



## Trabajo Original

Nutrición artificial

### Adherence of nutritional support prescriptions to clinical practice guidelines in patients with anorexia nervosa

*Adecuación de la prescripción de soporte nutricional a las guías de práctica clínica en pacientes con anorexia nervosa*

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#### Abstract

**Background:** nutritional support (NS) is a core element in the treatment of underweight patients with anorexia nervosa (AN).

**Objective:** to analyze the adherence of NS prescriptions to clinical practice guidelines (CPGs) for AN patients and to compare the effectiveness, safety, and cost of NS according to adherence.

**Methods:** this retrospective observational study included AN patients admitted to an Eating Disorders Unit between January 2006 and December 2009 and followed until December 2014. NS prescriptions were compared with guidelines published by the American Psychiatric Association (APA), the National Institute for Clinical Excellence (NICE), and the Spanish Ministry of Health and Consumption (SMHC). Adherence was defined as percentage of hospitalizations that followed all recommendations.

**Results:** adherence to APA and NICE/SMHC was observed in 10.2% and 73.4%, respectively, of the total of 177 hospitalizations. Body weight and body mass index were higher at admission in the NICE/SMHC adherence *versus* non-adherence group ( $p < 0.001$ ). Weight gain rate during hospitalization was higher ( $p = 0.009$ ) in "APA adherence" (135.5 g/day) *versus* "non-adherence" (92.1 g/day) group. Hospital stay was significantly shorter ( $p = 0.025$ ) in "NICE/SMHC adherence" (39.5 days) *versus* "non-adherence" group (50.0 days). NICE/SMHC adherence was associated with lower costs ( $p = 0.006$ ).

**Conclusions:** NS prescriptions for anorexic patients more frequently followed NICE/SMHC than APA recommendations. Over the short-term, APA adherence was associated with improved weight gain. Patients adhering to NICE/SMHC recommendations had shorter hospital stay and reduced costs, likely due to their more favorable nutritional status at admission.

#### Key words:

Eating disorders.  
Anorexia nervosa.  
Nutritional support.  
Guidelines.  
Adherence.

#### Resumen

**Introducción:** el soporte nutricional (SN) es un elemento clave en el tratamiento de la anorexia nervosa (AN).

**Objetivo:** analizar la adecuación de las prescripciones de SN en pacientes con AN a las guías de práctica clínica (GPC) y comparar la efectividad, seguridad y coste según la adecuación.

**Métodos:** estudio observacional retrospectivo en pacientes con AN ingresados en una Unidad de Trastornos de Conducta Alimentaria entre enero de 2006 y diciembre de 2009. Se hizo seguimiento hasta diciembre de 2014. Se compararon las prescripciones de SN con las GPC publicadas por la Asociación Americana de Psiquiatría (APA), el Instituto Nacional de Excelencia Clínica (NICE) y el Ministerio Español de Sanidad y Consumo (MSC). Se definió adecuación como porcentaje de ingresos que cumplieron todas las recomendaciones.

**Resultados:** el grado de adecuación a APA y NICE/MSC fue del 10,2% y 73,4%, respectivamente. El peso corporal y el índice de masa corporal al ingreso fueron mayores en el grupo "sí-adequación" al NICE/MSC *versus* "no-adequación" ( $p < 0,001$ ). La tasa de ganancia ponderal fue superior ( $p = 0,009$ ) en el grupo "sí-adequación" a APA (135,5 g/día) *versus* "no-adequación" (92,1 g/día). La estancia hospitalaria fue menor ( $p = 0,025$ ) en "sí-adequación" al NICE/MSC (39,5 días) *versus* "no-adequación" (50,0 días). La adecuación al NICE/MSC fue asociada con menores costes ( $p = 0,006$ ).

**Conclusiones:** las prescripciones de SN se ajustaron en mayor grado al NICE/MSC que a la APA. La adecuación a APA parece relacionarse con mayor tasa de ganancia ponderal. Los pacientes que se adecuaron al NICE/MSC presentaron menores estancias hospitalarias y costes, probablemente relacionado con su estado nutricional más favorable al ingreso.

#### Palabras clave:

Trastornos de conducta alimentaria.  
Anorexia nervosa.  
Soporte nutricional.  
Guías. Adecuación.

Received: 30/07/2018 • Accepted: 11/03/2019

Note: This article forms part of the doctoral thesis of María del Mar Alañón Pardo, Pharmacy Doctoral Program, University of Granada, Spain.

Alañón Pardo MM, Ferrit Martín M, Calleja Hernández MA, Morillas Márquez F. Adherence of nutritional support prescriptions to clinical practice guidelines in patients with anorexia nervosa. *Nutr Hosp* 2019;36(5):1001-1010

DOI: <http://dx.doi.org/10.20960/nh.02223>

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## INTRODUCTION

Anorexia nervosa (AN) is a life-threatening eating disorder associated with a higher chronification risk and mortality rate in comparison to other eating disorders (1-3). Its association with high hospital admission rates, long hospital stays, increased health costs, and severe physical, psychological, and social sequelae makes it an important social and health problem. Up to two-thirds of patients with AN are admitted to hospital at least once during the course of their disease (3,4).

Available treatments have very low success rates; thus, one review reported relapse in around half of AN patients within the first year after inpatient treatment (5). Little information is available on factors that may be associated with a favorable response. Low body weight at hospital discharge has been related to higher relapse and readmission rates (6,7), but the achievement of weight gain during hospitalization poses a major challenge in patients with AN (5).

