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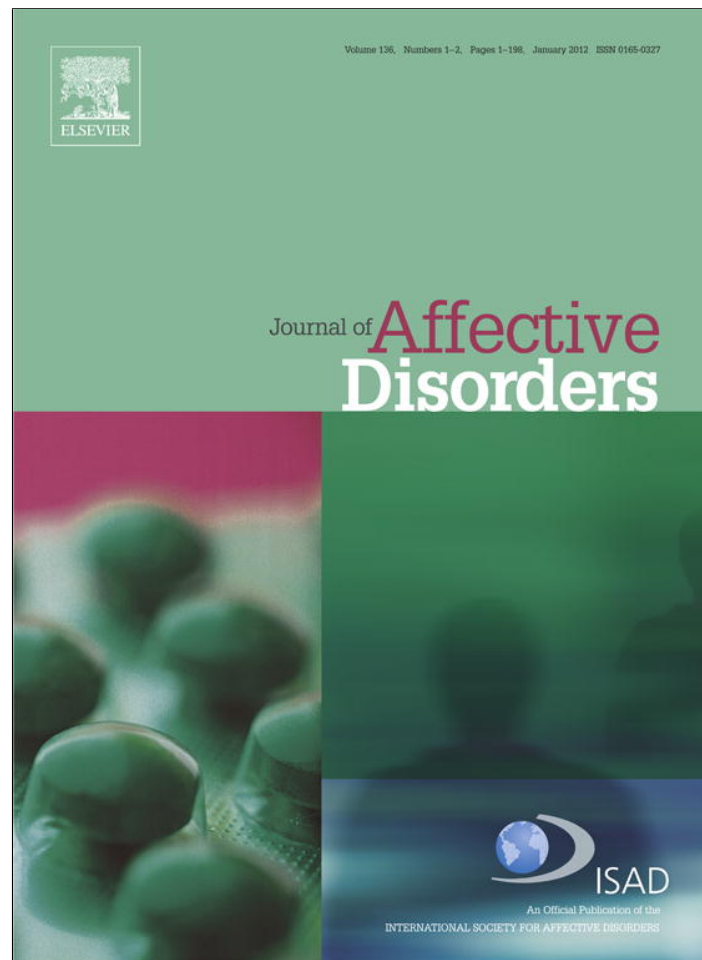
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## Mood disorders in eating disorder patients: Prevalence and chronology of ONSET



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### ABSTRACT

**Objectives:** In a clinical population, we estimated the frequency of mood disorders among 271 patients suffering from Anorexia Nervosa (AN) and Bulimia Nervosa (BN) in comparison to a control group matched for age and gender.

**Method:** The frequency of mood disorders was measured using the Mini International Neuropsychiatric Interview (MINI), DSM-IV version.

**Results:** Mood disorders were more frequent among eating disorder (ED) patients than among controls, with a global prevalence of the order of 80% for each ED group. The majority of the mood disorders comorbid with ED were depressive disorders (MDD and dysthymia). The relative chronology of onset of these disorders was equivocal, because mood disorders in some cases preceded and in others followed the onset of the eating disorders.

**Limitations:** Our sample was characterized by patients with severe ED and high comorbidities, and thus do not represent the entire population of AN or BN. This also may have resulted in an overestimation of prevalence.

**Conclusion:** Mood disorders appear significantly more frequently in patients seeking care for ED than in controls.

These results have implications for the assessment and treatment of ED patients, and for the aetio-pathogenesis of these disorders.

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**Abbreviations:** ED, Eating Disorders; AN, Anorexia Nervosa; BN, Bulimia Nervosa; MD, Mood Disorders; AN-R, Anorexia Nervosa Restrictive; AN-Rc, Anorexia Nervosa Restrictive-current; AN-BN, Anorexia Nervosa with bulimic symptoms (i.e. purging); AN-BNc, Anorexia Nervosa with bulimic symptoms – current; BN-P, Bulimia Nervosa with Purging; BN-Pc, Bulimia Nervosa with Purging-current; BN-NP, Bulimia Nervosa without purging; BN-NPc, Bulimia Nervosa without purging-current; MDE, Major Depressive Episode; MDD, Major Depressive Disorder; BD-I, Bipolar Disorder type I; BD-II, Bipolar Disorder type II; BMI, Body Mass Index; SPSS, Statistical Package for Social Sciences

