

Clinical Phenotypes of Anorexia Nervosa: Mathematical Models Based on Latent Class Analysis of Psychopathological Symptoms

Клинические фенотипы нервной анорексии: математические модели на основании анализа латентных классов психопатологических симптомов

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Original research

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ABSTRACT

BACKGROUND: Anorexia nervosa (AN) is characterized by heterogeneous clinical manifestations, which complicates diagnosis and treatment. It is important to define the clinical variants and therapeutic targets for AN.

AIM: To identify empirical patient phenotypes within the AN diagnostic category using Latent Class Analysis (LCA) of clinically assessed psychopathological symptoms.

METHODS: Psychiatrists clinically assessed psychopathological symptoms of AN using an original checklist (57 symptoms in total) and the Mini-International Neuropsychiatric Interview (M.I.N.I.) was used to identify mental disorders. Patients completed the Symptom Check List-90-Revised questionnaire (SCL-90-R) to self-assess psychopathological symptoms and distress. Clinically homogeneous patient subgroups were identified using LCA.

RESULTS: A total of 115 patients with AN were examined. Based on the LCA, four patient groups (C1–C4) were identified, with high classification certainty ($R^2=0.908$), model significance ($p<0.001$), and clear separation of the latent groups (class separation index = 0.957). ED-related symptoms were key determinants of class formation only in 68 patients (59%) — those in C1 and C3. No statistically significant differences were found between classes on any SCL-90-R subscales or most M.I.N.I. diagnoses. In C1 ($n=41$), core ED symptoms dominated: dysmorphophobia, fears related to eating, weight gain, loss of control. In C2 ($n=39$), low frequencies are observed for core ED symptoms; this group was characterized by a high incidence of sleep disturbances, anxiety, apathy, melancholy, and anhedonia. C3 ($n=27$) represents a polymorphic clinical profile with a combination of core ED symptoms, affective symptoms, thought disorders, cognitive impairments, and sleep disturbances. C4 ($n=8$) was defined by the presence of hypochondriacal concerns, somatoform autonomic symptoms, and apathy; none of the core ED symptoms were typical for C4.

CONCLUSION: Four empirically derived clinical phenotypes of AN were identified, each characterized by a distinct symptomatic profile. Each phenotype was defined by specific combinations of core ED symptoms and general psychopathological manifestations.

АННОТАЦИЯ

ВВЕДЕНИЕ: Нервная анорексия (НА) характеризуется гетерогенными клиническими проявлениями, что затрудняет ее диагностику и лечение. Описание клинических вариантов и мишеней терапии НА является актуальной задачей.

ЦЕЛЬ: Изучение наличия эмпирических фенотипов пациентов внутри диагностической категории «нервная анорексия» с применением анализа латентных классов (LCA) психопатологических симптомов, выявленных в результате клинической оценки психического состояния врачами-психиатрами.

МЕТОДЫ: Психопатологические симптомы НА были клинически оценены психиатрами с использованием оригинального чек-листа (всего 57 симптомов), для выявления психических расстройств применялся опросник Mini-International Neuropsychiatric Interview (M.I.N.I.). Для самооценки психопатологических симптомов и дистресса пациенты использовали опросник Symptom Check List-90-Revised (SCL-90-R). Клинически гомогенные подгруппы пациентов были выделены с помощью LCA.

РЕЗУЛЬТАТЫ: Обследовано 115 пациентов с НА. По результатам LCA выделены 4 группы пациентов (K1–K4) с высокой определенностью классификации ($R^2=0,908$), значимостью модели ($p<0,001$) и четким разделением латентных групп (индекс несходства классов = 0,957). Симптомы расстройства пищевого поведения (РПП) являлись ключевыми для формирования кластера только у 68 (59%) — в группах K1 и K3. Статистически значимых различий между классами по субшкалам SCL-90-R или большинству диагнозов M.I.N.I. выявлено не было. В группе K1 ($n=41$) доминировали ключевые симптомы РПП: дисморфофобия, страхи, связанные с едой, набором веса, потерей контроля. В группе K2 ($n=39$) наблюдалась низкая частота ключевых симптомов РПП, для этой группы была характерна высокая распространенность нарушений сна, тревоги, апатии, тоски и ангедонии. Группа K3 ($n=27$) представляет полиморфный клинический профиль с сочетанием ключевых симптомов РПП, аффективных симптомов, расстройств мышления, когнитивных нарушений и нарушений сна. Группа K4 ($n=8$) определялась наличием ипохондрических опасений, соматоформных вегетативных симптомов и апатии; ни один из ключевых симптомов РПП не был типичен для K4.

ЗАКЛЮЧЕНИЕ: Выделены 4 эмпирических клинических фенотипа НА, каждый из которых отличался уникальным симптоматическим профилем. Были определены специфичные для каждой группы симптомы, которые включали ключевые симптомы расстройства пищевого поведения и общие психопатологические проявления.

Keywords: *anorexia nervosa; latent class analysis; psychopathology; phenomenology*

Ключевые слова: *нервная анорексия; анализ латентных классов; психопатология; феноменология*

INTRODUCTION

Anorexia nervosa (AN) is an eating disorder (ED) characterized by diverse psychopathological manifestations, which may relate both to the disorder itself and to accompanying mental disorders. According to the International Classification of Diseases, 11th Revision (ICD-11), AN must be differentiated from schizophrenia and other primary psychotic disorders, obsessive-compulsive disorder (OCD), body dysmorphic disorder, bulimia nervosa and avoidant/restrictive food intake disorder [1]. AN is associated with high rates of psychiatric comorbidity, including depressive disorders (from 36 to 80%), anxiety disorders (up to 65%), autism spectrum

disorders (up to 22.9%), post-traumatic stress disorder (up to 22.7%), and OCD (up to 44%) [2–4]. The overlap between AN symptoms and those of other psychiatric disorders, combined with this high comorbidity, significantly complicates both the diagnosis and treatment of AN [3]. Moreover, there is still no robust evidence supporting the efficacy of pharmacotherapy either for core AN symptoms or for its concomitant mental disorders [5]. The marked heterogeneity of AN symptoms is widely regarded as a major barrier to developing effective treatment strategies [6–8].

Researchers increasingly recognize the need to reconceptualize AN [9, 10]. Empirical classifications of

the broader ED diagnostic category have been proposed, which use mathematical modeling of ED clinical features to integrate patient symptoms into the analysis. Latent Class Analysis (LCA) is applied to identify patient groups with similar symptoms [11–14], network analysis is used to detect symptom interrelationships in static and dynamic states [15, 16], and combinations of these methods are also used [17].

Identifying homogeneous patient subgroups may facilitate the development of more targeted and personalized therapeutic strategies, as well as the elucidation of biological factors contributing to the disorder [18]. LCA enables the detection of hidden, homogeneous patient groups within a population displaying diverse clinical manifestations, identifying discrete clinical categories of psychopathological symptom diversity [13, 16]. In this approach, patient characteristics cannot overlap between groups, allowing clear differentiation of patients based on the assessed features [19].

Over the past two decades, several studies have focused on the empirical identification of AN patient phenotypes using LCA. This approach formed the basis for modern ED classifications [20]. Some of these studies were conducted at the general population and aimed to: assess the prevalence of EDs variants based on clinical signs according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) [11]; identify phenotypes considering possible concomitant mental issues such as OCD, temperament, and personality traits (perfectionism and trait anxiety) [12]; and, determine the features of ED manifestation in different age groups [13]. Studies on clinical samples of patients diagnosed with AN identified latent classes based on the distribution of ED diagnostic criteria among classes [9, 14, 21], or focused on the combination of ED symptoms and patient personality traits [22], but without accounting concomitant psychopathological symptoms. However, the results of findings from network analysis studies on clinical samples highlight the importance of assessing symptoms beyond the behavioral manifestations of EDs [23, 24]. Despite this, to date, no studies have been conducted to identify latent classes within a clinical sample of patients with AN, considering the full spectrum of psychopathological manifestations.

