

Association of depressive symptoms with health status and markers of uncontrolled severe asthma

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ABSTRACT

Background: There are limited data that describe the association between markers of asthma control and depressive symptoms in severe asthma.

Objective: To evaluate the association between depressive symptoms and markers of asthma control in patients with uncontrolled severe eosinophilic asthma.

Methods: Baseline data from the MENSA and SIRIUS studies (N = 681) of mepolizumab intervention in severe eosinophilic asthma was used. We analyzed the relationships between depressive symptom severity by using the Beck Depression Inventory (BDI-II) and quality of life by using the St. George's Respiratory Questionnaire (SGRQ), asthma control questionnaire-5 (ACQ-5), polypharmacy, and sleep symptoms.

Results: When compared with patients with less severe depressive symptoms, patients with more severe depressive symptoms were predominantly female (81% versus 54%), had a higher mean body mass index (30.56 versus 27.67 kg/m²), were more likely to have a blood eosinophil count of ≥ 300 cells/uL within the previous 12 months (81% versus 68%), and to have experienced a near-fatal asthma event (16% versus 7%). The mean SGRQ score was higher in the severe BDI-II category compared with the minimal depressive symptoms category, which indicated a worse quality of life (71.6 versus 41.4, $p < 0.001$). Eighty-nine percent of the patients in the severe BDI-II category had poorly controlled asthma (ACQ-5 score ≥ 1.5) compared with 63% in the minimal category ($p < 0.001$).

Conclusion: Increased severity of depressive symptoms was associated with worse respiratory-related quality of life and asthma control in the patients with severe eosinophilic asthma. These findings highlight the need for a multidimensional approach for the management of uncontrolled asthma, including timely identification of depressive symptoms. Additional research is needed to further explore the interactions between the two common conditions.

Clinical trials NCT01691521 and NCT01619508, www.clinicaltrials.gov.

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Severe asthma is a complex heterogeneous disease that requires a structured and multidimensional approach to management.¹ An effective as-

essment and intervention strategy needs to focus on four key domains: behavioral modification, mitigation of risk factors, optimization of pharmacotherapy, and management of comorbidities. Depression is an important comorbidity in asthma, with a higher prevalence in patients with asthma compared with healthy controls.^{2,3} According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition⁴ depressive disorders include disruptive mood dysregulation, major depressive disorder, dysthymia, or substance and/or medication induced, or due to other medical condition. Common features are the presence of a sad, empty, or irritable mood as well as cognitive and somatic changes that significantly impact an individual's capacity to function. Major depressive disorder is characterized by discrete episodes of daily de-

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pressed mood or loss of interest or pleasure in nearly all activities, which lasts at least 2 weeks. Depressive symptoms can cause clinically significant distress or impairment.

The prevalence of asthma is also higher in patients with depression, as reported across multiple populations, which suggests a bidirectional relationship.^{1,2} Several longitudinal studies observed that depression increases the risk of incident asthma.^{3,5–7} A large study, of >85,000 people across 17 countries, found an age- and gender-adjusted odds ratio of 1.6 (95% confidence interval [CI], 1.4–1.7) for depressive disorders in persons with asthma relative to those without asthma.⁸ Similarly, a prospective analysis reported a 24% increased risk of asthma with each one standard deviation increase in depressive symptoms on the von Zerssen depression scale.⁹ Patients with severe asthma seem to have more depressive symptoms compared with patients with nonsevere asthma.^{10–12} Results of studies found significantly higher concentrations of certain cytokines (interleukin [IL] 1, IL-4, IL-5, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor, interferon alpha, and tumor necrosis factor alpha) in patients with depression compared with controls who were not depressed, which raised the possibility that inflammatory mechanisms could provide common pathways for both depression and asthma.^{13,14}

Although there are published data on the association between depressive symptoms and asthma, to our knowledge, the relationship with health status and markers of asthma control in patients with well-characterized severe eosinophilic asthma has not been previously described. We presented here a pooled analysis of the relationship between depressive symptomatology and baseline asthma characteristics in patients from two previously reported studies that evaluated efficacy of mepolizumab, a novel anti-IL-5 monoclonal antibody, in patients with severe eosinophilic asthma.^{15,16} We hypothesized that more-severe depressive symptoms are associated with worse health status and asthma control in this population.