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## 1. Introduction

The question as to whether mood disorders (MD) are particularly frequent in ED patients has interested clinicians for a number of years in part because their presence increase the severity of the ED (Brand-Gothelf et al., 2014). The answers to this question appear contrasted: in the literature, the frequency of MD in ED patients varies considerably from one study to another (Godart et al., 2007). For example, the lifetime prevalence of “at least one mood disorder” varies from 24% (Hatsukami et al., 1984) to 90% (Hudson et al., 1988) in BN patients and from 31% (Laessle et al., 1987) to 88.9% (Fornari et al., 1992) in patients suffering from AN. Few of

these studies included control groups, and, given that mood disorders are among the most frequent psychiatric disorders presenting in women, with an average lifetime prevalence of 20% (Kessler et al., 2005), there is little information about whether MD are more frequent among young women suffering from ED than in the general population, and particularly little information about the chronology of onset.

To explain the variable results reported in these studies, it is important to note that many of the studies conducted on this subject present the following serious methodological problems, which limit interpretation of the results (Godart et al., 2007): (1) sample sizes are often small (2) some of the studies include both men and women, without differentiating the results, although it is widely recognized that women suffer from MD more often than men (Kessler et al., 2005; Rouillon 2008); (3) the groups of AN patients evaluated differ between studies for age, BMI, clinical severity, duration of illness or clinical status, (4) few of these studies include control groups, and those that do are rarely matched for age or for other important characteristics; (5) the definition of “current” prevalence varies between studies, (6) over time, instruments and diagnostic criteria have changed, which has led to changes in estimations of prevalence. These elements taken together, and the fact that to date there is only one study published on the subject using DSM-IV criteria (Iwasaki et al., 2000) – without a control group – prompted us to undertake the present work, in which we compare a large group ( $N=271$ ) of subjects suffering from ED (AN and BN) with a group of control subjects matched for age and gender, as we have previously done with anxiety disorders (Godart et al., 2003). Our aims were to determine: (1) the frequency of mood disorders in all AN and BN subject groups, according to DSM-IV criteria; (2) whether mood disorders are significantly more frequent in ED patients than in the general population; (3) in cases with comorbidity, the relative chronology of onset of ED and mood disorder.

## 2. Method

### 2.1. Subjects

Women seeking treatment for an ED (AN or BN) were recruited as part of a larger French multicentre study on addictive disorders (ED, alcohol dependence, and illicit drug dependence; INSERM Network on Addictive Disorders, n 494013) (Godart et al., 2003). The inclusion criteria for ED patients were as follows: all consecutive female inpatients or outpatients, referred to one of the Network clinics (listed in Appendix A) with a current DSM-IV diagnosis of anorexia or bulimia nervosa, aged 15–30 years for anorexia nervosa, and 15–40 years for bulimia nervosa. Control subjects were recruited among patients referred to other departments of the same hospitals for a benign somatic disorder (e.g. stomatology), employees or students during systematic health visits, and high school or college students.

Exclusion criteria for both subjects with eating disorders and control subjects were a psychotic disorder and inability to read or complete the questionnaires. Additional exclusion criteria for the patients were as follows: a chronic or severe somatic disorder with possible effects on eating or weight (e.g. diabetes mellitus). Additional exclusion criteria for the controls were as follows: a lifetime DSM-IV diagnosis of anorexia or bulimia nervosa, alcohol abuse or dependence, illicit drug abuse or dependence, chronic or severe somatic disorder, or hospitalization for suicide attempt or severe accident (these situations being frequently linked to depressive or other psychiatric illnesses).

The controls were matched to the patients for gender, age (age of the patient 1 year for 15–24 year-olds, and 2 years for 25–40

year-olds, to take into account the significant variability of psychic and social characteristics in adolescents and young adults compared to adults), and socio-professional status, according to the following five broad categories defined by the French National Institute of Statistics and Economic Studies (INSEE): (1) farmers and workers; (2) self-employed tradespeople and employees; (3) managers and academic professionals; (4) high school and university students; (5) unemployed adults. In group 4, controls were matched to the patients according to whether they were high school or university students. The study group included 271 women with an ED (166 with AN and 105 with BN) and 271 individually-matched control women.

### 2.2. Ethical aspects

The protocol had been approved by the Consulting Committee for the Protection of Subjects in Biomedical Research (CCPPRB) of Hospital Cochin-Port Royal, Paris. After full information was provided, all subjects (and legal representatives for those below 18 years of age) gave written consent for their participation in the study. All data obtained were anonymous.

