Relations between Asthma and Psychological Distress: An Old Idea Revisited

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Abstract
Asthma has long been considered a condition in which psychological distress exerts a negative impact. Epidemiological studies confirm that depression and anxiety disorders, amongst the most common psychiatric disorders, occur in higher rates in people with asthma than in the general population. Alterations in the stress axis, immune and autonomic nervous systems appear to be involved in the pathogenesis of each disorder and may contribute to the observed associations between these conditions. Although there is increasing recognition of the importance of treating psychological distress to optimize symptom control in people with asthma, there are few studies examining whether specific treatments for depression or anxiety can improve symptom control in asthma and result in better overall function and outcome.

Links between psychological factors and allergic disorders have been observed in clinical practice for centuries [1]. More formalized hypotheses regarding the link between asthma and psychological factors were put forward in the 1930s by French and Alexander [2], who described asthma as one of the seven classic psychosomatic disorders caused by specific psychological conflicts. There has been a dramatic shift in the conceptualization and treatment of asthma in the last 50 years or so, but Douwes et al. [3] recently suggested that the original conceptualization of asthma being importantly influenced by psychological factors is experiencing something of a renaissance.

Depression and the anxiety disorders have diagnostic overlap and probably shared pathophysiological processes and are two of the most common psychiatric illnesses. Below, we focus prominently on the association between asthma and either depression or anxiety (depression/anxiety). Mood and anxiety disorders are associated with both a high burden of suffering and immense health care costs. Individuals with asthma and depression/anxiety may be disproportionately affected than those with
either condition alone. In youth with depression, asthma severity is increased relative to those with asthma alone [4]. In adults with asthma, mental health problems are also associated with poor asthma control [5]. Pulmonary function tends to be lower in people with asthma and depression or anxiety [6].

Why asthma and certain mental disorders commonly co-occur is not understood. It has been suggested that asthma increases the risk of developing anxiety and depression. Less frequently, it is proposed that mental disorders increase one’s risk of developing asthma, but as over half of people with asthma become symptomatic within the first decade of life, this is unlikely to account for the majority of cases. The most provocative explanation is that asthma, depression and anxiety share common pathophysiological pathways. Given that all these conditions are complex chronic illnesses that result from interacting genetic and environmental factors, it is conceivable that they share common susceptibility genes [7] and/or environmental risk factors which account for their high rates of comorbidity.

In this chapter, we examine the clinical and epidemiological evidence supporting the links between asthma and mental disorders and examine data that suggest that the high rate of co-occurrence between these illnesses may arise at least in part via common risk factors and pathways. We then review the evidence that outcome in asthma may be improved through psychiatric interventions that may act in part to decrease features of depression, anxiety and somatization.

### Epidemiologic Evidence of the Association between Asthma and Mood and Anxiety Disorders

Individuals with asthma appear to have about a twofold higher risk of having one or more anxiety or depressive disorders [8]. To date, the most methodologically rigorous and generalizable study of the comorbidity of asthma and mental disorders suggests that adults with asthma are at increased risk of manifesting major depressive disorder or dysthymia (OR = 1.6, 95% CI = 1.4–1.8), anxiety disorders including generalized anxiety disorder, panic disorder, posttraumatic stress disorder and social phobia (OR = 1.5, 95% CI = 1.4–1.7) [9]. In this synthesis of studies from 17 different countries, individuals with asthma had rates of major depressive disorder that ranged from 5 to 25.5%, and generalized anxiety disorder from 0 to 6.7%. Despite significant variability in the populations assessed, the sampling methods utilized and means of defining both asthma and mental disorders in studies done to date, the findings of this work generally support the majority of those in the published literature to date [10, 11]. In general, population-based studies have not reported rates of co-morbidity as high as studies that evaluated depression in clinical cohorts of patients with asthma, for whom lifetime rates of depression have been recorded to be as high as 41% [12]. This may represent an accurate reflection of variation in rates of depression occurring as a function of severity of asthma; as it is possible that the overall rates of psychiatric
illness in those with mild and well-controlled asthma are low, with elevated rates observed in patients surveyed in tertiary care clinical settings who are likely to have more severe and chronic asthma.