Clinical practice guidelines (CPGs) of the UK National Institute for Clinical Excellence (NICE, 2004; last revision in 2013), the American Psychiatric Association (APA, 2006; last revision in 2012), and the Spanish Ministry of Health and Consumption (SMHC, 2009) (8-10) provide evidence-based recommendations on the approach to patients with eating disorders. According to these CPGs, patients with AN require a multidisciplinary approach that includes dietary-nutritional and psychological therapies.

The therapeutic objective of nutritional support (NS) in hospitalized AN patients is to recover a healthy minimum weight, correcting the physical and psychological sequelae of malnutrition. An improvement in nutritional status has been found to enhance the cognitive status of these patients, increasing the effectiveness of psychological therapies (8-12).

Natural feeding should be the first option for NS, because it favors psychosocial abilities and behaviors that are hindered by artificial feeding. However, the diet can be supplemented with artificial nutrition, preferably enteral, in patients with a long history of early satiety, inadequate weight recovery, or severe malnutrition, or in those who will not cooperate with food intake (8,10,12). Thus, it has been reported that hypercaloric supplements are useful to recover weight and reduce hospital stays (12-15). Furthermore, multivitamin and mineral oral supplements (mainly phosphorus, potassium, and magnesium) have been used to prevent refeeding syndrome and treat nutritional deficiencies in highly malnourished patients (8-12), while zinc supplementation was reported to be effective for weight recovery in patients with AN (16,17).

We hypothesized that adherence of NS prescriptions to CPG recommendations for eating disorders would improve health outcomes and reduce costs. Few published data are available on the adherence to recommendations of NS prescriptions for patients with AN and its influence on long-term effectiveness and safety outcomes. With this background, the objectives of this study were to analyze the adherence of NS prescriptions for hospitalized AN patients to recommendations in APA, NICE, and SMHC CPGs and to compare the effectiveness, safety, and costs of NS as a function of CPG adherence.

## MATERIALS AND METHODS

### STUDY DESIGN AND POPULATION

This retrospective observational study included patients with AN admitted to a ten-bed in-patient Eating Disorders Unit (EDU) in a general university hospital between January 2006 and December 2009 and followed until December 2014. This unit is a nationally recognized specialist center for adolescents and adults with severe eating disorders.

Inclusion criteria were: age  $\geq 12$  years; weight  $< 85\%$  ideal weight, i.e., body mass index (BMI)  $\leq 17.5$  kg/m<sup>2</sup> according to the 10<sup>th</sup> edition of the International Classification of Diseases (ICD-10, WHO, 1992), and fulfillment of all diagnostic criteria for AN (restrictive [R-AN] and purging [P-AN] subtypes) according to the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition, text revision (DSM-IV-TR) (18,19). Exclusion criteria were: principle diagnosis of bulimia nervosa, eating disorder not otherwise specified (EDNOS), or psychiatric disease other than eating disorder; and the receipt of therapy at other centers.

### VARIABLES

#### Sociodemographic, clinical, anthropometric and therapeutic variables

Data were gathered from clinical records of the patients on sociodemographic variables (sex, age at admission, history of suicidal and/or self-harm behavior, consumption of toxic substances, consumption of psychopharmaceuticals, number of previous hospitalizations, and number of previous treatments for AN), clinical variables (R-AN or P-AN subtype, time with AN ["long" =  $\geq 7$  yrs], and physical and psychiatric comorbidities), and anthropometric variables (body weight [kg] and BMI [kg/m<sup>2</sup>] at hospital admission and discharge, and minimum BMI [kg/m<sup>2</sup>] reached during the course of their AN). Time with AN was defined as the interval (in years) between the diagnosis and first EDU admission.

Body weight was measured every morning after voiding, with patients in hospital gown and bare feet. Height was measured at admission. The BMI was calculated as weight (kg) divided by the square of height (m).

Plasma electrolytes, glucose levels, and deficiencies were closely monitored during the hospital stay.

NS prescriptions from psychiatrists during all hospital stays were gathered from the electronic prescription program for hospitalized patients (*ATHOS-Prisma*<sup>®</sup>). NS-related study variables were: type of artificial feeding (natural feeding [ordinary food] alone, supplementation with artificial nutrition, or solely artificial nutrition); intake cooperation (forced/unforced); administration route (enteral/parenteral); nasogastric feeding (yes/no) and administration (continuous [ $> 24$  h] or discontinuous [3-5 bolus feedings/day]); types of enteral nutrition formula; vitamin and

mineral supplements; maximum caloric supply (Kcal/day); dosage (mg/day, mEq/day, or IU/day) and duration (days) of NS; and reason(s) for NS prescription.

### Adherence of NS prescription to CPGs

CPGs adherence was defined as the fulfillment of all recommendations, considering the “degree of adherence” as the percentage of hospitalizations with NS prescriptions that followed all recommendations. Table I compiles the nutritional recommendations of APA (2006) and NICE (2004)/SMHC (2009) for patients with AN, and the reasons for non-adherence to CPG recommendations; SMHC recommendations are the same as those in NICE guidelines.