### 2.3. Instruments

A socio-demographic questionnaire was created for the study. The French edition of the Mini International Neuropsychiatric Interview (MINI, version 4.1) was used (Sheehan et al., 1997). The MINI is a structured diagnostic interview which assesses DSM-IV Axis I psychiatric diagnostic criteria in a standardized fashion with inter-rater reliability ranging from 0.88 to 1.0. All evaluators participating in this study received training in the use of the MINI by the authors of the instrument (E Weiller, INSERM U302, Paris, France).

The diagnoses assessed on the MINI in this study were the following: lifetime ED diagnosis (AN, AN-R or AN AN-BN; BN-P, BN-NP) and MD (MDE, dysthymia in the previous two years, hypomania and manic episode, mixed episode). For each episode present, the MINI assesses age at onset and age at end of episode (respectively: age at which the subject initially presented with disorders fulfilling the diagnostic criteria; age at which the subject no longer presented symptoms fulfilling the diagnostic criteria). According to the DSM-IV definitions, episodes are considered as disorders when at least one MDE has occurred (Major Depressive Disorder, MDD) or at least one MDE and one manic or mixed episode (BD-I) or at least one MDE and one hypomanic episode (BD-II). We defined the presence of “at least one mood disorder” as the presence of one or more of the three mood disorders evaluated and “at least one depressive disorder” as the existence of a MDD and/or dysthymia. Lifetime frequency was defined as: subjects presenting with a current and/or previous diagnosis of the disorder in question. We defined “current disorder” as occurring during the month preceding the evaluation, with the exception of dysthymia (assessed for the previous two years). BMI or Quetelet's index (weight in kilograms/height in meters<sup>2</sup>) was calculated to describe the subjects' nutritional state (Rolland-Cachera et al., 1991).

### 2.4. Statistical analyzes

Quantitative variables were described using the mean (m) and standard deviation (sd). Qualitative variables were described in percentages and proportions.

The proportions of subjects suffering from mood disorders among ED patients were compared to the control group, using MacNemar's  $\chi^2$  test. Regarding quantitative variables, the difference between means for subjects and controls was compared to

0, using the paired Student *t*-test; when the hypothesis of normal distribution of differences was not appropriate, we used Wilcoxon's test for paired samples. In order to compare the means of independent samples, we used Student's *t*-test or, where the necessary hypotheses were not verified, the Mann–Whitney test. Data were collected and analyzed using the SPSS 20 program.

### 3. Results

#### 3.1. Subject descriptions

Among the 271 participants suffering from current ED, 111 were classified as AN-R 55 were classified as AN-P, 86 were classified as BN-P and 19 were classified as BN-NP.

The descriptive characteristics and comparisons of the different subgroups are presented in Table 1.

AN-R patients were significantly younger than AN-BN and BN patients. BN patients were significantly older than AN-BN patients. AN-R participants had been ill for a significantly shorter period of time than the AN-BN and the BN groups. There was no significant difference in illness duration between AN-BN and BN groups. Patients with AN-R had a significantly lower BMI than that of AN-BN and BN patients, and BN patients had a significantly higher BMI than that of AN-BN patients. The proportion of inpatients was significantly higher in the AN-R group than in the AN-BN and BN groups, as well as in the AN-BN group compared to the BN group.

As regards socio-professional status, 92% of the AN-R group and 77% of the AN-BN group were students, whereas 40% of the BN were in employment. Most of the patients were unmarried (80.3% of the BN, 85.9% of the AN-BN and 98.1% of the AN-R).

The prevalence of anxiety disorders has been previously shown (Godart et al., 2005).

#### 3.2. Prevalence of mood disorder in AN and BN patients

##### 3.2.1. AN patients

Detailed results are presented in Tables 1 and 3.

Mood episodes were significantly more frequent among ED patients than among controls. Most of the mood disorders present in AN-R and AN-BN patients were MDE and dysthymia, whether lifetime or current disorders are considered. Mania or hypomania occurred only in subjects presenting with a MDE.

A comparison between sub-groups of AN patients showed that manic ( $p < 0.013$ ) and hypomanic episodes ( $p < 0.038$ ) were more frequent among AN-BN patients.

##### 3.2.2. BN patients

Detailed results are presented in Tables 2 and 3.

