). Importantly, this particular finding has to

305 be interpreted in light of the respective ages at onset (AAOs) of BD and AUD in non-  
306 comorbid individuals. AAO of BD usually stands around 20 years (Hasin and Grant, 2015),  
307 while that of DSM-5 AUD is ~25 . In our sample, the median AAO of BD was 21 years old in  
308 the AUD-BD group, which remained in the range of usual AAO of BD and supports the fact  
309 that our findings related to the comparison of the BD-AUD and AUD-BD groups reflect at  
310 least partially genuine trajectories of the comorbid BD+AUD condition. In the BD-AUD group,  
311 AAO of BD was particularly early and that, in the AUD-BD group, AAO of AUD was early as  
312 well. Therefore, the characteristics of these trajectories is likely to have been driven by the  
313 earlier AAO of the disorder, which began first. In the largest previous study on this issue,  
314 Azorin et al. also reported that BD AAO was higher in AUD-BD than in BD-AUD patients  
315 (Azorin et al., 2017).

316 Secondly, BD-AUD was also independently associated with a lower number of “up” episodes  
317 per year of illness and a lower prevalence of cannabis use disorder. We believe that this  
318 reflects previously-reported associations between AUD and increased risk for depressive  
319 episodes in BD (Janiri et al., 2017), whereas cannabis use and CUD have been linked to “up”  
320 episodes (Lagerberg et al., 2016). In our sample, this is further supported by the fact that the  
321 higher prevalence of past-year BD episodes (which shortly failed to reach significance in the  
322 sequence analysis, Table 2) in BD first patients was driven by depressive episodes (data not  
323 shown) and by a significant association between the presence of CUD and a higher rate of  
324 “up” episodes (median =0.29 vs. 0.2,  $p < 0.001$ ). Similar to our sample, there are also reports  
325 that “AUD first” BD patients have increased prevalence of CUD (Hunt et al., 2016) compared  
326 to BD first cases. In our sample, almost half (49%) of the AUD-BD patients had comorbid  
327 CUD, that is, three comorbid SUDs if tobacco use disorder is included. Our tentative  
328 interpretation is therefore that BD-AUD patients showing reduced prevalence of “up”

329 episodes due to lower prevalence of CUD. However, there was no difference between BD  
330 with or without AUD regarding the rate of depressive episodes in our sample, so that  
331 additional factors may be involved in these findings, warranting further investigation.

332 Interestingly, male gender was associated with the comorbid BD+AUD condition compared  
333 to BD alone, regardless of the sequence of onset. A reduction in gender differences for  
334 comorbid AUDs amongst individuals with BD had yet been previously evidenced (Frye et al.,  
335 2003). The lack of association between BD-AUD sequences of onset and comorbid anxiety  
336 disorder was unexpected. However, when investigating this issue in light of digestive system  
337 disorders and dyslipidemia, we found that the former was almost twice as frequent in cases  
338 with a positive history of anxiety disorders compared to those without (6% vs. 4%,  $p < 0.001$ ).  
339 These interactions should be investigated in a near future.

340 Finally, the sensitivity analysis aimed at estimating how the “same year” onset category of  
341 the sequence variable could have biased our results elicited similar patterns of association as  
342 with the dummy sequence variable (supplementary Table and Figure 1). However, a strong  
343 separate difference emerged regarding the rate of (hypo)manic episodes per year of bipolar  
344 illness, which was especially higher in the “same year” compared to the BD-AUD group. The  
345 speed of transition between the disorders could shed further light on these associations.

