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# **A specific association between laxative misuse and suicidal behaviours in patients with anorexia nervosa and bulimia nervosa**

Aiste Lengvenyte<sup>1,2,3</sup> · Robertas Strumila<sup>1,2,3</sup> · Laurent Maimoun<sup>4,5</sup> · Maude Seneque<sup>1,2</sup> · Emilie Olié<sup>1,2</sup> · Patrick Lefebvre<sup>6</sup> · Eric Renard<sup>1,7</sup> · Philippe Courtet<sup>1,2</sup> · Sebastien Guillaume<sup>1,2</sup>

## **\*Correspondence :**

Robertas Strumila robertas.strumila@gmail.com

1 Institute of Functional Genomics, University of Montpellier, CNRS, INSERM, 371 Av. du Doyen Gaston Giraud, 34090 Montpellier, France

2 Department of Urgent and Post Urgent Psychiatry, CHU Montpellier, 371 Av. du Doyen Gaston Giraud, 34090 Montpellier, France

3 Faculty of Medicine, Institute of Clinical Medicine, Psychiatric Clinic, Vilnius University, Vilnius, Lithuania

4 PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France

5 Département de Médecine Nucléaire, Hôpital Lapeyronie, Centre Hospitalier Régional Universitaire (CHRU) Montpellier, 34295 Montpellier, France

6 Department of Endocrinology, Diabetes, and Nutrition, CHRU Montpellier, Montpellier, France

7 UMR CNRS 5203, INSERM U1191, Institute of Functional Genomics, University of Montpellier, Montpellier, France

## **Keywords**

Brain–gut–microbiota axis · Eating disorders · Suicide · Laxatives · Anorexia nervosa · Bulimia nervosa

## **Acronyms**

5-HT 5-Hydroxytryptamine, serotonin; AN Anorexia nervosa; BD Bipolar disorder; BMI Body mass index; BN Bulimia nervosa; DSM-5 Diagnostic and statistical manual of mental disorders 5; ED Eating disorder; EDE-Q Eating disorders examination questionnaire; MDD Major depressive disorder; MINI Mini-International neuropsychiatric interview; OR Odds ratio AOR Adjusted odds ratio; SA Suicide attempt ; SI Suicidal ideation ; SB Suicidal behaviour ; SSRI Selective serotonin reuptake inhibitor.

# Abstract

## Objective

Eating disorders (ED) are associated with an increased risk of suicidal behaviours. Laxative abuse might alter the gut–brain axis signaling, that might be implicated in the pathophysiology of suicide. This study aims to determine the association between laxative misuse and suicide attempt (SA) and suicidal ideation (SI) in patients with ED.

## Methods

277 patients with ED were recruited from an Eating Disorder Unit of Lapeyronie Academic Hospital, Montpellier, France. Sociodemographic and clinical data were collected. Chi-square and *t* test were used, with Bonferroni corrections where required. Multiple regression models assessed the relationships between laxative misuse, SA, and SI.

## Results

62 (22.4%) patients reported lifetime laxative misuse. They were more likely to have a history of SA than nonmisusers [43.83 vs 19.9%,  $p < 0.001$ , odds ratio (OR) 3.68]. In the multivariate model, adjusted for other confounders, lifetime laxative misuse remained associated with SA (adjusted OR 3.79,  $p = 0.041$ ). In past 28 days, patients with SA history reported misusing laxatives for more days than patients without SA history (6 vs 1.5 days,  $p = 0.01$ , adjusted for vomiting and ED severity). Laxative use days during past 28 days was associated with current SI, adjusted for vomiting in the same period ( $p = 0.017$ ).

## Conclusions

Current and lifetime laxative misuse were associated with SA history and current SI in patients with ED, at least in part independently of other suicide-related factors.

## Level of evidence

Level III cohort, cross-sectional study.

