



Comorbidity Between Anorexia Nervosa and Depressive Disorder: A Narrative Review

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Objective Anorexia nervosa (AN) is a disorder with a significantly high prevalence. Affective disorders, including depressive disorder (DD), often coexist with this eating disorder (ED). In this review we will focus on its prevalence, associated vulnerability factors, clinical manifestations, possible etiological factors and its prognosis.

Methods A bibliographic search was carried out in the PubMed database selecting those articles that approached the subject of comorbidity between AN and DD. The search was limited to articles published from January 1990 to December 2021.

Results Of the 1891 abstracts reviewed, 33 studies met inclusion criteria. The prevalence of this comorbidity was extremely variable between studies, which exposed their heterogeneity. As to symptomatology this comorbidity presents itself with more severity, greater expression of psychological traits and greater cognitive impairment. Certain personality traits are postulated as vulnerability factors. Genetic factors such as neurochemicals seem to be involved in its pathogenesis.

Conclusion The comorbidity between DD and ED have important influence in its symptomatic expression, severity and prognosis. Some of the analyzed studies provide consistent data, but there are others that are contradictory. It would be necessary to increase the number of studies and use a unified methodology.

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Keywords Anorexia nervosa; Depressive disorder; Comorbidity; Narrative review.

INTRODUCTION

In recent years eating disorder (ED) and specifically anorexia nervosa (AN) have seen an increased both in their incidence as in their prevalence. These disorders have gone from being an epidemic limited to developed countries to becoming a pandemic as a result of the globalization of ideas and customs. We are faced with one of the most frequent pathological entities. Its incidence varies between 1%–10% depending on the culture. Its significances lie in its severity, as it is one of the ten most frequent causes of disability in women¹ and considered the mental disorder with the highest mortality rate.² This is

mainly due to the medical complications derived from malnutrition and its high suicide rate.

AN may present itself with various complications including those associated with family, physical and psychiatric symptoms that will affect its prognosis. Affective disorders are some of the most frequent psychiatric complications amongst which depressive disorder (DD) is of distinctive relevance and the object of our study. It has been postulated that the presence of depressive symptomatology in AN could be directly correlated to the severity of weight loss. Although this hypothesis does not account for every case of depression in AN, it does seem to explain a large proportion of them. We are faced with one of the most frequent pathological entities, so it is very important to identify it as soon as possible in order to improve the prognosis and therapeutic response in patients with AN.

Given the frequent association between AN and DD, it is essential to question how this relationship is established. In this regard, two types of hypotheses have been developed. The first one speaks of a genetic and/or experiential predisposition that would lead to the development of a DD. Suffering from a

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depressive state creates feelings of low self-esteem and greater self-criticism as well as a worsening of the self-image, which in turn would act as vulnerability factors for the appearance of an ED.³ The second of these hypotheses raises the possibility that an ED can appear in people without prior disposition for the development of an affective disorder. In this hypothesis, AN would develop in people with certain predisposing psychological factors that are subject to environmental risk factors. Once the ED has been established, the anorexic condition presents biological and cognitive-emotional characteristics that lead to the appearance of a concomitant DD.

We have conducted a narrative review to provide an up-to-date summary of the scientific evidence on the comorbidity between AN and DD, in order to clarify how these two entities are associated. The study population was those subjects who fulfilled the criteria for diagnosing AN and associated the presence of depressive symptoms. The intervention was to study the prevalence, prognosis, vulnerability and etiopathogenia of both comorbid entities, with the aim of seeing how both entities influence each other, compared to subjects in whom such comorbidity does not occur. Currently, our study takes on greater importance, given the significant increase in cases of AN that have arisen as a result of the COVID-19 pandemic, cases that stand out for their greater severity, which is why it is common for them to present greater comorbidity with depressive symptoms.^{4,5}

METHODS

Legibility criteria

The selected studies, dealt specifically with AN and its comorbidity with DD. Both longitudinal and cross-sectional studies were included, in the form of clinical trials, field studies or review articles. The inclusion criteria were the following: 1) diagnostic criteria for AN in International Classification of Dis-

eases-10, Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, DSM-IV, DSM-IV-R or DSM-5, 2) English published articles, 3) articles published between January 1990 and December 2021. The references of eligible articles were checked for any additional study not previously identified. All articles dealing with general ED without showing individualized results for AN were excluded. Clinical cases were also excluded, as well as those articles that did not deal with the previously mentioned items, such as prevalence, clinical features, vulnerability factors, etiopathogenesis, and prognosis.

