The use of systemic antimicrobial medication in patients with eating disorders

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Helsinki 19.8.2014

Tutkielma

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Tiedekunta/Osasto – Fakultet/Sektion – Faculty	Laitos – Institution – Department	
Lääketieteellinen tiedekunta	Hjelt-instituutti	
Tekijä – Författare – Author		
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Työn nimi – Arbetets titel – Title		
The use of antimicrobial medication in patients with eating disorders		
Oppiaine – Läroämne – Subject		
Lääketiede		
Työn laji – Arbetets art – Level	Aika – Datum – Month and year	Sivumäärä -Sidoantal - Number of pages
Tutkielma	19.8.2014	30

Tiivistelmä – Referat – Abstract

This study assessed the prevalence and number of antimicrobial prescriptions and defined daily doses (DDDs) in patients with eating disorders.

Patients (N=1592) treated at the Eating Disorder Unit of the Helsinki University Central Hospital were compared with matched controls (N=6368) on the prevalence and numbers of prescriptions and DDDs of antimicrobial drugs. The analyses were made using various regression models.

Patients with bulimia nervosa and binge-eating disorder had higher prevalence of prescription than their matched controls (OR 1.67, 95% CI 1.34-2.07 and OR 2.58, 95% CI 1.44-4.61, respectively). They also had generally larger number of DDDs. Patients with anorexia nervosa did not generally differ from their controls in the use of antimicrobial drugs.

The findings of this study demonstrated the increased use of antimicrobial medication in patients with bulimia nervosa and binge-eating disorder. The elevated number of infections in these patient populations might be associated with binge-eating related hyperglycemia. (149 words)

Avainsanat – Nyckelord – Keywords

Eating disorders; pharmacoepidemiology; antibacterial agents; antifungal agents; antiviral agents

Säilytyspaikka – Förvaringställe – Where deposited
Muita tietoja – Övriga uppgifter – Additional information

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1 INTRODUCTION

Eating disorders are psychiatric disorders in which abnormal eating patterns are typical. In ICD-10 (1), anorexia nervosa (AN) is characterized by extreme fear of getting fat, bodyweight more than 15% below expected and amenorrhea. Bulimia nervosa (BN) is characterized with episodes of binging large amounts of food followed by self-induced vomiting, misuse of laxatives or fasting. In addition, dissatisfaction with one's own body and fear of gaining weight are diagnostic features of BN (1). In DSM-4 and DSM-5 (2,3), typical features of binge-eating disorder (BED) are episodes of rapid uncontrolled food binges without the compensatory actions typical in BN. BED often leads to obesity, but can also occur in normal weight individuals.

Malnutrition, especially protein-energy malnutrition, and some micronutrient deficiencies are generally associated with impaired immunity and increased incidence of infections (4). Some malnutrition is often present in eating disorders (5,6). As well as deficiencies, also excess intake of some micronutrients, such as zinc (7), and some energy yielding nutrients, like certain dietary fatty acids (8), is associated with impairment of the immune function. In obesity, immune function is often compromised, but the underlying factors are not fully understood. It has been suggested to result from excessive intake of some nutrients but also deficiencies of some micronutrients have been reported in obese people. In addition, metabolic and endocrine changes, typical in obesity, could alter the immune system. (7) On the other hand, individuals overweight or obese are at increased risk for developing disordered eating behaviors (9,10), and both BN and BED might be associated with overweight or obesity at the acute stages of the disorder.

Several studies have demonstrated alterations in the immune function in patients with AN. Mild leukopenia and anemia have commonly been associated with AN (11–14). These seem to improve in AN after refeeding (15). Similar results have been presented in patients with BN (5), although controversial results have also been published (16,17). Lymphocyte proliferative responses, i.e. lymphocytes ability to respond to various stimuli such as antigens or mitogens, have been shown to correlate negatively with the level of anxiety in BN (16).

Reduced reactions or anegry, i.e. the secondary lack of cell mediated immunity, in delayed cutaneous hypersensitivity test, is common in patients with AN (11,12,18). In addition, reduction in the activation pathway, especially in T-lymphocytes CD2 and CD69, has been reported (15). Alterations in the function of the complement system of the immune defense have been associated both with AN and with obesity. Low bodyweight seems to associate with diminished complement proteins, whereas obesity is associated with the increased number of some proteins, for example complement proteins C3, B, AP50, H and I of the alternative pathway. (19,20)

Despite the alterations of the immune system, patients with AN rarely seem to develop bacterial or viral infections (14,21). This has been suggested to be due to the relatively good protein intake in many patients with AN (22). In addition, diminished febrile response in AN might complicate the diagnosis of infections and it might also be connected to increased complications (23,24).

According to the knowledge of the author, no previous pharmacoepidemiological or other studies of the use of antimicrobial medications among patients with eating disorders exist.

This study aimed to assess the use of antimicrobial medication in patients suffering from AN, BN and BED in comparison with matched control population. The incidence and the number of prescriptions as well as defined daily doses (DDDs) in all groups were examined. To exclude the potential effect of the treatment for an eating disorder on the number of prescriptions prescribed to the patients compared to the controls, the use of antimicrobial medication was assessed for five-year time period before the treatment onset.

Based on previous studies, the incidence and the number of prescriptions and DDDs were hypothesized to not differ in patients with AN compared to controls since the AN associated leukopenia have not been shown to increase the risk of infection; and, excluding Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS), which includes early onset AN, infections are not known to trigger the disorder. The numbers of prescriptions and DDDs were hypothesized to be elevated in patients with BED due to the elevated prevalence of overweight and obesity in this population; and as described, obesity is associated with impairment of the immune function. Because of lack consistent previous findings in BN, the analyses were exploratory and there was no specific hypothesis of the direction of the change in this population. As described, patients with BN have been noticed to have similar changes in the immune system as patients with AN, but on the other hand large weight fluctuations and overweight might also be present in BN.

2 METHODS

2.1 Study population

The study included patients (N=1592) treated in the Eating Disorder Unit at the Helsinki University Central Hospital between January 1st, 2000 and December 31st, 2010. For the majority of patients the treatment was on outpatient level, but day patient and inpatient treatments were also available. For each patient, four control individuals (N=6368) matched by sex, age and place of residence were selected from the Central Population Register of Finland. Each individual follow-up period started five years before the onset of the treatment and lasted until the start of the treatment at the Eating Disorder Clinic.

