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High Prevalence of Eating Disorders in Narcolepsy with Cataplexy: A Case-Control Study

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Study Objectives: To study the prevalence of and symptoms of eating disorders in patients with narcolepsy.

Design: We performed a case-control study comparing symptoms of eating disorders in patients with narcolepsy versus healthy population controls, using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1). To study whether an increased body mass index (BMI) could be responsible for symptoms of an eating disorder, we also compared patients with BMI-matched controls, using the SCAN as well as the Eating Disorder Examination-Questionnaire.

Setting: University hospital.

Patients and participants: Patients with narcolepsy/cataplexy (n = 60) were recruited from specialized sleep centers. Healthy controls (n = 120) were drawn from a population study previously performed in the Netherlands. Separately, 32 BMI-matched controls were recruited.

Interventions: N/A.

Measurements and Results: In total, 23.3% of the patients fulfilled the criteria for a clinical eating disorder, as opposed to none of the control subjects. Most of these were classified as Eating Disorder—Not Otherwise Specified, with an incomplete form of binge eating disorder. On the symptom level, half of the patients reported a persistent craving for food, as well as binge eating. Twenty-five percent of patients even reported binging twice a week or more often. When compared with BMI-matched controls, the significant increases persisted in symptoms of eating disorders among patients with narcolepsy. Except for a higher level of interference in daily activities due to eating problems in patients using antidepressants, medication use did not influence our findings.

Conclusions: The majority of patients with narcolepsy experience a number of symptoms of eating disorders, with an irresistible craving for food and binge eating as the most prominent features. Eating disorder symptomatology interfered with daily activities. These findings justify more attention for eating disorders in the treatment of patients with narcolepsy.

Keywords: narcolepsy, body weight, obesity, eating disorders, binge eating, bulimia

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NARCOLEPSY IS A CLINICALLY HETEROGENEOUS CONDITION.1,2 NEXT TO THE CORE FEATURES OF EXCESSIVE DAYTIME SLEEPINESS AND CATAPLEXY, there is a varying number of additional symptoms. Besides sleep-related symptoms, such as sleep paralysis, hypnagogic hallucinations and fragmented nocturnal sleep, non-sleep symptoms are often encountered. One of the more prominent of those is the increase in body weight in many patients. Already in the 1930s, Daniels reported that 57% of his patients with narcolepsy were overweight or obese.3 Recently, a number of epidemiologic studies showed a clear increase in body mass index (BMI) in narcoleptic patients compared with the general population,4,6 with a preferential storage of fat in the abdominal compartment.6 Several explanations for the weight gain have been put forward. Although the psychoanalytic theory of weight gain due to “substitutive oral activity” held for a while,7 recent discoveries into the biologic basis of narcolepsy provided more founded mechanisms.

Most cases of narcolepsy with cataplexy are caused by a deficiency in hypocretin (orexin) neurotransmission.8,9 The hypocretin neurons are located in the perifornical area of the lateral hypothalamus and are involved not only in the regulation of sleep, but in endocrine and autonomic regulation as well.10 The weight gain in narcolepsy could be caused by changes in energy expenditure due to excessive sleepiness, changes in basal metabolic rate,11,12 or endocrine disturbances.13,14 Excessive daytime sleepiness is not likely to be a major factor, as patients with narcolepsy have a significantly higher BMI than do patients with idiopathic hypersomnia.6 Interestingly, recent studies have shown that the hypocretin system may also be active in the psychiatric domain.15,16 This, in combination with the known stimulatory effect of hypocretin on food intake,17 raises the possibility that eating disorders may be present in narcolepsy.

