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Review Article

Principal Comorbidities in Severe Asthma: How to Manage and What is their Influence on Asthma Endpoints

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Abstract

Introduction: This is a review of the principal comorbidities of severe asthma (obesity, gastro-oesophageal reflux disease, obstructive sleep apnoea, and psychopathologies) with specific attention to their impact on pathophysiology and treatment. ERS/ATS or GINA guidelines on (severe) asthma provide limited information on comorbid conditions in these patients. These comorbidities are increasingly present in the growing population of older asthmatics and may result in additional asthma morbidity and mortality.

Materials and Methods: Review of 57 observational, interventional and review studies addressing comorbidities of severe asthma.

Conclusion: Weight loss of 10% in obese asthmatics increases asthma control significantly. CPAP use in asthmatics with OSA improves asthma symptoms, rescue bronchodilator use, peak flow and quality of life, especially in those > 60years. The impact of treatment of GERD and depression/anxiety is less clear. We propose a systematic history taking and screenings advice concerning the most important comorbidities.

Keywords: *Asthma; OSA; GERD*

Introduction

The small group of severe asthma patients accounts for most of the costs in asthma care. The definition of severe asthma is based on the 2014 ERS/ATS guidelines (Table 1). The criteria of uncontrolled asthma are listed in table 2.

1. Need for high dose inhaled corticosteroids(ICS) AND 2. Long acting β2 agonist, leukotriene modifier or theophylline AND/OR 3. Continuous or near continuous systemic CSs as background therapy to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy OR worsening on tapering of systemic corticosteroids

Table 1: *Definition of severe asthma (ATS/ERS guideline 2014).*

1. Poor symptom control: ACQ consistently > 1.5, ACT < 20 (or ''not well controlled'' by NAEPP/GINA guidelines) 2. Frequent severe exacerbations: two or more bursts of systemic CS (3 days each) in the previous year 3. Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year 4. Airflow limitation: pre-bronchodilator FEV1 < 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal). Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics).

Table 2: *Criteria for uncontrolled asthma.*

Nearly 3 - 5% of the total asthma population can be classified as having severe asthma which amounts to about 10 000 patients in Belgium. The ERS/ATS consensus document and the GINA guidelines provide limited information on comorbid conditions in severe asthma.

They conclude that although the impact of treatment of GERD on severe asthma is not yet clear, when this comorbidity is present, it should be treated as appropriate to improve this condition. Anxiety and depression are underdiagnosed, so appropriate psychiatric evaluation and referral to a specialist is recommended. Some assessment of family psychosocial stress using standardized questionnaires or direct interviews can be helpful. There is no evidence of clear benefit of psychiatric treatment on asthma outcomes [1,2]. There are some papers which focus on the role of anxiety and depression in patients with COPD [3]. The present paper reviews some of the most important comorbid conditions in asthmatics. These comorbidities are increasingly present in the growing population of older asthmatics and may result in extra asthma morbidity and mortality. Additional information about the relevance and the management of these comorbidities in asthma are needed.

Materials and Methods

The ethical committee of KU Leuven approved this study. We searched in Pubmed with queries "comorbidities and (severe) asthma", "obesity and asthma", "OSAS and asthma", "GERD and asthma", "anxiety and asthma", "depression and asthma". We selected the most recent and largest trials based on the number of patients included. The selection process is visualized in table 3.

