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Increased risk of suicide attempt in bipolar patients with severe tobacco dependence

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abstract

Background: The aim of our study was to investigate, in bipolar patients, the association between tobacco status (use and dependence) and history of suicide attempt, and to assess the possible role of inflammation as a missing link in the association between smoking status and history of suicide attempt.

Methods: A total of 453 adult bipolar out-patients recruited in the French FondaMental Advanced Centres of Expertise for Bipolar Disorder were divided into two subgroups: 274 patients without past history of suicide attempt (non-SA), and 179 patients with a past history of suicide attempt (SA). Tobacco use and dependence, psychiatric and somatic comorbidities, history of childhood abuse, family history of suicide were assessed. Fasting blood tests yielded samples collected for the measurement of high sensitivity (hs-)CRP.

Results: The risk of suicide attempt increased with smoking dependence. Notably, bipolar patients with a history of suicide attempt were three times more likely to have severe tobacco dependence, independently of confounding factors. However, we failed to find arguments promoting the hypothesis of inflammatory markers (through hs-CRP measure) in the link between tobacco dependence and suicidal behavior.

Conclusions: We found a significant association between severe tobacco dependence and history of suicide attempt, but not with level of CRP, independently of confounding factors. Longitudinal studies taken into account all these potential confounding factors are needed to confirm our results.

1. Introduction

With one million deaths by suicide every year and one billions of smokers all around the world, suicide and tobacco use disorder are two main public health concerns (World health organization, 2012, 2014). A meta-analysis based on fifteen prospective cohort studies

involving over one million participants found that former and current smokers had respectively 1.28 and 1.81 increased risk of completed suicide compared with never smokers, with a dose-response effect (Li et al., 2012). However, in this meta-analysis, only two studies took into account body mass index (BMI) as a potential confounder and none took into account personal history of suicide attempt and childhood trauma as potential confounder. In addition, significant associations have also been found between smoking and suicidal ideation or suicide attempts in both cross-sectional studies (Barbosa et al., 2014; Evren et al., 2014; Hallfors et al., 2004; Makikyro et al., 2004; Wu et al., 2004) and prospective studies (Breslau et al., 2005;

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Hintikka et al., 2001; Oquendo et al., 2007), mostly in general population. However, these results have not always been replicated when controlling for mental disorders (Boden et al., 2008; Kessler et al., 2007; McGee et al., 2005; Wilcox and Anthony, 2004). Similarly to studies on completed suicide, these studies had not controlled for personal history of childhood trauma, BMI, and somatic diseases. Interestingly, in the National Comorbidity Survey panel sample, Kessler et al. (2009) have found that the association between smoking and suicidal ideation did not remain significant after controlling for confounding factors including childhood trauma. However the association between early-onset nicotine dependence and suicide plans persisted after such adjustment. It might be due to the fact that the authors considered nicotine dependence instead of nicotine use. Thus, studies assessing the association between nicotine dependence and suicidal behaviors or ideation, considering confounding factors are largely needed. Finally, most of previous studies were conducted in non-psychiatric population although psychiatric patients have elevated rates of nicotine dependence (Grant et al., 2004) and are at high suicide risk.

The link between smoking and suicide remains poorly understood. Interestingly, several lines of evidence support a link between inflammation and suicidal behavior, with higher CRP levels in suicidal patients vs. healthy controls (Black and Miller, 2014) or psychiatric controls (Courtet et al. submitted). Besides, studies have found that cigarette smoking was positively associated with CRP plasma levels, after adjustment for other major cardiovascular risk factors (Vargas et al., 2013a; Wannamethee et al., 2005).

The aim of our study, based on a large cohort of bipolar patients followed in the French FondaMental Advanced Centers of Expertise for Bipolar Disorders (FACE-BD), was: (1) to investigate the association between tobacco status (use and dependence) and history of suicide attempt, after adjusting for potential confounders, and (2) to assess the possible role of inflammation on the association between smoking status and history of suicide attempt.

2. Methods

2.1. FondaMental advanced centers of expertise for bipolar disorders (FACE-BD)

The aims of bipolar expert centres are to offer a systematic and accurate assessment to provide advice on personalized treatment strategies. The centres are open to all bipolar subtypes (I, II, and not otherwise specified), patients being referred by a general practitioner or a psychiatrist. Each centre provides support to clinicians in delivering personalized care plans derived from systematic case assessments undertaken at the centre. Cross-centre reliability is monitored. A Web application, e-bipolar[®], is used to record data in a common computerized medical file. Anonymized data are entered into a shared national database for research. The assessment protocol was approved by an ethical review board and required only a letter of information for patients.