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## Introduction

Eating disorders (ED) are frequently mentioned among the most lethal conditions in psychiatry. ED display high mortality rates, with anorexia nervosa (AN) at the top of the list [1]. In a large survey study, the adjusted odds ratio (OR) of suicide attempt (SA) was 5–sixfold higher in individuals with lifetime history of ED, and 12-fold higher in those with the binge/purge type of AN [2]. One of the explanatory factors could be the high rates of psychiatric comorbidity, which augments the risk of SA in ED [3, 4]. However, an

independent association between bulimia nervosa (BN) and suicidality has been reported, even after controlling for psychiatric comorbidity [5]. Yet, studies on independent preventable factors associated with SB in ED are lacking.

Suicidal behaviours have been associated with purging behaviors in patients with ED [6]. In line, studies have associated SA history in ED with difficulties in emotion regulation and low reward dependence [7]. Yet, the higher risk of SA in ED cannot be entirely explained by the neuropsychological aspects of such disorders. For instance, patients with AN tend to have increased cognitive inhibition [8], which is generally considered a protective factor against suicidality. Indeed, several small-scale studies in patients with BN have found an association between laxative misuse and SA [9] or self-harming behaviors [10]. However, studies that included AN patients have reported mixed results [11–13].

Laxative use has been associated with marked changes in the gut microbiota composition [14], which is linked to the interoceptive signaling, and feeding behaviors via the gut–brain axis [15]. A change in any of the constituents of this delicate system has repercussions on the others. For example, gut microbiota alterations can influence the vagus nerve activation, the synthesis of neuro-active metabolites, such as serotonin (5-hydroxytryptamine, 5-HT) [16] and gamma-aminobutyric acid [17], and modulate the systemic and central inflammation responses [18, 19]. Since the 5-HT signaling and the immune system alterations are involved in the pathogenesis of SB [20], the gut–brain axis alteration might explain the possible association between laxative misuse and SB.

Compelling evidence on the role of 5-HT in suicide comes from a recent autoradiography study that showed higher 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> receptor binding and lower serotonin transporter levels in suicide victims compared with subjects with major depressive disorder (MDD) [21], suggesting lower 5-HT availability in the brain of suicide victims. Yet, it is frequently neglected that majority of all 5-HT in the human body is produced in the intestines, and gut bacteria have been shown to regulate the metabolism of the food derived 5-HT precursor tryptophan towards or from the synthesis of 5-HT [16]. Therefore, changes in gut bacteria composition might affect the production of 5-HT and other tryptophan metabolites.

To date, no big-scale study has investigated the link between misuse of laxatives, which might perturb the gut microbiota and 5-HT synthesis, and SB, controlling for putative cofactors. Therefore, the aim of the present study was to investigate whether the current or lifetime misuse of laxatives is specifically associated with SA history in patients with AN and BN, after controlling for eating disorder severity, psychiatric comorbidity and other purging behaviours.

## Methods

### Participants

The present study included 277 female patients with either AN or BN that were consulted for their ED in the Eating Disorder Unit of Lapeyronie Academic Hospital, Montpellier, France. The following inclusion criteria were used: (1) age between 15 and 45 years, (2) female gender, (3) native or fluent in French, (4) diagnosis of AN or BN according to the Diagnostic

and Statistical Manual of Mental Disorders 5 (DSM-5) criteria, and (5) ability to provide informed consent. Exclusion criteria were: (1) inability to understand and complete the clinical evaluation, (2) pregnancy or breastfeeding, and (3) deprivation of liberty by judicial or administrative decision. The study was carried out according to the Declaration of Helsinki. The informed consent was signed by all participants, in addition to official caregivers if the participant was younger than 18 years. This was an ancillary study in the framework of a larger project that was approved by the local ethics committee (CPP Sud Méditerranée IV).

### **Clinical assessment**

The diagnosis of AN or BN was based on the DSM-5 criteria. Patients were assessed by a senior psychiatrist and a senior nutritionist experienced in ED evaluation and management. In addition to the structured evaluation of ED, and screening for psychiatric comorbidity with the Mini-International Neuropsychiatric Interview (MINI, Version 5.0.0, [22]), sociodemographic and clinical data were collected from medical records and from relatives, when possible. All clinical diagnoses (current and lifetime) were confirmed by consensus.