### Variables related to NS effectiveness, safety, and cost

Evaluation of NS effectiveness considered the body weight (kg) and BMI (kg/m<sup>2</sup>) at discharge, weight gain rate (total weight gain in grams during hospitalization divided by days of hospitalization), hospital stay (number of days from admission to discharge), time to relapse (months between hospital discharge and next admis-

sion), body weight maintenance (yes/no), and number of EDU readmissions during 12 months post-discharge. Data on hospital stay and EDU admissions were furnished by the clinical documentation department of the hospital. Safety was evaluated according to the number and type of NS-related adverse effects. The NS cost (in euros) was the sum of direct costs for enteral nutrition formulas and vitamin and mineral supplements prescribed during hospital stays, extracted from the Pharmacy Department economic management program (*ATHOS-Stock*<sup>®</sup>).

### STATISTICAL ANALYSIS

IBM-SPSS V.21.0 was used for the statistical analysis. Quantitative variables were expressed as central tendency and dispersion measures and qualitative variables as absolute and relative frequencies. Proportions among groups were confirmed by bivariate analysis with Pearson's Chi-square test or, when conditions were not met, with Fisher's exact test. Quantitative variables were compared between independent groups with the Student's t-test or, when the distribution was non-normal, the Mann-Whitney U test. The normality of variables was verified using the Shapiro-Wilks test. Survival was analyzed using the Kaplan-Meier test, comparing survival between groups with the Log Rank test (Mantel-Cox).  $p < 0.05$  was considered as significant in all tests.

**Table I.** Nutritional recommendations for patients with anorexia nervosa during weight recovery, and reasons for non-adherence of nutritional support prescriptions to recommendations

American Psychiatric Association (APA, 2006) guidelines	Reason for non-adherence
“When life-preserving nutrition must be provided to a patient who refuses to eat, <i>nasogastric feeding</i> is preferable to intravenous feeding”	“Parenteral nutrition”
“When nasogastric feeding is necessary, <i>continuous</i> feeding may be better tolerated by patients and less likely to result in metabolic abnormalities than three to four bolus feedings a day”	“Discontinuous administration of nasogastric enteral feeding”
“Since zinc supplements have been reported to foster weight gain in patients with AN, these patients may benefit from daily <i>zinc-containing multivitamin tablets</i> ”	“Non-supplementation with zinc”
“ <i>Phosphorus, potassium and/or magnesium supplementation</i> should be given in <i>severely malnourished patients with AN</i> (particularly those whose weight is < 70% of their healthy body weight)* who undergo aggressive oral, nasogastric, or parenteral refeeding, in order to prevent refeeding syndrome”	“Non-supplementation with phosphorus, potassium, and/or magnesium for severely malnourished* patients with AN”
National Institute for Clinical Excellence (NICE, 2004) and Spanish Ministry of Health and Consumption (SMHC, 2009) guidelines	Reason for non-adherence
“In some cases*, treatment with a <i>multivitamin and/or mineral supplement in oral form</i> is recommended for patients with AN during weight restoration”	“Non-supplementation with multivitamins and/or minerals for severely malnourished* patients with AN”
“ <i>Total parenteral nutrition should not be used</i> for patients with AN, unless there is significant gastrointestinal dysfunction”	“Parenteral nutrition”
“ <i>Feeding against the will of the patient should be an intervention of last resort</i> in the care and management of AN”	“Force-feeding”

AN: anorexia nervosa. \*Considered as BMI  $\leq 15$  kg/m<sup>2</sup> (maximum level of severity according to the WHO categories for thinness in adults).

## ETHICAL APPROVAL

This study was approved by the Clinical Research Ethics Committee of the hospital and respected the confidentiality of personal data.

## RESULTS

### SOCIODEMOGRAPHIC, CLINICAL, ANTHROPOMETRIC AND THERAPEUTIC CHARACTERISTICS

During the study period, 128 patients were hospitalized in the EDU; 56 were excluded for: bulimia nervosa (n = 21), EDNOS (n = 20),

principle diagnosis of psychiatric disease other than an eating disorder (n = 3), and continued receipt of therapy at other centers (n = 12).

The study finally included 72 patients with R-AN (n = 45) or P-AN (n = 27). Table II lists their characteristics at baseline. All patients had malnutrition-related physical comorbidities, including endocrine (93.1%), hydroelectrolytic (70.8%), hematologic (63.9%), hepatic (41.7%), gastrointestinal (33.3%), cardiovascular (25.0%), bone (31.9%), and renal (12.5%) disorders. No significant differences in physical comorbidities were found between subtypes. The presence of psychiatric comorbidities was observed in 56.9% of the patients, including substance-related (30.6%), personality (22.2%), anxiety (16.7%), and mood (12.5%) disorders. Substance-related disorders were more frequent ( $p = 0.048$ ) in patients with P-AN (44.4%) versus R-AN (22.2%).

