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Sleep-Disordered Breathing and Psychopathology: A Complex Web of Questions and Answers

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Abstract

Sleep-disordered breathing is common but under-diagnosed. This is concerning given the emerging empirical relationships between severe forms of sleep-disordered breathing, such as obstructive sleep apnea syndrome, and various forms of psychopathology including major depressive disorder, attention deficit hyperactivity disorder, generalized anxiety disorder, schizophrenia and post-traumatic stress disorder. Inflammatory pathways may mediate part of the relationship between sleep-disordered breathing and psychopathology, but the strength and directionality of these processes and associations remains unknown. It may be appropriate to have a heightened index of suspicion for SDB and psychopathology in individuals at higher baseline risk for their co-morbidity. Further investigation in larger, longitudinal, well-controlled studies is needed to understand the relationship of SDB and psychopathology.

Keywords: Sleep-disordered breathing; Sleep apnea; Psychopathology; Major depressive disorder

Introduction

Sleep Disordered Breathing (SDB) characterizes a broad range of disorders described by abnormalities in respiratory pattern and intake during sleep [1]. These range from snoring to Upper-Airway Resistance Syndrome (UARS) to its most common form, Obstructive Sleep Apnea Syndrome (OSAS) [1]. SDB in adults is more prevalent than many clinicians realize, affecting approximately ten to seventeen percent overall [2,3] with its most severe form-Obstructive Sleep Apnea (OSA)-present in five to ten percent [4-6]. SDB is not uncommon in children, tends to increase with age, and may be increasing in incidence secondary to our national obesity epidemic [5]. However, it remains one of the most elusive conditions to diagnose-as many as eighty percent of patients at risk for OSA may escape formal diagnosis [2,7]. The prevalence and elusiveness of SDB are especially concerning considering the emerging associations between SDB and various forms of psychopathology [8,9].

The SDB-Psychopathology Web

To date, SDB has been found to be associated with many forms of psychopathology, the most well-studied of which include Major Depressive Disorder (MDD), [10-12] Attention Deficit/Hyperactivity Disorder (ADHD), [13-15] Generalized Anxiety Disorder (GAD), [16,17] schizophrenia [18,19] and Post-Traumatic Stress Disorder (PTSD) [20]. Additionally, theoretical evidence exists that may link SDB with worsened mood, memory and cognition. For example, the downfield sequalae of intermittent hypoxia and hypercapnia secondary to severe SDB (e.g., OSA) is associated with sympathetic activation and reduced vagal tone that is marked by release of pro-inflammatory cytokines and catecholamines. These deleterious mediators are known to contribute to relative cerebral under perfusion, neuronal oxidative stress, neurotransmitter imbalance (e.g., serotonin, glutamate), and decreased synaptic plasticity [21-24]. This may contribute to the various functional and structural abnormalities (e.g., in the frontal cortex, amygdala, basal ganglia, hippocampus, thalamus, cerebellum and cerebral ventricles) observed in many patients with severe SDB [25-27].

Thus, there exists a pathway by which the neurohumoral activation secondary to severe SDB may potentiate the impact of mental illness. In individuals with depression, for example, OSAS is associated with resistance to both pharmacological and cognitive behavioral therapy [28,29]. Patients with treatment-resistant depression and Cardiovascular Disease (CVD) have a higher rate of cardiovascular events than those with less severe depression [30], and sleep researchers have wondered whether this is explained in part by the underlying inflammatory cascade from incipient OSA that characterizes all three conditions [21,31,32]. This is especially important considering that Continuous Positive Airway Pressure (CPAP) has been shown to diminish the inflammatory cascade, improve symptoms of at least two forms of psychopathology (MDD and ADHD), [14,33-35] and reduce cardiovascular risk [36,37].

Many Important Questions Remain

Despite the emerging empirical associations and biochemical

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underpinnings, the SDB-psychopathology web may be more entangled than ever before.

For example, one of the primary concerns has been about the true strength of the SDB-psychopathology association. The literature linking SDB with some forms of psychopathology (e.g., ADHD) remains mixed [38,39] and the alleviation of SDB has not always produced improvements in mood symptoms [40]. Furthermore, much of the data linking SDB with different forms of psychopathology, and the effect of CPAP on neuropsychiatric improvement, come from small, short-term studies [41]. Additionally, the breadth of associations linking SDB to psychopathology-ranging from depressed mood to hyperactivity to psychosis-makes critical understandable skeptical of the strength of any one association. Lastly, the tendency for sleep-deprivation, independent of its underlying cause, to worsen neurocognitive function and mood has been well documented [42,43].

The second concern involves the directionality of the SDB-psychopathology association. Methodologically, even impressive associations in cross-sectional studies fail to demonstrate causality and should be interpreted with caution, especially in light of important potential confounders like obesity. This is perhaps best demonstrated from investigations of patients with SDB and PTSD, where SDB surely does not cause PTSD. Moreover, some have even suggested that certain psychopathological states may make one more likely to have SDB. In patients with MDD, for example, it is hypothesized that reduced serotonin delivery to the pharyngeal dilators may contribute to pharyngeal collapsibility observed in OSA [28,44]. Depressed patients may also have chemoreceptor dysregulation and blunted respiratory drive in response to hypercapnia, as evidenced by their tendency to have longer apneas than controls in recent studies [45-47]. However, the failure of antidepressants to consistently improve OSA in longitudinal studies tempers the enthusiasm for these findings [48].

Conclusions

Therefore, the take home message for clinicians and researchers is important but must be interpreted with caution. SDB has been empirically associated with various forms of psychopathology and some theoretical neurobiological links between the two may exist. Since these pathways share a profound inflammatory response that may potentiate the impact of each condition, it may be reasonable to have a heightened index of suspicion for the SDB-psychopathology relationship in certain high-risk patients.

For example, in patients with severe disorders of mood and risk factors for OSAS, it is appropriate to screen for OSAS. Clinicians should not only be aware of traditional risk factors for OSAS (e.g., obesity, family history, elderly), but also take notice of psychopathology in individuals who do not fit the high-risk stereotype but nonetheless are more likely to have an underlying sleep disorder (e.g., slender women with Chronic Fatigue Syndrome) [49]. The STOP-BANG questionnaire can be quickly administered in the office, and includes items related to snoring, feeling tired, observations of apneas, blood pressure, BMI greater than 35, age over 50, neck circumference greater than 40 cm, and male gender [50]. Positive responses to 3 or more items constitute high risk for OSA and warrants follow-up polysomnography. Given that the diagnosis of OSA is straightforward and treatment is relatively inexpensive and beneficial for select patients (e.g. with treatment-resistant depression and CVD), this may be an appropriate approach.

Conversely, individuals with OSA at high risk for perturbations of mood (e.g., genetic predisposition, personal history) may benefit from further psychopathology screening. For example, in some patients, one can at least rule out depression by administering the Patient Health Questionnaire (PHQ) 2. The PHQ 2 is 97 percent sensitive for detecting depression in adults and asks "Over the past two weeks, how often have you been bothered by either little interest or pleasure in doing things or feeling down, depressed, or hopeless" [51]. A positive response to either item merits further depression screening.

However, as we learn more about the SDB-psychopathology association, there are many significant questions that remain. Specifically, in individuals that are diagnosed with either OSAS or psychopathology with no other clues to suggest their co-morbidity, it may be reasonable to heed to the concerns raised by the body of research to date. Until larger, longitudinal, well-controlled studies are done to clarify the strength and directionality of the SDB-psychopathology association; it may be prudent to approach the matter of further mood and/or OSA screening for lower-risk patients on a case-by-case basis.

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