In prior studies of ED that used LCA or network analysis, the models relied on psychometric scales, self-report questionnaires, or participant reports on the presence or

absence of symptoms included in the ED diagnostic criteria [6, 13–15, 24–27]. Relying on self-report questionnaires instead of clinical assessment for constructing empirical classifications may lead to biased information about the patient's status into the model. This is a well-known limitation of the self-reported method compared with clinician evaluation [28–32].

For more detailed and personalized patients' assessment, the phenomenological approach, which captures phenomena of lived experience, has been increasingly used in recent years [33, 34]. This approach appears to be a promising direction for describing patient phenotypes in neurobiological research, developing therapeutic strategies, and incorporating the patients' subjective illness experience in care organization [33–35]. Phenomenological studies in AN have focused on manifestations that patients themselves view as important and that form part of their illness narrative. However, these studies have predominantly been limited to body image dissatisfaction and related phenomena [36].

A limitation of this approach is that information about the clinical condition is restricted to the patient's self-assessment. In addition to the methodological problem of data heterogeneity [35], this creates the risk of subjective selectivity, with some psychopathological phenomena omitted because patients do not recognize them or do not consider them significant. The egosyntonic nature of AN symptoms leads to discrepancies in the assessment of the condition by both patient and clinician assessments [36–38]. These limitations can be overcome by employing a clinical psychopathological assessment. This approach enables the psychiatrist not only to identify phenomena of the patient's mental functioning but also to perform their psychopathological qualification (the determination of symptoms and syndromes) [39, 40].

Thus, attempts are currently being made to identify subgroups of patients within ED diagnostic categories; however, there is a lack of research that would account for the entire complex of psychopathological manifestations observed in patients' mental status. Furthermore, there is a lack of research on empirical classifications of AN that incorporate psychopathological symptoms based on the results of clinical assessment by psychiatrists.

The aim of this study was to identify empirical patient phenotypes within the AN diagnostic category using LCA of psychopathological symptoms identified through clinical psychiatric assessment.

We hypothesized that within the single diagnostic category of “anorexia nervosa”, several clinical phenotypes would be identified, differing from one another in both ED symptoms and accompanying psychopathological symptoms.

METHODS

Study design

A cross-sectional study was conducted.

Setting

The study was conducted at the Eating Disorders Clinic (Clinic) inpatient and day hospitals of Mental-health clinic No. 1 named after N.A. Alexeev (Moscow) from April 2023 to September 2024. Psychiatrists from the Clinic ($n=6$) with 1–5 years of clinical experience participated in the patient assessment and data collection. Clinical assessment was supervised by department heads, who were psychiatrists with more than 20 years of work experience ($n=2$).

All study information was recorded in an electronic case report form (eCRF) developed specifically for the study.

Participants

The study included patients diagnosed with anorexia nervosa who were admitted for treatment at the Clinic. Non-inclusion criteria: refusal to participate. Exclusion criteria: duration of hospitalization less than 7 days.

The diagnosis of anorexia nervosa was established by psychiatrists during routine clinical assessment, according to the International Classification of Diseases, 10th Revision (ICD-10).

Measurements

Data were collected during the first week of hospitalization.

For all patients, age and duration of AN were recorded, and Body Mass Index (BMI) was calculated as weight (kg)/height² (m²). In addition, an ICD-11 ED diagnosis was assigned to each patient based on a clinical assessment by psychiatrists.

Evaluated parameters and study tools

To identify concomitant mental disorders, the semi-structured Mini-International Neuropsychiatric Interview, version 6.0 (M.I.N.I.) [41] was used by psychiatrists. All participating psychiatrists had previously undergone standardized training in its administration.

Patients also completed the Symptom Checklist-90-Revised (SCL-90-R) [42], a self-report questionnaire designed

to assess psychopathological symptoms and the severity of associated distress. The questionnaire comprises 90 items rated on a 5-point Likert scale from 0 (“not at all”) to 4 (“very strong”). Each item corresponds to one of nine subscales: “Somatization”, “Obsessive-compulsive symptoms”, “Interpersonal sensitivity”, “Depression”, “Anxiety”, “Hostility”, “Phobic anxiety”, “Paranoid ideation”, and “Psychoticism”. In addition, the questionnaire includes three global indices: the Global Severity Index, the Positive Symptom Distress Index, and the Positive Symptom Total. For the results, the mean score across all items within each subscale is calculated; higher scores indicate greater severity of the corresponding symptom.

Clinician-rated assessment of psychopathological symptoms of anorexia nervosa

The clinical-psychopathological evaluation, which was used to assess the patient’s mental state and inform decisions regarding psychopharmacotherapy, was conducted as part of routine clinical assessment. This included a structured clinical interview with the patient, behavioral observation during the inpatient stay, and collection of medical history from both the patient and their relatives.

For this study, a symptom checklist (see Table S1 in the Supplementary) was specifically developed to document psychopathological symptoms identified as treatment targets for psychopharmacotherapy. The checklist was completed by the patients’ physicians in the eCRFs at initiation of pharmacotherapy, as well as each time the medication dose was adjusted or a new medication was prescribed. One or several target symptoms could be noted depending on the reasons for prescribing the drug. Psychopharmacotherapy was prescribed by psychiatrists under routine clinical practice. In the eCRFs, psychiatrists indicated the specific symptoms being targeted and entered the name and dose of the medication prescribed to address those symptoms in designated fields of the electronic form. Data on target symptoms for psychopharmacotherapy were collected throughout the treatment period, encompassing both inpatient and day hospitals at the Clinic. The designation of target symptoms was reviewed and verified by department heads.

The checklist was based on a standardized mental status evaluation framework [43] routinely used by psychiatrists. It included a total of 54 psychopathological symptoms, categorized into nine subgroups: affective symptoms, neurotic and somatoform symptoms, thought

disorders, cognitive symptoms, behavioral disturbances, perceptual disturbances, obsessive-compulsive symptoms, physiological disturbances, and ED-specific symptoms. Additionally, the presence of three symptoms related to the management of antipsychotic side effects was assessed, allowing psychiatrists to evaluate 57 symptoms in each patient. Symptom selection for the checklist from the wide range of clinical manifestations based on the presence of two criteria: the symptom must be a potential target for psychopharmacotherapy, and the symptom must be potentially clinically present in patients diagnosed with AN. Before the study began, the completeness of symptom coverage and usability of the checklist were evaluated through iterative consultation with all participating investigators until it was considered sufficiently comprehensive and practical for describing psychopharmacotherapy targets in patients with AN.

Statistical analysis

No preliminary sample size calculation was performed; however, it was planned to include a minimum of 100 patients in the study.

Statistical data analysis was conducted by investigators who were not employed by the Clinic. They were provided with a fully de-identified dataset to ensure patient anonymity and minimize the risk of interpretation bias.

Data analysis included descriptive statistics, frequency analysis of psychopathological symptoms, the LCA, and comparative analysis of the characteristics of the groups identified using the LCA. Statistical significance was set at $p < 0.05$. Two-sided statistical tests were used in all cases. Quantitative and ordinal variables were summarized using either mean (standard deviation) or median values (first; third quartiles). The selection between mean (SD) and median (IQR) for describing quantitative variables was based on the results of the Shapiro–Wilk test for normality.

Preparation of data for statistical analysis

Data were extracted from the eCRFs into an Excel spreadsheet (Microsoft Corporation), and no imputation of missing values was performed.

Based on the documented target symptoms, a dedicated electronic dataset was created, with each row representing a unique “patient–drug–target symptom” entry. Binary values (0/1) were used to indicate whether the psychiatrist explicitly documented that a given medication was prescribed to

address a specific symptom. A symptom was considered clinically significant if it appeared as a treatment target in at least five cases. We chose this threshold value to exclude idiosyncratic or extremely rare symptoms that could introduce statistical noise and obscure the identification of stable latent classes. Following the exclusion of rare target symptoms, a binary “patient–symptom” matrix was constructed, reflecting all clinically relevant symptoms designated as treatment targets. This matrix served as the basis for LCA.