**Table II.** Sociodemographic, clinical and anthropometric characteristics in 72 patients with anorexia nervosa at first admission in the EDU

Variable	Total (n = 72)	R-AN (n = 45)	P-AN (n = 27)	p
<i>Sex, n (%)</i>				
Female	68 (94.4)	41 (91.1)	27 (100.0)	0.290
Male	4 (5.6)	4 (8.9)	0 (0.0)	
<i>Age at admission (yrs)</i>				
Mean (SD)	24.9 (8.6)	23.4 (8.8)	27.7 (7.6)	0.056
Range	13-47	13-47	16-39	
<i>History of suicidal and/or self-harm behavior, n (%)</i>				
Yes	16 (22.2)	7 (15.6)	9 (33.3)	0.079
No	56 (77.8)	38 (84.4)	18 (66.7)	
<i>Consumption of toxic substances, n (%)</i>				
Yes	23 (31.9)	10 (22.2)	13 (48.1)	0.022*
No	49 (68.1)	35 (77.8)	14 (51.9)	
<i>No. previous admissions, n (%)</i>				
No previous admission	45 (62.5)	30 (66.7)	15 (55.6)	0.265
1 previous admission	15 (20.8)	10 (22.2)	5 (18.5)	
> 1 previous admission	12 (16.7)	5 (11.1)	7 (25.9)	
<i>No. previous treatments, n (%)</i>				
No previous treatment	49 (68.1)	32 (71.1)	17 (63.0)	0.208
1 previous treatment	9 (12.5)	7 (15.6)	2 (7.4)	
> 1 previous treatment	14 (19.4)	6 (13.3)	8 (29.6)	
<i>Duration of AN, n (%)</i>				
Short (< 7 yrs)	53 (73.6)	36 (80.0)	17 (63.0)	0.093
Long ( $\geq$ 7 yrs)	19 (26.4)	9 (20.0)	10 (37.0)	
<i>Psychiatric comorbidities, n (%)</i>				
Yes	41 (56.9)	22 (48.9)	19 (70.4)	0.163
No	31 (43.1)	23 (51.1)	8 (29.6)	
<i>Body weight at admission (kg)</i>				
Mean (SD)	41.4 (7.2)	41.8 (7.7)	40.7 (6.7)	0.552
<i>BMI at admission (kg/m<sup>2</sup>)</i>				
Mean (SD)	15.7 (2.6)	15.9 (2.9)	15.4 (1.6)	0.440
<i>Minimum BMI (kg/m<sup>2</sup>)</i>				
Mean (SD)	14.4 (2.1)	14.7 (2.1)	13.9 (2.2)	0.066

BMI: body mass index; EDU: eating disorders Unit; P-AN: purging anorexia nervosa; R-AN: restrictive anorexia nervosa; SD: standard deviation. \*Statistical significance ( $p < 0.05$ ).

Almost half of the patients (47.2%) were admitted to EDU more than once (range: 1-15 admissions/patient); 177 hospitalizations were analyzed (112 for R-AN and 65 for P-AN), and the BMI at admission was  $\leq 15 \text{ kg/m}^2$  in 37.3% of these. Psychopharmaceuticals were prescribed in 71.8% of the 177 hospitalizations, finding no significant difference ( $p = 0.637$ ) between R-AN (70.5%) and P-AN (73.8%) patients. Feeding was exclusively natural in 50.8% of hospitalizations, supplemented with artificial nutrition in 46.3%, and completely replaced with artificial nutrition in 2.8%. Feeding was forced in 5.6% of hospitalizations (6.3% R-AN vs 4.6% P-AN,  $p = 0.748$ ), parenteral nutrition was used in 1.7% (0.9% R-AN and 3.1% P-AN,  $p = 0.226$ ) and nasogastric enteral feeding in 5.1% (6.3% R-AN and 3.1% P-AN,  $p = 0.489$ ), being continuous (24-h) in 44.4% of cases.

In 49.2% of hospitalizations, complete liquid enteral nutrition formulas were prescribed due to "lack of cooperation with oral intake" (44.8%), "insufficient weight recovery" (31.1%), or "life-threatening BMI" ( $\leq 12 \text{ kg/m}^2$ ) (24.1%). The mean maximum caloric supply *via* enteral nutrition was 716.9 Kcal/day (range: 100-2,100 Kcal/day), and the mean time with enteral nutrition was 41.8 days (range: 12-165 days); 93.1% of the formulas prescribed were standard, polymeric, hypercaloric (1.5 Kcal/ml), and fiber-free. The macronutrient composition of the total caloric supply was 15-17% proteins, 49-55% carbohydrates and 30-35% lipids.

Oral vitamin supplements were prescribed in 23.7% of hospitalizations. Out of the 66 prescriptions for these supplements, 36.4% were for multivitamins, 31.8% for vitamin D3, 25.8% for vitamins B1-B6-B12, 4.5% for vitamin B1, and 1.5% for vitamin B6. The mean duration of vitamin consumption was 50.9 days (range: 12-174 days). Drops of vitamin D3 (66.7 IU/drop) were administered (400-800 IU/day) to prevent and/or treat osteoporosis from the lack of dietary vitamin D intake and/or sunlight exposure. Supplementation with multivitamin pills (2,500-3,600 IU vitamin A, 1.6-15 mg vitamin B1, 1.8-15 mg vitamin B2, 2.6-10 mg vitamin B6, 4-10  $\mu\text{g}$  vitamin B12, 100-200 mg vitamin C, 400-500 IU vitamin D3, 15 IU vitamin E, 10-25 mg calcium pantothenate, 0.2 mg biotin, 19-50 mg nicotinamide, and 0.4-0.8 mg folic-acid per pill) or with 250-300 mg vitamin B1, 250-300 mg vitamin B6, and/or 0.5 mg vitamin B12 pills was used to prevent refeeding syndrome and treat vitamin deficiencies. Vitamins were administered once daily throughout the refeeding period. Mineral supplements were prescribed in 26.6% of hospitalizations. Out of the 65 prescriptions for these supplements, 44.6% were for calcium, 38.5% for potassium, 9.2% for phosphate, and 7.7% for magnesium. Calcium supplementation (500-1,500 mg/day) used lactogluconate/calcium carbonate pills (500 mg calcium/pill) to prevent and/or treat osteoporosis; potassium supplementation (20-80 mEq/day) used 600 mg potassium chloride capsules (8 mEq potassium/capsule) and/or injections of 1,491 mg potassium chloride (20 mEq potassium/injection); phosphate supplementation (800-1,000 mg/day) used monobasic sodium phosphate sachets (800 mg phosphate/sachet), and magnesium supplementation (53-212 mg magnesium/day) used pills

of 7.17 mg magnesium bromide, 0.34 mg magnesium fluoride, and 125.06 mg magnesium hydroxide.

