Allergy: A Risk Factor for Suicide?

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Opinion statement

The rates of depression, anxiety, and sleep disturbance (suicide risk factors) are greater in patients with allergic rhinitis than in the general population. The rate of allergy is also greater in patients with depression. Preliminary data suggest that patients with a history of allergy may have an increased rate of suicide. Clinicians should actively inquire to diagnose allergy in patients with depression and depression in patients with allergy.

Spring peaks of suicide are highly replicated, but their origin is poorly understood. Preliminary epidemiologic data suggest that seasonal spring peaks in aeroallergens are associated with seasonal spring peaks in suicide. Our research in Brown Norway rats demonstrates that sensitization and exposure to aeroallergens induces anxiety-like and aggressive behaviors as well as allergy-related helper T-cell type 2 (Th2) cytokine gene expression in the prefrontal cortex. Thus, it is possible that sensitization and exposure to aeroallergens, which peak in spring, may be conducive to seasonal exacerbation of suicide risk factors such as anxiety, depression, hostility/ aggression, and sleep disturbance. Connecting allergy with suicide and suicide risk factors adds to previous neurologic literature connecting allergy with migraines and seizure disorders.

Our recent report of Th2 (allergy-mediating) cytokine expression in the orbito-frontal cortex of suicide victims should lead to future studies to test the hypothesis that mediators of allergic inflammation in the nasal cavities may result in Th2 cytokine expression in the brain, influencing affect and behavioral modulation.

Certain medications used to treat allergy can exacerbate suicide risk factors, potentially worsening suicide risk and even triggering suicide. Systemic (but not topical) corticosteroids have been associated with manic and depressive episodes and mixed mood states. Recently, the US Food and Drug Administration started investigating the possibility that montelukast may trigger suicide. Although this association requires further exploration and confirmation, clinicians should err on the side of caution, inquiring about past suicide attempts; hopelessness; reasons for living; and suicidal ideation, intent, or plan; and referring the patient to a mental health professional for evaluation if appropriate.

Introduction

ALLERGY, DEPRESSION, AND SUICIDE

In 2004, suicide was the 11th leading cause of death in the United States, accounting for 32,439 deaths. For every suicide death, there are an estimated 8 to 25 attempted suicides. Most individuals who complete suicide are depressed [1, Class II]. Many short-term and long-term risk factors have been proposed, including socioeconomic factors and psychiatric symptoms and syndromes including depression, anxiety, sleep loss, and aggression. Asthma (with its

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treatment) is among the many chronic illnesses proposed to increase the risk of suicide, but allergic rhinitis has not made this list in any review or chapter known to us. The stress-diathesis model, currently one of the most accepted models of suicide vulnerabilities and triggering [1, Class II], proposes that a stressor leads to the exacerbation of a preexisting psychiatric disorder, triggering suicide. A highly replicated finding in epidemiology research is the spring peak in suicide from April to June with a mirror image in the Southern Hemisphere [2•, Class II]. There is a smaller and less consistent peak of suicide in late summer and early fall. Many factors have been implicated in contributing to the spring peak in depression and suicide, ranging from environmental (light) to social factors, but no single explanation has yet proven satisfactory [2•, Class II].

One of the most dramatic environmental changes, which coincides with physical symptoms, is the robust increase in pollen during the spring and the corresponding increased incidence of upper respiratory inflammation. Pollen is the most important and the most seasonal of the aeroallergens [3, Class III]. Every year, the air is flooded with pollen from wind-pollinated plants, and the development of allergies due to human exposure is an unfortunate consequence of this process. Tree pollination occurs in the spring and represents the largest source of airborne pollen (~ 75% of the yearly total). As an example of the time window of pollen peaks, we refer to the weekly mean values reported for total pollen production in the Baltimore, MD–Washington, DC area [4, Class I]. In April, the value typically increases from less than 100 grains/m^3 in the first week of the month to more than 1000 to 1300 grains/m^3 in the third week. The levels of pollen return to below 100 grains/m^3 by the first week of June. The dramatic increase in atmospheric concentration of tree pollen is highly relevant to human health. Another increase in atmospheric pollen occurs during the fall, mainly represented by the pollen of ragweed. Even though ragweed pollen amounts to only about 15% of the yearly pollen total, it is highly allergenic.

