Disturbed sleep: linking allergic rhinitis, mood and suicidal behavior

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1. ABSTRACT

Recent research has consistently shown an association between inflammation and sleep, with Th1 cytokines promoting NREM sleep and increasing sleepiness and Th2 cytokines (produced during allergic inflammation) impairing sleep. As sleep impairment is considered a treatable suicide risk factor strongly associated with mood disorders, we review the literature leading to the hypothesis that allergic rhinitis may lead to mood and anxiety disorders and an increased risk of suicide via worsening sleep. Allergic rhinitis can impair sleep through mechanical (obstructive) and molecular (cytokine production) processes. The high prevalence of mood and anxiety disorders and allergy, the nonabating suicide incidence, the currently available treatment modalities to treat sleep impairments and the need for novel therapeutic targets for mood and anxiety disorders justify multilevel efforts to test and better understand this pathophysiological link where, relatively limited if timely, interventions may have large beneficial effectgs. .

2. INTRODUCTION

Insufficient and disturbed sleep has been associated with suicide and suicidal ideation and behavior ("suicidality") (1-4). Thus, conditions resulting in disturbed sleep might also be associated with suicide and suicidal behavior. One frequently encountered somatic condition resulting in disturbed sleep is allergic rhinitis. Allergic rhinitis has a high prevalence, with 10-30% of adults and nearly 40% of children suffering from its symptoms (5, 6). Allergic rhinitis is associated with both sleep disturbance as well as mood disturbance (7). We discuss evidence suggesting a connection between allergic rhinitis (and its molecular mediators), depression, suicidal behavior and suicide.

3. SLEEP

Sleep is a biological process that appears to be essential for physical and mental well-being. Sleep not only has an influence on neurobehavioral functions such as

alertness, attention, cognitive functioning, memory consolidation, and mood, but also significantly affects the immune and neuroendocrine system. It may also be considered an evolutionary neurobehavioral state involving the interaction between neurons and neural circuits where excitatory and inhibitory changes occur intermittently. As first described by Borbely (8), two interconnected processes contribute to sleep and wake regulation: a circadian process driven by the suprachiasmatic nucleus of the hypothalamus (termed Process C) and an appetitive, homeostatic process (termed Process S). The mutual inhibition of wake-promoting and sleep-promoting regions, analogous to an electronic "flip-flop" switch, regulate Process S (9). This flip-flop switch maintains distinct sleep and wake states, with relatively sharp transitions, avoiding prolonged and dangerous intermediate states (10).

Sleep impairment may result in the deterioration of several aspects of mental functioning including, cognition(11), mood (12), and emotion (13). Chronic insomnia is a risk factor in the pathogenesis of psychiatric disorders such as depression and may act as a pre-indicator of future depressive episodes (14).

Sleep has several stages distinguishable by polysomnography (PSG). The awake brain emits predominantly alpha and beta waves. Alpha waves (8 to 13 Hz) are associated with a decrease in brain activity, generate while alert and relaxed with eyes closed, and become attenuated by open eyes and drowsiness. Beta waves (13 to 30 Hz) are expressed while in an aroused state such as during periods of alertness, attentiveness, and mental exertion. Sleep is comprised of two vastly different states categorized as either rapid eye movement (REM) or non-rapid eye movement (NREM) sleep. The first three stages of sleep comprise NREM sleep: a) stage 1 - transient period between wakefulness/sleep where alpha waves transition to theta waves (4 to 7 Hz); b) stage 2 - continuation of theta waves and presence of distinctive wave patterns of sleep spindles (12-16 Hz) and K-complexes accounts for 45-55% of total sleep; c) slow wave sleep or SWS (previously regarded as stages 3 and 4 during which greater than 20% of wave patterns are delta waves (0.5 to 4 Hz). The first episode of REM sleep appears within about 80 to 100 minutes of sleep onset, and usually lasts for approximately 10 minutes, shorter at the beginning of the night and longer towards the end of the night. REM sleep duration increases during each NREM-REM cycle resulting in the length of the final REM period of approximately 1 hour. During REM sleep, there is an abrupt loss of muscle tone, paralysis of skeletal muscles, as well as lowered heart rate and respiration. But brain activity remains similar to a wake status with a mixture of alpha, beta, and desynchronous waves. Adult sleep is generally composed of 75-80% NREM and 20-25% REM; however, these proportions vary with age (15). During NREM sleep, neuronal firings in the brainstem, cerebral cortex, and some forebrain regions are reduced. Presently it is believed that certain stages of sleep are required for the restorative qualities of feeling well rested and alert the following day, while other stages are required to establish and refine memories. The quality and quantity of sleep mediate

learning and memory, which may be influenced by three functions including acquisition of new information, consolidation of memory storage, and recall of information after storage. Evidence suggests that sleep promotes memory consolidation (16-18). Sleep disruption (19) and REM deprivation induce deficits of long-term potentiation (LTP), and underlying electrophysiological phenomenon linked with memory consolidation (20, 21). Sleep deprivation selectively affects certain molecular mediators of LTP and long-term depression (LTD). For instance, the loss of REM sleep corresponds to a reduction in brain-derived neurotrophic factor (BDNF), synapsin I, and cAMP response element-binding protein (CREB) mRNA levels, while the loss of NREM sleep results in the reduction of calcium/calmodulin-dependent protein kinase II (CaMKII) (22).

4. NEUROCHEMISTRY OF SLEEP

A number of neurotransmitters involved in sleep regulation have been incriminated in suicide and exacerbation or perpetuation of certain suicide risk factors, such as depression, anxiety, aggression and impulsivity.

4.1. Serotonin
Serotonin (5-HT) is a monoamine neurotransmitter released primarily by the dorsal raphe nucleus neurons located in the brainstem (23) implicated sleep/wake regulation. Early studies in animals showed that inhibiting serotonin synthesis caused complete insomnia, which could be reversed once 5-HT was repleted (24). Healthy human subjects given L-tryptophan, the precursor to serotonin, display decreased sleep latency (25). Conversely, healthy subjects depleted of tryptophan show decreased stage 2 sleep, increased REM density, and decreased sleep efficiency (26). Serotonin not only has a role in regulating the sleep-wake cycle but also correlates with mood and anxiety disorders, impulsivity and aggression (27, 28). Not surprisingly, as serotonin is involved in the regulation of suicide risk factors, there is further evidence implicating serotonin in completed suicide. The concentration of 5-hydroxyindoleacetic acid (5-HIAA), the serotonin metabolite in CSF, is a gross indicator of serotonin degradation, and thus turnover, in the brain (29). Among patients with major depressive disorders, two-thirds of those who attempted suicide had lower CSF 5-HIAA than those who made no attempt (30). Those with more frequent suicide attempts resulting in relatively more severe medical consequences had lower CSF 5-HIAA levels than those with milder or no medical consequences (31). In depressed inpatients, short-term suicide risk is greater with those with lower CSF 5-HIAA levels versus those with above median levels (32).