METHODS

Patients

For this analysis (GSK study number 209030), we included two previously reported studies: MENSA and SIRIUS.^{15,16} The MENSA study was a placebo-controlled double-dummy randomized study of mepolizumab administration for 32 weeks (NCT01691521).¹⁶ The SIRIUS study was a placebo-controlled randomized study of mepolizumab administration for 24 weeks (NCT01619508).¹⁵ The patients had baseline treatment requirements of ≥ 880 μg of inhaled fluticasone propionate equivalent per day and required additional controller medication(s). In addition, all the patients who participated in

the SIRIUS study¹⁵ and 25% in the MENSA study¹⁶ were on maintenance daily systemic corticosteroids. Although patients ≥ 12 years of age were included in the original studies, this meta-analysis was limited to patients ≥ 18 years old. Additional details are available in previous publications.^{15,16} All the participants provided written informed consent. The original protocols were approved by local or study research ethics committees and were conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. Disease severity was consistent with the most recent European Respiratory Society/American Thoracic Society definition for severe asthma.¹⁷ Eosinophilic inflammation was defined as a blood eosinophil count of ≥ 150 cells/ μL at screening or ≥ 300 cells/ μL during the previous year.

Instruments

The Beck Depression Inventory (BDI) is a 21-item self-report questionnaire designed to assess depressive symptomatology.^{18,19} The second edition (BDI-II) was revised in 1996 to better align with the diagnostic criteria used in Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV).²⁰ The BDI-II provides cutoff scores for symptom severity: 0–13, minimal; 14–19, mild; 20–28, moderate; and 29–63, severe.^{18,19} In this report, we used the term depressive symptoms to define the primary outcome of this analysis.

The Asthma Control Questionnaire (ACQ-5) is a five-item self-completed questionnaire, which has been developed as a measure of patients' asthma control that can quickly and easily be completed in clinical practice.²¹ The five questions inquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, shortness of breath, wheeze) over the previous week. The response options for all these questions consist of 0 (no impairment/no symptoms) to 6 (total impairment/symptoms) scale. The questionnaire is scored from 0 to 6, with higher numbers indicating poorer control.²² A score of ≤ 0.75 strongly indicates that asthma is well controlled; a score of ≥ 1.5 indicates poorly controlled asthma.

The St. George's Respiratory Questionnaire (SGRQ) is a well-established instrument, composed of 50 questions designed to measure overall health, daily life, and perceived well-being in patients with obstructed airways diseases, including asthma.²³ The three SGRQ domains include the following: Symptoms, Activity, and Impacts. SGRQ scores are based on a scale of 0 to 100, with lower scores indicating better health status. The Medical Outcomes Study (MOS) sleep scale is a 12-item questionnaire that assesses several dimensions of sleep, including initiation, maintenance, adequacy, somnolence, and respiratory impairments. Lower scores indicate worse sleep quality.²⁴

Table 1 Demographic and baseline clinical characteristics from the MENSA and SIRIUS studies

Characteristics	MENSA Study (n = 548)	SIRIUS Study (n = 133)	Total (N = 681)
Age, mean $\pm$ SD, y	51.7 $\pm$ 12.43	50.4 $\pm$ 11.71	51.4 $\pm$ 12.29
Females, no. (%)	313 (57)	73 (55)	386 (57)
BMI, mean $\pm$ SD, kg/m ²	28.04 $\pm$ 5.79	28.67 $\pm$ 6.03	28.16 $\pm$ 5.84
Duration of asthma, mean $\pm$ SD, y	20.4 $\pm$ 13.96	18.8 $\pm$ 13.22	20.1 $\pm$ 13.82
No. asthma exacerbations within previous 12 mo, mean $\pm$ SD	3.6 $\pm$ 2.57	3.1 $\pm$ 3.11	3.5 $\pm$ 2.69
ACQ-5 score, mean $\pm$ SD	2.23 $\pm$ 1.207	2.07 $\pm$ 1.227	2.20 $\pm$ 1.212
SGRQ score, mean $\pm$ SD	46.8 $\pm$ 19.45	47.3 $\pm$ 18.23	46.9 $\pm$ 19.20
Proportion of patients with blood eosinophils $\geq$ 150 cells/ μ L at screening, no. (%)	457 (83)	119 (89)	576 (85)
Proportion of patients with blood eosinophils $\geq$ 300 cells/ μ L within previous 12 mo, no. (%)	379 (69)	90 (68)	469 (69)
Proportion of patients on OCS, no (%)	135 (25)	133 (100)	268 (39)
Dose, mean $\pm$ SD, mg/day	13.2 $\pm$ 11.98	12.8 $\pm$ 6.77	13.0 $\pm$ 9.73
FEV ₁ % predicted, mean $\pm$ SD	60.1 $\pm$ 17.53	58.5 $\pm$ 17.66	59.8 $\pm$ 17.55
% reversibility, mean $\pm$ SD	26.8 $\pm$ 21.09	25.9 $\pm$ 17.79	26.6 $\pm$ 20.48
SABA use within previous 12 mo, no. (%)	328 (60)	99 (74)	427 (63)
History of near-fatal asthma event within previous 12 mo, no. (%)	39 (7)	19 (14)	58 (9)

SD = standard deviation; BMI = body mass index; ACQ-5 = Asthma Control Questionnaire; SGRQ = The St. George's Respiratory Questionnaire; OCS = oral corticosteroid; FEV₁ = forced expiratory volume in 1 s; SABA = short-acting β agonist.

