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Asthma and Mood Disorders

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Abstract

The high rate of comorbidity of asthma and mood disorders would imply the possibility of potential shared pathophysiologic factors. Proposed links between asthma and mood disorders include a vulnerability (trait) and state connection. Vulnerability for both asthma and mood disorders may involve genetic and early developmental factors. State-related connections may include obstructive factors, inflammatory factors, sleep impairment, psychological reactions to chronic medical illness, as well as exacerbation of asthma in individuals with chronic stress. Treatment for asthma may also exacerbate mood disorders. New research suggests involvement of the central nervous system in asthma and allergy. Further characterization of clinical, psychological, cellular and molecular interconnections between asthma and mood disorders is needed to better evaluate and treat these patients. A close collaboration between mental health professionals and allergists could result in improved symptom control, quality of life, overall functioning and ultimately, decreased mortality.

Keywords

asthma; major depression; mood disorders; suicide; anxiety disorders; inflammation; sleep

Introduction

Mood disorders, including major depressive disorder, dysthymic disorder and bipolar disorder, are common in the United States (US). Approximately 20.9 million American adults (9.5% of people ages 18 and older in a given year) have a mood disorder. Major depressive disorder is the leading cause of disability in the US for ages 15 to 44 years [1]. They are among the most expensive medical conditions and cost the US economy over $83 billion in 2000 [2]. Depressive disorders may affect children and adolescents of all ages, with an onset as early as preschool [3]. Suicide, the eleventh leading cause of death in the US representing over 32,000 deaths, occurs most often in depressed individuals. Anxiety, including panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, and phobias frequently co-occur with depressive disorders. Approximately 40 million American adults ages 18 and older have an anxiety disorder [1]. These disorders are among the most common psychiatric conditions in children and adolescents, affecting more than 10% of the youth in the general population [3].

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A chronic physical condition, such as asthma is described as one that interferes with daily functioning for more than 3 months a year and/or may cause prolonged hospitalizations [4]. Many of these conditions start in childhood, but then continue into adulthood because they are incurable. Hence, throughout a person's life, he or she may experience exacerbations of a chronic physical condition similar to flares that can occur with mood disorders and anxiety disorders. Many medical conditions can present or be associated with psychiatric symptoms. Sometimes these psychiatric symptoms can be so prominent that they can overshadow the underlying pathophysiologic process that accounts for them. Patients with a chronic medical illness and comorbid depression or anxiety report significantly more medical symptoms compared to those without depression or anxiety. Research points to a bidirectional effect between depression/anxiety and severity of the medical illness. Depression and anxiety are associated with lower adherence rates to personal care regimens and increased morbidity in patients with chronic medical illness, which may lead to increased symptoms. Mood disorders and anxiety may lead to a keen awareness of physical symptoms. An exacerbation of physical symptoms and resulting functional impairment can exacerbate episodes of depression or anxiety. In turn, an exacerbation of these symptoms can worsen the physical symptoms associated with the medical illness [5]. Chronic physical conditions are also associated with higher-than-expected rates of suicidal ideation [6].

Asthma is a prototypical chronic physical condition that has been linked with mood disorders and anxiety. It is one of the most common chronic health problems in the US and is characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. The interaction of these factors influences the clinical manifestations, severity of disease and the response to treatment [7]. According to the Centers for Disease Control and Prevention (CDC), an estimated 7.7% of the US population (22.2 million) have asthma, including 6.5 million children. Approximately 4,000 Americans die each year from asthma. Asthma accounted for 1.8 million emergency room visits and approximately 500,000 hospitalizations in 2004 [8]. In 1998, the cost of asthma was approximately $12.7 billion in the US [9]. A number of studies have investigated the interaction between asthma and mood disorders, such as depression, anxiety and suicidal ideation. These are common comorbid conditions with potential shared pathophysiology, impacted by treatment choices, adherence and level of control. A number of studies are ongoing to further investigate this relationship.