Latent class analysis

LCA was performed to identify latent, homogeneous subgroups (classes) of patients characterized by similar patterns of binary symptom features (i.e., combinations of target symptoms). The unit of analysis was the individual patient. The analysis was conducted using XLSTAT software (version 2024.2.2.1422, Addinsoft, Paris, France), with the number of latent classes varied automatically from 1 to 4. Model parameters were estimated using the Expectation–Maximization (EM) algorithm refined by the Newton–Raphson method. To ensure stability of solutions, a fixed random number seed (seed=123456789) and multiple random starting conditions (16 distinct initializations) were employed, which minimized the risk of local minima. The model assumed local independence of symptom indicators; therefore, covariance parameters between symptoms were not included. The optimal model was selected based on the following criteria: Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), Consistent Akaike Information Criterion (CAIC) and Sample-Adjusted Bayesian Information Criterion (SABIC), the highest classification entropy (Entropy R^2); and the lowest classification error rate. Additionally, the model fit was evaluated using the likelihood-ratio chi-square statistic (L^2) and the associated degrees of freedom. This approach ensured a balanced assessment of both model fit and the discriminative power of the resulting solution [19]. After determining the optimal number of classes according to these criteria, classification function coefficients were computed for each class. These coefficients correspond to the parameters of multinomial logit models and enable the calculation of the post-hoc probability that a given patient belongs to a specific class, based on the presence or absence of particular target symptoms. Positive coefficient values indicate that the presence of a given symptom increases the likelihood of a patient’s membership in the corresponding class, whereas

negative values indicate that the symptom decreases this likelihood.

Subsequently, a comparative analysis of classes characteristics was performed, including demographic variables (age), clinical features (body mass index, ICD-11 diagnosis, duration of AN), psychometric data (results from the M.I.N.I. and SCL-90-R questionnaires), and psychotropic medications prescribed to address psychiatric symptoms. For continuous variables, normality was assessed using the Shapiro–Wilk test. When the assumption of normality was met, one-way analysis of variance (ANOVA) was employed, reporting the F-statistic, statistical significance level (p -value), and effect size (η^2). In cases of asymmetrical distributions, the Kruskal–Wallis H test was used, with estimation of the proportion of explained variance (ϵ^2). Categorical variables were analyzed using Pearson’s chi-square (χ^2) test. When expected cell frequencies in contingency tables were less than 5, Fisher’s exact test was applied. Effect sizes for categorical comparisons were quantified using Cramér’s V coefficient. Comparisons between classes were conducted without a priori grouping, and multiple comparison corrections were applied using the Bonferroni adjustment for post hoc tests. Interpretation of results was based on both statistical significance ($p < 0.05$) and effect size magnitude to assess the practical and clinical relevance of observed differences.

Ethical considerations

The study was approved by the local ethics committee of Mental-health clinic No. 1 named after N.A. Alexeev (Minutes No. 2 dated March 9, 2023). Before the inclusion in the study, the patients signed the informed consent form for participation.

RESULTS

Participants

A total of 115 patients were enrolled in the study. Clinical and demographic parameters of the sample are presented in Table 1.

According to the M.I.N.I. questionnaire (data available for 110 patients), the most common comorbid disorders were current major depressive episode ($n=27$, 24.5%); recurrent depressive episode ($n=48$, 43.6%); OCD ($n=50$, 45.5%); generalized anxiety disorder (GAD) ($n=39$, 35.5%). Four (3.6%) patients had an ongoing psychotic disorder. All M.I.N.I. diagnoses are presented in Table S2 in the Supplementary.

Table 1. Clinical and demographic characteristics of the sample

Parameter	Value ($n=115$)
General characteristics Me (Q1; Q3)	
Age, years	22.0 (19.0; 26.0)
BMI, kg/m ²	14.6 (12.7; 16.3)
Duration of the disease, years	5.0 (2.0; 9.0)
Diagnosis according to the ICD-11 ($n=111$), n (%)	
AN with significantly low body weight, restricting pattern (6B80.00)	39 (35.1%)
AN with significantly low body weight, binge-purge pattern (6B80.01)	33 (29.7%)
AN with dangerously low body weight, restricting pattern (6B80.10)	28 (25.2%)
AN with dangerously low body weight, binge-purge pattern (6B80.10)	10 (9.1%)
AN in recovery with normal body weight	1 (0.9%)
SCL-90-R	
Scale	Me (Q1; Q3)
Somatization	0.8 (0.5; 1.4)
Obsessive-compulsive symptoms	1.4 (0.7; 2.1)
Interpersonal sensitivity	1.3 (0.6; 2.0)
Depression	1.5 (0.9; 2.1)
Anxiety	0.9 (0.4; 1.6)
Hostility	0.7 (0.2; 1.3)
Phobic anxiety	0.4 (0.0; 0.9)
Paranoid ideation	0.7 (0.2; 1.2)
Psychoticism	0.6 (0.3; 1.3)
GSI	1.0 (0.6; 1.6)
PST	50.0 (31.0; 64.0)
PSDI	1.9 (1.5; 2.3)

Note: AN — anorexia nervosa; BMI — body mass index; GSI — Global Severity Index; ICD-11 — International Classification of Diseases, 11th Revision; Me — median; PSDI — Positive Symptom Distress Index; PST — Positive Symptom Total; SCL-90-R — Symptom Checklist-90-Revised.

Frequency of the target symptoms for psychopharmacotherapy in the sample

All patients received psychopharmacotherapy, and information about the treatment-target symptoms was available for all 115 patients. Forty-six of the possible 57 symptoms were present in the sample. Eleven symptoms were not specified as targets for psychopharmacotherapy (euphoria; delusional mania; depersonalization and

derealization; contrasting obsessions; aggression; decreased appetite; decreased libido; increased somnolence; epilepsy syndrome; and delirium). The distribution of symptom frequencies is presented in Table 2.

Symptom frequencies showed high variability. The most frequent targets of psychopharmacotherapy were mood-related symptoms — anxiety, apathy, melancholy, anhedonia, and mood swings — as well as sleep-onset difficulties and AN-specific symptoms, including fears related to eating, weight gain, loss of control, and body-image-related dysmorphic symptoms.

Latent class model

LCA enabled the identification of the most probable latent structure of therapy-target symptoms of the 115 patients.

The total number of recorded clinically significant target symptoms (with a frequency of occurrence ≥ 5) in the sample was 830, indicating sufficient data saturation for LCA [19]. Twenty-six of the 46 symptoms were clinically significant (with a frequency of ≥ 5). The final data matrix for LCA comprised “115 patients \times 26 symptoms”. To assess the number of latent classes, models of one to four classes were built. The selection of the optimal number of classes was based on information criteria and classification quality indices (see Table S3 in the Supplementary).

