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REVIEW ARTICLE

Psychopathology in difficult asthma

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Abstract

Objective: Within the asthma population, difficult asthma (DA) is a severe condition in which patients present with frequent exacerbations, hospitalizations and emergency room visits. The identification and treatment of psychopathology is included in the management of DA. Psychopathology is supposed to predispose patients to DA or vice versa; psychopathology may develop as a consequence of DA. We reviewed the available literature on empirical findings regarding psychopathology in adult patients with DA. *Methods*: Studies in English language journals using MEDLINE, Cochrane and PsycINFO databases, were retrieved by an electronic search published from 1990 till July 2014. *Results*: Literature on psychopathology in DA is scarce. The search identified 16 articles of which only 6 articles were specifically about psychopathology in adult patients with DA. Almost half of the patients with DA had evidence of psychopathology at both syndrome and symptom level. Moreover, psychopathology appeared to be related to frequent exacerbations in patients with DA. *Conclusions*: This literature review suggests a high prevalence of psychopathology of patients with DA, although it remains unclear whether psychopathology occurs more often in DA compared to ''stable asthma''. More research is needed on a possible role of psychopathology on clinical signs and symptoms in DA.

Keywords

Difficult asthma, psychopathology, psychology

History

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Introduction

Asthma is a respiratory disease characterized by airway obstruction, airway inflammation and bronchial hyper responsiveness [1,2]. Asthma is a common and increasing problem in our society [2,3]. About 8% of the adult population in Europe, North America and Australia has asthma [4]. Asthma can be a life-threatening condition although usually, asthma is well controlled with standard treatment. Standard treatment is directed at maximizing the symptom-free periods and keeping the airways in the best possible physical state [2–4].

Treatment mostly involves the prescription of medication, avoiding asthma triggers and improving self-management strategies. Recent guidelines classify severity based on responsiveness to treatment [2,5]. Approximately 5% of patients with asthma have difficult asthma (DA) [6], as defined by the European Respiratory Society (ERS) task force [7], i.e. these patients do not reach an acceptable level of control at step 4 or 5 of prescribed treatment [3]. DA is defined as a failure to reduce the clinical manifestation of asthma symptoms despite maximal treatment [8–10]. As a result patients with DA have frequent exacerbations, hospital admissions and emergency room (ER) visits [8–10]. Patients with DA form a heterogeneous group with ''uncontrollable symptoms''. DA includes clinical subgroups with refractory asthma, near fatal asthma (NFA) [11], brittle asthma, nocturnal asthma, corticosteroid-resistant asthma, corticosteroid-dependent asthma and therapy-resistant asthma [6].

Although DA consists of a small group of patients, the impact on healthcare is significant. A substantial part of the overall costs of asthma is consumed by patients with DA because of the many hospitalizations, ER visits and high medication use [3,8,12,13]. Moreover, DA influences the quality of life of patients themselves as well as their environment [8]. Ultimately DA can even lead to death. Reasons why asthma symptoms in these patients are difficult to manage are not well understood [3]. Management programs concerning the treatment of DA propose a stepwise management of the disease [6,14]. One step in the treatment of DA is the modification of socioeconomic factors influencing disease control and the identification and treatment of psychopathology, mental disorders as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [15], the standard classification used by mental health professionals. Psychopathology is suggested to obscure diagnostics and to complicate the treatment of asthma [14].

In the asthma population, the prevalence of psychopathology is significantly higher compared to the general

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population [16–18], both at syndrome and symptom level. Feldman et al. [19] reported a prevalence of 46% of psychiatric diagnoses in asthma patients and the estimation of psychopathology in severe asthmatics ranges between 30 and 63% [20,21]. Asthmatic patients with psychopathology achieve fewer goals related to asthma control, have more asthma associated ER visits and use more medication, all independent of the severity of asthma and demographics. Moreover, these patients tend to report higher levels of asthma symptoms than expected by their pulmonary function [19].

Psychopathology can be both causal and secondary to DA. Psychopathology may predispose asthma patients directly to an exacerbation through psychophysiological processes or it may predispose asthma patients indirectly through factors like non-adherence, and maladaptive coping styles [6,22,23] or misinterpretation of symptoms resulting in improper asthma management leading to poor asthma control [19,21–25]. Vice versa asthma, especially with frequent exacerbations as in DA, may increase the risk of developing psychopathology.