Mood episodes were significantly more frequent among ED patients than among controls. The majority of mood disorders present among BN-P and BN-NP patients were MDE and dysthymia, whether for lifetime frequency or current disorder. Manic episode and hypomania occurred only in subjects presenting with

a MDE (Table 4).

#### 3.2.3. Chronology of onset

For each disorder, we present the proportions of cases occurring prior to ED (at least the year before the onset of the ED), simultaneous with the onset of ED (within the same year) or following the onset (at least the year after the onset of ED), as well as the mean age at onset (Tables 5 and 6).

#### 3.2.4. AN patients

Detailed results are presented in Table 5.

81% of AN-R patients were hospitalized and 19% were outpatients against respectively 65% and 35% of AN-BN patients.

At least one “mood disorder” proceeded AN in almost a third of comorbid cases (AN-R: 34.5%; AN-BN: 29.7%) and around a quarter of the total sample (respectively 29/111 = 26.1 and 14/55 = 25.5).

#### 3.2.5. BN patients

Detailed results are presented in Table 6.

81% of AN-R patients were hospitalized and 19% were outpatients against respectively 65% and 35% of AN-BN patients.

“At least one mood disorder” preceded BN-NP in 25% and BN-P in 41.2% of comorbid cases, respectively between 4/19 = 21.1% and 26/86 = 30.2% of the total sample.

## 4. Discussion

#### 4.1. Diagnosis of “at least one mood disorder”

We confirm the high frequency of mood disorders (almost 80%) among both AN and BN patients. These disorders were significantly more frequent than among controls. Lifetime prevalence of mood disorders (MD) observed in the literature range from 38.1% to 40% in AN-R patients and from 61% to 70% in AN-BN patients for three DSM-IV disorders [major depression disorder (MDD), bipolar disorder (BD) and dysthymic disorder (DD)] (Iwasaki et al., 2000), or four DSM-III disorders [MDD, BD, DD and atypical depression (AD)] (Laessle et al., 1989). Our figures are higher (respectively 76.4% and 85.5% for AN-R and AN-BN patients), and this can be explained mainly by the high frequency of MDD (see the MDD section below), but also by the use of different diagnostic instruments, and the respective proportions of hospitalized patients in the samples.

The current prevalence of MD among patients in our study (AN-R 54.3%, AN-BN 61.5%) was higher than for the controls (AN-R and AN-BN control groups respectively 1.8% and 3.8%), and close to the estimated rates in the literature; for example 68.6% of 51 AN patients and 9.8% of 51 controls in a study by Rastam (1992), significantly more than in controls.

Lifetime prevalence of “at least one mood disorder” in BN patients (BN-NP 89.5% and BN-P 82.2%) is close to previous estimates, given the number of disorders we observed and various criteria used. Previous studies, in clinical samples of BN patients,

**Table 1**

Description of AN sub-groups and their controls.

	AN	CONTROLS	AN-R	CONTROLS	AN-BN	CONTROLS
Number	166	166	111	111	55	55
Age (years) $m \pm sd$	19.7 $\pm$ 3.1	19.9 $\pm$ 3.2	19.2 $\pm$ 2.9	19.5 $\pm$ 3.2	20.6 $\pm$ 3.0	20.7 $\pm$ 2.9
ED Duration (years) $m \pm sd$	2.8 $\pm$ 2.4	–	2.4 $\pm$ 2.1	–	3.5 $\pm$ 2.9	–
BMI $m \pm sd$	15.1 $\pm$ 1.5 **	20.9 $\pm$ 2.6	14.9 $\pm$ 1.9 *	20.7 $\pm$ 2.4	15.6 $\pm$ 2.0 *	21.5 $\pm$ 3.0

AN: Anorexia nervosa; AN-R: Anorexia nervosa restrictive type; AN-BN: Anorexia nervosa with bulimic symptoms; Comparison with controls

\*  $p < 0.0001$

\*\*  $p < 0.004$

**Table 2**  
Description of BN sub-groups and controls.

	BN	CONTROLS	BN-P	CONTROLS	BN-NP	CONTROLS
Number	105	105	86	86	19	19
Age (years) m ± sd	23.1 ± 5.0	23.1 ± 5.1	22.8 ± 4.5	22.7 ± 4.6	24.6 ± 6.9	24.5 ± 6.9
ED Duration (years) m ± sd	5.6 ± 4.8	–	4.9 ± 4.9	–	7.4 ± 7.5	–
BMI m ± sd	21.2 ± 3.9	20.9 ± 2.5	20.3 ± 3.3	20.9 ± 2.6	24.8 ± 4.2 *	20.6 ± 1.6