Although a controlled diary study showed no differences in total caloric intake between patients with narcolepsy and controls,18 there have been some reports on symptoms of eating disorders. Kotagal et al found a history of binge eating in 5 out of 31 children with narcolepsy.19 Recently, Chabas et al reported a mild eating disorder, classified as eating disorder not otherwise specified (EDNOS), in 6 patients with narcolepsy-
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METHODS

General Study Design

We conducted 2 separate cross-sectional case-control studies. In study I, we compared symptoms of eating disorders in 60 patients with narcolepsy-cataplexy with 120 age- and sex-matched controls taken from a large population-based study. In study II, 32 patients with narcolepsy were compared (using an additional diagnostic instrument) with 32 specifically recruited controls, matched not only for age and sex, but also for BMI. This study was conducted according to the guidelines of the medical ethics committee of the Radboud University Nijmegen Medical Center. All subjects gave informed consent prior to entering the study.

Participants

Narcoleptic patients were recruited from the outpatient clinics of Sleep-Wake Center ‘Kempenhaeghe’ (Heeze, The Netherlands) and the Department of Neurology, Leiden University Medical Center (Leiden, The Netherlands). All patients fulfilled the ICSD-2 diagnostic criteria of narcolepsy with cataplexy.20 All were HLA-DQB1*0602 positive, and multiple sleep latency testing showed a mean sleep latency of less than 8 minutes as well as 2 or more sleep-onset rapid eye movement periods. In only a minority of patients, cerebral spinal fluid hypocretin-1 measurements were performed.9 Other sleep disturbances, such as sleep-related breathing disorders, were excluded as the cause for the excessive daytime sleepiness.

In study I, 60 narcoleptic patients were compared with 120 control subjects. Controls were randomly taken from the cross-sectional population-based Nijmegen-Health-Area-2 study, in which psychiatric symptoms were assessed in 368 people from the Dutch population.21 Controls were matched for age, sex, and urban environment (living in residential area with less or more than 100,000 inhabitants).

In study II, 32 narcoleptic patients were compared with 32 controls, recruited by advertisement in a local newspaper. Here, subjects were also matched for BMI, as BMI has been shown to influence eating attitudes and behavior.22-24

Measurements

Symptoms of eating disorders were assessed using chapter 8 and 9 of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1. The SCAN consists of a semi-structured interview that incorporates the Present State Examination, version 10.25 The SCAN is a validated diagnostic instrument that is widely endorsed.25-28 Both the patients and the population controls were interviewed by trained and certified SCAN investigators. From the SCAN data, symptoms of eating disorders can be assessed on the item level. In addition, it is possible to classify symptoms into the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic classification for eating disorders: anorexia nervosa, bulimia nervosa, and EDNOS.29 EDNOS contains incomplete forms of anorexia nervosa or bulimia nervosa, as well as binge eating disorder. To enable classification as binge eating disorder with more certainty, we added 1 question from the Structured Clinical Interview for DSM-IV to our SCAN interview. Section 8 of the SCAN assesses physical functions such as changes in BMI over time. Section 9 assesses various symptoms of eating disorders, as well as the interference with daily activities due to these symptoms. We added section 6 and 7 from the SCAN, which cover depressive symptomatology, in order to assess the influence of mood symptoms on eating behavior.

In study II, besides the SCAN, subjects completed the Eating Disorders Examination-Questionnaire (EDE-Q 4th edition).30 The EDE-Q is a self-report version of the Eating Disorder Examination.31 It is a 36-item scale that assesses features of eating disorders, generating 4 subscale scores: dietary restraint, eating concern, weight concern, and shape concern. Respondents rate the items on a 7-point scale, indicating the number of days out of the previous 28 in which specific behaviors and attitudes occurred. The EDE-Q has received psychometric support, including adequate test-retest reliability32,33 and a good convergence with the EDE-interview.30,34,35 Disordered eating was defined when subjects scored 4 or greater on either the weight concern or the shape concern subscale, had a mean global score of 4 or greater, or had more than 1 episode of self-induced vomiting, binging with loss of control or diuretic or laxative use over the last 4 weeks.34,36

Statistical Analysis

All data are presented as mean ± standard deviation. Mean item scores and item frequencies were compared between groups using student t-test and Fisher exact test, respectively. To obtain DSM-IV diagnostic classifications from the SCAN interview, we used the software algorithm written by C.R. in SAS version 8, in consultation with and after approval of the World Health Organization SCAN workgroup. All other statistical comparisons were done using SPSS version 14 (SPSS, Inc., Chicago, IL). Significance level was set at P = 0.05.