Information sources and search

Studies were identified by searching the electronic database PubMed and Web of Science up to until the end of December 2021. The search criteria used were the following: Title: (depression) AND Title: (anorexia nervosa) OR Title: (depressive disorder) AND Title: (anorexia nervosa) OR Title (depressive symptoms) AND (anorexia nervosa).

Study selection

Screening and selection of articles is displayed in Figure 1. Where titles of articles appeared relevant, abstracts were screened for eligibility, and full texts of potentially eligible studies were then retrieved. Any full texts that did not meet full eligibility criteria were excluded from the review.

Data collection

Independent study searches were carried out by two authors (MPCR and MINP). The selected articles were then classified according to the main subject at study: prevalence, clinical features, etiopathogenesis, and prognosis.

Synthesis of results

Studies were grouped by the main subject at study: three

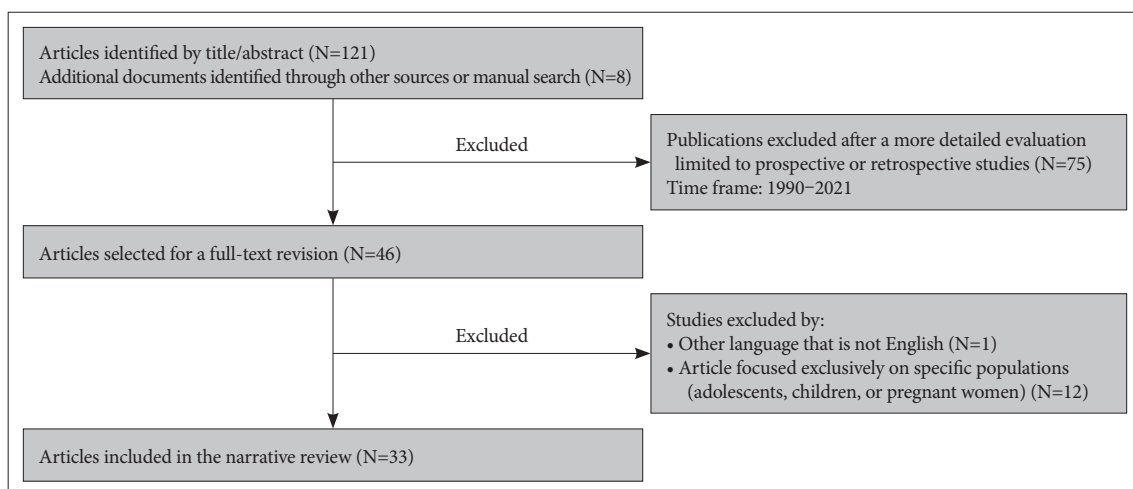


Figure 1. Flow chart of the article selection process.

prevalence articles, nine clinical manifestations articles, two vulnerability articles, ten etiopathogenesis articles, and finally seven prognosis articles.

RESULTS

Prevalence

The results found in relation to the prevalence of AN and DD's comorbidity are dissimilar, resulting from the heterogeneity of the different studies. It is worth mentioning that in recent years there has been a lack of studies focusing on prevalence (Table 1). Due to the great heterogeneity of the methodology used in the studies and of the samples analyzed, we have found a great variability in the prevalence between both pathologies, ranging from 36% to 80%.^{6,7}

Finally, in a recent analysis on psychopathology and psychiatric symptoms observed in patients with AN, it was noted that depression was one of the symptoms with the highest prevalence score.⁸

Clinical features

Regarding clinical features, several studies have reflected that patients with AN and comorbid DD have a higher severity of eating symptoms (Table 2).^{9,10} Furthermore, the Eating Disorder Inventory (EDI) scale scores vary significantly depending on the severity of the depressive symptoms.¹⁰ In addition, it has been observed that patients with comorbid depression present a greater number of suicides attempts^{9,11} higher hospitalization rates⁹ and greater physical complications such as an increased risk of long-term osteoporosis¹² than those without this comorbidity.