Consistent with the hypothesis that allergens trigger suicide in those with a triple vulnerability (ie, for suicide, mood disorders, and allergic reactions) (Fig. 1), we have found a twofold increase in the rate of nonviolent completed suicides among women younger than 65 years during the spring tree allergy season in the high-exposure period compared with the pre-exposure period (95% CI, 1.3−3.0) [5•, Class II]. This finding is consistent with the findings of Timonen et al. [6, Class II], who reported a greater seasonality of suicide in those with a history of allergy than in those without such a history. One possible explanation for this phenomenon is that one or more of the known suicide risk factors—depression, anxiety, aggression, or sleep impairment—may be affected by exposure to allergens in vulnerable individuals. Marshall et al. [7, Class II] used the Multi-Dimensional Fatigue Inventory and the Positive Affect–Negative Affect mood rating scales in patients sensitized to ragweed and reported higher levels of general and mental fatigue (but not physical fatigue), reduced motivation, increased sadness, and reduced pleasurable engagement during the ragweed pollen season as compared with the off-season. Our own work in a student population has shown that seasonality of mood is directly related to self-reported sensitivity to pollen counts [8, Class II]. Finally, we have shown that changes in allergy symptoms from low to high tree-pollen seasons correlate with changes in depression scores [9, Class II] and anxiety scores [10, Class II] in patients with recurrent mood disorders.

Increasing evidence suggests an association between recurrent depression and allergic diseases [6,11-14, Class II]. In addition, a shared risk for allergic and depressive symptoms has been described among adult Finnish twins [15, Class II].

NEUROPSYCHIATRIC SYMPTOMS ASSOCIATED WITH ALLERGEN EXPOSURE

When exposed to pollen, subjects with allergic rhinitis had decrements in reaction time, attention, and vigilance [16, Class I]. Others have reported an association of increased fatigue

and depressed mood in individuals with sensitivity to ragweed during the ragweed season [1, Class II]. Another suicide risk factor, anxiety, has been associated with allergy in women [17,18, Class II].

Immune function may play a role in depression and suicide [19-25,26•, Class II]. It is known that treatment of hepatitis C with the cytokine interferon-α, resulting in the reduction of viral titers, induces depression in a significant proportion of patients [27-29, Class II], as does treatment with the cytokine interleukin (IL)-2 in melanoma patients [30,31, Class II]. A causal relationship between cytokine treatment and depression is further suggested by the cessation of depressive symptoms when cytokine treatments are discontinued [22,32, Class II].

Moreover, several studies have reported the presence of elevated proinflammatory cytokines in depressed patients [33,34, Class II] and a reduction in these mediators of inflammation after treatment with antidepressants [35, Class II]. However, because cytokines induce sickness behavior, the validity of these studies has been limited by the overlap with the sickness syndrome. (For studies and reviews on this issue, see references 36-38, Class I.) Although the degree to which sickness, rather than depression, is involved in these effects is under debate, studies show that healthy individuals receiving low doses of lipopolysaccharides (LPS), components of bacterial cell walls, had elevated anxiety and depressive scores in the absence of sickness behavior [39, Class I]. In animal studies, behaviors that resembled depression [40, Class I] and anxiety [41, Class I] were induced by activation of the immune system with LPS. These effects have been shown to be mediated by the actions of cytokines in the brain, likely as an adaptive mechanism to cope with potentially lethal infectious agents. Although the involvement of the immune system and cytokines in the pathophysiology of depression has not been fully addressed, it is an active area of research that may contribute to fundamental advances in the understanding of mood disorders.

BRAIN CYTOKINES

We have recently reported an elevated expression of helper T-cell type 2 (Th2) cytokines in the human orbito-frontal cortex in suicide victims [42••, Class II]. We have also reported an increased tumor necrosis factor-α (TNF-α) and IL-6 cytokine expression in the hippocampus of rats after intranasal immune challenge with LPS [43•, Class I], anxiety-like behaviors in Brown Norway rats sensitized and exposed to tree pollen [44, Class II], and aggression (seen in the resident-intruder test) in rats sensitized and exposed to allergens after a swim stress [45, Class II]. The anxiety-like behaviors and aggression-like behaviors have been replicated using mice and with a different allergen, ovalbumin (Tonelli, personal communication).

Although no data show conclusively that peripheral cytokines can cross the blood-brain barrier, these cytokines can signal cells within the brain through several mechanisms. These include direct actions of circulating cytokines via circumventricular organs, cytokine signaling through the vagus nerve [46, Class II], de novo transcription of cytokine genes in astrocytes, and microglia induced by inflammatory mediators produced by endothelial cells of the cerebrovasculature [47-52, Class II].

Several mechanisms have been proposed to explain how cytokines may affect brain function and behavior. Two of the most important are interactions with the hypothalamic-pituitary-adrenal (HPA) axis and with the indoleamine deoxygenase enzyme. Cytokines can induce activation of the HPA axis [53, Class III], resulting in altered levels of corticotropin-releasing hormone and cortisol with detrimental effects for neurons. Activation of the indoleamine deoxygenase enzyme steals tryptophan from serotonin synthesis toward production of kynurenines and reduces serotonin production. Moreover, direct interactions between brain cells and cytokines also have been proposed [54, Class II].

