Comorbidity studies of eating disorders and mood disorders.
Critical review of the literature

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Abstract

Objective: We conducted a critical literature review of studies assessing the prevalence of mood disorders (MD) in subjects with eating disorders (ED; anorexia nervosa and bulimia nervosa). In the first part of this article, we discuss methodological issues relevant to comorbidity studies between ED and MD. In the second part, we summarize the findings of these studies in light of the methodological considerations raised.

Method: A manual computerised search (Medline) was performed for all published studies on comorbidity between ED and MD. In order to have sufficiently homogeneous diagnostic criteria for both categories of disorders, this search was limited to articles published between 1985 and 2006.

Results: Too few studies include control groups, few studies compared diagnostic subgroups of ED subjects, and results are scarce or conflicting.

Discussion: The results are discussed in the light of the methodological problems observed. The implications when reviewing the results of published studies and planning future research are set out.

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Keywords: Anorexia nervosa; Bulimia nervosa; Mood disorders; Comorbidity; Review

Contents

1. Methods ........................................................ 38
2. Results — part 1: methodological issues. ....................... 38
   2.1. Population sources ........................................... 38
   2.2. General methodological issues .............................. 39
   2.3. Diagnostic criteria for eating disorders .................... 40
   2.4. Diagnosis of mood disorders ............................... 40
   2.5. Sample composition. ........................................ 41

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In comorbidity studies published over the past two decades, the lifetime prevalence of mood disorders varies considerably, from 24.1% to 90% (Hatsukami et al., 1984a,b; Hudson et al., 1988) in subjects with bulimia nervosa (BN), and from 31% to 88.9% in those with anorexia nervosa (AN) (Laessle et al., 1987; Fornari et al., 1992).

The only articles we found reviewing the relationships between ED and mood disorders explore different types of arguments in favour of a link between these categories of disorders, including symptoms, personal and family comorbidity, overlap with biological findings, and treatment results, but they do not review in detail available comorbidity data (Sours, 1981; Hatsukami et al., 1984a,b; Altshuler and Weiner, 1985; Rothenberg, 1986; Swift et al., 1986; Vandereycken, 1987; Herzog et al., 1996; Wondelich and Mitchell, 1997; Casper, 1998; Mury et al., 1995; McElroy et al., 2005).

Consequently, the aim of this paper is to conduct a critical literature review on studies assessing the prevalence of mood disorders in subjects with a lifetime diagnosis of AN or BN (two studies are included twice in the following report, because they include two different samples of subjects, making a total of 57 samples).

Most studies (34/55) were conducted among in-or outpatients with a current diagnosis of ED admitted for treatment in specialised clinics or on waiting lists, or among volunteers for research (treatment or evaluation) in such clinics. Other studies were part of the long-term follow-up of ED patients (15 studies). Finally, a few studies (8 studies) were conducted in the community, including three studies in populations of twins.

Even after exclusion of problematic studies (for references see below, Part 1), the diversity of inclusion and exclusion criteria, diagnostic criteria, diagnostic instruments, in-or outpatient status, age, and body weight status, made it impossible to conduct a meta-analysis of all available studies. Therefore, the following is a descriptive review of methodological issues and prevalence findings (for references see Tables 1–4).

2. Results — part 1: methodological issues

2.1. Population sources

Studies on referred patients, follow-up samples, and community samples should be considered separately for several reasons. First, patients in clinical settings may not be representative of all those with the disorder because of
the «Berkson Bias» (Berkson, 1946; for further detail, see Godart et al., 2002). Second, follow-up studies of ED patients evaluate subjects with a lifetime diagnostic of ED, either past or current; as a consequence, they differ from those with a current ED on many factors (age, duration of illness ...), which will be discussed below.

Finally, community-based samples are heterogeneous, since they include subjects with either a current or a past diagnosis, seeking or not seeking treatment, and a broad range of symptom severity.

