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Anxiety, depression and personality traits in severe, prednisone-dependent asthma

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Summary
Background: Anxiety and depression are prevalent in patients with asthma, and associated with more exacerbations and increased health care utilization. Since psychiatric intervention might improve asthma control, we examined whether patients with severe, prednisone-dependent asthma are at higher risk of these disorders than patients with severe non-prednisone dependent asthma or mild-moderate asthma, and whether they exhibit different personality traits.
Methods: Sixty-seven adults with severe prednisone-dependent asthma, 47 with severe non-prednisone dependent and 73 patients with mild-moderate asthma completed the HADS depression and anxiety subscale and the NEO-FFI for personality traits. In addition, asthma duration, body mass index and FEV_1 were measured.
Results: The prevalence of clinically significant depressive symptoms (9% vs. 0 vs. 0%; $p = 0.009$) and anxiety symptoms (19% vs. 6.4 vs. 5.5%; $p = 0.01$), was higher in patients with severe, prednisone-dependent asthma than in patients with severe non-prednisone dependent or mild-moderate asthma. Patients with prednisone-dependent asthma were respectively 3.4

List of abbreviations: FEV_1, forced expiratory volume in one second; HADS, hospital anxiety and depression scale; HADS-A, hospital anxiety and depression scale anxiety; HADS-D, hospital anxiety and depression scale depression; NEO-FFI, NEO-Five-Factor Inventory; BMI, body mass index; OR, odd ratio; SD, standard deviation; OCS, oral corticosteroids; CS, inhaled corticosteroids; LABA, long acting beta agonist.

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(95%CI: 1.0—10.8 $p = 0.04$) and 3.5 (95%CI: 1.3—9.6 $p = 0.01$) times more likely to have significant depression symptoms and 1.6 (95%CI: 0.7—3.7, $p = 0.2$) and 2.5 (95%CI: 01.1—5.5, $p = 0.02$) times more likely to have symptoms of anxiety than patients with severe non-prednisone dependent or mild-moderate asthma. There were no differences found in personality traits between the 3 groups.

Conclusion: Patients with severe, prednisone-dependent asthma have more often psychological distress as compared to patients with severe non-prednisone dependent or mild-moderate asthma.

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Introduction

Mental disorders, including anxiety and depression are more prevalent in asthma as compared to the general population [1—8]. Although there is a clear relationship between anxiety, depression and asthma, the association with asthma severity is controversial. Some studies have shown significant differences in anxiety [9] and depression [10] in patients with severe asthma as compared to those with milder disease, while other studies did not find such differences [11—13].

Although these results are inconsistent, it has been clearly demonstrated that psychiatric morbidity in asthma is associated with reduced adherence to treatment [14], loss of asthma control [10,15], increased medical consumption [16] and increased exacerbations requiring bursts of oral corticosteroids [17,18]. Moreover, it has been shown that depression in chronic diseases such as asthma, has a greater effect on general health than depression or asthma alone [7].

Patients who use chronic oral corticosteroids are at higher risk of developing psychiatric comorbidities [19,20]. In patients with severe, prednisone-dependent asthma this may be bi-directional. On the one hand, the use of oral corticosteroids in severe asthma may lead to higher levels of anxiety and depression; while on the other hand, the underlying psychopathology may lead to less asthma control and thereby more prednisone dependence. Patients with steroid-dependent asthma seem therefore to be at highest risk of developing depression and anxiety disorders, and might benefit most from psychiatric interventions that contribute to asthma control.

In addition to anxiety and depression, specific personality traits have been associated with disease severity and poor outcome. Patients with near-fatal asthma have been shown to have less adaptive personality characteristics [15], and patients with severe asthma according to ATS criteria [21] appeared to have maladaptive coping styles [13] as compared to patients with milder disease. There are no reports comparing other personality traits between patients with mild-moderate and severe asthma.

Therefore, the aim of the present study was to investigate the prevalence of anxiety and depression symptoms in patients with severe, prednisone-dependent asthma and to investigate whether these patients have elevated dysfunctional personality traits as compared to patients with severe, non-prednisone dependent and mild-moderate disease. If so, this might have important implications for the management of patients with this disabling disease.