Patients completed the Eating Disorders Examination Questionnaire (EDE-Q) [23], a 33-item screening tool to evaluate the core clinical dimensions of ED over the last 28 days. For scoring, questions are subdivided in four subscales that explore four ED dimensions: eating concern, body shape concern, weight concern, and restraint. The total score is calculated by adding the scores of the four subscales and dividing the sum by 4. In this study, the Cronbach alpha value for the four subscales and the total score was 0.945. Lifetime laxative misuse was defined as current or past self-reported use of laxatives for weight control, with a binary “Yes” or “No” answer to a question “Have you ever used laxatives to control weight?”. Same procedure was used applied for other purging behaviors (vomiting, use of diuretics, or both). Despite being a compensatory behaviour, compulsive exercise was not included in our analyses, because we were interested in behaviours that targets gastrointestinal tract. Also, the level when exercise is abused is much more subjective. Current laxative misuse was defined as reporting one or more times of laxative misuse during the past 28 days on the item 17 of the EDE-Q questionnaire.

History of SA was assessed using the suicidality section of the MINI. If the patient answered that he or she has attempted suicide in the past (“Yes” or “No”), a direct question was then asked during the psychiatric interview (i.e., “Have you ever attempted to take your own life?”), and the number of the attempts ascertained. The severity of the current suicidal ideation (SI) was measured with the Beck Depression Inventory Short Form (BDI-SF) item 7, which measures SI from 0 points (no SI) to 4 points (active SI) [24].

### **Statistical analysis**

Categorical variables are presented as percentages, and quantitative variables as means with standard deviations. Differences between categorical variables were analyzed with the Chi-square ( $\chi^2$ ) test. Before the comparison of continuous variables, the data was assessed for normality with Levene’s test for equality of variances. The *t* test was used in case of normal variance, and the non-parametrical Mann Whitney *U* test in all other cases. Odds ratios (OR) with 95% confidence intervals (CI) were then computed with risk analysis function for categorical data, and exp(b) function for continuous data using logistic regression. Missing data were not imputed, and comparisons were performed based on individuals for whom data for the exact comparison were available. Percentages are reported for valid cases.

A linear regression model was used to test the multicollinearity of all variables. Each independent variable was used as dependent variable and compared to all the other independent variables. Multicollinearity was quantified by computing the variance inflation factor (VIF) that measures the relationship between the dependent variable and the other independent variables. Multicollinearity was rejected in all cases, because VIF was never  $> 3$ . A multiple logistic regression model was then used to measure the associations between significant factors and SA history.

To assess whether laxative misuse was associated with SA history independently of other significant factors, a multivariate logistic regression model was performed. In the model, SA was entered as the dependent variable, while laxative misuse and ten other variables most significantly associated with SA history were entered as covariates. Another multivariate logistic regression was then performed, evaluating the relationship between the recent laxative misuse (prior 28 days) and SA. The association between current SI severity and current laxative misuse severity was assessed with the Pearson correlation coefficient. A linear regression model was then used to see whether laxative misuse is associated with SI independently of vomiting.

Significance in multivariate models was set at  $p < 0.05$ . Where necessary, Bonferroni corrections were used. All analyses were performed using the SPSS statistical software (version 23.0.0.2; IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp).

## Results

### Characteristics of the included patients stratified according to suicide attempt history

The present study included 277 patients with AN (65%,  $n = 180$ ) and BN (35%,  $n = 97$ ) diagnoses, among whom 62 had a history of SA. Both AN-R (AN restrictive) and AN-BP (AN binge-eating purging) were included into the analyses. The sociodemographic and clinical characteristics of the participants in function of SA history are presented in Table 1. Current and lifetime laxative misuse, higher EDE Q score, lifetime vomiting, history of major depressive disorder, and use of tobacco were more frequent in patients with SA history. They also had a higher BDI-SF score and a BDISF item 7 score (all aforementioned relationships significant after the Bonferroni correction for multiple comparisons, at  $p < 0.0025$ ). History of anxiety disorders, diuretics use, substance use disorders, higher current body mass index (BMI), and history of bipolar disorders were also more frequent in the SA group, but significance was lost after Bonferroni correction (see Table 1).