The model with four classes demonstrated the lowest BIC value (BIC=2951.94) compared with the one- to three-class models and the lowest classification error (0.041) as well as a high entropy value ($R^2=0.908$), and minimal probability of misclassification of patients into multiple

Table 2. Ranking of target symptoms in the sample by frequency

Symptoms	n (%)	Symptoms	n (%)
Anxiety	98 (85.2%)	Memory deficits	5 (4.3%)
Apathy	92 (80.0%)	Vomiting	5 (4.3%)
Difficulties falling asleep	78 (67.8%)	Akathisia*	5 (4.3%)
Fears related to eating, weight gain, loss of control	56 (48.7%)	Pain	4 (3.5%)
Melancholy	54 (47.0%)	Conflict behavior	4 (3.5%)
Anhedonia	50 (43.5%)	Suicidal thoughts	4 (3.5%)
Mood swings	44 (38.3%)	Hallucinations	4 (3.5%)
Dysmorphophobia (regarding body size)	39 (33.9%)	Ideas of reference (except for EDs)	3 (2.6%)
Formal thought disorders	36 (31.3%)	Impulsive actions	3 (2.6%)
Superficial sleep	35 (30.4%)	Cenesthopathies	3 (2.6%)
Delusional level of anxiety	34 (29.6%)	Rituals (except for EDs)	3 (2.6%)
Prevention of EPS*	33 (28.7%)	Fears (except for ED-related symptoms)	2 (1.7%)
Irritability	22 (19.1%)	Self-harm	2 (1.7%)
Obsessive ideas (regarding food, weight, and body shape)	21 (18.3%)	Early awakening	2 (1.7%)
Hypochondriacal concerns	20 (17.4%)	Rituals (food, evaluation of one's own body)	2 (1.7%)
Overvalued ideas (regarding food, weight, and body shape)	20 (17.4%)	Compulsions as part of EDs	2 (1.7%)
Reduced attentional focus	19 (16.5%)	Elevated mood	1 (0.9%)
Extrapyramidal effects*	19 (16.5%)	Dysmorphophobia (except for body size)	1 (0.9%)
Somatoform autonomic dysfunction	12 (10.4%)	Delusional level of depression	1 (0.9%)
Sensitive ideas of reference	12 (10.4%)	Overvalued ideas (except for EDs)	1 (0.9%)
Obsessive thoughts (except for EDs)	8 (7.0%)	Compulsions (except for ED-related symptoms)	1 (0.9%)
Delusional ideas (except for EDs)	7 (6.1%)	Fatigue	1 (0.9%)
Dysmorphomania	6 (5.2%)	Decreased appetite	1 (0.9%)

Note: *Additional signs introduced as indications for prescribing “agents to treat the side effects of antipsychotics”. ED — eating disorder; EPS — extrapyramidal symptoms.

classes. The L^2 statistic value ($L^2=1,359.49$, $df=8$, $p<0.0001$) confirmed the model's significance, while the dissimilarity index between classes (dissimilarity index=0.957) indicated a clear separation of latent groups. Thus, the model with four latent classes was considered statistically justified and the most appropriate for describing the existing data structure.

The final distribution of patients across classes was: class 1 (C1) — 41 patients (35.7%), class 2 (C2) — 39 (33.6%),

class 3 (C3) — 27 (23.5%) and class 4 (C4) — 8 (7.0%). Table 3 demonstrates the classification matrix showing the estimated likelihood of being in each class based on the results of the multinomial logistic regression. Regression coefficients (logits) reflect the contribution of each symptom to class membership: positive values indicate that a symptom increases the likelihood of belonging to a given class, whereas negative values suggest that the symptom is not typical for that class.

Table 3. Regression coefficients* of the multinomial logistic model for estimating the post-hoc probabilities of belonging to each class

Groups of symptoms	Symptoms	Class 1	Class 2	Class 3	Class 4
	<i>Intercept</i>	-1.286	-7.962	13.960	-4.713
Affective disorders	Anxiety	-0.063	0.128	0.214	-0.279
	Apathy	-0.194	-0.394	-0.849	1.437
	Melancholy	-0.967	0.193	0.985	-0.212
	Anhedonia	-0.199	0.721	1.049	-1.570
	Mood swings	0.086	0.021	0.468	-0.576
	Irritability	0.514	0.206	0.707	-1.427
ED-related symptoms	Fears related to eating, weight gain, loss of control	0.813	-1.288	1.113	-0.638
	Dysmorphophobia (concerns regarding body size or its parts)	0.877	-0.861	1.305	-1.321
	Obsessive ideas (regarding food, weight, and body shape)	0.514	-0.185	1.039	-1.368
	Overvalued ideas (regarding food, weight, and body shape)	0.846	-1.657	1.723	-0.913
	Sensitive ideas of reference ("others are critically judging me")	1.511	-1.566	0.854	-0.799
	Vomiting	-1.034	-1.032	2.323	-0.257
Neurotic and somatoform symptoms	Hypochondriacal concerns	-2.608	-0.440	0.450	2.598
	Somatoform autonomic symptoms	-0.459	-2.275	0.494	2.239
OCD	Obsessive thoughts (except for EDs)	-2.199	0.434	0.645	1.120
Thought disorders	Delusional level of anxiety (including regarding EDs)	0.525	-0.851	0.071	0.255
	Dysmorphomania (including regarding body size or its parts)	0.623	-2.117	0.596	0.898
	Formal thought disorders (associative process disorders)	-0.438	0.098	0.466	-0.126
	Delusional ideas (except for EDs)	0.440	-2.151	0.530	1.180
Psychological disorders	Difficulties falling asleep	-1.369	0.066	1.962	-0.658
	Superficial sleep	-0.051	0.643	0.836	-1.427
Cognitive impairments	Reduced attentional focus	-0.018	0.414	0.994	-1.390
	Memory deficits	-1.075	-0.967	2.311	-0.270
Treatment of adverse effects	Extrapyramidal symptoms**	-0.926	-0.187	0.774	0.338
	Prevention of EPS**	0.211	-0.768	0.342	0.215
	Akathisia**	-2.134	0.759	0.365	1.011

Note: *Regression coefficients are calculated as the logarithm of the odds ratio of a patient being assigned to a given class in the presence of a particular symptom. **Additional signs introduced as indications for prescribing "agents to treat the side effects of antipsychotics". ED — eating disorder; EPS — extrapyramidal symptoms; OCD — obsessive-compulsive disorder.

The quality of classification based on modal and proportional probability of belonging is presented in Table S4 in the Supplementary. The classification matrix confirmed the model's high accuracy, demonstrating that the vast majority of patients were unambiguously assigned to one Class.

Clinical characteristics of the classes

The analysis of the regression coefficients allowed the identification of the key symptoms determining the patients' membership in specific class. Table 4 presents the frequency of symptom occurrence in each Class. Table 5 provides a comparison of Classes based on clinical characteristics