Alexithymia is a term used to designate a difficulty in identifying and expressing emotions. It has been noted that patients with AN have higher levels of alexithymia than those of the general population. It is considered a characteristic feature in patients with this diagnosis. In the present review, several studies have been identified that focus on the investigation of how depressive symptomatology influences the expression of alexithymia in AN. A study of 160 women (80 with AN diagnosis

and 80 controls), studied the presence of alexithymia based on several variables. The study concluded that the variable that best explained the variation in alexithymia was depression.¹³ This points to the fact that the severity of depression would probably be related to a higher degree of alexithymia in patients with AN.

Another article aimed to study alexithymia's relationship with ED based on the presence of depressive symptomatology as well as axis II psychopathology. For this they used the Toronto Alexithymia Scale (TAS) finding statistically significant differences with one of the factors that forms the scale: "difficulty in expressing emotions." Higher scores were noted among patients with AN compared to patients with BN as well as compared to the control group.¹⁴ Likewise, the severity of the depression as well as an avoidant personality was the variables that were most associated with alexithymia.¹⁴ Finally, in patients with AN, higher levels of both depressive symptomatology and alexithymia were found when compared to control groups.^{14,15}

Other concepts, such as concern for weight loss and body image as well as self-esteem, were also the main focus of various researchers. Thus, in a study conducted on 60 patients (19 with AN, 20 with food restriction and 21 controls), it was perceived that patients with AN had a greater body image concern and lower self-esteem than patients who only had a restrictive diet.¹⁶ These statistically significant results were correlated to the presence of concomitant DD, since once the depressive symptomatology was controlled, these significant differences found between both groups tended to disappear.¹⁶

DDs usually co-exist with cognitive, physical, emotional and functional alterations. One of the most prevalent and important alterations are cognitive dysfunctions which can be observed in the comorbidity between AN and DD. A review including 62 studies intended to approach this matter by evaluating the impact of depressive symptoms on cognitive flexibility, coherence and decision-making capacity in individuals diagnosed with AN. Statistically significant differences were observed in 48% of the studies when approaching neurocognitive alterations and depressive symptomatology in these patients. This leads to show that the greater the severity of the depressive

Table 1. Studies on the prevalence of AN and depression

Study	Sample	Diagnostic criteria/evaluation	Results of OR and prevalence of depression
Solmi et al., 2019 ⁹	955 patients with AN diagnosis (631 with RAN and 324 with PAN)	SCL-90/EDI/Tridimensional Personality Questionnaire	OR for PAN (1.19–1.35) and OR for RAN (1.15–1.51)
Godart et al., 2015 ⁶	271 patients with ED (AN and BN)	MINI (DSM-IV-Version)	80% prevalence of depression in AN
García-Alba., 2004 ⁷	150 subjects (50 with RAN, 50 MDD and 50 C)	Rorschach Test/MMPI	36% prevalence of depressive symptoms in AN

AN, anorexia nervosa; BN, bulimia nervosa; C, controls; ED, eating disorder; MDD, major depressive disorder; MINI, Mini International Neuropsychiatric Interview; MMPI, Minnesota Multiphasic Personality Inventory; OR, odds ratio; PAN, purgative anorexia nervosa; RAN, restrictive anorexia nervosa; SCL-90, Symptom Check-List-90; EDI, Eating Disorder Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders

Table 2. Studies on comorbidity between AN and depression clinical features

Study	Sample	Diagnostic criteria/evaluation	Results of eating behaviour disorder
Abbate-Daga et al., 2015 ¹⁷	Revision of 62 articles	Wisconsin Card Sorting Test, the Trail Making Task parts A and B, the Brixton Test, the Rey-Osterrieth Complex Figure Test and/or Iowa Gambling Task	Significant relationship between the degree of depression and the degree of cognitive impairment in patients with AN
Torres et al., 2015 ¹³	160 subjects (80 with AN and 80 C)	TAS-20/SDS	The greater the severity of depression is associated with a greater degree of alexithymia in AN
Brand-Gothelf et al., 2014 ⁹	88 patients with AN	EDI-2	The greater the severity of the eating behaviour, the greater the risk of suicide attempt and the greater the number of hospitalizations
Lulé et al., 2014 ¹⁵	30 women (15 with AN and 15 C)	WISC/EDQ/EDI-2/YSR/CBCL/BDI-II/STAI/TAS-20/SPF	Higher degree of alexithymia in AN than in control group
Wildes et al., 2007 ¹¹	50 patients with AN	Mood Spectrum Self-Report	The greater the severity of depressive symptoms is associated with a higher risk of suicide attempt
Konstantynowicz et al., 2005 ¹²	45 patients with AN (14 with depressive symptomatology)	HRSD/MADRS	Comorbidity entails a higher risk of osteoporosis
Wilksch and Wade, 2004 ¹⁶	60 women (19 with AN, 20 RE and 21 C)	CES-D/EDE-Q/SSPA	Subjects with AN have greater concern for body silhouette and lower self-esteem than RE in the presence of depressive symptoms
Bizeul et al., 2003 ¹⁰	193 patients with AN (55 with severe depression, 77 with moderate depression and 32 with mild depression)	EDI/BDI	The greater the severity of depressive symptoms the greater the severity of eating behaviours
Sexton et al., 1998 ¹⁴	53 with ED and 14 C	TAS/BDI/SCID	Alexithymia scores higher in RAN. Alexithymia presents a strong association with the severity of the depression and avoidant personality

AN, anorexia nervosa; BDI, Beck Depression Inventory; BN, bulimia nervosa; C, controls; CBCL, Child Behaviour Checklist; CES-D, Center for Epidemiological Studies Depression Scale; ED, eating disorder; EDI, Eating Disorder Inventory; EDQ, Eating Disorder Questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; HRSD, Hamilton Rating Scales for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; SCID, Structured Clinical Interviews for DSM-III-R; SDS, Zung-Self Rating Depression Scale; SSPA, Self-Perception Profile for Adolescents; STAI, State-Trait Anxiety Inventory; SPF, Saarbrücker Persönlichkeitsfragebogen; RE, restrictive eaters; TAS, Toronto Alexithymia Scale; YSR: Youth Self Report; WISC, Wechsler Intelligence Scale for Children

symptoms, the higher neurocognitive deterioration.¹⁷

Vulnerability factors

Several investigations have noted how specific personality and character aspects can act as vulnerability factors in the comorbidity between AN and DD (Table 3).

Alexithymia would also act as a vulnerability factor for comorbidity between AN and DDs. Patients with associated AN and DD were found to score higher in the Difficulty in Describing Emotions factor of the TAS as well as presenting higher levels of dependence and self-criticism.¹⁸

Body image distortion is one of the nuclear symptoms of AN. A study conducted on a sample of 242 patients with AN between the ages of 18 and 56, studied the relationship between body image distortion's severity and the appearance of depressive symptoms throughout the treatment. The results found that the degree of body image distortion in early stages would predict the appearance of depressive symptomatology throughout the course of the disorder. Moreover, it was noted that the maintenance of this distortion even after an increase in the body mass index (BMI), which would therefore be considered a good evolution, acted as a factor for the presence of depres-

sive symptomatology.¹⁹ Thus the persistence of body image distortion acts as a vulnerability factor for the appearance of comorbid DD.