Multivariate logistic regression analysis using the variables most related to SA history (reported in Table 1) was performed. After controlling for vomiting, diuretics use, current BMI, EDE-Q total score, BDI-SF total score, use of tobacco, anxiety disorders, history of bipolar disorders, and history of major depressive disorder, lifetime laxative misuse remained significantly associated with lifetime SA history (aOR 3.79, 95% CI 1.056–13.603,  $p = 0.041$ ). Four other factors also remained significantly associated with SA history: vomiting, current BMI, BDI-SF total score, and use of tobacco (Table 2).

**Table 1** Sociodemographic and clinical characteristics of patients

	Mean $\pm$ SD or <i>N</i> (%)			<i>p</i> value	OR or exp( <i>b</i> ) (95% CI)
	All	SA history	No SA history		
<b>Sociodemographic characteristics</b>					
Age	27.65 $\pm$ 10.17	29.49 $\pm$ 11.87	26.87 $\pm$ 9.75	0.07	1.025 (0.99–1.05)
Female gender	262 (95.3%)	60 (96.77%)	202 (94.84%)	0.53	1.63 (0.35–7.57)
Professional situation: in employment	95 (34.3%)	21 (34.43%)	69 (34.27%)	0.98	1.07 (0.55–1.83)
Marital status: in couple/married	88 (31.8%)	20 (33.33%)	67 (31.60%)	0.80	1.08 (0.59–1.99)
<sup>b</sup> Education, years	13.26 $\pm$ 2.33	13.40 $\pm$ 2.05	13.21 $\pm$ 2.42	0.62	1.04 (0.91–1.17)
<b>Clinical characteristics</b>					
<b>BMI<sup>a</sup></b>					
Current	18.40 $\pm$ 3.58	19.46 $\pm$ 3.82	18.05 $\pm$ 3.30	0.005*	1.12 (1.03–1.21)
Illness duration, years	10.01 $\pm$ 9.41	11.89 $\pm$ 8.07	9.07 $\pm$ 9.95	0.20	1.03 (0.98–1.08)
EDE-Q score	3.33 $\pm$ 1.58	3.95 $\pm$ 1.43	3.17 $\pm$ 1.58	<0.001**	1.43 (1.15–1.78)
Lifetime laxative use	62 (22.4%)	26 (42.93%)	34 (16.43%)	<0.001**	3.68 (1.97–6.86)
<sup>b</sup> Current Laxative use, days	2.46 $\pm$ 9.32	5.93 $\pm$ 16.41	1.49 $\pm$ 5.68	0.002**	1.047 (1.01–1.09)
Lifetime vomiting	125 (45.1%)	43 (34.4%)	19 (12.75%)	<0.001**	3.59 (1.96–6.58)
Current vomiting, days		11.58 $\pm$ 18.49	7.13 $\pm$ 15.55	0.073	1.02 (0.99–1.03)
Diuretics	16 (5.8%)	8 (50%)	52 (22.08%)	0.007*	3.77 (1.36–10.58)
<b>Comorbidity</b>					
Substance use disorder history	26 (9.4%)	10 (38.46%)	50 (20.24%)	0.033*	2.46 (1.05–5.76)
Anxiety disorder history	106 (38.3%)	32 (30.18%)	26 (16.46%)	0.008*	2.20 (1.22–3.96)
Major depressive disorder history	189 (68.2%)	52 (27.66%)	7 (8.97%)	<0.001**	3.88 (1.68–8.98)
<sup>b</sup> BDI-SF	14.57 $\pm$ 8.02	19.92 $\pm$ 9.15	13.12 $\pm$ 7.06	<0.001**	1.12 (1.06–1.17)
<sup>b</sup> BDI-SF suicidal ideation	0.54 $\pm$ 0.91	1.26 $\pm$ 1.20	0.34 $\pm$ 0.71	<0.001**	2.57 (1.75–3.77)
Bipolar disorder history	22 (7.9%)	9 (40.90%)	52 (20.63%)	0.028*	2.66 (1.08–6.57)
Use of tobacco	114 (42.4%)	39 (34.21%)	23 (15.03%)	<0.001**	2.94 (1.63–5.29)