Asthma may be more deleterious to emotional well-being than other chronic illnesses. Children with asthma appeared to be at higher risk for depression than children with other illnesses including cancer and cystic fibrosis [13] and asthmatic children seem to have more problems with affective adjustment and functional impairment than children with a cancer diagnosis [14]. In adults, particularly older adults [11], asthma is associated with higher rates of depression than other chronic illnesses, even after adjusting for psychosocial factors, physical comorbidity and the use of medications linked to depression. The study of Ortega et al. [15] of 2,554 American Latinos showed that of cardiovascular disease, diabetes and asthma, only persons with asthma had an increased risk of a depressive disorder. Ng et al. [11], compared rates of depression in older adults with doctor-diagnosed asthma to nonasthmatic controls including those with chronic illness. They found an increased risk of depressive disorders relative to controls (OR = 2.45, 1.06–5.69) and controls with chronic illnesses even after adjusting for potential confounders (OR = 2.42, 1.04–5.64). Finally, Niti and colleagues compared the rates of depression among older Asian adults with chronic medical illnesses to controls and between the types of illness. In addition to finding that depressive symptoms were higher in those with chronic illness overall, crude odds ratios were elevated for only certain chronic illnesses after adjustment for a number of relevant variables, of which asthma/COPD was the one with the highest risk (OR = 2.85, 1.36–5.98) [16]. Interestingly, though subjective health and functional status explained most of the link between depression and chronic illness, in those with asthma/COPD, these variables did not completely explain depression rates. As a result, the authors concluded that chronic respiratory illness might have a direct psychobiological link to depression.

**Mechanisms Underlying the Association between Asthma and Mood and Anxiety Disorders**

Why asthma and depression/anxiety are frequently comorbid is not well understood. One cognitive theory posits that asthma produces mental disorders because the repeated experience of asthma produces fearful or catastrophic thoughts about respiratory symptoms that produces anxiety problems over time [17]. It has also been suggested that the experience of unpredictable asthma attacks can lead to a state of learned helplessness that can produce depression [18]. Finally, others believe that the family’s exposure to asthma can produce a depressogenic environment, overwhelming parents with excessive care and financial demands [19]. One biological theory that supports the asthma→mental disorder hypothesis suggests that repeated episodes of hypoxia and hypercapnia leads brain circuits that modulate responses to
fear including those in the locus ceruleus and amygdala to become hyperreactive in response to asthma attacks or the experience of shortness of breath [17]. Over time this is thought to result in states of anxiety that can become clinical in severity.

Few studies have examined the possibility that asthma and mental disorders share common pathophysiologic pathways. The potential environmental and molecular pathways that might underlie this finding are myriad and could include diverse environmental and genetic influences potentially mediated by dysregulation of a plethora of biological pathways. We have previously reviewed these [20] and here only briefly discuss the range of genetic, familial and environmental factors that may link asthma and depression.

Familial and Genetic Associations between Asthma and Depression
It has been hypothesized that individual genes or even multiple genes in close proximity to one another (and under the control of similar regulatory elements) may be involved in the causal pathways of asthma and depression. However, while heritability estimates for asthma and depression vary from 60 to 80% [21], there is little extant evidence to support the existence of shared polymorphisms between these conditions. Indirect proof of a link between asthma and depression comes from family studies that suggest that the prevalence of one disorder is increased in the family members of index cases with the other [22]. Wamboldt et al. [23] reported that mood but not anxiety disorders were increased in the relatives of adolescents with severe asthma and that the onset of these problems was equally likely to have occurred before as after the proband’s asthma diagnosis. More recent studies provide further proof that the prevalence of mood disorders is increased in the parents of children with asthma [24] even when childhood mental illness is considered [25].