Methods

Patients

Adult patients (18—80 yr) were recruited from the outpatient departments of 2 academic and 3 non-academic teaching hospitals in The Netherlands. Patients with mild-moderate asthma had to have a history of episodic dyspnea and wheezing, a documented reversibility in forced expiratory volume in 1 s (FEV_1) of >12% predicted [22] or hyperresponsiveness to histamine ($PC_{20} < 8$ mg/ml) [23]. Patient with severe asthma and prednisone-dependent and non-prednisone-dependent asthma had to meet the ATS criteria of severe asthma [21]. In addition, patients with prednisone dependent asthma were on maintenance therapy with prednisone (≥2.5 mg/day) for at least three months. Current smokers and patients with a smoking history of more than 15 packyears were excluded. The study was approved by the Leiden University Medical Centre Hospital Medical Ethics Committee and all patients gave written informed consent (P06.191).

Design

In this cross-sectional study all patients with asthma were asked to participate at their visit to the pulmonary outpatient clinics for a regular doctor's appointment.

In one visit, patients' characteristics were documented according to a structured questionnaire. Then the patients completed the 2 self-report questionnaires on psychological functioning. Finally, postbronchodilator FEV_1 was assessed using a handheld spirometer (Ferraris Respiratory Piko-1) according to ERS criteria [22].

Psychological questionnaires

The Hospital Anxiety and Depression Scale (HADS) is a widely used screening questionnaire to identify possible and probable cases [24] of depression (HADS-D) and anxiety (HADS-A) [25], which is reliable in patient and healthy populations [24]. The questionnaire contains 7 anxiety and 7 depression questions, each scoring 0—3 points. A cut off score of ≥11 points was used to define a probable case of anxiety or depression [26].

The NEO-Five-Factor Inventory (NEO-FFI) contains 60 multiple choice questions with a score ranging 1—5 for each answer. The questionnaire measures the 5 leading dimensions of the Big Five-model [27], neuroticism

(emotional stability vs. lability), openness (susceptibility to new experiences), extraversion (out- or inwards directed energy and orientation), agreeableness (orientation towards others) and conscientiousness (conscience towards own behavior). In the present study the authorized Dutch translations were used for all questionnaires.

Statistical analysis

Demographic and psychopathological differences between patients with severe, prednisone-dependent asthma, non-prednisone dependent asthma and mild-moderate asthma were analyzed using one-way anova, chi-square tests and kruskall wallis tests. The sum scores obtained on the anxiety (HADS-A), depression (HADS-D), neuroticism, openness, extraversion, agreeableness and conscientiousness subscales (NEO-FFI) were analyzed as continuous variables.

Potential factors associated with anxiety and depression were analyzed as dichotomous independent variables, using the following contrasts: HADS-D $\geq$11 vs. <11, HADS-A $\geq$11 vs. <11, asthma duration $\geq$15 yr vs. <15 yr (median) and BMI $\geq$28 vs. <28 (median), age $\geq$49 vs.<49 (median). Odds ratios for anxiety and depression as reference group were obtained by logistic regression analyses.

Asthma duration was defined as the number of years since asthma diagnosis. Number of smoking packyears was calculated by defining 1 packyear of smoking 20 cigarettes/day for a whole year. Chronic use of oral corticosteroids was defined as the daily use of prednisone for at least 1 month before entering the study. Analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). *p*-Values less than 0.05 were considered significant.

Power

As a clinical meaningful difference on the HADS scale we defined a 2 unit difference. Because the HADS has a standard deviation of 4[25], we needed to include 128 patients in total to achieve 80% power for this medium effect size (significance level 0.05). As a clinical meaningful difference on the NEO-FFI scale we defined a 3 unit difference. Because the NEO-FFI has a standard deviation of 6[27], we needed to include 128 patients in total to achieve 80% power for this medium effect size (significance level 0.05).

Results

Patient characteristics

One-hundred-eighty-seven patients, 67 patients with severe, prednisone-dependent asthma (20—77 yr), 47 with severe non-prednisone dependent asthma (19—70 yr) and 73 patients with mild-moderate asthma (18—75 yr) participated in the study. There was no significant difference between the prednisone-dependent patients and the group of severe, non-prednisone dependent patients and mild-moderate asthma patients with respect to gender, BMI and atopy (Table 1). However, prednisone-dependent asthma patients were older, had longer asthma duration and showed more severe airflow limitation as compared to the other patients.