Diagnoses were based on The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5)

Missing data were not imputed, and comparisons were performed based on individuals for whom data for the comparison were available. Percentages are reported for valid cases. Categorical variables were compared using test. Means were compared using the Students *t* test. For continuous data, normality assumption was tested. *T* test was used if normality was assumed, and Mann Whitney *U* test was used in other cases, marked in the table as<sup>b</sup>

*Exp(B)* is an odds ratio for continuous variables

*BDI-SF* Beck Depression Inventory Short Form, *BDI-SF suicide* Beck Depression Inventory Short Form item 7, *BMI* body mass index, *EDE-Q* Eating Disorder Examination Questionnaire, *OR* odds ratio, *SA* suicide attempt, *SD* standard deviation

<sup>a</sup>Of note, BMI is presented for the whole sample of patients. Mean current BMI for AN was (16.41  $\pm$  1.90), for BN was (22.10  $\pm$  2.99)

\*Significant at *p* < 0.05, two-sided. \*\*Significant with Bonferroni-corrected *p* < 0.0025 (0.05 divided by *N* = 20 comparisons), two-sided

**Table 2** Multivariate logistic regression model of the association between history of suicide attempt and laxative misuse

	B	(S.E.)	Wald	p value	aOR (95% CI)
History of laxative misuse for weight control	1.332	0.652	4.175	0.041*	3.790 (1.056–13.603)
History of vomiting for weight control	1.856	0.618	9.010	0.003*	6.396 (1.904–21.485)
History of diuretics use for weight control	1.017	1.361	0.559	0.455	2.765 (0.192–39.803)
Current BMI	0.206	0.100	4.266	0.039*	1.229 (1.011–1.494)
EDE-Q score	– 0.609	0.251	5.882	0.15	0.544 (0.333–0.890)
Use of tobacco	1.775	0.616	8.317	0.004*	5.901 (1.766–19.718)
History of any anxiety disorder	0.658	0.583	1.274	0.259	1.931 (0.616–6.056)
History of major depressive disorder	0.870	0.758	1.317	0.251	2.388 (0.540–10.557)
History of bipolar disorder	– 0.345	1.034	0.111	0.793	0.708 (1.060–1.261)
BDI-SF score	0.145	0.044	10.768	0.001*	1.156 (1.060–1.261)

Multiple logistic regression analysis using the factors most related to suicide attempt history from Table 1

Laxative misuse was defined as having used laxatives to control weight at any moment in life

*BDI-SF* Beck Depression Inventory Short Form, *BMI* body mass index, *EDE-Q* Eating Disorder Examination Questionnaire, *aOR* odds ratio, *SE* standard error

\*Significant at  $p < 0.05$ , two-sided; \*\*Significant at  $p < 0.001$ , two sided

**Table 3** Association between laxative misuse and suicide attempt history

	<i>N</i> (%) of suicide attempters			
	Laxative misuse	no laxative misuse	p value	OR
All patients	26 (41.94%)	34 (16.43%)	<0.001*	3.68
Diagnosis				
Anorexia nervosa	11 (30.56%)	20 (14.18%)	0.021*	2.66
Bulimia nervosa	15 (57.7%)	14 (21.2%)	<0.001**	5.07
Comorbidity				
Major depressive disorder history	24 (46.15%)	43 (19.70%)	<0.001**	3.50
Bipolar disorder history	6 (66.67%)	5 (25.00%)	<0.001**	6.00
Anxiety disorder history	14 (46.67%)	17 (23.29%)	0.019*	2.88
Substance use disorder (except tobacco) history	8 (88.89%)	1 (6.25%)	<0.001**	120.0
Tobacco use	18 (52.94%)	20 (25.97%)	<0.006**	3.21