In light of the management strategies prescribed [3,14,26], which involves treating psychopathology if diagnosed, there is a need to study the association between psychopathology and disease outcome [27]. However, to our knowledge, a review of evidence from the literature on the importance of the identification and treatment of psychopathology in DA, has not yet been undertaken. Therefore, the aim of the present study was to review the literature with regard to (1) the prevalence of all psychopathology in general DA and in subcategories of DA; (2) evidence of associations between specific syndrome and symptoms of psychopathology and poor disease outcome in DA.

Methods

Search

A comprehensive literature search of the PsycINFO database, MEDLINE database and Cochrane Library of English-language abstracts was conducted on literature published from 1990 till July 2014 on psychopathology in DA. The search was conducted by pairing ''difficult asthma'' with keywords: psychological, psychology, psychiatric comorbidity, psychiatry, alexithymia, anxiety, panic, depression, affective, personality and psychopathology. Another search was conducted including subgroups of patients with DA by separately pairing ''refractory asthma'', ''near fatal asthma'', ''brittle asthma'', ''nocturnal asthma'', ''corticosteroid-resistant asthma'', ''corticosteroid-dependent asthma'', and ''therapy-resistant asthma'' with the same keywords as mentioned above.

Selection criteria

Psychopathology can be described both at syndrome and symptom level. Psychopathological syndromes refer to a specific set of symptoms and can be diagnosed with a semi-structured interview by trained professionals. Psychopathology at symptom level can be determined by self-report questionnaires. Studies meeting the following criteria were included in this review: (a) participants were patients with DA as defined by the ERS task force [26], or were patients with asthma in the following subgroups; refractory asthma, near fatal asthma, brittle asthma, nocturnal asthma, corticosteroid-resistant asthma, corticosteroid-dependent asthma and therapy-resistant asthma, (b) participants were adults above 18 years, (c) psychopathology was studied at symptom level or syndrome level, measured with standardized instruments, (d) statistical analyses were well described and (e) studies were published in English.

Once an initial pool of articles was obtained, titles were screened on inclusion criteria. Abstracts from retained records were assessed to identify potentially relevant articles and duplicates were removed. For the remaining records full texts were obtained and articles were added to the search by cross reference of full texts (Figure 1). All eligible papers were submitted to close reading and were coded by two readers (L. P. and A. P.) on the following characteristics: (a) number of participants, (b) asthma diagnosis of participants, (c) instruments used to measure psychopathology, (d) statistical analysis, (e) design of the study and (f) main findings concerning psychopathology in DA. The results of the search are summarized in Tables 1, 2 and 3, describing results separately for DA in general and for each subgroup of DA.

Results

The search initially identified 267 hits, of which 54 were potentially relevant, as is shown in Figure 1. After applying the above mentioned inclusion criteria, removing duplicates and adding 3 articles by cross referencing, the search resulted in 16 articles. The studies are described in the tables; first specifically for DA (Table 1), second for the subgroups NFA and brittle asthma (Tables 2 and 3, respectively) to give a nuanced picture of the studies on psychopathology in DA.

Prevalence of all psychopathology in general DA

Four studies measured psychopathology at syndrome level (Tables 1, 2 and 3). Heaney et al. [30,31] reported 48% psychopathology in DA, Garden et al. [42] 40% and Rocco et al. [37] reported 11.7%.

At symptom level Robinson et al. [32] reported 46%, Campbell et al. [35] 43%, Garden et al. [42] 40%, Ten Brinke et al. [29] 20.4% and Van Veen et al. [33] 20.11% psychopathology in DA. Only Miles et al. [43] and Garden et al. [42] studied psychopathology in patients with DA in comparison to patients with stable asthma. Miles et al. [43] found higher prevalence rates of psychopathology while Garden et al. [42] found no differences.