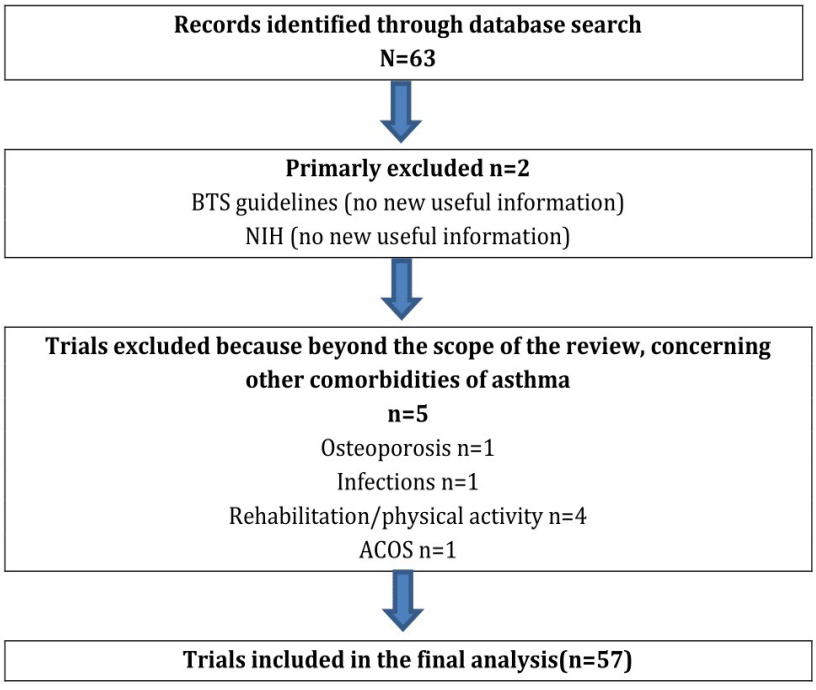


Table 3: *Selection process for the trials included in this review.*

Results

57 studies were included of which 2 were guidelines, 21 observational trials, 17 interventional trials (12 RCT), 14 systematic reviews, 2 meta-analyses and one case report.

Obesity

Prevalence

Epidemiological studies have shown an association between obesity and asthma with a relative risk of 3 and an increased odds ratio for asthma of 1.9 in obese subjects versus those with a normal weight [4]. Studies have also shown that there might be sex-specific differ-

ences in the association between asthma and obesity [4]. Nystad., *et al*. found a 10% increase in asthma prevalence per unit of increase in BMI in men and 7% in women. More than 50% of poorly controlled asthmatics are obese in the United States [5].

Impact on asthma outcome/control

Cohort studies show that obesity in young (< 12 years of age) asthmatics is an independent risk factor for developing unremitting asthma beyond puberty [5]. Holguin., *et al*. concluded that asthmatics are differentially affected by obesity based on the age of onset of asthma. The early onset asthmatics (< 12yr), especially severe asthmatics become obese in contrast with the late onset asthmatics (> 12yr) where obesity can give rise to more asthma severity/morbidity [5,6]. Most although not all studies have shown worsened asthma control, quality of life, and/or severity in obese asthmatics [5,6]. A cross sectional study in severe asthma showed that obese patients had more asthma exacerbations, increased usage of oral corticosteroids and higher long acting beta 2 agonist (LABA) dosage requirements [7,8].

Pathophysiology

It remains unclear if obesity in asthmatics is merely a comorbidity or a specific "subphenotype" of asthma.Two phenotypes of asthma in obese patients have been described [5].

The first phenotype comprises patients with (early onset) allergic asthma that is characterized by T2 driven inflammation and overproduction of IL-5 (resulting in airway eosinophilia) and IL-13 (resulting in airway smooth muscle hyperresponsiveness and mucus hypersecretion) and that is complicated by the development of obesity [5].

Adipose tissue produces several cytokines and adipokines that may worsen the pathophysiology of asthma [9]. Leptin, a proinflammatory cytokine is increased and adiponectin, an anti-inflammatory cytokine is decreased in obese individuals. Airway epithelial cells express multiple receptors for leptin and adiponectin. These cytokines may have direct effects on the airway epithelium and increase hyperreactivity rather than enhancing airway inflammation [9]. More macrophages infiltrate the adipose tissue and an increase in IL-1β induces proliferation of IL-17 producing cells and increased airway hyperresponsiveness [6]. Markers of metabolic inflammation are higher in visceral adipose tissue and serum in obese asthmatics compared to obese non-asthmatics [9].

The second phenotype links obese, mostly female patients with later onset (non-allergic) asthma. These patients have less T2 inflammation and lower markers of airway hypereosinophilia than the first phenotype. In this phenotype, mechanical changes affecting the lung function (restrictive pattern) and airways may play an important role in addition to the increased airway hyperresponsiveness caused by the previously mentioned cytokines/adipokines. Tidal volumes are lower as a result of less chest expansion because of the impact of body weight on the thorax and flattening of diaphragm due to increased abdominal fat. FRC and ERV decrease with increasing BMI and lung resistance increases because of the adipose tissue distribution [5].

The relation between obesity and asthma may be even more complex and involve other theories including mechanical, dietary and genetic factors. One theory proposed that individuals with asthma restrict their levels of activity in fear of inducing an asthma exacerbation, resulting in a more sedentary lifestyle and an increased risk of obesity. Boudreau showed in a recent Canadian study with 798 asthma patients that the relationship between BMI and worse asthma control can be mediated by depressive symptoms [10].

Diagnostics, when and how?

GINA emphasizes the importance of documenting obesity to avoid under or overtreatment of asthma. Weight reduction should be included in the treatment plan for obese asthmatics. BMI (evolution over time) is important to monitor in severe asthmatics. A BMI > 30 should prompt action to lower weight and be more active.

How to treat and what is the impact on asthma therapy?