2.2. Sample (see supplemental material for flow chart)

Among 1304 outpatients evaluated in the French FACE-BD centers from January 2009 and July 2014, we recruited 453 bipolar (according to DSM-IV criteria) outpatients aged over 18 years. Exclusion criteria were the presence of medical comorbidities including multiple sclerosis, inflammatory bowel disease, HIV infection, allergic diseases, cancer. Indeed, all these conditions are known to share peripheral inflammation and cell-mediated immune activation (Leonard 2012 *Neurosci. Biobehav. Rev.*) We also excluded patients with hepatic diseases as CRP is an

inflammatory marker produced by liver and those without information concerning history of suicide attempt, CRP levels or tobacco status.

Finally the sample was divided into two subgroups: 1) 274 patients without past history of suicide attempt (non-SA), and 2) 179 patients with a past history of suicide attempt (SA).

A suicide attempt was defined as a self-damaging act carried out with some intent to die, distinguished from other self-destructive types of behavior such as self-mutilation, non-compliance with medical treatment in severely ill individuals, and the use of substances such as alcohol and tobacco (Mann, 1998).

2.3. Clinical assessment

Psychiatric assessment. Diagnoses were determined using the Structured Clinical Interview for DSM-IV-R (SCID) for axis I. The following symptom and mood ratings were administered to participants: MADRS (Montgomery and Asberg, 1979) for depressive symptoms, YMRS (Young et al., 1978) for manic symptoms, the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) for the history of childhood abuse. Family history of suicide was also recorded.

2.3.1. Tobacco use patterns

For smoking status, participants were classified as non-smokers (had never smoked or smoked less than 100 cigarettes), ex-smokers (had smoked more than 100 cigarettes, but had not smoked in the past 30 days), or current smokers (had smoked more than 100 cigarettes and had smoked in the past 30 days) (World health organization, 1998). Assessment of tobacco dependence was using Fagerstrom Test for Nicotine Dependence (FTND) (Fagerstrom and Schneider, 1989), a self-questionnaire scoring from 0 to 10. Severe tobacco dependence was defined for FTND score ≥ 7 .

Clinical somatic assessment. We measured BMI, arterial tension. We recorded medical comorbidities such as arterial hypertension (i.e. systolic and/or diastolic blood pressure $\geq 140/90$ mmHg (World health organization, 2007)), diabetes (i.e. patient taking insulin or oral hypoglycaemic drugs or with fasting plasma glucose concentration ≥ 7.0 mmol/l (World health organization, 2007)), thyroid dysfunction (euthyroidism is defined by the Thyroid Stimulating Hormone: 0.45–4.50 mIU/L (Cappola et al., 2006)), dyslipidemia (i.e. fasting triglyceride level ≥ 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level ≥ 440 mg/dl (men) or ≥ 50 mg/dl (women) (World health organization, 2007)), and cardiovascular diseases (including history of coronary heart disease and myocardial infarction).

2.3.2. Biological assessment

Fasting blood samples were collected between 7:00 and 9:00 AM, and used to measure high sensitivity hs-CRP. Samples were collected in 5 ml EDTA coated tubes (BD Vacutainer, Franklin Lakes, NJ). We used the immunoturbidimetric method for quantifying serum concentration of hs-CRP via the Cobas8000 biochemistry analyzer (Roche Diagnostic, Meylan, France). Reagents and calibrators were used according to manufacturer guidelines with analytic measuring ranges set at 0.3–350 mg/L.

Because of a clinically predictive value, results for the categorical measure of inflammation were classified as follows: CRP < 1 mg/L for low cardiovascular risk/low level of systemic inflammation; 1.01–3.0 mg/L for moderate cardiovascular risk/moderate level of systemic inflammation; 3.01–10.00 mg/L for high cardiovascular risk/high level of systemic inflammation (Pearson et al., 2003). This cut-off was provided by a workshop entitled "CDC/AHA Workshop on Inflammatory Markers and

Table 1
Clinical characteristics of the 453 patients according to history of suicidal behavior.

