

Treatment of *Anorexia Nervosa*: The Importance of Disease Progression in the Prognosis



Tratamento da Anorexia Nervosa: A Importância da Evolução da Doença no Prognóstico

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ABSTRACT

Introduction: *Anorexia nervosa* is a severe, usually chronic, life-threatening disease of complex etiology characterized by food restriction, overestimation of the importance of body weight and image, intense fear of weight gain and distortion of body image. *Anorexia nervosa* is associated with high rates of mortality, suicide and decreased quality of life. Our aim is to present an *anorexia nervosa* treatment program offered in a major university hospital in Portugal, and to determine the impact of illness duration before admission on the outcome. Our hypothesis is that patients with greater disease longevity may have worse prognosis and poorer outcome.

Material and Methods: The sample included data from case records of 169 patients seen consecutively and for the first time at Centro Hospitalar São João, between 2010 and 2015. We performed a retrospective observational study which included data collected at admission and from later follow-up years.

Results: From the initially selected patients, 14.8% reached total remission, 16% accomplished partial remission and 14.2% ended up with exacerbation/stagnation of the disease. The dropout rate was of 55% throughout our study period. We found significant differences on outcome rates between distinct illness duration groups ($p = 0.007$).

Discussion: There are several factors frequently associated with poor outcome for *anorexia nervosa*. The interpretation of outcome findings was limited by the high rate of dropout and lack of consistent definition criteria.

Conclusion: Our results support the idea that illness duration has an important role on the outcome and prognostic features of these patients.

Keywords: Anorexia Nervosa/therapy; Disease Progression; Prognosis; Treatment Outcome

RESUMO

Introdução: A anorexia nervosa é uma doença severa, geralmente crónica e potencialmente fatal, de etiologia complexa e caracterizada por restrição alimentar, sobrevalorização da importância do peso corporal e da imagem, medo intenso de ganho ponderal e distorção da imagem corporal. A anorexia nervosa está associada a altas taxas de mortalidade, suicídio e diminuição da qualidade de vida. O nosso objetivo é apresentar um programa de tratamento da anorexia nervosa de um hospital universitário português e determinar o impacto da duração da doença, antes da admissão, no *outcome*. A nossa hipótese é que pacientes com maior longevidade da doença apresentam piores prognóstico e *outcome*.

Material e Métodos: A amostra incluiu dados de 169 pacientes vistos consecutivamente e pela primeira vez no Centro Hospitalar de São João, entre 2010 e 2015. Realizámos um estudo observacional retrospectivo, que incluiu os dados colhidos na admissão e durante o seguimento.

Resultados: Dos doentes inicialmente selecionados, 14,8% alcançaram remissão total, 16% remissão parcial e 14,2% terminaram com exacerbção/estagnação da doença. A taxa de *dropout* foi 55% durante o nosso período de estudo. Encontrámos diferenças estatisticamente significativas relativamente ao *outcome* para diferentes tempos de duração da doença ($p = 0,007$).

Discussão: Existem vários fatores frequentemente associados com mau *outcome* na anorexia nervosa. A interpretação dos resultados foi limitada pela alta taxa de *dropouts* e falta de critérios de definição consistentes.

Conclusão: Os nossos resultados apoiam a ideia de que a duração da doença tem um papel preponderante no *outcome* e prognóstico da doença.

Palavras-chave: Anorexia Nervosa/tratamento; Prognóstico; Progressão da Doença; Resultado do Tratamento

INTRODUCTION

Eating disorders (ED), such as *anorexia nervosa* (AN), *bulimia nervosa* (BN) and binge-eating disorders,¹ although representing different diagnostic identities, share psychopathological characteristics, particularly anxiety and mood disorders. These conditions affect particularly young women² and are associated with significant morbidity and mortality rates. These disorders are difficult to resolve and represent a challenge for health professionals.³

Anorexia nervosa is a severe, usually chronic and potentially fatal disease⁴ of complex etiology and characterized by starvation imposed by the individual, overestimation of body weight and image importance, intense fear of weight gain, body image distortion which results in rigid restriction of caloric intake. *Anorexia nervosa* is associated with high rates of mortality, suicide, and decreased quality of life.⁵ The recently published

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Diagnostic and Statistical Manual of Mental Disorders, 5th ed., (DSM-5) includes a diagnostic category for AN in two types - restricting type (AN-R) and binge eating/purging type (AN-BP) - which does not refer to a specific amount of weight loss required for the diagnosis, but instead provides guidelines for specifying the severity of weight loss (mild, moderate, severe or extreme), based on ranges of current body mass index (BMI).⁶ However, it is important to notice that cross-over between the two subtypes is common.⁷