The diagnoses were made by the attending psychiatrist on the arrival at the Eating Disorder Unit on the grounds of International Classification of Disease (ICD-10) of the World Health Organization (1992) (1). The diagnostic groups within the patients were F50.0, F50.1, F50.2, F50.3 and F50.8 indicating AN, atypical AN, BN, atypical BN and BED, respectively. The diagnosis for atypical AN was made in case of patients who otherwise presented a fairly typical clinical picture of AN, but were missing one or more key features of the disorder; for example amenorrhea or weight loss below 85% of expected. Similarly, the diagnosis for atypical BN was made for patients who were missing one or more key features of BN, but otherwise presented a fairly typical clinical picture.

For AN and BN broader definitions were used, since the current diagnostic criteria for eating disorders in DSM-5 (3) have been relaxed compared to DSM-4 (2) and ICD-10 (1). In this study ICD-10 classifications F50.0 and F50.1 indicate AN (N=701) and ICD-10

classifications F50.2 and F50.3 indicate BN (N=747). Patients with BED (F50.8; N=144) were diagnosed at the Eating Disorder Unit using the DSM-4 research criteria (2).

2.2 Antimicrobial medication

The study utilized the Medical Reimbursement Register of the Social Insurance Institution of Finland. The register includes data on all redeemed reimbursed prescriptions and individuals in this register can be identified by a personal identification number. These medication data were available from January 1st, 1995 to December 31st, 2011; all the study participants had medication data for five-year period before the onset of the treatment. The numbers of prescriptions as well as DDDs were assessed. DDD denotes a statistical value of average maintenance dose per day for a drug used for its main indication in adults, defined by the World Health Organization (25). Personal identification number was used for linkages between the study population and the data from the Medical Reimbursement Register on prescriptions of systemic antibacterial, antifungal and antiviral medication (Anatomical Therapeutic Chemical [ATC] groups J01, J02 and J05, respectively; see Appendix 1 for the list all drugs assessed).

This study assessed the use of systemic antibacterial, antifungal and antiviral medication. Antibacterial drugs are used for defense against bacterial infections and can be targeted to effect on bacteria's metabolism, cell wall synthesis, protein synthesis, nucleic acid synthesis or sometimes cell membrane permeability. Antifungal drugs are used against fungal infections usually caused by yeast, mold or dermatophyte. Many of the antifungal drugs prevent the synthesis of ergosterol, which is an essential component of the fungal cell wall. Virus is a strand of genetic material surrounded by a protein envelope. The majority of antiviral drugs are purine or pyrimidine analogs that compete with the natural components of the viral nucleic acids. (26)

2.3 Statistical analyses

Conditional logistic regression model was used to analyze the difference in the prevalence of prescriptions between patients and matched controls with dichotomous manner (no prescription=0, one or more prescriptions=1). I.e., the numbers of prescriptions or DDDs were not taken into account in this test. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Multivariate regression model was used to test the differences in DDDs in all ATC groups within each diagnostic group comparing the patients to the control population. To compare the prevalence of prescriptions within patients in three diagnostic groups, logistic regression analysis was used and AN group was used as the reference. Results are reported as ORs with 95% CI. Also prevalence adjusted by sex and age were modeled.

Because of the overdispersed data, quasipoisson regression model was used to make predictions on the number of prescriptions for individuals of different age and sex. This quasi-likelihood allows greater variability in the data than would be predicted by the Poisson model (27). Linear regression model was used to assess the number of DDDs during the five-year follow-up period. DDD was set as the dependent variable and age, sex and diagnostic groups were set as the independent variables. Predictions of the estimated values for individuals of different age and sex were calculated using these models. Results are presented as predictions with 95% CIs.

The author performed all the analyses using R software.

2.4 Ethical considerations

Ethical permits for the study were obtained from the Ethics committee of National Institute of Health and Welfare (Dnro THL/184/6.02.00/2011), and the permission of the use of the data of The Social Security Institution was obtained. The study was conducted according to the Helsinki Declaration. Data handling was performed according to the Finnish data protection legislation and the rules of National Institute of Health and Welfare. The author did not have access to the personal identification data, only research codes were used in the analyses.

3 RESULTS

3.1 Basic characteristics of the study population

The basic characteristics of the patients of the study population are presented in Table 1. The study population consisted of 1592 patients (1515 females and 68 males) and 6368 control individuals (6096 females and 272 males). There were 701 (4.71% males) patients with AN, 747 (2.01% males) patients with BN and 144 (13.89% males) patients with BED. The mean age of the whole population was 26.0 years (SD ±8.4); 23.6 years (SD ±6.9) in patients with AN, 25.9 (SD ±7.2) in patients with BN and 38.0 (SD ±10.5) in patients with BED.

Table 1. Basic characteristics of the patients of the study population by diagnostic groups. The age of the patients was recorded at the beginning of the treatment at the Eating Disorder Unit of the Helsinki University Central Hospital.

SD, Standard Deviation

	All eating disorders		**Anorexia nervosa (F50.0+F50.1)**		**Bulimia nervosa (F50.2+F50.3)**		**Binge-eating disorder (F50.8)**	
	Patients (N)	**%**	**Patients (N)**	**%**	**Patients (N)**	**%**	**Patients (N)**	**%**
Number	1592	100.00%	701	100	747	100.00%	144	100.00%
Sex								
Female	1515	95.16%	668	95.29%	723	96.79%	124	86.11%
Male	68	4.27%	33	4.71%	15	2.01%	20	13.89%
Age groups, years								
(0,20]	385	24.18%	252	35.95%	130	17.40%	3	2.08%
(20,25]	565	35.49%	263	37.52%	291	38.96%	11	7.64%
(25,30]	285	17.90%	97	13.84%	171	22.89%	17	11.81%
(30,35]	147	9.23%	39	5.56%	80	10.71%	28	19.44%
(35,40]	78	4.90%	18	2.57%	32	4.28%	28	19.44%
(40,45]	58	3.64%	14	2.00%	21	2.81%	23	15.97%
(45,50]	40	2.51%	12	1.71%	14	1.87%	14	9.72%
(50,Inf]	34	2.14%	6	0.86%	8	1.07%	20	13.89%

	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Age, years	26.0±8.4	23.6±6.9	25.9±7.2	38.0±10.5
Min.	17.4	17.4	17.6	18.7
Q_1	20.1	19.2	20.8	30.6
Med.	23.2	21.1	24.0	36.8
Q_3	28.8	25.3	28.8	44.6
Max.	64.8	64.8	64.5	64.2

3.2 The numbers of prescriptions and defined daily doses

Appendix 1 summarizes the numbers of prescriptions and DDDs with the mean values in each diagnostic group of all the drugs assessed in the study. The total number of prescriptions in this study was 25 869 (mean 3.25 prescriptions per person) and the total number of DDDs was 263 533 (mean 33.11 DDDs per person).