Prevalence of all psychopathology in subcategories of DA

Anxiety and depression symptoms were studied in NFA-type of DA (Table 2). The reported prevalence rates ranged between 16.7% for state anxiety and 40.5% for depression [38]. Vázquez et al. [41] found no difference of prevalence of alexithymia (a personality trait which in a literal sense means ''without words for emotions'' [44]) between patients with NFA-type of DA and normal asthma while Plaza et al. [36] and Serrano et al. [40] reported more alexithymia in patients with NFA.

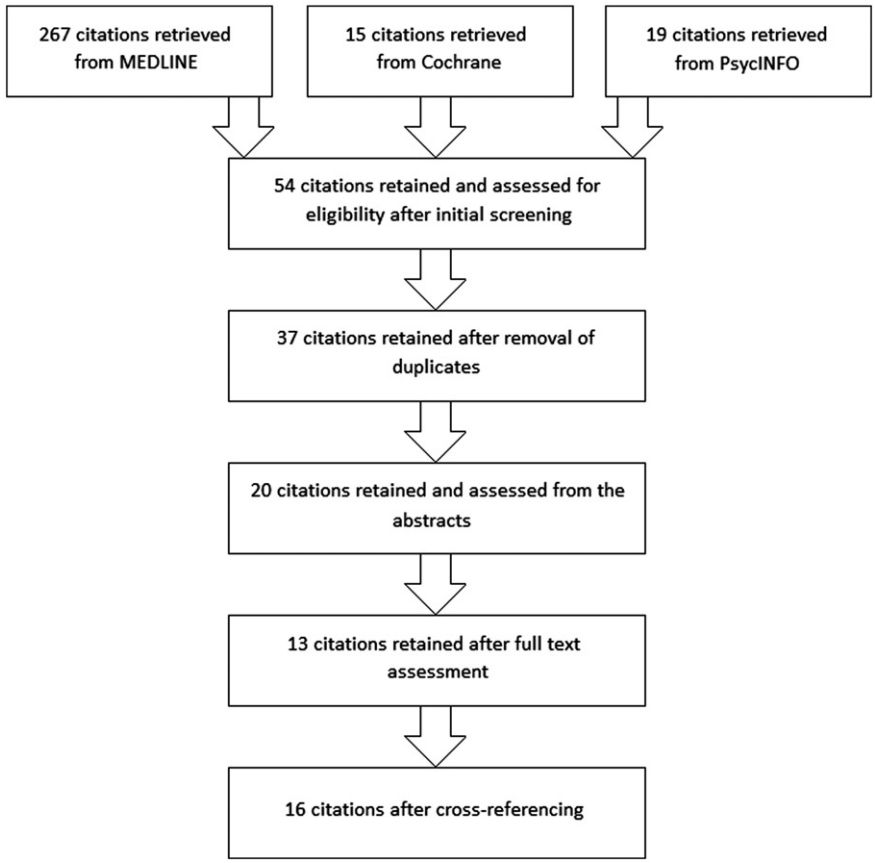

Figure 1. Flow diagram of the literature search.

Table 1. Psychopathology in DA.

Study (first author)	Participants	Instrument	Statistical analysis	Main findings
Ten Brinke [28]	98 DA; 21 psychiatric caseness, 77 non-caseness	GHQ-12, Healthcare utilization questionnaire	Unpaired Student's *t*-tests, chi^2 analyses, nonparametric tests	Patients with psychiatric caseness have more: GP visits $p = 0.02$, ER visits $p = 0.01$, exacerbations $p = 0.02$, hospitalizations $p = 0.04$.
Ten Brinke [29]	136 DA; 39 > 3 exacerbations, 24 one exacerbation	GHQ-12	Unpaired *t*-tests, chi^2 analyses, logistic regression, nonparametric tests	20.4% Psychiatric caseness in total of 136 patients, 18.4% in 63 patients. Patients with frequent exacerbations had higher score on psychological dysfunctioning $p < 0.05$.
Heaney [30]	34 DA, 39 NDA	HADS, psychiatric interview	Unpaired *t*-tests, chi^2 analyses, logistic regression	48% Psychiatric disorder, 45% unrecognized. No difference for psychiatric disorder, anxiety and depression scores.
Heaney [31]	33 DA, 32 NDA	HADS, systematic psychiatric interview, Juniper scale, AQLQ	Unpaired *t*-tests, chi^2 analyses	49% ICD10 psychiatric diagnoses, 48% in DA, 50% in non DA (ns). Anxiety and depression scores are higher in patients with ICD10 diagnosis ($p < 0.01$). No relation ICD10 diagnosis and outcome of asthma. Better outcome for QoL in NDA $p < 0.001$, More depression in DA $p < 0.05$.
Robinson [32]	56 DA	GHQ-30, psychiatric interview	Descriptive statistics	10 Patients had a major psychiatric contribution to asthma (17.9%), psychiatric caseness in 26 patients (46%).
Van Veen [33]	136 DA; 29 obese, 107 nonobese	GHQ-12	Logistic regression analyses	20.11% Psychiatric caseness. 32% Psychiatric caseness in obese patients, 16.9% psychiatric caseness in non-obese patients ($p = 0.10$).