#### 346 *Limitations*

347 Our findings must be interpreted in light of several limitations. Data regarding lifetime  
348 events were retrospective, thus subject to recall or classification bias. Recent substance use  
349 was not included in our analyses, and excessive alcohol use - whether AUD is present or not -  
350 has also been shown to alter BD course (Gordon-Smith et al., 2020). We merged the  
351 category of BD and AUD onset when they occurred the same year with the BD-AUD  
352 category, expecting that keeping all three categories would yield too small subgroups for

353 adequate statistical power. Overall, the prevalence of comorbid SUDs is rather lower in the  
354 FACE-BD sample than in a recent meta-analysis of BD-AUD in clinical samples (Hunt et al.,  
355 2016). We believe this might be due to the FACE-BD network selection bias that is both due  
356 to how patients are referred to the network and to the euthymia criterion – a state that is  
357 less frequent in BD comorbid with SUDs than without - that is applied so that patients are  
358 able to undergo all assessments, which include full neuropsychological testing. The cross-  
359 sectional nature of the study meant that we could not address issues of cause and effect.

360 Both the presence and the sequence of onset of the comorbidity between BD and AUD,  
361 showed a wide range of associations with important clinical factors indicating increased  
362 severity in comorbid patients. For most these factors, the sequence of onset of the disorders  
363 was not associated with different association patterns, suggesting that AUD comorbidity in  
364 BD has such a devastating effect on illness course that it overcomes the potential effect of its  
365 sequence of onset with BD. Having a close look still highlighted that the sequence of onset of  
366 BD and AUD had a few, yet relevant clinical implications with regards to AAO of BD, gender,  
367 risk of (hypo)manic episodes and comorbidity with CUD. Importantly, our results overall  
368 argue against previous findings that BD occurring after SUDs in general could represent a  
369 less severe illness presentation as compared to BD alone (Pacchiarotti et al., 2009) (although  
370 this may stand for substances, other than alcohol). This should encourage clinicians to  
371 consider intensive care for all BD patients with AUD without focusing much on their  
372 sequence of onset. Likewise, when considering young alcohol-using BD individuals, who may  
373 not have developed AUD yet, full abstinence from alcohol (and possibly other addictive  
374 substances as well) should be discussed during the stabilization phase of BD treatment.  
375 Similar strategies should also be discussed in order to reduce the risk of developing BD in  
376 alcohol-using individuals with prodromal BD symptoms.



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589 Table 1: Characteristics of patients in the FACE-BD sample, according to the presence of alcohol use disorder  
590 (AUD). N(%) or median (interquartile range, IQR) and raw p-values are shown. \* $p < 0.001389$ . Unadjusted odds  
591 ratios (OR) are displayed for categorical variables. BD, bipolar disorder; MDE, major depressive episode; AAO,  
592 age at onset; BIS10, Barratt Impulsiveness Scale - 10th version; ALS, affective lability by the Affective lability  
593 scale; CTQ, Childhood Trauma Questionnaire – short form; FAST, Functional Assessment Short Test (FAST);  
594 MADRS, Montgomery-Asberg Depression Rating Scale (MADRS); YMRS, Young Mania Rating Scale (YMRS); BMI,  
595 Body mass index.