Statistical Analysis

This was a cross-sectional analysis that used baseline data collected before patients received the investigational product. A modified intent-to-treat population, defined as all patients $\geq$ 18 years of age at screening who were randomized and completed a baseline BDI-II assessment, was used for analysis. Data from the two studies^{15,16} and across treatment groups were pooled, and no comparison of treatments were made. Summary tables and plots were generated to characterize the relationship between baseline BDI-II measures and other variables of interest. SAS software was used (SAS Institute, Cary, NC) for all statistical analyses of the data. Statistical analyses were performed by using the Fisher exact test for categorical data and analysis of variance for continuous data. To assess the relationship between BDI-II scores and baseline characteristics, separate linear regression analyses of the BDI-II total score as a continuous variable against each of ACQ-5, body mass index (BMI), SGRQ total, symptoms, activity, and impacts scores were also carried out.

RESULTS

Demographic Characteristics

Of the 684 patients $\geq$ 18 years old randomized, 551 were from the MENSA study¹⁶ and 133 from the SIRIUS study.¹⁵ Of these, 681 (548 and 133, respectively) completed a baseline BDI-II questionnaire and formed the basis for this analysis. The demographic and baseline clinical characteristics from the MENSA and SIRIUS studies^{15,16} were similar (Table 1). The overall population was stratified by BDI-II scores into groups with minimal (score 0–13 [n = 495]), mild (score 14–19 [n = 91]), moderate (score 20–28 [n = 58]), and severe (score 29–63 [n = 37]) depressive symptoms. Compared with the BDI-II group with minimal symptoms, the patients in the BDI-II severe category were predominantly female (81% versus 54%), had a higher mean BMI (30.56 vs. 27.67 kg/m²), were more likely to have a blood eosinophil count in the previous 12 months of $\geq$ 300 cells/ μ L (81% versus 68%), and more likely to have experienced a near-fatal asthma event (16% versus 7%) (Tables 1 and 2). Regression analyses also

Table 2 Demographic and baseline clinical characteristics by BDI-II scores

Characteristics	BDI-II Score			
	Minimal (n = 495)*	Mild (n = 91)#	Moderate (n = 58)§	Severe (n = 37)¶
Age, mean ± SD, y	51.3 ± 12.69	52.1 ± 11.07	52.2 ± 0.81	50.8 ± 12.34
Females, no. (%)	265 (54)	55 (60)	36 (62)	30 (81)
BMI, mean ± SD, kg/m ²	27.67 ± 5.46	29.77 ± 6.61	28.32 ± 6.00	30.56 ± 7.32
Duration of asthma, mean ± SD, y	20.0 ± 13.75	19.3 ± 13.94	21.0 ± 14.57	22.0 ± 13.65
No. asthma exacerbations within previous 12 mo, mean ± SD	3.5 ± 2.73	3.7 ± 2.41	3.6 ± 2.37	3.8 ± 3.37
Proportion of patients with blood eosinophils ≥150 cells/μL at screening, no. (%)	422 (85)	73 (80)	51 (88)	30 (81)
Proportion of patients with blood eosinophils ≥ 300 cells/μL within previous 12 mo, no. (%)	335 (68)	59 (65)	45 (78)	30 (81)
Proportion of patients on OCS no. (%)	184 (37)	40 (44)	30 (52)	14 (38)
OCS dose, mean ± SD, mg/day	12.8 ± 10.12	14.0 ± 9.12	13.0 ± 9.55	12.9 ± 6.78
FEV ₁ % predicated, mean ± SD	60.3 ± 17.65	58.7 ± 17.50	56.0 ± 17.48	61.5 ± 16.24
% reversibility in FEV ₁ , mean ± SD	25.4 ± 19.22	32.1 ± 25.24	25.7 ± 21.34	32.2 ± 20.08
SABA use within the previous 12 mo, no. (%)	297 (60)	62 (68)	43 (74)	25 (68)
History of near-fatal asthma event within the previous 12 mo, no. (%)	37 (7)	11 (12)	4 (7)	6 (16)

BDI-II = Beck Depression Inventory second edition; BMI = body mass index; FEV₁ = forced expiratory volume in one second; OCS = oral corticosteroids; SABA = short acting β agonist; SD = standard deviation.

* Minimal, 0–13.

Mild, 14–19.

§ Moderate, 20–28.

¶ Severe, 29–63.

indicated that higher BDI-II scores were associated with higher BMI (coefficient, 0.220; $p < 0.001$; R^2 , 0.021). Lung function measures (forced expiratory volume in the first second of expiration percentage predicted and percentage bronchodilator reversibility) were similar across the four BDI-II categories.