Anorexia nervosa is predominantly diagnosed in young women and adolescents, where approximately 40% of new cases are found among women aged 15 - 19 years.^{8,9} Even though almost 90% of all diagnosed cases relate to women, the incidence among men has been increasing.¹⁰ Epidemiological data in Portugal are quite scarce, but a recent study suggests similar data to other western countries with the mean prevalence rate of 0.3% in young female, and a 10:1 female to male ratio.^{6,11,12}

According to the American Psychiatric Association, AN can be subdivided into two subcategories: the first concerns the restrictive type, in which patients would have to present in the last three months a weight loss that had been achieved mainly through diet, fasting and/or excessive exercise without the existence of binge eating or purging behavior; the second type, the binge-eating/purging, is accompanied by episodes of recurrent binge-eating or purging behavior during the last three months. These two types of AN are also differentiated by their hormonal and behavioral profiles. In the first type the levels of the hormone leptin are lower and, on the other hand, the second type shows higher levels of impulsivity and a higher rate of self-harm behaviors.¹³

The treatment of this ED is a complex, multidisciplinary process that includes nutritional rehabilitation, psychotherapy, psychopharmacotherapy and treatment of medical complications that appear during disease progression and that may interfere with its prognosis. However, the psychological background that characterizes this disease is often difficult to modify.¹⁴ A large number of studies have admitted that the early identification of prognostic features has a significant result in the therapeutic strategy and outcome of the disease, which may lead to a more effective intervention.¹⁵⁻¹⁷

The CHSJ is a university hospital responsible for the treatment of several ED, including, in its range, patients from all over northern Portugal. The therapeutic program of this hospital is guided mainly by the consciousness of the importance of developing autonomy and self-initiative in these patients. It consists of several phases with the ultimate goal of encouraging a gradual change in eating behavior and subjective experience of patients.¹⁸ Regarding the therapeutic approach, the scientific evidence is limited and a greater knowledge about response predictors and resistance to treatment is needed.

The main objective of this dissertation is to determine the influence of illness duration before admission on patient outcome. Our hypothesis intends to consider that patients with a perpetuation of disease may have a worse prognosis,

as well as higher dropout rates than those with a shorter disease duration at the date of admission.

MATERIAL AND METHODS

Participants

Our sample included 169 patients (159 female, 10 male) seen for the first time at CHSJ in Porto and evaluated consecutively on clinical psychiatric interview by two experienced senior psychiatrists.

The most recent edition of the DSM-5 includes significant differences on what refers to the ED chapter. The review of the diagnostic criteria resulted, therefore, in significant changes in the prevalence of ED, including an increase in the diagnosis of AN, due to the exclusion of the amenorrhea criterion.¹⁹ According to these changes in relation to DSM-IV, all diagnoses were reviewed and all patients meeting the latest AN diagnostic criteria were admitted. Participants were referred to our unit by General Practitioners and Family Physicians (MGFs) or psychiatrists. Some of them sought intervention on their own initiative or on the advice of family members, others were directly transferred from the emergency department to the psychiatric ward, being admitted either immediately at the hospital due to severe electrolytic disturbances, psychological instability, very low body mass index – BMI – (< 13 kg/m²) or due to risk of suicide. Participants fulfilled the criteria for AN diagnosis according to DSM-5 and were included only those older than 13 years of age. Additional exclusion criteria used were pregnancy and lactation.

This study was approved by the CHSJ Ethics Committee.

Data collection

Data was collected from records of patients admitted from January 2010 to December 2015. Patients' follow-up continued until their last consultation in 2016. Treatment outcome was evaluated in December 2016. A retrospective cohort study was conducted, which included sociodemographic variables (date of birth, sex, marital status and educational status), and clinical variables (BMI at admission, duration of illness in years and good or bad treatment outcome).

Treatment program

All patients were treated according to the standards of the Department of Psychiatry and Mental Health of CHSJ, which has developed its own model of care.¹⁸ The treatment plan has as main principle the consideration that AN is a self-autonomy conflict with three main aspects to be emphasized: motivation to change based on respect for autonomy and responsibility, food intake seen not as a choice but rather a mandatory requirement of nature; nutritional rehabilitation, with establishment of diet based on health control; involvement of the family but leaving the patient responsible for his/her eating behavior learned during the treatment.