Interventional studies showed that obese individuals with moderate asthma do not respond as well to ICS or ICS+LABA [6,8]. Systemic

steroids are less efficient and have to be avoided in this population because of the weight gaining side effect. On the other hand, frequent use of (long acting) β_2-adrenergic receptor (β_2-AR) agonists may attenuate its protective effect against bronchial hyperresponsiveness and may result in β_2-AR desensitization due to downregulation of the receptors [11]. International Asthma Treatment Guidelines have emphasized that overuse of β_2-AR should be avoided and that LABA should not be used as monotherapy in asthma.

A systematic review of the effect of all means of weight loss interventions on asthma control in 2012, concluded an overall positive effect [12,13]. A recent Cochrane review was inconclusive on the effect of nonsurgical weight loss interventions in asthma [13]. This was confirmed by Ma., *et al*. in 2015 as there was no better asthma control after 12months of diet and training. A weight loss of > 10% seems to result in better asthma control to a clinically meaningful degree but was not achieved in Ma's and other trials without surgery [14].

Several small studies showed an improved asthma control, asthma quality of life, spirometry as well as a reduced inhaled corticosteroid use after bariatric surgery in obese asthmatics (Table 4). Decreased systemic/airway inflammation (leptin, adiponectin, high sensitivity C-reactive protein, number of mast cells) and airway hyperresponsiveness after surgery was seen in several trials [12,15]. Significant weight reduction in obese adults with asthma has also a positive impact on emergency department visits for asthma and hospital admissions for asthma [16]. Aggressive weight reduction strategies should thus be the cornerstone in the management of obese patients with asthma.

Source	Intervention	Study duration	Lung function	ACQ	AQLQ	Airway inflammation	PD20	Systemic markers of inflammation	Inhaled corticoid use N=number of patients (µg)=dose of ICS	ED visit/hospitalisation for asthma exacerbation	Small airway functions
Dávila-Cervantes., *et al*. 2004	BS+A (BMI40-50) (n=30)	12M	BS+A: Baseline-12M FEV1:89-103%* FVC: 84-97,5*	NA	NA	NA	NA	NA	NA	NA	NA
Maniscalco., *et al*. 2008	1.BS+A (females, mean BMI 45) (n=12) 2.NBS+A (n=10)	12M	BS+A: Baseline-12M FEV1: 83-87,2%*	BS+A: 18,7-22,2* NBS+A: 18,8-18,5	NA	NA	NA	NA	NA	NA	NA
Dixon., *et al*. 2011	1.BS+A (n=23) 13% banding, rest bypass 2. BS-A (n=21) 48% banding, rest bypass	12 M	BS+A: Baseline-12M FEV1: 82,4-90,4*	BS+A: Baseline-12M 1,64-0,63*	BS+A: Baseline-12M 4,87-5,87*	BS+A: BAL Baseline-12M Lymphocytes: 3,5-7,9* Adiponectin: 1527-4530*	BS+A: Baseline-12M 3,9-7,28*	BS+A: Baseline-12M Leptin: 30,2-17,1* Adiponectin: 13,8-25,2*	BS+A: Baseline-12M N=16-10(331-238µg Fluticsasone) p>0,05	NA	NA
Van Huisstede., *et al*. 2015	1.BS+A(n=27) BMI>35 63% gastric sleeve, rest, bypass 2. BS-A (n=39) 69% gastric sleeve, rest bypas 3. NBS+A (n=12)	12 M	BS+A Baseline-12M FEV1: 86-95%* BS-A Baseline-12M FEV1: 97-106%*	NBS+A: Baseline-12M 1,7-1* BS+A: Baseline-12M 1,2-0,4*	NBS+A: Baseline-12M 6,3-6,9* BS+A: Baseline-12M 5,6-6,6*	BS+A: biopsies Baseline-12M mastcells decreased *	BS+A PD20 Baseline-12M Median 0,22-1,46mg*	BS+A Baseline-12M Hs-CRP(36-7,1)* Leptin(69-11)*, adiponetin(12-22,5)* BS-A Baseline 12M: Hs-CRP(3à,4-5,3)* Leptin(55-6)* Adiponectin(14,1-23,3)*	NBS+A: no difference BS+A: n=6-4(600µg budesonides/day)	NA	BS+A: Baseline-12M R5-R20 0,25-0,07kPa/s* BS-A: Baseline-12M R5-R20: 0,17-0,07*
Hasegawa., *et al*. 2015	BS+A (n=2261)	24 M	NA	NA	NA	NA	NA	NA	NA	Baseline-12M -24M 22-10,9-10,9%*	NA

Table 4: *Studies analyzing effects of bariatric surgery in asthma*

*Abbreviations: BS+A= Bariatric Surgery and Asthma; BS-A: Bariatric Surgery Without Asthma; NBS+A: No Bariatric Surgery and Asthma; NA; Not Applicable; *: significant or p < 0,005, Baseline-12M: before and 12months after (no) bariatric surgery*

Gastro-oesophageal reflux disease (GERD)

Prevalence

The prevalence of GERD in asthma patients is significantly higher than in healthy controls and varies from 35 to 82% depending on the definition and means of establishing GERD [17].