Prevalence of Depression and Anxiety in Asthma

Asthma was previously thought to be a psychosomatic disease because of the episodic nature in which symptoms would suddenly appear without warning or apparent cause. Emotional causes were frequently thought to lead to asthma exacerbations [10]. Several clinical studies have found patients with asthma have higher rates of depressive and anxiety symptoms than healthy controls. Studies also suggest that asthma is associated with increased likelihood of suicidal ideation [6]. In 2000, Zielinski et al [11] performed a literature search and reviewed eight studies specifically directed at the prevalence of depressive symptoms in children and adults with asthma. All eight studies indicated that depressive symptoms were more common in children and adults with asthma than in the general population. However, only one of the eight actually looked at the prevalence of major depressive disorder in asthma patients so no conclusion with respect to the rate of formal mood disorders in asthma patients could be made [11]. Eisner et al [12] studied 743 adults with asthma who were recruited after a hospitalization for asthma. They looked at depressive symptoms based on the Center for Epidemiologic Studies Depression Scale and found that these subjects had an 18% prevalence rate of depressive symptoms [12]. Goodwin et al [13] found that German adults 18 to 65 years old with physician diagnosed current (previous 4 weeks) and lifetime severe and non-severe asthma had a significantly higher likelihood of any anxiety disorder. Mental disorders were assessed using

the German National Health interview and Examination Survey-Mental Health Supplement (GHS-MHS) [13]. Suicidal ideation and suicidal attempt have been shown to be more prevalent among asthmatic adults and this was independent of a major depression diagnosis [5].

Adolescents and young adults similarly have been found to have higher rates of depressive and anxiety disorders. Goodwin et al prospectively examined the likelihood of depressive and anxiety disorders in a birth cohort of over 1,000 young people with asthma studied to the age of 21 years. At ages 18 and 21 years, participants were questioned about their experience with depressive and anxiety symptoms since the previous assessment, using the Composite International Diagnostic Interview (CIDI). Asthma in adolescence and young adulthood was associated with increased likelihood of major depression, panic attacks and any anxiety disorder [14]. Adolescents frequently take risks with their health, such as drug use. The Youth Risk Behavior Survey (YRBS) assesses health risk behaviors in high school students in the US. Bender recently reported that the survey found high school students with asthma report higher rates of depressive symptoms such as feeling sad or hopelessness (45.3 vs. 29.3%) than their non-asthmatic peers. He also found that they considered suicide at a higher rate than their non-asthmatic peers (31% vs. 16.2%) and the suicide attempt rate was twice the national population rates [15].

Asthma is the most common chronic illness in children accounting for most hospitalizations in pediatrics [8]. Inner city children with asthma tend to have a higher burden of disease. Goodwin et al studied a sample of 74 patients 5 to 11 years old who were screened for mental disorders with the National Health's Diagnostic Interview Schedule for Children (DISC) Predictive Scale (DPS) while in the waiting room of an inner city asthma clinic. They found almost 26% of patients had a probable depressive or anxiety disorder [16]. Morrison et al studied 46 patients ages 6 to 17 years who presented to the Children's Medical Center Asthma Clinic which primarily treats children from low-income families. Eighty-six percent of the children were on medium or high doses of inhaled corticosteroids for their asthma and 41% had mild to moderate airway obstruction even on inhaled steroids. Thirty percent of patients had Children's Depression Rating Scale, Revised (CDS-R) scores consistent with likely, very likely, or almost certain depressive disorder [17].

Most studies have depended upon patient self-report of asthma and although the diagnosis of asthma depends primarily on the history, spirometry provides an objective measure of lung function in these patients. Few studies have investigated the association between asthma based on spirometry and depression or anxiety. Goodwin et al found that adults with obstructive lung disease had significantly lower scores on the overall General Well-Being scale and a higher odds of depressive symptoms compared to subjects with no lung function abnormalities. There was no association seen with anxiety symptoms. It should be noted, however, that there was no information available for subjects' specific respiratory conditions [18]. Lavoie et al confirmed the diagnosis of asthma with spirometry and found rates of depressive and anxiety disorders in asthmatic adults (20% and 23%, respectively) to be twice as likely as the general population [19]. Meanwhile, Rimington et al found only weak correlations between anxiety and depression with 2 spirometry measures [peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1)] [20].