	no AUD N=2259	lifetime AUD N=768	OR	p	N
Gender (W vs. M)	812 (36%)	368 (48%)	1.6 (1.4-1.9)	<0.001*	3025
Age	40 (31-50)	39 (31-48)		0.09	3027
Referral (vs. other modes)				0.215	2628
GP	248 (13%)	66 (10%)	0.9 (0.5-1.8)		
Patient	56 (3%)	25 (4%)	1.5 (0.7-3.3)		
Psychiatrist	1620 (82%)	552 (84%)	1.1 (0.6-2.2)		
Finished high school education	290 (15%)	92 (15%)	1 (0.8-1.3)	0.983	2564
Current relationship status (vs. single)				<0.001*	2586
Married / with partner	1015 (52%)	276 (44%)	0.7 (0.6-0.8)		
Separated	220 (11%)	79 (12%)	0.9 (0.7-1.2)		
Current professional status (vs. other modes)				<0.001*	2549
Student	182 (9%)	57 (9%)	1 (0.7-1.4)		
Inactive	585 (30%)	234 (38%)	1.3 (1.1-1.6)		
Disability leave	77 (4%)	26 (4%)	1.1 (0.7-1.7)		
Retired	146 (8%)	14 (2%)	0.3 (0.2-0.5)		
Family history of BD	470 (21%)	154 (20%)	1.0 (0.8-1.2)	0.693	3027
Family history of AUD	458 (20%)	282 (37%)	2.3 (1.9-2.7)	<0.001*	3027
BD subtype type 2 (vs. 1)	1070 (47%)	394 (51%)	1.2 (1.0-1.4)	0.065	3027
AAO BD	21 (17-28)	20 (17-25)		<0.001*	2905
Polarity at BD onset (depressive vs. “up”)	681 (30%)	208 (27%)	0.9 (0.7-1.0)	0.118	3027
BD duration	15 (7-24)	16 (10-24)		0.013	2903
Lifetime SA	766 (35%)	358 (48%)	1.7 (1.4-2.0)	<0.001*	2958
Past-year BD episode	1598 (77%)	576 (84%)	1.5 (1.2-1.9)	<0.001*	2767
Number of inpatient stays (lifetime)	2 (1-3)	2 (1-4)	1.0 (1.0-1.1)	0.08	2738
Number of MDE per year of bipolar illness <sup>b</sup>	0.3 (0.18-0.5)	0.30 (0.17-0.51)		0.841	2317
Number of “up” episodes per year of bipolar illness <sup>b</sup>	0.19 (0.06-0.4)	0.21 (0.07-0.44)		0.194	2903
History of psychosis	771 (40%)	209 (32%)	0.7 (0.6-0.8)	<0.001*	2597
BIS10 total score	65 (58-73)	71 (64-79)		<0.001*	2862
CTQ total score	38 (31-48)	42 (35-54)		<0.001*	2887
ALS total score <sup>b</sup>	1 (1-2)	2 (1-2)		<0.001*	2845
MADRS total score	7 (2-14)	11 (5-19)		<0.001*	2991
YMRS total score	0 (0-3)	1 (0-4)		<0.001*	2985
FAST total score	18 (8-30)	24 (13-34)		<0.001*	2880
FAST – cognitive subscale	3 (1-6)	3 (1-7)		<0.001*	2925
BMI	24 (22-28)	25 (22-28)		0.533	2859
Waist circumference (cm)	91 (82-101)	93 (83-103)		0.015	2711

	<b>no AUD N=2259</b>	<b>lifetime AUD N=768</b>	<b>OR</b>	<b>p</b>	<b>N</b>
History of any non-psychiatric disorder	1712 (84%)	598 (87%)	1.2 (1.0-1.6)	0.118	2730
History of cardiovascular disorder	262 (12%)	107 (16%)	1.3 (1.0-1.6)	0.045	2796
History of dyslipidemia	313 (15%)	124 (18%)	1.2 (1.0-1.6)	0.071	2843
History of digestive system disorder	86 (4%)	45 (6%)	1.6 (1.1-2.3)	0.014	2790
Comorbid anxiety disorder	904 (41%)	393 (53%)	1.6 (1.4-1.9)	<b>&lt;0.001*</b>	2938
Tobacc smoking (vs. never-smoking)				<b>&lt;0.001*</b>	2871
Former smoking	247 (12%)	103 (14%)	2.9 (2.2-3.9)		
Current smoking	844 (40%)	482 (66%)	4.0 (3.2-4.9)		
Sedative use disorder	51 (2%)	90 (12%)	5.7 (4.0-8.2)	<b>&lt;0.001*</b>	3027
Cannabis use disorder	288 (13%)	312 (41%)	4.7 (3.9-5.7)	<b>&lt;0.001*</b>	3027
Stimulant use disorder	46 (2%)	125 (16%)	9.3 (6.6-13.3)	<b>&lt;0.001*</b>	3027