Psychological characteristics in prednisone-dependent vs. severe non-prednisone dependent and mild-moderate asthma

Patients with severe prednisone-dependent asthma had significant higher scores on depression symptoms (HADS-D mean (SD) 4.5 (3.6) vs. 2.4 (2.4) and 3.4 (2.5), $p = 0.002$) and showed a trend towards higher anxiety symptoms (HADS-A 6.2 (4.4) vs. 4.8 (3.6) and 5.0 (2.9), $p = 0.06$) as compared to patients with severe or milder disease resp. (Table 2).

The prevalence of clinically significant depressive symptoms (HADS-D score $\geq$11) and anxiety symptoms

Table 1 Baseline characteristics of patients with severe prednisone-dependent asthma vs. moderate-severe and mild-moderate asthma.

	Prednisone-dependent $n = 67$	Severe non-prednisone dependent $n = 47$	Mild-moderate $n = 73$	*p*-Value
Age (yr)[a]	49.6 (12.9)	40 (16.5)	46.6 (15)	0.003
Female gender %	58.2	53.2	60.3	0.7
Asthma duration (yr)[b]	21 (9—36)	16 (5—21.8)	10 (2—27)	0.005
BMI[a]	28.2 (5.6)	26.5 (5.4)	26.1 (4.8)	0.07
Ex-smoker %	43.3	17	37	0.01
Packyears[b]	0 (0—4.1)	0 (0—0)	0 (0—3.3)	0.013
Atopy%	54.5	66.7	60.7	0.4
OCS dose (mg/day)[b]	10 (5—15)	0 (0—0)	0 (0—0)	<0.001
Duration of daily OCS (mth)	44 (3—360)	0 (0—0)	0 (0—0)	<0.001
ICS dose (μg/day)[b]	1000 (625—1250)	750 (500—1500)	250 (250—500)	<0.001
LABA%	100	91.5	68.5	<0.001
$pbFEV_1$	81.0 (23.5)	96 (23.6)	102.4 (14.3)	<0.001

BMI, body mass index; OCS, oral corticosteroids; ICS, inhaled corticosteroids fluticason equivalent; LABA; long acting beta agonist, $pbFEV_1$, forced expiratory volume in 1 s postbronchodilator.
[a] Mean (SD).
[b] Median (range).

Table 2 Psychological Questionnaire scores for patients with severe prednisone-dependent, moderate-severe and mild-moderate asthma.

		Prednisone-dependent $n = 67$	Severe non-prednisone dependent $n = 47$	Mild-moderate $n = 73$	p-Value
HADS	Anxiety	6.2 (4.4)	4.8 (3.6)	5.0 (2.9)	0.07
	Depression	4.5 (3.6)	2.5 (2.4)	3.4 (2.5)	0.002
NEO-FFI	Neuroticism	33.7 (5.6)	32.2 (3.9)	31.8 (2.8)	0.07
	Extraversion	38.6 (4.7)	39 (4.1)	39 (3.6)	0.8
	Openness	37.4 (4.2)	36.4 (4.2)	37.4 (3.3)	0.3
	Agreeableness	35 (4.3)	36 (5.2)	35.8 (4.5)	0.4
	Conscientiousness	40.2 (4.3)	39.9 (4.1)	40.8 (3.1)	0.4

Values expressed in mean (SD); HADS, Hospital Anxiety and Depression Scale; NEO-FFI, Neo-Five-Factor Inventory.

(HADS-A score $\geq$11) was higher in patients with severe, prednisone dependent asthma than in patients with severe non-prednisone-dependent or mild-moderate asthma (9% vs. 0% and 0%; $p = 0.004$) and (19% vs. 6.4% and 5.5%; $p = 0.01$), respectively (Fig 1). There were no differences in personality traits between the three groups (Table 2).