4.2. Norepinephrine and histamine
The noradrenergic neurons are found mostly in the locus coeruleus of the pons, while the histaminergic neurons are located in the tuberomammillary nuclei of the hypothalamus. Both neuron groups fire faster during wakefulness than sleep and remain completely silent during REM sleep. The loss of muscle tone during sleep may relate to the inactivity of norepinephrine cells (33).

Forebrain arousal is effectively associated with histaminergic cell groups (33, 34), while muscle tone, and possibly motor activity, is intrinsic to both norepinephrine and serotonin cell groups (33, 35). Norepinephrine has been associated with suicidal behavior as well. Tyrosine hydroxylase, the key biosynthetic enzyme for the synthesis of norepinephrine, as well as alpha2- and beta2-adrenergic receptors, are increased in the postmortem brain of suicide victims (36, 37). Compared to healthy controls, there are also fewer noradrenergic neurons in the locus coeruleus in brains of those who committed suicide (38).

4.3. Orexins

Discovered in 1998, orexin-A and -B, also known as hypocretin-1 and -2, are neuropeptides released from the lateral hypothalamus (39, 40). Orexin stimulates wakefulness and inhibits sleep, underscoring its primary role in sleep regulation. Injection of orexin-A into the laterodorsal tegmental nucleus (LDT) results in prolonged wakefulness and less time in the sleep state (41). The administration of orexin-A in sleep-deprived rhesus monkeys was also found to improve performance in cognitive tasks (42). Orexin neurons stimulate "wake-active" (i.e., on during wake, quiet during NREM, not active during REM) monoaminergic (noradrenergic cells of locus coeruleus, dopaminergic cells of ventral tegmental area, serotonergic cells of dorsal raphe, histaminergic cells of the tuberomammillary nucleus) and cholinergic neurons to allow a sustained wake period (43). Orexin is thought to stabilize the flip-flop switch based on its asymmetrical behavior of reinforcing the arousal systems, while not directly inhibiting the sleep-promoting ventral posterior lateral nucleus (VPLO) area.

Although orexin abnormalities are best known to be associated with narcolepsy, they are also are associated with depression and potentially with suicidality. For instance, the Wistar-Kyoto rat model of depression displayed 18% fewer and 15% smaller hypothalamic orexin neurons compared to controls (44). Also, in a study of 101 patients with various psychiatric diagnoses who attempted suicide, it was observed that low CSF orexin levels correlated significantly with both patient rated lassitude and clinician-scored ratings of slowness in movement and global illness. Among those who had attempted suicide, lower CSF-orexin levels corresponded with higher illness severity. Furthermore, those with major depressive disorder had a lower CSF-orexin level than those with adjustment disorder or dysthymia (45). As it is the case in many similar studies of suicidality, it is yet unknown if these changes in orexin levels are the cause of, the consequence of, a modulator or the effect of a common mediator of psychiatric disorder, psychological distress or suicidality.

4.4. Cytokines

Cytokines belong to a class of extracellular signaling proteins, which, similar to hormones, act in regulating the functioning of cells and tissues. In general, cytokines are classified according to their functional association with T-helper type 1 (Th1) or type 2 (Th2) cells. They play an important role in the immune response by directing the proliferation and differentiation of immune cells. Besides their role in the immune system, research has shown that certain cytokines affect brain structure and function (46). With particular reference to sleep, the following section will discuss studies suggesting that specific cytokines including tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) promote sleep, while the cytokines interlukin-4 and 13 (IL-4 and IL-13) cause sleep disturbance.

Early cerebrospinal fluid research on dogs, goats, and rats resulted in the identification of a factor "s" that accumulated during wakefulness and known to induce sleep. A putative component of factor s is considered to be muramyl dipeptide, which was shown to induce the synthesis and secretion of interleukin-1 (IL-1)(47).

Interleukin-1β (IL-1 β) and tumor necrosis factor-α (TNF-α) promote physiologic NREM sleep (47, 48) in addition to interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-18 (IL-18), growth-hormone releasing hormone (GHRH), prostaglandin D_2 (PGD$_2$), nitric oxide, adenosine, uridine, neurotropin 1 and 2 (48-53). On the other hand, interleukin-4 (IL-4), interleukin-13 (IL-13), interleukin-10 (IL-10), and transforming growth factor-β1 (TGF-β1) have been shown to reduce NREM sleep (50-52). In an early study, IL-1 was observed to affect SWS, varying in phase during the sleep period among normal healthy male subjects (54). The administration of IL-1 and TNF-α by different routes have been somnogenic in every species tested, usually with the observation of increasing NREM (50-52, 55-57). TNF-α receptor knockout mice demonstrated decreased total sleep time, and upon IL-1β administration, both SWS and REM sleep decreased (55). IL-1 may exert its influence by reducing the discharge rates of wake-active neurons and increasing the discharge of sleep-active neurons during sleep, which has been observed in the lateral preoptic area, median preoptic nucleus, and basal forebrain (44, 51, 58). The inhibition of serotonergic neurons in the dorsal raphe nucleus may be one possible mechanism by which IL-1 promotes NREM due to the presence of IL-1 receptors in that region (47, 59). In guinea pig brain stem slices, IL-1β injections into rat dorsal raphe nuclei increased NREM sleep and reduced the discharges of serotonergic neurons (60).

Most of the cytokines noted to decrease sleep, including the primary cytokines involved in allergic inflammation IL-4 and IL-13, may work directly or indirectly , by reducing the production of sleep-promoting cytokines. For instance, antiinflammatory cytokine IL-4 inhibits proinflammatory cytokines IL-1 and TNF-α production *in vitro* and *in vivo*, and promotes the production of sleep-inhibitory substances IL-1 receptor antagonist and soluble TNF receptor (53,). IL-8 production is promoted by IL-1, TNF-α, IFN-γ, and IL-18 and when injected introcerebroventrically in rats and rabbits, increased NREM sleep (62). Similarly, IL-10 inhibits spontaneous NREM sleep in rats when injected intracerebroventricularly (63). IL-13 and IL-4 share 20-25% of their amino acid structure and have a common receptor moiety. It is thus not surprising that IL-13 has similar actions to that of IL-4 (52). TGF-β1 is an important

immune and inflammatory process regulator of the central nervous system and works similarly to IL-4 and IL-13 to decrease NREM sleep. Interestingly, its expression in glial cells is stimulated by IL-1 (52), resulting in a regulatory feedback loop. It is thought that IL-13 and TGF-β1inhibit proinflammatory cytokines through dissimilar mechanisms (52).

IL-6 is unique in that it is considered the most "endocrine" of the cytokines, being also produced by adipose tissue with a role in lipid metabolism and HPA axis stimulation (50, 64). Sleep onset is associated with an increase in circulating IL-6 in stages 1, 2 and REM sleep; but there are no changes in levels during SWS (65). IL-6 has a possible role in sickness behavior with diurnal variation (elevated during daytime), and its secretion varies with sleep deprivation (47, 50, 66). IL-6 is considered to have a different effect on REM sleep than IL-1 or TNF-α at baseline, the IL-6 knockout mice spent 30% more time in REM sleep throughout the recording period (67).