Table 4. Frequency of symptoms in the classes

Groups of symptoms	Symptoms	Class 1 (n=41)	Class 2 (n=39)	Class 3 (n=27)	Class 4 (n=8)	χ^2 (df), p
Affective disorders	Anxiety	34 (82.9%)	34 (87.2%)	24 (88.9%)	6 (75.0%)	$\chi^2(3)=1.24, p=0.743$
	Apathy	36 (87.8%)	31 (79.5%)	17 (63.0%)	8 (100.0%)	$\chi^2(3)=8.47, p=0.037$
	Melancholy	4 (9.8%)	23 (59.0%)	24 (88.9%)	3 (37.5%)	$\chi^2(3)=44.39, p<0.001$
	Anhedonia	7 (17.1%)	23 (59.0%)	20 (74.1%)	0 (0.0%)	$\chi^2(3)=31.88, p<0.001$
	Mood swings	15 (36.6%)	13 (33.3%)	15 (55.6%)	1 (12.5%)	$\chi^2(3)=6.12, p=0.106$
	Irritability	9 (22.0%)	5 (12.8%)	8 (29.6%)	0 (0.0%)	$\chi^2(3)=5.03, p=0.170$
ED-related symptoms	Fears related to eating, weight gain, loss of control	31 (75.6%)	1 (2.6%)	23 (85.2%)	1 (12.5%)	$\chi^2(3)=63.69, p<0.001$
	Dysmorphophobia (concerns regarding body size or its parts)	19 (46.3%)	1 (2.6%)	19 (70.4%)	0 (0.0%)	$\chi^2(3)=40.04, p<0.001$
	Obsessive ideas (regarding food, weight, and body shape)	8 (19.5%)	2 (5.1%)	11 (40.7%)	0 (0.0%)	$\chi^2(3)=15.48, p=0.001$
	Overvalued ideas (regarding food, weight, and body shape)	6 (14.6%)	0 (0.0%)	14 (51.9%)	0 (0.0%)	$\chi^2(3)=32.43, p<0.001$
	Sensitive ideas of reference ("others are critically judging me")	10 (24.4%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	$\chi^2(3)=14.28, p=0.003$
	Vomiting	0 (0.0%)	0 (0.0%)	5 (18.5%)	0 (0.0%)	$\chi^2(3)=17.04, p<0.001$
Neurotic and somatoform symptoms	Hypochondriacal concerns	0 (0.0%)	3 (7.7%)	9 (33.3%)	8 (100.0%)	$\chi^2(3)=53.96, p<0.001$
	Somatoform autonomic symptoms	1 (2.4%)	0 (0.0%)	4 (14.8%)	7 (87.5%)	$\chi^2(3)=58.74, p<0.001$
OCD	Obsessive thoughts (except for EDs)	0 (0.0%)	3 (7.7%)	3 (11.1%)	2 (25.0%)	$\chi^2(3)=7.84, p=0.049$
Thought disorders	Delusional level of anxiety (including regarding EDs)	20 (48.8%)	3 (7.7%)	8 (29.6%)	3 (37.5%)	$\chi^2(3)=16.47, p<0.001$
	Dysmorphomania (including regarding body size or its parts)	3 (7.3%)	0 (0.0%)	2 (7.4%)	1 (12.5%)	$\chi^2(3)=3.63, p=0.304$
	Formal thought disorders (associative process disorders)	6 (14.6%)	14 (35.9%)	14 (51.9%)	2 (25.0%)	$\chi^2(3)=11.13, p=0.011$
	Delusional ideas (except for EDs)	3 (7.3%)	0 (0.0%)	2 (7.4%)	2 (25.0%)	$\chi^2(3)=7.72, p=0.052$
Psychological disorders	Difficulties falling asleep	11 (26.8%)	35 (89.7%)	27 (100.0%)	5 (62.5%)	$\chi^2(3)=53.07, p<0.001$
	Superficial sleep	6 (14.6%)	16 (41.0%)	13 (48.1%)	0 (0.0%)	$\chi^2(3)=14.40, p=0.002$
Cognitive impairments	Reduced attentional focus	3 (7.3%)	6 (15.4%)	10 (37.0%)	0 (0.0%)	$\chi^2(3)=12.38, p=0.006$
	Memory deficits	0 (0.0%)	0 (0.0%)	5 (18.5%)	0 (0.0%)	$\chi^2(3)=17.04, p<0.001$
Treatment of adverse effects	Extrapyramidal effects*	1 (2.4%)	4 (10.3%)	12 (44.4%)	2 (25.0%)	$\chi^2(3)=22.69, p<0.001$
	Prevention of EPS*	15 (36.6%)	3 (7.7%)	12 (44.4%)	3 (37.5%)	$\chi^2(3)=13.23, p=0.004$
	Akathisia*	0 (0.0%)	3 (7.7%)	1 (3.7%)	1 (12.5%)	$\chi^2(3)=4.23, p=0.239$

Note: *Additional signs introduced as indications for prescribing "agents to treat the side effects of antipsychotics". ED — eating disorder; EPS — extrapyramidal symptoms; OCD — obsessive-compulsive disorder.

Table 5. Comparison of classes by clinical characteristics* and psychopharmacotherapy prescriptions*

Variable	Class 1 (n=41)	Class 2 (n=39)	Class 3 (n=27)	Class 4 (n=8)	Total (n=115)	Test
Age, Me (Q1; Q3), years	21.0 (18.0; 24.0)	22.0 (19.0; 26.0)	27.5 (21.3; 31.0)	21.0 (20.5; 25.0)	22.0 (19.0; 26.0)	H(3)=10.05, p=0.018, ε²=0.091
BMI, M±SD, kg/m²	14.2±2.0	15.5±1.9	14.2±2.6	14.8±2.3	14.7±2.2	F(3; 107)=3.21, p=0.026, η²=0.083
Current suicidal risk Moderate (n (%))	3 (7.5%)	2 (5.4%)	6 (24.0%)	0 (0.0%)	11	χ²(3)=7.48, p=0.058
Ongoing OCD (n (%))	19 (47.5%)	14 (37.8%)	11 (44.0%)	6 (75.0%)	50	χ²(3)=3.77, p=0.287
Psychotic disorders. Current episode (n (%))	1 (2.5%)	1 (2.6%)	0 (0.0%)	2 (28.6%)	4	χ²(3)=13.78, p=0.003
Antidepressants						
Agomelatine	1 (2.4%)	1 (2.6%)	4 (14.8%)	0 (0%)	6	χ²(3)=6.67, p=0.083
Amitriptyline	0 (0%)	1 (2.6%)	1 (3.7%)	1 (12.5%)	3	χ²(3)=4.24, p=0.236
Venlafaxine	6 (14.6%)	6 (15.4%)	9 (33.3%)	0 (0%)	21	χ²(3)=7.14, p=0.068
Vortioxetine	2 (4.9%)	1 (2.6%)	1 (3.7%)	1 (12.5%)	5	χ²(3)=1.63, p=0.652
Duloxetine	1 (2.4%)	1 (2.6%)	1 (3.7%)	3 (37.5%)	6	χ²(3)=18.18, p<0.001
Clomipramine	0 (0%)	1 (2.6%)	2 (7.4%)	0 (0%)	3	χ²(3)=3.70, p=0.296
Mirtazapine	12 (29.3%)	8 (20.5%)	8 (29.6%)	0 (0%)	28	χ²(3)=3.23, p=0.357
Paroxetine	1 (2.4%)	0 (0%)	0 (0%)	0 (0%)	1	χ²(3)=1.82, p=0.610
Sertraline	13 (31.7%)	17 (43.6%)	7 (25.9%)	2 (25.0%)	39	χ²(3)=4.41, p=0.221
Trazodone	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)	1	χ²(3)=1.94, p=0.585
Fluvoxamine	5 (12.2%)	10 (25.6%)	15 (55.6%)	3 (37.5%)	33	χ²(3)=17.10, p<0.001
Fluoxetine	1 (2.4%)	0 (0%)	0 (0%)	0 (0%)	1	χ²(3)=1.82, p=0.610
Escitalopram	10 (24.4%)	7 (17.9%)	8 (29.6%)	1 (12.5%)	26	χ²(3)=1.81, p=0.613
Antipsychotic drug						
Alimemazine	3 (7.3%)	3 (7.7%)	3 (11.1%)	1 (12.5%)	10	χ²(3)=0.56, p=0.906
Aripiprazole	3 (7.3%)	3 (7.7%)	5 (18.5%)	0 (0%)	11	χ²(3)=3.90, p=0.273
Brexpiprazole	0 (0%)	0 (0%)	1 (3.7%)	0 (0%)	1	χ²(3)=3.25, p=0.355
Haloperidol	6 (14.6%)	0 (0%)	2 (7.4%)	3 (37.5%)	11	χ²(3)=12.58, p=0.006
Cariprazine	0 (0%)	5 (12.8%)	7 (25.9%)	4 (50.0%)	16	χ²(3)=18.32, p<0.001
Quetiapine	10 (24.4%)	24 (61.5%)	17 (63.0%)	5 (62.5%)	56	χ²(3)=21.43, p<0.001
Clozapine	0 (0%)	0 (0%)	1 (3.7%)	0 (0%)	1	χ²(3)=3.25, p=0.355
Lurasidone	2 (4.9%)	1 (2.6%)	5 (18.5%)	0 (0%)	8	χ²(3)=7.71, p=0.052
Olanzapine	30 (73.2%)	11 (28.2%)	19 (70.4%)	3 (37.5%)	63	χ²(3)=11.75, p=0.008
Paliperidone	1 (2.4%)	0 (0%)	1 (3.7%)	0 (0%)	2	χ²(3)=1.56, p=0.669
Pericizazine	2 (4.9%)	2 (5.1%)	4 (14.8%)	0 (0%)	8	χ²(3)=3.72, p=0.294
Perphenazine	3 (7.3%)	0 (0%)	2 (7.4%)	1 (12.5%)	6	χ²(3)=3.59, p=0.309
Risperidone	6 (14.6%)	5 (12.8%)	7 (25.9%)	3 (37.5%)	21	χ²(3)=4.77, p=0.190
Sulpiride	0 (0%)	3 (7.7%)	9 (33.3%)	8 (100%)	20	χ²(3)=53.38, p<0.001
Tiapride	0 (0%)	1 (2.6%)	5 (18.5%)	0 (0%)	6	χ²(3)=12.75, p=0.005
Triptazine	0 (0%)	0 (0%)	3 (11.1%)	0 (0%)	3	χ²(3)=9.93, p=0.019
Flupentixol	1 (2.4%)	0 (0%)	0 (0%)	0 (0%)	1	χ²(3)=1.82, p=0.610