ACQ

Asthma control was categorized based on ACQ-5 scores as well controlled (≤ 0.75), borderline controlled (> 0.75 to < 1.5), and poorly controlled (≥ 1.5). An association between depressive symptoms, as categorical and continuous variables, and asthma control was assessed within each ACQ-5 score category. The cumulative distribution of depressive symptoms by three categories of ACQ-5 score is shown in Fig. 1. Patients with an ACQ-5 score of ≥ 1.5 have quartiles of the BDI-II distribution higher than patients with an ACQ-5 score of < 1.5 , which indicated that worse asthma control is associated with more severe depressive symptoms. A similar observation that used individual data points is illustrated in Supplemental Fig. 1. Regression analysis also showed this association (coefficient, 2.826; $p <$

0.001; R^2 , 0.148). Eighty-nine percent of the patients in the severe BDI-II category had poorly controlled asthma (ACQ-5 score ≥ 1.5) compared with 63% in the minimal category, $p < 0.001$. When the ACQ-5 scores were analyzed across BDI-II categories, a higher proportion of patients with uncontrolled asthma (ACQ-5 score ≥ 1.5) clustered in the BDI-II moderate and severe (88% and 89%, respectively) categories compared with minimal and mild (63% and 81%, respectively) categories (Table 3). When we combined the BDI-II categories, 88% of the combined moderate-severe depressive symptoms group had uncontrolled asthma and 66% of the combined minimal-mild depressive symptoms group had uncontrolled asthma.

Asthma Quality of Life

Cumulative distribution of SGRQ scores across BDI-II subgroups are presented in Fig. 2, and a scatter plot with representation of individual data points is presented in Supplemental Fig. 2. Higher BDI-II scores were associated with higher SGRQ scores, which indicated poorer quality of life. The mean SGRQ score was higher in the severe BDI-II category

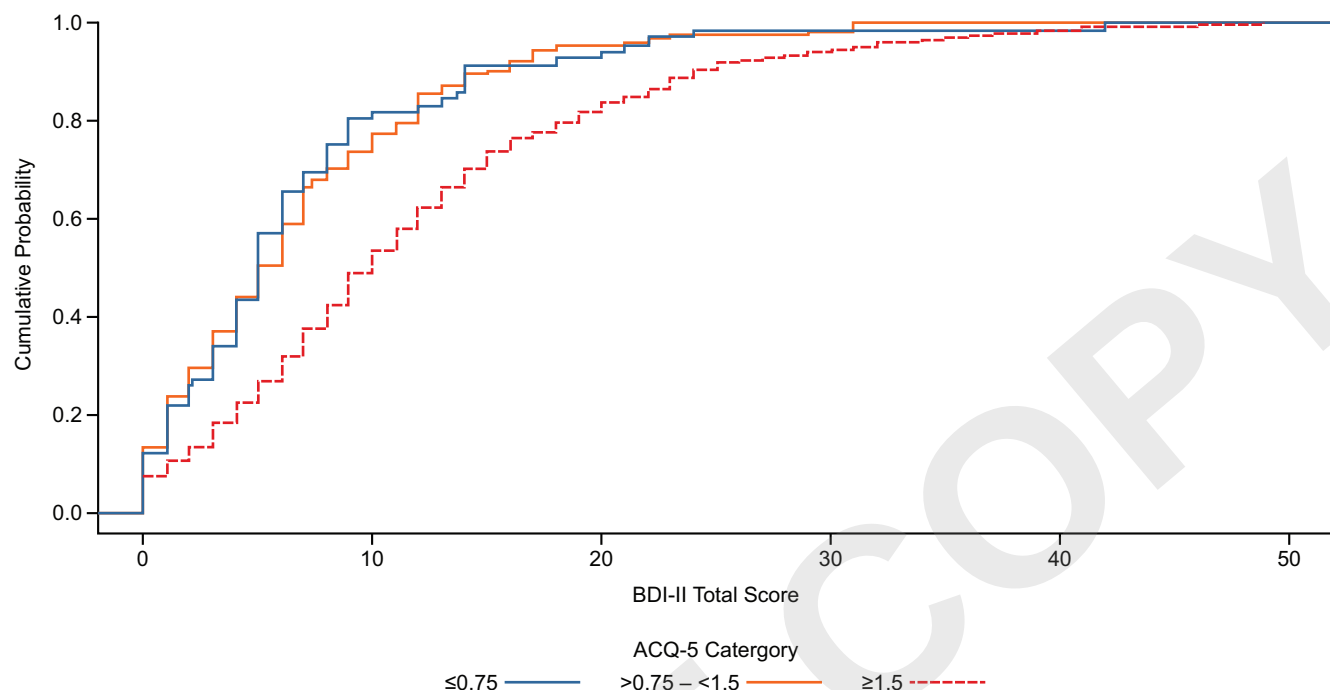


Figure 1. Cumulative distribution function of asthma control by using BDI-II scores. BDI-II = Beck Depression Inventory second edition; ACQ = Asthma Control Questionnaire.