Not only can immune activation alter sleep and wakefulness, but also conversely, sleep disorders can affect immunity. Narcolepsy, for example, involves elevated TNF-α and IL-6. The current hypothesis, based on its strong association with the HLA subtype DQB1*0602, is that it is caused by an auto immune-mediated process directed at orexin neurons (51). Chronic insomniacs have significantly lower levels of IFN-γ, as well as a lower IFN-γ to IL-4 ratio than those without insomnia. In one study, subjects with difficulties in sleep initiation, maintaining sleep, and attaining sufficient sleep had a significantly lower IFN-γ to IL-4 ratio than those who did not have such problems (68). Meanwhile, in subjects with medical illnesses, those with comorbid insomnia had significantly higher IL-4 than those without insomnia, showing a shift in the Th1/Th2 balance toward Th2 dominance (68). These studies provide further evidence supporting the link between sleep restriction and cytokine regulation (69). In addition, sleep deprivation activated the production of both pro- and anti-inflammatory cytokines including increases in IL-1α and IL-1β and increases in IL-6 and C-reactive protein (CRP) (70). An animal model of sleep deprivation supports the immune reaction by demonstrating significant alterations in the levels of pro-inflammatory cytokines including IL-1α, IL-1β, TNF-α, and IL-6. The authors contend that cytokine secretion following sleep deprivation operates in a different manner than its pattern of production following stress (71).

5. CYTOKINES, DEPRESSION AND SUICIDE

Healthy subjects, with no preexisting diagnostic illnesses, injected with low doses of endotoxin developed significant exacerbations in anxiety and depressive symptoms along with impaired memory performance, which followed increases in TNF-α, IL-1, IL-6, and cortisol as compared to subjects injected with placebo(72). The blinding was successful, ad the does of endotoxin was bellow the level necessary to making the participants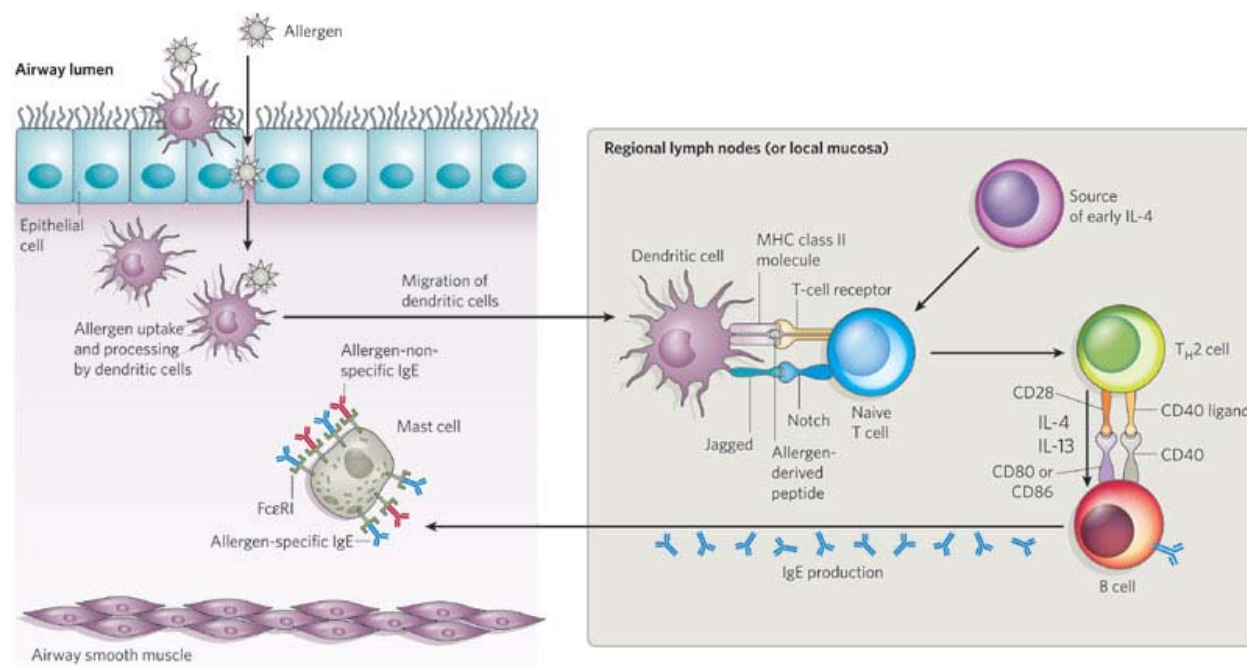 feel sick. Together, these findings evidence a role for immunological activation in inducing emotional and cognitive changes independant of illness (73).

Stimulated by infection and/or inflammation, the peripheral immune system can signal the brain and cause cytokine-induced "sickness behavior," manifested as specific and nonspecific symptoms including fatigue, diminished eating and drinking, somnolence, psychomotor retardation, anhedonia, and cognitive impairment (74). It is important to keep in mind that peripheral cytokine activation may or may not translate into activation of cytokines within the cerebrum, traditionally considered an immune-privileged organ. Individuals with major depressive disorders exhibiting sickness behavior showed increased proinflammatory cytokine levels in their blood and cerebrospinal fluid, with IL-1, IL-6, and IFN-γ being especially evident (75).

The cytokine hypothesis of depression theorizes that immune activation results in the predisposition, triggering, and perpetuation of depression (76-78). Physical, psychological, and physiological stress activates the immune response, prompting the production and proliferation of proinflammatory cytokines such as IL-1, TNF-α, and IFN-γ. These operate essentially as neuromodulators, becoming the primary mediators of the behavioral, neuroendocrine, and neurochemical attributes of depressive disorders (79, 80).

One mechanism that might explain the depressogenic effect of cytokines is tryptophan (TRP) depletion, induced by cytokine elevation. It has been shown that certain cytokines, such as IL-1, IL-2, IL-4, and IFN- γ, induce the expression of the enzyme indoleamine-2,3-dioxygenase (IDO), which shifts TRP metabolism from serotonin synthesis toward the kynurenine (KYN) pathway and the production of neurotoxic compounds resulting in TRP depletion (81, 82). TRP availability is the rate-limiting step in the synthesis of serotonin, and its reduced availability is linked to depressive relapses in vulnerable patients. That treatment with IFN-α or IL-2 is associated with significant decreases in TRP, increases in KYN, and decreases in the TRP/KYN ratios has been consistently evidenced in patients with cancer and hepatitis (83). Moreover, the decrease in TRP, the increase in KYN, and the decrease in TRP/KYN ratio have been correlated with the severity of depression (84).