Impact on asthma outcome/control

A strong association between GERD and asthma exists but the nature of the relationship is controversial. In some studies GERD in asthmatics was associated with lower scores on ACT and AQLQ and more exacerbations [18]. It is unlikely that asymptomatic gastro-esophageal reflux is an important cause of poorly controlled asthma.

Pathophysiology

Two theories suggest how GERD can exacerbate pre-existing asthma. The "reflux" theory is based on animal and scintigraphic studies and suggests that symptoms of asthma are due to reflux of acid into the oesophagus followed by micro-aspiration into the tracheobronchial tree. The "reflex" theory suggests that distal oesophageal acidification results in vagal stimulation and consequent bronchoconstriction. The latter may explain why some asthmatics with GERD may develop bronchospasm without proximal oesophageal acidification. Bronchoconstriction inducing an increase in negative pleural pressure, the mechanical influence of a depressed diaphragm caused by hyperinflation and increased abdominal pressure induced by coughing, may all adversely affect the pressure gradient between the thorax and the abdomen and contribute to gastroesophageal reflux [19]. In addition, β_2AR agonists and theophylline may promote gastroesophageal reflux by causing relaxation of the lower oesophageal sphincter and increasing the gastric acid secretion [20].

Diagnostics: when and how?

Symptoms of GERD need to be questioned in severe asthmatics. Suggestive symptoms include nocturnal cough, worsening of asthma symptoms after eating large meals, drinking alcohol, or lying supine. Half of the asthma patients with GERD do not have any of this symptoms. GERD should also be considered as a possible cause of a dry cough, in asthmatics who present in adulthood and in those not responding to bronchodilator or steroid therapy. In the absence of GERD symptoms, it is not advised in the current guidelines to screen patients with uncontrolled asthma for GERD.

If GERD symptoms do not resolve, specific investigations such as pH monitoring or endoscopy may be considered. An endoscopy can confirm the diagnosis of GERD with reflux esophagitis. Oesophageal manometry can identify specific oesophageal motility abnormalities as ineffective oesophageal motility (in 53.3% of asthmatics); nutcracker oesophagus in 7.6%; and lower oesophageal sphincter pressure in 15.4%. The gold standard to diagnose GERD, remains 24h pH monitoring [19]. Sensitivity is improved by using a combination of pH- and impedance-monitoring, recently recognized as superior to pH monitoring alone for evaluation of the temporal relations between symptoms and GERD [21].

How to treat and what is the impact on asthma therapy?

The GINA guidelines stipulate that symptomatic reflux in patients with asthma should be treated for its general health benefits, but anti-reflux therapy will not reduce asthma symptoms or exacerbations [2]. Interventional studies resulted in inconsistent results but overall results are regarded as negative. A first systematic review in 1998 concluded that medical treatment for GERD improved asthma symptoms in 69% of the patients, reduced asthma medication use in 62%, and improved evening PEFs in 26% of the patients but without effect on lung function [22]. In 2003; Gibson., *et al*. performed a new systematic review of 12 randomized, placebo-controlled trials using the Cochrane methodology, and concluded that there was no overall improvement in asthma following treatment for GERD. No definite conclusions could be drawn at that moment because of the diversity in study designs and methodologies [23,24]. The largest and most recent systematic review/meta-analysis was published in 2011. Overall, patients had a higher mean morning PEF rate (primary outcome

parameter) after treatment with PPIs compared to placebo; with a mean improvement of 8.7 L/min. Although this small effect is statistically significant, it is unlikely to be of clinical significance because it falls below the range of minimal perceivable improvement for PEF (18.8l/min) rate and moreover, this effect was smaller than the improvement with other medical therapies (25 – 40 l/min). PPI therapy failed to improve PEF rate, FEV1, asthma symptoms, or quality of life. Further trials should focus on clarifying the pathologic roles of symptomatic and silent GERD in patients with severe asthma table 3 [25-34].