The impact of depression and anxiety has been investigated in relation to asthma symptoms. Richardson et al conducted a large population-based sample of adolescents with asthma (767 youth aged 11 to 17) and found that those with an anxiety or depressive disorder reported significantly more asthma symptom days in the previous 2 weeks than those without anxiety or depressive disorders. Youth with ≥1 DSM-IV anxiety and depressive disorder and asthma had significantly more asthma symptom days over the prior 2 weeks than those with asthma alone [21]. For adults recently hospitalized with asthma, depressive symptoms were associated

with poorer asthma-related health status, greater severity of asthma, poorer asthma-specific quality of life, and poorer physical health status [12]. Rimington et al measured the effect of anxiety and depression using the Hospital Anxiety and Depression (HAD) scale on asthma symptoms as measured by the Asthma Quality of Life Questionnaire (AQLQ) in 114 adults from general practitioner practices. Anxiety and depression were strongly correlated with severity of asthma symptoms [17]. Martinez-Moragon et al investigated possible determinants of dyspnea in 153 adult patients with different levels of severity of asthma using spirometry, dyspnea scales, and the Beck Depression Inventory (BDI). Independent of the severity of obstruction that the patients demonstrated, patients showed more dyspnea when they had higher levels of anxiety and depressive symptoms [22]. Anxiety and depression were shown to increase complaints of respiratory troubles in asthma patients, even when no quantitative differences in measured respiratory function were present. [23].

Few studies have evaluated whether depression or anxiety treatment affects a patient's asthma. Brown et al conducted a randomized, double-blind, parallel-group, placebo-controlled trial of citalopram in 90 depressed adults followed in an asthma clinic. Multiple visits were conducted and at each visit, the Hamilton Rating Scale for Depression (HSRD), Inventory of Depressive Symptomatology-Self Report (IDS-SR_{30}), Asthma Control Questionnaire (ACQ), and Asthma Quality of Life Questionnaire (AQLQ) were administered in addition to an assessment of oral corticosteroid use. HSRD scores decreased in both groups. Although there were no significant differences between the citalopram and placebo groups in change in ACQ or AQLQ scores, the citalopram group had significantly fewer follow-up assessments in which they required systemic corticosteroids compared to placebo group [24].

In an attempt to establish which diagnosis comes first in asthmatic patients, Solis, et al [25] collected data on patients with both asthma and major depression. They found that asthma heralded the onset of the first depressive symptoms in 62% of patients while depression preceded asthma in 24% and both presented at the same time in 14% of participants [25].

It has been difficult to establish a link between asthma and depression/anxiety. Goodwin et al suggested that the presence of specific personality factors, like neuroticism, could explain the association between mental and physical disorders. In a 2006 study, the group investigated the importance of neuroticism in those with allergy and depression. Over 3,000 adults between 25 and 75 years of age underwent the Midlife Development in the United States (MIDUS) Survey that involved a telephone interview and 2 mailed questionnaires. Multiple logistic regression analyses were used to investigate the association between depression and allergy and the role of neuroticism in these relationships. Among their male subjects they found that higher neuroticism was associated with a significantly increased likelihood of allergy. After adjusting for demographics, depression, and neuroticism, neuroticism remained significantly associated with increased likelihood of allergy. Among females, there was a significant relationship between allergy and depression but this was independent of the effects of neuroticism [26].

Pathophysiologic Connection between Asthma and Mood Disorders

Asthma is a chronic inflammatory disorder which involves airway hyperresponsiveness and bronchial obstruction. These factors lead to symptoms and signs such as cough, dyspnea, wheezing, and chest tightness. Although symptoms are easily appreciated, the fundamental pathophysiology of asthma is underlying airway inflammation, which can be present without overt symptoms.