Laxative misuse was defined as having used laxatives to control weight at any moment in life

Statistical analyses were performed using the  $\chi^2$  or Fisher's exact tests for categorical variables

*OR* odds ratio

\*Significant at  $p < 0.05$ , two-sided

\*\*Significant with Bonferroni-corrected  $p < 0.00625$  (0.05 divided by  $N = 8$  comparisons)

### **Lifetime laxative misuse and suicide attempt history**

Among 277 patients, 62 (22.88%) reported lifetime misuse of laxatives. The percentage of patients with a history of laxative misuse was not significantly different between patients with AN (20%) and BN (28%),  $p > 0.05$ .

SA history was statistically significantly associated with laxative misuse in all patients (41.94 vs 16.42%, OR 3.68,  $p < 0.001$ , Table 3), as well as subsamples stratified by diagnoses and major comorbidities. In both AN ( $p = 0.021$ ) and BN ( $p < 0.001$ ) patients, lifetime laxative misuse was associated with lifetime history of SA (only the association in BN patients remained significant after the Bonferroni correction). Laxative misuse was associated with SA history in patients regardless of psychiatric comorbidity (MDD, bipolar disorders, and anxiety disorders, use of tobacco and other substance use disorders, with associations remaining significant in MDD, bipolar disorder, substance use disorders and tobacco users, after Bonferroni correction  $p < 0.00625$  (0.05 divided by  $n = 8$  comparisons).

Further analysis of the continuous data revealed that there was a tendency for laxative misuse to be associated with a higher number of lifetime SA ( $4.76 \pm 6.25$  in laxative misusers vs  $2.33 \pm 2.56$  in non-misusers,  $p = 0.077$ ). The mean EDE-Q score was higher in the laxative misuse group than in the non-misuse group ( $4.11 \pm 1.27$  vs  $3.06 \pm 1.59$ ,  $p < 0.001$ ). Meanwhile, mean current BMI ( $19.05 \pm 3.84$  vs  $18.18 \pm 3.50$ ,  $p > 0.05$ ) and minimal lifetime BMI ( $15.86 \pm 2.77$  vs  $15.38 \pm 2.39$ ,  $p > 0.05$ ) did not differ significantly between laxative misusers and non-misusers.

Table 3 Characteristics of the patients with suicide attempt history stratified in function of laxative misuse.

SA history was also associated with the higher number of times of laxative use during past 28 days (EDE-Q item 17):  $5.93 \pm 16.41$  vs  $1.49 \pm 5.68$ ,  $p = 0.01$ , aOR 1.05. In a multivariate model with the severity of the ED psychopathology (EDE-Q score) and vomiting as confounders during the past 28 days, current laxative misuse remained significantly associated with the lifetime history of SA,  $p = 0.048$ , OR = 1.054. EDE-Q score, but not recent vomiting remained significantly associated with SA history ( $p = 0.026$ , aOR 1.306 and  $p = 0.387$ , aOR 1.008, accordingly).

### **Laxative misuse and the severity of current suicidal ideation**

A further post-hoc exploratory analysis was performed to assess the association between laxative misuse and current SI. The severity of current SI (BDI-SF item 7 score) was higher in patients with the lifetime laxative misuse history, as compared to those without such history ( $0.94 \pm 1.09$  vs  $0.45 \pm 0.85$ ,  $p = 0.006$ , OR 1.65). The number of reported times of laxative use during the past 28 days correlated positively with the severity of current SI (Pearson's correlation coefficient  $r = 0.187$ ,  $p = 0.017$ ). In a linear regression model, controlling for current another purging behaviour vomiting, laxative misuse during the past 28 days was associated with current SI ( $p = 0.017$ ), while vomiting was not ( $p = 0.597$ ).