In multivariate regression analyses, patients had more DDDs than the controls as follows. There was significantly higher number of DDDs of all drugs together in patients with BN and BED ($P<0.001$ and $P<0.001$, respectively) compared to the controls. There was also significantly larger number of DDDs in both BN and BED groups when assessing all antibacterial drugs together ($P<0.001$ and $P<0.001$, respectively) and specifically, tetracyclines (ATC code J01A; $P<0.001$ and $P<0.001$), beta-lactam antibacterials, i.e. penicillins (ATC code J01C; $P= 0.05$ and $P= 0.04$) and other beta-lactam antibacterials (ATC code J01D; $P= 0.008$ and $P<0.001$). In addition, there was more DDDs of macrolides, lincosamides and streptogramins (ATC code J01F) in the BN group ($P= 0.005$) and quinolone antibacterials (ATC code J01M) in the BED group ($P= 0.04$). BED patients had also significantly more DDDs of antifungal drugs (ATC code J02) than the controls ($P= 0.03$).

Of the individual drugs, there was increased number of DDDs in doxycycline (ATC code J01AA02; $P=0.03$), amoxicillin (ATC code J01CA04; $P= 0.05$), cephalexin (ATC code J01DB01; $P=0.01$) and fluconazole (ATC code J02AC01; $P= 0.02$) in the BN diagnostic group. In the BED diagnostic group, there was increased number of DDDs in phenoxymethyl penicillin (ATC code J01CE02; $P= 0.02$) and cephalexin (ATC code J01DB01; $P<0.001$). There

were no significant differences between AN patients and controls except in ATC group J01F indicating macrolides, lincosamides and streptogramins (P=0.005).

3.3 The use of antimicrobial medication

The results of conditional logistic regression analyses are presented in Table 2. In addition, the numbers of patients positive and negative for prescriptions with the percentage of the positive are presented. Assessing all prescriptions as a composite showed significantly higher prevalence of prescriptions in all patients compared to the matched controls (OR 1.22, 95% CI 1.06 - 1.40, P= 0.004). Patients with BED had the highest prevalence of all prescription (OR 2.58, 95% CI 1.44 - 4.61, P= 0.001), of antibacterial prescriptions (OR 2.37, 95% CI 1.39 - 4.06, P=0.002) and of antifungal prescriptions (OR 1.70, 95% CI 1.09 - 2.66, P= 0.02).

BN patients had significantly higher prevalence of prescriptions compared to their matched controls in all drug groups assessed, and BN group was the only eating disorder group showing significant difference in antiviral drugs (OR 1.61, 95% CI 1.14 - 2.29, P= 0.007). There was no difference between patients with AN and their controls in any of the drug groups.

Table 2. The prevalence of prescriptions in patients with different eating disorders compared to the matched controls. The numbers of patients positive and negative for prescriptions (YES/NO) with the percentage of the positive are presented as well as odds ratios with 95% confidence interval and P-values.

OR, Odds Ratio; CI, Confidence Interval

	N (positive/negative for prescription, % of positive)						**OR (95% CI)**	**P-value**
	Patients			**Controls**				
All Prescriptions	YES	NO	%	YES	NO	%		
All eating disorders	1260	332	79.15%	4825	1543	75.77%	1.21 (1.06 - 1.40)	**0.004**
Anorexia Nervosa	499	202	71.18%	2082	722	74.25%	0.85 (0.71 - 1.03)	0.100
Bulimia Nervosa	632	115	84.61%	2296	692	76.84%	1.67 (1.34 - 2.07)	**<0.001**
Binge Eating Disorder	129	15	89.58%	447	129	77.60%	2.58 (1.44 - 4.61)	**0.001**
Prescriptions of Antibacterial Drugs								
All eating disorders	1225	367	76.95%	4692	1676	73.68%	1.20 (1.05 - 1.36)	**0.007**
Anorexia Nervosa	490	211	69.90%	2035	769	72.57%	0.88 (0.73 - 1.05)	0.200
Bulimia Nervosa	609	138	81.53%	2224	764	74.43%	1.52 (1.24 - 1.86)	**0.001**
Binge Eating Disorder	126	18	87.50%	433	143	75.17%	2.37 (1.39 - 4.06)	**0.002**
Prescriptions of Antifungal Drugs								
All eating disorders	293	1299	18.40%	1037	5331	16.28%	1.17 (1.01 - 1.35)	**0.040**
Anorexia Nervosa	83	618	11.84%	395	2409	14.09%	0.81 (0.63 - 1.05)	0.100
Bulimia Nervosa	170	577	22.76%	531	2457	17.77%	1.38 (1.13 - 1.68)	**0.002**
Binge Eating Disorder	40	104	27.78%	111	465	19.27%	1.70 (1.09 - 2.66)	**0.020**
Prescriptions of Antiviral Drugs								
All eating disorders	73	1519	4.59%	254	6114	3.99%	1.16 (0.886 - 1.51)	0.300
Anorexia Nervosa	18	683	2.57%	93	2711	3.32%	0.77 (0.46 - 1.28)	0.300
Bulimia Nervosa	47	700	6.29%	120	2868	4.02%	1.61 (1.14 - 2.29)	**0.007**
Binge Eating Disorder	8	136	5.56%	41	535	7.12%	0.76 (0.35 - 1.68)	0.500

Logistic regression analyses results are shown in Table 3. There was a higher prevalence of prescriptions in patients with BN and BED compared to the patients with AN (used as reference). The prevalence was higher also when adjusted by sex and age.