AQLQ = asthma quality of life score; DA = difficult asthma; ER = emergency room; GHQ = General Health Questionnaire; GP = general practitioner; HADS = Hospital Anxiety and Depression Scale; ICD10 = International Classification of Diseases 10; NDA = non-difficult asthma; ns = non-significant; PC = poorly compliant; QoL = quality of life.

Table 2. Psychopathology in NFA.

Study (first author)	Participants	Instrument	Statistical analysis	Main findings
Campbell [34]	154 NFA, 80 died of asthma	GHQ-28, IBQ, interview questionnaire	Mann–Whitney, chi2, Fishers-exact	No difference in psychiatric caseness and denial.
Campbell [35]	77 NFA	GHQ-28, Asthma Attitudes and Beliefs Questionnaire, IBQ	Spearman's correlation coefficient	43% Psychiatric caseness, 57% denial. Positive correlation GHQ with morbidity ($p<0.05$) and stigmatization ($p=0.02$). No association GHQ and severity of asthma.
Plaza [36]	50 NFA, 25 asthmatic controls, 25 non-asthmatic controls	TAS, Borg scale,	Chi^2 analyses, Oneway ANOVA, Kruskal–Wallis, Mann–Whitney, Spearman's correlation coefficient	24% Alexithymia in NFA. More alexithymia in NFA ($p<0.001$). Higher mean TAS score in NFA ($p=0.007$). Alexithymia is associated with more hospitalizations in NFA and non NFA ($p=0.036$). No difference for dyspnea.
Rocco [37]	17 NFA, 17 asthmatic controls	MMPI, HDA, Zung AD, psychiatric interview	*t*-Tests	11.7% Minor psychiatric episodes, no significant differences.
Romero [38]	42 NFA	STAI, BDI, p-f scale of ASC	Spearman's rho coefficients, logistic regression analyses	21.4% p-f, 40.5% Depression, 2.4% severe depression (of 42 persons).16.7% State anxiety, 38.1% trait anxiety. State anxiety is a risk factor for the prescription of oral steroids ($p=0.015$). Panic-fear and trait anxiety were no risk factors.
Sández [39]	40 NFA	SF-36, BDI, p-f scale of ASC	Multiple regression	Depressive symptoms and p-f are associated with worse HRQL ($p<0.01$).
Serrano [40]	179 NFA (64 alexithymic, 115 non-alexithymic), 40 asthmatic controls	TAS, GHQ-28	*t*-Tests, Mann–Whitney, chi^2 analyses, Fishers' exact test logistic regression	36% Alexithymia in NFA. More alexithymia ($p=0.004$) in NFA. Patients with NFA and alexithymia have more psychiatric caseness ($p=0.002$). Alexithymia is related to recurrent exacerbations ($p=0.049$).
Vázquez [41]	44 NFA, 44 asthmatic controls	TAS, CDI, STAI-T, HSPK, BSSMA	Chi^2 analyses, student's *t*-test, multivariate analyses	36.4% Trait anxiety. Higher levels of trait anxiety ($p=0.001$), depression ($p=0.021$). 9% was alexithymic. There was no difference for TAS overall score, there were more problems in describing feelings in NFA ($p=0.002$). No differences for self-management and adherence.