Etiopathogenia

Focusing on the underlying causes behind AN and DD's strong association, many authors have pointed out that genetics may play an important role (Table 4). Thus a 58% of heri-

Table 3. Studies on vulnerability factors in comorbidity between AN and depressive disorder

Study	Sample	Diagnostic criteria/evaluation	Results of eating behaviour disorder
Junne et al., 2016 ¹⁹	242 women with AN	CBT-E, FPT	Body image distortion in AN is associated with symptoms of anxiety and depression in all stages of the treatment
Speranza et al., 2005 ¹⁸	531 subjects (105 with RAN, 49 with PAN, 98 with BN and 279 C)	TAS-20, BDI, DEQ	Subjects with RAN present greater difficulty to describe feelings and greater self-criticism

AN, anorexia nervosa; BDI, Beck Depression Inventory; BN, bulimia nervosa; CBT-E, enhanced cognitive behavioural therapy; C, controls; DEQ, Disordered Eating Questionnaire; FPT, focal psychodynamic therapy; PAN, purgative anorexia nervosa; RAN, restrictive anorexia nervosa; TAS, Toronto Alexithymia Scale

Table 4. Studies on the etiopathogenesis of the comorbidity between AN and depressive disorder

Study	Sample	Diagnostic criteria/evaluation	Results of eating behaviour disorder
Boehm et al., 2018 ²⁴	130 subjects (35 with severe AN, 33 recovered from AN, 62 C)	Self-reports in which depressive and anhedonia symptoms were collected	No direct relationship between BMI and depression in AN. Anhedonia in AN is not related to depression
Thornton et al., 2016 ²¹	6,899 women from the Swedish study in twin adults	SCID-I	Shared genetic factors were observed for AN, depression and suicide risk
Lawson et al., 2013 ²⁵	35 women (13 with AN, 9 recovered from AN and 13 C)	STAI, BDI-II/DSM-IV-TR	Abnormal postprandial secretion of oxytocin is associated with anxiety and depression in AN
Mattar et al., 2012 ²²	24 women with AN	BMI, Y-BOCS/DSM-IV	Anxiety symptoms and depression improve with nutritional rehabilitation in AN. However, they are not directly related to the BMI
Mattar et al., 2011 ²³	Revision of 7 studies on AN, depression, anxiety and malnutrition	BMI, Y-BOCS/DSM-IV	Contradictory results were observed in the relationship between malnutrition, and anxiety and depression in AN
Lawson et al., 2009 ²⁶	52 women (21 C, 13 with hypothalamic amenorrhea and 18 with AN and amenorrhea)	HRSA/HRSD	Higher levels of cortisol were found in patients with AN. Higher levels of cortisol were positively associated with depression and anxiety
Miller et al., 2007 ²⁷	43 subjects with AN	HRSA/HRSD	Lower testosterone levels were associated with anxiety and depression in AN
Wade et al., 2000 ²⁰	2,163 twin women (including 1,030 twin partners)	DSM-III-R structured clinical interview for anorectic and depressive symptoms	AN has a heritability of 58%. Genetic factors would be involved in the comorbidity between AN and depression
Berk et al., 1997 ²⁹	12 patients with AN, 11 patients with BN and 17 C	HRSD	Patients with AN and depressive comorbidity, have an increased response to intracellular calcium, which is related to depression
Schweitzer et al., 1990 ²⁸	20 subjects with AN	Dexamethasone suppression test	50% of the sample obtained an abnormal response in the dexamethasone suppression test. No relationship was found with weight. Higher scores in depression were found in those with an abnormal response

AN, anorexia nervosa; BN, bulimia nervosa; BDI, Beck Depression Inventory; BMI, body mass index; C, controls; HRSA, Hamilton Rating Scales for Anxiety; HRSD, Hamilton Rating Scales for Depression; SCID-I, Structured Clinical Interviews for DSM-IV; STAI, State-Trait Anxiety Inventory; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised

tability was observed in a sample of 2,163 twins with AN.²⁰ This same study mentioned that the comorbidity between AN and DD is probably due to genetic factors that influence the risk of occurrence of both disorders.²⁰ It has also been noted that both disorders would share common genes with the presence of a higher risk of suicide.²¹