Thus, one important mechanism of neuroimmune interactions is the brain's capacity to produce cytokines in response to peripheral immune challenge [47,55-57, Class II]. This mechanism may change the balance of cytokine expression in the brain and, in turn, may affect neuronal function in response to inflammatory processes initiated in the periphery.

SLEEP IMPAIRMENT

Insomnia, hypersomnia, nightmares, and sleep panic attacks are important suicide risk factors [58, Class III]. Correcting them may reduce suicide risk relatively swiftly [59, Class III]. Proinflammatory cytokines, such as TNF-α, IL-1, IL-6, and interferons, tend to induce sleepiness and sleep [60-64, Class II]. In contrast, "anti-inflammatory cytokines" have been reported to disrupt sleep. For instance, it has been reported that IL-4 [65, Class II] and IL-10 [66, Class II] inhibit spontaneous sleep. Sleep, suicide, and cytokines could also be interconnected via HPA axis activation [67, Class II].

Moreover, in addition to the effects of cytokines, mechanical obstruction secondary to mucosal edema and secretions in the upper respiratory tract could be a direct cause of sleep disturbance and daytime sleepiness and may exacerbate or make manifest an obstructive sleep apnea. Intranasal corticosteroids are effective agents in improving sleep in patients with allergy [68, Class II].

GENDER EFFECTS

A stronger association between allergy, depression, and suicide in women may be explained in part by an increased incidence of allergy and depression in women, or by increased anxiety associated with depression in women [18, Class II]. To a certain degree, the effects could be hormonal. Specifically, beta estradiol and progesterone significantly increase the production of IL-4 and IL-13 [69, Class II], whereas testosterone inhibits histamine release and eosinophil degranulation [70, Class II]. Estrogens favor a Th2 IgE–mediated response, which may explain, in part, the increased prevalence of allergic disease in women of reproductive age as compared with men [71, Class II].

INTRANASAL-INTRACRANIAL COMMUNICATION

As much as the brain is (incorrectly) considered an "immune-privileged organ," the relationship between the nasal cavity and the brain is also a "privileged" and "intimate" one. First, the nasal cavity is the only place in which central nervous tissue (ie, the olfactory neurons) is directly exposed to air carrying chemicals, pathogens, pollutants, and allergens. Second, the transfer of large molecules and pathogens into the brain via the intranasal pathway has been reported [72-75, Class II]. It is important to mention that the intranasal pathways may, via olfactory and trigeminal pathways, deliver large molecules into brain areas that play a key role in mood regulation and dysregulation more efficiently than intravascular administration [73, Class II]. In addition, it has been shown that intra-nasal instillation of recombinant cytokines, including IL-6 and IL-12, affects the course of experimentally induced neurologic disorders in rats [76,77, Class II].

ALLERGIC RHINITIS: CLINICAL CONSIDERATIONS

Allergic diseases affect 10% to 30% of adults and nearly 40% of children [78,79, Class II] and are increasing in prevalence for unknown reasons [80, Class II]. Symptoms of allergy are occasionally life-threatening, sometimes debilitating, and frequently very bothersome. In the lungs, allergy is manifested by bronchoconstriction or asthma; in the nose, by rhinitis; in the skin, by urticaria; and in the eyes, by conjunctivitis. Anaphylaxis—the systemic and life-threatening manifestations of allergy—requires immediate medical attention. For several reasons, this article focuses on allergic rhinitis. First, in contrast to allergic rhinitis, asthma is

often treated with systemic corticosteroids, which may themselves cause neuropsychiatric symptoms. Second, because of anatomic proximity, inflammation of the nasal cavities may have a closer relationship with the brain than inflammation of the skin, lungs, or digestive tract. The distinction between asthma and nasal inflammation is somewhat illusory, however, because more than 60% of individuals with rhinitis also have asthma, and allergic rhinitis frequently progresses toward allergic asthma [81, Class II].

Rhinitis symptoms include rhinorrhea, nasal congestion, sneezing, itching of the nose, postnasal drainage, or a combination of these. Allergic rhinitis also is often associated with symptoms of allergic conjunctivitis, including tearing, redness, ocular itch, and sometimes swelling and photophobia. In addition to allergic variables, irritant, infectious, hormonal, occupational, and other factors may predispose individuals to rhinitis or may trigger or aggravate it [82, Class II].