More direct evidence supporting a genetic link between asthma and depression comes from the study of Wamboldt et al. [26] of Finnish twin pairs in which they assessed the prevalence of atopic disease and depressive symptomatology. They found a within-person correlation between atopic and depressive symptoms of 0.103 and, using a best-fit model, estimated that 64% of this association was due to shared familial vulnerability, mainly additive genetic factors.

Hypothalamic Pituitary Adrenal Axis
Exposure to highly and/or chronically psychologically stressful environments in early life may also contribute to the increased risk of comorbid asthma and depression or anxiety. Indeed, research in both animals and humans suggests that chronic stress disrupts a series of physiological systems that may actually increase the risk of both asthma and mental disorders. Some have proposed that perinatal exposure to stress in youth at risk of asthma results in alterations of the hypothalamic pituitary adrenal (HPA) axis that is at first hyperresponsive but that becomes hyporesponsive over time. This downregulation of stress hormones and their effects on their receptors
may lead to reduced regulation of inflammatory responses in response to asthma triggers [27].

Maternal experience of stress in pregnancy can affect the development of central nervous, immune and respiratory systems. Indeed, the fetus is particularly sensitive to stressful environmental stimuli in utero since DNA synthesis rates are highest at that time. A recent study in humans demonstrated that prenatal psychologic stress can induce alterations in both innate and adaptive immune responses as measured in cord blood [28]. Additional physiologic stresses encountered in pregnancy could also confer risk for depression or asthma to offspring. Maternal smoking in pregnancy appears to increase the risk of mental disorders [29], and asthma [30]. Given obesity's association with a systemic inflammatory milieu [31] and since exposure to maternal obesity in pregnancy may increase the risk of psychiatric illness in offspring [32] and the likelihood that they will develop asthma later in life [33], obesity in pregnancy might also be a shared risk factor for asthma and psychiatric illness.

Postnatal stress also appears to play a role in the genesis of asthma. Childhood stress exposure is associated with an increased risk of developing asthma [34] and it is well known that stresses experienced in childhood increase the risk of a variety of psychiatric disorders. Stresses relevant to the pathogenesis of asthma and mental disorders are not merely limited to those experienced in or as a result of the child's proximal physical environment, however. Stress exposure often occurs in multiple contexts in those chronically exposed to it. Children who grow up poor not only experience more family violence, separation, and chaos but have parents who are more authoritarian and less responsive. They are also exposed to higher levels of air and water pollution, more dangerous neighborhoods and attend poorer schools and day cares [35]. The prevalence of asthma also appears to be inversely related to levels of social support [11]. In light of this evidence, it is not difficult to extrapolate this to the conclusion that early life stress may trigger genetic predispositions to asthma as well as to mental disorders.

The Immune System

Given the multiple, complex and reciprocal links between stress response systems and the immune system and the importance of both to the pathogenesis of asthma and certain mental disorders, it would not be surprising if the immune system mediated some of the effects of environmental stresses on asthma and depression. While the immune alterations in asthma, including a predilection for Th2-based immune responses are well known, immune dysregulation is also present in people with depression [36]. Sickness behavior, the emotional and behavioral symptoms that develop as a consequence of acute infection or cytokine therapy, can result from increased levels of interleukin-1 and tumor necrosis factor, and is a frequently cited link between cytokine activation and major depressive disorder (MDD) [37].

A bidirectional relationship seems to exist between cytokine and glucocorticoid (GC) signaling pathways that might explain how stress links asthma and mental
illness via the immune system. Cytokine effects on GC signaling are complex as proinflammatory cytokines seem to increase expression of the β-isoform of human GC receptor relative to the α-isoform. This imbalance contributes to GC resistance in a number of disorders, including asthma and may also be important to the development of depression. Certainly, numerous cytokines and their signaling pathways can inhibit glucocorticoid receptor signaling by downregulating the translocation and function of these receptors [20].