Table 3. Results of logistic regression analyses of the prevalence of prescription presented as odds ratios with 95% confidence intervals with and without adjustments by sex and age. Patients with anorexia nervosa were used as reference.

OR, Odds Ratio; CI, Confidence Interval

		Adjusted by sex and age	
	OR (95% CI)		**OR (95% CI)**
	Prescriptions of All Antimicrobial Drugs		
		Sex, female	1.57 (0.88 - 2.80)
		Age	**1.02 (1.00 - 1.04)**
Bulimia nervosa	**2.23 (1.72 - 2.88)**	**Bulimia nervosa**	**2.12 (1.63 - 2.75)**
Binge-eating disorder	**3.48 (1.99 - 6.09)**	**Binge-eating disorder**	**2.91 (1.58 - 5.37)**
	Prescriptions of Antibacterial Drugs		
		Sex, female	1.34 (0.76 - 2.39)
		Age	1.01 (0.99 - 1.03)
Bulimia nervosa	**1.90 (1.49 - 2.43)**	**Bulimia nervosa**	**1.84 (1.43 - 2.36)**
Binge-eating disorder	**3.01 (1.79 - 5.07)**	**Binge-eating disorder**	**2.67 (1.51 - 4.72)**
	Prescriptions of Antifungal Drugs		
		Sex, female	**7.02 (2.14 - 23.09)**
		Age	**1.03 (1.02 - 1.05)**
Bulimia nervosa	**2.19 (1.65 - 2.92)**	**Bulimia nervosa**	**2.00 (1.50 - 2.67)**
Binge-eating disorder	**2.86 (1.86 - 4.41)**	**Binge-eating disorder**	**2.04 (1.24 - 3.34)**
	Prescriptions of Antiviral Drugs		
		Sex, female	2.28(0 - Inf)
		Age	1.02 (0.99 - 1.05)
Bulimia nervosa	**2.55 (1.47 - 4.43)**	**Bulimia nervosa**	**2.36 (1.35 - 4.12)**
Binge-eating disorder	2.23 (0.95 - 5.24)	**Binge-eating disorder**	1.82 (0.70 - 4.75)

3.4 Predictions of the use of antimicrobial medication

Quasipoisson model was used to make predictions of the number of antimicrobial prescriptions prescribed for individuals during the five-year time period (Table 4). The predicted numbers of prescriptions were higher for females than for males (P<0.001) (Appendix 2). The number of prescriptions rose with age (P<0.001) (Appendix 2). The predicted number of prescriptions was highest in BED patients; 5.15 antimicrobial prescriptions (95% CI 4.41 - 6.02) for a 25-year-old female compared to 3.13 prescriptions (95% CI 3.03 - 3.23) for a control of a same age. A female BN patient of 25 years of age had a prediction of 4.05 prescriptions (95% CI 3.74 - 4.38) during the five-year time period. The patients with AN did not differ significantly from the controls when assessing all antimicrobial prescriptions; the prediction for a 25-year old female was 2.92 prescriptions (95% CI 2.64 - 3.22). The only significant difference in patients with AN was in antifungal prescriptions that they had less than the controls (P=0.03).

Table 4. The predicted numbers of prescriptions in the course of five years for 20-, 25- and 40-year-old females and males with 95% confidence intervals.

CI, Confidence Interval

	20-year-old female	25-year-old female	40-year-old female
	Number of prescriptions (95% CI)	**Number of prescriptions (95% CI)**	**Number of prescriptions (95% CI)**
All Antimicrobial Drugs			
Controls	2.88 (2.77 - 2.99)	3.13 (3.03 - 3.23)	4.01 (3.82 - 4.22)
Anorexia nervosa	2.68 (2.43 - 2.97)	2.92 (2.64 - 3.22)	3.75 (3.36 - 4.18)
Bulimia nervosa	**3.72 (3.43 - 4.04)**	**4.05 (3.74 - 4.38)**	**5.20 (4.75 - 5.68)**
Binge-eating disorder	**4.74 (4.04 - 5.56)**	**5.15 (4.41 - 6.02)**	**6.62 (5.70 - 7.68)**
Antibacterial Drugs			
Controls	2.52 (2.43 - 2.62)	2.68 (2.60 - 2.76)	3.22 (3.06 - 3.39)
Anorexia nervosa	2.40 (2.18 - 2.64)	2.55 (2.32 - 2.80)	3.06 (2.75 - 3.41)
Bulimia nervosa	**3.13 (2.89 - 3.40)**	**3.33 (3.08 - 3.60)**	**4.00 (3.66 - 4.37)**
Binge-eating disorder	**4.00 (3.41 - 4.70)**	**4.26 (3.64 - 4.98)**	**5.11 (4.39 - 5.94)**
Antifungal Drugs			
Controls	0.29 (0.26 - 0.32)	0.35 (0.32 - 0.38)	0.58 (0.52 - 0.65)
Anorexia nervosa	**0.08 (0.05 - 0.15)**	0.25 (0.18 - 0.33)	0.41 (0.30 - 0.57)
Bulimia nervosa	0.14 (0.09 - 0.22)	**0.52 (0.43 - 0.63)**	**0.87 (0.71 - 1.08)**
Binge-eating disorder	0.05 (0.02 - 0.18)	**0.80 (0.58 - 1.10)**	**1.33 (0.98 - 1.81)**
Antiviral Drugs			
Controls	0.07 (0.06 - 0.09)	0.09 (0.07 - 0.11)	0.19 (0.15 - 0.24)
Anorexia nervosa	0.08 (0.05 - 0.15)	0.11 (0.06 - 0.20)	0.22 (0.12 - 0.42)
Bulimia nervosa	**0.14 (0.09 - 0.22)**	**0.18 (0.12 - 0.28)**	0.38 (0.24 - 0.59)
Binge-eating disorder	0.05 (0.02 - 0.18)	0.07 (0.02 - 0.23)	0.14 (0.04 - 0.46)