One of the main theories of the aetiology behind AN and DD's comorbidity is its association with malnutrition. Thus, in a prospective study, it was pointed out that some of the depressive and anxious symptoms observed in patients with AN were partially reduced after nutritional rehabilitation.²² However, it failed to find a direct association between the psychometric scales and the BMI modification.²² In this regard, a review analyzed seven studies that dealt with malnutrition's role in the appearance of depressive features in AN with contradictory and inconsistent results.²³ On the other hand, a recent study suggests that depressive symptoms found in AN are related to malnutrition, with a negative association between the BMI and depressive symptoms in acute patients.²⁴

Moreover, several studies have suggested that the etiopathogenesis of the comorbidity between AN and DD could be mediated by the existence of both endocrine and neurochemical factors.

A recent study carried over 35 women of which 13 had been diagnosed with AN, studied its association with oxytocin. The study concluded that the abnormal secretion of postprandial oxytocin in patients with AN was associated with a greater severity of anxiety and depressive symptoms. Thus, oxytocin secretion was able to explain up to 24% of the variation in the Beck Depression Inventory-II.²⁵ Another study chose to observe the association between cortisol levels in AN, hypothalamic amenorrhea and its association with the presence of affective disorders and bone density levels. The results showed that patients with AN had higher scores in depression and anxiety and higher cortisol levels than patients with functional hypothalamic amenorrhea.²⁶ Cortisol levels were positively related to anxiety and depression scores and negatively so to bone density levels. Therefore, this study suggests that hypercortisolemia could act as a mediator in the appearance of affective symptoms and low bone density in patients with AN.²⁶ Continuing with endocrinology, another study focused on androgen levels and its association with depressive and anxious symptoms in patients with AN. Low androgen levels have been linked to affective and behavioral alterations. Thus, it was found that testosterone levels were inversely related to the severity of anxiety and depressive symptoms, as well as the presence of thoughts and behaviors related to this ED.²⁷ Lastly, one final article sought to study the test results of dexamethasone suppression in a sample of 20 patients with AN and its relationship with various parameters. Half of these patients initial-

ly presented an altered dexamethasone suppression test that was not related to the percentage of weight loss. However, it was associated with a higher percentage of depressive symptoms.²⁸

Several research have studied the possible role of serotonin on the neurochemical factors involved in the pathogenesis between AN and DD. It was noted that those patients with AN and associated depressive symptomatology had an intracellular calcium increase in response to serotonin that was not observed in those patients with AN who scored low on depression scales. Thus, this serotonergic dysregulation appeared to a common trait, understanding that it could be mediated not so much by the ED as it would be by the affective disorder.²⁹

Prognosis of the comorbidity

Regarding the evolution of depressive symptomatology in patients with AN, it seems that patients that have recovered from long-term AN have higher depression levels than those who have never suffered from an ED³⁰ (Table 5). The relationship between nutritional recovery and improvement of depressive symptoms is contradictory, and some studies point to improvement of depressive symptoms with weight gain;³¹ however, others suggest that they are not statistically significant.³²

Additionally, recovering from these depressive symptoms is highly related to the ED's subtype, with restrictive AN bearing the worst prognosis.³³ However, despite weight restoration, anxious and depressive symptoms can remain mild or moderate in subjects who have suffered from AN, which could mean that these symptoms are indeed linked to AN's pathogenesis.³¹

Focusing on the role of depressive symptomatology in AN's evolution, it has been noticed that the presence of onset depressive symptoms³¹ does not act as a prognostic indicator.³⁴ However, the persistence of depressive symptomatology throughout the follow-up of AN is firmly associated with its evolution.³⁴⁻³⁶ Likewise, another study carried on AN hospitalized patients observed that depressive symptoms during the disease's onset did not predict the results of the treatment; however, higher relapse rates were observed in those hospitalized patients who presented depressive symptomatology after one month of hospital admission.³⁵

DISCUSSION

Prevalence

In regard to the prevalence of this comorbidity, the first thing that attracts our attention is the lack of studies that have been carried out in recent years in order to determine its prevalence. Furthermore, the prevalence figures are very disparate ranging from 36% to 80%, thus it is difficult to establish an average prevalence.