RESULTS

Demographic and Clinical Variables

In Table 1, the demographic characteristics of the participants are listed. In both studies, patients and controls were well matched for sex and age. On average, patients had narcolepsy symptoms for approximately 20 years at the time of study. Fifty-two percent of patients used stimulant medication (modafinil...
or methylphenidate), 12% used sodium oxybate, and 43% used antidepressants for cataplexy.

In study I, we again confirmed that patients with narcolepsy are overweight: there was a significant difference in BMI between patients (27.8 ± 5.7) and controls (24.6 ± 3.3, P = 0.001). BMI was not influenced by sex. In study II, patients and controls were well matched for BMI.

### Symptoms of Eating Disorders

The percentages of participants scoring positive on the various items of the SCAN are listed in Table 2. In study I, patients with narcolepsy scored significantly higher on all items, except for “actions to lose weight through purgation.” About half of the patients reported a persistent craving for food, experienced an earlier episode of overeating, and experienced binge eating. Twenty-five percent of patients even reported binging twice a week or more often. The majority of patients reported a dread of becoming fat, a self-perception of fatness, or both. Patients also took more measures for weight control, such as the avoidance of fattening foods or trying to lose weight through self-restriction. No endocrine disturbances were reported, such as delayed onset of puberty or amenorrhea.

Female patients showed significantly higher scores than males on the following items: dread of becoming fat (78% vs 43%, P = 0.001) and dread of getting too fat in spite of craving (44% vs 15%, P = 0.02). Furthermore, women more often reported a certain level of interference of symptoms of eating disorders in daily life (72% vs 43%, P = 0.013).

In study II, BMI-matched controls also reported symptoms of eating disorders, such as a self-perception of fatness and measures for weight control (Table 2). However, even when compared with BMI-matched controls, patients with narcolepsy had a significantly increased frequency of episodes of overeating, binge eating, and a persistent craving for food. Furthermore, within the patient group, there was no difference in BMI between subjects who reported binge eating and those who did not. There were also no significant correlations between BMI and the presence of eating disorders.

### Table 1—Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Age, y</td>
<td>43.5 ± 15.6</td>
<td>40.4 ± 15.1</td>
</tr>
<tr>
<td>Males, no.</td>
<td>28 (47%)</td>
<td>11 (34%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.8 ± 5.7</td>
<td>27.6 ± 7.1</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>20.1 ± 9.2</td>
<td>19.7 ± 7.6</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>30.6 ± 11.6</td>
<td>28.2 ± 10.8</td>
</tr>
<tr>
<td>Duration of symptoms, y</td>
<td>23.9 ± 15.8</td>
<td>20.4 ± 13.0</td>
</tr>
<tr>
<td>Duration since diagnosis, y</td>
<td>10.5 ± 11.0</td>
<td>11.10 ± 9.4</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD unless otherwise indicated. BMI refers to body mass index.