	20-year-old male	25-year old male	40-year-old male
	Number of prescriptions (95% CI)	**Number of prescriptions (95% CI)**	**Number of prescriptions (95% CI)**
All Antimicrobial Drugs			
Controls	1.47 (1.23 - 1.76)	1.60 (1.34 - 1.90)	2.05 (1.73 - 2.44)
Anorexia nervosa	1.37 (1.13 - 1.67)	1.49 (1.23 - 1.81)	1.91 (1.57 - 2.33)
Bulimia nervosa	1.90 (1.57 - 2.31)	2.07 (1.71 - 2.50)	2.66 (2.20 - 3.21)
Binge-eating disorder	**2.42 (1.92 - 3.06)**	**2.63 (2.10 - 3.31)**	**3.38 (2.72 - 4.21)**
Antibacterial Drugs			
Controls	1.49 (1.27 - 1.27)	1.59 (1.35 - 1.86)	1.91 (1.63 - 2.23)
Anorexia nervosa	1.42 (1.18 - 1.71)	1.51 (1.26 - 1.81)	1.81 (1.51 - 2.18)
Bulimia nervosa	**1.85 (1.55 - 2.22)**	1.97 (1.65 - 2.35)	2.37 (1.98 - 2.82)
Binge-eating disorder	**2.37 (1.90 - 2.96)**	**2.52 (2.03 - 3.13)**	**3.02 (2.45 - 3.73)**
Antifungal Drugs			
Controls	0.03 (0.01 - 0.08)	0.04 (0.02 - 0.09)	0.07 (0.03 - 0.15)
Anorexia nervosa	0.02 (0.01 - 0.06)	0.03 (0.01 - 0.07)	0.05 (0.02 - 0.12)
Bulimia nervosa	0.05 (0.02 - 0.12)	0.06 (0.02 - 0.14)	0.10 (0.04 - 0.24)
Binge-eating disorder	0.08 (0.03 - 0.19)	0.09 (0.04 - 0.22)	0.15 (0.06 - 0.37)
Antiviral Drugs			
Controls	0.02 (0.01 - 0.08)	0.03 (0.01 - 0.09)	0.05 (0.02 - 0.19)
Anorexia nervosa	0.02 (0.01 - 0.10)	0.03 (0.01 - 0.12)	0.06 (0.02 - 0.25)
Bulimia nervosa	0.04 (0.01 - 0.16)	0.05 (0.01 - 0.20)	0.11 (0.03 - 0.40)
Binge-eating disorder	0.02 (0.00 - 0.09)	0.02 (0.00 - 0.11)	0.04 (0.01 - 0.22)

Linear regression model was used to make predictions of the number of DDDs. As in quasipoisson model, the results are presented as predicted numbers of DDDs with 95% CI for 20-, 25- and 40-year-old females and males in table 5. The predicted number of all DDDs for a 25-year-old female with BED is 62.1 (95% CI 51.7 - 72.6), which is nearly double to the number of a control of a same age with 31.8 DDDs (95% CI 30.3 - 33.4). BN patient had a prediction of a total of 42.4 DDDs (95% CI 37.9 - 46.8), which is significantly higher

than the prediction for a control. Patients with AN did not have significantly different prediction of DDDs in any drug groups tested with linear regression model. The number of DDDs rose with age and females had higher number of DDDs than males. (Appendix 3)

Table 5. Predicted numbers of defined daily doses in the course of five years for 20-, 25- and 40-year-old females and males with 95% confidence intervals.

DDD, Defined Daily Dose; CI, Confidence Interval

	20-year-old female	**25-year-old female**	**40-year-old female**
	Number of DDDs (95%CI)	**Number of DDDs (95%CI)**	**Number of DDDs (95%CI)**
All Antimicrobial Drugs			
Controls	30.5 (28.6 - 32.3)	31.8 (30.3 - 33.4)	35.8 (32.9 - 38.7)
Anorexia nervosa	32.2 (27.6 - 36.9)	33.6 (28.9 - 38.2)	37.6 (32.1 – 43.0)
Bulimia nervosa	**41.0 (36.4 - 45.6)**	**42.4 (37.9 - 46.8)**	**46.3 (41.2 - 51.4)**
Binge-eating disorder	**60.8 (50.1 - 71.5)**	**62.1 (51.7 - 72.6)**	**66.1 (55.8 - 76.4)**
Antibacterial Drugs			
Controls	29.9 (28.1 - 31.6)	30.6 (29.1 - 32.1)	32.8 (30.0 - 35.5)
Anorexia nervosa	31.3 (26.8 - 35.8)	32.0 (27.6 - 36.5)	34.2 (29.0 - 39.4)
Bulimia nervosa	**40.2 (35.8 - 44.6)**	**40.9 (36.6 - 45.2)**	**43.1 (38.2 - 47.9)**
Binge-eating disorder	**55.4 (45.2 - 65.6)**	**56.2 (46.1 - 66.2)**	**58.3 (48.5 - 68.2)**
Antifungal Drugs			
Controls	0.5 (0.3 - 0.7)	0.9 (0.7 – 1.0)	2.0 (1.7 - 2.2)
Anorexia nervosa	0.5 (0.0 - 0.9)	0.9 (0.4 - 1.3)	1.9 (1.4 - 2.5)
Bulimia nervosa	0.7 (0.2 - 1.1)	1.0 (0.6 - 1.5)	2.1 (1.6 - 2.6)
Binge-eating disorder	**3.3 (2.3 - 4.3)**	**3.7 (2.7 - 4.7)**	**4.8 (3.8 - 5.8)**
Antiviral Drugs			
Controls	0.2 (0.0 - 0.3)	0.3 (0.2 - 0.5)	0.8 (0.6 - 1.1)
Anorexia nervosa	0.5 (0.0 – 1.0)	0.7 (0.2 - 1.1)	1.2 (0.6 - 1.7)
Bulimia nervosa	0.3 (-0.2 - 0.7)	0.4 (0.0 - 0.9)	0.9 (0.4 - 1.5)
Binge-eating disorder	0.2 (-0.9 - 1.2)	0.3 (-0.7 - 1.4)	0.9 (-0.2 - 1.9)

