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Tobacco Smoking and other Substance Use Disorders Associated with Recurrent Suicide Attempts in Bipolar Disorder

R. Icick^{1,2,3,4,5*}, I. Melle^{6,7}, B. Etain^{1,2,3,4,5}, P.A. Ringen⁶, S.R. Aminoff^{7,8}, M. Leboyer^{4,5,9,10}, M. Aas^{6,7}, C. Henry^{4,5,9,10}, T.D. Bjella^{6,7}, O.A. Andreassen^{6,7}, F. Bellivier^{1,2,3,4,5}, T.V. Lagerberg⁶.

¹Inserm, U1144, Paris, F-75006, France ;

²Paris Diderot University, UMR-S 1144, Paris, F-75013, France ;

³Assistance Publique – Hôpitaux de Paris, University Hospitals Saint-Louis – Lariboisière – F. Widal, Department of Psychiatry and Addiction Medicine, Paris, F-75010, France;

⁴FondaMental Foundation, Créteil, F-94000, France;

⁵LabEx ‘Bio-Psy’, 17 rue du Fer à Moulin, 75005 Paris, France.

⁶NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway;

⁷NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway;

⁸Department of Specialized Inpatient Treatment, Division of Mental Health Services, Akershus University Hospital, Norway;

⁹Inserm U955, Psychiatric Genetics Team, Créteil, F-94000, France ;

¹⁰Paris Est University, Faculty of medicine, Créteil, F-94000, France ;

¹¹Assistance Publique – Hôpitaux de Paris, University Hospitals Henri Mondor, DHU PePsy, Psychiatry Center, Créteil, F-94000, France.

***Corresponding author :** romain.icick@aphp.fr. CSAPA « Espace Murger », Département de Psychiatrie et de Médecine Addictologique, Hôpital Fernand Widal, 200 rue du Faubourg Saint-Denis, 75010 Paris, France. Tel: +33140054275 / Fax : +33140054213.

Abstract

Background: Suicide attempts (SA) are more frequent in bipolar disorder (BD) than in most other mental disorders. Prevention strategies would benefit from identifying the risk factors of SA recurrence in BD. Substance use disorders (SUD) (including tobacco-related) are strongly associated with both BD and SA, however, their specific role for the recurrence of SA in BD remains inadequately investigated. Thus, we tested if tobacco smoking - with or without other SUDs – was independently associated with recurrent SA in BD. **Methods:** 916 patients from France and Norway with ascertained diagnoses of BD and reliable data about SA and SUD were classified as having no, single, or recurrent (≥ 2) SA. Five SUD groups were built according to the presence/absence/combination of tobacco, alcohol (AUD) and cannabis use disorders. Multinomial logistic regression was used to identify the correlates of SA recurrence. **Results:** 338 (37%) individuals reported at least one SA, half of whom (173, 51%) reported recurrence. SUD comorbidity was: tobacco smoking only, 397 (43%), tobacco smoking with at least another SUD, 179 (20%). Regression analysis showed that tobacco smoking, both alone and comorbid with AUD, depressive polarity of BD onset and female gender were independently associated with recurrent SA. **Limitations:** Lack of data regarding the relative courses of SA and SUD and cross-national differences in main variables. **Conclusion:** tobacco smoking with- or without additional SUD can be important risk factors of SA recurrence in BD, which is likely to inform both research and prevention strategies.

Keywords: bipolar disorder; substance use disorder; tobacco smoking; alcohol; cannabis; suicide attempt; recurrent suicide attempts; comorbidity; dual disorder.

Metrics: word count - abstract=243; manuscript=4876; number of tables=3; number of figures=3; number of supplementary tables=3; number of supplementary figures=0; number of supplementary methods file=2.

Introduction

The lifetime prevalence of attempted (SA) and completed suicides is higher in bipolar disorder (BD) than in most other mental disorders: 50% for SA (Singhal et al., 2014) and 11-19% for completed suicide (Pompili et al., 2013). This corresponds to a 20-30 fold risk for SA in BD (Costa et al., 2015), and to a suicide-specific standardized mortality rate of 14.4 [95% confidence interval (CI) 12.4-16.8] (Hayes et al., 2015). The risk factors for SA in BD [see (Schaffer et al., 2015) for review] include longer illness duration (especially untreated phases), family history of suicidal behavior, depressive polarity at onset and as the predominant polarity over the course of BD, in addition to comorbidity with addictive and anxiety disorders. SAs occur 25 times more often during depressive episodes than during euthymia (Jylhä et al., 2016).

Above all, a history of SA remains the strongest predictor for future SA and completed suicides. It has been prospectively observed that each attempt increased the probability of repetition by about 30% in people with major mood disorders (Oquendo et al., 2002). Recurrent SAs [defined as having attempted suicide twice or more in a lifetime (Large et al., 2016)] are also associated with a significant further increase in completed suicides. Importantly, the lethal intent or medical seriousness of SAs does not decrease with the number of repetitions in BD (Michaelis et al., 2003). Comparisons between recurrent vs. single suicide attempters have mostly been conducted in non-BD samples. Overall, recurrent SAs are associated with psychiatric (Lopez-Castroman et al., 2011; Monnin et al., 2012; Perquier et al., 2017) and non-psychiatric comorbidities (Vajda and Steinbeck, 2000; Zatzick et al., 2017). They are also associated with high levels of hopelessness, hostility and aggressiveness (Sher et al., 2017) which, altogether, indicate that recurrent SA are associated with a high morbidity load. Both SUDs (Mitchell and Potenza, 2014) and SAs (American Association of Suicidology, 2013) have been associated with trait-impulsivity. As such, it

could represent a common denominator of the risk of SA hypothesized to be increased in BD-SUD individuals. Of note, impulsivity is a highly complex construct (Dalley and Robbins, 2017) and there have been associations of various SA subtypes with different impulsivity subtypes, the most constant likely being the relationship between motor impulsivity and recurrent SAs (Colborn et al., 2017). However, several studies also reported a lack of association between impulsivity and SA, regardless of SA subtypes (recurrent, violent) in BD (Etain et al., 2013; Perroud et al., 2011). Regarding sociodemographic characteristics, a family history of suicidal behavior (Liu et al., 2017), female gender, younger age, and living alone (Lopez-Castroman et al., 2011; Monnin et al., 2012; Zahl and Hawton, 2004) have been associated with recurrent SA, although most these associations were inconstant across studies. Substance use disorders (SUD) seemed particularly involved in the recurrence of SA in such non-BD samples, e.g., in follow-up studies based on an index attempt assessed in the emergency room (Lopez-Castroman et al., 2011; Monnin et al., 2012). However, there are noticeable substance-specific differences in associations between SAs and SUD. For instance, alcohol use disorders (AUD) and SUD [other than cannabis use disorders (CUD)] have been repeatedly associated with SA (Østergaard et al., 2017), but the study of CUD have so far yielded equivocal findings (Carrà et al., 2015; Østergaard et al., 2017). This may be due to the confounding effects of the almost constant overlap between tobacco and cannabis use, which are often overlooked in cannabis studies (Peters et al., 2012).