Non-or weakly acidic reflux can be diagnosed with the impedance measurement and does not respond to PPI treatment. Several animal studies suggest that GABA agonists such as baclofen may inhibit bronchial responsiveness to various stimuli. In chronic cough patients, small studies suggest a minor effect of baclofen on the cough symptoms [38]. In asthma patients, a trial with Baclofen resulted in a paradoxically increased bronchial hyperresponsiveness. This can be due to dysfunctional GABA-B prejunctional receptors in asthmatics [39]. Additional studies are needed.

Reference	Patient characteristics PPI vs control	PPI treatment	AM PEF (L/min)	PM PEF (L/min)	FEV1 (L)	Asthma symptom score	AQLQ (S)Score
Ford., *et al*. 1994	Clinical Asthma and GERD diagnosis (endoscopy/pHmetry) N = 10 PPI, 10 control	Omeprazole 20mg, od, 4wk	7 (-63 to 82)	3 (-67 to 73)	NA	0 (-0,57 to 0,57)	NA
Teichtahl., *et al*. 1996	Clinical Asthma and GERD diagnosis (pH metry) N = 20 PPI, 20 control	Omeprazole 40mg, od, 4wk	14 (-46 to 74)	10 (-82 to 102)	NA	NA	NA
Levin., *et al*. 1998	Clinical Asthma and GERD (pH metry and symptoms) N = 9 PPI, 9 controls	Omeprazole 20mg, od, 8wk	38 (11 to 65)*	32 (3 to 60)*	0,13 (0,17 to 0,43)	NA	1,18 (0,18 to 2,18)*
Boeree., *et al*. 1998	Pos Metacholine test, reversibility and GERD (pH metry) N = 15 PPI, 13 controls	Omeprazole 40mg, bd, 12 wk	-13 (-90 to 64)	NA	-0,02 (-0,56 to 0,52)	-0,03 (-0,46-0,40)	NA
Littner., *et al*. 2005	Clinical asthma diagnosis + reversibility or ICS And GERD (symptoms) N = 99 PPI, 108 controls	Lansoprazole 30mg, bd, 24wk	-6 (-19 to 31)	0 (-25 to 35)	-0,1 (-0,31 to 0,11)	0,14 (-0,03 to 0,31)	NA
Kiljander., *et al*. 2006	Clinical asthma diagnosis and +provovacation test or reversibility (15%) No GERD diagnosis N = 387 PPI, 384 controls	Esomeprazole 40mg, bd, 16wk	6 (0 to 13)	5 (0 to 11)	NA	NA	0,03 (-0,1-0,15)
Dos Santos., *et al*. 2007	Clinical asthma diagnosis + FEV1/FVC <90%+ reversibility (7%) or +provocation test of 20% PEF diurnal variation and GERD (pH Metry) n = 22 PPI, 22 controls	Pantoprazole 40mg, od, 12wk	60 (13- 107)*	54 (-8 to 116)*	NA	NA	NA
Peterson., *et al*. 2009	Clinic of exercise triggered asthma, no GERD N = 22 PPI, 8 controls	Rabeprazole 20mg, od/bd, 10-12wk	NA	NA	NA	NA	0,53 (0,29 to 1,34)
Mastronarde., *et al*. 2009	Clinical diagnosis of asthma and reversibility or +provocation test and ICS>8w, no GERD N = 200 PPI, 193controls	Esomprazole 40mg, bd 40 wk	6 (-4-16)	NA	0,025 (-0,03 to 0,08)	NA	-0,098 (-0, 21 to 0,17)
Kiljander., *et al*. 2010	Clinical asthma diagnosis + reversibility (>12%), ICS+LABA 3m and 1 exacerbation last year, GERD symptoms or pH metry N = 632 PPI, 328 controls	Esomeprazole 20mg, od/bd, 26wk	Od 4 (-3 to 10) Bd 6 (-1 to 12)	Od -0,2 (no CI) Bd 3,2 (no CI)	Od 0,09 (0,03 to 0, 0,15) Bd 0,12 (0,06- 0,18)*	NA	Od 0,28 (0,12 to 0,44) Bd 0,41 (0,27 to 0,57)*

Table 5: *Summary of results of RCT's of PPI therapy and asthma outcomes.*

*Abbreviations: AM PEF: Morning Peak Flow; PM PEF: Evening Peak Flow; od: Once Daily, bd: Twice Daily; AQLQ: Standardized Asthma Quality of Life questionnaire; CI: Confidence Interval; NA: Not Available; PPI: Proton Pump Inhibitor; Results are expressed as mean change vs placebo (95%CI); *: statistically significant result*

OSA/sleep quality

Prevalence

Poor sleep quality and sleep disordered breathing, especially obstructive sleep apnoea (OSA) is common in asthmatics. A study by Shen et al concluded that the overall incidence of OSA was 2.5-fold higher in asthmatics than in the control group [40]. The effect of sleep quality on asthma (severe and non-severe) control and quality of life is independent of GERD and OSA [41].