Immune responses are regulated by T lymphocytes. Naïve CD4+ T cells can either develop into Th1 (T helper type 1) cells or Th2 cells. Th1 cells are primarily involved in response to infection; whereas, Th2 cells are primarily involved in the allergic response. Asthma is a disorder of the conducting airways characterized by Th2 cell mediated inflammation and

increased mediator release. Asthma begins early in life often in response to viral infections and in addition, in response to allergen exposure. Allergens are recognized by the immune system and taken up by antigen presenting cells (APCs). After the antigen is broken down into short polypeptides, APCs present them to T lymphocytes. For those predisposed to an allergy phenotype and in the presence of allergy-promoting cytokines, such as IL-4 and IL-13, T helper cells will develop into Th2 cells. These Th2 cells induce B lymphocytes to undergo a class switch from immunoglobulin M (IgM) to allergen-specific IgE, levels of which are increased in atopic asthma. IgE molecules will bind to receptors on effector cells, such as mast cells, basophils and eosinophils, in the respiratory mucosa leading to sensitization. Once the allergen is encountered again, it will cross-link IgE molecules and induce the effector cells to degranulate and release a host of mediators. Mediators including histamine, tryptase, cytokines, leukotrienes, and prostaglandins induce asthma symptoms [27].

For years, psychological stress has been thought to play an important role in asthma as these patients tend to have higher levels of stress and negative emotions such as panic, fear, irritability and depression. Evidence indicates that emotional stress may exacerbate the physical symptoms of atopic disorders such as asthma [3]. Some data suggest that psychological stress may shift the Th1/Th2 cytokine balance towards type 2 and cause an immune dysregulation with more allergic or asthmatic reactions during periods of high stress. Psychological stress activates the hypothalamic-pituitary-adrenocortical axis and sympathetic nervous system, leading to an increase in cortisol and catecholamine secretion. Cortisol and catecholamines can suppress Th1 cytokines such as IL-12 and IFN-γ which may then shift the immune response toward a Th2 phenotype [28]. This dysregulation is believed to play a role in the pathogenesis of asthma and allergic diseases with increased levels of IL-4, IL-5, and IL-13 in cells obtained from asthmatic patients and may further aggravate existing inflammation after an inhaled antigen exposure [29].

Liu et al [30] conducted an antigen challenge on 20 college students with mild asthma during both a low-stress phase and a stress phase. The low-stress phase was conducted during mid-semester or at least 2 weeks after final examinations while the stress phase took place during the final examination week. Questionnaires assessed for anxiety and depression. Sputum samples were collected before the challenge, and at 6 hours, 24 hours and 7 days post-challenge. Sputum eosinophils and eosinophil derived neurotoxin levels were significantly increased at 6 hours and 24 hours post-challenge and were enhanced during the stress phase. IL-5 generation was also increased at 24 hours during stress and correlated with increased sputum eosinophils. The investigators suggested that stress can act as a cofactor to increase eosinophilic airway inflammatory responses to antigen challenge and in this way increases asthma severity. It should be noted, however, there was no significant deterioration in lung function or increase in reported asthma symptoms associated with these inflammatory changes [30]. Stress management should be routinely recommended for asthmatics. Smyth et al investigated adults with mild to moderate severe asthma and stress and found that asthmatics who wrote about their most stressful experience from the past had improvements in lung function and decreases in self-reported distress levels [31].

Asthma is frequently associated with noctural symptoms and a decrease in lung function. Nocturnal cough and dyspnea are associated with cyclic shifts in airway inflammation and hyperresponsiveness. A survey study conducted in 1988 of 7,729 asthmatics found 74% of these patients awoke once a week with asthma symptoms. In the same study, 40% of the subjects actually reported symptoms every night. Sleep disturbances can manifest as difficulty in sleep onset and early arousals, sleep apneas [23,32], less time spent in the stages of deep sleep, and microarousals [32]. Microarousals can be especially frustrating, as the individual may not even realize he is awakening from sleep, yet will still experience significant negative effects to the same extent as with the other noticeable disturbances. Impaired sleep leads to

daytime fatigue, difficulty in concentration, reduced productivity, worsened mood, and, in general, a lower quality of life. Sleep impairment itself can also exacerbate or bring about depression in vulnerable individuals [33]. Moreover, the functional impairment induced by asthma may reduce participation in physical, social, and outdoor activities, the last of which means decreased exposure to natural light. All of these factors can be depressogenic. In addition, anxiety is associated with the inherent uncertainty of asthma and its attacks [34]. Interestingly, several reports have posited that hypercapnia can result in changes in activity in the locus coerulus, leading to increased anxiety [35,36].