Peak presentations of allergic rhinoconjunctivitis occur between ages 10 and 25 years. Rhinitis has traditionally been classified as "seasonal" or "perennial," but recently there has been a tendency to classify rhinitis as intermittent ($\leq$ 4 days per week or, if > 4 days per week, then total duration of < 4 weeks) or persistent [83, Class III]. Allergic rhinitis is classified as moderate/severe rather than mild if symptoms are severe or if they result in impairment of sleep, daily activities, work, or school.

RESEARCH DIRECTIONS

Animal studies, as an immediate priority, can test the effect of medications used to treat allergy in behavioral analogues of suicide risk factors (eg, aggression, behaviors resembling depression or anxiety, impulsivity, sleep impairment) at baseline and after sensitization and exposure to antigens. Animal studies also can elucidate mechanisms of transmission of inflammation from the nasal cavity to the brain and test mechanisms of interventions. Larger postmortem studies with better controls are needed to localize the cellular substrate of Th2 inflammation in the brain using in situ hybridization. Large-scale clinical trials could compare the effect on suicide risk factors of intranasal corticosteroids, antihistamines, and leukotriene inhibitors in patients with recurrent mood disorders (preferably those with a history of suicide attempts). Functional neuroimaging studies are needed to determine brain activity changes with exposure to aeroallergens in sensitized individuals stratified by diagnosis of mood disorders and suicide attempt history (number, severity). Epidemiologic studies are needed to study completed suicide; for replication, it is essential to confirm a relationship between suicide (completed and attempted) and prior history of allergy and timing of exposure to allergens, ideally with adjustment for history of mental and medical illness and socioeconomic factors previously implicated in suicide.

The relationships described in this article add to previously reported associations between allergy and neurologic conditions such as migraines [84,85, Class II] and epilepsy [86, Class II], between mast cells as central cells in both allergy and migraine pathophysiology [87, Class II], and between intranasal administration of cytokines and seizure thresholds [76]. To move our knowledge further, from association toward causation, it is important to study (probably at multiple levels) the effects of allergen exposure (intensity and timing), allergic sensitization, and nasal inflammation in general (allergy-induced, viral, bacterial, cold-induced, or idiopathic) on brain function and dysfunction. In parallel, clinicians should be familiar with the current standards of treatment of allergic rhinitis. Animal studies are needed to systematically examine the effects on suicide risk factors. of medications used to treat allergy. Understanding the interface between allergic inflammation and brain function requires multilevel observational—and especially interventional—approaches (epidemiologic, treatment trials, imaging, animal, postmortem).

PATHOPHYSIOLOGY

Certain individuals with an atopic predisposition synthesize IgE antibodies upon initial exposure to allergen. IgE binding to mast cells and basophils sets the stage for the allergic response. Upon re-exposure, allergen binds and crosslinks IgE bound to the cell surface, resulting in the release of inflammatory mediators. Early response mediators include lipid mediators (leukotrienes, prostaglandins) and granule mediators (histamine, tryptase). Minutes to hours later, cytokines such as TNF-α, IL-4, IL-5, and IL-6 and chemokines (IL-8, monocyte chemotactic protein-1, macrophage inflammatory protein-1α) are released [88, Class II]. The type of allergen, the degree and length of exposure, and the atopic tendency of the individual determine the manifestation of symptoms. Allergen contact occurs via the air (seasonal aeroallergens tree, grass, and weed pollen and perennial dust mite protein, animal dander, and mold), food, drugs, and skin (stinging insects).

Allergic rhinitis pathophysiology is characterized by edema of the nasal mucosa as a result of IgE-mediated release of early-phase and late-phase mediators and Th2 cytokines, which promote the infiltration of mucosa with inflammatory cells: eosinophils, neutrophils, basophils, T cells, and macrophages [79, Class I].

DIAGNOSIS

In addition to the symptoms of allergy, in vivo and laboratory-based testing for allergen sensitivity may objectively support the diagnosis of allergic disease [79,82,89,90, Class II]. Skin prick and intradermal testing measure IgE-mediated hypersensitivity in the skin, quantifying the wheal and flare response within 15 minutes of allergen contact. The skin prick and intradermal testing lose their value if skin response is decreased through treatment with antihistamines, antihistaminic effects of other medications (including many psychotropic agents), or increased skin sensitivity from dermatographism. In that case, specific IgE antibodies may be detected in serum with comparable sensitivity and specificity [91, Class I].

Treatment

- There are no current data on the treatment of allergic rhinitis in individuals with a history of neuropsychiatric conditions. Nevertheless, good management of nasal inflammation may be very important for the general management of neuropsychiatric conditions, specifically recurrent mood disorders with an increased risk for suicide. The general principles of treatment are given here. Future studies ideally will successfully focus on the treatment of allergic rhinitis in patients with depression, the treatment of depression in patients with allergic rhinitis, and the effects on specific suicide risk factors of each medication from the antiallergy arsenal.