The CHSJ program consists of an interdisciplinary project using the support of professionals in the areas of

Psychology, General Medicine, Nutrition and Nursing. Psychiatric consultations are regularly done. Psychotherapy is initiated as soon as the refeeding process is started and must persist through all stages of treatment. It focuses primarily on eating behavior and weight gain, without neglecting the emotional component of the disease. The cognitive behavioral approach aims to change behavior but always respecting the individual, its own autonomy, emotions and thoughts. Attempts to promote weight gain can provoke tension and anxiety, and therefore a non hypercaloric diet (1700 Kcal/day, distributed over six meals a day) is usually proposed in order to achieve a minimum weight compatible with health. The goal is not for the patient to stop being thin but to accept his decision without jeopardizing his health. This intervention emphasizes nutritional reeducation instead of total weight recovery, accepting the temporary persistence of low weight since there are assured improvements in other health indicators. Finally, the importance of family involvement in patient recovery is well recognized,²⁰ but sometimes the family structure can interfere, restricting the autonomy and independence of the patient.²¹ From the beginning of the treatment, feeding of patients' own responsibility, obviously according to their age, without family interference and with medical support whenever necessary. This assures the principle of autonomy by encouraging the patients to actively participate in their therapy, helping with the fear of losing control over food, which is a characteristic psychological mechanism of the anorexic behavior.

Inpatient care is justified when it is expected a fatal outcome of the disease and it is a decision that must be taken according to medical, psychopathological and familiar reasons. It consists in a therapeutic plan structured with patient and family which may imply the absence of visits or contact with relatives. Depending on the progress made, it can be restarted by the therapist's decision.

The use of pharmacotherapy has been disappointing and, therefore, is not considered in the therapeutic strategy. However, it can be important especially regarding other comorbidities.

Outcome of patients

An agreement has not been reached yet as to what is considered to be a positive or negative outcome. In this study, we considered the following treatment outcome: good outcome (total remission or partial remission) and poor outcome (exacerbation/stagnation, death or dropout).

The definition of total remission goes according to the DSM-5 criteria for AN, which is, total absence of the previously presenting symptoms.⁶ Partial remission is considered when the patient does not meet the criteria of low body weight but there is still some resistance to weight gain and/or disturbances in self-perception.

Stagnation consists on the persistence of the clinical manifestations of AN, defined by the DSM-5, while exacerbation refers to clinical aggravation during follow-up, despite the treatment. The meaning of dropout is of

high importance; in this study, it refers to the withdrawal of the treatment or follow-up, by patient's own initiative. The distinction between early and late dropout is also established. Early dropout occurs when the patient abandons during the first month or only attended to three or less sessions.

Statistical analysis

Descriptive statistics was used to characterize the sample. Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables as frequency and percentages. Since not all data was normally distributed, both parametric (*t*-test for independent samples and One-Way ANOVA) and non-parametric (Mann-Whitney) tests were used for continuous data, and Chi square test for categorical data. All tests were two tailed and $p < 0.05$ was established. All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 24.0

RESULTS

Overall sample description

This study's population included 169 patients (159 female, 10 male) with a mean age of 22.61 ± 7.95 years and a mean BMI of 15.00 ± 2.00 Kg/m², at admission.

At admission most of the participants was single (85.8%). On the matter of the educational status, more than a half were students (67.5%), 46 (40.4%) of them were attending high school and 60 (52.6%) were graduating or had already completed a college degree. Participants had median illness duration of 2.0 years (mean 3.68 ± 5.09 years, range 0.17 – 28 years) and the mean age of onset was 19.04 ± 6.07 years.

Clinical characteristics considering AN subtypes

Table 1 presents the patient's characteristics at admission according to AN subtype. Within the sample, 66 (39.1%) patients had AN-BP subtype and 103 (60.9%) had AN-R subtype.

The mean illness duration was significantly higher for AN-BP 6.05 ± 6.5 years, than for AN-R 3.13 ± 3.97 years ($p = 0.001$). Mean age at first appointment was higher for the AN-BP subtype, with 25.23 ± 9.06 years, when compared with the AN-R subtype, with 20.93 ± 6.67 years ($p = 0.001$). When considering differences between illness duration groups (< 1, 1 - 2, > 2 years) and mean age at first appointment, we found that only the subgroup of AN-R with < 1 year of illness duration had a statistically significant difference in the age at first appointment comparing to the subgroup of > 2 years (18.51 vs 24.61 years old, $p < 0.001$).