BN: Bulimia; BN-P: Bulimia with purging; BN-NP: Bulimia without purging Comparison to controls

\*\*p < 0.001

\* p < 0.0001

found that prevalence varied from 50% for two disorders (MDD and BPD), using DSM-III-R criteria (Powers et al., 1988) to 90% for five disorders [MDD, BPD, DD, CD (cyclothymic disorder) and atypical depression (AD)], using DSM-III criteria (Hudson et al., 1988). Three clinical studies compared BN patients to control subjects (Hudson et al., 1988; Bushnell et al., 1994; Schwalberg et al., 1992) and also found a significantly higher lifetime prevalence for BN patients.

The global current prevalence of MD evaluated in one study (Schwalberg et al., 1992) was 40% for two disorders, which does not differ greatly from our results (BN-NP: 61.1% and BN-P: 47.6%).

#### 4.2. Major depressive disorders

We observed a high prevalence for MDD in AN patients (63.9% for AN-R and 74.5% for AN-BN patients). Previous studies described a prevalence of 64.7% in AN-R patients (Herzog et al., 1999), and from 50% (Iwasaki et al., 2000) to 71.3% (Herzog et al., 1999) in AN-BN patients. It can be thought that the prevalence of MDD in AN subjects is likely to be lower in subjects treated in outpatient settings (9.5%) (Laessle et al., 1989) than in hospitalized patients (85%) (Viesselman & Roig, 1985). The high prevalence observed in our study is probably at least in part due to the fact that most of the AN patients were in hospital (81% of AN-R and 64% of AN-BN patients). In line with previous reports in the literature, we found a lifetime prevalence of MDD that was significantly higher in AN-R patients than in controls (Godart et al.,

2007).

The prevalence of MDD in BN patients was also high in our population (BN-NP: 78.9%; BN-P: 74.4%). This can be explained by the fact that our sample included severely ill subjects, as there were 4.2 times more depressed inpatients than outpatients, not taking account of anxiety disorders (Godart et al., 2007).

Previous studies in clinical populations having samples of at least 50 BN patients find a high lifetime prevalence for MDD, but slightly different from ours, between 61% and 63% (Hudson et al., 1987; Hudson et al., 1988; Brewerton, 1995; Herzog et al., 1999; Iwasaki et al., 2000).

Comorbid depression in AN and BN patients was almost always present at the time of the evaluation, whereas it was more often a past event in the lives of controls (who were paired for age to the ED patients). We can legitimately wonder whether some depressive symptoms, related to eating symptoms, explain a “false” comorbidity which could be partly an artifact, since some symptoms commonly occur in AM and MDD, such as menstrual disturbances, weight loss, sleeping and libido disorders and loss of interests (Godart et al., 2007).

It is indeed known that binge-eating is often followed by a depressed mood involving both sadness and anxiety (Paxton and Diggins, 1997). Therefore, at certain periods, the presence of depressive symptoms could be the result of the emergence of bulimic symptoms, which thus also leads to a diagnostic artefact.

**Table 3**  
Sub-groups of AN patients and their controls: lifetime and current comorbidity with mood disorder.

	AN-R (111)		Controls AN-R (111)		AN-BN (55)		Controls AN-BN (55)	
	Number	%	Number	%	Number	%	Number	%
<b>Lifetime episode</b>								
At least one mood episode	84 <sup>a</sup>	75.7	21	18.9	47 <sup>a</sup>	85.5	12	21.8
Major depressive episode	80 <sup>a</sup>	72.1	18	16.2	46 <sup>a</sup>	83.6	11	20.0
Hypomania episode	2	1.8	0	0	2	3.7	0	0
Maniac episode	5	4.5	1	0.9	9 <sup>d</sup>	16.4	2	3.6
Mixed episode	2	1.8	0	0	5 <sup>c</sup>	9.3	0	0
<b>Lifetime disorder</b>								
Major depressive disorder	71	63.9	16	14.4	41	74.5	11	20
Bipolar disorder	9	8.1	1	0.9	16	29.1	2	3.6
<b>Current episode (past six months)</b>								
Current mood episode	57 <sup>a</sup>	54.3	2	1.8	33 <sup>a</sup>	53.5	2	3.8
Current major depressive episode	49 <sup>a</sup>	44.1	0	0	27 <sup>a</sup>	49.1	2	3.8
Current hypomania episode	0	0	0	0	0	0	0	0
Current manic episode	2	1.8	0	0	4	7.3	0	0
Current mixed episode	1	0.9	0	0	0	0	0	0
Current diagnostic								
Dysthymia	8 <sup>b</sup>	7.6	2	1.8	5 <sup>c</sup>	9.6	0	0