Variable	Whole Sample N:453		Non-SA N:274		SA N:179		OR [95% CI]		p
	n	%	n	%	n	%	OR [95% CI]		
Gender									
Men	199	43.93	134	48.91	65	36.31	1		0.009
Women	254	56.07	140	51.09	114	63.69	1.68 [1.14; 2.47]		
Age (in years), mean (SD)	42.27 (13.06)		42.49 (13.52)		41.94 (12.35)		1.00 [0.98; 1.01]		0.66
Marital status									
Non-married	200	48.66	119	47.98	81	49.69	1		0.73
Married	211	51.34	129	52.02	82	50.31	0.93 [0.63; 1.39]		
Study level									
<12 years of study	166	40.29	91	36.55	75	46.01	1		0.06
≥12 years of study	246	59.71	158	63.45	88	53.99	0.68 [0.45; 1.01]		
Present occupation									
Not employed	216	52.43	125	50.20	91	55.83	1		0.26
Employed	196	47.57	124	49.80	72	44.17	0.80 [0.54; 1.19]		
Substance dependence or abuse (within the last month)									
No	373	93.02	230	92.74	143	93.46	1		0.78
Yes	28	6.98	18	7.26	10	6.54	0.89 [0.40; 1.99]		
Anxiety disorder (lifetime)									
No	252	59.43	171	65.52	81	49.69	1		0.001
Yes	172	40.57	90	34.48	82	50.31	1.92 [1.29; 2.87]		
Bipolar type									
I	212	46.80	138	50.36	74	41.34	1		0.08
II	173	38.19	102	37.23	71	39.66	1.30 [0.86; 1.96]		
Nos	68	15.01	34	12.41	34	18.99	1.86 [1.07; 3.24]		
Current depression level (MADRS score)									
Absent (r6)	217	48.87	143	53.76	74	41.57	1		0.02
Mild (7–19)	172	38.74	97	36.47	75	42.13	1.49 [0.99; 2.26]		
Moderate to severe (≥20)	55	12.39	26	9.77	29	16.29	2.16 [1.18; 3.92]		
Body mass index (kg/m ²)									
Normal (<25)	215	49.09	130	48.87	85	49.42	1		0.09
Overweight (25–29)	155	35.39	102	38.35	53	30.81	0.79 [0.52; 1.22]		
Obese (≥30)	68	15.53	34	12.78	34	19.77	1.53 [0.88; 2.65]		
Arterial hypertension									
No	393	92.47	235	91.09	158	94.61	1		0.18
Yes	32	7.53	23	8.91	9	5.39	0.58 [0.26; 1.29]		
Diabetes									
No	412	96.71	247	96.11	165	97.63	1		0.39
Yes	14	3.29	10	3.89	4	2.37	0.60 [0.18; 1.94]		
Thyroid dysfunction									
No	374	87.79	233	90.31	141	83.93	1		0.05
Yes	52	12.21	25	9.69	27	16.07	1.78 [1.00; 3.20]		
Dyslipidemia									
No	357	84.40	219	84.88	138	83.64	1		0.73
Yes	66	15.60	39	15.12	27	16.36	1.10 [0.64; 1.88]		
Cardiovascular disease									
No	405	95.97	245	96.08	160	95.81	1		0.89
Yes	17	4.03	10	3.92	7	4.19	1.07 [0.40; 2.87]		
CTQ: Total score									
<34	148	34.02	105	40.08	43	24.86	1		<0.0001
35–45	144	33.10	93	35.50	51	29.48	1.34 [0.82; 2.19]		
≥45	143	32.87	64	24.43	79	45.66	3.01 [1.86; 4.89]		

Non-SA : no personal history of suicide attempt/SA : personal history of suicide attempt; Nos: Non-specified.

Cardiovascular Disease: Applications to Clinical and Public Health Practice”, based on distributions of hs-CRP samples from 415 populations involving 440,000 persons.

2.4. Statistical analysis

Associations between patient's characteristics, smoking status, hs-CRP levels and history of suicide attempt were quantified with odds ratio (OR) and their 95% confidence interval (CI). Socio-demographic and clinical variables associated with history of suicide attempt (at $p < 0.15$) were included in logistic regression models to estimate adjusted OR for smoking status and CRP levels. Significance level was set at $p < 0.05$. Analyses were performed using SAS statistical software (version 9.3; SAS Inc., Cary, NC).

3. Results

3.1. Sociodemographic and clinical data (Table 1)

In comparison to non-SA, SA were more likely to be female ($p = 0.009$) and obese ($p = 0.09$), to have thyroid dysfunction ($p = 0.05$), a personal history of childhood maltreatment ($p < 0.0001$), and a lifetime history of anxiety disorder ($p = 0.001$). SA had higher current depression levels ($p = 0.02$) compared to non-SA. Finally, in comparison to non-SA, SA were more likely to be bipolar II and Non-Specified than bipolar I ($p = 0.08$).