Identifying the characteristics associated with recurrent SAs in BD represents a crucial step to decrease the burden of suicidal behavior in this population (Malhi et al., 2018), as was suggested for other clinical conditions (Lopez-Castroman et al., 2016b; Sher et al., 2017). Yet, to our knowledge, only two studies to date have addressed this issue as their main objective. The first (Michaelis et al., 2003) examined the lifetime characteristics of first *vs.* recurrent attempters assessed after an index SA. SUDs were not associated with the presence *vs.*

absence of previous SA, however, the study lacked statistical power (N=52). The second (Arici et al., 2018) identified psychiatric comorbidity and living alone as specific risk factors for recurrent SA, in a larger sample (N=362, including 95 suicide attempters). The most frequent comorbidity pattern associated with recurrent SA was 'anxiety + SUD', but separate results for SUDs were not reported. Two studies also reported associations between recurrent SA and repeated and refractory mood episodes [especially mixed states (Goldberg et al., 1998)], and having a depressive onset of BD (Neves et al., 2009), respectively. Also relevant to the focus of the present study is the frequently reported association between mixed states and SUDs in bipolar disorders (Schaffer et al., 2015). As for onset/predominant polarity, a complex pattern emerged from extant literature. In a study comparing manic to depressive polarity at onset, authors reported that SUD were associated with the former and suicide attempts to the latter (Popovic et al., 2014). Comparing three groups of BD without SUD, BD-AUD and BD-other SUD, another study reported that BD without SUD had a more frequent manic predominant polarity whilst BD with any SUD were associated with depressive polarity (Janiri et al., 2017). Given the strong association between mixed states and SUD with inconstant findings regarding onset/predominant polarity, further study was warranted to address these course specifiers of BD in relation to suicide attempts.

Thirty to seventy percent (30-70%) of individuals with BD have at least one comorbid SUD (Hunt et al., 2016a, 2016b) [including tobacco smoking/nicotine dependence (Thomson et al., 2015)], and these comorbidities have been repeatedly associated with suicidal behavior (Carrà et al., 2014; Schaffer et al., 2015). A growing body of evidence also designates tobacco smoking as a potentially independent risk factor for SA in BD (Ducasse et al., 2015; Ostacher et al., 2009) and, in non-BD samples, specific associations between tobacco smoking and recurrent SA have been reported (Icick et al., 2018; Lopez-Castroman et al., 2016a). However, according to our literature search (including 'nicotine dependence' or 'cigarette

smoking' as entry terms), whether tobacco smoking is independently associated with recurrent SA in BD remains to be investigated, especially as regards former *vs.* current smoking.

In summary, recurrent SAs represent a distinct and burdensome suicidal phenotype in BD, the prevention of which would largely benefit from a better characterization of the addictive comorbidity patterns associated with recurrent SA in this high-risk population. Therefore, we aimed at studying the effects of comorbid tobacco smoking and other common SUDs in the recurrence of SAs in a large sample of patients with BD. More specifically, we investigated (i) whether tobacco smoking was associated with recurrent SA independently from AUD and CUD and (ii) if increasing SUD burden, i.e. presenting with one or more SUDs in addition to tobacco smoking, was associated with further increased risk for recurrent SA. We hypothesized that the risk of recurrent SA would increase with the number of SUDs comorbid with tobacco smoking.

Methods

This was a cross-sectional study including a multicenter sample.

Participants (Figure 1)

Treatment-seeking individuals presenting to specialized clinics in Norway and France, as inpatients or outpatients, and with symptoms suggesting the presence of BD were screened for the study. Inclusion criteria were: (i) age \geq 18 years; (ii) meeting DSM-IV criteria for a diagnosis of BD-I or BD-II disorder; and (iii) willingness and ability to provide written informed consent. In France, additional criteria for inclusion were: (i) being euthymic at inclusion, as defined by a Montgomery-Asberg Depression Rating Scale (MADRS) score \leq 8 (Montgomery and Asberg, 1979) and a Mania Rating Scale (YMRS) score of \leq 5 (Young et

al., 1978); (ii) mastering the French language; and (iii) having at least three grandparents born in France due to the initial purpose of the study (genetic analyses). In Norway, euthymia was not an inclusion criterion, but patients had to be clinically stable and to master a Scandinavian language. Additional inclusion criteria in Norway were: (i) absence of history of severe head trauma and (ii) $IQ \geq 70$. In both samples, lifetime schizophrenia was also an exclusion criterion, so that there were no cases with affective psychosis/schizo-affective disorder in the final sample.

Thirty-three cases were excluded due to missing data about SA (17 for lifetime SA and 16 for the number of SA), 35 because they had missing data regarding SUD diagnoses, and 17 due to missing data about smoking status. Given their small number and in order to limit the number of subgroups, we also excluded non-tobacco smokers with AUD (N=27) and/or CUD (N=5) and/or other SUDs (N=49), leaving a final sample of 916 participants. The flowchart of participant selection and incomplete cases exclusion is presented Figure 1.

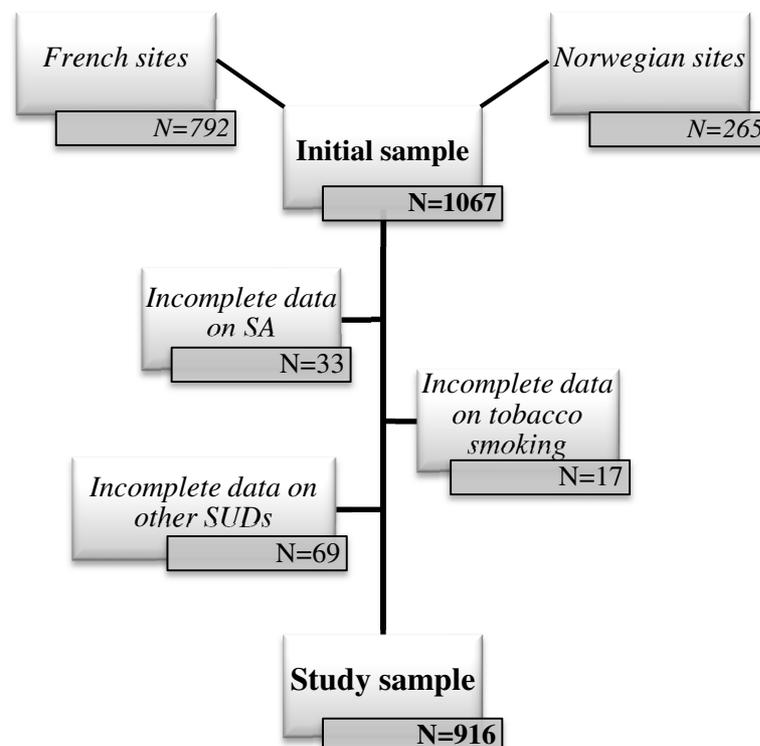


Figure 1: flowchart for sample selection

SA, suicide attempt; SUD, substance use disorders.