Table 3 Characteristics of the ACQ-5 score categories by BDI-II subgroups

ACQ-5 Threshold	BDI-II Score			
	Minimal (n = 495)	Mild (n = 91)	Moderate (n = 58)	Severe (n = 37)
n	484	88	57	35
<0.75, no.(%)	62 (13)	6 (7)	4 (7)	1 (3)
0.75 to <1.5, no. (%)	118 (24)	11 (13)	3 (5)	3 (9)
≥1.5, no. (%)	304 (63)	71 (81)	50 (88)	31 (89)

ACQ = Asthma Control Questionnaire; BDI-II = Beck Depression Inventory second edition.

(mean 71.6 [95% CI, 66.2–76.9]) compared with minimal depressive symptoms category (mean 41.4 [95% CI, 39.8–42.9]), which indicated a worse quality of life ($p < 0.001$). Depressive symptoms separated by SGRQ domains (Symptoms, Activity, and Impacts) are shown in Table 4. The mean total SGRQ scores and domain scores consistently increased across BDI-II severity categories. Regression analyses also indicated that higher BDI-II scores were associated with higher SGRQ scores (SGRQ total score coefficient, 0.264 [$p < 0.001$; R^2 , 0.324]; SGRQ Symptoms coefficient, 0.116 [$p < 0.001$; R^2 , 0.081]; SGRQ Activity coefficient, 0.180 [$p < 0.001$; R^2 , 0.210]; and SGRQ Impacts coefficient, 0.259 [$p < 0.001$; R^2 , 0.365]).

Comorbidities

The association between depressive symptoms and common comorbidities is presented in Table 5. Com-

mon self-reported comorbidities in this age group were selected, in addition to mood changes, anxiety, and depression, which were all captured in the original case report form. Interestingly, the distribution of BDI-II mean and median scores was similar between the groups with and without comorbid diabetes and hypertension. As expected, we observed higher mean BDI-II scores in patients with a diagnosis of mood disorders, including anxiety, depression, and mood changes. We also evaluated the MOS Sleep scale by using BDI-II categories in the SIRIUS study only.¹⁵ The mean MOS Sleep scores ranged from 49.2 in the group with minimal depressive symptoms ($n = 93$) to 33.5 in the group with severe depressive symptoms ($n = 8$) (data not shown) (lower scores indicate worse sleep quality). However, the interpretation of the data was limited by the small sample size, and, therefore, any conclusions would have been speculative.