Logistic regression analyses showed that patients with prednisone-dependent asthma were respectively 3.4 (95% CI: 1.0—10.8 $p = 0.04$) and 3.5 (95%CI: 1.3—9.6 $p = 0.01$) times more likely to have clinically significant symptoms of depression as compared to non-prednisone dependent severe asthma and mild-moderate asthma. In addition, as compared to mild-moderate asthma, patients with prednisone-dependent asthma were 2.5 (95%CI: 01.1—5.5, $p = 0.02$) times more likely to have significant symptoms of anxiety and 1.6 (95%CI: 0.7—3.7, $p = 0.2$) times more likely as compared to non-prednisone dependent severe asthma, although the latter one was not significant. In addition, there were no associations found between depression or anxiety and age, asthma duration, BMI, smoking history and dose of OCS. Also, there was no association found between the dose of prednisone and anxiety or depression.

Discussion

In the present study we found a higher prevalence of psychological distress (depression and anxiety) in patients with severe, prednisone-dependent asthma as compared to patients with severe, non-prednisone dependent or mild-moderate disease. Patients with prednisone-dependent asthma were 3.5 times more likely to have clinically significant depression symptoms, and about 2.5 times more likely to have significant anxiety symptoms as compared to patients with severe or mild-moderate disease. With respect to personality traits we found no differences in patients with severe, prednisone-dependent asthma and the other groups. This implies that this particular group of patients with prednisone-dependent asthma should be screened routinely for anxiety and depression symptoms and offered psychiatric care if needed.

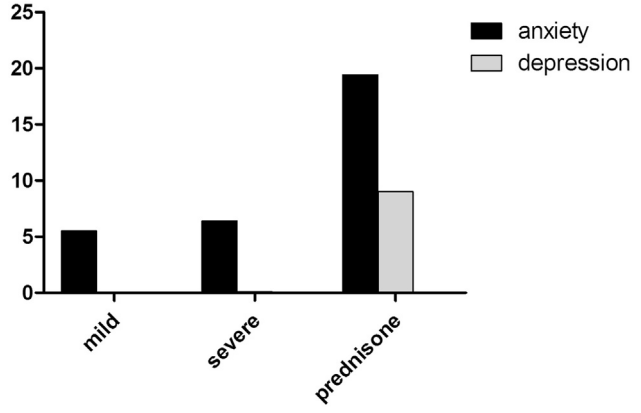

Figure 1 Percentage of patients with high anxiety and depression symptoms in severe prednisone-dependent asthma as compared to patients with severe non-prednisone dependent asthma and mild asthma.

The present study is the first, to our knowledge, to systematically investigate psychological distress and personality traits in patients with severe, prednisone-dependent asthma as compared to less severe, non-prednisone dependent asthma. Previous studies have investigated the prevalence of depression or anxiety symptoms (HADS score >11) in asthma irrespective of disease severity. They found prevalences ranging from 10 to 13.6% and 9—31.6% respectively [18,28,29].

The non-prednisone dependent asthma patients in our study had HADS-A and HADS-D scores similar to that of the general population [25,30]. However, patients with severe prednisone-dependent asthma had higher scores, similar to those of (non-psychiatric) medical outpatients [25]. This indicates that the prevalence of anxiety and depression symptoms in severe prednisone-dependent asthma is high, but not higher than in other outpatients. The prevalence of anxiety and depression in severe non-prednisone dependent asthma and mild-moderate asthma is within the normal range.

Studies that compared the prevalence of anxiety and depression between patients with severe and milder forms of asthma found conflicting results. Several studies showed no differences between patients with severe and mild-moderate asthma [11—13], while other studies found higher levels of psychopathology in patients with more severe disease [31—33]. The present study sheds new light on these conflicting findings by showing that only prednisone-dependent severe asthma patients have more anxiety and depression, which suggests that these psychological conditions are associated with prednisone treatment rather than with disease severity *per se*.

With respect to personality traits, relatively few studies have been performed in severe asthma. Several studies

found that patients with severe asthma [13] and near-fatal asthma [15] show less adaptive personality characteristics as compared to those with milder disease, although this relationship was not always found [12]. In these studies different methods were used to measure personality traits, and therefore the results are difficult to interpret. One study investigated the "Big 5" personality profile in a Portuguese asthma population [34]. Neuroticism scores were positively associated with asthma severity, which is consistent with the trend we found in our study. They also found extraversion and openness scores to be lower with increasing asthma severity, which we did not find. Interestingly, all patients with asthma in our study had relatively low scores on conscientiousness and very low scores on agreeableness as compared to the general population [35], for which we have no explanation. Obviously, more studies are needed to further investigate the relationship between personality traits and asthma severity.