<sup>a</sup> Comparison with the control group p < 0.0001

<sup>b</sup> Comparison with the control group p < 0.045

<sup>c</sup> Comparison with the control group p < 0.027

<sup>d</sup> Comparison with the control group p < 0.026

**Table 4**  
Sub-groups of BN patients and their controls: lifetime and current comorbidity with mood disorder.

	BN without purging (19)		Controls of BN without purging (19)		BN with purging (86)		Controls of BN with purging (86)	
	Number	%	Number	%	Number	%	Number	%
<b>Lifetime episode</b>								
At least one mood episode	17 <sup>a</sup>	89.5	5	26.3	70 <sup>a</sup>	82.4	21	24.4
Major depressive episode	15 <sup>b</sup>	78.9	5	26.3	64 <sup>a</sup>	74.4	21	24.4
Hypomania episode	0	0	0	0	3	3.5	0	0
Manic episode	1	5.3	1	5.3	12 <sup>d</sup>	14.0	0	0
Mixed episode	1	5.3	1	5.3	7 <sup>e</sup>	8.3	0	0
<b>Lifetime disorder</b>								
Major depressive disorder	11	57.9	4	21.1	52	60.5	18	20.9
Bipolar disorder	2	10.5	2	10.5	22	25.6	0	0
<b>Current episode (past six months)</b>								
Current mood episode	11 <sup>a</sup>	61.1	1	5.3	39 <sup>a</sup>	47.6	5	5.8
At least one MDD	11	61.1	1	5.3	39 <sup>a</sup>	47.6	5	5.8
MDD	7	36.8	0	0	27 <sup>a</sup>	31.4	3	3.5
Manic episode	1	5.3	0	0	4	4.7	0	0
Mixed episode	1	5.3	0	0	1	1.2	0	0
<b>Current disorder</b>								
Dysthymia (past two years)	4	22.2	1	5.3	12 <sup>c</sup>	14.6	2	2.3

<sup>a</sup> Comparison with the control group  $p < 0.0001$

<sup>b</sup> Comparison with the control group  $p < 0.001$

<sup>c</sup> Comparison with the control group  $p < 0.004$

<sup>d</sup> Comparison with the control group  $p < 0.0001$

<sup>e</sup> Comparison with the control group  $p < 0.006$

**Table 5**  
Mean age of onset (in years) and chronology of appearance of mood disorders.

	Age of onset m ± sd	Chronology of appearance			
		Anterior	Simultaneous	Posterior	
AN-R	MDE (N=79)	16.1 ± 3.1	26 (34.2)	30 (39.5)	20 (26.3)
	Dysthymia (N=8)	16.8 ± 2.6	4 (50)	4 (50)	–
	Manic episode (N=4)		1 (25)	2 (50)	1 (25)
AN-BP	MDE (N=44)	16.3 ± 3.0	12 (27.3)	21 (47.7)	11 (25)
	Dysthymia (N=5)	15.2 ± 2.9	3 (60)	2 (40)	–
	Manic episode (N=11)		2 (18.2)	4 (36.4)	5 (45.5)
Controls AN-R	MDE (N=8)	16.3 ± 4.2			
	Dysthymia (N=2)	15.0 ± 2.8			
Controls AN-BP	MDE (N=8)	17.8 ± 3.4			
	Dysthymia (N=0)	– ± –			
	Manic episode				

### 4.3. Bipolar disorder

This disorder is rare in the general population [1.1% in women (Merikangas et al., 2011)], and is rarely assessed in ED (McElroy et al., 2011). In the present study, the prevalence of bipolar disorder (BD) is high. In comparable studies, the lifetime prevalence of BD was negligible in AN-R patients (Piran, Kennedy, Garfinkel, & Owens, 1985; Laessle et al., 1989; Iwasaki et al., 2000); but in AN-BN patients it was estimated at 6% for BD and 3% for hypomania (Iwasaki et al., 2000). In BN patients, the lifetime frequency for BD varies considerably in the clinical population, from 0% (Piran et al., 1985) to 17% (Laessle et al., 1989). These variations have been previously discussed as resulting from a possible selection bias: certain recruitment sites have a dual specialization in ED and