Impact on asthma outcome/control

A high OSA risk on the sleep apnoea scale of the sleep disordered questionnaire (SA-SDQ) was associated with an almost 3 times higher OR for not well controlled asthma(ACQ) independent of obesity or other factors affecting asthma control [42]. Other predictors of symptoms of OSA in patients with asthma in addition to asthma severity, include coexistent GERD (OR, 2.70), and use of an ICS (OR, 4.05) [43].

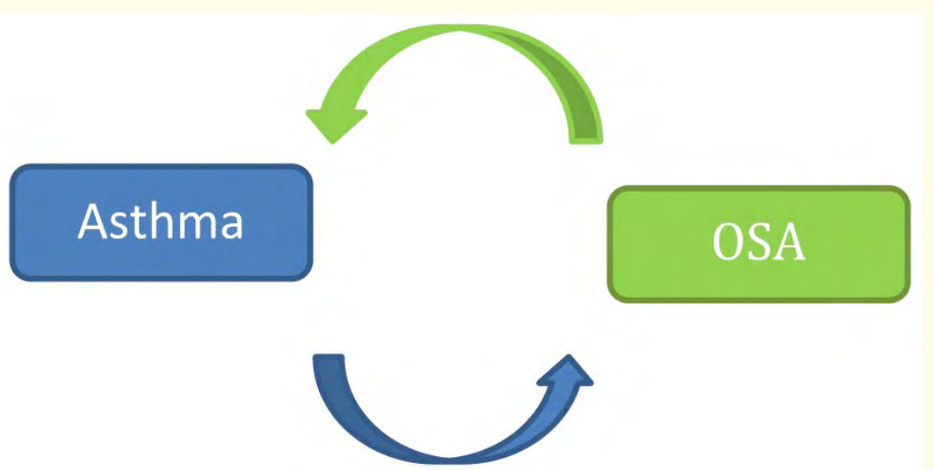
A cross sectional study showed a strong correlation between moderate to severe asthma and OSA (apnoea hypopnoea index >= 5/u), using the Apnoea Link; a validated simplified portable screening tool for OSA, without EEG [44]. Obesity in asthmatics seems also a promoting factor to develop OSA, especially in children.

The association of OSA with worse asthma control is more pronounced in older (60 - 75yr) than younger asthmatics (13 vs 7%) [45]. High dose inhaled corticosteroids also increased the risk of developing OSA with 5,4 vs 3,7 for medium dose and 2,3 times for the low dose [46,47].

Pathophysiology

The relationship between OSA and severe asthma is based on shared pathophysiological factors. Bidirectional direct and indirect interactions of asthma and OSA have been studied repeatedly (Figure 1) [48]. One plausible explanation is the theory of "the integrated airway"; an inflammatory process within a continuous airway. Upper airway obstruction results in intrathoracic pressure swings, frequent arousals and intermittent hypoxia that contribute to an inflammatory milieu, as demonstrated by associations of OSA with cardiovascular and cerebrovascular disease [45]. OSA also promotes inflammatory responses by means of hypoxia, hypercapnia and sleep fragmentation, resulting in a reversible increase in CRP, similarly to asthma. TNFalfa, a proinflammatory cytokine, is elevated in OSA and plays an important role in collapse and reopening of the airways. Both proinflammatory factors decrease with CPAP treatment [46,47].

Direct (nerve reflex, intermittent hypoxia, sleep fragmentation, VEGF, leptin, inflammation)
Indirect (GERD, cardiac dysfunction)



Direct (mechanical)
Indirect (smoking, obesity and prolonged cortisteroid effect)

Figure 1: *Potential bidirectional relationship between asthma and obstructive sleep apnoea.*

Diagnostics, when and how?

Polysomnography is indicated in asthmatics with inadequate control of nocturnal symptoms despite adequate treatment [47].

How to treat and what is the impact on asthma therapy?

Most interventional studies with CPAP treatment reduced asthma symptoms and bronchodilator use, and improved PEF and quality of life [49]. Asthmatics with OSA older than 60 years benefit more from CPAP treatment. This can be due to age related changes in upper airway anatomy and an increase in pharyngeal collapsibility and resistance independent of BMI and gender [45]. Serrano-Pariente showed recently in a prospective trial that the mean ACQ decreased from 1.39 ± 0.91 at baseline to 1.0 ± 0.78 at 6 months, the percentage of uncontrolled asthma patients decreased from 41.4% to 17.2%, and the percentage of patients with asthma attacks in the 6 months before and after treatment from 35.4% to 17.2% when using CPAP [49].