BDI = Beck depression inventory; BSSMA = Brooks self-report Scales of Medication Adherence; CDI = Cognitive Depression Index; GHQ = General Health Questionnaire; HDA = Hamilton depression and anxiety scales; HRQL = Health-related quality of life; HSPK = hypothetical scenarios of practical knowledge; IBQ = Illness Behavior Questionnaire; MMPI = Minnesota multiphasic personality inventory; NFA = near fatal asthma; p-f = panic and fear; p-f scale of ASC = panic fear scale of the Asthma Symptom Checklist; SF-36 = Short Form Health Survey; STAI = State Trait Anxiety Index; STAI-T = State Trait Anxiety Index, Trait; TAS = Toronto Alexithymia Scale; Zung AD = Zung Anxiety and depression scales.

Table 3. Psychopathology in brittle asthma.

Study (first author)	Participants	Instrument	Statistical analysis	Main findings
Garden [42]	20 BA, 20 asthmatic controls	GHQ-60, EPI, SCID, Life events interview	Binomial test, Shapiro–Wilk test, paired *t*-test	40% Psychiatric caseness and 40% current disorders; 3 mood disorders, 1 substance disorder, 6 anxiety disorders and 1 adjustment disorder. More current and past psychiatric disorders in brittle asthma ($p=0.02$). No difference in personality profiles or GHQ scores.
Miles [43]	29 BA, 29 asthmatic controls	GHQ, LAQ, ASC, Clinical Interview	Chi^2 analyses	More psychiatric caseness in brittle asthma ($p=0.0002$). More problems in living with asthma in brittle asthma ($p=0.002$). In brittle asthma 55.2% of patients delayed seeking help, 20.7% in non-brittle asthma.

ASC = Asthma Symptom Checklist; BA = Brittle asthma; EPI = Eysenck Personality Inventory; GHQ = General Health Questionnaire; LAQ = Living with Asthma Questionnaire; SCID = Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders.

Associations between psychopathology syndrome and symptoms and poor disease outcome in DA

There were no studies on the relationship between disease outcome and psychopathology at syndrome level. At symptom level Heaney et al. [31] reported no relationship between psychopathology at symptom level and outcome in DA. Ten Brinke et al. [28] did report significantly more GP visits, ER visits, exacerbations and hospitalizations in patients with DA who displayed more psychopathology at symptom level. Campbell et al. [34] studied psychopathology in DA compared to patients who died of asthma and found no differences between groups for psychopathology. And vice versa, DA patients with worse outcomes, i.e. more exacerbations, reported significantly more psychopathology [29]. Alexithymia was associated with more hospitalizations [36] and more exacerbations [40] in patients with DA. Sández et al. [39] reported an association of reduced health-related quality of life and depressive symptoms.

Discussion

Given the burden of DA and the role psychopathology plays in the treatment protocols of DA [2], it is remarkable that there are just few empirical literature studies on the association between psychopathology and DA. No studies were found on psychopathology in refractory asthma, nocturnal asthma, corticosteroid-resistant asthma, corticosteroid dependent asthma and therapy-resistant asthma.

Results on the prevalence of psychopathology on both symptom and syndrome level in DA were mixed but there is some evidence to indicate a higher prevalence of psychopathology in DA. The mixed findings are predominantly to be explained by the use of different instruments to assess psychopathology at different levels (symptoms versus syndrome). Another explanation could be the underestimation of symptoms in DA patients, possibly due to a high prevalence of alexithymia. Patients with alexithymia have difficulty discriminating between emotions and physical symptoms, which will limit the ability to recognize psychopathology and can possibly result in insufficient asthma management.

There were no studies at *syndrome* level on the association between psychopathology and exacerbations, but four studies [28,29,36,40] showed a relationship between psychopathology and exacerbations in DA at *symptom* level. Patients with DA as well as psychopathology experienced more asthma hospitalizations and exacerbations in comparison to patients with DA and less psychopathology [28]. And vice versa, patients with more exacerbations reported more psychopathology compared to patients with fewer exacerbations [29]. Although the direction of this relationship is still speculative, it supports not only the importance of diagnosing psychopathology in DA, but also the extension of the medical examination after an exacerbation with a psychiatric evaluation. We can only speculate whether the treatment of psychopathology also positively influences outcome in DA.