Asthma Pharmacotherapy and Effects on Mood Disorders

Pharmacotherapy for asthma is divided into controller medications which are taken on a daily basis and rescue medications which are used for treatment of acute exacerbations. These medication regimens need to be monitored closely for adverse events, such as exacerbations of depression or anxiety symptoms. Rescue medications include short acting beta-adrenergic agonists (SABAs), anticholinergics, and systemic corticosteroids. Controller medications include inhaled corticosteroids (ICS), leukotriene modifiers, long-acting beta-adrenergic agonists (LABAs), cromones, methylxanthines and immunomodulators [7].

Inhaled corticosteroids are the most potent and most effective long-term anti-inflammatory medication available for treatment of asthma. Oral corticosteroid (OCS) bursts, such as prednisone and prednisolone, are frequently prescribed for patients with acute asthma exacerbations. Corticosteroids inhibit cytokine, prostaglandin and leukotriene production, prevent inflammatory cell activation and migration, and decrease microvascular leakage, in addition to enhancing the action of β-adrenergic receptors on airway smooth muscle. Systemic corticosteroids have been associated with depression, mania and psychosis. Brown et al evaluated adults receiving at least seven days of a minimum of 40 mg of prednisone for asthma exacerbations. Patients were assessed before, during and after systemic corticosteroid therapy with the HRSD, the Young Mania Rating Scale (YMRS), the Brief Psychiatric Rating Scale (BPRS), and the Internal State Scale (ISS). They found significantly increased manic symptoms compared to baseline. Patients with depression actually showed a decrease in symptoms compared to those without depression. These changes resolved with discontinuation of the steroids. Some suggest that mood changes seen with corticosteroids may be due to improvement in the symptoms of the physical condition; however, in this study, changes in mood measures did not show significant associations with changes in peak expiratory flow readings in a subset of patients [37]. Some patients with difficult to control severe persistent asthma on maximal medical therapy may require chronic oral steroids. Chronic steroid use seems to be associated with an increase in depressive symptoms [31]. Brown et al conducted a small follow-up study on 13 patients with either asthma or rheumatologic conditions, 6 of whom were on chronic prednisone. The HRSD, YMRS, and BPRS were administered. The prednisone treated group had higher scores on psychiatric measures than those not on chronic steroids [38]. ICS are considered the mainstay of chronic asthma management. There are concerns about the long-term safety of such medications; however, their bioavailability is significantly less than that of oral corticosteroids and numerous studies have demonstrated the relative safety of ICS in children and adults. However, if they are used at high doses for an extended period of time (i.e., years) and accompanied by frequent OCS bursts, similar adverse effects may be seen as with chronic OCS therapy [7]. For this reason, those patients with moderate and severe persistent asthma may require adjunct therapy that may also serve as steroid sparing agents, such as leukotriene modifiers, LABAs, chromones, theophylline, and omalizumab. The impact of these medications on comorbid depressive and anxiety disorders in patients with asthma have not been extensively studied.

Leukotriene modifiers, including inhibitors of leukotriene production and leukotriene receptor antagonists, affect a specific component of the inflammatory process. Leukotrienes affect bronchoconstriction, mucus secretion, and the activation and infiltration of inflammatory cells in the airway. Leukotriene modifiers have been shown to decrease rescue medication use, decrease symptoms including nighttime awakenings and improve lung function. When combined with ICS, montelukast has shown to significantly increase lung function [7]. Montelukast, a leukotriene receptor antagonist, has been rarely been associated with dream abnormalities, hallucinations, drowsiness, psychomotor hyperactivity (including irritability, agitation, aggressive behavior, restlessness, and tremor), insomnia, depression, and suicidal thinking [39].