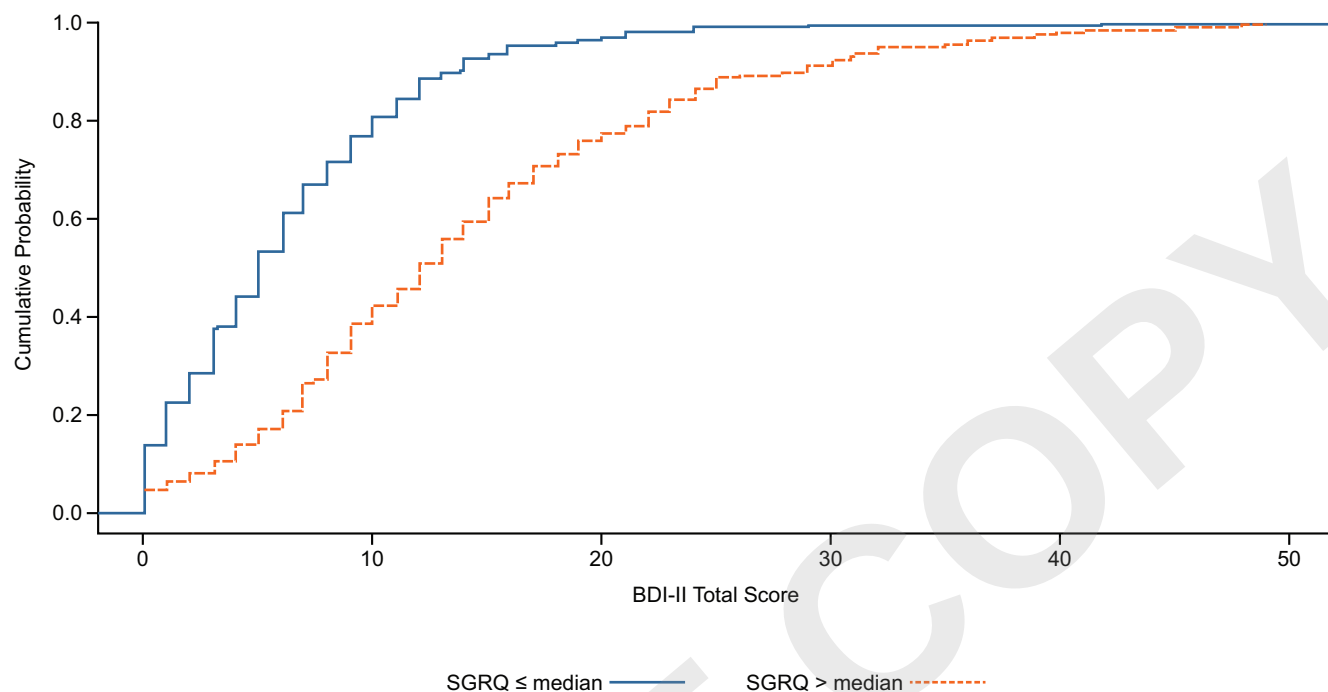


Figure 2. Cumulative distribution function of median SGRQ by using the BDI-II score. SGRQ = The St. George's Respiratory Questionnaire; BDI-II = Beck Depression Inventory second edition.

Table 4 Characterization of depressive symptoms at baseline by SGRQ domains

SGRQ Domain		BDI-II Score			
		Minimal (n = 495)	Mild (n = 91)	Moderate (n = 58)	Severe (n = 37)
Symptoms	LS mean	57.3	66.7	69.6	72.8
	95% CI	55.4–59.2	62.3–71.1	64.1–75.1	65.9–79.7
	Median	59.5	70.1	71.9	80.1
Activity	LS mean	51.4	65.2	73.8	79.8
	95% CI	49.5–53.2	60.9–69.5	68.4–79.3	73.1–86.5
	Median	53.6	66.2	73.0	85.8
Impacts	LS mean	30.8	48.1	56.1	66.3
	95% CI	29.3–32.4	44.5–51.8	51.5–60.7	60.6–72.1
	Median	29.9	51.0	57.0	68.2
Total	LS mean	41.4	56.4	63.9	71.6
	95% CI	39.9–42.8	53.0–59.8	59.5–68.2	66.2–76.9
	Median	41.4	57.3	64.9	75.1

SGRQ = The St. George's Respiratory Questionnaire; BDI-II = Beck Depression Inventory second edition; LS = least squares; CI = confidence interval.

Polypharmacy

We also evaluated the relationship between the number of nonasthma medications and depressive symptoms. A higher mean BDI-II score was observed in the patients who received more than four nonasthma medications when compared with one or fewer nonasthma medications (11.5 versus 8.7). Patients who took three or more nonasthma medications were more likely to have severe depressive symptoms (Fig. 3).

DISCUSSION

We identified an association between depressive symptoms and markers of asthma health status as well as asthma control in patients with severe eosinophilic asthma. Higher depressive symptom scores were associated with lower quality of life and asthma control. This study highlighted the need for a comprehensive multidimensional approach to management of this complex and challenging disease. Analysis of previously

Table 5 BDI-II mean and median score in subgroups with key comorbidities

Comorbidity		<i>n</i>	Mean ± SD	95% CI	Median
Any condition	Yes	401	11.5 ± 9.71	10.5–12.4	9.0
	No	280	8.3 ± 7.20	7.4–9.1	7.0
Diabetes mellitus	Yes	65	11.4 ± 9.42	9.0–13.7	10.0
	No	611	10.0 ± 8.77	9.3–10.7	8.0
Hypertension	Yes	185	10.6 ± 8.96	9.3–11.9	8.0
	No	494	10.0 ± 8.89	9.2–10.8	8.0
Weight gain	Yes	82	14.4 ± 10.79	12.0–16.8	12.5
	No	592	9.6 ± 8.39	8.9–10.2	8.0
Obesity	Yes	223	11.7 ± 9.88	10.4–13.0	10.0
	No	458	9.4 ± 8.29	8.7–10.2	7.4
Sleep disorders	Yes	90	12.3 ± 8.98	10.4–14.2	11.0
	No	581	9.8 ± 8.86	9.1–10.5	8.0
Mood disorders	Yes	103	14.9 ± 10.92	12.7–17.0	13.0
	No	573	9.3 ± 8.12	8.6–9.9	7.4
Anxiety	Yes	64	14.5 ± 10.22	12.0–17.1	12.5
	No	608	9.7 ± 8.56	9.0–10.4	8.0
Depression	Yes	58	18.3 ± 11.47	15.3–21.3	17.5
	No	618	9.4 ± 8.14	8.7–10.0	7.7
Mood changes	Yes	38	16.2 ± 10.47	12.7–19.6	14.5
	No	633	9.8 ± 8.62	9.1–10.4	8.0

BDI-II = Beck Depression Inventory second edition; SD = standard deviation; CI = confidence interval.