### Table 2—SCAN Section 9 (Item Level Symptoms of Eating Disorders)

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Dread of becoming fat</td>
<td>62%</td>
<td>78%</td>
</tr>
<tr>
<td>Earlier episode of undereating</td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td>Irresistible and persistent craving for food</td>
<td>67%</td>
<td>66%</td>
</tr>
<tr>
<td>Earlier episode of overeating</td>
<td>42%</td>
<td>50%</td>
</tr>
<tr>
<td>Self-perception of fatness w/ intrusive dread of becoming too fat</td>
<td>33%</td>
<td>38%</td>
</tr>
<tr>
<td>Imposes low weight threshold</td>
<td>5%</td>
<td>13%</td>
</tr>
<tr>
<td>Avoidance of fattening foods</td>
<td>45%</td>
<td>53%</td>
</tr>
<tr>
<td>Actions to lose weight through self restriction</td>
<td>42%</td>
<td>43%</td>
</tr>
<tr>
<td>Actions to lose weight through purgation</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Binge eating w/ sense of lack of control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>45%</td>
<td>31%</td>
</tr>
<tr>
<td>Binges but retains control</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Binges infrequently w/ feeling of loss of control</td>
<td>18%</td>
<td>28%</td>
</tr>
<tr>
<td>Binges twice a week, w/ a feeling of lack of control</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>Binges more frequently w/ a feeling of loss of control</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Dread of getting too fat in spite of craving</td>
<td>30%</td>
<td>28%</td>
</tr>
<tr>
<td>Actions to correct binging through purgation</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Restrictive actions to correct binging</td>
<td>18%</td>
<td>25%</td>
</tr>
</tbody>
</table>

*χ² test. SCAN refers to Schedules for Clinical Assessment in Neuropsychiatry.
between treated and untreated patients and, separately, between patients with or without the use of antidepressants or stimulants. The results are shown in Table 4. Interestingly, medication use did not increase BMI. Treated patients even tended toward a lower BMI. Furthermore, medication use did not influence the prevalence of symptoms and diagnoses of eating disorders, except for a trend toward more irresistible craving in the patients using antidepressants. Furthermore, the patients who received treatment reported a significantly higher level of interference with activities due to eating problems.

Mood disorders may interact with the presence of diagnoses and symptoms of eating disorders. The number of patients fulfilling the criteria for depression or bipolar disorder was too small to make any comparisons. We therefore compared patients with and without the SCAN-symptom “depressive mood” and “anhedonia” on BMI, key symptoms of eating disorders, and diagnoses of eating disorders. We found no effect of these mood symptoms, except for a higher prevalence of binge eating with lack of control (with depressive mood: 67% vs 33%, P = 0.024; with anhedonia: 75% vs 32%, P = 0.004) and a higher number of EDNOS diagnoses (with depressive mood: 39% vs 5%, P = 0.002; with anhedonia 38% vs 7%, P = 0.008). So, especially for the diagnosis EDNOS, there seems to be a relation with the presence of depressed mood and anhedonia.

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and the EDE-Q subscales on objective and subjective bulimic episodes.

Symptoms of eating disorders posed a clear interference with daytime activities in patients. More than 30% of patients reported moderate to severe (and incapacitating) interference with activities, compared with 1% of controls in the general population and 6% in BMI-matched controls (P < 0.001).

**DSM-IV Classification of Eating Disorders**

Using the SCAN data, subjects were classified in the DSM-IV eating disorders diagnoses (Table 3). In total, 23.3% of the patients fulfilled the criteria for a clinical eating disorder, against none of the control subjects. Only 1 patient was classified as having anorexia nervosa. Four patients (6.7%) fulfilled the criteria of bulimia nervosa. Nine patients (15%) were classified as EDNOS. Within this category, 2 patients were subthreshold anorexia nervosa cases (having all criteria except amenorrhea); 1 patient had subthreshold bulimia nervosa (having all criteria, but binge frequency was less than twice a week). Six patients met the criteria for binge eating disorder, 5 of whom were subthreshold because of missing the DSM-IV criterion of “marked distress regarding binge eating.” In study II, the results regarding DSM-IV eating disorders diagnoses were essentially the same as in study I.

