Obstructive Sleep Apnea and Psychiatric Disorders

Steven H. Woodward, PhD; Ruth M. Benca, MD, PhD

In this issue of *JAMA Network Open*, Shah et al.\(^1\) show that increasing posttraumatic stress disorder (PTSD) symptom severity is associated with increasing severity of obstructive sleep apnea (OSA), confirming what a number of prior studies have shown using weaker methods. Their study leverages a twin study methodology in which monozygotic and dizygotic twins discordant for PTSD severity and diagnosis were assessed with objective sleep laboratory measures and found to have higher rates of OSA. It eliminates many potential confounders that might cast doubt on the PTSD-OSA association. No association with zygosity was observed, which aligns with the heterogeneity of both conditions; nevertheless, the question of whether rates of OSA are elevated in PTSD, which has occupied researchers for more than 2 decades since first proposed by Krakow et al.\(^2\) has now been answered in the affirmative. We are in complete agreement with the authors’ statement that their “findings emphasize the need for more studies to examine mechanisms underlying endotypes of OSA that incorporate psychological stress pathways.”

The commonsense proposition that inadequate sleep, whether too short or too fragmented, can exacerbate or contribute to the onset of psychiatric disorders is beyond debate and now considered principally from the perspective of best practices. The obverse and more intriguing idea raised by Krakow et al.\(^2\) Shah et al.\(^1\) and others is that psychiatric “stress pathways” could play independent causal roles in OSA. The study of PTSD has enjoyed special prominence in this domain, though stress is not unique to PTSD. We recommend that researchers interested in this question maintain an even broader scope. This recommendation is based on 2 lines of argument. The first highlights findings contrary to the proposition that PTSD is mechanistically associated with OSA. The second highlights the strength of associations between OSA and major depressive disorder in particular, as well as bipolar disorder and schizophrenia.

Shah et al.\(^1\) and others have pointed to a number of possible mechanisms that might, alone or in combination, enhance the risk for OSA. Perhaps the most direct mechanism yet proposed is that sleep fragmentation secondary to reduced arousal thresholds in PTSD may lead to increased upper-airway collapsibility. We note that the study commonly referenced in this connection, Sériès et al.\(^3\) has not been replicated. Brooker et al.\(^4\) recently compared airway collapsibility across 2 older veterans subsamples, both exposed to combat but differing in PTSD. No difference in airway collapsibility was observed.

Almost universally invoked in this context is the presumed lowering of sleep arousal thresholds in PTSD. Such lowering would seem consistent with both hyperarousal and dyssomnia but has been surprisingly difficult to demonstrate. In fact, a study by Lavie et al.\(^5\) addressing this question found exactly the opposite. While this important issue remains to be settled and may yield to studies performed outside the sleep laboratory, a positive result would still lack a direct connection to upper-airway function.

A novel candidate proposed by Shah et al.\(^1\) is exaggerated loop gain, the compensatory response of a control system (in this case, respiratory control) to a disturbance. In such a system, an overcorrection following a respiratory disturbance, such as an hypopnea, would lead to hyperpnea, or overly deep breathing. This overcorrection, in turn, may lead to a drop in partial pressure of carbon dioxide, reducing drive to the upper-airway muscles and leading to airway collapse and obstruction. We note that Brooker et al.\(^4\) also found no evidence of differential loop gain in their comparison of combat veterans with and without PTSD. Theirs is only 1 study, and episodic hyperpnea would seem...
to be a straightforward target for sleep researchers to address. In fact, the Shah et al\textsuperscript{1} dataset would seem ideal for this purpose.

Though associations between other psychiatric disorders and OSA have not garnered the same level of attention as that between PTSD and OSA, it is not for lack of evidence. Meta-analyses,\textsuperscript{6} systematic reviews,\textsuperscript{7} and large archival studies\textsuperscript{8} have provided evidence that psychiatric disorders, such as bipolar disorder, schizophrenia, and, in particular, major depressive disorder, are strongly associated with elevated rates of OSA. Drawing from Veterans Health Administration records, Sharafkhaneh et al\textsuperscript{8} examined diagnostic associations in 118,105 veterans diagnosed with OSA between 1998 and 2001 and found OSA to be associated with depression in 22.8%. While the relative low rate of association with PTSD they observed (11.9%) could be ascribed to the missed diagnoses Krakow et al\textsuperscript{2} warned of, no corresponding bias toward overdiagnosis of OSA in people with depression has been alleged. This qualification applies also to the recent finding of Mi et al\textsuperscript{9} of a causal effect of depression on OSA in their large study (38,998 case and 336,659 control individuals) using Mendelian randomization. No reverse causation was observed, and no other psychiatric diagnosis was implicated.

In sum, we do not believe that a fair reading of the current literature supports a conclusion that PTSD bears an association with OSA that does not overlap with those manifested by other psychiatric disorders. The set of identified stress pathways is increasing rapidly and does not promise to be effectively segmented by our current diagnostic categories. Furthermore, while Shah et al\textsuperscript{1} suggest that it is PTSD that increases risk for OSA, it is also possible that the presence of OSA may exacerbate PTSD symptoms through episodes of hypoxemia and arousals, as discussed by McCall and Watson.\textsuperscript{10} The current study was performed in older participants, making it difficult to ascertain directionality of the association.

This commentary is not intended to discourage any specific line of inquiry. Rather, we seek to keep the door open as wide as possible to hypotheses and research designs aimed at elucidating the relationships between OSA and psychiatric disorders. This landscape is complex given the multiplicity of endotypes of the conditions involved. Accordingly, an effort considering all possibilities, be they diagnosis-specific mechanisms, transdiagnostic mechanisms, directly causative, or attributable to shared risk factors, might converge most quickly on a body of findings affording the greatest benefit to the greatest number of patients.

ARTICLE INFORMATION
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Corresponding Author: Steven H. Woodward, PhD, VA Palo Alto Health Care System, 3801 Miranda Ave, Palo Alto, CA 94350 (steve.woodward@va.gov).

Author Affiliations: VA Palo Alto Health Care System, California.

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REFERENCES