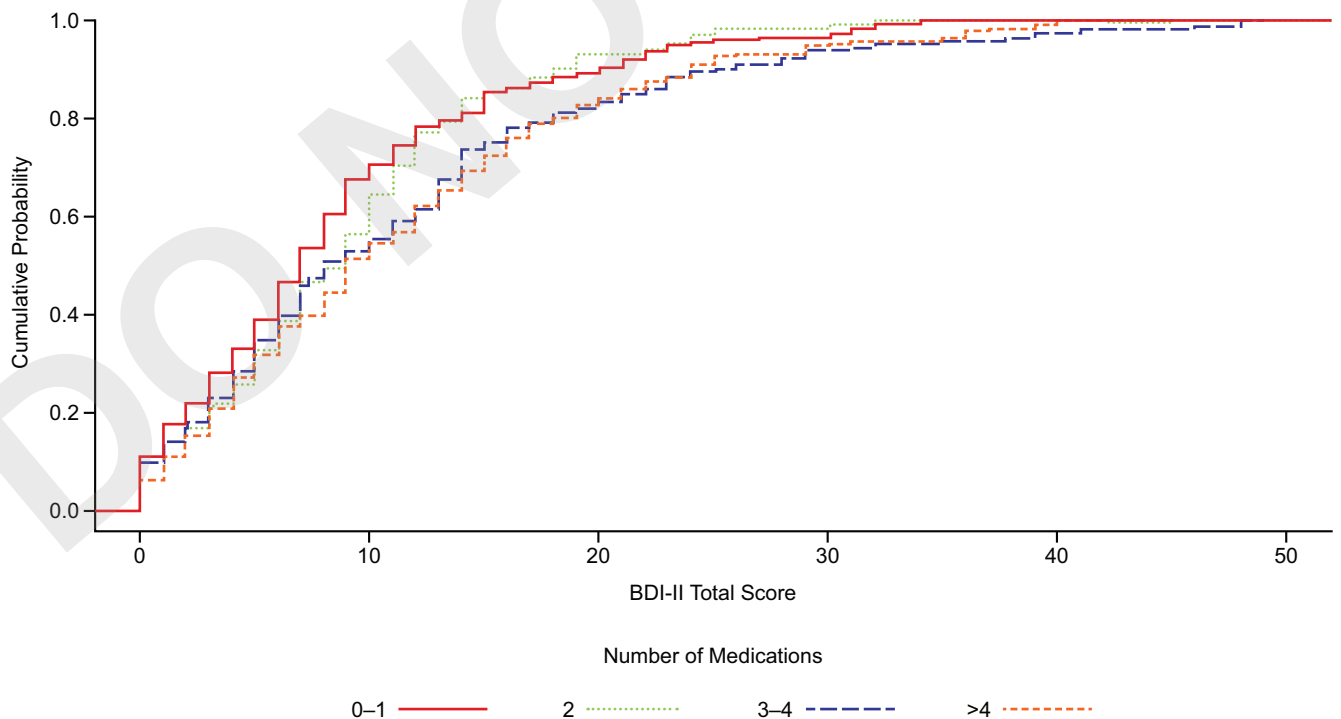


Figure 3. Cumulative distribution of the BDI-II scores by nonasthma polypharmacy use. BDI-II = Beck Depression Inventory second edition.

published data showed an association between asthma and depressive symptoms.^{2,3,5–11,13,25} However, to our knowledge, ours was the first study that evaluated this relationship in a well-characterized cohort of patients

with severe eosinophilic asthma. An historical cohort and nested case-control study from the United Kingdom found an association between depression and health-seeking behavior.⁶ The same study also found

an increased mortality rate in patients with asthma and who were depressed. In our study, although the number of events was small, we found an association between greater depressive symptoms and a history of a near-fatal asthma event. Further study is needed to assess the direction of this relationship.

Depression can be a risk factor for medication non-adherence. In another study, which used the Centers for Epidemiologic Studies–Depression questionnaire, investigators reported an association between depression and inappropriate medication use among 416 patients with mild asthma. The investigators found that rescue-medication overuse and controller-medication underuse were associated with greater depressive symptoms.²⁶ Another relevant factor could be the complexity of prescribed medical regimen, including polypharmacy. We explored this relationship in our study and found higher depressive symptom scores in patients who received three or more nonasthma medications. This observation underscored the challenges associated with polypharmacy in patients with more-severe disease.^{27,28}

Carvalho-Pinto *et al.*¹¹ evaluated clinical characteristics and phenotypes of a Brazilian adult severe asthma cohort. Results of this study highlighted the high burden of disease, the persistence of inflammation, and the existence of possible clinical phenotypes, which shared common features with published cohorts.¹¹ Thirty-one percent of their study population reported moderate-severe depressive symptoms (BDI-II scores ≥ 19).¹¹ Although the prevalence of moderate-severe depressive symptoms in our cohort was lower (14% with a BDI-II score ≥ 20), it is important to highlight that the level of uncontrolled asthma in the Brazilian cohort (mean ACQ score, 3.2) was considerably higher than in our study population (mean ACQ score, 2.2). Nonetheless, markers of disease severity, such as asthma control and quality of life, in our analysis were clearly associated with a higher degree of depressive symptoms.

