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The Potential Role of Melatonin in Combat-Related Post-Traumatic Stress Disorder

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Dear Editor,

Combat-related post-traumatic stress disorder (PTSD) remains among the most debilitating psychiatric consequences of military service. Despite advances in trauma-focused psychotherapy and pharmacological interventions, a substantial proportion of veterans and active-duty military personnel continue to experience persistent symptoms, including intrusive memories, hyperarousal, sleep disturbances, anxiety, and emotional dysregulation (1, 2). The limited efficacy of currently available treatments highlights the need for safe adjunctive therapeutic strategies. In this context, melatonin has emerged as a promising candidate because of its multifaceted neuroprotective, anti-inflammatory, antioxidant, and chronobiotic properties (2, 3).

Sleep disruption is a hallmark of combat-related PTSD and often precedes or exacerbates other clinical manifestations (4, 5). Altered circadian rhythms and impaired endogenous melatonin secretion have been reported in individuals exposed to severe psychological trauma. Consequently, restoration of normal circadian function may represent an important therapeutic target. Unlike conventional hypnotic agents, melatonin improves sleep architecture while preserving physiological sleep patterns and has a favorable safety profile, making it particularly attractive for long-term use in military populations (6, 7).

Beyond its effects on sleep, melatonin may directly influence the biological mechanisms involved in PTSD pathogenesis. Chronic psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, increases oxidative stress, promotes neuroinflammation, and disrupts synaptic plasticity within brain regions critical for fear processing, including the amygdala, hippocampus, and prefrontal cortex (5). Experimental studies have shown that melatonin suppresses the production of proinflammatory cytokines, such as interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin 1 beta (IL-1β), while enhancing endogenous antioxidant defenses through the activation of enzymes, including superoxide dismutase and glutathione peroxidase. These biological actions may reduce neuronal injury associated with chronic traumatic stress (8, 9).

Furthermore, accumulating evidence suggests that melatonin modulates neurotransmitter systems implicated in PTSD, including γ-aminobutyric acid (GABA), glutamate, serotonin, and dopamine pathways. Through these mechanisms, melatonin may attenuate hyperarousal, reduce anxiety-like behaviors, and improve emotional regulation. Preclinical animal models have also shown that melatonin enhances hippocampal neurogenesis and supports synaptic remodeling, processes considered essential for

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extinction learning and recovery following traumatic experiences (8).

The potential role of melatonin extends beyond symptom management. Emerging molecular evidence indicates that melatonin regulates mitochondrial function, inhibits apoptosis, and modulates signaling pathways such as nuclear factor-kappa B (NF-κB), nuclear factor erythroid 2-related factor 2 (Nrf2), and sirtuin 1 (SIRT1). These pathways are increasingly recognized as contributors to neuropsychiatric disorders characterized by chronic inflammation and oxidative injury. Consequently, melatonin may provide disease-modifying benefits rather than merely symptomatic relief (5, 8, 9).

Another important consideration is the practicality of melatonin administration in military settings. Compared with many psychotropic medications, melatonin has minimal adverse effects, lacks dependence potential, and is well tolerated across a wide range of clinical populations. These characteristics make it particularly suitable as an adjunctive therapy during rehabilitation or for individuals who cannot tolerate conventional pharmacotherapy (6, 7).

Nevertheless, current clinical evidence remains insufficient to support the routine implementation of melatonin for combat-related PTSD. Most available data originate from animal studies or investigations focused primarily on sleep disorders rather than PTSD-specific outcomes. Large-scale randomized clinical trials are therefore required to determine the optimal dosage, treatment duration, timing of administration, and long-term safety of melatonin in military personnel and veterans. Future studies should also evaluate objective biomarkers of inflammation, oxidative stress, circadian rhythm restoration, and neuroimaging changes to better elucidate the mechanisms underlying its therapeutic effects (6, 8).

In conclusion, melatonin represents a biologically plausible and clinically attractive adjunctive intervention for combat-related PTSD. Its combined chronobiotic, antioxidant, anti-inflammatory, neuroprotective, and anxiolytic properties target several interconnected mechanisms involved in PTSD pathophysiology. Although current evidence is encouraging, robust clinical investigations are essential before melatonin can be incorporated into evidence-based treatment guidelines for military-related PTSD.

Footnotes

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