Chlorpromazine	4 (9.8%)	3 (7.7%)	7 (25.9%)	0 (0%)	14	$\chi^2(3)=7.16, p=0.067$
Chlorprothixene	1 (2.4%)	1 (2.6%)	6 (22.2%)	0 (0%)	8	$\chi^2(3)=12.78, p=0.005$
Agents to treat the side effects of antipsychotics						
Biperiden	16 (39.0%)	10 (25.6%)	20 (74.1%)	4 (50.0%)	50	$\chi^2(3)=19.94, p<0.001$
Trihexyphenidyl	0 (0%)	0 (0%)	2 (7.4%)	1 (12.5%)	3	$\chi^2(3)=7.58, p=0.056$
Mood stabilizers						
Valproic acid	0 (0%)	0 (0%)	3 (11.1%)	0 (0%)	3	$\chi^2(3)=9.93, p=0.019$
Carbamazepine	7 (17.1%)	6 (15.4%)	5 (18.5%)	1 (12.5%)	19	$\chi^2(3)=0.25, p=0.969$
Lamotrigine	5 (12.2%)	6 (15.4%)	4 (14.8%)	0 (0%)	15	$\chi^2(3)=1.64, p=0.651$
Lithium carbonate	0 (0%)	1 (2.6%)	2 (7.4%)	0 (0%)	3	$\chi^2(3)=3.70, p=0.296$
Oxcarbamazepine	1 (2.4%)	1 (2.6%)	2 (7.4%)	0 (0%)	4	$\chi^2(3)=1.76, p=0.624$
Tranquilizers						
Hydroxyzine	9 (22.0%)	10 (25.6%)	13 (48.1%)	3 (37.5%)	35	$\chi^2(3)=8.07, p=0.045$
Diazepam	0 (0%)	0 (0%)	1 (3.7%)	0 (0%)	1	$\chi^2(3)=3.25, p=0.355$
Tofisopam	11 (26.8%)	3 (7.7%)	3 (11.1%)	0 (0%)	17	$\chi^2(3)=5.32, p=0.150$

Note: *Only variables that demonstrated statistically significant differences between classes at $p<0.05$, or the most frequent features in the sample, are presented. BMI — body mass index; M — mean value; Me — median; SD — standard deviation; OCD — obsessive-compulsive disorder.

with statistically significant differences and on the frequency of drug prescriptions. Notably, no statistically significant differences were found between Classes in terms of any subscales of the SCL-90-R questionnaire or most of the diagnoses stated in the M.I.N.I. Data for all evaluated parameters across Classes are presented in Table S2 in the Supplementary.

Class1 (C1) is dominated by symptoms typical for AN. Dismorphophobia, fears related to eating, weight gain, loss of control and sensitive ideas of reference are defining symptoms of C1. The presence of target symptoms — specifically, hypochondriacal concerns, akathisia, and obsessive thoughts unrelated to the ED — indicates that a patient is unlikely to belong to C1. These patterns are reflected in the clinical presentation of C1 patients: fears related to eating, weight gain, or loss of control were present in 75.6% of patients; dysmorphophobia in 46.3%; sensitive ideas of reference in 24.4%; while hypochondriacal concerns, akathisia, and obsessive thoughts unrelated to the ED context are entirely absent in this class. Apathy was highly prevalent (87.8%), in contrast to the relatively low frequencies of melancholy (9.8%) and anhedonia (17.1%). A high frequency of delusional anxiety (48.8%) is noteworthy in C1.

The most commonly prescribed agents for these symptoms are antidepressants — sertraline, mirtazapine, and escitalopram. Among antipsychotics, olanzapine

was prescribed most frequently; among tranquilizers, tofisopam and hydroxyzine. Patients in the first class had the lowest BMI of 14.2 ± 2.0 kg/m² and were the youngest, with a median age Me (Q1; Q3)=21 (18; 24) years.

In class 2 (C2), somatoform autonomic symptoms, delusional ideas and dysmorphomania demonstrated strong negative regression coefficients, indicating their lack of contribution to the formation of this class. In C2, notably low frequencies are observed for core ED symptoms such as fears of eating, weight gain, or loss of control; dysmorphophobic concerns regarding body size or its parts; and obsessive or overvalued ideas about eating, weight, or body shape (see Table 4). Clinically, this group was characterized by a high incidence of difficulties falling asleep, anxiety, apathy, melancholy, and anhedonia. The most commonly prescribed drugs were the antidepressants sertraline, fluvoxamine, and mirtazapine. Quetiapine was the primary antipsychotic, while hydroxyzine is the most commonly used anxiolytic agent. The patients in this class had the highest BMI in the sample (15.5 ± 1.9 kg/m²).

Class 3 (C3) represents a polymorphic clinical profile with a combination of AN-specific symptoms, affective symptoms, thought disorders, cognitive impairments, and sleep disturbances. Leading symptoms determining the attribution to this class are vomiting, memory disturbances, difficulties falling asleep, and overvalued ideas regarding diet, weight, and body shape. The most common affective

symptoms include melancholy, anhedonia, and mood swings. In addition to the listed symptoms, such AN-specific symptoms as fear of eating / gaining weight / losing control, dysmorphophobia, overvalued ideas about weight and body shape, obsessive thoughts within the ED context were also common. The range of ED-specific symptoms in C3 is more heterogeneous than in C1. Moreover, C3 is characterized by frequent disturbances in the associative thinking. Cognitive impairments — specifically, reduced attentional focus and memory deficits — occur more commonly in this class than in the others. Pharmacologic management typically includes quetiapine, olanzapine, cariprazine, and risperidone. A distinctive feature was the frequent prescription of chlorpromazine, likely due to vomiting as a treatment target, as well as tiapride. Biperiden was actively prescribed to prevent extrapyramidal effects. In this class, the most commonly prescribed antidepressants include fluvoxamine, venlafaxine, mirtazapine, and escitalopram. Hydroxyzine was used more frequently than in the other class. Patients in this class had the highest median age (Me [Q1; Q3]=27.5 [21.3; 31.0] years). A binge-purge pattern was present in 53.8% of patients, and a moderate suicide risk was identified in 23.1%.

Class 4 (C4) was defined by the presence of hypochondriacal concerns, somatoform autonomic symptoms, and apathy, alongside a strong negative contribution of anhedonia, superficial sleep, and obsessive or overvalued ideas concerning eating, weight, or body shape, as well as dysmorphophobia. As in C2, none of the ED-specific symptoms were typical for C4. Clinically, all patients in C4 exhibited hypochondriacal concerns and apathy, and somatoform autonomic symptoms were highly prevalent in this class. Patients typically exhibited obsessive thoughts and delusional ideas outside the ED context. The class was notable for the near-complete absence of most ED-related symptoms and for the absence of anhedonia. Treatment typically included sulpiride, quetiapine, cariprazine, and haloperidol. The most commonly prescribed antidepressants include fluvoxamine and duloxetine. Hydroxyzine was used in one third of cases, and biperiden in one half of the patients. Notably, two patients within this class were diagnosed with an ongoing psychotic episode.