Diet and lifestyle

- Minimize contact with allergens. Avoid outdoor exposure when aeroallergen counts are high. For seasonal aeroallergens, a useful resource is the National Allergy Bureau, which provides the most accurate and reliable pollen and mold counts from approximately 75 counting stations throughout the United States and two counting stations in Canada.

- Reduce the aeroallergen load to the mucosa. Saline nasal irrigation is a safe and effective method of cleansing the nasal mucosa of allergens and improving sinus symptoms [92, Class II].

- Reduce allergen load in microclimates. Vacuum cleaning, furnace filters, dehumidifiers, "allergy bedding," and washing bed linens in hot water may reduce

exposure to dust mites (the most important perennial allergen) and other perennial allergens (Class III).

Pharmacologic treatment

Choice of medications

- Drug therapy for allergic rhinitis has many aims: stabilizing mast cells, reducing the effects of histamine, reducing inflammation, reducing secretions, reducing the production and effects of inflammatory mediators, reducing activation of prostaglandin pathways, maintaining the patency of sinuses and lacrimal channels, treating pain from sinus infection, and desensitization.

- Clinicians should ask about depression, anxiety, and sleep disturbance, and treat them if present.

- Clinicians also should ask about suicidal ideation and consider whether medications the patient is taking are increasing the risk of suicide. Referral for evaluation of suicide risk and preventive treatment may be appropriate.

- Drugs used to treat allergic rhinitis (Table 1) include decongestants (oral and intranasal), antihistamines (oral and intranasal) (Table 2), corticosteroids (intranasal, rarely oral or parenteral) (Table 3), cromolyn (intranasal), anticholinergics (intranasal), and some newer combinations.

- Debate on the sequence of use or combination of these agents has generated many studies. Weiner et al. [93, Class I] completed a worldwide meta-analysis of intranasal corticosteroids versus oral antihistamines, including 2267 patients with allergic rhinitis in 16 studies. End points were nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, nasal discomfort, total nasal symptoms, nasal resistance, eye symptoms, and global ratings. The results demonstrate a superiority of intranasal corticosteroids over antihistamines. This conclusion was confirmed by Yáñez and Rodrigo [94, Class I], who showed the superiority of intra-nasal corticosteroids for ameliorating nasal blockage, sneezing, nasal discharge, nasal itch, and total nasal symptoms.

- Antileukotrienes have been shown to be effective for treating daytime symptoms of allergic rhinitis but not for night symptoms [95, Class I].

- Decongestants such as pseudoephedrine and phenylpropanolamine are effective in reducing nasal congestion from rhinitis, but they can cause insomnia, loss of appetite, and excessive nervousness [96, Class II]. Topical alpha-adrenergic nasal decongestants are commonly used but may cause rhinitis medicamentosa, a syndrome of rebound nasal congestion, when overused.

- Antihistamines are commonly used to treat symptoms of allergic rhinoconjunctivitis. Antihistamines have long been the standard therapy for allergic rhinitis and are effective in relieving symptoms of itching, sneezing, and rhinorrhea, as well as allergic conjunctivitis. They have been shown to relieve symptoms of seasonal and perennial rhinitis [97, Class I].

- A recent investigation by the US Food and Drug Administration (FDA) of the possibility that montelukast (Singulair; Merck & Co., White-house Station, NJ) may trigger suicide awaits additional data and conclusions. As montelukast neither improves sleep in allergic rhinitis (sleep disruption being a suicide risk factor) nor reduces production of cytokines (as would an intranasal corticosteroid), it may be possible that montelukast does not directly trigger suicide but rather fails to reduce suicide risk mediators elevated by the allergic inflammation. This question will

require additional longitudinal studies. In the meantime, Merck has updated the prescribing information and patient information for Singulair to include the following postmarketing adverse events: depression (April 2007), suicidality (suicidal thinking and behavior) (October 2007), and anxiousness (February 2008). The FDA [98, Class III] currently recommends monitoring patients taking Singulair for suicidality and changes in mood.

Sequence of treatment

- Recent recommendations [99, Class II] suggest a stepwise approach:

  Mild, intermittent allergic rhinitis can be treated with 1) avoidance of allergens and irritants, 2) an oral or local nonsedating H1 histamine blocker, or 3) an intranasal or oral decongestant, each for fewer than 10 days.

  Moderate to severe or persistent allergic rhinitis can be treated with intranasal corticosteroids as a first-line treatment. If major blockage occurs, add a short course of decongestant. Reassess in 2 to 4 weeks; if symptoms persist, add an oral antihistamine (with or without decongestants) and ipratropium.