Bronchodilators are important medications for acute and chronic management of asthma. Inhaled SABAs are preferred for acute asthma exacerbations. Side effects include tachycardia, tremor, and hypokalemia. They have been proven safe and effective in all age groups; however, if used regularly instead of as-needed, they may be associated with diminished control of asthma and increased bronchial reactivity [40]. Salmeterol and formoterol are the two LABAs approved for use in asthma in the US. They are only used in conjunction with ICS and when they are used as adjuncts, they decrease the risk of exacerbations requiring OCS, significantly improve lung function, and increase symptom-free and rescue medication-free days. They can also produce similar side effects to SABAs [7].

The chromones, cromolyn and nedocromil, are mast cell stabilizers that are alternatives, but not preferred, for mild persistent asthma. They inhibit early- and late-phase response to allergen and can be used as preventive treatment prior to exercise or unavoidable exposure to known allergens. They are the safest medications for asthma available, but because of frequent dosing, adherence is often an issue [7].

Theophylline is a phosphodiesterase inhibitor which has some bronchodilator effects and at low doses, some possible anti-inflammatory effects. It is approved for patients 5 years and older and is used for mild persistent asthma and as an adjunct to ICS in moderate and severe persistent asthma. Its use has diminished in recent years due to its potential side effects such as seizures, insomnia, anxiety, and tachyarrhythmias. Because of its narrow therapeutic range, frequency of concomitant illnesses that change its kinetics, and many drug interactions that affect its clearance, it is essential to monitor blood levels [40].

Research is being conducted on the use of immunomodulators for asthma. Omalizumab is FDA approved for the treatment of moderate to severe persistent asthma in patients 12 years and older who have proven allergen sensitivity. It is a monoclonal antibody that selectively binds to free IgE. It prevents IgE from binding to the high-affinity receptors on mast cells and basophils and, hence, prevents release of mediators that can cause airway inflammation and bronchial hyperreactivity. Postmarketing surveys have identified anaphylaxis in an estimated 0.2 percent of treated patients, which resulted in an FDA black box warning. As it is an injectable medication, there are frequent reports of injection site pain [7]. No effects on depression or anxiety have been reported.

Ongoing Research and Preliminary Clinical Implications

Evidence suggests a high rate of co-occurrence of depression/anxiety and asthma for children, adolescents and adults. More research is needed to establish the link between these conditions. More studies are also needed to determine whether concurrent treatment of depression and anxiety in asthma patients improves asthma symptoms. It is equally important for mental health providers to screen their mood disorder patients for symptoms of asthma such as persistent cough, shortness of breath, or wheezing and primary care providers to screen their asthma

patients for depressive and/or anxiety symptoms. Since, during times of high pollen counts in the spring, mood worsens [41,42] and the suicide rate is increased [43,44] we recommend paying attention to environmental pollen counts. They can, thus, identify possible periods of increased vulnerability for decompensation and suicide attempts for patients with comorbid allergy and mood disorders. This is particularly important, as molecular and cellular mediators of allergy have been identified in the brain in response to allergic sensitization and exposure [45,46]. Moreover, Th2 cytokines gene expression has been found to be increased in the brains of victims of suicide as compared with controlled subjects who died from other causes [47]. A functional imaging study has identified a neuroanatomical substrate for the interaction between emotion and asthma symptom exacerbation in the subgenual anterior cingulate cortex and insula [48]. It is important to mention that in the subgenual anterior cingulate cortex in patients with recurrent major depression a reduction of gray matter thickness has been previously reported, across episodes of illness [49,50].

Appropriate evaluation and treatment of patients with comorbid asthma and mood disorders is not only important to maintain lung function and respiratory-related quality of life, but it may also negatively impact the mood disorder if not recognized and treated appropriately. It is equally important for primary care providers and asthma specialists to recognize the association between asthma and mood disorders and screen their patients for depression and anxiety. Patients exhibiting psychiatric symptoms should be referred to mental health services. Comprehensive treatment of patients with psychiatric symptoms due to a medical condition may require multi-disciplinary care involving primary care, mental health, and specialty care personnel. If underlying depression or anxiety is not considered, this may lead to unnecessary medication changes and testing, poor adherence, higher rate of symptoms, higher medical costs and potentially higher mortality.

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