	20-year-old male	25-year-old male	40-year-old male
	Number of DDDs (95%CI)	**Number of DDDs (95%CI)**	**Number of DDDs (95%CI)**
All Antimicrobial Drugs			
Controls	14.8 (7.8 - 21.8)	16.1 (9.3 - 23)	20.1 (13.3 - 27)
Anorexia nervosa	16.6 (8.4 - 24.7)	17.9 (9.9 - 25.9)	21.9 (13.7 - 30.0)
Bulimia nervosa	25.3 (17.0 - 33.6)	26.7 (18.5 - 34.8)	30.7 (22.5 - 38.8)
Binge-eating disorder	**45.1 (32.6 - 57.6)**	**46.4 (34.2 - 58.6)**	**50.4 (38.6 - 62.2)**
Antibacterial Drugs			
Controls	15.8 (9.1 - 22.5)	16.5 (10.0 - 23.0)	18.7 (12.2 - 25.2)
Anorexia nervosa	17.2 (9.4 - 25.0)	17.9 (10.3 - 25.6)	20.1 (12.3 - 27.9)
Bulimia nervosa	26.1 (18.1 - 34.0)	26.8 (19.0 - 34.6)	29.0 (21.2 - 36.8)
Binge-eating disorder	**41.4 (29.4 - 53.3)**	**42.1 (30.4 - 53.8)**	**44.3 (33.0 - 55.6)**
Antifungal Drugs			
Controls	-0.4 (-1.1 - 0.3)	0.0 (-0.7 - 0.6)	1.1 (0.4 - 1.7)
Anorexia nervosa	-0.4 (-1.2 - 0.4)	-0.1 (-0.8 - 0.7)	1.0 (0.3 - 1.8)
Bulimia nervosa	-0.2 (-1.0 - 0.6)	0.1 (-0.7 - 0.9)	1.2 (0.4 - 2.0)
Binge-eating disorder	**2.4 (1.2 - 3.6)**	**2.8 (1.6 - 3.9)**	**3.9 (2.7 - 5.0)**
Antiviral Drugs			
Controls	-0.3 (-1.0 - 0.4)	-0.1 (-0.8 - 0.6)	0.4 (-0.3 - 1.1)
Anorexia nervosa	0.0 (-0.8 - 0.8)	0.2 (-0.6 - 1.0)	0.7 (-0.1 - 1.5)
Bulimia nervosa	-0.2 (-1.0 - 0.6)	0.0 (-0.8 - 0.8)	0.5 (-0.3 - 1.3)
Binge-eating disorder	-0.3 (-1.5 – 1.0)	-0.1 (-1.3 - 1.1)	0.4 (-0.8 - 1.6)

4 DISCUSSION

This study demonstrated that the patients with BN and BED had higher prevalence and higher number of prescriptions and DDDs compared to the control population in many antimicrobial drug groups. Compared to the controls, patients with BED had substantially higher prevalence and larger number of antibacterial and antifungal prescriptions as well as larger number of DDDs of those drug groups. Patients with BN had higher prevalence and number of antibacterial, antifungal and antiviral prescriptions and larger number of DDDs of antibacterial and antiviral drugs. Generally AN patients seemed to have less prescriptions and DDDs than their controls, the results did not however reach the statistical significance except in the number of antifungal prescriptions. The numbers of prescriptions and DDDs were higher among females than males in the whole study population, except in antiviral drugs. The findings of this study provide support for the association between eating disorders with binge-eating patterns and the increased number of infections.

The prevalence of antimicrobial drug prescriptions and DDDs can be considered as an indicator of the number of infections. BED is often, but not always, associated with overweight or obesity. This might partly explain the highly increased use of antimicrobial medication within patients with BED, since overweight and obesity are linked to increased number of infections (4,7). During the five-year follow up in this study, BED patients had nearly double the number of DDDs of anti-bacterial drugs and 2.6 times more DDDs of antifungal drugs than the controls. There was no prominent increase in the number of antiviral prescriptions in patients with BED, which might be due to the generally lower tendency to prescribe antiviral drugs. Various physical and psychiatric health problems, such as diabetes, depression and anxiety disorders, associate with binge-eating (28).

Comorbidity of binge-eating and psychiatric disorders has been shown to be independent of BMI (29). Depression has been reported to be linked to the activation of the immune system (30).

Of all the eating disorder groups, patients with BED had the highest prevalence of prescription in all other drug groups except for antiviral drugs, even when adjusted by age and sex. BED and BN patients had higher number of DDDs of antifungal drugs than the controls. Binge-eating considerably increases the blood sugar levels and hyperglycemia, at least in diabetes mellitus, has been associated with the higher prevalence of oral *Candida* infections (31) and also deaths caused by candidaemia, i.e. invasive candidiasis (32). B lymphocyte function has been reported to be impaired in high glucose concentrations (33). In addition, surgical patients with postsurgical non-diabetic hyperglycemia seem to develop more surgical site infections than the patients without hyperglycemia (34,35). Acute hyperglycemia after overfeeding in non-diabetic rats also promotes the inflammation in severe infections (36). The high acute blood glucose levels caused by binge-eating might therefore explain the elevated number of infections and hence the use of antimicrobial medication in patients with BN and BED.

BN was the only diagnostic group with higher prevalence of antiviral drug prescriptions. Aciclovir was the only individual antiviral drug assessed in this study, and in adults it is mainly used systemically as an acute or preventive medication in *Herpes simplex* virus (HSV) infections or sometimes against shingles or chickenpox (26). *Herpes simplex* virus has two subtypes: HSV-1, which produces most cold sores, and HSV-2, which produces most genital herpes. BN has been associated with early puberty and early sexual activity (37) as well as childhood sexual abuse (38). Individuals with BN, and especially those with early sexual abuse, are prone to have multi-impulsivity (38,39), which is characterized by

another impulsive behavior, such as alcohol or drug abuse or sexual disinhibition. In addition, association between extreme weight control methods and unprotected sexual activity have been reported (40). Together with previous studies, our results suggest that patients with BN are at increased risk for sexually transmitted HSV-2 infections.

Previous studies (14,21) have shown that patients with AN do not seem to develop more infections than the control population. This is in line with the results of this study where patients with AN did not have any more prescriptions or DDDs of systemic antimicrobial drugs than the matched controls. This might be due to the relatively good protein intake in many patients with AN (22) since especially protein-energy malnutrition is associated with increased amount of infections (4). Diminished febrile response in AN might also complicate the diagnosis of infections (23,24). It has been suggested that streptococcal infections might play a role in the development of some subtypes of early onset AN (PANDAS-AN) (42). In addition, elevated proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, have been hypothesized to contribute to the development of psychiatric disorders like depression, anxiety and AN (43,44). Also some physical diseases, such as cardiac and autoimmune diseases, have been hypothesized to develop by the interaction between immune system and central nervous system (45). The low numbers of prescriptions and DDDs in the patients with AN before the treatment in this study suggests that the infection-triggered inflammation do not play a major role in the development of AN on a larger population, even though it might be true in some individual cases. However, it is possible that increased amount of infections, revealed in BN and BED patients, precedes the eating disorders with binge-eating patterns. The immunological (5) and inflammatory (41) changes present in eating disorders could be the possible initiators of binge-eating, since, as mentioned, proinflammatory cytokines might be involved in the development of some psychiatric disorders.