  For persistent allergic rhinitis, regardless of severity, consider the addition of allergen immunotherapy.

- For specific drugs, see Table 1.

- For dosages, see Table 2 (antihistamines), Table 3 (intranasal corticosteroids), and Table 4 (leukotriene inhibitors).

Interventional procedures

Subcutaneous immunotherapy—For effectiveness, see reference 100•• (Class I).

Standard procedure: Patients with allergic rhinitis, allergic conjunctivitis, allergic asthma, or insect allergy who have evidence of specific IgE antibodies correlating with suspected environmental triggers, patient exposure, and clinical history may be candidates for subcutaneous immunotherapy (SCIT). Once the potential benefit is established (taking into consideration response to standard pharmacotherapy, convenience, cost, and risks of anaphylaxis), an extract of the specific allergens likely to cause allergic symptoms is made. The immunotherapy begins with a build-up phase of injections, with the ultimate goal of reaching a maintenance phase. The maintenance phase is the dose that achieves clinical efficacy. For inhalant allergens, it is generally administered every 2 to 4 weeks.

Contraindications: Medical conditions that may impair a patient's ability to survive an anaphylactic reaction or the necessary treatment of this reaction. Examples are severe asthma, cardiovascular disease, and β-blocker use.

Complications: Anaphylaxis, large local reactions, cellulitis.

Special points: Effect size with SCIT (standardized mean difference, 95%) is −0.73 (95% CI, −0.97 to −0.50). The comparable figures with medications are −0.57 (95% CI, −0.82 to −0.33) [100••, Class I].

Sublingual immunotherapy—Clinical efficacy has been supported by several studies [101, Class II]. However, the optimal maintenance dose, dosing schedule, and mechanism of action have not been established.

Standard procedure: Standard procedure has not been established. Current protocols include a sublingual tablet or liquid containing allergen extract that is ingested daily.

Contraindications: Same as for subcutaneous immunotherapy.

Complications: Anaphylaxis; gastrointestinal symptoms such as mouth, throat, and tongue irritation or swelling. Headaches have been reported [102, Class II].

Special points: The effect size (standardized mean difference, 95%) is −0.43 (95% CI, −0.57 to −0.28). With medications it is −0.41 (95% CI, −0.55 to −0.28) [97, Class II].

Emerging therapies

Anti-IgE antibodies

- Given the central role of IgE in the pathogenesis of allergic disease, it stands to reason that inhibiting IgE responses by using anti-IgE antibodies would decrease its sensitizing effects on mast cells and basophils. Several studies indeed indicate that anti-IgE therapy is effective in treating asthma and allergic rhinitis [103, Class II].

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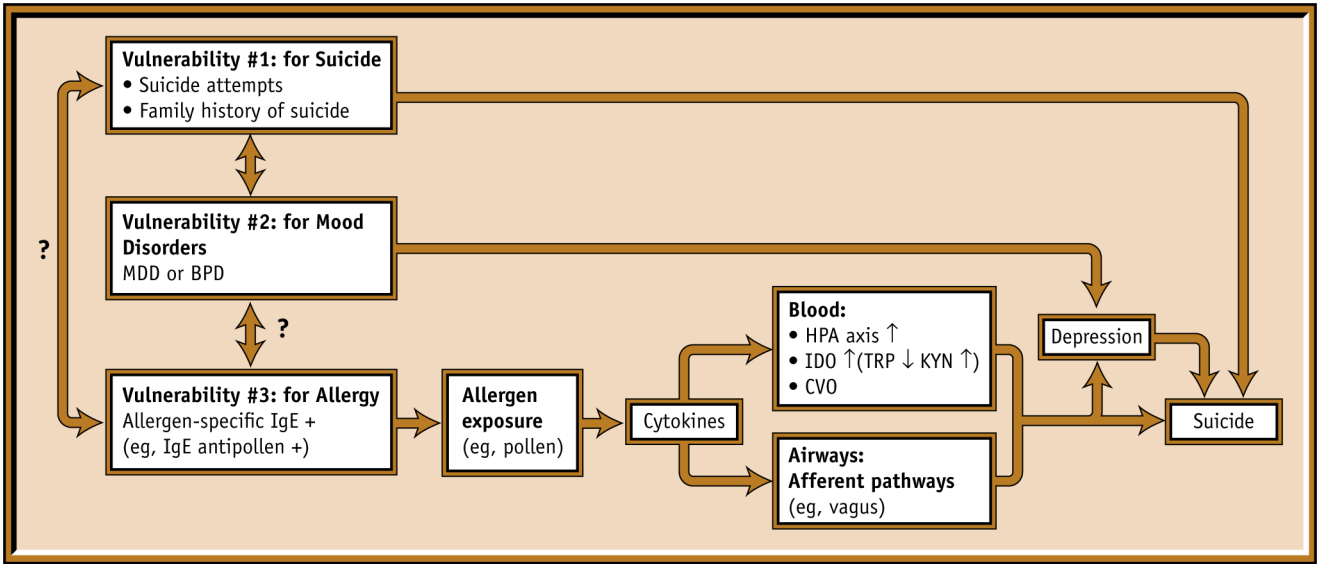
Figure 1.
Triple vulnerability for suicide, mood disorders, and allergic sensitization with an environmental trigger (allergen). Mechanisms by which cytokines affect the brain include activation of the hypothalamo-pituitary-adrenal (HPA) axis and the actions of indoleamine deoxygenase (IDO), an enzyme involved in the catabolism of tryptophan (TRP), stealing it from the TRP hydroxylase pathway and serotonin synthesis and producing potentially neurotoxic compounds such as kynurenine (KYN). In addition, several small areas of the brain (the circumventricular organs, CVO) lack a blood-brain barrier and allow larger molecules such as cytokines to interact with neurons, their terminals, and glial cells. BPD—bipolar disorder; MDD—major depressive disorder.

