Sleep Medicine Reviews 48 (2019) 101220

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

GUEST EDITORIAL

# A new meta-analysis of sleep findings in PTSD, toward integration and coherence

By providing a comprehensive, up-to-date, methodologically sound review and meta-analysis of sleep studies of posttraumatic stress disorder (PTSD) with analysis of multiple relevant covariates, Zhang et al. [1] have made a valuable contribution to the literature on a critically important aspect of PTSD. The last inclusive meta-analysis of sleep findings in PTSD was published by Kobayashi and colleagues in 2007 [2]. Zhang et al. were able to include 11 additional studies to their meta-analysis, and in doing so, substantially increasing the representation of civilians and women from studies reported before 2007.

Reviews of this topic often note that while disturbed sleep is a prominent feature of PTSD and multiple lines of evidence implicate disrupted sleep in the pathogenesis and maintenance of the disorder, specific sleep abnormalities that are consistently associated with PTSD have not been identified. The search for sleep-related biomarkers (or any biomarker) of PTSD is challenged by the heterogeneous nature of the disorder. Specification of common reactions to severely threatening experiences that can maladaptively persist, as currently codified in the DSM5 criteria for PTSD [3], and previously in its two DSM predecessors, has been critically important in providing a framework for investigating mechanisms and interventions. The complexity inherent to characterizing and understanding PTSD, however, is underscored by the fact that the diagnostic criteria are and have been set up so that two individuals can meet diagnostic criteria for the disorder and have completely non-overlapping symptoms. Heterogeneity is further indicated by specification a subtype in the DSM-5 (dissociative) and removal of PTSD from the anxiety disorders, where PTSD had been categorized in two previous editions of the diagnostic system. This discrepancy reflects that some (many) but not all presentations of PTSD are paradigmatic of a conditioned fear response. Gender affects the risk of developing PTSD after trauma exposure [4]. Finally, symptoms of PTSD typically emerge in the early aftermath of trauma exposure and the disorder can be diagnosed one month after the exposure, and can resolve within an acute time frame, remit and recur, or persist chronically, at relatively equal frequencies [4]. It is unlikely that the biology would remain static over these varying courses. Thus Zhang et al.'s analysis [1] of the influences of sex, age, severity, type of control, study location, among other potential covariates, contribute importantly to an emerging coherence of findings from the sleep PTSD field.

The first set of notable findings from the meta-analysis is that in the aggregate, research participants with PTSD have reduced total sleep time (TST), sleep efficiency (SE), and percent of slow wave (deep) sleep, and increased wake after sleep onset (WASO) compared with the studies controls. Kobayashi et al. [2] found evidence for lighter sleep (decreased slow wave and increased stage 1) but not disrupted sleep continuity as evidenced here by differences in TST, SE, and WASO. The contrasting results of these reports is consistent with the characteristics of the more recently studied samples analyzed by Zhang and colleagues, and their findings regarding moderators of these differences. Specifically, the current report identified relationships of indices of disrupted sleep continuity with younger age, female gender, and PTSD related to non-combat (civilian) trauma, precisely the representations that have increased by studies reported subsequent to 2007. While significant, the magnitude of these differences across studies tends to be small. An oft made assertion that the magnitude of subjective reports of sleep disturbance with PTSD exceed what is objectively measured may generally still hold true, however, there are caveats beyond the likelihood that people with PTSD tend to be sensitive to sleep loss and disruption. There is emerging evidence associating PTSD with risk for sleep apnea [5]. Sleep breathing events that increase with age, and are unmeasured or not excluded in studies, could counter increases in awakening and time awake. While there was analysis of effects of study setting, there are still relatively few in-home PTSD sleep studies and a paradoxical salutary effect of a laboratory setting on sleep with PTSD has been observed. The findings of Zhang et al. [1] increase confidence that, overall, there is objective evidence of disrupted sleep with PTSD and that the evidence is stronger for younger, female, and civilian trauma-exposed populations. Of further interest is that the differences were a function of comparisons with controls characterized as healthy as opposed to controls who were recruited for being trauma-exposed. A factor contributing to differences not being observed with trauma-exposed controls could be the insomnia/sleep disturbance that develops post-trauma absent a diagnosis of PTSD that is not uncommon in trauma-exposed cohorts [6].

In addition to whether there is objective evidence of sleep disruption in PTSD, another fundamental question that has resisted resolution is the role of rapid eye movement sleep (REMS) in PTSD. Interest in this question was stimulated by a seminal paper by Ross et al. [7], which emphasized the prominence and specificity of the occurrence of trauma-related nightmares in PTSD [7]. In addition, there has been accumulating evidence that REMS has a role in learning processes that appear to underly adaptative processing of trauma memory including extinction learning and affective depotentiation [8]. Prior work led by this author found fragmentation of REMS within a month of traumatic injury to be associated with the development of PTSD [9]. While studies of established PTSD have not consistently “replicated” this finding, none have studied participants during the acute period following trauma exposure. In fact, a unique, albeit anecdotal report of sleep with acute combat fatigue noted “marked fragmentation” of REMS

https://doi.org/10.1016/j.smrv.2019.101220

[10]. In a more recent cross-sectional study of civilian PTSD we reported that the duration of PTSD was inversely associated with the latency to, and the percentage of REMS [11]. Zhang et al. [1] found that REMS percentage is diminished in PTSD, compared with controls, among studies with participants less than 30 y of age. PTSD related to childhood trauma is not well represented in the sleep PTSD literature, so it is likely (as suggested by the authors) that younger age is a surrogate for more recent onset of PTSD in their analysis. Therefore, the extant literature continues to support that during acute and early phases of PTSD there are factors inhibiting and/or disrupting REMS. Adrenergic neuronal activity is both implicated in PTSD pathogenesis and in terminating the REM sleep stage in the traditional model of REM/non-REM sleep regulation [12]. (More recent models provide a more complex picture but do not negate involvement of reciprocal inhibition of adrenergic/cholinergic systems in REM/non-REM sleep regulation [13].) It is likely that dynamic processes would alter neuronal activity and sensitivity over time and not surprising that sleep regulation in PTSD would not be static. While preliminary reports of the adrenergic blocking agent prazosin diminishing nightmares and improving sleep included Veterans with chronic PTSD, a relatively large study which found efficacy was conducted among (younger and more recently deployed) active duty military personnel [14], whereas a large VA cooperative multi-site study of Veterans with chronic PTSD did not [15]. In a secondary analysis of the former study, a physiological marker of adrenergic activity (standing systolic blood pressure) was associated with response to prazosin [16].

Much like the meta-analysis by Kobayashi et al., of 2007 was an important contribution, the new report by Zhang et al. adds coherence to conceptualizing findings and provides a point of reference for future studies. Understanding sleep patterns with PTSD is critical for effectively target distressing symptoms that exacerbate other features of the disorder and interfere with adaptive emotional processing. In addition, sleep is a state that when achieved is relatively unencumbered by the environment and an individual's intent, and the neurobiological regulation and substrates of sleep are relatively well understood. Hopefully, with nuanced consideration of individual/clinical factors, and further application of emerging molecular, neuroimaging and other research tools, continuing investigation of sleep in PTSD will contribute to realizing personalized/precision approaches to preventing and promoting recovery from PTSD.

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Available online 17 October 2019