2.2. General methodological issues

Many studies suffer from general methodological limitations: (1) Samples are small (32/55 studies have at least one group including less than 30 subjects). (2) The earliest studies did not use any diagnostic instrument; in later studies, instruments have varied, and differences in diagnostic procedures may have resulted. (3) Refusal to participate in the study, a possible selection bias, is mentioned for only a few studies (Bulik et al., 1997; Bushnell et al., 1994; Herpertz-Dahlmann et al., 2001; Herpertz-Dahlmann et al., 1996; Herzog et al., 1992; Herzog et al., 1999; Keel et al., 1999; Pla and Toro, 1999; Toner et al., 1988). Longitudinal studies carry the risk that subjects lost to follow-up may compromise the representativeness of the sample. (4) Some studies include both males and females (Fornari et al., 1992; Garfinkel et al., 1995; Herpertz-Dahlmann et al., 2001; Herpertz-Dahlmann et al., 1995; Herpertz-Dahlmann et al., 1996; Hudson et al., 1983a; Hudson et al., 1988; Laessle et al., 1987; Viesselman and Roig, 1985), even though women are more likely to be affected by lifetime mood disorders than men (Kessler et al., 1994). (5) Less then half of the studies examined (20/55) included a control group, and only seven matched the control group to the ED group for age and socio-economic status (Gershon et al., 1984; Halmi et al., 1991; Lilenfeld et al., 1998; Rastam, 1992; Rastam et al., 1995; Smith et al., 1993; Stern et al., 1984). (6) The definition of ‘current’ prevalence varies across

<table>
<thead>
<tr>
<th>References country</th>
<th>Diagnostic criteria</th>
<th>Subjects</th>
<th>N</th>
<th>Prevalence period</th>
<th>At least one mood disorder</th>
<th>Major depressive disorder</th>
<th>Bipolar disorder</th>
<th>Dysythmic disorder</th>
<th>Cyclothymic disorder</th>
<th>Atypical depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piran et al. (1985) Canada</td>
<td>DSM-III RA</td>
<td>14</td>
<td>Lifetime</td>
<td>6 (42.8%)</td>
<td>0</td>
<td>13 (92.9%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laessle et al. (1989) Germany</td>
<td>DSM-III RA</td>
<td>21</td>
<td>Lifetime</td>
<td>8 (38.1%)</td>
<td>2 (9.5%)</td>
<td>0</td>
<td>6 (28%)</td>
<td>3 (14.3%)</td>
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</tr>
<tr>
<td>Lilenfeld et al. (1998) USA</td>
<td>DSM-III-R RA</td>
<td>26</td>
<td>Lifetime</td>
<td>(46%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
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</tr>
<tr>
<td>Herzog et al. (1999) USA</td>
<td>DSM-III-R AN-R</td>
<td>51</td>
<td>Lifetime</td>
<td>64.7%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iwasaki et al. (2000) Japan</td>
<td>DSM-IV AN-R</td>
<td>62</td>
<td>Lifetime</td>
<td>25 (40%)</td>
<td>20 (32%)</td>
<td>0</td>
<td>6 (10%)</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Miles et al. (2003) Switzerland</td>
<td>DSM-IV AN</td>
<td>77</td>
<td>Lifetime</td>
<td>41 (53%)</td>
<td>AN et BN</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

AN: Anorexia Nervosa; AN-BN: Anorexia Nervosa and Bulimia Nervosa; BN: Bulimia Nervosa; RA: Restrictive AN; AN-R: Anorexia Nervosa restricting type; AN-BP: Anorexia Nervosa binge eating purging type; BN-P: Bulimia Nervosa purging type; BN-NP: Bulimia Nervosa non purging type; CW: Control women from the community; Hx: with past history of aComparison versus CW, p<0.05.b Comparison versus BN-P, p<0.05.
studies, and is used to refer to 1-week (Herzog, 1984), to 6-month (Herpertz-Dahlmann et al., 2001; Herpertz-Dahlmann et al., 1996; Rastam et al., 1995) or to 1-year prevalence (Halmi et al., 1991), as well as to unspecified prevalences (Brewerton et al., 1995; Garfinkel et al., 1995; Garfinkel et al., 1996; Pla and Toro, 1999; Rastam et al., 1995; Schwalberg et al., 1992).

2.3. Diagnostic criteria for eating disorders

Changes in diagnostic criteria for ED and mood disorders over the past 15 years obviously have an impact on patient selection and comorbidity findings (Wittchen and Essau, 1993). For example, Feighner’s criteria for AN require that there is no other known psychiatric disorder — including primary affective disorder — while the DSM-III, in its definition of BN, includes a criterion for «depressed mood and self-depreciating thoughts following eating binges». The weight criterion for AN has changed, from loss of at least 25% of original body weight in Feighner’s criteria, to 15% below expected weight in the DSM-III-R and DSM-IV (APA, 1987, 1994). What are the consequences of such changes since the degree of malnutrition seems to be linked to depressive symptoms (Pollice et al., 1997)?