Table 1

Pharmacologic treatment of allergic diseases related to mental health

Drug	Mode of action	Uses	Comments	Suicide risk considerations
Antihistamines	Histamine antagonist at HI receptor site	Allergic rhinitis and conjunctivitis, urticaria, allergic asthma	First-line therapy for mild or intermittent symptoms	1st generation: somnolence, cognitive dysfunction
Oral, 1st generation			Often combined with oral decongestant	2nd generation: less prominent, although sedation possible
Oral, 2nd generation			For symptoms rhinorrhea, sneezing, nasal and ocular itch	Attention to combinations; propensity to potentiation of ethanol and other sedating medications
Intranasal			2nd generation: less significant CNS side effects	
Topical (optical)			Not very effective for congestion (may require addition of decongestant); minimal effect on cytokine production	
Corticosteroids	Anti-inflammatory	Treatment of many allergic diseases: allergic rhinitis and conjunctivitis, asthma, urticaria	First-line therapy for moderate/severe and persistent symptoms	Systemic: may cause depression, mania, psychosis
Oral			Potent anti-inflammatory; reduces cytokine production and effects	Local (eg, intranasal): compliance often is not very good; some mild systemic effects with local administration
Inhaled			Intranasal first-line therapy for moderate to severe symptoms of rhinitis	
Intranasal			Oral: severe exacerbations of asthma, urticaria	
Topical (skin)				
Decongestants	Alpha adrenergic agonist causes nasal vasoconstriction	Rhinitis	Reduce nasal congestion	Phenylephrine, phenylpropanolamine, pseudoephedrine, and synephrine may cause agitation, restlessness, insomnia, anxiety
Oral			Intranasal may cause rebound nasal congestion (rhinitis medicamentosa)	
Intranasal				
Cromolyn/nedocromil sodium	Mast cell stabilizer; inhibits degranulation	Asthma, allergic rhinitis	Nonsteroidal anti-inflammatory	Few, if any, CNS effects
Oral			Minimal side effects	
Inhaled			Mild efficacy	
Intranasal			Requires frequent administration (daily dosing, poor compliance)	
Anticholinergics	Muscarinic receptor antagonist	Asthma, rhinitis	Effectively reduces rhinorrhea	May add to anticholinergic effects of psychiatric medications
Inhaled			Role in acute bronchospasm	
Intranasal				
Leukotriene inhibitors	Phospholipid metabolism inhibition	Asthma	Effective for daytime symptoms	Depression, anxiety, suicidal ideation
Oral (montelukast, zafirlukast, zileuton)			Steroid-sparing	Ongoing investigation of possibility of increased suicide risk with montelukast (check FDA website)
			Adjust for liver impairment, monitor liver enzymes	
			Zafirlukast and zileuton inhibit metabolism of warfarin	

Drug	Mode of action	Uses	Comments	Suicide risk considerations
Allergen immunotherapy	Th2 response suppression, Th1 response stimulation	Allergic rhinitis and conjunctivitis, asthma	Clinical efficacy confirmed in allergic rhinitis and allergic asthma (SCIT)	Unknown, caution recommended considering possible immune connections
Subcutaneous (SCIT)			Emerging evidence efficacy in allergic rhinitis (SLIT)	
Sublingual (SLIT)				
Anti-IgE antibody	Reduces serum IgE	Severe asthma, possibly chronic urticaria and other IgE-mediated diseases	Approved for severe asthma	Unknown
IM injection			Requires multiple IM injections Expensive	

CNS—central nervous system; FDA—US Food and Drug Administration; IM—intramuscular; Th1—T helper cell type 1; Th2—T helper cell type 2.