Patients who have dispensed cytokines as an immunological booster have also expressed marked symptoms of depression including despondent mood, sleep disturbances, decreased energy, irritability, and loss of appetite. Therapeutic administration of cytokines and the influx of cytokines caused by immunotherapy for various medical illnesses including cancer, hepatitis, and multiple sclerosis have been etiologically linked to the concomitant onset of depression, suicidal ideation, suicide attempts and occasionally completed suicide (85-88). The cessation of depressive symptoms in patients after the suspension of cytokine treatment further supports this association between cytokines and depression (84, 89). These occurrences, though pervasive, are not universal as confirmed in a study in which 45% of a sample (N = 20)

Figure 1. Allergic sensitization: Air allergens penetrate tissues through disrupted epithelium or using their protease activity. Peptides resulting from the processing of aeroallergens are presented by activated dendritic cells to naïve T cells in regional lymph nodes or local mucosa. Influenced by "early" interleukin 4 (IL-4) naive T cells transform in T helper 2 (TH2) cells. TH2 cells then secrete IL-4 and IL-13, which induce immunoglobulin class-switch recombination of B cells, involving a rearrangement of gene segments that encode the immunoglobulin heavy chain. As a result, antibodies of the IgE class are produced. Then IgE binds, on tissue-resident mast cells, to the high-affinity receptor for IgE (Fc RI), thereby sensitizing them to respond upon re-exposure to the allergen. Reproduced with permission from (97).

treated with IFN-α developed major depression over the course of 12 weeks (88). Patients treated with IFN-α experienced fever, anorexia, fatigue, headache, myalgia, and arthralgia (90-92). Those treated with IL-2 manifest depressive symptoms within a few days, while those treated with IFN-α may take a few weeks (89). Sporadic accounts of individuals who attempted suicide after being exposed to immuno-boosting therapy for various medical conditions including melanoma, hepatitis C, HIV, and multiple sclerosis have been documented (87, 93, 94).

We recently analyzed the expression of cytokines specifically in the orbitofrontal cortex (Brodman area 11, are previously reported to show histopathological changes in victims of suicide) in suicide victims (95). Real-time RT-PCR was performed to evaluate the expression of mRNA species of six targeted cytokines, which included TNF-α, IL-1β, IL-4, IL-5, IL-6, and IL-13. The results indicated an elevated expression of IL-4 and IL-13 in females and IL-13 in males who committed suicide, suggesting that Th2 cytokines in the brains of these suicide victims may be related to neuroimmunological abnormalities.

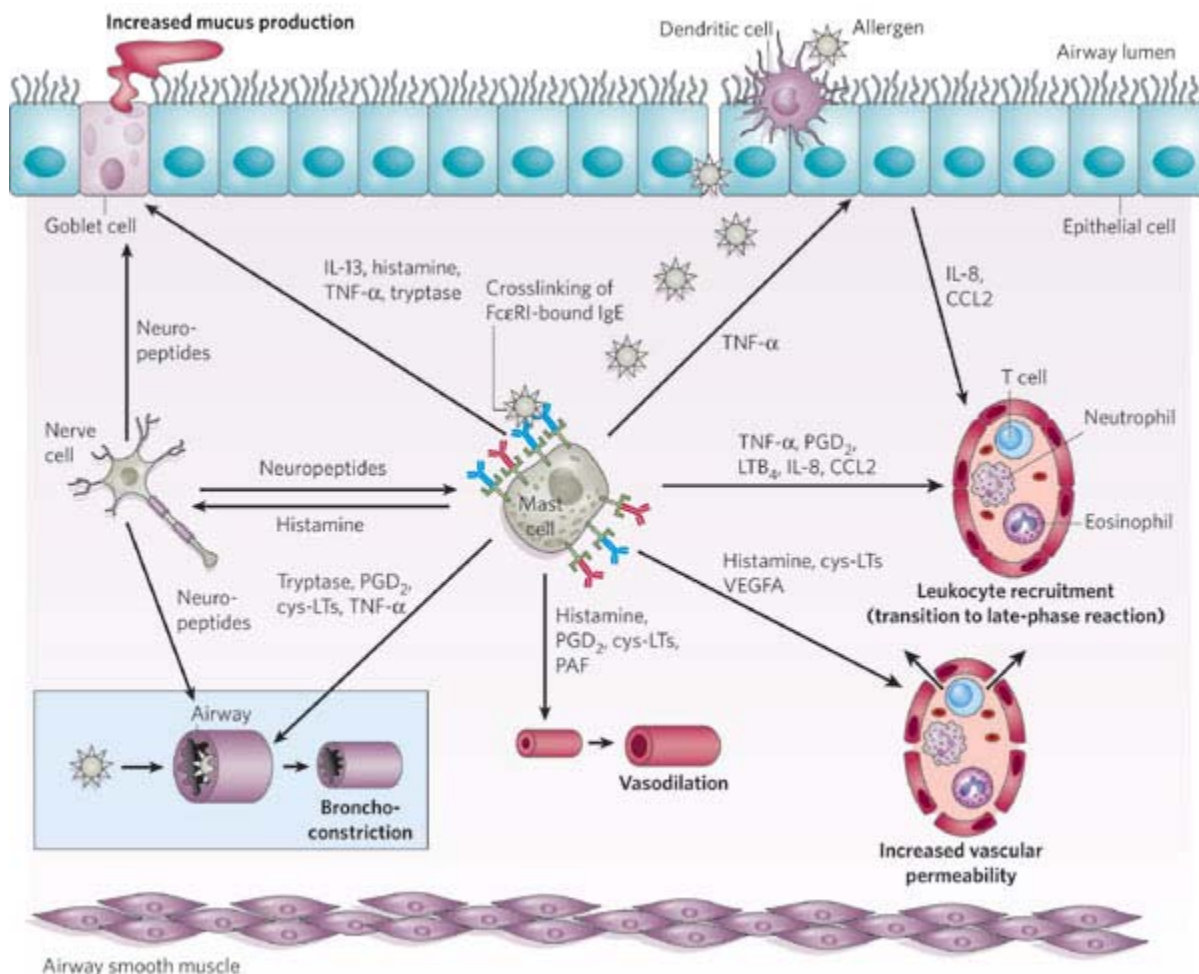## 6. ALLERGIC RHINITIS, IMPAIRED SLEEP, AND SUICIDE

Allergic rhinitis is a common condition, affecting 20-40 million people in the United States and 10-25% of the world's population. The more common symptoms include nasal congestion in up to 90% of patients, runny nose, postnasal drip, red itchy eyes (rhinoconjunctivitis), and headaches. Along with physical symptoms, patients may display symptoms similar to depression: mental fatigue, amotivation, dysphoria, and social withdrawal. Rhinitis is classified as intermittent (< 4 days per week with a duration of < 4 weeks) or persistent (96).

For a recent detailed review on the molecular and cellular events characterizing allergic inflammation, and especially on cellular and molecular mediators of allergic sensitization (Figure 1), immediate (Figure 2) and delayed (Figure 3) phases of the inflammatory events during atopic reactions, refer to the recent review by Galli *et al* 2008 (97).