4.1 Strengths and limitations

The strengths of this study were the large patient sample with different eating disorders and the relatively long follow-up period of five years preceding the treatment. Assessing the use of antimicrobial medication before the start of the treatment made it possible to rule out the potential influence of the treatment on the amount of prescriptions in patients compared to the controls, who were not necessarily under a regular medical observation.

The most important limitation of this study is the dearth of information about the date of the onset of a patient's eating disorder. There was no certainty on how long a patient had the eating disorder before the start of the treatment and therefore how long of a period of the five-year follow-up each individual had the disorder. The limitations also include the lack of BMI information about the patients and their controls. However, according to the experience at the Eating Disorder Unit, the majority of the patients with BN were within the normal weight range (BMI 18.5-24.9), whereas most of the patients with BED were overweight (BMI 25.0-29.9) or obese (BMI $\geq$30.0). In addition, the long follow-up period decreases the significance of the lacking BMI information, since large weight fluctuations are very common among patients with eating disorders.

4.2 Conclusion

In conclusion, the results of this study showed increased use of antimicrobial medication in patients with BN and BED. This indicates the elevated number of infections in these patient groups, which might be a consequence of hyperglycemia caused by binge-eating. On the other hand, increased number of infections, and thus inflammation mediators, might contribute to the onset of binge-eating. The future studies should concentrate on

the underlying mechanisms causing increased number of infections in patients with binge-eating behavior as well as the possible effect of infections and inflammatory mediators on the pathophysiology of binge-eating.

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APPENDICES

Appendix 1. The numbers and means of prescriptions and defined daily doses of all the drugs assessed in the study in patients with eating disorders and in controls. The significant differences between patients and controls in multivariate regression analyses on the number of DDDs are bolded with *.

ATC, Anatomical Therapeutic Chemical; DDD, defined daily dose

Drug or a drug group (ATC code)		All eating disorders and controls		Anorexia nervosa				Bulimia nervosa				Binge-eating disorder			
				Patients		Controls		Patients		Controls		Patients		Controls	
		N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
All drugs															
	Prescriptions	25869	3.25	1964	2.80	8181	2.92	3058	4.09	9573	3.20	868	6.03	2225	3.86
	DDDs	263533	33.11	22760	32.47	87212	31.10	31582	**42.28***	93321	**31.23***	9130	**63.41***	19528	**33.9***
Antibacterial drugs															
All (J01)	**Prescriptions**	21957	2.76	1729	2.47	7214	2.57	2503	3.35	8064	2.70	681	4.73	1766	3.07
	DDDs	252206	31.68	21842	31.16	84646	30.19	30426	**40.73***	89469	**29.94***	8077	**56.09***	17747	**30.81***
Tetracyclines (J01A)	**Prescriptions**	3485	0.44	323	0.46	1144	0.41	447	0.60	1224	0.41	104	0.72	243	0.42
	DDDs	100553	12.63	9929	14.16	35535	12.67	13307	**17.81***	33715	**11.28***	2999	**20.83***	5069	**8.80***
Doxycycline (J01AA02)	**Prescriptions**	1813	0.23	123	0.18	518	0.18	220	0.29	703	0.24	61	0.42	188	0.33
	DDDs	26771	3.36	1859	2.65	7620	2.72	3410	**4.56***	10232	**3.42***	843	5.85	2809	4.88
Beta-lactam antibacterials, penicillins (J01C)	**Prescriptions**	6640	0.83	536	0.76	2412	0.86	715	0.96	2368	0.79	157	1.09	452	0.78
	DDDs	65676	8.25	5199	7.42	23529	8.39	6965	**9.32***	23644	**7.91***	1622	**11.27***	4716	**8.19***
Amoxicillin (J01CA04)	**Prescriptions**	2889	0.36	246	0.35	1016	0.36	336	0.45	1018	0.34	75	0.52	198	0.34
	DDDs	34228	4.30	2813	4.01	11752	4.19	3945	**5.28***	12471	**4.17***	836	5.81	2411	4.19
Pivmecillinam (J01CA08)	**Prescriptions**	1057	0.13	75	0.11	418	0.15	103	0.14	381	0.13	17	0.12	63	0.11
	DDDs	7370	0.93	508	0.72	2828	1.01	714	0.96	2756	0.92	116	0.80	448	0.78
Phenoxymethylpenicillin (J01CE02)	**Prescriptions**	1854	0.23	142	0.20	656	0.23	219	0.29	690	0.23	39	0.27	108	0.19
	DDDs	14486	1.82	1042	1.49	5158	1.84	1686	2.26	5350	1.79	378	**2.63***	871	**1.51***
Amoxicillin and enzyme inhibitor (J01CR02)	**Prescriptions**	814	0.10	72	0.10	310	0.11	55	0.07	271	0.09	24	0.17	82	0.14
	DDDs	9310	1.17	828	1.18	3604	1.29	605	0.81	3022	1.01	272	1.89	979	1.70