The causality of the association between prednisone dependent asthma and anxiety and depression, might be bidirectional. The most likely explanation is that depression and possibly anxiety are a direct effect of corticosteroid treatment. One study found an association between the use of inhaled corticosteroids and depressive symptoms [36] and it has been shown that patients taking (long term) prednisone therapy tend to show higher scores on psychiatric symptoms [19,37,38]. This result is consistent with the observation of an increased prevalence of psychopathology in patients with long-term cured Cushing's disease, suggesting irreversible effects of previous glucocorticoid excess on the central nervous system [39].

Alternatively, psychological stress might be the cause of prednisone-dependency in patients with asthma. Psychological distress has been shown to be associated with more severe asthma symptoms [40], increased health care utilization [16], and frequent exacerbations [17] requiring oral corticosteroid bursts. It could be speculated that psychological stress leads to increased perception of asthma symptoms or even more severe airway inflammation [41], which may the cause of failure to control asthma with inhaled medications alone or to discontinue oral corticosteroids after an acute exacerbation.

Finally, psychosocial stress could be the consequence of chronic severe asthma itself. The experience of frequent asthma attacks and/or chronic impairment in social functioning might obviously result in anxiety and depression [42]. However, our results show an association with prednisone dependent asthma and not with severe non-prednisone dependent asthma. Therefore, this explanation is the least likely.

Although this study was performed in a well-defined group of patients and was adequately powered, it might have some limitations. The design of the present study is cross-sectional; therefore we cannot be certain that the results are consistent over time. Asthma as well as anxiety and depression are conditions with variable degrees of symptoms, and consistency over time in these patients has never been investigated. Nevertheless, the HADS has been well validated in the general population, in general practice and in psychiatric patients [26]. In addition, the HADS has proven to be adequate for repeated assessment of probable anxiety and depression at subsequent visits for follow-up [26].

Second, patients had to use prednisone on a daily basis for at least one month. It could be speculated that, if anxiety and depression are adverse effects of oral corticosteroids, this period may be too short. However, at least one study showed that anxiety and depression can develop within 5 days after starting oral corticosteroids [19]. In addition, the vast majority of our patients used chronic oral prednisone for many years. Therefore, we do not think this influenced the results of the present study.

The results of the present study have clinical and research implications. Physicians should be aware that oral corticosteroids may induce psychiatric adverse effects, such as anxiety and depression which may in turn influence asthma severity and control. Therefore, it might be worth to screen patients with severe prednisone-dependent asthma for anxiety and depression symptoms. In short-term intervention studies promising effects of pharmaceutical or psychosocial interventions have been observed [43,44], but more prospective studies are needed in this category of patients to see if better asthma control or less oral corticosteroid-dependency can be obtained on the long term.

In conclusion, we found significantly more anxiety and depression symptoms in patients with severe prednisone-dependent asthma as compared to patients with non-steroid dependent severe asthma or mild-moderate asthma. Patients with prednisone dependent asthma are 3.5 times more likely to have significant symptoms of depression and 2 times more likely to have significant symptoms of anxiety than their non-steroid dependent counterparts. Therefore, these patients deserve to be screened for depression and anxiety, and offered psychiatric or psychosocial care if needed. Hopefully, such interventions will lead to better control of the disease and less need for oral corticosteroids.

Author contributions

M. Amelink, MD: contributed to development of the study design, subject recruitment, collecting study data, performed statistical analysis and wrote the manuscript.

S. Hashimoto, MD: contributed to development of the study design, subject recruitment, collecting study data and manuscript preparations and writing.

Prof. P. Spinhoven: contributed in statistical analyses, interpretations and manuscript preparations.

H.R. Pasma MD: contributed in subject recruitment and manuscript preparations.

Prof. dr. P.J. Sterk MD: Principal Investigator, contributed to the study design and manuscript preparation.

Prof. dr. E.H. Bel MD: Contributed to study design, data analysis and manuscript preparation.

Dr. A. ten Brinke MD: contributed to development of the study design, statistical analysis and manuscript preparation.

Conflicts of interest

For all authors there are no known conflicts of interest associated with this publication. In addition, there has been no financial support for this work that could have influenced it's outcomes.

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