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The Riddle of the Sphinx: Sleep, Pain, and Depression

Michael T. Smith* and Phillip J. Quartana
Johns Hopkins University School of Medicine

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In this issue of *Sleep Medicine*, Chung et al. [1] report on associations between sleep-related parameters and pain in participants with an acute major depressive episode. The authors highlight the growing recognition of the active role that sleep plays in the trajectory of both depression and clinical pain. Chung et al. found that compared to baseline, sleep was correlated more robustly with pain at three months (i.e., following pharmacotherapy for depressive symptoms) and that baseline wake after sleep onset time and changes in total sleep time correlated with changes in pain. These data provide momentum for future studies to determine whether prophylactic sleep-specific interventions can diminish pain above and beyond traditional pharmacotherapy or behavioral interventions for depression.

This said, the ability of sleep to explain pain in this study was somewhat modest. Anxiety symptoms emerged consistently as the most robust correlate of pain in both the cross-sectional and prospective analyses. On one hand, these data suggest that hybrid interventions targeting sleep in addition to mood/anxiety disturbances hold promise for ameliorating pain comorbid with depression. On the other hand, the analytical approach was data-driven (i.e., stepwise regressions). Hence, the unique proportion of variance in pain at baseline and 3 months, as well as changes in pain, accounted for by sleep disturbance above and beyond anxiety and depressive symptoms, were not ascertained. Future investigations should prioritize entry of covariates in multivariate analyses based on theory-driven hypotheses (i.e., hierarchical multivariate analysis) versus the strength of zero-order correlations.

Chung et al.'s finding that actigraphic measure of sleep, i.e., wake after sleep onset time and total sleep time emerged as significant correlates of pain in major depression, is promising. This is one of first studies to examine sleep-pain interactions in depression using actigraphy. It should be emphasized, however, that the validity of actigraphy to measure sleep continuity in depression has not been adequately established (2;3). Specifically, actigraphy directly measures movement and not sleep. Motoric agitation and/or retardation are features of depression, which potentially confound actigraphy algorithms derived predominantly from healthy normal sleeper samples.

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*Corresponding Author: Michael T. Smith, Ph.D., Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Behavioral Sleep Medicine Program, 5510 Nathan Shock Drive, Suite 100, Baltimore, MD 21224, msmith62@jhmi.edu, Phone: 410-550-7000, Fax: 410-550-117.

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Pain is experienced by the majority of clinically depressed patients (4), but few longitudinal studies have sought to treat or identify potentially modifiable risk factors of pain in depression, a major void in the literature. As Chung et al. highlight, this gap is surprising because pain occurring in the context of depression is related to poorer treatment response, increased healthcare utilization and suicidality. It is also surprising because the high co-occurrence of sleep disruption, pain, depressive symptoms and anxiety has long been recognized.

Seeking to understand idiopathic pain disorders, syndromes in which clear evidence of peripheral insult is often lacking, early psychodynamically-influenced theories went so far as to conceptualize these conditions as variants of a masked depressive illness (5). This conceptualization has since been criticized as lacking empirical support (6). With the development of modern neuroimaging techniques and advances in the neuroscience of pain (7), it is becoming increasingly evident that sleep-wake systems, affect regulation, and pain processing mechanisms share a common neurobiological substrate providing the groundwork for interactions between sleep, pain, and affect (8;9). As one example, well defined opioidergic descending pain inhibition circuits in the medullary brainstem are under serotonergic and noradrenergic control (10;11). These pain inhibitory mechanisms are often impaired in chronic pain disorders (12–14), though, to our knowledge, they have yet to be studied in the context of major depression. We have experimentally demonstrated that sleep disruption in healthy females reduces the efficacy of these endogenous analgesic systems (15). In addition to the well established role of serotonergic and noradrenergic reuptake inhibitors (SNRIs) in treating depression (16) and anxiety (17), studies which demonstrate the efficacy SNRIs as analgesics for chronic pain syndromes are rapidly accumulating (18;19). It is interesting that in the Chung et al. study, SNRIs and tricyclic antidepressants were not associated with differences in pain symptoms over time. Recent work, however, has demonstrated the efficacy of duloxetine to ameliorate pain in depressed older adults (20).

Unraveling the shared and unique neurobiological underpinnings of sleep, pain and affect is likely to yield novel and critical insights into the functions of sleep and the pathophysiology of chronic pain, anxiety and depressive disorders. If prior research and Chung et al.'s work is any indication, this pursuit might prove akin to solving the riddle of the sphinx, as the nexus of sleep, pain, and affect poses many seeming contradictions once the surface is broken. In healthy subjects, for example, sleep deprivation induces hyperalgesia (21), depressed mood (22), and spontaneous pain (23). Similarly, negative mood induction augments sensitivity to laboratory pain tests (7). Reduced REM latency is a heritable risk factor for depression (24), and this polysomnographic marker has been linked to enhanced pain sensitivity in healthy controls (25). Clinical depression, however, is often associated with *hypoalgesia* (7), and a substantial number of depressed patients respond to sleep deprivation with dramatic improvements in mood coupled with *hyperalgesia* (26)—changes that reverse after recovery sleep (27).

The mythical sphinx guarding the entrance to Thebes asked, “Which creature in the morning goes on four legs, at mid-day on two, and in the evening upon three, and the more legs it has, the weaker it be?” Of all people, Oedipus, fresh from killing his father, solved the riddle by answering it, “Man—who crawls on all fours as a baby, then walks on two feet as an adult, and then walks with a cane in old age” (27).

Perhaps the seeming contradictions in the pain, sleep, depression triangle will be similarly resolved by considering the development of these interactions over time in both clinical and healthy samples. Chung et al.'s data suggest that these relationships may change or strengthen over time, i.e., the inverse relationship between sleep quality and pain, for example, strengthened considerably at three months, relative to baseline, possibly an unmasking due the waning of depressive symptoms with treatment. Similar “unmasking effects” have been

observed in depressed participants undergoing quantitative sensory testing using a pharmacologic challenge (28).

Ultimately, there is much to be gained in conducting more systematic and intensive research that incorporates polysomnography and quantitative sensory testing to map the developmental trajectory of these symptoms over longer periods of time while simultaneously assessing changes in candidate neurobiological mechanisms. Until then, interpretations of sleep, pain and affect interactions place us all at risk of being devoured by the sphinx.

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