DISCUSSION

This study aimed to identify symptomatically homogeneous subgroups of patients diagnosed with AN, based on clinically significant psychopathological symptoms.

Symptoms explicitly designated by psychiatrists as targets of psychopharmacotherapy were considered clinically relevant. LCA of the psychopathological symptom dataset identified four distinct patient subgroups within the diagnostic category of “anorexia nervosa”. The classification demonstrated high certainty (entropy $R^2=0.908$), high statistical significance of the model ($p<0.0001$), and clear separation between latent groups, as evidenced by a high inter-class dissimilarity index (0.957).

It should be noted that direct comparison of our findings with those of other studies is challenging, because our model was built on results of psychopathological assessment of symptoms by clinicians, whereas previous research typically relied on psychometric scores or ED diagnostic criteria derived from classification systems. No prior study has used a detailed clinical assessment of psychopathological symptoms as the foundation for an empirical classification models.

Each of the four identified classes (C1–C4) was characterized by a distinct constellation of symptoms, predominantly involving either ED-related symptoms or/and affective symptoms. It is noteworthy that among the 115 patients in the sample, ED symptoms were key determinants of class formation only in 68 (59%) patients (C1 and C3). This finding aligns with data from idiographic studies of ED psychopathology, which report that only about 50% of patients with diagnosis of ED exhibit ED-specific symptoms among clinically significant manifestations [8]. Among the remaining 47 patients in our sample (C2 and C4), affective symptoms, somatoform symptoms, and hypochondriacal concerns were the primary determinants of class formation. ED symptoms showed negative regression coefficients, indicating that they did not contribute to class formation.

The ED symptoms that determined patient allocation to C1 and C3 shared a common core — predominantly dysmorphophobic concerns with body shape and fears related to eating, weight gain, or loss of control. However, these two classes diverged markedly in their additional symptom profiles. Patients in C1 were characterized by sensitive ideas of reference (e.g., “others are critically judging me”), whereas patients in C3 exhibited overvalued ideas and obsessive thoughts specifically focused on eating, weight, and body shape. C3 was also notably associated with self-induced vomiting, reflected in the high prevalence (53.8%) of the binge-purge pattern in this class. C1 and C3 also differed substantially in their non-ED-related symptoms. Compared with C1, patients in C3 showed significantly

higher rates of sleep disturbances, associative thinking disturbances, and mood swings. Affective symptoms in C3 were dominated by anxiety, melancholy, and anhedonia, whereas C1 was characterized primarily by anxiety and apathy. Hypochondriacal concerns were absent in C1, but present in one third of C3 patients. These results are consistent with findings from other AN studies confirming that body dissatisfaction and fear of weight gain represent core diagnostic features of AN. Nevertheless, additional ED-related symptoms contribute to individualized symptomatic profiles, helping to explain the clinical heterogeneity among patients with AN [7, 8, 23, 26].

Interestingly, despite extensive literature documenting frequent comorbidity between AN and OCD [4], patients in C1 exhibited no obsessive thoughts unrelated to the ED context, and such symptoms were rarely reported in C3 (11.1%). At the same time, both C1 and C3 patients presented with obsessive thoughts directly related to ED context. In C4, patients exhibited obsessive thoughts unrelated to the ED context and ED-related symptoms were absent. This observation contrasts with our findings from the M.I.N.I. diagnostic interview, which indicated OCD in 47.5% of C1 and 44.0% of C3 patients in our sample. The obtained contradictory data may point to the importance of identifying the content of obsessive thoughts when assessing the mental state of patients with AN, which is not always possible using standardized questionnaires. These findings highlight the potential for distinguishing between OCD and AN through clinical assessment. Notably, across the entire sample, no compulsive symptoms — the core behavioral manifestations of OCD — were identified as therapeutic targets. This finding contrasts with other studies reporting a strong association between key AN symptoms (e.g., body dissatisfaction and drive for thinness) and compulsions [4].

A high prevalence of negative affect symptoms was observed across all classes, consistent with prior researchers' observations regarding the involvement of affective disorders in shaping the clinical presentation of ED [11, 15, 23, 25, 26]. Anxiety was typical for patients in all four classes, and in C1 patients, it reached the delusional level. Other affective symptoms differed between classes in terms of frequency and contributed differently to class formation. Anhedonia and melancholy were most commonly observed in C2 and C3.

The combination of affective symptoms within classes is also of interest, as it may indirectly indicate differences

in the nature and phenomenological content of the same symptom. For example, apathy was observed in C1, C2, and C4. C2 was distinguished by the prominent presence of melancholy and anhedonia, whereas they were less frequent in C1 and C4. At the same time, C1 was characterized by symptoms of AN, while C4 exhibited delusional ideas unrelated to the ED context, hypochondriacal concerns and somatoform symptoms. This may suggest that apathy in patients of C1 and C4 falls outside the realm of affective disorders. Whereas, patients in C2 and C3 exhibited anxiety, apathy, and anhedonia, combined with sleep disturbances. Additionally, patients in C3 had cognitive impairments such as decreased concentration and memory disorders. Such affective symptoms combination may indicate an affective core of apathy in C2 and C3.

Further we would like to discuss the rationale for the symptom assessment using clinical psychopathological method.

We used the checklist of pharmacotherapy target symptoms as a psychopathological assessment tool, to provide a more detailed description of the clinical condition of patients with AN. According to the literature [7] and our own clinical observations, considerable heterogeneity exists in ED symptoms among patients with the same AN diagnosis. The clinical presentation of these patients often includes symptoms of other mental disorders, which do not fully meet the operational criteria of ICD-10; therefore, no diagnosis other than AN can be assigned. Available psychometric tools for assessing EDs focus more on the patient's behavior than on the mental phenomena, for example, the widely used Eating Disorder Examination (EDE) [44]. Moreover, scales and questionnaires designed to assess EDs do not address comorbid psychopathology, making it necessary to employ multiple assessment tools in research to evaluate the patient's condition comprehensively.

Our symptom-oriented approach is consistent with recent trends in psychiatry. Given the assumption that symptoms, rather than syndromes or even diagnostic categories, are linked to the biological factors underlying mental disorders, increasing attention is being paid to approaches based on symptomatic assessment of patients' mental states [45]. To more accurately determine therapeutic targets and incorporate treatment response into the diagnostic process, using data on the efficacy of psychopharmacotherapy for individual symptoms is proposed [46].

In describing patients' mental states, we found it most appropriate to record individual symptoms based on

clinical psychopathological assessment. We did not intend to assign symptoms to established diagnostic categories. Instead, the set of symptoms served as a mean of comprehensive description for clinical manifestations in patients diagnosed with AN according to ICD-10. Basically, this approach to mental state assessment is trans-diagnostic.

The symptom checklist was developed based on signs assessed in the mental status during routine clinical evaluation [43], and which may serve as targets for psychopharmacotherapy. A similar approach was developed by psychiatrists from the Association for Methodology and Documentation in Psychiatry (AMDP) in the 1960s and was named the AMDP system. The AMDP system includes symptom checklists for documenting psychopathological phenomena and their severity. This tool is used in clinical psychiatry and research, particularly for validating psychometric questionnaires during their development and for evaluating the efficacy of psychopharmacotherapy [47].

One of our objectives in the Psychopathological Symptom Checklist for Patients with AN (symptom checklist) was to distinguish ED-related symptoms from other symptoms.

For example, dissatisfaction with appearance (dysmorphophobia) is a symptom central to EDs but also seen in body dysmorphic disorder or as a feature of depressive or delusional disorders. Dysmorphophobia in our study was assessed in two content-dependent variants and placed in different symptom subgroups: 1) concerns about body size or specific body parts (an ED-related symptom), and 2) dissatisfaction with appearance not related to body size or body parts (a neurotic and somatoform symptom). Notably, dysmorphomania — defined as dissatisfaction with one's appearance reaching delusional levels — was included as a separate item in thought disorders subgroup. In our study, dissatisfaction with appearance outside the ED context did not emerge as a therapeutic target, whereas concerns about the body size or specific body parts were typical of C1 and C3. Dysmorphomania was rare and was mostly reported in C4 patients. Thus, the symptom of dysmorphophobia in AN is limited to concerns regarding body size and do not include other aspects of the appearance. Similar findings were found for obsessive thoughts, which were also differentiated by the content, as we discussed earlier.