6.1. Association between seasonal allergies and suicides

Epidemiological studies have reported a highly replicated peak in suicide from April to June and a smaller less consistently observed peak in the late summer/early fall (98). Many factors have been suggested to cause these peaks, ranging from environmental to social causes, but no single explanation has yet proved satisfactory (98). Pollen is the most important seasonal aeroallergen, and comes primarily from wind-pollinated plants, with tree pollen the most important source of spring aeroallergens. Atmospheric pollen also increases during the fall, mainly by the pollen of ragweed. Even though ragweed pollen amounts to only about 15% of the yearly pollen total, it is

Figure 2. Early Phase of allergic inflammation: IgE molecules are bound to the FcRI molecules mast cells. Allergen recognition of a particular allergen by FcRI-bound IgE specific for antigen derived from that allergen (allergen-specific IgE) induces FcRI aggregation, which, through a phosphorilation cascade activates mast cells to secrete preformed mediators and synthesize many cytokines, chemokines and growth factors. The secreted mediators result in rapid onset of vasodilatation, increased vascular permeability and mucus production, as well as, in the lungs, bronchoconstriction (lower left). Reproduced with permission from (97).
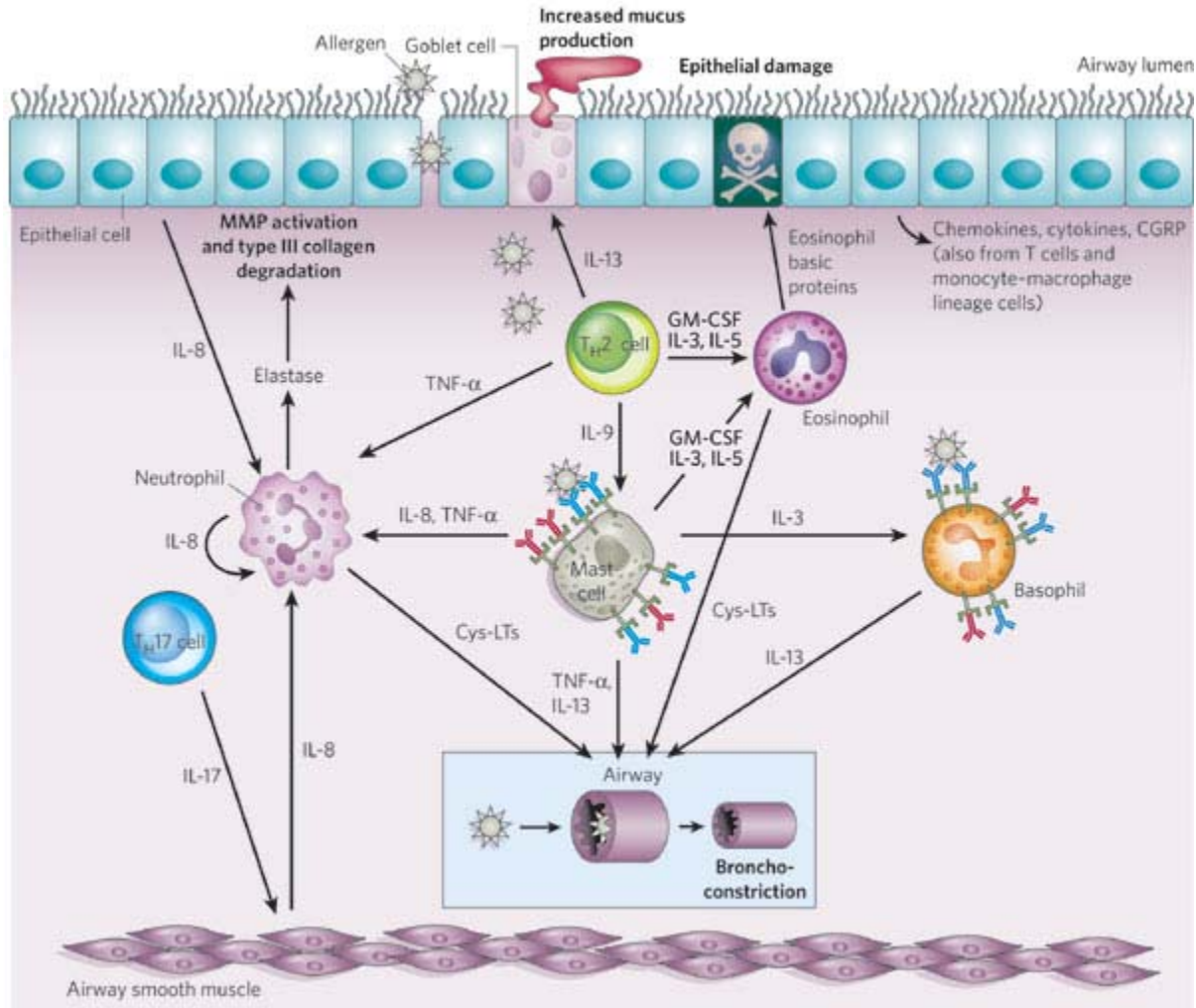
highly allergenic. We have recently reported a twofold increase in suicides among women below the age of 65 during the spring tree allergy season in the high-exposure period compared to the pre-exposure period (95% confidence interval [CI], 1.3–3.0) (99). This finding is consistent with the study done by Timonen *et al* (100), who reported a greater seasonality of suicide among those with a history of allergy than those without such a history.

Increasing evidence suggests an association between allergy and recurrent depression (101-103). In addition, a shared risk for allergic and depressive symptoms has been described among adult Finnish twins (104). Exposure to allergens in vulnerable individuals may affect one or more of the known suicide risk factors—depression, anxiety, aggression, or sleep impairment. Marshall *et al* 2002 rated mood and fatigue 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 (105). Our own work in a student population has shown that seasonality of mood is directly related to self-reported sensitivity to pollen counts (106). We have shown that changes in allergy symptoms from low to high tree-pollen seasons correlate with changes in depression and anxiety scores in patients with recurrent mood disorders scores (107).