Psychopathologies: depression, anxiety and self-harm

Prevalence

The risk of clinical depression (Beck depression inventory) is doubled in severe asthmatics, especially in the more symptomatic patients [50].

Asthma is also associated with a two-fold risk of an anxiety disorder and vice versa [51]. In a cross-sectional trial excluding known psychopathologies, 70% of moderate to severe asthmatics suffered from anxiety symptoms (Self-Anxiety Scale (SAS) and the State–Trait Anxiety Inventory (STAI–Y)) [52]. Rural residence, depression and prednisone use were additional risk factors for anxiety disorders in asthmatic patients [53].

Generalized anxiety disorder is diagnosed in 4% of asthmatics in a prospective analysis, especially in the worse controlled and independent of age, sex, smoking, and asthma severity with covariates as major depressive disorder and low asthma self-efficacy [54]. Self-harm is also associated with asthma after adjustment for demographic, socio-economic and health factors independent of age and sex in a large controlled prospective trial [55].

Impact on asthma outcome/control

A cohort study showed that in severe asthma, increased respiratory symptoms was associated with more depressive symptoms [50]. Sleep disturbance and limited physical activity because of activity limitation show the strongest association to develop a depression. On the other hand, an underlying psychiatric morbidity, such as a depression, has been associated with non-adherence with treatment and reduced perception of asthma symptoms and may result in increased asthma severity [50].

Asthmatics with a perception of impaired breathing (ie, visual analog scale score of < 6) have above-normal anxiety scores. This is consistent with the hypothesis that anxiety may negatively affect asthma [56].

Pathophysiology

Several pathophysiological theories link anxiety and asthma. The cognitive theory connects the long-term experience of respiratory symptoms with the generation of fear. Hypoxia and hypercapnia as factors sensitizing the neural circuits that control fear responses are named in biological theories and psychological theories point the role of stress affecting respiration [56].

Diagnostics, when and how?

Severe asthmatics or those with poor asthma control should be screened for depression and anxiety disorders. The Beck depression inventory is a useful tool to classify the severity of clinical depression [50]. The STAI can diagnose and distinguish between anxiety dis-

orders and depression. The SAS can quantify the anxiety level [52]. Referral to a psychiatrist/psychologist is mandatory if the questionnaires are positive.

How to treat and what is the impact on asthma control?

Interventional trials using non-pharmacological interventions have inconsistent results. A recent meta-analysis of 23studies showed that relaxation and cognitive behavioural therapy (CBT), may have a positive effect on asthma-related quality of life, some psychological outcomes, and lung function (relaxation only) [57]. A pilot study with escitalopram in 26 depressive asthmatics showed a trend favouring escitalopram to reduce depressive symptoms, without significant results. There was no effect on asthma symptoms [58]. Future trials should harmonize the interventions under study and outcome measures used to determine their effectiveness.

Discussion and Conclusion

Obese individuals have a threefold relative risk to develop asthma and obesity worsens asthma control. The relation between obesity and asthma is complex and differs depending on the age, phenotype of asthma and gender. Mechanical impact of obesity on pulmonary function test may also mimic asthmatic symptoms. Weight loss of > 10% results in clinically improved asthma control. Significant weight loss, especially with bariatric surgery improves asthma control, lung function and quality of life. Bariatric surgery is indicated in severely obese and inadequately controlled asthmatics if conservative measures result in < 10% weight loss.

A strong association between GERD and asthma exists with prevalence rates of 30 - 90% of GERD in asthmatics. Several RCT's and meta-analysis with PPIs in asthmatics (with and without diagnosed GERD), concluded that PPIs only result in a small but probably not clinically significant improvement in morning/evening PEF. Routine use of PPI in (severe) asthmatics is not indicated at the moment. Future research should focus on the role of impedance and pH measurements to identify subgroups of asthmatics who may benefit from PPI therapy. Nissen fundoplication, radiofrequency technique and magnetic sphincter augmentation are more effective in improving asthma control than medical therapy and can be an option in highly symptomatic patients. Non/weakly acidic reflux, known as a cause of chronic cough, responding to Baclofen but that drug showed paradoxical enhancement in bronchial hyperresponsiveness in asthmatics.

A bidirectional relationship OSA is more prevalent in asthma especially in the more severe, obese and older asthmatics. CPAP treatment improves asthma symptoms and quality of life. Screening of OSA in insufficiently controlled asthmatics is mandatory, as well as in the obese and older asthmatics (> 60y). SA-SDQ, the Apnoea Link and the classical polysomnography are possible screenings tools. More investigation is needed to determine which tool suits the best.