Written informed consent was obtained from all participants in both countries. This involved being registered in the database and having one's de-identified data analyzed for research purposes. In France, the Research Ethics Board of Pitié-Salpêtrière Hospital reviewed and approved this study. In Norway, the project was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Clinical Assessment

In both countries, trained psychiatrists, medical doctors and clinical psychologists carried out the clinical assessments. After the verification of euthymia, defined as a Montgomery-Asberg Depression Rating Scale (MADRS) < 8 (Montgomery and Asberg, 1979) and Young Mania Rating Scale (YMRS) < 4 (Young et al., 1978), French participants were interviewed with the Diagnostic Interview for Genetic Studies (DIGS) (Preisig et al., 1999). In the Norwegian sample, diagnoses were established using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I), modules A to E. Diagnostic concordance between the DIGS and the SCID has previously been reported to be excellent (Aas et al., 2014), and these questionnaires have been validated in French (Preisig et al., 1999) and Norwegian language (Ringen et al., 2008), respectively. Thus, they provided reliable lifetime DSM-IV Axis I diagnoses in both samples.

Bipolar illness

Participants were asked about their age at first major mood episode and their respective lifetime numbers of depressive, hypomanic, manic and mixed episodes. The lifetime occurrence of psychotic symptoms during a mood episode was also collected. The polarity and age at onset (AAO) of the first major depressive, manic, hypomanic or mixed episode

defined those of onset of BD [depressive *vs.* (hypo)manic/mixed]. AAO of BD was used to calculate duration of illness until age at inclusion in the study. The minimum duration of BD was set to 1 year because 1/ of the way it was calculated by using age *vs.* date data and 2/ in order to avoid division by 0 in our estimate of the relative lifetime exposure of individuals to their bipolar illness, obtained by dividing the duration of bipolar illness by participants' age at interview ('% of lifetime spent with BD'). Rates of mood episodes and hospital stays due to a mood episode per year of BD were calculated from the number of (hypo)manic and/or depressive episodes / hospital stays divided by the number of illness years (one per type of episode and one for the total number of episodes). These calculations were performed in order to limit the right-censoring of events inherent to the study cross-sectional design and to take the duration of exposure to BD into account.

Suicide attempts

In both countries, history of SA was collected through semi-structured instruments (Supplementary Methods I), SA being identically defined as self-harm with any intent to die (Goodfellow et al., 2017):

- In France, by the relevant section of the DIGS, the opening question being about 'killing oneself'.
- In Norway, by a specific questionnaire derived from a European study of self-harm (CASE-study) following the *National Institute for Clinical Excellence (NICE)* guidelines (National Collaborating Centre for Mental Health (UK), 2004), and previously used in psychiatric populations (Mork et al., 2013), the opening question being about 'hurting oneself with further specification of the suicidal intent'.

Participants were then asked how many times they had attempted suicide. SA recurrence was set to “0” for the absence of lifetime SA, “1” if only one SA was reported, and “2” if two or more SAs were reported, which corresponded to recurrent SA.

Substance use assessments

Tobacco smoking was defined as ‘smoking on a daily basis’, a widely used and reliable marker of DSM-IV nicotine dependence with low intra-individual variability (Hughes et al., 2017). For current smokers, pack-years (the theoretical number of years during which a subject has smoked 20 cigarettes/day) were also calculated, as a rough estimate of lifetime exposure to tobacco. In the French subsample, lifetime tobacco smoking (former + current) was assessed, while in the Norwegian subsample, only current tobacco smoking was considered. As such, tobacco smokers (N=413) in the French subsample were both current (N=294) and former smokers (N=119), whereas those from the Norwegian subsample were current smokers only (N=163). Both the DIGS and the SCID generated DSM-IV diagnoses of abuse or dependence to other substances, which were compiled to obtain a single binary variable of ‘use disorder’ for each substance.

Substance Use Disorder (SUD) groups

A single ‘SUD groups’ variable was built according to whether participants reported tobacco smoking and/or were diagnosed with SUDs: (i) neither tobacco smoking nor any other SUD, which was the reference group in our analyses, (ii) tobacco smoking without any other SUD (tobacco), (iii) tobacco smokers with AUD but no CUD (tobacco + AUD), (iv) tobacco smokers without AUD but with CUD (tobacco + CUD) and (v) tobacco smokers with both AUD and CUD (tobacco + AUD + CUD). Groups were mutually exclusive.

Statistics

Data are described as medians (interquartile range, IQR) since all had non-normal distribution according to the Shapiro-Wilk test (all p -values <0.001), or counts (frequency). Bivariate analyses used Kruskal-Wallis H for quantitative variables or Chi^2 for categorical variables. Fisher's exact tests were used when calculation tables for qualitative variables had cells with less than five expected cases. Statistical significance was set at $p < 0.05$, two-tailed tests applied to the three groups altogether, with Bonferroni correction for pairwise *post hoc* tests. In order to discuss the reliability of our findings, we indicate which variables remained statistically significant after Bonferroni correction (21 tests, significant raw $p < 0.00238$).

Multinomial logistic regression was then performed with recurrent SA as a dependent variable (see above). We forced the entry of SUD groups, country of inclusion and the rate of mood episodes per year of illness (as our main objective was to uncover the correlates of SA recurrence that were independent from mood episodes – during which most SA in BD occur) into the regression model. The variables associated with SA groups at $p < 0.05$ in bivariate analyses were also entered in the model. In case of collinearity, defined as a variance inflation factor (VIF) > 2.5 , variables were excluded. The model ran twice: once with the absence of SA as the reference group, and once with 'single lifetime SA' as the reference group. This allowed for testing factors that specifically differentiated single and recurrent SA, as previously published (Olié et al., 2015). Models were backward, stepwise based on largest to smallest p -values for association with recurrent SA. Finally, a sensitivity analysis was conducted by performing both bivariate and regression analyses separately in both countries, which are summarized in the discussion section and presented in Figure 2, Table 1 & Supplementary Table 2.