(*Modified from* Komarow HD, Postolache TT: Seasonal allergy and seasonal decrements in athletic performance. Clin Sports Med 2005, 24:e35—e50, and Postolache et al.: Allergy, depression, and suicide. Directions of Psychiatry 2005, 25:59−70.)

Table 2

Dosage and administration of antihistamines for allergic rhinitis

Generic name	Trade name	Available with decongestant?	Dosage
Diphenhydramine HCl	Benadryl[*]	No	Adults: 25−50 mg tid Children 6−11 years: 5 mg/kg/d
Chlorpheniramine maleate	Chlor-Trimeton[†]	Yes	Adults: 8−12 mg bid Children: 6−11 y, 0.35 mg/kg/d; 2−5 y, 1.25 mg bid
Hydroxyzine HCl	Atarax[*]	No	Adults: 25−50 mg bid Children: 2 mg/kg/d
Loratadine	Claritin[†]	Yes	Adults: 10 mg qd Children 6−11 y: 10 mg qd
Desloratidine	Clarinex[†]	Yes	Adults: 5 mg qd Children: 6−11 y, 2.5 mg qd; 1−5 y, 1.25 mg qd
Cetirizine HCl	Zyrtec[‡]	No	Adults: 5−10 mg qd Children: 6−11 y, 5−10 mg qd; 2−5 y, 2.5−5 mg qd
Fexofenadine	Allegra[§]	Yes	Adults: 60 mg bid, 120 mg qd
Azelastine HCl	Astelin[¶]	No	Adults: 2 sprays/nostril bid Children 5−11 y: 1 spray/nostril bid (0.1% solution)

bid—twice a day; qd—every day; tid—three times a day.

[*] Pfizer.

[†] Schering-Plough.

[‡] McNeil-PPC.

[§] Aventis.

[¶] AstraZeneca.

Table 3

Dosage and administration of topical corticosteroids for allergic rhinitis

Generic name	Trade name	Delivery	Dosage
Beclomethasone	Beconase,[*] Vancenase,[*] Beconase AQ,[*] Vancenase AQ[*]	Fluorocarbon aerosol, liquid spray	1 spray = 42 μg; 1−2 sprays/nostril bid to tid
Triamcinolone	Nasacort,[†] Nasacort AQ[†]	Fluorocarbon aerosol, liquid spray	1 spray = 55 μg; 1−2 sprays/nostril qd to bid
Flunisolide	Nasalide,[‡] Nasarel[‡]	Liquid spray	1 spray = 25 μg; 1−2 sprays/nostril bid
Mometasone	Nasonex[§]	Liquid spray	1 spray = 50 μg; 2 sprays/nostril qd
Budesonide	Rhinocort,[¶] Rhinocort AQ[¶]	Fluorocarbon aerosol, liquid spray	1 spray = 32 μg; 1−4 sprays/nostril qd
Fluticasone	Flonase[*]	Liquid spray	1 spray = 50 μg; 1−2 sprays/nostril qd

AQ—aqueous; bid—twice a day; qd—every day; tid—three times a day.

[*] GlaxoSmithKline.

[†] Aventis.

[‡] Ivax Laboratories.

[§] Schering-Plough.

[¶] AstraZeneca.

Table 4

Leukotriene inhibitors for the treatment of allergy and asthma

Generic name	Trade name	Dosage	Therapeutic issues
Montelukast	Singulair[*]	Adults: 10 mg qhs Children: 6−14 y, 5 mg qhs; 2−5 y, 4 mg qhs	Renal adjustments: none Hepatic adjustments: in mild to moderate disease
Zafirlukast	Accolate[†]	Age ≥ 12 y: 20 mg bid 5−11 y: 10 mg bid	Renal adjustments: none Hepatic adjustments: not defined Monitor hepatic enzymes every 2−3 mo Administration with meals decreases bioavailability; take at least 1 h before meals or 2 h after Inhibits metabolism of warfarin (Coumadin), increasing prothrombin time
Zileuton	Zyflo[‡]	Patients > 12 y: 600 mg with meals and qhs	Can inhibit metabolism of warfarin, theophylline, and propanolol Monitor hepatic enzymes every 2−3 mo

bid—twice a day; qhs—at bedtime.

[*] Merck.

[†] AstraZeneca.

[‡] Critical Therapeutics, Inc.