Stress-elicited changes in the immune and central nervous systems may occur as early as fetal life. Indeed, maternal stress responses involving the HPA axis in pregnancy and leading to cortisol release affect fetal immunomodulation and induce a Th2 cell predominance by directly affecting cytokine production [38] and preventing the development of regulatory T cells [39]. Postnatal stresses can affect immune development just as prenatal exposures can [40].

The Autonomic Nervous System
The ANS is comprised of the sympathetic (adrenergic, noradrenergic) and parasympathetic (cholinergic) systems. Depression is associated with parasympathetic, vagal or cholinergic bias [41] and people with asthma may also manifest dysregulation of cholinergic systems. As stress can affect the development of the ANS, its dysregulation could be another mechanism by which stress increases the risk of developing both asthma and emotional problems. In addition to being affected by stress, the balance between parasympathetic and sympathetic nervous system activity occurring in response to emotions may be also be germane to immune system alterations that result in airway inflammation and hyperreactivity [42]. Both GC and sympathovagal balances play a role in the development of the immune system as well as intrauterine and postnatal lung maturation [43]. Stress in utero as well as postnatally can also alter sympathovagal balance [44] and affect immunoregulation [45]. In one study, children without asthma and exposed to maternal distress showed an elevation of cortisol in response to acute stressors while asthmatic children had lower cortisol levels. The results of this work suggest that changes in the HPA axis and potentially also the ANS alter inflammatory responses to asthma triggers and may contribute to the association [46] between asthma and certain mental disorders.

While stress generally decreases parasympathetic nervous system activity in healthy persons, Lehrer et al. [47] proposed that in those with asthma, stress may lead to an increased response of both parasympathetic and sympathetic nervous systems. Miller [48] has suggested that depression is accompanied by a pattern of autonomic dysregulation that entails a cholinergic or vagal bias (i.e. vagal over sympathetic reactivity) that amplifies airway instability in asthma. He proposes that depression alters the extent of the vagal or cholinergically mediated response of airways to asthma triggers. Indeed, his group has recently demonstrated that children with asthma and depression demonstrate vagal bias when stressed, as well as increased airway resistance. While this model was not designed to assess the etiologies of asthma or depression,
it may provide a framework by which stress increases the risk of this comorbidity via the ANS.

It is apparent that the pathways linking asthma and mental disorders are complex. This is illustrated in a study by Chen et al. [49] in which low family support was associated with worse asthma symptoms via allergic inflammation and worse neighborhood conditions led to worsened morbidity via smoking. As Shalowitz [50] has noted, the studies required to understand these associations require the collection of a wide variety of variables at the individual, family, neighborhood and societal level.

**Examining Psychological Influences on Asthma Using Neuroimaging**

In addition to the impact psychosocial stress can have on the immune and autonomic nervous systems, it is possible that stress can modulate asthma symptoms [51] via direct effects on the brain [52]. There is anecdotal and empirical evidence that the stable variable of nonhypnotic suggestibility can determine the susceptibility of asthmatic patients to suggestion of bronchoconstriction, providing a construct for understanding how some, but not all, patients with asthma might be influenced by asthma-related cues [53]. Until recently, however, there were no studies that directly imaged the brain during exposure to asthma-related stimuli.

In a seminal study, Rosenkranz et al. [54] used functional magnetic resonance imaging (fMRI) to examine activity in the anterior cingulate cortex (ACC) and insula during exposure to asthma-related words when patients with asthma were exposed to allergen. The results provide provocative evidence that these brain regions were hyperresponsive to asthma-related emotional cues and afferent physiologic signals. As Rosenkrantz and Davidson [55] subsequently noted, the relative interoceptive ability of asthmatics is unknown. Asthma is characterized by hypersensitive airways, including the sensory nerves that innervate the airway; it is unknown whether this sensitization to noxious stimuli extends to the cortex. Other chronic inflammatory conditions, such as irritable bowel syndrome, show this form of sensitization [56]. The ACC receives input regarding key physical symptoms (e.g. shortness of breath) of relevance to asthma (for an extensive review of the ACC, see Devinsky et al. [57]). Along with the insula, the ACC is also crucial for the processing of emotional stimuli and is implicated in the pathophysiology of MDD. Rosenkranz et al. [54] contextualized their study by stating that 'despite the compelling support for a model integrating psychological and physiological factors in asthma, the brain has been largely absent from any discussion of its mechanistic underpinnings'.