All analyses were conducted with R version 3.5.2 (R Core Team, 2019) through R studio version 1.1.463 (R Studio Team, 2019) for Mac OS® X.12.6. The whole script and a summary of the packages that we used are available in the supplementary methods file.

Results

Nine hundred sixteen (916) cases with complete data on SUDs (diagnoses+groups, including tobacco smoking) and SA were eventually analyzed (Figure 1). Cases were 59% women (N=542), 74% BD-I (N=675) and 26% (N=241) BD-II. Four French university-affiliated psychiatry departments recruited 623 (68%) cases (Créteil, Bordeaux, Marseille, Nancy), the remaining 293 (32%) were recruited across all major hospitals in the Oslo area for the Thematically Organized Psychosis (TOP) Study (Norway). There were 338 (37%) participants with lifetime SA in the sample, 173 (51%) of whom reported recurrent SA. Three hundred and forty participants (340, 37%) had neither tobacco smoking nor SUD, 397 (43%) had tobacco smoking only, 99 (11%) had tobacco smoking+AUD, 42 (5%) had tobacco smoking+CUD and 38 (4%) had tobacco smoking+AUD+CUD. One-hundred seventy-nine participants (20%) had tobacco smoking and at least another SUD.

Several variables exhibited cross-national differences (Table 1, Figure 2), namely: age ($p < 0.001$), marital status ($p < 0.001$), ancestry ($p < 0.001$), AAO and duration of BD ($p < 0.001$, Figures 2b&2d), the number of both any and depressive mood episodes per year of BD ($p < 0.001$), the presence ($p < 0.001$) and recurrence ($p = 0.04$) of SA, current smoking ($p = 0.021$), smoking pack-years ($p = 0.001$, Figure 2a), SUD groups ($p < 0.001$, Figure 2c) and family history of BD ($p < 0.001$).

Table 1: Country specific data distribution and cross-national differences in demographic and clinical characteristics

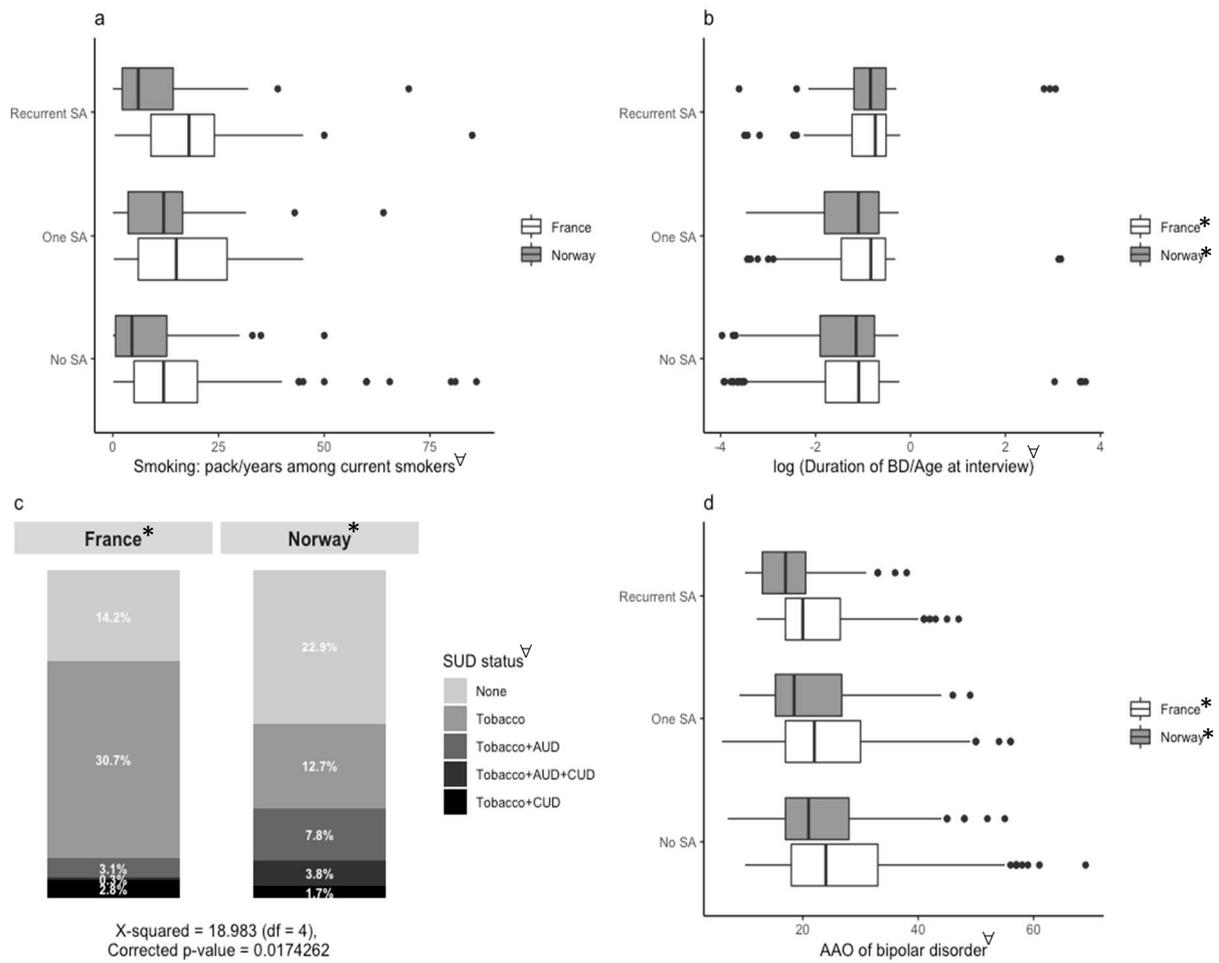
N (%) or median (IQR)		Norway, N=293	France, N=623	All	Norway vs. France Statistics ^a	p-value	Sample size
	Gender	181 (62%)	361 (58%)	542 (59 %)	1.06	0.304	916
	Age	34 (26-44)	42 (33-52)	40 (30-49.3)	17.695	<0.001	
Marital status	<i>Currently married</i>	73 (25%)	215 (35%)	288 (32%)			
	<i>Divorced/Widowed</i>	43 (15%)	381 (62%)	424 (47%)	397.38	<0.001	910
	<i>Never married</i>	177 (60%)	21 (3%)	198 (21%)			
	Caucasian ancestry	268 (91%)	613 (100%)	881 (97 %)	40.4	<0.001	909