The reason of this disparity could be the heterogeneity of

Table 5. Studies on prognosis in the comorbidity between AN and depressive disorder

Study	Sample	Diagnostic criteria/evaluation	Results
Carretier et al., 2021 ³²	Eight studies dealing with 10–18 year old inpatient or outpatient adolescents presenting an AN complicated by a major depressive disorder	DSM-5	There is a need to identify faster severe depressive disorders in adolescents with AN in order to provide a more intensive treatment of mood symptoms
Kahn et al., 2019 ³⁵	56 patients with AN	EDE/BSI	During hospitalization depression in AN has not an association with a bad prognosis. If depressive symptoms persist beyond 1 month during hospitalization the risk of relapsing back to AN is higher
Mischoulon et al., 2011 ³³	51 patients with RAN, 85 with PAN and 110 with BN	LIFE-EAT-II	A higher severity in depression was noted in RAN
Holtkamp et al., 2005 ³⁰	39 patients with AN and 39 C	BMI	Patients with anxiety, depression and obsessive symptoms scored higher than those with just AN
Pollice et al., 1997 ³¹	Women with AN in different stages (low weight, short-term weight restoration and long-term weight restoration) are compared with a group of healthy women	BDI/HRSD/STAI/Y-BOCS	Malnutrition aggravates anxiety-depressive and obsessive symptoms. Anxious-depressive symptoms persist mildly or moderately in AN and could be related to their pathogenesis
Herpertz-Dahlmann et al., 1995 ³⁴	34 patients with AN	HRSD/SDS	Depression at the start of AN holds no association with its prognosis. Throughout the follow-up, a statistically significant relationship was observed between depression and AN prognosis

AN, anorexia nervosa; BN, bulimia nervosa; BDI, Beck Depression Inventory; BMI, body mass index; BSI, Brief Symptom Inventory; C, controls; EDE, Eating Disorder Examination; HRSD, Hamilton Rating Scales for Depression; LIFE-EAT-II, Eating Disorders Longitudinal Interval Follow-up Evaluation; PAN, purgative anorexia nervosa; RAN, restrictive anorexia nervosa; SDS, Zung-Self Rating Depression Scale; STAI, State and Trait Anxiety Inventory; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

the studies. Furthermore, the scales and measuring instruments used for the assessment of depressive symptomatology were not homogeneous. However, despite these dissimilarities, final results seem to point to a considerable prevalence of this comorbidity. Therefore, the detection of depressive symptoms in patients with AN is of great importance for both its treatment and its prognosis. In recent years, given the impact of COVID-19 on AN cases,^{4,5} more studies will be needed to establish the current prevalence of this comorbidity.

Clinical manifestations

Regarding clinical manifestations, the studied articles confirm that certain character traits are closely linked to AN and, in short, to those with comorbid depressive symptoms.

Thus, depressive symptoms would act as modulators of alexithymia's severity degree in patients with AN.^{13,14} Ultimately, we can state that the comorbidity under study leads to an aggravation of those psychological factors that have been classically related to AN.

In scientific literature it is pointed out that both DD and

ED present somatic, cognitive and functional complications, amongst other symptoms. Many studies to this date suggest that depressive symptoms significantly influence the aggravation of neurocognitive alterations in patients with AN.¹⁷ Studies on cognition in AN adjusted for depressive symptoms are scarce, however, given the role of depression in neurocognition that many articles suggest, it would be of great clinical utility to explore the presence of comorbid depressive symptoms in patients with AN and marked alterations in the cognitive spheres.

Vulnerability factors

The reviewed articles suggest that the main vulnerability factors for the development of a comorbid DD in patients with AN are those associated with personality traits and certain psychological features of the patients in question.