Severe asthmatics has a twofold risk to develop a depression compared to healthy people. A bidirectional relation exists between asthma and anxiety. Anxiety seems to influence the perception of asthma symptoms. Severe asthmatics with poor asthma control should be screened for mood disorders (Beck, STAI/SAS) and referred to a psychiatrist on a regular basis. Only few data exist on the effect of antidepressants/non-pharmacological therapy for depression/anxiety in asthmatics and the effect on asthma control. CBT and relaxation therapy showed some positive effects on quality of life and lung function. Further research with interventional trials is urgently needed to make clear conclusions.

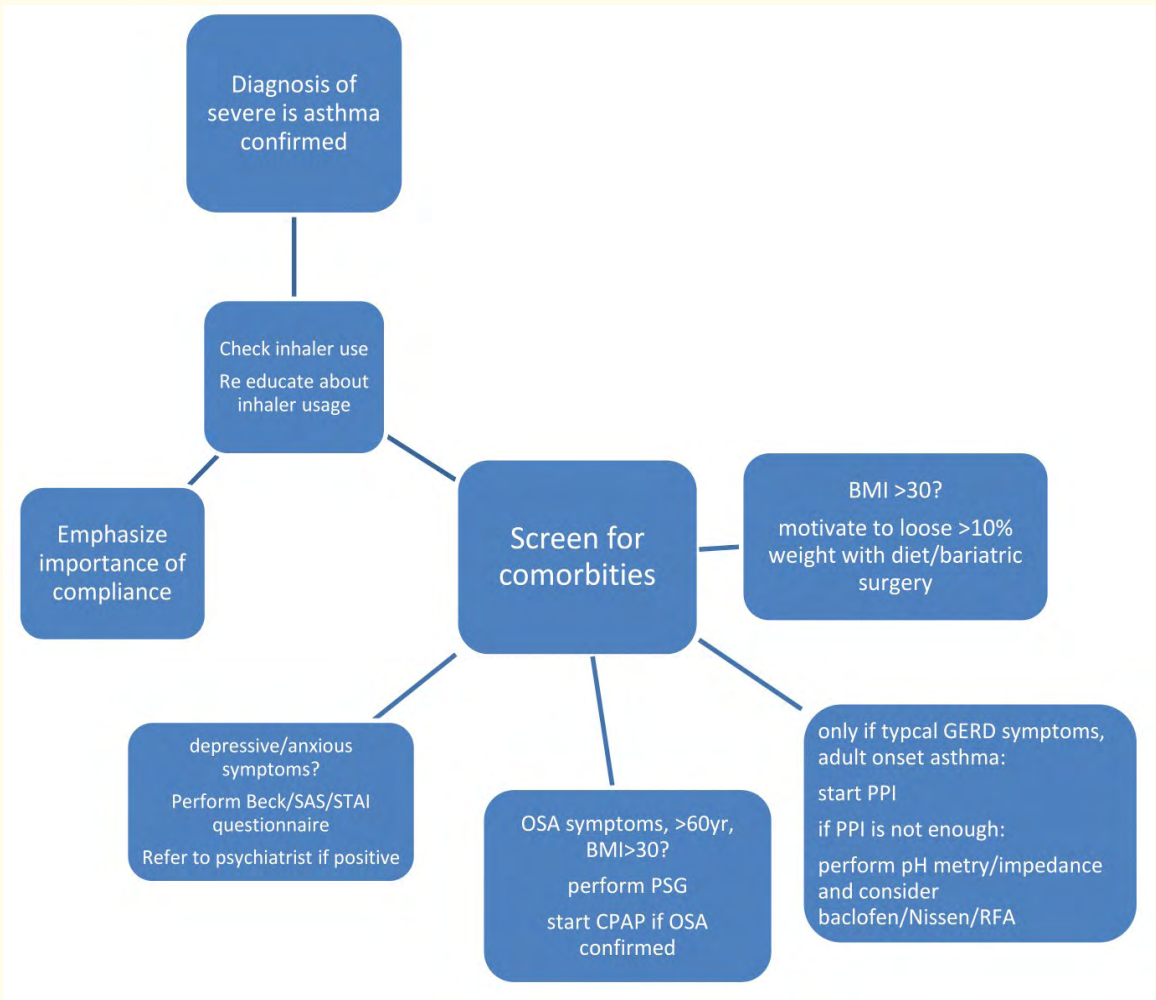


Figure 2: *Proposal of systematic history taking and screening for comorbidities in severe asthma.*

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