N (%) or median (IQR)	<i>Norway, N=293</i>	<i>France, N=623</i>	<i>All</i>	<i>Norway vs. France</i> Statistics ^a	<i>p-value</i>	<i>Sample size</i>
Bipolar subtype	87 (30%)	154 (25%)	241 (26 %)	2.29	0.13	916
Depressive polarity at onset	162 (62%)	387 (63%)	549 (63 %)	0.02	0.892	877
AAO of BD	20 (16-28)	22 (18-31)	22 (17-30)	54.558	<0.001	905
Duration of BD	10 (5-19)	15 (7-25)	13 (6-23)	25.45	<0.001	
Percent of lifespan spent with BD	0.33 (0.17-0.51)	0.39 (0.2-0.56)	0.37 (0.2-0.55)	5.95	0.015 ^b	905
MDE / year of BD	0.43 (0.19-1)	0.25 (0.12-0.5)	0.29 (0.14-0.61)	29.32	<0.001	850
(Hypo)manic episodes / year of BD	0.38 (0.15-1)	0.33 (0.14-0.78)	0.33 (0.14-0.94)	1.4	0.237	830
Mood episodes / year of BD	0.99 (0.43-1.81)	0.60 (0.32-1.17)	0.67 (0.35-1.5)	15.19	<0.001	873
Any lifetime SA	84 (29%)	254 (41%)	338 (37 %)	12.02	0.001	916
Number of SA / year of BD	0.14 (0.06-0.33)	0.1 (0.06-0.25)	0.11 (0.06-0.27)	4.2	0.04	338
Recurrent SA	46 (16%)	119 (19%)	165 (18 %)	13.89	0.001	916
Ever presented with psychotic characteristics	156 (55%)	365 (59%)	521 (58 %)	1.52	0.218	903
Current smoking	163 (56%)	294 (47%)	457 (50 %)	5.35	0.021	916
Smoking: pack/years	6 (0.85-15)	12 (5-22)	10 (3.4-20)	30.55	0.001	529
Lifetime AUD	31 (11%)	106 (17%)	137 (15 %)	5.99	0.014	916
Lifetime CUD	19 (6%)	61 (10%)	80 (9 %)	2.33	0.127	
Family history of BD	36 (13%)	220 (40%)	256 (30 %)	64.62	<0.001	841

IQR, interquartile range; AAO, age at onset; SA, suicide attempt; BD, bipolar disorder; MDE, major depressive episode; SUD, substance use disorder; AUD, alcohol use disorder; CUD, cannabis use disorder.

^aChi² for categorical variables and Kruskal-Wallis *H* for quantitative variables, unless otherwise specified. ^bStatistics performed on the log (BD duration/age).

Figure 2: Factors associated with SA groups according to the country of inclusion



AAO, age at onset; SA, suicide attempt; BD, bipolar disorder; SUD, substance use disorder; AUD, alcohol use disorder; CUD, cannabis use disorder.*Denotes Bonferroni-corrected p -values < 0.05 according to Kruskal-Wallis test, by country

[∇]Denotes variable differences between countries at $p < 0.05$

Table 2: Bivariate tests of sociodemographic and clinical factors for the presence and recurrence of suicide attempts

<i>N (%) or median (IQR)</i>	<i>Never attempted suicide, N=578</i>	<i>One lifetime SA, N=165</i>	<i>Recurrent lifetime SA, N=173</i>	<i>Statistics[#]</i>	<i>raw p-value</i>	<i>Sample size</i>
Included in France^{§,c}	369 (64%)	119 (72%)	135 (78%)	13.891	0.001*	916
Women	321 (56%)	100 (61%)	121 (70%)	11.609	0.003	
Age	39 (29-50)	42 (31-49)	41 (33-48)	0.9533	0.621	910
<i>Currently married</i>	185 (32%)	55 (34%)	48 (28%)			
Marital status^c <i>Divorced/Widowed</i>	242 (42%)	81 (49%)	101 (59%)	21.473	<0.001*	
<i>Never married</i>	148 (26%)	28 (17%)	22 (13%)			916
Diagnosis of BD-I[‡]	420 (73%)	128 (78%)	127 (73%)	1.6056	0.92	
Ever presented with psychotic characteristics	326 (57%)	97 (59%)	98 (58%)	0.16764	0.448	903
History of mixed episode^{a,c}	82 (15%)	29 (19%)	42 (26%)	9.4564	0.009	847
Depressive polarity at onset of BD^c	315 (58%)	112 (70%)	122 (72%)	15.713	<0.001*	877
Age at onset of BD	23 (18-32)	22 (16.5-30)	20 (16-25.75)	22.847	<0.001*	905
Duration of bipolar disorder	12 (5-22)	17 (8-23)	18 (10-27)	26.5368	<0.001*	905
<i>Range</i>	1-61	1-39	1-58			905
Percent of lifespan spent with BD	32 (16.2-50.2)	39 (22.2-55.9)	47 (30.4-60)	39.9776	<0.001* [§]	
Number of MDE per year	0.29 (0.12-0.67)	0.28 (0.13-0.58)	0.33 (0.17-0.5)	2.9708	0.226	850
Number of (hypo) manic episodes per year	0.38 (0.17-1)	0.32 (0.14-0.67)	0.25 (0.12-0.67)	5.424	0.066	830
Number of mood episodes per year	0.73 (0.36-1.5)	0.64 (0.33-1.53)	0.62 (0.33-1.29)	0.2385	0.888	873
Rate of hospital admissions in relation to affective episodes	0.17 (0.05-0.5)	0.21 (0.11-0.5)	0.25 (0.14-0.5)	19.6155	<0.001*	889
Lifetime tobacco smoking^{†a,c}	335 (58%)	116 (70%)	125 (72%)	16.407	<0.001*	916
Smoking pack years	8 (3-20)	15 (5-25)	13 (4-22)	10.8865	0.004	916
<i>Tobacco smoking only</i>	247 (43%)	65 (39%)	85 (49%)			
Comorbid SUD(s)^c <i>Tobacco+AUD</i>	44 (8%)	29 (18%)	26 (15%)	37.949	<0.001*	
<i>Tobacco+CUD</i>	24 (4%)	8 (5%)	10 (6%)			916
<i>Tobacco+AUD+CUD</i>	20 (3%)	14 (8%)	4 (2%)			
Family history of SA	115 (21%)	42 (27%)	37 (23%)	2.7463	0.253	864
Family history of bipolar disorder	160 (30%)	50 (33%)	46 (30%)	0.54027	0.763	841
Family history of mood disorder^c	300 (53%)	89 (55%)	111 (66%)	8.5689	0.014	898

IQR, interquartile range; SA, suicide attempt; BD, bipolar disorder; MDE, major depressive episode; SUD, substance use disorder; AUD, alcohol use disorder; CUD, cannabis use disorder.