Drug or a drug group (ATC code)		All eating disorders and controls		Anorexia nervosa				Bulimia nervosa				Binge-eating disorder			
				Patients		Controls		Patients		Controls		Patients		Controls	
		N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Antibacterial drugs															
Other beta-lactam antibacterials (J01D)	**Prescriptions**	5110	0.64	358	0.51	1645	0.59	584	0.78	1935	0.65	183	1.27	405	0.70
	DDDs	31485	3.96	2138	3.05	10082	3.60	3466	**4.64***	11491	**3.85***	1669	**11.59***	2639	**4.58***
Cephalexin (J01DB01)	**Prescriptions**	4378	0.55	306	0.44	1404	0.50	507	0.68	1644	0.55	166	1.15	351	0.61
	DDDs	26442	3.32	1765	2.52	8461	3.02	2891	**3.87***	9510	**3.18***	1565	**10.87***	2250	**3.91***
Sulfonamides and trimethoprim (J01E)	**Prescriptions**	881	0.11	53	0.08	286	0.10	106	0.14	345	0.12	24	0.17	67	0.12
	DDDs	10583	1.33	810	1.16	3226	1.15	1178	1.58	4477	1.50	193	1.34	699	1.21
Macrolides, lincosamides and streptogramins (J01F)	**Prescriptions**	4650	0.58	377	0.54	1370	0.49	520	0.70	1737	0.58	163	1.13	483	0.84
	DDDs	34543	4.34	3089	**4.41***	9229	**3.29***	4738	**6.34***	12674	**4.24***	1114	7.74	3698	6.42
Roxithromycin (J01FA06)	**Prescriptions**	988	0.12	69	0.10	297	0.11	116	0.16	380	0.13	33	0.23	93	0.16
	DDDs	9611	1.21	631	0.90	2512	0.90	1055	1.41	3886	1.30	303	2.10	1226	2.13
Azithromycin (J01FA10)	**Prescriptions**	2219	0.28	157	0.22	681	0.24	235	0.31	816	0.27	73	0.51	257	0.45
	DDDs	10558	1.33	720	1.03	3219	1.15	1085	1.45	3806	1.27	340	2.36	1388	2.41
Quinolone antibactrials (J01M)	**Prescriptions**	1075	0.14	77	0.11	307	0.11	122	0.16	412	0.14	49	0.34	108	0.19
	DDDs	7094	0.89	575	0.82	1840	0.66	671	0.90	2686	0.90	478	**3.32***	845	**1.47***
Other antibacterials (J01X)	**Prescriptions**	116	0.02	5	0.01	50	0.02	9	0.01	43	0.01	1	0.01	8	0.01
	DDDs	2274	0.29	103	0.15	1206	0.43	100	0.13	783	0.26	1	0.01	81	0.14
Antifungal drugs															
All (J02)	**Prescriptions**	3010	0.38	162	0.23	771	0.27	406	0.54	1192	0.40	165	1.15	314	**0.55**
	DDDs	7800	0.98	501	0.72	1857	0.66	816	1.09	2981	1.00	649	**4.5***	996	**1.73***
Fluconazole (J02AC01)	**Prescriptions**	2602	0.33	138	0.20	665	0.24	357	0.48	1031	0.35	143	0.99	268	0.47
	DDDs	3943	0.50	265	0.38	894	0.32	486	**0.65***	1316	**0.44***	431	2.99	552	0.96
Antiviral drugs															
All (J05)	**Prescriptions**	893	0.11	73	0.10	190	0.07	149	0.20	317	0.11	19	0.13	145	0.25
	DDDs	3093	0.39	417	0.59	573	0.20	341	0.46	872	0.29	105	0.73	785	1.36
Aciclovir (J05AB01)	**Prescriptions**	677	0.09	63	0.09	150	0.05	92	0.12	246	0.08	15	0.10	111	0.19
	DDDs	2206	0.28	379	0.54	458	0.16	218	0.29	659	0.22	97	0.67	395	0.69

Appendix 2. Results of quasipoisson regression analyses with number of prescriptions as an outcome.

	Estimate	Standard Error	P-value
All Antimicrobial Drugs			
Intercept	0.05	0.102	0.610
Age	0.02	0.002	**<0.001**
Sex, female	0.67	0.089	**<0.001**
Anorexia nervosa	-0.07	0.053	0.190
Bulimia nervosa	0.26	0.043	**<0.001**
Binge-eating disorder	0.50	0.080	**<0.001**
Antibacterial Drugs			
Intercept	0.16	0.096	0.100
Age	0.01	0.002	**<0.001**
Sex, female	0.52	0.082	**<0.001**
Anorexia nervosa	-0.05	0.051	0.320
Bulimia nervosa	0.22	0.043	**<0.001**
Binge-eating disorder	0.46	0.080	**<0.001**
Antifungal Drugs			
Intercept	-4.10	0.455	**<0.001**
Age	0.03	0.004	**<0.001**
Sex, female	2.18	0.437	**<0.001**
Anorexia nervosa	-0.34	0.162	**0.030**
Bulimia nervosa	0.41	0.107	**<0.001**
Binge-eating disorder	0.83	0.167	**<0.001**
Antiviral Drugs			
Intercept	-4.87	0.724	**<0.001**
Age	0.05	0.008	**<0.001**
Sex, female	1.27	0.660	0.060
Anorexia nervosa	0.16	0.321	0.620
Bulimia nervosa	0.68	0.236	**0.004**
Binge-eating disorder	-0.28	0.613	0.650

Appendix 3. Results of linear regression analysis with number of defined daily doses as an outcome.

DDD, Defined Daily Dose

	Estimate	Standard Error	P-value
All Antimicrobial Drugs			
Intercept	9.47	4.421	**0.032**
Age	0.27	0.087	**0.002**
Sex, female	15.69	3.524	**<0.001**
Anorexia nervosa	1.75	2.499	0.483
Bulimia nervosa	10.53	2.421	**<0.001**
Binge-eating disorder	30.30	5.375	**<0.001**
Antibacterial Drugs			
Intercept	12.87	4.223	**0.002**
Age	0.15	0.083	0.080
Sex, female	14.08	3.370	**<0.001**
Anorexia nervosa	1.44	2.390	0.548
Bulimia nervosa	10.29	2.316	**<0.001**
Binge-eating disorder	25.57	5.140	**<0.001**
Antifungal Drugs			
Intercept	-1.85	0.424	**<0.001**
Age	0.07	0.008	**<0.001**
Sex, female	0.91	0.338	**0.007**
Anorexia nervosa	-0.02	0.240	0.920
Bulimia nervosa	0.16	0.232	0.490
Binge-eating disorder	2.80	0.516	**<0.001**
Antiviral Drugs			
Intercept	-0.97	0.440	**0.027**
Age	0.03	0.009	**<0.001**
Sex, female	0.46	0.350	0.190
Anorexia nervosa	0.33	0.249	0.188
Bulimia nervosa	0.10	0.241	0.682
Binge-eating disorder	0.01	0.535	0.979