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Table 2: Characteristics of patients in the FACE-BD sample according to the sequence of onset of alcohol use disorder (AUD) and bipolar disorder (BD). N(%) or median (interquartile range, IQR) and raw p-values are shown. \* $p < 0.00208$ . <sup>a</sup>Although the distribution was highly skewed, we report means (SD) for interpretability. N/A, not applicable; MDE, major depressive episode; AAO, age at onset; BIS10, Barratt Impulsiveness Scale - 10th version; ALS, affective lability by the Affective lability scale; CTQ, Childhood Trauma Questionnaire – short form; FAST, Functional Assessment Short Test (FAST); MADRS, Montgomery-Asberg Depression Rating Scale (MADRS); YMRS, Young Mania Rating Scale (YMRS).

	AUD first N=276	BD first N=269	Odds Ratio (95% CI)	p-value	N
Gender	151 (55%)	112 (42%)	0.6 (0.4-0.8)	0.003	545
Current professional status (vs. other modes)					
Student	27 (12%)	17 (7%)	0.6 (0.3-1.1)	0.3421	456
Inactive Disability leave	83 (37%)	85 (37%)	0.9 (0.6-1.4)		
Retired	7 (3%)	11 (5%)	1.4 (0.5-4.1)		
Current relationship status (vs. single)				0.8344	473
Married / with partner	102 (43%)	107 (45%)	1.1 (0.8-1.6)		
Separated	27 (11%)	29 (12%)	1.1 (0.6-2.1)		
Family history of AUD	105 (38%)	103 (38%)	1.0 (0.7-1.4)	1.0000	545
AAO BD	21 (18-27)	18 (15-22)		<0.0001*	545
AAO AUD	18 (16-20)	27 (20-34)		<0.0001*	545
Past-year BD episode	202 (79%)	226 (89%)	2.2 (1.3-3.7)	0.0026	508
Number of MDE per year of bipolar illness <sup>a</sup>	0.43 (0.34)	0.34 (0.25)		0.0225	417
Number of “up” episodes per year of bipolar illness <sup>a</sup>	0.45 (0.39)	0.32 (0.31)		<0.0001*	321
Lifetime SA	119 (44%)	132 (50%)	1.3 (0.9-1.8)	0.1598	535
History of psychosis	87 (36%)	70 (29%)	0.7 (0.5-1.1)	0.1626	483
BIS10 total score	71 (12)	71 (11)		0.4364	514
CTQ total score	53 (49-58)	54 (50-60)		0.0569	520
ALS total score	1 (1-2)	2 (1-2)	1.6 (1.2-2.1)	<0.0001*	509
MADRS total score	9 (4-16)	12 (5-21)		0.0081	541
YMRS total score	2 (0-4)	1 (0-4)		0.7878	537
FAST total score	21 (11-31)	25 (14-34)		0.0186	515
FAST – cognitive subscale	3 (1-6)	3 (1-7)		0.1283	524
Comorbid anxiety disorder	136 (51%)	158 (60%)	1.5 (1-2.1)	0.0335	530
Tobacc smoking (vs. never-smoking)				0.6024	530
Former smoking	40 (15%)	31 (12%)	0.8 (0.4-1.4)		
Current smoking	174 (64%)	171 (66%)	0.9 (0.6-1.5)		
Sedative use disorder	23 (8%)	36 (13%)	1.7 (1-3)	0.0786	545
Cannabis use disorder	136 (49%)	91 (34%)	0.5 (0.4-0.7)	<0.0001*	545
Stimulant use disorder	48 (17%)	31 (12%)	0.6 (0.4-1)	0.0682	545

**Figure 1: Binary logistic regression with the sequence of onset of bipolar disorder (BD) and alcohol use disorder (AUD) as the dependent variable (BD-BD patients are the reference group). Bars represent 95% CI. \*p <0.05, \*\* p <0.001, \*\*\* p <0.0001. ALS, Affective lability scale; AAO, age at onset; “UP” represents (hypo)manic episodes.**