Furthermore, in the DSM-III, concurrent diagnoses of AN and BN were not allowed. Thus, BN samples could, at this time, have included patients now classified, according to DSM-IV, as «AN binge-eating/purging type»: in the Piran et al. (1985) study, for example, 67% of the bulimics were below 85% of normal weight (Walsh et al., 1985).

2.4. Diagnosis of mood disorders

Across studies, the number of diagnoses taken into consideration for definition of a comorbid mood disorder varies from two [major depressive disorder and cyclothymia (Laessle et al., 1987)] to nine [bipolar I and II,
cyclothymic disorder, intermittent depressive disorder, labile major mood disorder, minor depressive disorder, numerous probable hypomanic episodes, schizoaffective disorder) (Herzog et al., 1992).

Some categories, mainly from the RDC criteria (e.g., labile major affective disorder, minor depressive disorder, numerous probable hypomanic episodes, are no longer used.

For dysthymic disorder, the DSM-III did not include any criteria on appetite, and allowed simultaneous diagnosis of MDD, unlike the DSM-III-R and the DSM-IV.

In addition, some authors made their own alterations to usual diagnostic criteria, such as the exclusion of ‘appetite or weight change’ in the RDC definition of depression, leading to very low prevalence findings for depression (Herzog, 1984), or they refer to specific instructions, e.g., “the interviewers are trained to make clear distinction between anorexic and depressive symptoms” (Herzog et al., 1992).

2.5. Sample composition

The studies reviewed with samples of referred patients include inpatients, or outpatients, or both. It is difficult to consider all these patient groups together, as inpatients are likely to have more severe ED and higher rates of major mood disorders than outpatients. (93% of inpatients have a mood disorder versus 68% of outpatients, p<0.02; Hudson et al., 1983b).

Despite these findings, this important issue has not been taken into consideration in subsequent studies.

Some studies excluded all subjects with comorbid substance abuse (Bossert-Zaudig et al., 1993; Keck et al., 1990; Walsh et al., 1985; Bulik et al., 1996), yet individuals with a lifetime history of major depression have been shown to be 3.7 times more likely to have experienced alcohol dependence and 3.6 times more likely to have experienced drug dependence in the previous year (Wittchen et al., 1996). Several studies excluded patients currently taking psychoactive medication, possibly excluding subjects treated for anxiety or depression (Deep et al., 1995; Keck et al., 1990; Bulik et al., 1996), and a few studies excluded psychotic patients (Brewerton et al., 1995; Walsh et al., 1985).

Inclusion and exclusion criteria vary from only one simple indication [e.g., consecutive female inpatients (Grilo et al., 1996)] to a complex list of strict criteria for inclusion in particular treatment protocols (Keck et al., 1990). Some authors added their own personal criteria to those classically used for ED, regarding frequency of binges, percentages of ideal body weight, or illness duration (Iwasaki et al., 2000; Keck et al., 1990; Powers et al., 1988).

The age of the ED subjects (when reported) in the studies reviewed varies from 11 to 65 years. When comparing different diagnostic subgroups, ages are not taken into account, although the age ranges concerned by the different subgroups sometimes differ significantly (Herzog et al., 1992; Keck et al., 1990; Laessle et al., 1989; Schwalberg et al., 1992).

Studies selected. After reviewing the methods used in the 55 studies, 30 were excluded from this analysis because of the following methodological problems which could have affected comparability of their results with those of the other studies: no diagnostic instrument (Deter and Herzog, 1994; Gershon et al., 1984; Hatsukami et al., 1984a,b; Herpertz-Dahlmann and Riemenschmidt, 1993b; Herpertz-Dahlmann et al., 1995; Hsu et al., 1992; Rastam, 1992; Saccomani et al., 1998; Stern et al., 1984; Viesselman and Roig, 1985); authors’ own diagnostic criteria for ED (Bulik et al., 2000; Viesselman and Roig, 1985); lack of distinction between AN and BN groups for all results (Geist et al., 1998; Grilo et al., 1996; Woodside et al., 2001) or part of the results (current prevalence) (Laessle et al., 1987); mixed groups of subjects in early phase of inpatient treatment and at 1 year after discharge (Laessle et al., 1987); mixed groups of subjects with current and past diagnosis of ED (Hudson et al., 1983b); studies concerning only men (Carlat et al., 1997; Striegel et al., 1999); studies using RDC criteria, since some categories (e.g. labile major affective disorder, minor depressive disorder, numerous probable hypomanic episodes) are no longer used (Biederman et al., 1985; Formari et al., 1992; Gershon et al., 1984; Herzog, 1984; Herzog et al., 1992; Simpson et al., 1992; Stern et al., 1984); studies excluding ED subjects with comorbid substance abuse and/or taking psychoactive medication. Seven studies report exclusion of substantial numbers of particular categories of subjects because of missing information [33/138 subjects in the Braun et al. (1994) study]; high rates of subjects lost for follow-up outcome studies, 32% (47/147) for Toner et al. (1988) and 90% (153/169) for Hsu, Crisp, and Callender (1992).