Among personality traits, self-direction, harm avoidance, self-criticism or dependence are factors that have classically been related to an emotional disorder of the depressive pole. Likewise, these traits have also been associated to restrictive AN so they appear to be common features for both disorders.³⁷

If we focus on the above-mentioned hypotheses, we can establish an association between the existence of an ED and a comorbid DD. Thus, in the first hypothesis, it was pointed out that biological and/or experiential factors would contribute to the appearance of a DD. The presence of depression would produce a worsening of body image as well as greater self-criticism, both which would in turn act as vulnerability factors for the development of a comorbid ED.^{18,19} The research that we have found points to the confirmation of this hypothesis. However, the temporal sequence of both disorders still has not been established, which means that which of these disorders would act as a predisposing agent for the other one cannot be established yet.³⁸

Etiopathogenia

Regarding the role of genetics, studies have pointed to the existence of genetic factors that increase the risk of both AN and DD.^{20,21} However, these studies only provide approximate data, so we are far from determining exactly which genetic factors are involved.

As to the role of malnutrition as a causal element of the appearance of depressive symptomatology in patients with AN, the results seem to be contradictory. As noted in the scientific literature, although many depressive symptoms can be explained by weight loss, it cannot explain every case of comorbidity between AN and DD.²³

Finally, studies suggest that the cause of this frequent association could rely on biological factors. However, most results are not too specific. For example, there seem to be higher plasma levels of cortisol in AN as well as in patients with associated depressive and/or anxious symptoms.²⁶ However, cortisol levels are increased in any given situation that causes stress, so such finding would lack specificity. Regarding the dexamethasone suppression test, there existed a limitation of the sample size ($n=20$), so conclusive results cannot be obtained. However, previous studies point to a close relationship between non-suppression and low weight, which in turn was related to the appearance of greater depressive symptomatology.²⁸

Prognosis of this comorbidity

Depressive symptomatology seems to be related to the severity of the eating symptoms, being more severe among restrictive disorders and improving with weight gain. However, regarding ED's evolution and its association with depressive symptomatology, most of the reviewed studies suggest depressive symptoms do not condition the final outcome of the treatment. The only exception would be the presence of depressive symptomatology after one month's hospitalization which would be related to the appearance of greater depressive symptoms.³⁵ Therefore, it seems that the influence of both disorders is not

clearly bidirectional.

Finally, it should be noted that the majority of studies present in this review have a cross-sectional design and of great heterogeneity, which makes it difficult not only to establish causal relationships, but also to compare the results.

Limitations

The main limitation of this article is that it has not been possible to perform a meta-analysis that would provide more scientific evidence, due to the heterogeneity in the methodology of the articles included, as well as the diversity of variables that have been analysed.

Conclusions

Affective disorders and among them DD constitute one of the main comorbid disorders of AN. This is due both to its prevalence and to its influence over the symptomatic expression and evolution of AN. Throughout this article, relevant data has been found that points to a symptomatic aggravation, to the existence of vulnerability factors and to common etiopathogenic pathways. However, this bibliography is not exempt from some contradictory data.

This may be due to the fact that a large part of the studies we have worked with generalized depressive symptomatology instead of making it specific for DD.

Availability of Data and Material

All the data are extracted from the articles reviewed.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Maria Pilar Calvo-Rivera, Luis Gutiérrez-Rojas. Data curation: all authors. Formal analysis: Maria Pilar Calvo-Rivera, Luis Gutiérrez-Rojas. Investigation: Maria Pilar Calvo-Rivera. Methodology: Maria Pilar Calvo-Rivera, Luis Gutiérrez-Rojas. Project administration: Luis Gutiérrez-Rojas. Resources: Maria Pilar Calvo-Rivera. Software: Luis Gutiérrez-Rojas. Supervision: Luis Gutiérrez-Rojas. Validation: Maria Isabel Navarrete-Páez, IB. Visualization: Luis Gutiérrez-Rojas. Writing—original draft: Maria Pilar Calvo-Rivera, Luis Gutiérrez-Rojas. Writing—review & editing: all authors.

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