At the time of study, 17 out of 60 patients (28.3%) did not receive treatment for their narcolepsy, with stimulants, sodium oxybate, or antidepressants. Only 6 control subjects (5%) used antidepressant drugs. We compared BMI, diagnoses of eating disorders, and the most salient symptoms of eating disorders between treated and untreated patients and, separately, between patients with or without the use of antidepressants or stimulants. The results are shown in Table 4. Interestingly, medication use did not increase BMI. Treated patients even tended toward a lower BMI. Furthermore, medication use did not influence the prevalence of symptoms and diagnoses of eating disorders, except for a trend toward more irresistible craving in the patients using antidepressants. Furthermore, the patients who received treatment reported a significantly higher level of interference with activities due to eating problems.

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**EDE-Q Results**

Results from the EDE-Q auto-questionnaire are presented in Tables 5 and 6. Several measures of attitudes in eating behavior (dietary restraint, eating and weight concern) were significantly
In this study, we showed that a considerable number of patients with narcolepsy-cataplexy display various symptoms of eating disorders, with an emphasis on a craving for food and binge eating behavior. In almost a quarter of patients, it was even possible to make a formal DSM-IV eating disorder classification. Many patients reported a dread of becoming fat, and the eating problems posed a clear interference with activities in more than one third of our cohort. Eating disorders seem to be an integral part of the narcolepsy phenotype and not only due to the increase in BMI, as narcoleptic patients scored significantly higher on various items of both the SCAN and EDE-Q when compared with BMI-matched healthy controls.

On the symptom level, narcoleptics reported irresistible and persistent craving for food, binge eating with lack of control, and restrictive actions to correct binging. However, there was no single specific eating disorder classification within the patient group: bulimia nervosa (4/60), anorexia nervosa (1/60), and EDNOS (9/60) were all present. Within the EDNOS group, however, 6 of 9 patients could indeed be categorized into binge eating disorder, whereas the others had subthreshold bulimia or anorexia. These prevalence numbers are clearly higher than those in the overall population. In our control cohort, no formal eating disorders could be diagnosed, and this is in line with previous studies that found very low prevalences, even in selected populations that would be at higher risk, such as young females (in the range of 0.7% for anorexia nervosa to 1% to 2% for bulimia nervosa). The prevalence of EDNOS has been established less extensively; a recent study of 2018 Portuguese young females found a prevalence of not more than 2.4%. Interestingly, the effect of the various medications used for narcolepsy had no clear influence on the prevalence of diagnoses and symptoms of eating disorders, nor on BMI. In fact, medication use tended to be associated with a lower BMI. There was as slight trend toward more craving in patients using antidepressants, and these patients also report more interference in activities due to eating problems. Regarding the influence of symptoms of mood disorders, patients with depressive mood and/or anhedonia had a higher number of EDNOS diagnoses, as well as binge eating with lack of control. However, in our cross-sectional study design, it is not possible to decipher the “direction” of this correlation. Further (longitudinal) studies may shed light on this issue.

The few other reports on eating disorder symptomatology in narcolepsy also found an emphasis on binge eating. Recently, Chabas et al reported that half of 6 typical and 7 atypical patients with narcolepsy could be classified as EDNOS, with features of bulimia nervosa. Diagnosis of EDNOS seems to have been made on a rough exclusion of anorexia and bulimia nervosa without precise criteria, however. Because of the small sample size, the influence of sex on eating behavior could not be assessed. In our study, we did not find a difference in binging behavior between men and women. However, women more often reported a dread of becoming fat and a higher level of interference in activities. So, despite binging to the same extent, women are more worried about their eating behavior.

Previous studies into binge eating disorder have shown a positive correlation between binge eating and obesity. Chabas et al also showed a trend toward more pronounced symptoms in the narcoleptics who were overweight, compared with those with a normal BMI. However, in our study, we could not establish a relationship between BMI and binge eating. In fact, the relationship between symptoms of eating disorders and BMI may be the other way: a higher BMI has been...
shown to influence eating attitudes and behaviors. The control subjects in study II (matched with the patients for BMI) indeed showed an increase in symptoms, compared with the general population controls in study I. However, even when compared with BMI-matched controls, patients had significantly more eating disorder symptomatology. This suggests that the eating disorder is an integral part of the narcolepsy phenotype and not a pure consequence of the obesity per se. We propose that the eating disorder could be a direct consequence of the hypocretin deficiency. This is not in contradiction with the fact that Chabas et al found that both “typical” and “atypical” patients displayed symptoms of eating disorders; in that study, hypocretin levels were not measured, and, even in patients with normal hypocretin levels, it remains possible that the hypocretin system is dysfunctional, for example through postsynaptic mechanisms.