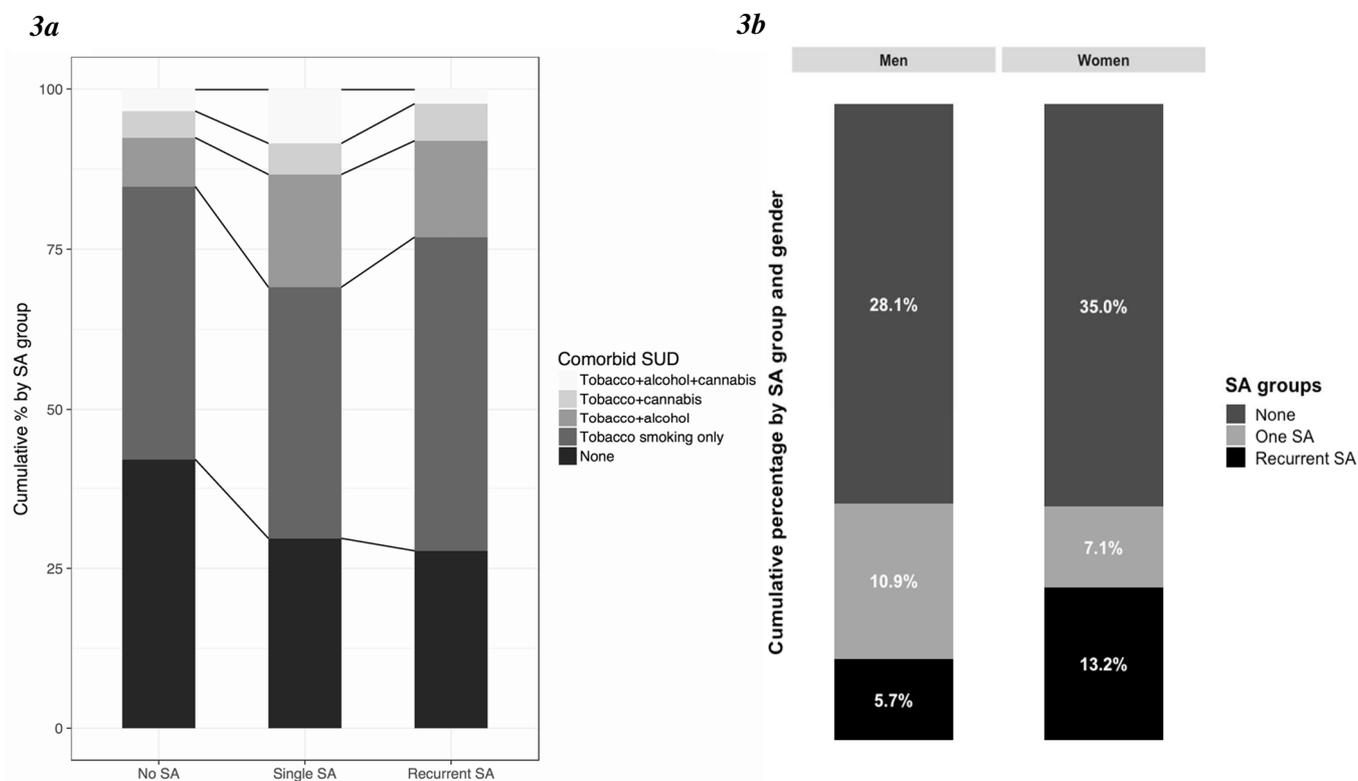
[#]Chi² for categorical variables and Kruskal-Wallis *H* for quantitative variables, unless otherwise specified. [§]Compared to participants included in Norway. [‡]Compared to participants with BD-II diagnosis. [§]Statistics performed on log(BD duration/age). [†]Corresponds to former + current tobacco smokers in France and to current smokers only in Norway. *Denotes *p* < 0.00238 (significance after Bonferroni correction for 21 tests). Significant pairwise comparisons after Bonferroni correction are

flagged with superscript letters: ^adenotes no SA vs. one SA, ^bdenotes one SA vs. recurrent SA, ^cdenotes no SA vs. recurrent SA.

The variables that were significantly associated with SA groups were (Table 2): country of inclusion (France>Norway, $p = 0.001$, more frequent in recurrent vs. non-SA), gender (women>men, $p = 0.003$), marital status (separated vs. other statuses, $p < 0.001$), BD duration and age at onset (respectively shorter and lower in ever suicide attempters, both $p < 0.001$), history of mixed episode (more frequent in ever suicide attempters, $p = 0.0088$), the depressive polarity at BD onset (more frequent in ever suicide attempters, $p < 0.001$), the rate of hospital admissions in relation to affective episodes ($p < 0.001$), lifetime tobacco smoking (more frequent in ever suicide attempters, $p < 0.001$), smoking pack-years (higher in single SA vs. both non and recurrent suicide attempters, $p < 0.001$), SUD status (the comorbidity load seemed higher for all SUD groups in case of single SA, except for tobacco smoking). Recurrent SA were not associated with the yearly episode rate of a specific polarity, so we chose to incorporate that of any mood episode /year as a covariate for regression analysis (see *Methods* section).

The cumulative proportions of SA groups with respect to SUD status and gender are shown Figure 3a & 3b, respectively. Fig. 3a illustrates the association between recurrent SA and tobacco smoking without another SUD and that of AUD with any SA, while Fig. 3b shows that, conversely to men, women presented a majority of recurrent vs. single SA in the sample.

Figure 3: Cumulative % of SA groups according to SUD status (3a) and gender (3b)



SUD, substance use disorder; SA, suicide attempt; AUD, alcohol use disorder; CUD, cannabis use disorder. Fig. 3a: Chi-squared =37.949, $p < 0.001$; fig. 3b, Chi-squared =11.609, $p = 0.003$.

Multinomial logistic regression (Table 3) showed that tobacco smoking was associated with recurrent SA independently from other SUDs. SUD profiles consisting of one SUD in addition to tobacco smoking showed the strongest associations with single (tobacco+AUD) and recurrent SA (tobacco+AUD, tobacco+CUD). Finally, tobacco+AUD+CUD was specifically associated with single SA, while female gender was linked to any SA. There was no evidence of multicollinearity (all VIF < 1.52) and Hosmer-Lemeshow test was not significant.

Table 3: multinomial logistic regression with the presence or recurrence of SA as dependent variable and the absence of SA as reference variable.