An evaluation between subtypes did not show any statistically significant difference on gender, marital status, educational status, age at onset or BMI at admission.

Considering severity based on BMI groups (mild/moderate ≥ 16 and severe/extreme < 16), there were no significant differences on the number of cases between the AN subtypes ($p = 0.295$).

Table 1 - Sample characteristics at admission according to type of *anorexia nervosa*

	AN-R n = 103	AN-BP n = 66	p-value*
Demographic %			
Gender			
Female	93.2	95.5	0.742
Male	6.8	4.5	
Marital status			
Single	90.3	78.8	0.120
Married	5.8	15.2	
Common law marriage	2.9	3.0	
Divorced	1.0	1.5	
Widowed	0.0	1.5	
Educational status			
University	38.8	47.0	0.246
High school	42.7	30.3	
Junior high school (9 th grade)	10.7	12.1	
Preparatory education (6 th grade)	1.0	1.5	
Primary education (4 th grade)	0.0	3.0	
Illiterate	0.0	1.5	
Clinical history			
Age at onset	18.4 ± 5.86	19.89 ± 6.31	0.139
Age at first appointment	20.93 ± 6.67	25.23 ± 9.06	0.001
Illness duration	3.13 ± 3.97	6.05 ± 6.5	0.001
BMI at admission	15.98 ± 1.72	16.49 ± 2.12	0.091
Severity based on BMI (DSM-5)%			
Mild/Moderate	47.6	59.1	0.295
Severe/Extreme	50.5	39.4	

* Significant at $p < 0.05$

Data is presented as mean ± standard deviations or percentages and is based on available data only (i.e. missing or unknown data was excluded)

At the end of follow-up

From the 169 patients, 76 (45%) completed treatment and follow-up, and 93 were lost during the follow-up, which means a 55% dropout rate. The rate of early dropout was 11.2% corresponding to 19 patients. Analysis of treatment results revealed that 52 patients (30.8%) achieved good outcomes, 27 of them (16%) met partial remission criteria and 25 (14.8%) reached full remission, while 24 (14.2%) had poor outcome, either with exacerbation or stagnation of their condition.

At the end of follow-up there were no significant differences in remission or dropout rates among the two AN subtypes ($p = 0.636$). When looking at the AN-R subtype there were 35.9% patients with good outcome, comparing to the 25.8% of the AN-BP patients. Dropout rate reached 53.4% ($n = 55$) in patients with AN-R and 57.6% ($n = 38$) of those with AN-BP.

Outcomes between different severity groups at admission (mild/moderate and severe/extreme) were similar; 34.6% of the patients with severe/extreme level achieved remission (partial or full) compared to the 29.5% of those who met mild/moderate level ($p = 0.782$). Dropout

rate reached 48.7% ($n = 38$) in patients admitted at BMI < 16 and 61.4% ($n = 54$) of those admitted at BMI ≥ 16, however differences did not fulfill statistical significance ($p = 0.197$).

Follow-up data considering illness duration

Table 2 summarizes results of follow-up according to illness duration before admission.

We observed that there were significant differences on the outcome between different illness duration groups ($p = 0.007$). From the group of patients with less than one year of illness durability ($n = 65$), 53.8% completed the follow-up with a poor outcome, while in the 1 - 2 years group ($n = 25$), 68% ended up with the same results and, finally, the poor outcome rate in the more than two years group ($n = 66$) was 77.3%.

At the end of follow-up there were no significant differences in dropout rates among different illness duration groups ($p = 0.139$).

DISCUSSION

The primary aim of the current project was to explore

Table 2 - Follow-up data according to illness duration

	Illness duration			p-value*
	< 1 year n = 65	1 - 2 years n = 25	> 2 years n = 66	
Clinical History of follow-up				
Outcome				
Remission (partial/full)	46.2	32.0	22.7	0.007
Poor outcome	53.8	68.0	77.3	
Various outcomes %				
Full remission	30.8	8.0	4.5	
Partial remission	15.4	24.0	15.2	
Exacerbation/stagnation	10.8	4.0	24.2	
Dropout	43.1	64.0	56.1	
Early dropout	7.7	12.0	13.6	
Dropout				
Yes	43.1	64.0	56.1	0.139
No	56.9	36.0	43.9	

* Significant at $p < 0.05$ Data is presented as mean \pm standard deviations or percentages and is based on available data only (i.e. missing or unknown data was excluded)

the impact of illness duration at the start of treatment on the outcome and patient prognosis. According to our research, the period of disease before admission seems to have a considerable importance in the outcome or prognosis, since patients with longer illness duration seem to reveal a tendency to have a worse outcome.