6.2. Sleep and daytime alertness is adversely affected by untreated allergic rhinitis

There is a close association between allergic rhinitis and disturbed sleep. In a web-based survey of 1,322 people with self-reported rhinitis, 68% of those with
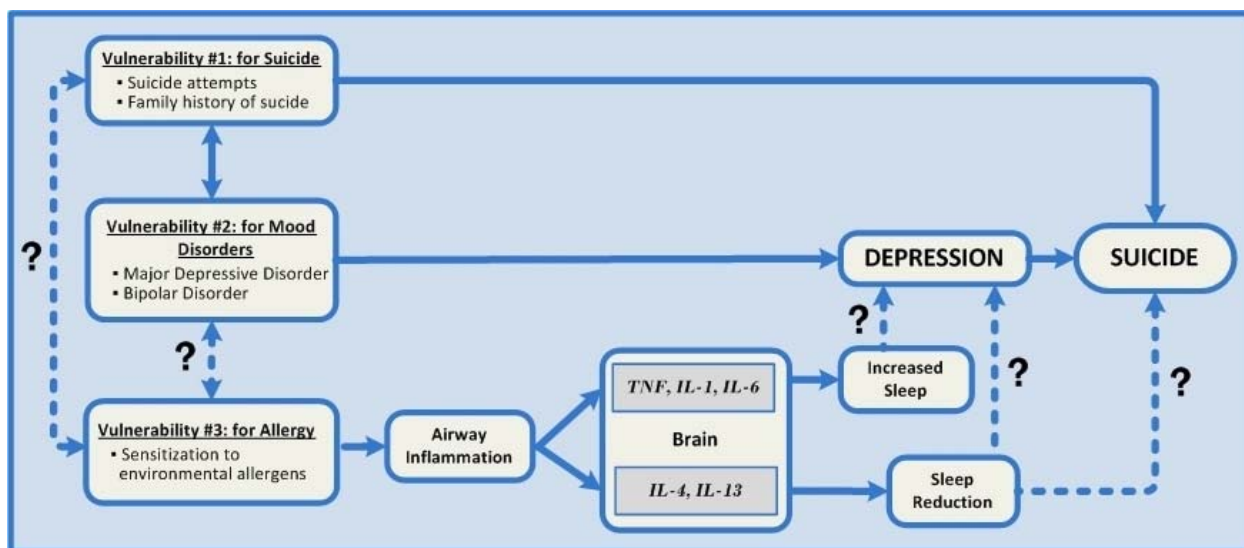
Figure 3. Late phase of allergic inflammation: occur hours after allergen challenge and are mediated by both innate and adaptive immune mechanisms. Innate immune cells include eosinophils, monocytes (not shown) neutrophils, and basophils. Mast cells that have been activated by IgE- and allergen-dependent Fc RI aggregation continue to secrete and synthesize mediators of inflammation. Tissue-resident or recruited T cells that recognize allergen-derived peptides are also locally active. Thus there is a plethora of both Th2 ("anti-inflammatory") as well as Th1 cytokines ("proinflammatory"), as well as many other molecular mediators locally active during this phase. Reproduced with permission from (97).

perennial rhinitis and 51% of those with seasonal allergic rhinitis had sleep problems (108). In a controlled cross-sectional study of 591 allergic rhinitis patients, the severity of allergic rhinitis rather than the frequency (intermittent or persistent) was more closely associated with insomnia, hypersomnia (defined as occurrence of sleepiness during daily life), and daytime somnolence (7). Eighty percent of 2,355 self-reported allergic rhinitis patients identified nasal congestion as the most bothersome symptom (109). Not only is nasal obstruction a subjectively bothersome complaint, it has deleterious effects on the quality of sleep. In a study of normal subjects, those with nasal obstruction complained of poor sleep quality (110). Patients had difficulty initiating sleep and had an increased number of nocturnal arousals (109). In a naturalistic study involving 404 outpatients with self-reported allergic rhinitis, confirmed as congestion by physical exam or with a positive skin test in the last 12 months, nasal congestion alone was associated with sleep problems, fatigue and daytime sleepiness (111). During the inspiratory phase of the respiratory cycle, increased effort is needed to inhale through the nose as the airflow decreases (112). The nose is the primary route of breathing during sleep. The negative pressure that is created is exacerbated by nasal congestion, which can limit maximal upper airway flow (113). With the negative pressure, the nasal passages collapse, leading to obstruction and associated microarousals (112, 113). In the same survey of 2,500 adults with self-reported allergic rhinitis, 44% reported frequent fatigue during the allergy season, whereas 36% reported sometimes feeling tired (114).

The sheer number of nocturnal arousals has been associated with excessive daytime sleepiness (115). Of interest was that certain sleep problems relate to particular

Figure 4. Allergy, mood disorders, sleep impairment and suicide. A model of triple vulnerability for suicide, for major recurrent mood disorder and allergic sensitization (marker is allergen specific IgE). As trigger, after the contact with the aeroallergen in sensitized individual a cascade of molecular and cellular events (see Figures 1-3) results in secretion of both Th1 and Th2 cytokines. Peripheral cytokines could reach the brain via circumventricular organs, altered blood brain barrier (BBB) permeability, or via nasocerebral molecular transport. Peripheral activation of cytokines may result in secondary production of cytokines in the brain and affect brain function. Cytokine activation in the prefrontal cortex (see Tonelli *et al* 2008) may impair the "breaking" function of the prefrontal cortex on impulsivity, aggression, depression and anxiety (not shown). Th1 cytokines may promote sleep and drowsiness and Th2 cytokines may impair sleep onset and continuity, which could indirectly worsen risk of suicide. In addition, sleep could be affected by nasal airway obstruction (not shown). Finally, antiallergy medications could induce sleep and sleepiness changes that may have effects of their own (not shown). Although sleep impairment is known to exacerbate mood disorders and elevate the risk for suicide, its possible connecting role between allergic inflammation, mood disorders and suicide requires additional research (question marks).

types of arousals. Those with apneas had more numerous, shorter arousals, and less EEG and SWS disturbance. This contrasted with insomnia patients whose length of time awake more highly corresponded to daytime sleepiness (115). In an early study of sleep disturbances in patients with allergic rhinitis, 14 patients went through overnight polysomnograms. Those with allergic rhinitis had an average of 49.1 microarousals, mostly occurring in stages 1 and 2 sleep. Normal controls had just an average of 4.7 microarousals, just before REM periods. Also observed were increased episodes of periodic breathing, hypopnea, and hyperpnea. No one had specific sleep complaints. But, of the allergic rhinitis group, three had difficulty initiating sleep, five noticed frequent awakenings, and four had excessive daytime sleepiness and fatigue (116).

In patients with allergic rhinitis verified by skin testing for allergy and with complaints of nasal congestion, objective measurements using both polysomnography (PSG) for sleep and a pneumotachygraph to assess nasal resistance as a surrogate for nasal congestion were taken. The results showed an increased number and duration of obstructive apneas during allergy season, with the frequency of apneas associated with nasal resistance (117). The number of sleep apnea episodes in this sample with seasonal allergic rhinitis was greater than in healthy individuals, although less than in individuals with clinically severe sleep apnea. Oxygen saturation only decreased

mildly, although the study population was young and not obese (117). Similarly, a study of 4,927 middle-aged adults with allergic rhinitis symptoms of ≥ 5 nights a month, found that those with nasal congestion secondary to allergy were 1.8 times as likely to have moderate-to-severe sleep-disturbed breathing (SDB) than those with nasal congestion unrelated to allergy. Those with allergic rhinitis are also more likely to snore 3-7 nights a week and have chronic excessive daytime sleepiness and chronic nonrestorative sleep (118). In a study of non-obese obstructive sleep apnea (OSA) patients, nasal resistance was also shown to be an independent predictor of the apnea-hypopnea index (AHI) (119).

6.3. Treatment of allergic rhinitis improves sleep

Several studies have demonstrated that treatment with intranasal corticosteroids not only decreased nasal congestion, but also improved sleep quality and decreased daytime sleepiness. Intranasal corticosteroid therapy inhibits both early and late inflammatory responses (120). In at least 75% of adult and child patients, nasal symptoms (nasal congestion, itching, sneezing, rhinorrhea) were controlled (120). A small placebo-controlled crossover trial in perennial allergic rhinitis patients resulted in significant improvements in subjective ratings of nasal congestion and sleep after 8 weeks of topical nasal flunisolide treatment (112). Open label treatment with intranasal budesonide on children with allergic rhinitis showed conspicuous

reductions in arousals from a baseline of 8.4 arousals (apneas and hypopneas) per hour to 1.2 and corresponding decreases in sleep and rhinitis symptoms according to the Rhinoconjunctivitis Quality of Life Questionnaire (RQLG) (121). In a similarly designed placebo-controlled crossover trial in perennial allergic rhinitis, there were significant improvements over an 8-week period in nasal congestion, subjective sleep, and daytime somnolence with intranasal budesonide (122). An open label study using intranasal triamcinolone acetonide for three weeks also restored sleep quality (123).