Capuron et al. [58] also used fMRI to examine patients receiving interferon (IFN) therapy, finding that IFN-treated patients had activation of the dorsal ACC during a visuospatial task that was not present in control subjects. Interestingly, IFN-treated patients performed well on the task but appeared to require more extensive involvement of the ACC than was necessary from control subjects. Although indirect, this
study supports the hypothesis that the ACC may be important for understanding the interface of cognition, emotion, and peripheral inflammation. Studies such as these, which integrate brain imaging with physiologic symptoms or inflammatory markers, are complex to undertake but represent extraordinary opportunities to reveal the role of the brain in modulating various components of the asthmatic response.

Treatment of Psychiatric Symptoms to Improve Asthma and Health-Related Quality of Life

Katon et al. [59] examined depression and anxiety in adolescents with asthma, reporting that only about one-third of youth with anxiety had the condition recognized within the last year, and only about one in five youth with depression had adequate treatment. A commentary accompanying this article concluded that the methods used by Katon et al. [59] were probably conservative in the estimates of rates receiving treatment, so the actual rates of treatment of depression or anxiety in youth with asthma may be even lower than 20% [60]. Thus, there appears to be a significant dissociation between studies that, despite limitations, suggest that anxiety and MDD occur frequently in asthma and studies that suggest that in routine clinical practice comorbid psychiatric conditions are infrequently recognized in patients with asthma and even less frequently treated.

There does, however, appear to be increasing recognition of the importance of attending to psychological function in order to optimize outcome in patients with asthma, particularly children and youth. In general, such treatment could involve the direct treatment of symptoms of depression or anxiety in patients with asthma, or it may involve the use of psychological therapies targeted directly at the management of symptoms of asthma [61].

Pharmacologic Treatment

There is a notable paucity of data examining whether treating depression in people with asthma will improve asthma outcome. Brown et al. [62] randomized 90 patients with asthma and an episode of depression to citalopram, a commonly used antidepressant, or placebo. The impact of this intervention on asthma symptoms was difficult to evaluate between antidepressant- and placebo-treated patients because at end point there was no difference in depression scores between antidepressant- and placebo-treated patients. Nonetheless, antidepressant-treated patients required fewer oral corticosteroids and there was a correlation between asthma symptom severity and depression symptoms. Patients who had substantial improvement in depressive symptoms (regardless of whether they were medication or placebo treated) had greater improvement in a variety of asthma-related scales than patients whose depressive symptoms did not improve significantly. These results do, therefore, support the
notion that improvement in depressive symptoms may improve outcome in patients with asthma.

Another trial, conducted several decades ago, evaluated the impact of antidepressant treatment on asthma outcome. Completed in 1969, investigators examined whether the antidepressants amitriptyline and doxepin improved depressive and anxiety symptoms in patients with allergic diseases, including some patients with asthma [63]. Doxepin appeared to have a more pronounced benefit than amitriptyline but the particularly potent antihistaminergic properties of doxepin may have mediated the observed effect.

There is some evidence that tianeptine, a selective 5HT reuptake enhancer, reduces respiratory symptoms in those with asthma [64]. A small study that treated depressed people with asthma [65] found that bupropion treatment improved depressive and anxiety symptoms, but this did not translate into significant impact on FEV1 or self-reported asthma control.

In contrast to improved asthma control following treatment of depression, therapeutic agents used for asthma may worsen symptoms of depression and anxiety. Exogenous steroid administration commonly induce mood shifts and experience with immune-based therapies for other conditions highlights the fact that profound changes in mood can occur with immunotherapy, making CNS side effects, including depressive symptoms, a leading reason for treatment discontinuation. More recently, concerns were raised that the leukotriene receptor antagonist montelukast could produce suicidal thinking though thorough reviews of the evidence leading to this assertion suggest that this finding may have been spurious [66]. Studies that consider the pathophysiological points of convergence between MDD and asthma may result at a minimum in the development of new therapies that do not worsen symptoms of the other condition, increasing the likelihood that novel therapeutics will be acceptable to clinicians, patients and regulatory bodies.