Another purpose of the checklist was to assess the varying phenomenological content of ED-related symptoms and to determine how they should be qualified.

For example, symptoms such as “eating concern” (fear of food, preoccupation with food) or “shape concern” and “weight concern” (preoccupation with shape or weight), which are included in one of the main ED questionnaires, EDE [44], as well as in the diagnostic criteria for ED in the ICD-11, were divided into the following symptoms: fear of eating / gaining weight / losing control, obsessive thoughts, and overvalued ideas about food/weight/shape based on several considerations. Firstly, in clinical psychopathology, there is no such concept as “concern/preoccupation”; rather, specific symptoms such as fear, obsessive thoughts, and overvalued ideas are distinguished. Secondly, dividing “concern/preoccupation” into fear, obsessive, and overvalued ideas allows us to determine the psychopathological register and clinical significance of the symptoms, which ultimately implies different therapeutic strategies and clinical prognoses. As a result of our study, obsessive and overvalued ideas regarding food, weight, and body shape were distributed differently across the classes: they were typical for patients in C3, less typical for patients in C1, and not typical for patients in C2 and C4. Fear of eating / weight gain / loss of control was the most common ED-related symptom in C1 and C3. These findings indicate the need to clarify the phenomenological content of “concerns/preoccupation” about food, weight, and body shape in patients with AN.

Combining symptoms such as a fear of food, fear of weight gain, and fear of loss of control into a single symptom may not be fully justified in terms of clinical reality, as a given patient might not exhibit all three (which indicates that these symptoms might be a different therapeutic targets) [8, 48]. However, we decided to consolidate them under the grouping element of “fear” as a potential therapeutic target for psychopharmacotherapy.

The symptom “delusional level of anxiety” was proposed by us based on clinical observations of AN patients and by analogy with established psychopathological entities (“delusional level of depression”, “OCD with poor insight”). Our rationale was to describe a condition where patients, due to rigidity and high anxiety levels, are entirely overwhelmed by anxious concerns and unresponsive to reassurance, however, phenomenologically these symptoms are closer to intense anxiety than to delusion. Although “delusional level of anxiety” has not been previously described in the literature, clinicians in our study frequently identified it as a therapeutic target: it was present in 48.8% of patients in C1, 29.6% in C3, and 37.5% in C4.

Other findings in the present study also emphasize the importance of delineating phenomenological nuances of patients' clinical states and highlight the advantages of a symptom-based approach to describe the psychopathological profile of AN patients. In addition to the symptom checklist, standard instruments for psychopathological assessment — specifically the M.I.N.I. and the SCL-90-R — were used. However, based on the results of these instruments, the patient classes did not differ significantly from one another, whereas clinically assessed psychopathological symptoms showed significant differences. This may indicate a low sensitivity of these scales with respect to individual aspects of mental state. A characteristic example from our study is the discrepancy between the M.I.N.I. questionnaire results, which indicated the presence of OCD within the sample, and the relatively low prevalence of OCD symptoms outside the ED content when the same patients were evaluated clinically.

The SCL-90-R self-report inventory not only failed to show differences between patient classes in terms of psychopathology but also did not indicate distress (PSDI Me [Q1; Q3]=1.9 [1.5; 2.3]) despite the sample comprising recently hospitalized patients with severe AN, which suggests a high level of distress in these patients due to their symptoms. These findings indicate a low accuracy of self-reporting questionnaires for characterizing the clinical status of patients with AN, largely because these patients tend to have limited self-reflective capacity, that is known from the previous research [49]. However, SCL-90-R questionnaire data are frequently used in building empirical models of EDs [15, 26].

The first limitation of the present study is the use of a checklist as an evaluation tool, developed based on the consensus of nine psychiatrists involved in the study and not subjected to clinical validation or pilot testing. However, there are studies on EDs that employed an identical consensus-based approach to creating a symptom checklist [8].

The obtained data should be interpreted keeping in mind that the described symptoms were the rationale for psychopharmacotherapy prescriptions. This limited the potential set of symptoms in the checklist. Moreover, the absence of a specific clinical symptom as a therapeutic target in a patient does not imply its absence in a particular patient's mental state.

With regard to the more detailed differentiation of ED symptoms commonly used in studies, we did not elaborate

on all cases to avoid overloading the checklist with symptoms that, in essence, represent a single therapeutic target (e.g., grouping fear of eating, weight gain, and loss of control into one target symptom, as discussed above). At the same time, we identified dysmorphic ideas as a distinct symptom, separated from the fear of eating, weight gain, or loss of control due to the high likelihood that different therapeutic strategies will be required, consistent with recommendations from earlier studies [50].

Potential objections may arise from the fact that patients were prescribed psychopharmacotherapy, despite the lack of evidence of its efficacy in AN [51]. However, there has been a growing discussion recently about prescribing pharmacotherapy based on specific symptoms rather than diagnoses [46]. The absence of data for psychopharmacotherapy effectiveness in AN patients might be attributed to the fact that clinical approaches to symptom evaluation and response to treatment are not consistently implemented in studies assessing the efficacy of pharmacological interventions. In our study, describing patients based on treatment-target symptoms can be considered a strength, as it demonstrates the potential of a clinical-psychopathological approach to identifying pharmacotherapy targets in AN. This may be useful for future research on the efficacy of psychopharmacotherapy.

This study has several noteworthy strengths. First, the sample consisted exclusively of individuals with AN who were treated under uniform clinical conditions. Second, the primary method of evaluating patients' mental states was clinical psychopathological assessment conducted by qualified psychiatrists with expertise in EDs. This method differentiates the study from others where empirical models were built on data obtained from patients' self-reporting or psychometric scales. Third, the clinical method enabled an individualized and nuanced evaluation of each patient's mental state, incorporating multiple clinical nuances and ensuring a comprehensive assessment.

The development of personalized approaches is a priority in mental health [52]. Our study allowed identification of key treatment-target symptoms in AN patients, as well as their combinations, which may be important for a better understanding of the psychopathology of AN, greater personalization of therapeutic strategies, and more precise diagnostics.

Moreover, we developed and applied an original tool based on the clinical psychopathological method — a checklist of psychopathological symptoms, which can be used in future

research. The advantages of this tool are: 1) unification of clinical assessment due to the checklist format; 2) the possibility of identifying clinically significant symptoms by determining the treatment-target symptoms; 3) it can be used to collect information on the use of a specific drug to treat a specific symptom. The limitation of this approach is the essential role of a psychiatrist trained in clinical psychopathology, which may not be available in some countries [33, 53].

Future research may verify the identified patient classes on a larger sample size or in different clinical settings. Studies of biological markers in patients may also be required to determine common biological factors within the classes. It would be useful to follow-up mental state changes during treatment and the response to treatment in patients of different classes in future studies. The psychopathological assessment tool we proposed can be used in further research on the response to therapy in AN patients.

CONCLUSION

Four empirical phenotypes with unique symptomatic profile were identified within the diagnostic category of “anorexia nervosa” based on a comprehensive clinical psychopathological assessment. Unique symptomatic profile of each class encompassed both core ED symptoms and general psychopathological symptoms. We proposed an original tool for assessing clinically relevant psychopathological symptoms in patients with AN.

The results highlight the importance of detailed psychopathological qualification of symptoms. Attribution of overlapping clinical manifestations in AN patients to specific phenomena allowed us to identify key differences between patient groups. This approach opens prospects for a more accurate diagnosis and more personalized therapy for AN.

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