6.4. Disrupted sleep in patients with allergic rhinitis may increase risk of suicide

Sleep disturbances, which are known suicide risk factors, are common consequences of allergic rhinitis. Mann proposes a stress diathesis model that incorporates typical stressors, like acute intrinsic psychiatric illness, acute medical illness, and acute drugs, as well as factors for the vulnerability toward suicide including chronic illness and genetics (124). As we know, sleep disturbances and allergic rhinitis can contribute to both acute and chronic medical and psychiatric illnesses. One possible formulation is that acute allergic rhinitis symptoms may cause severe sleep fragmentation either directly, via cytokine expression in the brain or indirectly, via exacerbation of a pre-existing mood disorder, possibly triggering suicidal behaviors in individuals with genetic or developmental vulnerabilities for suicide in the presence of other suicide precipitants. Figure 4 summarizes our view on the possible connections between allergy, depression, sleep impairment and suicide.

7. SLEEP, DEPRESSION AND SUICIDE

Previously thought of as a symptom of a psychiatric disorder, there now appears to be a bi-directional relationship between sleep disturbances and psychiatric illness. As the majority of suicide victims are depressed at the time of suicide, the consistently reported relationship between sleep and recurrent depression is of major clinical importance (98). Sleep impairment is not only a symptom of the syndrome of depression, but may also herald the onset of depressive episodes. For instance, Perlis *et al* reported that sleep disturbances were seen up to 5 weeks prior to the recurrence of depression (125). It was observed that a history of insomnia and hypersomnia even without a psychiatric diagnosis could predict the onset of major depression (126-128). A review of eight epidemiologic studies of primary insomnia revealed that insomnia symptoms lasting for more than 2 weeks had an increased risk for depression onset within 1-3 years (129). Not only can sleep disturbances predict episodes, it can also indicate how a patient is progressing through his or her psychiatric illness. It has been reported that sleep disturbances in mood disorders, in which insomnia is the chief complaint, are more pronounced during acute episodes as opposed to remission periods (130).

7.1. Sleep and psychiatric disorders: epidemiological and clinical evidence

Subclinical sleep fragmentation in normal healthy subjects, which did not result in arousals on EEG,

corresponded with dysphoria (131). There is a clear association between sleep disorders and psychiatric disorders. One study concluded that 40% of insomniacs and 46.5% of hypersomniacs had a comorbid psychiatric disorder (126). Nocturnal awakenings, also known as middle insomnia, also have a high comorbidity with major depressive disorder, bipolar disorder, and anxiety disorders (132).

A population-based cohort study was conducted using the UK General Practice Research Database, perhaps the largest longitudinal medical records database used extensively in epidemiological studies, in an effort to determine the demographics of comorbid mental health disorders and their outcomes (133). Data on 12,437 individuals newly diagnosed with sleep disorders was compared to matched controls, and results indicated sleep disorders had the highest incidence rate for psychiatric stress (OR=3.6) and depression (OR=3.1).

7.2. Sleep architecture in patients with psychiatric disorders

In an early review, depressive disorders associated with disturbed sleep continuity, decreased SWS, shortened latency to the first REM period, and an increased amount of REM early in the sleep period (134). In the initial meta analysis by Benca *et al* (135) and others since, affective disorders differed from controls in many sleep-related measurements including decreased total sleep time, decreased sleep efficiency, prolonged sleep latency, significant reduction in SWS time and SWS percentage (136), shortened REM latency, increased REM density (137), increased total REM time (137-140), and increased REM percentage with the duration of the first REM period increased significantly (135).

8. SLEEP DISTURBANCES AND SUICIDALITY

8.1. Shortening of sleep duration; insomnia, sleep fragmentation

Sabo *et al* performed one of the initial investigations in determining the association between sleep disturbance and suicidality. The study included 21 matched depressive patients with previous suicide attempts, depressive patients without previous suicide attempts, and a control group of individuals without depressive disorders or previous suicide attempts. Depressed individuals who had a history of suicide attempts had longer sleep latency, lower sleep efficiency, and less SWS than the control group (141). Depressed patients without suicide attempts had more delta counts in the fourth NREM period and less REM in the second period than depressed patients with previous suicide attempts. The length of the second REM period correlated with a history of suicide attempts (141).There was also a significant difference in REM latency (defined as ≤ 60 minutes) among 19% controls, 42.9% attempters, and 66.7% non-attempters out of the population. Subjective measures of sleep, assessed by the Pittsburgh Sleep Questionnaire Index (PSQI), showed that depressed patients who were suicidal, according to the Schedule for Affective Disorders and Schizophrenia (SADS) suicide subscale, had a significantly higher global

PSQI score. They also had significantly higher scores in four components of the PSQI including subjective sleep quality, sleep latency, sleep duration, and habitual sleep efficiency (2). In addition, self- reported questionnaires of 763 adolescents in a French secondary school showed a significant relationship between poor sleep and suicidal ideations (38%) and attempts (9%) (142). In a study of 27 adolescents with major depressive disorder, based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) interview, those who were suicidal had significantly increased sleep latency compared to adolescents with major depressive disorder who were not suicidal. There was a trend in reduced REM latency, increased REM density and increased stage REM (143).

Depressive symptoms had the strongest association with suicide in a study of those ≥ 65 years old, comprised primarily of males (144). Symptoms were solicited approximately 2 years before the 21 completed suicides in a study population of 14,456 (144). The risk for suicide increased by 34% for each symptom endorsed on the 10-item CES-D (Center for Epidemiologic Studies-Depression Scale). However, poor sleep quality, perceived poor health, and having relatively few friends or relatives also predicted suicide (144). In a population of volunteers undergoing no treatment for depression, there was a significant association between disturbed REM sleep, decreased mean REM latency, increased REM sleep percentage and suicidality, as measured by particular items on the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS) (145). Reports have also observed significantly greater levels of general sleep disturbance, insomnia, and hypersomnia in both the previous week and the current affective episode in suicide victims (3). Wallander *et al* 2007 has recently reported that the percentage of suicides was significantly higher in those with sleep disorders (4.2%) versus controls (0.6%) (133). Insomnia has been associated with increased psychological strain, subjective stress, arousal predisposition, and health problems (146) and is considered an important suicide risk factor (147). The prevalence of insomnia within the major depressive disorder population has been estimated to be 70%, with comorbidity significantly associated with suicidal ideation (148). Of 100 consecutive patients examined in an emergency room after severe suicide attempts, global insomnia was present in 46% and partial insomnia (defined as either having difficulty falling asleep, staying asleep or early morning awakenings) was present in 92% (147). Sleep less than 3.5 to 4.5 hours in duration was associated with a 15% increased mortality hazard in a large questionnaire survey involving 1.1 million adult Americans (149). Adolescents sleeping <8 hours were three times as more likely to have had a suicide attempt in the last 6 months than those sleeping over nine hours (150). A recent study also found an association between short sleep (≤5 hours sleep), significant odds ratios of both suicidal ideation (OR = 2.5), and suicidal attempts (OR = 3.0) in the National Comorbidity Survey (4). Short sleep was found to have a prevalence of 7.37% and was more common among older, separated and divorced individuals (151).