## Discussion

To our knowledge, this is the first study to explore the association between laxative misuse and SB in patients with ED while controlling for a number of possible covariates. The present study found that SA history was significantly more frequent (increase by almost fourfold) in AN and BN patients who had used laxatives to control weight, after adjusting for other significant clinical characteristics and psychiatric comorbidities, notably, other purging behaviours, comorbidities, eating disorder and depression severity. Moreover, SA history was also associated with the current (past 28 days) laxative misuse. The current use of laxatives was also associated with the current SI severity, even after controlling for another purging behaviour—vomiting.

There are several possible explanations for the current findings. First, patients with more severe ED might be more prone to use laxatives for weight control. Laxative misuse involves advanced planning and is less compatible with everyday life compared with some other means of weight control. Indeed, ED was more severe in patients with laxative misuse history. However, the association between laxative misuse and SA remained significant after controlling for the general severity of ED. Second, laxative misuse is a type of compensatory behaviour, that have been associated with suicidality as a group in previous studies [6]. It has been suggested that impulsivity might underlie this association, because it is strongly related to both purging [25] and SA [26]. Furthermore, impulsivity is regarded as a clinical hallmark of borderline personality disorder, and a study by Tozzi et al. has reported an association between laxative abuse and borderline personality disorder in ED patients [13]. Other studies have also demonstrated an association between laxative abuse and sexual abuse history [27, 28], which, in addition to being associated with increased impulsivity, might cause the laxative misuse as a way to increase control over the body and affects.

In our multivariate model, SA history was associated with both laxative misuse and vomiting, after adjusting for other purging behaviors, ED severity, BMI, comorbidity, and depressive symptomatology severity, suggesting the independent association between SA and both purging behaviours. Yet, only laxative misuse, and not vomiting, during the past 28 days was associated with both SA history and current SI. This suggests that misuse of laxatives remains a risk factor for SB, independently of other purging behaviors, possibly implicating mechanisms other than impulsivity.

The independent association between laxative misuse and SB suggests that a specific process, not directly related to the clinical presentation of ED and the presence of psychiatric comorbidity, might underlie this link. First, patients with ED and SB might have shared interoceptive deficits, as decreases ability to interpret body signals have been described in both ED [29, 30] and in SB [31]. AN patients have impaired ability to predict and interpret interoceptive signals, such as feelings of fullness and pain [32], and activation of brain regions known to be implicated in the interoceptive process in response to aversive stimuli are altered in patients remitted from AN [33]. Either restriction or bingeing and engaging in compensatory behaviours, such as laxative misuse, have been proposed to reflect initial difficulty in regulating misinterpreted hunger and satiety signals [30]. Meanwhile, interoceptive awareness impairments have been reported to be more frequent suicide attempters [34], and are proposed to facilitate the passing to act in patients with SI [35]. Indeed, increased pain tolerance (related to both hunger and to compensatory behaviours) and fearlessness of death have been proposed to mediate the relationship between ED and SB [36]. Finally, it should be noted that while laxative abuse was conceptualised as a purging behaviour in the present study, this behaviour can be also be regarded as a mean to regulate affects, bringing it closer to self-harm behaviours. However, this model does not explain why laxative misuse is independently associated with SA history, regardless of other purging behaviors and minimal BMI, that could also reflect affect control via vomiting or restriction.

An alternative explanation for the observed association could be associated with the mechanism of action of laxatives. Laxative use reduces nutrient absorption [37], causes disturbances in electrolyte and acid/base balance [38], and perturbs the gut microbiota composition, by increasing the relative

number of *Bacteroides* and *Alistipes* [14]. As transient osmotic perturbations cause long-term alterations in the composition of gut microbiota [39], even an episodic use of laxatives might have long-term repercussions. Meanwhile, microbiota alterations have been linked to ED [40], mood disorders and stress-related behaviors [41, 42], as well as susceptibility to learned helplessness [43]. Biologically, changes in the hippocampus neuroplasticity [44], and differences in the responses to negative emotional stimuli in relation to gut microbiota have been described [45]. Both *Bacteroides* and *Alistipes* have been associated with proinflammatory states [46, 47], which, in turn, are associated with SB [20]. A recent review analysed these issues in detail [48].