Results from the remaining 25 studies are presented in the following part.

3. Results — part 2

3.1. What is the convincing evidence that mood disorders are more frequent among women with an ED than among women from the community?

We will first present the range of the estimated prevalence (lifetime and current when mentioned) across studies for all specific mood disorders in subjects
<table>
<thead>
<tr>
<th>References</th>
<th>Diagnostic criteria</th>
<th>Subjects</th>
<th>N</th>
<th>Prevalence period</th>
<th>At least one mood disorder</th>
<th>Major depressive disorder</th>
<th>Bipolar disorder</th>
<th>Dysthymic disorder</th>
<th>Cyclothymic disorder</th>
<th>Atypical depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudson et al. (1982) USA</td>
<td>DSM-III</td>
<td>BN</td>
<td>10</td>
<td>Lifetime</td>
<td>–</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Piran et al. (1985) Canada</td>
<td>DSM-III</td>
<td>BN</td>
<td>33</td>
<td>Lifetime</td>
<td>–</td>
<td>12 (36.3%)</td>
<td>0</td>
<td>24 (72.7%)</td>
<td>3 (9.1%)</td>
<td>0%</td>
</tr>
<tr>
<td>Bulik (1987) USA</td>
<td>DSM-III</td>
<td>NC</td>
<td>35</td>
<td>Lifetime</td>
<td>–</td>
<td>21 (60%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hudson et al. (1987a,b) USA</td>
<td>DSM-III</td>
<td>BN</td>
<td>51</td>
<td>Lifetime</td>
<td>36 (71%)</td>
<td>30 (59%)</td>
<td>6 (12%)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hudson et al. (1987a,b) USA</td>
<td>DSM-III</td>
<td>BN</td>
<td>19</td>
<td>Lifetime</td>
<td>13 (68%)</td>
<td>9 (47%)</td>
<td>2 (11%)</td>
<td>2 (11%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hudson et al. (1988) USA</td>
<td>DSM-III</td>
<td>BN</td>
<td>105</td>
<td>Lifetime</td>
<td>95 (90%)</td>
<td>67 (64%)</td>
<td>14 (13%)</td>
<td>11 (10%)</td>
<td>2 (1.9%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Powers et al. (1988) USA</td>
<td>DSM-III-R</td>
<td>BN</td>
<td>30</td>
<td>Lifetime</td>
<td>15 (50%)</td>
<td>14 (47%)</td>
<td>1 (3%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Laessle et al. (1989) Germany</td>
<td>DSM-III</td>
<td>BN Hx</td>
<td>23</td>
<td>Lifetime</td>
<td>16 (69.6%)</td>
<td>8 (34.8%)</td>
<td>4 (17.4%)</td>
<td>0</td>
<td>8 (34.8%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>Schwalberg et al. (1992) USA</td>
<td>DSM-III-R</td>
<td>BN</td>
<td>20</td>
<td>Lifetime</td>
<td>(60%)</td>
<td>?</td>
<td>–</td>
<td>?</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Brewerton (1995) USA</td>
<td>DSM-III-R</td>
<td>BN</td>
<td>59</td>
<td>Lifetime</td>
<td>44 (75%)</td>
<td>37 (63%)</td>
<td>(41%)</td>
<td>0</td>
<td>11 (19%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Herzog et al. (1999) USA</td>
<td>DSM-III-R</td>
<td>BN</td>
<td>110</td>
<td>Lifetime</td>
<td>(60.7%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Iwasaki et al. (2000), Japan</td>
<td>DSM-IV</td>
<td>BN-P</td>
<td>57</td>
<td>Lifetime</td>
<td>42 (74%)</td>
<td>35 (61%)</td>
<td>2 (4%)</td>
<td>8 (14%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Milos et al. (2003), Switzerland</td>
<td>DSM-IV</td>
<td>AN</td>
<td>77</td>
<td>Lifetime</td>
<td>71 (52%)</td>
<td>AN et BN</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
with ED, shown in Tables 1–4; separate consideration is
given to studies in referred samples of subjects currently
suffering from an ED (Table 1 for AN, Table 3 for BN),
outcome studies (Table 2 for AN and BN), and com-
community studies (Table 4 for AN and BN). Then, the
comparative studies between ED and control groups will
be considered: for AN, only one referred sample (table 1)
and three outcome studies (table 2); for BN, four
referred samples (Table 3) and three community studies
(table 4). It should be noted that community estimates
of MD (lifetime prevalence) from the National Comor-
dbidity Study (Kessler et al., 1994) are as follows: in
women, MDD is 21.3%; dysthymia is 8% and BD is
1.7%.