Behavioral Treatment
A number of studies have examined the efficacy of psychological therapies at improving various aspects of asthma control or quality of life. These studies have been reviewed for both adults [67] and children [68] and are briefly reviewed here.

Cognitive behavior therapy (CBT) incorporates the key elements of both behavioral and cognitive models. Two studies measuring asthma knowledge as an outcome reported benefits of CBT [69], and CBT has been reported to have a positive effect on self-efficacy measures. The cognitive element of therapy tends to focus on identification and constructive management of incorrect and damaging thoughts, such as perceptions of helplessness or inappropriate fear of asthma attack that can trigger episodes. Information (e.g. about the relations between anxiety and bronchoconstriction) also targets cognitions. Behavioral elements of therapy focus on identifying the processes by which behavior has been learned and modifying behavior using methods such as systematic desensitization, selective reinforcement, and positive modeling.
Dahl found positive results following behavioral therapy when school absenteeism and use of as-needed medications were the outcome measures in young people with asthma [70].

Relaxation techniques are generally conducted with or without biofeedback and were the focus of several earlier studies of psychological interventions in asthma. Such programs generally include progressive relaxation, autogenic training, which focuses on attending to bodily feelings and mentally controlling them, and hypnosis or deep relaxation, which may be induced using mental imagery. This is often accompanied by autosuggestion to create positive thoughts and feedback of biologic indicators, which the subject must control via relaxation. Alexander et al. [71] measured the effect of relaxation therapy on peak expiratory flow and found effects favoring the treatment group compared with the control group. In addition, self-hypnosis assisted relaxation reduced emergency room visits, again in a single study that also found that self-reports of asthma improved in the self-hypnosis group [72]. In contrast, hospital admission rates were not decreased following biofeedback [73], nor were self-hypnosis rates or use of as-needed medications [74], but emergency room visits were in a single study [75]. The results from these studies highlight the variability in outcome measures employed and the difficulty of understanding these studies in a systematic manner given this variability. Breathing retraining exercises include a range of techniques for improving breathing control in asthma. These are not regarded as standard psychotherapies, although aspects of breathing retraining may be included in behavioral therapy or CBT. A Cochrane review [76] has previously examined the effectiveness of breathing retraining exercises, suggesting that conclusions must be viewed with caution.

Despite the trials of various psychological approaches in asthma, there are no sufficiently powered studies of any single therapy to draw conclusions regarding the utility of these approaches for improving asthma-related outcome. In addition to adequate power, a key issue limiting the interpretation of these studies is how to select patients with asthma for psychological intervention. It may be that a randomized controlled trial that includes patients with very mild or well-controlled asthma or only minimal psychological distress may not yield much evidence of improvement in asthma symptoms following intervention.

**Conclusions**

Psychiatric illnesses, particularly depression and anxiety, occur at higher rates in individuals with asthma than in the general population and perhaps at elevated levels compared to those with other chronic illnesses. Alterations in the HPA axis, immune system and ANS may confer risk of both disorders and account for a major component of the co-occurrence of the conditions. Work is required to understand the environmental and genetic factors relevant to the development of asthma and depression/
anxiety and the molecular pathways that underlie this. Given the high rates of depression and anxiety in people with asthma, the detection and management of psychiatric symptoms should be an integral component of medical care for people with asthma, perhaps children and youth in particular. Pharmacological and nonpharmacological treatments for depression may translate into better control of asthma, but trials are needed to determine the optimal approach to managing depression and anxiety in people with asthma.

References

76 Holloway E, Ram FSF: Breathing exercises for asthma. Cochrane Database Syst Rev 2004;CD001277

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