**Table 6**  
Mean age of onset (in years) and chronology of appearance of mood disorders.

	Age of onset m ± sd	Chronology of appearance			
		Anterior	Simultaneous	Posterior	
BN-BP	MDE (N=63)	16.8 ± 3.5	26 (41.3)	21 (33.3)	16 (25.4)
	Dysthymia (N=11)	16.1 ± 4.3	5 (45.5)	5 (45.5)	1 (9.1)
	Manic episode (N=15)		5 (33.3)	5 (33.3)	5 (33.3)
BN-NP	MDE (N=15)	17.7 ± 5.6	4 (26.7)	6 (40)	5 (33.3)
	Dysthymia (N=3)	13.5 ± 3.3	1 (33.3)	1 (33.3)	1 (33.3)
	Manic episode (N=1)		–	1 (100)	–
Controls BN-BP	MDE	18.8 ± 4.4			
	Dysthymia	8.5 ± 10.6			
Controls BN-NP	MDE	18.6 ± 4.5			
	Dysthymia	26.0 ± –			
	Manic episode				

manic depression treatment (Mury et al., 1995). This is not the case for our work. However, this is not the opinion of McElroy et al. (2011), who, in contrast, have demonstrated that ED are frequent in BD. In addition, a recent study has revived the debate, as it has been shown that familial BD increases the risk of developing an ED (Bould et al., 2014). Thus on the basis of these studies and clinical practice, we hypothesize that the frequency of BD in ED samples could be higher in severe ED samples than in the general population.

### 4.4. Relative chronology of onset of depression and eating disorder

One important result of this study is the relative chronology for onset of MDD and ED, which contributes to knowledge about the relationship between these two disorders.

In our study, MDD was the most frequent disorder preceding

AN or BN in around a quarter of the cases. Thus, we will focus here on MDD.

The relationship between depression and ED is complex and should be considered along with the following factors: the mean age at onset of ED varies from one diagnostic type to another (for example, the onset of BN is later than that of AN); by way of an artefact between ED and MDD symptoms, ED symptoms could enhance the diagnosis of depressive comorbidity (malnutrition leads to mood symptoms (Mattar et al., 2011, 2012a, 2012b) and binge-eating can also lead to depressive symptoms); also, ED are chronic disorders and can lead to social disability and secondarily to depression (Godart et al., 2003). Moreover, it has recently been shown that the presence of Axis-I comorbidities, and depressive disorders in particular, increases the crossover within ED diagnoses (Castellini et al., 2011; Milos et al., 2013). Thus, it would facilitate the move from AN-R to AN-BN or BN and the appearance of depressive symptoms which darkens the outcome.

In addition, the relative chronology of appearance of depression varies: depression can be prior, simultaneous, or posterior to the ED (Godart et al., 2007). Authors have generally focused on one aspect of the comorbidity between ED and depression, which leads to false conclusions, either that ED are mood disorders, or that they are the cause or the consequence of mood disorders (Cantwell et al., 1977; Hudson et al., 1982; Strober et al., 1985; Pope and Hudson, 1988; Keck et al., 1990). Some authors hypothesized that mood disorders may be due solely to malnutrition (Pollice et al., 1997), but we have developed an integrative point of view, in which all of these elements coexist and contribute to depression, which is a complex phenomenon in ED.