3.1.1. Diagnosis of “at least one mood disorder”

The prevalence rates for the «at least one mood
disorder» diagnosis increase with the number of mood
disorders, whatever the type of ED studied.

In referred anorexic patients, two studies estimated
the overall lifetime prevalence of three and four mood
disorders respectively, finding around 40% in AN-R,
and over 60% in AN-BN (Table 1). No comparison was
made with a control group.

In regards to follow-up of AN, lifetime prevalence of
mood disorders is estimated in four studies — for two or
three disorders depending on the study. These studies
estimate lifetime prevalence from 64.1% to 96%,
significantly more prevalent than in a normal control
group in 2 out of the 3 controlled studies. The current
prevalence varies from 12.7% to 68.6% but does not
differ from that for controls (Table 2).

Lifetime occurrence of at least one MD is reported
in eight clinical sample studies of BN; prevalence
ranges from 50% to 90%. There is a significantly
higher lifetime prevalence of MD in the BN group
compared to controls and compared to bipolar disorder
or schizophrenia probands (Table 3). Current preva-
lence is estimated by only one study at 40% (for two
disorders).

One outcome study gives a prevalence of at least one
MD that is significantly higher for BN in remission and
for patients with current eating disorders (62.8% versus
71.2%, p = 0.028) (Keel et al., 1999).

3.1.2. Major depressive disorder (MDD)

MDD is the most frequently assessed disorder in the
studies under consideration here (22/24). MDD preva-
ience rates are always high in AN and BN, and signi-
ificantly higher than in control groups. However, there
are variations in connection with the type of recruitment
and/or the sample numbers considered.

Five referred sample studies estimate the lifetime
prevalence of MDD in AN-R to be between 9.5% and
64.7%, significantly more than in controls for the last
value (Table 1). It is between 50% and 71.3% in AN-BN.

Of the two controlled follow-up studies of anorexics,
the first (N=62) finds a significantly higher rate of
lifetime MDD in AN (67.7%) than in normal controls
(21%), while the second (N=39) does not. The current
prevalence of MDD in seven follow-up studies of
anorexics varies from 2.2% to 35.3%, and differs
significantly from that in controls in 1/3 of the controlled
studies (Table 2).

In the community, the lifetime prevalence of MDD is
found to be 2.6 to 4 times higher in AN than in control
subjects (Table 4).

In 12 studies of referred BN subjects, the range of
lifetime prevalence estimates for MDD varies in inverse
proportion to the number of subjects included in the
sample. The range in the smallest samples is 20% to
80% while it is 60.7% to 70% in the 5/12 samples that
include more than 50 patients. In addition, the highest
rates are found with DSM-III criteria (which include, for
a diagnosis of BN, «depressed mood and self-depreci-
ating thoughts following eating binges»). The four
controlled studies find significantly lower prevalence in
normal controls. (Table 3). Current prevalence of MDD
in referred BN patients is estimated at 41% in one study.

In the community, the lifetime prevalence of MDD
ranges from 30% to 51% in BN or “partial BN syn-
drome”. Current prevalence is 20% for BN and 18.2%
for partial BN syndrome. Both lifetime and current
prevalence in BN or partial BN syndrome are signi-
ificantly higher than in controls in all studies (Table 4).