Initial model (not shown): gender, country of inclusion, marital status, polarity at onset of BD, rate of mood episodes per year of illness, history of mixed episode, SUD groups, 1st-degree family history of mood disorder.

Final model (presented): variables that remained significant after backward, stepwise elimination based on largest to smallest p-values.

Odds ratios (ORs) and 95% confidence intervals (95% CIs) are displayed.

		<i>One lifetime SA</i>	<i>Recurrent lifetime SA</i>	<i>Recurrent vs. single SA</i>
Gender (women vs. men)		1.48 (1.01-2.18)*	2.23 (1.51-3.29)***	1.5 (0.93-2.41)
Country (France vs. Norway)		1.38 (0.92-2.08)	1.98 (1.3-3.03)**	1.43 (0.85-2.41)
Polarity at onset of BD (depressive vs. (hypo)manic)		1.61 (1.1-2.37)*	1.78 (1.22-2.62)**	1.11 (0.68-1.79)
Comorbid SUD (no SUD as reference group)	<i>Tobacco smoking only</i>	1.36 (0.89-2.08)	1.75 (1.16-2.63)**	1.29 (0.76-2.17)
	<i>Tobacco + AUD</i>	3.7 (2.05-6.67)***	3.58 (1.94-6.59)***	0.97 (0.49-1.92)
	<i>Tobacco + CUD</i>	1.71 (0.68-4.26)	2.65 (1.15-6.1)**	1.55 (0.54-4.46)
	<i>Tobacco + AUD + CUD</i>	3.73 (1.67-8.18)*	1.11 (0.35-3.5)	0.3 (0.09-0.99)*

N =752. Chi-squared =76.368, p <10⁻⁹. McFadden R²=0.049.

SA, suicide attempt; SUD, substance use disorder; BD, bipolar disorder; AUD, alcohol use disorder; CUD, cannabis use disorder. *p<0.05;**p<0.01;***p<0.001.

Finally, we conducted sensitivity analysis by performing multinomial regression with recurrent SA as a dependent variable in each country subsample separately, limited to current tobacco smokers in the French subsample so as to maintain comparability (Supplementary Table 2), and based on the independent factors listed in Table 3. This analysis confirmed the three main findings obtained in the whole sample: significant relationships between recurrent SA and tobacco smoking and depressive onset polarity, and between both single and recurrent SA and comorbid tobacco smoking + AUD. History of mixed episode shortly failed to reach

significance of association in the French subsample ($p = 0.056$). In the Norwegian subsample, tobacco+CUD were further associated with both SA phenotypes, although with borderline statistical stability given the very wide confidence intervals of both odds ratios. We took advantage from this country-specific analysis to test the differences in SA history between current *vs.* former tobacco smokers, thus in the French subsample only (supplementary Table 3). We found that current, but not former daily tobacco smokers, had an increased risk of recurrent SA (OR = 1.83, 95% CI = 1.08-3.12, $p = 0.0025$).

Discussion

In a large sample of patients with BD, tobacco smoking was independently associated with recurrent SA, even in the absence of other SUDs. When tobacco smoking was comorbid with AUD or CUD, this association was stronger. Concurrently, the present study also evidenced associations between recurrent SA and depressive polarity at onset of BD, history of mixed episodes and female gender, the latter encouraging further gender-stratified analyses. Associations between current tobacco smoking and recurrent SA, as well as those between AUD and both SA phenotypes and polarity at BD onset and recurrent SA, were replicated independently in both country subsamples. Moreover, in the French subsample where the group of former smokers was sub-categorized, we found that current smoking, but not former smoking, was independently associated with recurrent SA as compared to never smoking.

The association between tobacco smoking and recurrent SA may be dependent on the level of exposure to tobacco smoking (Lopez-Castroman et al., 2016a). Thus, current smokers had a significantly higher median of pack-years in the SA and recurrent SA groups than in the non-SA group (Table 2), but this relationship was lost after adjustment for confounders (regression analysis on current smokers, pack-years not shown in supplementary Table 2 due to lack of significance with both p -values = 1). Current, but not former smokers in the French subsample

had an increased risk for recurrent SA (supplementary Table 3), the results overall highlighting that the risk of recurrent SA was carried by the current smokers' group.

In preclinical models, the modulation of nicotinic receptors in the brain increased impulsivity and altered decision-making (Nees, 2015), both being involved in SA risk (Dalley and Robbins, 2017; Dombrowski and Hallquist, 2017). In patients assessed after an index SA from the emergency room, an interaction between heavy tobacco smoking and impulsivity was found to increase the repetition of SA during prospective follow-up (Lopez-Castroman et al., 2016a). However, in BD patients, this link was first suggested in 2009 (Ostacher et al., 2009), but not confirmed in a more recent study that included BD patients thoroughly assessed for impulsiveness, clinical course and suicidal behavior (Etain et al., 2013). Although these data help prefiguring a neurobiological framework to the links between tobacco smoking and SAs, further studies in BD should use more experimental designs to assess the associations between tobacco smoking and impulsivity levels, together with clinical studies incorporating possible risk factors for recurrent SA.

AUD (combined with tobacco smoking) was strongly associated with both single and recurrent SA in the present sample and in both country subsamples (supplementary Table 2), which may reflect the strong relationship between AUD and SA in BD in general, regardless of recurrence (Schaffer et al., 2015).

Conversely, CUD (combined with tobacco smoking) was independently associated with recurrent SA in the present sample (but it was only replicated in the Norwegian subsample, supplementary Table 3). We previously reported the absence of association between lifetime CUD and lifetime SA (without further specification) (Lagerberg et al., 2016), but it seems that focusing on a more severe suicidal outcome uncovered a more specific link. Indirect evidence support this association, since CUD has been associated with (i) any SA in a national registry study (Østergaard et al., 2017), but only in people with BD; (ii) recurrent suicidal ideation,

among other substances of abuse, in young adults without psychiatric disorders (Dugas et al., 2015); (iii) a lower age at first SA in psychiatric inpatients (Slama et al., 2009) and (iv) an early AAO of BD and a higher number of previous SA in a first-treatment BD sample (Kvitland et al., 2016). These data suggest, at least, that cannabis misuse is associated with a larger window of exposure to risk factors for recurrent SA. In the present sample, participants with CUD were significantly younger than those without, and both groups tended to exhibit higher rate of SA/year of BD than their counterparts (data not shown). Moreover, continued cannabis use has been associated with mixed episodes in BD (Bally et al., 2014), as was CUD in the present sample ($\text{Chi}^2 \text{ test}=16.965, p=9.4 \times 10^{-3}$). Further investigation regarding the pathway between tobacco and cannabis misuse and their links with mixed episodes, AAO of BD and age at first SA is warranted to better characterize their relationships with recurrent SA. The lack of association between the combination of tobacco smoking, CUD and AUD and recurrent SA was somewhat unexpected. This may be a false negative due to the low number of cases presenting with all three SUDs ($n=4$) in the recurrent SA group, which was conserved in all analyses for the sake of clinical representativeness.