Gut microbiota might also modulate vagal signaling [49], which is crucial in ED. A cyclic increase in vagal activity have been suggested to drive the urge to binge-eat and vomit in BN [50], and ondansetron, a vagal activity modulator, has been used to treat BN [51]. Meanwhile, in a 5-year followup study, vagal stimulation resulted in reduced depressive symptomatology and suicidality [52], suggesting vagal nerve involvement in their pathophysiology. Indeed, oral serotonin reuptake inhibitors (SSRIs) have been shown to induce vagus nerve-dependent activation of the gut–brain axis, and the subsequent improvement of depressive-like behaviors in mice [53]. Gut bacteria also affect tryptophan availability and the synthesis of 5-HT, indoles and kynurenine [16]. Therefore, putative laxative-induced dysbiosis might ultimately result in lower 5-HT availability in the brain, which is an established finding in suicide attempters [21]. Treatment with the “good bacteria” *Lactobacillus reuteri*, for example, increases the blood levels of 5-HT in mice [54]. On the other hand, both *Alistipes* and *Bacteroides* metabolize tryptophan mostly via alternative ways, favouring production of indoles [55] and suicidality-linked quinolinic acid [56], in disadvantage of 5-HT production.

## Limitations

Results from this study should be interpreted considering some important limitations. First, this is a cross-sectional observational study, and causality cannot be inferred from the present results. Second, symptomatology, purging behaviour history and psychiatric comorbidity history were assessed via an interview; therefore, results are susceptible to recall bias. Yet, the same recall bias applies to both laxative use and other types of behaviours (vomiting). This study also did not discriminate among different types of laxatives that might have different effects on the gut health and SB, as well as the exact amount of laxatives used per one time of ingestion. Moreover, while the sample size was comparatively large for the question explored, it was too small to measure the association between laxative use and violent SA history. Indeed, it has been previously shown that SA in patients with AN is more severe and lethal compared with controls and patients with BN [57]. Therefore, it would have been interesting to determine whether laxative misuse plays a role in patients with ED and history of severe SA.

## Conclusion and future directions

In conclusion, both current and lifetime laxative misuse were associated with an increased risk of SA history in patients with AN and BN, independently of other purging behaviors, psychiatric comorbidity, ED severity, and depressive symptomatology. Current SI was also associated with the current laxative misuse, enforcing the reported relationship. Future studies should explore the differences in 5-HT system functioning, inflammation and gut microbiota in laxative misusers. The effects of different types of laxatives should be assessed. The anti-suicidal effect of gut bacteria supplements, such as *Lactobacillus reuteri* [54], should also be investigated in ED patients who misuse laxatives.

## **What is already known on this subject?**

The risk of suicidal behaviours in patients suffering from eating disorders is elevated compared to both general population and other mental disorders. Suicidal behaviour is associated with comorbid psychiatric conditions, such as depression, but is not fully explained by them. Some preliminary studies have associated laxative abuse and suicidal behaviours. Yet, larger studies examining the link between laxative misuse and suicidal behaviours, controlling for putative cofactors, were lacking.

## **What this study adds**

The present study has demonstrated an independent association between laxative abuse and suicidal behaviours. A multivariate model showed that, after eliminating effects of related psychiatric comorbidities and other compensatory behaviours such as vomiting, laxative abuse remained in the model as a significant predictor of a suicide attempt history. This is true for both lifetime and past month temporal periods. Therefore, awareness regarding the possible laxative abuse-related increase in risk of suicidal behaviours is needed.

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## **Declarations**

### **Conflict of interest**

No conflicts of interest to declare. Ethical approval This was an ancillary study in the framework of a larger project that was approved by the local ethics committee (CPP Sud Méditerranée IV).

### **Consent to participate**

All the patients signed the informed consent form.

### **Consent for publication**

All the patients agreed that anonymised data would be published.

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