3.1.3. Bipolar disorder (BD)

BD was assessed only 11 times in 24 studies. In
clinical samples (Table 1), no cases are found in AN-R;

Notes to Table 3:
AN: Anorexia Nervosa; AB: Bulimic AN; AN-BN: Anorexia Nervosa and Bulimia Nervosa; RA: Restrictive Anorexia Nervosa; AN-R: Anorexia Nervosa restricting type; AN-BP: Anorexia Nervosa binge eating purging type; BN: Bulimia Nervosa; BN-P: Bulimia Nervosa purging type; BN-NP: bulimia nervosa non purging type; BPP: Bipolar Disorder Proband; MD: mood disorder; OBE: Obese; ScPP: Schizophrenia Proband; P: Panic Disorder; SP: Social phobia; C: Controls; CW: Control Women from the community; NC: Normal controls; Hx: with past history of: a: comparison versus NC, p < .0001; b: comparison versus NC, p < .05; c comparison versus NC, p < .05; d comparison versus Bipolar Disorder Proband and Schizophrenia Proband, p < .001; e comparison versus C, p < .01; f comparison versus C, p < .001; g comparison versus CW, p < .05; h comparison versus AN-R, p < .05.
in AN-BN, lifetime prevalence BD is estimated at 6% for bipolar II disorder and 3% for hypomaniac disorder.

One outcome study of AN patients evaluates the lifetime and current prevalence of BD at 3.2%, significantly more than controls, while one other study finds no cases (Table 2). Finally, Rastam et al. (1995), in a follow-up of their sample over 6.7 years, found no cases, as compared with 6% after 10 years for Ivarsson et al. (2000).

For BN, the lifetime frequency of BD varies, in eight referred samples, from 0% to 17% (Table 3). Bulimic inpatients had higher rates of bipolar disorders (36%) than bulimic outpatients (7% p<0.01) (Hudson et al., 1988).

### 3.1.4. Dysthymic disorder (DD)

14/24 studies estimate the frequency of this disorder. Only three clinical sample studies estimate lifetime prevalence of DD in AN-R, with highly divergent results (10% to 92.9%), and two studies give rates (40% and 8%) in AN-BN (Table 1; Iwasaki et al., 2000; Piran et al., 1985). The outcome studies of AN estimate the lifetime prevalence of DD at between 17.9% and 32%. Only the last result shows a significant difference with controls. The current prevalence varies from 13% to 33%, significantly higher than in controls for the last result (Table 2).

Lifetime prevalence of DD in BN varies widely, between 3% and 72.7%. As remarked above, the highest rates are found with DSM-III criteria which, as previously noted, allow a diagnosis of dysthymia simultaneously with MDD. The two most recent studies, with sample sizes over 50, find concordant results, with lifetime prevalence between 14% and 19% for BN. There is no difference with normal controls for one study, while there is in the other study (Table 3).

Cyclothymic disorder is very rarely evaluated (4/24 studies). One study in a small referred AN-R sample does not find any cases. The lifetime prevalence of cyclothymic disorder in BN, estimated in four clinical samples, varies from 1.9% to 20%.

Atypical depression is a diagnosis specific to DSM-III studies. It is very rarely evaluated (4/24). In clinical
samples, the upper estimate for lifetime prevalence is 14.3% in AN-R and 17% in BN, with no significant difference from controls.

3.2. Is there convincing evidence that prevalence of mood disorders differs across diagnostic types or subtypes of eating disorders?

Research findings are contradictory in the studies examined. However, sample numbers are very small, and the age of subjects and their outpatient/inpatient status are never taken into account.

Concerning the prevalence of MDD in AN subtypes (AN-R and AN-BN), the studies usually found no differences except for one (Halmi et al., 1991) found a difference, with major depression occurring more frequently in a group of 62 AN patients who had at some time engaged in bingeing compared to those who never binged ($p = 0.09$).

In BN, one study found no significant differences in the rates for any disorder between subjects with and without a past history of anorexia nervosa. No differences were found for the lifetime prevalence of MD between current BN and patients with a past history of BN, between BN-P and BN-NP, between clinical BN and BN from the general population.

However, Garfinkel et al. (1996) noted significantly higher rates of MDD in BN-P (64%) than in BN-NP (24.4%).

Two studies found increased presence of depression in BN compared to AN-R; conversely, three other studies found no differences between BN and AN-R regarding the prevalence of MD.

3.3. When both an eating disorder and a mood disorder are present, what is the chronology of appearance of the two disorders?

In case of comorbidity, few studies have looked at the relative onset chronology of the ED and the MD. Some have estimated the anteriority of the MD in general in relation to the ED, others have considered only one MD (MDD) or two disorders (MDD and BD). Some studies pooled AN and RA (Piran et al., 1985) or BN and past history of BN (Hudson et al., 1987a) and will be excluded from this discussion. Results are summarized in Table 5. As shown, at least one MD preceded the onset of AN and BN in respectively 25% and 36% to 61% of the cases. MDD preceded BN in 32% to 71% of the cases.