Recurrent SA have been associated with female gender in clinical samples (Icick et al., 2018; Monnin et al., 2012) but was not identified in a meta-analysis of unselected population studies (Cornaggia et al., 2013) nor, to the best of our knowledge, in BD (Arici et al., 2018; Michaelis et al., 2003). The discrepancy between the present study and these two previous BD studies may be explained by increased statistical power due to our larger sample size or to sampling issues. Likewise, the association between mixed episodes and recurrent SA had not been consistently evidenced, although there are reports linking mixed episodes with recurrent suicidal ideation (Goldberg et al., 1998) and repetition of SA (Persons et al., 2018). It is noticeable that mixed episodes have also been associated with rapid cycling and SUD (Carvalho et al., 2014), both being plausibly associated with recurrent SA. We also confirmed

a previously-reported association between depressive polarity at onset of BD and recurrent SA (Neves et al., 2009), which was replicated in both country subsamples. Both results regarding mixed episodes and polarity at onset seemed specific in our sample, given that it was not confounded by the rate of mood episodes over the course of BD.

The present study has several strengths. It relies on the extensive assessment of a large sample of patients by structured interviews across a wide range of clinical variables, while using stringent phenotypes for BD, suicidal outcomes and SUDs. The data on SA is expectedly reliable, because the risk of misclassification bias was reduced by using multiple-items assessment (Hom et al., 2016) (supplementary Methods) and by focusing on a stringent phenotype (Forman et al., 2004), which may have further limited the risk for inconsistent reporting of SA (Hart et al., 2013). Cases with BD ‘not otherwise specified’ were excluded to enhance the face validity of the sample. Not applying correction for multiple testing decreased type II error, since it allowed for identifying both female gender and mixed states as risk factors for recurrent SA, noticing that the selection of variables would have eventually been similar under Bonferroni correction. The regression model was performed with 752 cases and yielded high significance and good stability. Finally, in our sample, both the rates of SA and the proportion of recurrent *vs.* single SAs fell within the range of BD samples described elsewhere (Arici et al., 2018; Michaelis et al., 2003; Schaffer et al., 2015). The relatively low prevalence of comorbid SUD in our sample may reflect a common issue when studying addictive comorbidity among participants referred to specialized care for BD (Henry et al., 2015), as compared to those referred to acute inpatient wards or addiction clinics (Langås et al., 2012). It may also be related to issues in diagnostic accuracy (Hasin et al., 2006) and, possibly, to the underreporting of substance use and misuse by patients seen in psychiatric *vs.* addiction settings.

The study also has limitations. The study was retrospective, which may have introduced recall bias that could be more important in participants with more severe/comorbid BD. The study was a secondary analysis of primary data collected from studies with somewhat different foci (genetics in France, early illness phases in Norway), which is likely to have introduced some selection biases. Thus, recurrent SA were significantly more frequent in the French *vs.* Norwegian sample (Table 1), even after controlling for confounding factors (Table 3). Table 1 and Figure 2 show further subsample differences. Compared to Norwegian participants, the French were also significantly older, which is likely explained by the focus of the Norwegian study toward first treatment patients. Besides, Norwegian participants lived more frequently alone than the French, probably due to their younger age. French participants also had a higher prevalence of lifetime SA and mixed episodes. It is noticeable that both suicidal behavior and tobacco smoking are highly prevalent in France (Giovino et al., 2012; Nock et al., 2009). As regards the inclusion of former tobacco smokers in the Norwegian non-smokers group, whilst they were regarded as lifetime tobacco smokers in France, we performed sensitivity analyses in current smokers only and to compare former *vs.* current smokers with regards to SA risk (supplementary Tables 1 & 3). Overall, there might have been some residual confounding effects of cross-national sampling and assessment procedures, although they were mostly similar (see supplementary Methods for SA history collection). Finally, it is noticeable that adjusting the duration of BD by the age at interview – both being lower in the Norwegian subsample - the resulting ratio did not differ between participants from Norway *vs.* France.

There were other limitations. The study was retrospective, which may have introduced recall bias that could be more important in participants with more severe/comorbid BD. We did not assess distal/lifetime risk factors such as childhood trauma, anxiety and personality disorders, which are possibly associated with with recurrent SA (Arici et al., 2018) in complex clinical

patterns including increased risk for SUD comorbidity (Salloum and Brown, 2017) and shared psychological dimensions (e.g. affective lability, impulsiveness, hostility) (Aas et al., 2017; Etain et al., 2017, 2013). This is especially lacking regarding impulsivity and reward processing, which are major modulators of the link between trait and state vulnerability to suicidal behavior, in the framework of the stress-diathesis theory of suicidal outcomes (Malhi et al., 2018). Apart from tobacco smoking, we did not consider quantitative measures of exposure to addictive substances, although they may have been useful in terms of relative exposure to different risk factors and outcomes (Kennedy et al., 2015). Finally, due to cross-sectional design, lifetime suicidal behavior was a right-censored variable in the study, so that new SAs may have occurred after participants' assessments (thus with potential misclassification in terms of SA group).

The associations evidenced in the present study are likely bi-directional and partly result from a shared liability of BD-SUD toward recurrent SA without any possible conclusion about causal inference. It is noticeable, however, that emerging data suggest such a causal relationship between smoking outcomes and both mood states (Taylor et al., 2014) and suicide risk (Evins et al., 2017; Grucza et al., 2014). With that regard, all their possible links (Hughes, 2008) will have to be investigated if one were to address the causality issue. Still, we have added important pieces of evidence regarding liability patterns of recurrent SA and SUDs in BD, especially by attempting to differentiate the factors associated with either single, recurrent SA, or both. Such vulnerability could further interact with specific stress comorbidity patterns to increase suicidal risk, especially toward the most burdensome suicidal outcomes. To our knowledge, no study to date has sought to determine whether treating SUD could decrease the incidence of SAs in BD, although this benefit has been strongly established as regards e.g. the specialized treatment of heroin dependence (Darke and Ross, 2002). This would be particularly relevant as regards nicotine dependence, the treatment of which is well-

defined and shows fair to good response rates, even in people with BD, a majority of whom are willing to undergo such treatment (Evins et al., 2015; West et al., 2018).

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