Minerals were included in the composition of 83.3% of multivitamin pills (61.8-125 mg calcium, 15.6-60 mg iron, 38.9-100 mg magnesium, 0.5-1 mg manganese, 1 mg copper, and 30-125 mg phosphorus per pill). In 11.3% of hospital stays, zinc was supplemented by the daily administration of a single multivitamin pill with 20.6 mg zinc sulfate (7.5 mg zinc elemental).

Oral supplements with multivitamins, potassium, phosphorus, and/or magnesium were prescribed in 43.9% of the 66 hospitalizations with admission BMI  $\leq 15 \text{ kg/m}^2$  in order to prevent refeeding syndrome.

## ADHERENCE OF NS PRESCRIPTIONS TO CPGs

NS prescriptions followed all APA recommendations in 18 (10.2%) hospitalizations and all NICE/SMHC recommendations in 130 (73.4%). Among hospitalizations for R-AN ( $n = 112$ ), 9.8% adhered to APA and 73.2% to NICE/SMHC CPGs. Among hospitalizations for P-AN ( $n = 65$ ), 10.8% adhered to APA and 73.8% to NICE/SMHC CPGs. Table III exhibits the adherence to CPGs as a function of sociodemographic, clinical, and anthropometric variables. Causes of "non-adherence" in the 159 hospitalizations that did not meet APA recommendations were "non-supplementation with zinc" (98.7%), "non-supplementation with phosphorus, potassium, and/or magnesium" in patients with BMI  $\leq 15 \text{ kg/m}^2$  (23.3%), "discontinuous administration" of nasogastric enteral feeding (3.1%), and "parenteral nutrition" (1.9%). Causes of "non-adherence" in the 47 hospitalizations that did not meet NICE/SMHC recommendations were "non-supplementation with multivitamins and/or minerals" in patients with BMI  $\leq 15 \text{ kg/m}^2$  (78.7%), "force-feeding" (21.3%), and "parenteral nutrition" (6.4%).

## NS EFFECTIVENESS, SAFETY AND COST AS A FUNCTION OF ADHERENCE TO CPGs

Table IV compares the effectiveness, safety, and cost of NS in patients with AN between the adherence and non-adherence of prescriptions to the CPGs. After correcting for the longer hospital stay of the patients receiving nutritional supplements, the weight gain rate was significantly higher in patients receiving zinc supplementation (Table V). A total of 65 adverse effects of the NS were recorded in 28.9% of hospitalizations, including dyspepsia (30.8%), flatulence (29.2%), abdominal distension (18.5%), abdominal pain (12.3%), nausea (4.6%), regurgitation (3.1%), and vomiting (1.5%), which were all attributed to the enteral nutrition formulas. Before the initiation of NS, hypopotassemia was observed in 10.2% of hospitalizations, hypophosphatemia in 1.7%, and hypomagnesemia in 1.2%. During NS treatment, plasma levels of these electrolytes were normal. No symptoms of refeeding syndrome (e.g., cardiac arrest, rhabdomyolysis or encephalopathy) were recorded.

**Table III.** Distribution of adherence of hospitalizations (n = 177) as a function of sociodemographic, clinical and anthropometric variables