4. Discussion

Our literature review highlights the heterogeneity of samples and methods in numerous studies on comorbidity between ED and MD, and calls for caution in the interpretation of results. We do not aim to underestimate the value of findings from previous studies, but to reconsider the literature from the past 25 years in view of the advances that have occurred in terms of methodology and clinical knowledge of ED. Published research has provided valuable information in the field, but should now be re-examined, keeping in mind the fact that hidden biases are present in many studies, which is indeed the reason why more than half the studies initially identified were excluded from the results.

In addition, the studies retained pose problems that interfere with results. The wide age range of patients observed in the studies reviewed above is an important concern. Epidemiological research has shown that the prevalence of depression increases between childhood and adulthood (Rutter et al., 1976) and it would seem that this remains true for subjects suffering from ED, since, the youngest patients in a multi-dimensional study on depression tended to be the least depressed (Heebink et al., 1995). Therefore, it is very important that age be considered when

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Age (m±ds)</th>
<th>Type of disorder</th>
<th>At least 1 year before AN or BN</th>
<th>The same year</th>
<th>At least 1 year after AN or BN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piran et al.</td>
<td>18 BN or AN-R</td>
<td>22,2±4,6</td>
<td>MDD</td>
<td>44%</td>
<td>22%</td>
<td>34%</td>
</tr>
<tr>
<td>Hudson et al.</td>
<td>47 BN or phBN</td>
<td>26,3±5,4</td>
<td>MDD</td>
<td>32%</td>
<td>32%</td>
<td>36%</td>
</tr>
<tr>
<td>Hudson et al.</td>
<td>81 BN</td>
<td>27,2±7,1</td>
<td>MoD</td>
<td>41%</td>
<td>31%</td>
<td>28%</td>
</tr>
<tr>
<td>Schwalberg et al.</td>
<td>20 BN</td>
<td>26,3±6,4</td>
<td>MoD</td>
<td>36,4%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kendler et al.</td>
<td>63 BNB</td>
<td>20,9±6,5</td>
<td>MDD</td>
<td>71%</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>23 AN</td>
<td>22,1±2,1</td>
<td>MDD</td>
<td>25%</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Brewerton et al.</td>
<td>44 BN</td>
<td>28,4±6,6</td>
<td>MoD</td>
<td>27 (61%)</td>
<td>2 (5%)</td>
<td>15 (34%)</td>
</tr>
</tbody>
</table>

* Comparison with « at least 1 year before AN or BN ».

ph: past history of; AN: Anorexia Nervosa; AN-R: Anorexia Nervosa Restricting type; BN: Bulimia Nervosa; BNB: BN broad definition; MDD: Major Depressive Disorder; MoD: Mood Disorder.
recruiting control group subjects and when comparing different subgroups of ED patients. In part, this might explain why studies that compared diagnostic subgroups of ED subjects yielded scarce or conflicting data: higher prevalence of depression sometimes noted in AN-BNs or BNs compared to AN-Rs could be related to age, since the latter are often younger (Laessle et al., 1989). In addition, duration of illness often differs between subgroups of ED, due to clinical history: onset for anorexia is earlier, on average, than for bulimia. Thus, AN-Rs usually have a significantly shorter duration of illness than AN-BNs (Laessle et al., 1989). Age or duration of illness should be taken into account in future studies.

Likewise, the sources for sample recruitment are not taken into account, possible causing bias in results: in youth, depression prevalence varies in relation to patient status: 15.9% in the general population, 31.5% in outpatients and 55.2% in in-patients (Kendall et al., 1992).

Anxiety and depression are not always evaluated together. However, in women with BN, the presence of either depressive or anxiety disorder reciprocally increases likelihood of presence of the other by 3.6 (Bulik et al., 1996). Conversely, in the general population, eating disorders are significantly more frequent among adolescents with depressive or anxiety disorders than among those without depressive or anxiety disorders. (Zaider et al., 2000).

Nevertheless, regarding overall lifetime prevalence of MD, studies on referred anorexics find rates of around 40%, which is about twice as high as in the community (23.9%; Kessler et al., 1994). However, we found no controlled studies on this subject. In addition, outcome studies show contradictory results.