Although the hypocretin system was initially proposed to be mainly stimulating feeding, it is now clear that it subserves a broad range of functions, including metabolic and endocrine regulation. One tantalizing link between hypocretin defects and binge eating forms the melanocortin system. Binge eating has been reported as a major phenotype of mutations in the melanocortin-4 receptor (MC4-R). The hypocretin system has connections with cells in the arcuate nucleus that produce pro-opiomelanocortin, the precursor of melanocortin. So, hypocretin deficiency may directly influence melanocortin signaling, which in turn may cause eating disorders.

The increased scores on weight and eating concern in the EDE-Q data reflect the impact that the symptoms of eating disorders have on the lives of patients. This was further corroborated with the high levels of interference with activities, as assessed in the SCAN. Clearly, symptoms of eating disorders pose a great burden on the patients. Now that obesity has become a social and even political issue, the pressure to correct the increase in body weight may even add to the suffering and concern of patients. It is not improbable that shame around this theme suppresses communication, partly explaining that eating disorders in narcolepsy are a relatively unknown issue to physicians. It is important that doctors treating patients with narcolepsy discuss these symptoms and give proper information and guidance. In patients with prominent symptoms of eating disorders, referral to a specialized psychiatrist may be indicated. Cognitive behavior therapy can be useful in certain eating disorders, such as bulimia, binge eating disorder, and other EDNOS subtypes. Guided weight-reduction programs may also be used. Although we did not have information on formal diagnoses of the metabolic syndrome in our cohort, patients with a BMI greater than 30 more often used cardiovascular and antidiabetic medication than did those with a BMI less than 30 (6/7 vs 4/43, P = 0.004). An increased BMI has been reported as a major phenotype of mutations in the melanocortin-4 receptor (MC4-R). The hypocretin system has connections with cells in the arcuate nucleus that produce pro-opiomelanocortin, the precursor of melanocortin. So, hypocretin deficiency may directly influence melanocortin signaling, which in turn may cause eating disorders.

This is the first epidemiologic study assessing eating disorder symptomatology in narcolepsy with cataplexy, using a cross-sectional case-control design in a large number of subjects. Furthermore, we not only used auto-questionnaires, but also a semistructured interview to assess symptoms. We used both a general population control group, as well as controls matched for BMI. All patients fulfilled the ICSD-2 criteria for narcolepsy with cataplexy. Hypocretin-1 levels were known in only a small number of subjects, so we were not able to directly assess the influence of hypocretin deficiency. However, it is known that in patients with sporadic and clear-cut cataplexy, more than 90% of subjects are hypocretin-1 deficient. Although we used validated instruments to assess symptoms, we did not systematically collect data to measure the timing of binges and craving for food. We were thus unable to assess the presence of the night eating syndrome. Six out of 32 patients in study II spontaneously mentioned binging at night; other patients reported that, with a build-up of sleep pressure throughout the day, the resistance against binging diminished. Future studies should include a formal assessment of the night eating syndrome and address circadian, sleep homeostatic, and mood influences on the frequency and severity of binging. Furthermore, the prevalence of the metabolic syndrome and other cardiovascular and endocrine complications should be assessed in narcolepsy. Finally, it would be of great interest to study the direct effect of hypocretin disturbances and associated endocrine changes in narcolepsy, for example in leptin or ghrelin levels.

ACKNOWLEDGMENTS

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