Limitations

Although in the last two decades, substantial efforts have been made in appropriately defining asthma [2,3] and specifically DA, the concept of DA is still not well described which makes it a very heterogeneous group of patients to study. Because of the small number of studies as well as the heterogeneity between studies, the use of different instruments, small sample sizes, it is also difficult to make cross study comparisons. Also, it is a question whether it is acceptable to compare DA to NFA and brittle asthma since they are subcategories of DA.

In summary, there is a higher prevalence rate of psychopathology in DA compared to the general population. Studies showing higher prevalence in DA compared to patients with stable asthma are equivocal. Alexithymia seems to be more common in DA compared to stable asthma and the general population but this association needs further consideration since all studies were performed in one country and only included patients/participants with a subcategory of DA (NFA). These findings should be replicated in other ethnic groups with DA.

Clinical relevance and future recommendations

There is some preliminary evidence that psychiatric evaluation should be included in medical examinations for individuals with DA who present with an exacerbation. Subsequently, psychological interventions could become a more prominent part of the rehabilitation program. The treatment of psychopathology could have an influence on outcome in DA, but further study is needed to increase insight into the relevance of treating psychopathology in DA.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH. Psychopathology in patients with severe asthma is associated with increased health care utilization. Am J Respir Crit Care Med 2001;163:1093–1096.
2. Global Inititiative for Asthma (GINA). Global strategy for asthma management and prevention; 2011; Available from: http://www.ginasthma.org/guideline [last accessed Sep 2014].
3. Wenzel SE, Fahy JV, Irvin C, Peters SP, Spector S, Szefler SJ. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. Am J Respir Crit Care Med 2003;162:2341–2351.
4. Burney P. Epidemiology of asthma. Allergy 1993;17:17–21.
5. National Heart, Lung, and Blood Institute (NHLBI). Guidelines for the Diagnosis and Management of Asthma (EPR-3). 2007. Available from: http://www.nhlbi.nih.gov [last accessed Sep 2014].
6. Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J 1998;12:1209–1218.
7. Chanez P, Godard P. Is difficult asthma still clinically meaningful? Eur Respir J 2006;28:897–899.
8. Wenzel SE. Severe asthma in adults. Am J Respir Crit Care Med 2005;172:149–160.
9. Bateman ED. Severity and control of severe asthma. J Allergy Clin Immunol 2006;117:519–521.
10. Chanez P, Wenzel SE, Anderson GP, Anto JM, Bel EH, Boulet L, Brightling CE, et al. Severe asthma in adults: what are the important questions? J Allergy Clin Immunol 2007;119:1337–1348.
11. Alvarez GG, FitzGerald JM. A systematic review of the psychological risk factors associated with near fatal asthma or fatal asthma. Respiration 2007;74:228–236.
12. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, Weiss S, et al. Design and baseline characteristics of the

epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2004;92:32–39.
13. Sullivan SD, Rasouliyan L, Russo PA, Kamath T, Chipps BE. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. Allergy 2007;62:126–133.
14. Le AV, Simon RA. The difficult-to-control asthmatic: a systematic approach. Ann Allergy Asthma Immunol 2006;2:109–116.
15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text revised. Washington, DC: American Psychiatric Association; 2000.
16. Nouwen A, Freeston MH, Labbé R, Boulet L. Psychological factors associated with emergency room visits among asthmatic patients. Behav Modif 1999;23:217–233.
17. Lehrer P, Feldman J, Giardino N, Song H, Schmaling K. Psychological aspects of asthma. J Consult Clin Psychol 2002;70: 691–711.
18. Lavoie KL, Bacon SL, Barone S, Cartier A, Ditto B, Labrecque M. What is worse for asthma control and quality of life: depressive disorder, anxiety disorder, or both? Chest 2006;130:1039–1047.
19. Feldman JM, Mahmood IS, Morales E, Kaminski B, Lu SE, Lehrer PM. Psychiatric disorder and asthma outcomes among high-risk inner-city patients. Psychosom Med 2005;67:989–996.
20. Yellowlees PM, Haynes S, Potts N, Ruffin RE. Psychiatric morbidity in patients with life-threatening asthma: initial report of a controlled study. Med J Australia 1988;149:246–249.
21. Wamboldt MZ, Weintraub P, Krafchick D, Wamboldt FS. Psychiatric family history in adolescents with severe asthma. J Am Acad Child Adolesc Psych 1996;35:1042–1049.
22. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. Lancet 2006;368:780–793.
23. Barton C, Clarke D, Sulaiman N, Abramson M. Coping as a mediator of psychosocial impediments to optimal management and control of asthma. Respir Med 2003;97:747–761.
24. Adcock IM, Kazahiro I. Steroid resistance in asthma: a major problem requiring novel solutions or a non-issue? Cur Opinion Pharmacol 2004;4:257–262.
25. Rimington LD, Davies, DH, Lowe D, Pearson MG. Relationshipship between anxiety, depression, and morbidity in adult asthma patients. Thorax 2001;56:266–271.
26. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, Bel EH, et al. ERS task force 1998 Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. Eur Respir J 1999;13:1198–1208.
27. Bosley CM, Corden ZM, Cochrane GM. Psychosocial factors and asthma. Respir Med 1996;90:453–457.
28. Ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH. Psychopathology in patients with severe asthma is associated with increased health care utilization. Am J Respir Crit Care Med 2001;163:1093–1096.
29. Ten Brinke A, Sterk PJ, Masclee AAM, Spinhoven P, Schmidt JT, Zwinderman AH, Rabe KF, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005;26: 812–818.
30. Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, Gamble J. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. Thorax 2003;58: 561–566.
31. Heaney LG, Conway E, Kelly C, et al. Prevalence of psychiatric morbidity in a difficult asthma population: relationship to asthma outcome. Respir Med 2005;99:1152–1159.
32. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF. Systematic assessment of difficult-to-treat asthma. Eur Respir J 2003;22:478–483.
33. Van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. Allergy 2008;63:570–574.
34. Campbell DA, McLennan G, Coates JR, Frith PA, Gluyas PA, Latimer KM, Luke CG, et al. A comparison of asthma deaths and near-fatal asthma attacks in South Australia. Eur Respir J 1994;7: 490–497.
35. Campbell DA, Yellowlees PM, McLennan G, Coates JR, Frith PA, Gluyas PA, Latimer KM, et al. Psychiatric and medical features of near fatal asthma. Thorax 1995;50:254–259.
36. Plaza V, Giner J, Picado C, Sureda B, Serrano J, Casan P, De Pablo J, et al. Control of ventilation, breathlessness perception and alexithymia in near-fatal asthma. J Asthma 2006;43:639–644.
37. Rocco PL, Barboni E, Balestrieri M. Psychiatric symptoms and psychological profile of patients with near fatal asthma: absence of positive findings. Psychother Psychosom 1998;67: 105–108.
38. Romero-Frais E, Vázquez MI, Sández E, Blanco-Aparicio M, Otero I, Verea H. Prescription of oral corticosteroids in near-fatal asthma patients: relationship with panic-fear, anxiety and depression. Scand J Psychol 2005;46:459–465.
39. Sández E, Vázquez MI, Romero-Frais E, Blanco-Aparicio M, Otero I, Verea H. Depression, panic-fear, and quality of life in near-fatal asthma patients. J Clin Psychol Med 2005;12:175–184.
40. Serrano J, Plaza V, Sureda B, De Pablo J, Picado C, Bardagi S, Lamela J, et al. Alexithymia: a relevant psychological variable in near-fatal asthma. Eur Respir J 2006;28:296–302.
41. Vázquez MI, Romero-Frais E, Blanco-Aparicio M, Seoane G, Otero I, Rodríguez-Valcarcel ML, Pértega-Díaz S, et al. Psychological and self-management factors in near-fatal asthma. J Psychsosom Res 2010;68:175–181.
42. Garden GM, Ayres JG. Psychiatric and social aspects of brittle asthma. Thorax 1993;48:501–505.
43. Miles JF, Garden MF, Tunnicliffe WS, Cayton RM, Ayres JG. Psychological morbidity and coping skills in patients with brittle asthma and non-brittle asthma: a case controlled study. Clin Exp Allergy 1997;27:1151–1159.
44. Sifneos PE. Alexithymia: past and present. Am J Psychiatry 1996; 15:137–142.