Variable	Adherence to APA guidelines			Adherence to NICE/SMHC guidelines		
	Yes (n = 18)	No (n = 159)	p	Yes (n = 130)	No (n = 47)	p
<i>Sex, n (%)</i>						
Female	18 (100)	155 (97.5)	0.351	127 (97.7)	46 (97.9)	0.943
Male	0 (0.0)	4 (2.5)		3 (2.3)	1 (2.1)	
<i>Age at admission</i>						
Mean (SD)	26.7 (8.5)	25.0 (8.5)	0.420	25.3 (8.5)	24.9 (8.5)	0.811
<i>History of suicidal and/or self-harm behavior, n (%)</i>						
Yes	5 (27.8)	28 (17.6)	0.294	28 (21.5)	5 (10.6)	0.100
No	13 (72.2)	131 (82.4)		102 (78.5)	42 (89.4)	
<i>Consumption of toxic substances, n (%)</i>						
Yes	8 (44.4)	47 (29.6)	0.196	40 (38.8)	15 (31.9)	0.884
No	10 (55.6)	112 (70.4)		90 (69.2)	32 (68.1)	
<i>Consumption of psychopharmaceuticals, n (%)</i>						
Yes	10 (55.6)	117 (73.6)	0.107	96 (73.8)	31 (66.0)	0.303
No	8 (44.4)	42 (26.4)		34 (26.2)	16 (34.0)	
<i>No. previous admissions, n (%)</i>						
No previous admission	4 (22.2)	39 (24.5)	0.284	30 (23.1)	13 (27.7)	0.820
1 previous admission	1 (5.6)	31 (19.5)		24 (18.5)	8 (17.0)	
> 1 previous admission	13 (72.2)	89 (56.0)		76 (58.5)	26 (55.3)	
<i>No. previous treatments, n (%)</i>						
No previous treatment	15 (83.3)	93 (58.5)	0.111	84 (64.6)	24 (51.1)	0.272
1 previous treatment	0 (0.0)	19 (11.9)		13 (10.0)	6 (12.8)	
> 1 previous treatment	3 (16.7)	47 (29.6)		33 (25.4)	17 (36.2)	
<i>Anorexia nervosa subtype, n (%)</i>						
Restrictive	11 (61.1)	101 (63.5)	0.841	82 (63.1)	30 (63.8)	0.927
Purging	7 (38.9)	58 (36.5)		48 (36.9)	17 (36.2)	
<i>AN duration, n (%)</i>						
Short (< 7 yrs)	10 (55.6)	115 (72.3)	0.139	96 (73.8)	29 (61.7)	0.117
Long (≥ 7 yrs)	8 (44.4)	44 (27.7)		34 (26.2)	18 (38.3)	
<i>Psychiatric comorbidities, n (%)</i>						
Yes	13 (72.2)	103 (64.8)	0.529	90 (69.2)	26 (55.3)	0.085
No	5 (27.8)	56 (35.2)		40 (30.8)	21 (44.7)	
<i>Body weight at admission (kg)</i>						
Mean (SD)	40.5 (6.9)	40.4 (6.7)	0.784	41.8 (6.6)	36.5 (4.9)	< 0.001*
<i>BMI at admission (kg/m<sup>2</sup>)</i>						
Mean (SD)	15.2 (2.1)	15.3 (1.7)	0.838	15.8 (1.7)	14.0 (1.3)	< 0.001*
<i>Minimum BMI (kg/m<sup>2</sup>)</i>						
Mean (SD)	13.9 (2.4)	13.9 (2.1)	0.855	14.1 (2.1)	13.1 (1.8)	0.003*

APA: American Psychiatric Association; AN: anorexia nervosa; BMI: body mass index; NICE: National Institute for Clinical Excellence; SD: standard deviation; SMHC: Spanish Ministry of Health and Consumption. \*Statistical significance ( $p < 0.05$ ).

**Table IV.** Treatment effectiveness, safety and cost in patients with anorexia nervosa

Variable	Total	Adherence to APA guidelines			Adherence to NICE/SMHC guidelines		
		Yes	No	p	Yes	No	p
<i>Body weight (kg) at discharge</i>							
Mean (SD)	45.1 (5.8)	42.5 (4.8)	45.4 (5.8)	0.026*	45.1 (5.8)	41.0 (6.0)	0.923
n	169	18	151		123	46	
<i>BMI (kg/m<sup>2</sup>) at discharge</i>							
Mean (SD)	17.2 (1.4)	16.5 (1.4)	17.3 (1.4)	0.032*	17.2 (1.4)	17.2 (1.5)	0.832
n	169	18	151		123	46	
<i>Weight gain rate (g/day)</i>							
Median (IQR)	97.3 (95.1)	135.5 (110.4)	92.1 (91.6)	0.009*	84.2 (94.9)	103.5 (90.9)	0.236
n	169	18	151		123	46	
<i>Hospital stay (days)</i>							
Median (IQR)	42.0 (50.0)	48.0 (48.3)	42.0 (49.0)	0.091	39.5 (46.0)	50.0 (55.5)	0.025*
n	177	18	159		130	47	
<i>Time to relapse (months)</i>							
Median (IQR)	3.5 (5.1)	2.9 (2.7)	3.5 (6.1)	0.117	3.0 (5.0)	5.6 (10.6)	0.073
n	112	10	102		87	25	
<i>Weight maintenance one year after discharge, n (%)</i>							
Yes	51 (32.7)	1 (5.9)	50 (36.0)	0.013*	37 (33.3)	14 (31.1)	0.789
No	105 (67.3)	16 (94.1)	89 (64.0)		74 (66.7)	31 (68.9)	
n	156	17	139		111	45	
<i>No. readmissions during the year after discharge, n (%)</i>							
No readmission	81 (45.8)	13 (72.2)	68 (42.8)	0.062	52 (40.0)	29 (61.7)	0.033*
1 readmission	47 (26.6)	2 (11.1)	45 (28.3)		37 (28.5)	10 (21.3)	
> 1 readmission	49 (27.7)	3 (16.7)	46 (28.9)		41 (31.5)	8 (17.0)	
n	177	18	159		130	47	
<i>Adverse effects, n (%)</i>							
Yes	33 (18.6)	8 (44.4)	25 (15.7)	0.007*	22 (16.9)	11 (23.4)	0.328
No	144 (81.4)	10 (55.6)	134 (84.3)		108 (83.1)	36 (76.6)	
n	177	18	159		130	47	
<i>NS cost/day (€)</i>							
Median (IQR)	0.4 (2.4)	1.4 (4.1)	0.3 (2.2)	0.790	0.2 (2.1)	1.1 (3.4)	0.006*
n	114	12	102		74	40	
<i>Total NS cost (€)</i>							
Median (IQR)	17.6 (115.3)	21.7 (461.9)	13.2 (111.4)	0.518	7.3 (106.3)	73.5 (229.4)	0.002*
n	114	12	102		74	40	

BMI: body mass index; IQR: interquartile range; NS: nutritional support; SD: standard deviation. \*Statistical significance ( $p < 0.05$ ).