Marshall and Agarwal²⁹ reviewed the role of stress and immune regulation related to asthma. The rationale for stress management in asthma is based on the notion that chronic stress induces a shift in the type-1/type-2 cytokine balance toward a predominant type-2 cytokine response, which favors asthma activity in susceptible individuals. In our study, 81% of the patients with severe depressive symptoms had a blood eosinophil count ≥ 300 cells/ μ L over the previous 12 months compared with 68% in the minimal category. However, this difference was not evident when we compared severe and minimal BDI categories by using blood eosinophils of ≥ 150 cells/ μ L at baseline (81% versus 85%), respectively. Glucocorticoids and inflammation have been implicated in the pathogenesis of depression.³⁰ Results of a study indicate that hyperac-

tivity of the hypothalamic-pituitary-adrenal axis and glucocorticoid receptor dysfunction are present in a significant number of patients who are depressed; also there is evidence of increased inflammatory processes in depressed populations, with higher levels of cytokines being a prominent finding, including raised levels of IL-6, IL-5, IL-4, and IL-1.¹⁴ Although we did not directly measure cytokine levels in our population, the phenotype of our study population was indicative of type 2 T-helper cell high phenotype.

A study by Amelink *et al.*³¹ found a higher prevalence of clinically significant depressive symptoms (9% versus 0%; $p = 0.009$) in patients with severe, prednisone-dependent asthma compared with patients with severe non-prednisone-dependent asthma. Patients with prednisone-dependent asthma were 3.4 (95% CI, 1.0–10.8; $p = 0.04$) times more likely to have significant depressive symptoms than patients with severe non-prednisone-dependent asthma. There were no differences found in personality traits between the groups studied. In our study, a significant proportion of patients were dependent on oral corticosteroids (39% [$n = 268$]), but neither the percentage of patients who were dependent on oral corticosteroids or the prednisone dose was different across the BDI-II categories of severity.

A recent study reported an association between glucocorticoid levels and the pathophysiology of depressive disorders in the context of changes in levels of estrogen, another steroid hormone that may play a role in depressive behavior in postpartum females.³² In our analysis, 81% of females were clustered in the category of severe depressive symptoms compared with 54% in the minimal symptom category. This observation opens the question of the potential role of estrogen and hormonal disruption in patients with more severe disease. Our study showed an association with more depressive symptoms across all three domains (Symptoms, Activity, and Impacts) of the SRGQ scores as well as ACQ-5 scores that define uncontrolled asthma. In addition, the mean sleep scores (MOS questionnaire) ranged from 49.2 in the group with minimal depressive symptoms to 33.5 in the group with severe depressive symptoms. Although the observation regarding sleep was not surprising, the small sample size precluded making any conclusions. Overall, analysis of the data indicated that patients with more depressive symptoms had asthma that was affected at multiple levels or domains that made the management and control of asthma more challenging.

There were some limitations related to this study. In this study, the selection of the patient population was based on markers of type 2 inflammation “eosinophilic phenotype”; therefore, these findings were not generalizable to other asthma phenotypes. In addition, in this analysis, we could only determine an association but could not determine

causation. Moreover, the comparison of BDI-II categories (minimal and mild versus moderate and severe) are descriptive, and formal statistical hypotheses, therefore, were not defined. In the regression analyses, the R^2 values were relatively low, which indicated a high level of variability of individual patient values around each fitted regression line; therefore, any prediction of the level of depression in an individual patient based on the regression would have a relatively low level of precision. Nonetheless, each coefficient could be interpreted in terms of the average increase in BDI-II score for each unit increase in the covariate (e.g., per unit increase of BMI in kg/m^2). The analysis was retrospective in nature, and, as a result, there was a possibility for misclassification and selection bias. Also, there was a risk that some associations were spurious due to the number of comparisons.

CONCLUSION

Analysis of our data confirmed that depressive symptoms were associated with poor quality of life and uncontrolled disease in patients with well-characterized severe eosinophilic asthma. The relationship between asthma and depressive symptoms seemed to be bidirectional, but this needs further study. These findings highlighted the need for a comprehensive and multidimensional approach to management of patients with uncontrolled asthma and comorbid depressive symptoms. Further research is urgently needed to explore the potential causal and/or moderating interactions between these two common conditions.

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