Subsequent analyses were thus adjusted for all these factors plus others characteristics associated with SA with $p < 0.15$. In the whole sample, duration of bipolar disorder was 17.30 (SD = 11.09) years and patients have been treated for 14.80 (SD = 10.21) years.

Table 2
Tobacco status and CRP levels according to suicidal behavior.

Variable	Non-SA N%274		SA N%179		Model 0 ^a		Model 1 ^b		Model 2 ^c	
	n	%	n	%	OR [95% CI]	p	OR [95% CI]	p	OR [95% CI]	p
Smoking status										
Never	131	47.81	73	40.78	1	0.05	1	0.22	1	0.17
Current	104	37.96	88	49.16	1.52 [1.01; 2.27]		1.44 [0.87; 2.37]		1.58 [0.94; 2.67]	
Past	39	14.23	18	10.06	0.83 [0.44; 1.55]		0.86 [0.41; 1.77]		0.98 [0.46; 2.06]	
Tobacco										
Never smoker	131	55.27	73	45.91	1	0.21	1	0.46	1	0.36
10 packs per year	41	17.30	27	16.98	1.18 [0.67; 2.08]		1.14 [0.57; 2.27]		1.29 [0.63; 2.62]	
10–20 packs per year	34	14.35	32	20.13	1.69 [0.96; 2.96]		1.48 [0.77; 2.83]		1.59 [0.81; 3.09]	
420 packs per year	31	13.08	27	16.98	1.56 [0.87; 2.82]		1.62 [0.81; 3.25]		1.76 [0.85; 3.62]	
Tobacco										
Not current smoker (never or past smoker)	170	62.04	91	50.84	1	0.002	1	0.02	1	0.01
Current Fagerstromo7	84	30.66	56	31.28	1.25 [0.82; 1.90]		1.15 [0.68; 1.95]		1.21 [0.70; 2.07]	
Current FagerstromZ7	20	7.30	32	17.88	2.99 [1.62; 5.52]		2.80 [1.34; 5.88]		3.23 [1.50; 6.96]	
CRP levels (mg/l)										
1	60	21.90	32	17.88	1	0.23	1	0.35	1	0.22
1.01–3.00	165	60.22	104	58.10	1.18 [0.72; 1.94]		0.85 [0.46; 1.58]		0.81 [0.43; 1.54]	
3.01–10.00	49	17.88	43	24.02	1.65 [0.91; 2.98]		1.33 [0.62; 2.83]		1.41 [0.64; 3.09]	
CRP levels (mg/l) ^d	1.67 (1.72)		2.03 (1.84)		1.26 [1.02; 1.55]	0.03	1.17 [0.88; 1.55]	0.27	1.18 [0.88; 1.58]	0.26

Non-SA: no personal history of suicide attempt/SA : personal history of suicide attempt.

^a Model 0: crude association.

^b Model 1: model adjusted for gender, educational level, body mass index, thyroid dysfunction, anxiety disorder, current depression level, Bipolar type.

^c Model 2: model was adjusted for all the covariates on model 1 plus CTQ-Score Total.

^d Geometric mean (SD).

3.2. History of suicide attempt and tobacco use pattern

Overall, 204 patients (45.03%) had never smoked, 192 patients (42.38%) were current smokers and 57 patients (12.58%) were past smokers. Duration of tobacco use was 23.97 (SD \pm 12.74) years.

A significant association was found between smoking status and history of suicide attempt; but this association did not remain significant after adjustment for potential confounders. Furthermore, history of suicide attempt was associated with tobacco dependence: the risk of suicide attempt was higher in severe dependent smokers than non-severe dependent smokers (model 0, $p=0.002$) according to FTND score. This association remained significant after adjustment for gender, educational level, BMI, thyroid dysfunction, anxiety disorder, current depression level and bipolar subtype (model 1, $p=0.02$, OR \pm 2.80; 95% CI [1.34–5.88] for current FTNDZ7), and also after adding adjustment on childhood maltreatment (model 2, $p=0.01$, OR \pm 3.23; 95% CI [1.50–6.96] for current FTNDZ7) (Table 2). Moreover, this association remained significant after adjustment for familial history of suicidal behavior (suicidal attempt and completed suicide) ($p=0.02$, OR \pm 3.61; 95% CI [1.50–8.67]) after having excluded patients with data unavailable ($n=188$).