Major depressive disorder appears significantly more frequently in AN than in controls in all types of studies (clinical population, outcome studies, general population) but malnutrition is a major factor that is often neglected in studies exploring comorbidity between eating disorders and depression. However, most of the patients included in clinical studies are extremely malnourished, and it is widely thought that malnourishment leads to depressive symptoms (Keys et al., 1950; Pollice et al., 1997). There is also a correlation between severity of eating disorder and severity of depression (Herpertz-Dahlmann and Remschmidt, 1993a). Although the impact of malnutrition on the prevalence of depressive symptoms has been widely studied, its impact on depressive comorbidity has not. It is therefore possible that the present (and lifetime) frequency of depressive disorders in malnourished (or previously malnourished) subjects is overestimated due to the many depressive symptoms present. In a group of undernourished anorexics, the current prevalence of depression was about 40% upon entry into the study while it was about 1.9% in a group of anorexics seen 10 years later (Ivarsson et al., 2000). In addition, Ivarsson notes that long-term resolution of the eating disorder (ED) was associated with the absence of mood disorder and vice versa. What proportion of MDD diagnoses can be seen as an artefact related to malnutrition, or at least to symptom overlap?

A recent review concludes that there is little doubt that BD and ED are related, particularly BN and bipolar II (McElroy et al., 2005). Likewise, this issue deserves more detailed study in anorexics. Indeed, studies that follow their samples over long periods (at least 10 years) are dealing with a population that is growing older (mean age 24), and BD prevalence rates increase significantly more in ED patients than among controls (Halmi et al., 1991), or else increase from no cases to 6% of the sample (10% of MDD subjects), a prevalence rate that is above that observed in the general population (Rastam et al., 1995; Ivarsson et al., 2000). However frequency may not be as high, if it is considered that on the one hand 25% of the children and adolescents who present a depressive episode develop a bipolar disorder in the 2 to 5 years following (Akiskal, 1995), and on the other that the samples include hospitalised subjects. Thus, on the basis of the study by Ivarsson et al. (2000) 56% of the subjects with AN onset in adolescence have suffered MDD by the age of 24, but only 6% (or only 11% of the MDD subjects) present BD. It would however be interesting to characterize the subjects presenting both disorders more accurately, since the resolution of the ED is associated with that of the MD (Ivarsson et al., 2000): what is the link between BD and chronology of ED?

The relative chronology of onset for MD and ED is an element that requires consideration in relation to the links between these disorders. However, in interpreting onset chronology, it is important to consider the following: (i) the average age of ED onset is usually younger in AN (mean=17 years) than in BN (mean=18 years; APA, 1994); (ii) the age of onset for depressive disorder varies according to type of disorder [e.g., MDD generally starts during adulthood, while DD appears in childhood (APA, 1994)]. Therefore, it is not certain that the relative chronology of onset between MD and ED derives solely from the natural course of each disorder. It would be interesting to compare age of onset for MD in ED subjects and controls.

Ivarsson et al. (2000) concluded that MDD is concomitant with, not a precursor of ED. However, chronology of appearance as reported in the literature is not in line with this finding, since in at least 25% of cases MDD precedes
ED. The relative chronology of the onset of MDD could differentiate two types of ED: those preceded by MDD and those where MDD is consecutive (part of which could be related to the malnutrition artefact mentioned above) — these could be different clinical profiles, or even different phenotypes.

5. Conclusion

Our review highlights the need for further studies, which should address several requirements: studies on comorbidity should be designed with this specific goal in mind, rather than as a secondary aim within other types of studies (such as treatment studies, follow-up studies, etc...). New studies should include control subjects, matched (at least) for gender and age with ED subjects. Studies should evaluate prevalence of all types of MD in order to yield comparable estimates for MD in general. Comorbidity studies should be conducted on both current and recovered patients, compared to subjects from the community. It is still necessary to demonstrate the specificity of certain findings, for instance that early onset MD is of specific etiological importance to ED and does not simply increase the risk of later psychopathology in general. Studies should be conducted on larger samples, and diagnostic subgroups should be considered on a lifetime basis, as Kaye et al. (2004) did for anxiety disorders. Multivariate comparisons should be performed to compare group and sub-group prevalence, taking into account subject age, gender (if men are included), in-and outpatient status, BMI and/or malnutrition markers, duration of illness, and other possibly relevant variables. Thus, more reliable estimates of the frequency of MD in subjects with ED could provide us with valuable etiological, therapeutic and prognostic information.

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References