Table V. Treatment with nutritional supplements in patients with anorexia nervosa

Variable	Supplementation with enteral nutrition formulas		Supplementation with multivitamins		Supplementation with minerals		Supplementation with zinc	
	Yes	No	Yes	No	Yes	No	Yes	No
Weight (kg) at admission Mean (SD)	38.2 (6.9)	42.5 (5.7)	35.8 (7.7)	41.1 (6.2)	34.8 (6.0)	42.4 (5.7)	40.8 (6.7)	40.3 (6.7)
BMI (kg/m <sup>2</sup> ) at admission Mean (SD)	14.8 (1.9)	15.8 (1.4)	13.7 (2.1)	15.6 (1.6)	13.8 (1.9)	15.9 (1.4)	15.3 (2.1)	15.3 (1.7)
Minimum BMI (kg/m <sup>2</sup> ) Mean (SD)	13.1 (2.1)	14.6 (1.8)	12.5 (1.8)	14.1 (2.1)	12.4 (1.8)	14.3 (1.9)	13.8 (2.3)	13.9 (2.1)
Weight (kg) at discharge Mean (SD)	44.7 (6.2)	45.4 (5.4)	42.7 (5.4)	45.4 (5.7)	43.3 (5.8)	45.7 (5.7)	41.9 (4.9)	45.5 (5.8)
BMI (kg/m <sup>2</sup> ) at discharge Mean (SD)	17.1 (1.6)	17.3 (1.3)	16.3 (1.6)	17.3 (1.4)	17.0 (1.6)	17.3 (1.4)	16.4 (1.4)	17.3 (1.4)
Weight gain rate (g/day) Median (IQR)	84.3 (82.2)	108.2 (113.8)	112.3 (103.4)	91.7 (93.5)	99.4 (95.1)	97.3 (94.2)	127.0 (110.3)	95.1 (91.7)
Hospital stay (days) Median (IQR)	55.0 (45.3)	30.0 (33.0)	53.0 (62.0)	41.5 (46.5)	63.0 (56.0)	39.0 (41.0)	49.5 (49.8)	42.0 (48.0)
Time to relapse (months) Median (IQR)	3.5 (4.9)	3.4 (6.5)	2.1 (2.6)	3.5 (6.8)	2.7 (7.1)	3.5 (5.6)	2.9 (4.0)	3.5 (6.1)
	61	57	16	96	29	83	12	100
Weight maintenance at 12 months post-discharge n (%)								
Yes	25 (30.9)	26 (34.7)	7 (31.8)	44 (32.8)	11 (26.8)	40 (34.8)	1 (5.3)	50 (36.5)
No	56 (69.1)	49 (65.3)	15 (68.2)	90 (67.2)	30 (73.2)	75 (65.2)	18 (94.7)	87 (63.5)
	81	75	22	134	41	115	19	137
No. readmissions during the year after discharge, n (%)								
N° readmission	35 (40.2)	46 (51.1)	10 (41.7)	71 (46.4)	23 (48.9)	58 (45.4)	13 (65.0)	68 (43.3)
1 readmission	20 (23.0)	27 (30.0)	8 (33.3)	39 (25.5)	14 (29.8)	33 (26.9)	2 (10.0)	45 (28.7)
> 1 readmission	32 (36.8)	17 (18.9)	6 (25.0)	43 (28.1)	10 (21.3)	39 (27.7)	5 (25.0)	44 (28.0)
	87	90	24	153	47	130	20	157

BMI: body mass index; IQR: interquartile range; SD: standard deviation. \*Statistical significance ( $p < 0.05$ ).

## DISCUSSION

NS prescriptions for these hospitalized AN patients showed a low degree of adherence to APA recommendations. Force-feeding by nasogastric tube was more frequent than parenteral nutrition, considered as a last resort, although nasogastric feeding was more often discontinuous than continuous, while the main cause of "non-adherence" was "non-supplementation with zinc". Supplementation with phosphorus, potassium, and/or magnesium was not always offered to severely malnourished patients during the first few days of NS treatment. NS prescriptions showed a higher degree of adherence to NICE/SMHC recommendations, largely attributable to the scant utilization of force-feeding and parenteral nutrition, while the main cause of "non-adherence" was non-supplementation with multivitamins and/or minerals for severely malnourished patients.

Among reported prognostic factors for AN chronification (age at admission, history of suicidal/self-harm behavior, consumption of toxic substances, number of treatments and hospitalizations,  $\geq 7$  yrs with AN, psychiatric comorbidities, and low body weight/BMI) (1,20,21), the only statistically significant differences as a function of CPG adherence were the lower body weight and BMI at admission and the lower minimum BMI reached during the course of their AN in the NICE/SMHC non-adherence *versus* adherence group. This apparently greater severity of illness in the NICE/SMHC "non-adherence" group may have increased the frequency of force-feeding and parenteral nutrition in life-threatening situations.