1. In our sample, a MDD appears for a almost third of cases simultaneously with ED. Thus, a possible explanation, developed many times in the past, could be that MD comorbidity is at least in part an artefactual phenomenon (Eckert et al., 1982; Channon, DeSilva 1985; Wittchen, 1996; Bogenschutz & Nurnberg, 2000). Depression may be related to the physiological state of malnutrition (Mattar et al., 2011) via, for example, a reduced availability of tryptophan (Gauthier et al., 2013). In this way, ED and MD could at least in part be the result of a diagnostic bias (Bogenschutz & Nurnberg, 2000). Indeed, as mentioned above, binge-eating can lead to depressive symptoms (Kennedy et al., 1994).
2. Secondly, we found that for about a third of our sample (AN: 28.9%; BN: 30.5%), the first MD precedes the ED. Thus, the MD can be considered at least in part as independent from the nutritional state. In this case, depression and ED can be considered as two different entities. In addition, it is well known that the presence of a MDE in the teenage years is associated with a higher risk of developing bipolar disorder thereafter (Akiskal, 1995); 25% of children and adolescents who have suffered from a MDD will develop a BD in the 2–5 years following. That could explain the frequency of BD we observed in our sample.
3. Finally, we found that for respectively 18.7% and 20.0% of the AN and BN patients in our sample, MDD onset is posterior to the onset of the ED. Consequently, it could be considered as a social consequence of a chronic disorder such as AN or BN (Blumer, Dietrich 1982; Banks, Kerns 1996; Ivarsson et al., 2000; Flament et al., 2001; Moussavi et al., 2007; Keyes et al., 2014) or as a relapse of an earlier MD (Ivarsson et al., 2000; McElroy et al., 2005).

#### 4.5. Limitations

Our study raises several biases. First, as indicated above, we

recruited patients who had asked for care in specialized tertiary centers, and who therefore do not represent the entire population of AN or BN patients (Godart et al., 2007). In fact, they are severe ED patients with high comorbidity as a result of the “Berkson bias” (Berkson, 1946; Godart et al., 2007). We consequently found an elevated frequency of mood disorder, that reported in this study being among the highest in the literature for both controls and patients. Secondly, it is well known that this comorbid relationship increases the risk of mortality of those patients (Keel et al., 2003) which could induce a « prevalence-incidence bias ». This bias in our study leads to the fact that our sample represents only the leaving patients who did not die consequently to this comorbidity. That would mean that our prevalence of mood disorders is slightly undervalued. Thus, the presence of such a bias in our study will only decrease the power of our prevalence of mood disorders (MD) which is already very high and significantly higher than controls. Third, the “membership bias” which limits the interpretation of our results, and especially the nature of the comorbidity between ED and MD.

It is unfortunate that, because of the recruitment criteria used for the study (where controls were not chosen if they presented with past or current drug or alcohol dependence, which could affect the frequency of mood disorder) we were naturally prevented from comparing frequencies of alcohol and drug dependency in the control group.

The small size of the BN-NP sub-group (the only other study having recruited such subjects according to DSM-IV criteria only included 18) (Iwasaki et al., 2000), is related to difficulties in recruiting these subjects because they rarely seek medical care. This limits our conclusions concerning this little-known diagnostic group.

As in previous studies, the retrospective nature of data collection could be a source of memory bias, whether for earlier disorders or for the relative chronology of the onset of disorders (Wittchen, 1996).

It should also be noted that the majority of the patients evaluated in this study were adolescents or young adults, so it is important to note that any mood disorders that might develop after this inquiry were necessarily neglected, and as a result we overestimate the proportion of mood disorders occurring prior to ED.

Others factors that may have an influence on the development of MD or ED, such as family history of either disorders (Bould et al., 2014), have not been taken into account. Unfortunately, we did not have any information concerning family history.

Thus, future studies, which could control for the effects of malnutrition, taking into account the relative chronology of onset, family history of mood disorders or eating disorders, and the impact of different kinds of depression observed on outcome are needed. They could deepen our understanding of the nature of mood disorders in ED and as a result, in clinical practice, when we evaluate depression in ED patients, we need to evaluate the different components in order to determine whether antidepressant treatment is needed or not. Thus, research is needed on the therapeutic rules of treatment for MD in ED patients in order to improve their clinical treatment.

## 5. Conclusions

In conclusion, through the results of this study and those of the literature including our previous studies (Mattar et al., 2011, 2012a, 2012b; Gauthier et al., 2013) and review of international literature, we could hypothesis that the presence of depression in ED have a different meaning depending of it chronology of appearance. It's a sort of chimera whose composition varies from one individual to another and in a same individual at different



moments in time. Thus, when depression precedes the ED, it could represent a risk for its development (through the negative self-image bias and biological disturbances-in particular serotonin-related); when in some cases these two disorders appear simultaneously, depression could be at least partly the consequence of major malnutrition; finally, when the MDD is posterior to the ED, it could be in part the consequence of the length of the illness negatively affecting the social life of the subject, or a genuine comorbidity. Nonetheless, futures studies are needed in order to test each of those hypotheses above.

#### Conflict of interest

The authors declare that they have no competing interests.

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