3.3. History of suicide attempt and CRP levels

As a continuous variable, plasma hs-CRP levels was associated with history of suicide attempt (model 0, $p=0.03$, OR \pm 1.26; 95% CI [1.02–1.55]), but this association did not remain significant after adjustment for potential confounders. No association was found between hs-CRP levels and history of suicide attempt when hs-CRP was divided into 3 classes.

4. Discussion

We have found that the risk of suicide attempt increased with smoking dependence. Notably, bipolar patients with a history of suicide attempt were twice as likely to have severe tobacco dependence, independently of confounding factors. Of note, given that one mechanism linking smoking and suicidal risk is likely to

involve tobacco-related disease (Hawton and van Heeringen, 2009; Hughes, 2008), we have excluded chronic inflammatory diseases such as cancer, and we have assessed cardiovascular disease as potential confounding factor.

The association between severe tobacco dependence and suicidal behavior is promoted by common biological mechanisms of these two conditions, which might potentiate each other. First, smoke exposure has been shown to reduce serotonin and its metabolites in animal studies (Hughes, 2008; Olausson et al., 2002). Notably, serotonin depletion has been related to suicidal risk in several studies. Second, nicotine is a strong activator of hypothalamic-pituitary-adrenal (HPA) axis (Rohleder and Kirschbaum, 2006), and a dose-dependency of nicotine-induced HPA axis stimulation has been observed in animal studies (Cam et al., 1979). Importantly, HPA axis overactivity has been associated with increased risk of suicidal risk (Jokinen et al., 2007; Mann et al., 2006; Mathew et al., 2003). Third, inflammation should be involved in association between tobacco use and suicidal risk. Suicide attempters have significantly higher levels of nitric oxide metabolites (products of nitrates and nitrites) and lipid hydroperoxides (a biomarker of oxidative damage to lipids or lipid peroxidation) as well as lower levels of plasma total antioxidant potential TRAP (a biomarker of total antioxidant defenses) than non attempters (Vargas et al., 2013b). Proinflammatory cytokines have been implicated in depressed smokers (Nunes et al., 2012). Finally, inflammation and oxidative stress is a mechanism activating production of kynurenine, which may deplete tryptophan and lead to decreased levels of serotonin. However, we failed to find arguments promoting the hypothesis of inflammatory markers through hs-CRP in the link between tobacco dependence and suicidal behavior. One explanation could be that bipolar patients in our sample had low levels of depression (mean MADRS \pm 9.09 (SD \pm 8.01)). Notably, the only one study conducted in non-depressed suicidal patients failed to find differences in CRP levels between suicidal and non-suicidal patients. On the contrary, other studies finding elevated CRP levels in suicidal vs. non-suicidal patients included individuals suffering from moderate to severe depression (Karlovic et al., 2012; O'Donovan et al., 2013). Indeed, depression is associated with increased inflammatory levels. We have chosen hsCRP as inflammatory marker given that it is an easily accessible biomarker of low-grade systemic inflammation (Guarner

and Rubio-Ruiz, 2015), which can be obtained from a non-fasting peripheral blood sample. However, we cannot exclude CRP is not the best marker for testing the hypothesis of inflammatory marker in the link between tobacco dependence and suicidal behavior. Further studies would benefit from interleukin investigations. Moreover, mood stabilizers might have an anti-inflammatory action; indeed, lithium, lamotrigine, valproic acid and atypical antipsychotics reduce oxidative stress (Berk et al., 2011; Malhi et al., 2013). Some atypical agents, such as olanzapine have been associated with a reduction of inflammatory markers (Berk et al., 2011).

4.1. Strengths and limitations

The main strength of this study is the inclusion of multicentric representative bipolar patients. Then, there is a large standardized assessment for each patient admitted in FondaMental Advanced Centers of Expertise for Bipolar Disorders, which have permit to take into account a wide range of potential cofounders (including sociodemographic characteristics, BMI, somatic and psychiatric comorbidities, and history of childhood trauma).

However, the cross-sectional data does not allow concluding on temporal relationship between history of suicide attempt and tobacco dependence. Then, we have used only CRP levels for assessing inflammation, which might have limited our results.

4.2. Conclusion

We found a significant association between severe tobacco dependence and history of suicide attempt, independently of potential confounders. Longitudinal studies taken into account all these potential confusing factors are needed to confirm our results.

Role of funding source

None.

Conflict of interest

None of the authors declare conflict of interests related to this manuscript.

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The group of Ph Courtet is affiliated with the Bio-PsyLaboratory of Excellence.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2015.04.038>.

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