8.2. Hypersomnia

Increased sleepiness and sleep duration have also been linked to depression and increased suicidality. In a Breslau *et al* 1996 study, 8.2% had hypersomnia alone, with hypersomnia in that study defined as having at least 2 weeks of feeling as if one slept too much every day, and was associated with a gender-adjusted relative risk of 2.9 for the onset of major depression (127). Agargun *et al* 1997 were among the first to demonstrate that hypersomnia related to suicidal tendencies (2). They found that 50% of hypersomnia patients (classified using SADS questions involving sleep) were considered suicidal (≥3 on SADS suicidal subscale), which differed markedly from the proportions of major depressive patients without sleep disturbance (2). In Ford and Kamerow's study, 3.2% in the community had hypersomnia (subjective assessment of having too much sleep), and among those 46.5% had a psychiatric disorder (126). However in Chellapa's study, excessive somnolence was not as greatly associated with suicidal ideation. The authors thought the result may have been secondary to the heterogeneity in the definition (148).

8.3. Nightmares

A disorder classified as a parasomnia in DSM-IV and ICD-10, nightmares are described as awakenings from major sleep or nap episodes with quick and detailed recollections of dreams, usually involving threats to security, survival or self-esteem. They tend to occur in the second half of the sleep period, not generally associated with vocalizations or increased body movements, and usually involve autonomic activation. Nightmares are also associated with psychiatric disorders, including depression and suicidality. A twin study conducted in Finland determined a genetic predisposition for nightmares and a temporal relationship between nightmare frequency and ensuing psychiatric disorders (152). From a sample of individuals with nightmares, 32% had concomitant major depression and anxiety disorders (153). Another study observed a positive correlation between frequency of nightmares and suicide risk (154), which was later quantified by Bernert *et al* 2005 (155) as a two-fold risk increase and later by Sjöström *et al* 2007 as a five-fold increase in elevated suicidality (156). Two studies of adolescents with nightmares also found an association with suicidal ideation (157) and 6-month prior suicide attempts (150).

8.4. Nocturnal panic attacks

Nocturnal panic attacks are another sleep phenomena associated with psychiatric disorders and suicidality. Apprehension or fear upon awakening that often "jolt" the patient from sleep characterize sleep panic attacks. However, the experience is not associated with dream recall. Sleep panic attacks occur in NREM sleep, either in stage 2 or SWS, usually during periods of transition to deeper sleep stages (158). The physical symptoms are similar to the patient's wake panic attacks, but less likely to include fears of insanity or death. Similar to agoraphobia, some among those with recurrent sleep panic attacks may develop a fear of falling asleep (159). In an outpatient study comparing 45 panic disorder patients with 26 non-psychiatric controls, 69% of those with panic

disorder said they had sleep panic attacks at some point in their lives, with 33% having recurrent panic attacks versus 8% of the controls (158). Recurrent middle and late insomnia was more common in panic disorder patients than in controls, with no difference in recurrent initial insomnia between the groups. Among those with a lifetime history of sleep panic, all types of insomnia were more prevalent. They had longer histories of depression and were more likely to report sleep deprivation and relaxation as panic attack precipitants (158). Agargun *et al* 1998 conducted a study of panic disorder patients with sleep panic attacks of ≥ 4 per month and found that they were more suicidal on the SADS suicidal subscale than those who did not have sleep panic attacks (151). Since those with comorbid major depression were more suicidal than those with isolated panic disorder, the authors felt that panic disorder was not an independent factor, (160). This conclusion was supported by Rudd *et al* who found that isolated panic disorder was rarely associated with suicide, but the mean scores for suicidal ideation and hopelessness were significantly higher in those with comorbid panic and mood disorders (161).

9. CONCLUDING REMARKS

In recent decades, much progress has been made in addressing sleep problems in allergy treatments, underscoring unimpaired sleep as a goal and using sleep (normal versus abnormal) to determine the difference between mild and moderate-severe allergic rhinitis (162) (163). Confirming and better understanding the correlations between allergy, sleep, suicide, and suicide risk factors, including mood and anxiety disorders will necessitate concentric studies at clinical, epidemiological, postmortem, and animal levels. Uncovering and treating sources of sleep impairment, including allergic rhinitis, in patients with an increased risk for suicide has a potential to reduce mortality, morbidity, improve symptomatic control, and enhance the functioning and quality of life. In all cases, however, professional mental health evaluations in settings, which temporarily increase the separation between the suicidal individual and suicidal means, are critical whenever acute risk for suicide is uncovered or even suspected.

10. ACKNOWLEDGEMENTS

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Abbreviations: Th1/Th2: T-helper type 1/2 cells, NREM: non-rapid eye movement, REM: rapid eye movement, LTP: long-term potentiation, LTD: long-term depression, BDNF: brain-derived neurotrophic factor, CREB: cAMP response element-binding protein, CaMKII: calcium/calmodulin-dependent protein kinase II, 5-HT: serotonin, 5-HIAA: 5-hydroxyindoleacetic acid, CSF: cerebrospinal fluid, CSF 5-HIAA: cerebrospinal fluid 5- hydroxyindoleacetic acid, LDT: laterodorsal tegmental nucleus, VPLO: ventral posterior lateral nucleus, TNF: tumor necrosis factor, IFN: interferon, IL: interleukin, TGF: transforming growth factor, SWS: slow wave sleep, HPA: hypothalamic-pituitary-adrenal axis, HLA: human leukocyte antigen, CRP: C-reactive protein, TRP: tryptophan, IDO: indoleamine-2,3-dioxygenase, KYN: kynurenine, RT-PCR: reverse transcription polymerase chain reaction, CI: confidence interval, EEG: electroencephalography, PSG: polysomnography, AHI: apnea-hypopnea index, RQLG: Rhinoconjunctivitis Quality of Life Questionnaire, OR: odds ratio, PSQI: Pittsburgh Sleep Questionnaire Index, SADS: Schedule for Affective Disorders and Schizophrenia, K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime, CES-D: Center for Epidemiologic Studies-Depression Scale, BDI: Beck Depression Inventory, HDRS: Hamilton Depression Rating Scale, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition, ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

Key Words: Sleep Disturbance, Sleep Impairment, Insomnia , Suicide, Suicide Attempts, Suicide Ideation, Suicidality, Allergic Rhinitis, Allergy, Depression, Immune Response, Immunology, Allergic Inflammation, Allergic Sensitization, Allergens, Quality Of Life, Review

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