Body weight and BMI at discharge were significantly lower in hospitalizations with "adherence" *versus* "non-adherence" to APA. After correcting for longer hospital stay in the "APA adherence" group, a significantly higher weight gain rate was obtained in the latter in comparison to the "non-adherence" group, which may be attributable to the zinc supplementation. Daily supplementation with 7.5 mg elemental zinc increased the weight gain rate in these AN patients. This finding is consistent with two randomized, double blind, placebo-controlled clinical trials (16,17) in which anorexic patients receiving 28 mg or 50 mg elemental zinc daily showed higher weight gain and improved anxiety and depression symptoms. Zinc is present in large amounts in brain areas involved in food intake, body weight control, and serotonin metabolism, and zinc deficiencies and serotonergic activity disorders are frequent in anorexic patients (17). However, the prescription of zinc supplementation to hospitalized patients with AN was infrequent in the present study.

No statistically significant differences were found in body weight or BMI at discharge or in weight gain rate during hospitalization between NICE/SMHC adherence and non-adherence, likely attributable to the more severe malnutrition at admission in the (non-adherence) group. Hospital stay was significantly shorter in the NICE/SMHC "adherence" *versus* non-adherence group, which may be explained by the superior nutritional status of the former at admission. Accordingly, force-feeding and parenteral nutrition do not appear to favor weight gain or reduce the hospital stay in hospitalized patients with AN. There have been reports that a greater caloric intake and weight gain are obtained by force-feeding these patients with a nasogastric tube in comparison to oral feeding, although these benefits are not maintained over the long

term (13,22-25). Moreover, force-feeding may damage the relationship between patients and healthcare professionals and has been criticized on ethical grounds (12).

CPGs recommend multivitamin and mineral supplementation in severely malnourished AN patients. According to the present results, this supplementation does not appear to increase the weight gain rate in hospitalized AN patients, likely due to the greater severity of illness (lower body weight and BMI) at admission of the patients who received it. A double-blind controlled clinical trial with placebo also found that vitamin and mineral supplementation was not useful for weight gain in anorexic patients and did not enhance the effects of pharmacological treatment (26). However, the administration of multivitamins with zinc proved to be the only NS component that significantly increased the weight gain rate in the present patients.

Most enteral nutrition formulas were hypercaloric, the type most frequently indicated in AN to reduce gastric distension and hydric overload during refeeding (27). However, fiber-enriched formulas were not routinely administered, despite the benefits of fiber for these frequently constipated patients (27). Administration of enteral nutrition formulas had no effect on weight gain and was associated with longer hospital stays, likely due to the higher malnutrition severity at admission of those treated with enteral nutrition. These findings support the proposal that exclusively natural feeding should be the first option for NS in AN patients (12,27). It was reported that enteral nutrition formulas do not yield major benefits and may possibly reinforce avoidance behavior towards normal food (12), although other researchers observed increased weight gain and reduced hospital stay with the administration of hypercaloric formulas (13-15,23,28).

Over the longer term, relapse was observed within 12 months post-discharge after 54.2% of hospitalizations, similar to previous observations (5), and most of the patients failed to maintain their body weight during this follow-up period. Nova et al. described a tendency for anorexic patients to reduce food intake after hospital discharge due to dissatisfaction with their body image, returning to their pre-admission size (29). In the present study, CPG adherence did not appear to contribute to weight maintenance or reduce the time to relapse or readmission rate.

NS-related adverse effects were mild and infrequent, and vitamin and mineral supplements were better tolerated than enteral nutrition formulas. No refeeding syndrome was observed in any hospitalizations. The risk of refeeding syndrome increases with parenteral nutrition, but this was very rarely utilized (8-10,22). The incidence of adverse effects appears to be higher for NS prescriptions that adhere to APA *versus* NICE/SMHC guidelines. This may be because the former support nasogastric tube feeding in patients who do not acknowledge their disease, refuse oral intake, or feel guilty when eating (9). Force-feeding with nasogastric tube has been associated with more frequent adverse effects in anorexic patients (24).

NICE/SMHC adherence was associated with a significant reduction in NS-related costs, mainly due to the shorter hospital stay. Enteral nutrition formulas were more frequently administered to patients with a greater degree of malnutrition at admission, who represented a higher proportion of the NICE/SMHC "non-adherence" than "adherence" group, increasing costs in the former.

One strength of this study was the setting of an EDU in which an AN-specific multimodal treatment program is provided; these patients are frequently admitted to general or psychiatric hospitals, in which multiple factors can influence treatment effectiveness. Study limitations include its retrospective design and the lack of randomization. Moreover, clinical records were used as the main source of information, and possible under-recording cannot be ruled out.

## CONCLUSIONS

NS prescriptions for anorexic patients showed a higher degree of adherence to NICE/SMHC than APA recommendations. APA adherence was associated with improved weight gain during hospitalization but only over the short term. Patients whose NS prescriptions followed all NICE/SMHC recommendations had shorter hospital stay and reduced costs, likely due to their more favorable nutritional status at admission.

## ACKNOWLEDGEMENTS

The authors thank Amanda Rocío González Ramírez for her assistance with the statistical analysis, Richard Davies for the translation into English, and the Clinical Documentation Department and Medical Library of the hospital for their collaboration. They are also grateful to the Doctoral Program in Pharmacy of the University of Granada for supporting the PhD thesis of the first author (María del Mar Alañón Pardo), entitled "*Evaluation of pharmacotherapy and nutritional support in patients with Eating Behavior Disorders*", whose results are in part reported in the present article.

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