An additional purpose of the present study present the AN treatment program offered in a major university hospital in Portugal. The goal of CHSJ program is not only to achieve a healthy weight but specially to provide skills to promote a full sustained recovery. The main innovative feature of our therapeutic strategy is to ensure the principle of autonomy while working in three essential aspects: motivation to change, nutritional education with non hypercaloric diet and family therapy encouraging the patient to take an active role on its own treatment. Accordingly, and in line with previous guidelines,^{20,22} we believe that outpatient programs should be privileged, allowing individuals to maintain their routines and social life, applying the newly learned skills in their usual environment.²³

The problem of very high rate of treatment dropout has been long recognized.²³ Data from standard clinical practice reveal that dropout rates have not changed over the course of time, regardless of country or treatment modality, reaching 50% or more for both outpatient and inpatient samples.^{24,25} In our program we had 55% dropout rate, 11.2% of which matching early dropouts, a favorable value compared to previous estimates among outpatient eating disorder services of 13 – 32%.²⁶ We do not know exactly the major reasons for premature treatment termination of our patients but resistance to treatment and reluctance to recovery have been long recognized as key-problems in the treatment, as well as illness duration, treatment type and family variables.²⁴

The discussion of outcome findings between studies

was limited by the lack of consistent definitions of outcome criteria.²⁷ After follow-up, 14.8% of our patients had recovered, no longer fulfilling any of diagnostic criteria of AN and 16% achieved partial remission, having a normal body weight but maintaining some psychological symptoms, what makes a 30.8% rate of good outcome. This is compatible with the literature remission rates that range from 13.2% to 40.5%, depending on the used definition.²⁸ This wide range rates could be explained not only by the absence of commonly accepted outcome criteria, but also by different study methodologies or DSM diagnostic criteria along the years.²⁷ On the other hand, reports on long-term course of AN in adults suggested that recovery increased with longer follow-up periods²⁹ reaching almost half of the surviving patients, while about 20% remained chronically ill,¹⁶ so that we considered our mean follow-up period (1.29 years – approximately one year and four months) a short term to successfully achieve and/or interpret conclusions on the global AN outcome.

There are many factors which have been frequently associated with poor outcome for AN related with a short or long-term follow-up.¹⁵ One of the most reported prognostic indicators in literature is the body weight at the start of the treatment.^{15,16,30} Contrary to previous findings that have related a lower BMI on admission to outpatient treatment with a lower rate³⁰ or even a higher rate of treatment completion,^{16,30} there were no statistically significant differences in dropout rates among the current study groups. The findings of our research do not suggest a direct relationship between initial BMI and outpatient treatment outcome. Therefore, according to our study, low body weight at the start of the treatment, which is one factor that has been suggested to strongly influence treatment outcome,^{30,31} does not seem to affect clearly our outpatient results. These findings oppose other studies that had considered that

BMI at admission to inpatient units seems to select severe patients who are less compliant with treatment, which leads to dropout and contributes to poor prognosis.^{31,32}

The present study has several limitations that should be considered. It was a retrospective medical chart review whereby the information collected was dependent exclusively on case records. Since standardized measures were not used, our data are mainly clinical which limits the generalizability of our findings. On the other hand, the recruitment of subjects from a single center with a large catchment area, treated by the same experienced therapists, can be considered an added value of this study.

CONCLUSION

In conclusion, this paper presents a particular model of care for AN patients based on outpatient treatment that in general leads to relevant weight gains and decreased psychopathology during the therapeutic approach and follow-up. The lack of consensual definition of remission creates difficulties when comparing outcome data from treatment modalities and centers, so we emphasize the need for uniform adoption of remission definitions.²⁸ Furthermore, the high incidence of dropout as in the case of the majority of literature,^{24,33} as well as in our study, largely decreases the power and generalization of the results.

Nevertheless, one of our main goals has been achieved by demonstrating a significant difference in patients' outcome according to their illness duration. Thereby, we may conclude that the longer illness duration, the worst the

outcome, thus it can be considered an important factor of worse prognosis.

However, many other factors are related to the recovery process despite the treatment, therefore illness duration should only be a guide.

In order to fully understand it, future research with longer follow-up period must be done to evaluate how differences in areas like motivation to change, therapeutic alliance or treatment acceptance, considered the biggest challenges in the management of patients with AN,³⁴ may influence the treatment outcome.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

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