REVIEW

Wound-healing and benzodiazepines: does sleep play a role in this relationship?

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Patients who have suffered burns frequently experience psychological consequences, among which anxiety disorders are prominent. Benzodiazepines are commonly administered to treat these symptoms. The effects of benzodiazepines on healing may not be direct but rather are modulated by alterations of the sleep architecture. This hypothesis is supported by studies that demonstrate the effects of benzodiazepines on the immune system and the inflammatory profile under both normal sleep conditions and during sleep deprivation, particularly rapid eye movement sleep deprivation.

KEYWORDS: Benzodiazepines; Sleep Deprivation; Wound Healing; Burns; Immune System.

Egydio F, Pires GN, Tufik S, Andersen ML. Wound-healing and benzodiazepines: does sleep play a role in this relationship? Clinics. 2012;67(7):827-830.

Received for publication on January 10, 2012; **First review completed on** January 31, 2012; **Accepted for publication on** February 22, 2012

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INTRODUCTION

Damage to the skin triggers mechanisms of repair that are collectively called healing. This process commences immediately after injury and is composed of the following three main phases: inflammatory, proliferative, and maturation. The wound-healing process is not linear, and these phases depend on various intrinsic and extrinsic factors. Several factors may influence the healing process, including age, nutritional status, diabetes, atherosclerosis, stress, lack of sleep, and the integrity of the immune system (1-3). The integrity of the immune system is indispensable during the healing process, particularly during the recovery of tissue after burns, when defense cells and inflammatory mediators act in unison to promote tissue regeneration, cytokine production, and bacterial clearance.

Among patients who have suffered burns, a common sequela is the psychological consequences, among which anxiety disorders are the most prevalent (4). A therapeutic option for anxiety is the prescription of benzodiazepines (BDZ) to deal with the ensuing stress caused by the injury. The choice of this drug for burn patients has grown considerably in the past years and 77% of burn patients received this drug in 2001 (5,6).

Recently, some studies examined the effects of midazolam, a commonly used BZD, upon the burn wound. Babcock et al. treated mice with midazolam (1 mg/kg) daily after a burn injury and observed a decrease in IL-1β, TNF-α, IL-6, IL-10, and TGF-β levels compared to saline-treated mice (7). Moreover, the chemokines (MIP-1α, MIP-1β, and MIP-2) in the wound were increased significantly by midazolam. Another study by this group, using the same treatment with midazolam, investigated whether psychological stress (e.g., predator exposure) could alter survival following *Pseudomonas aeruginosa* infection. The results showed that midazolam had a protective effect in mice (8). Together, these studies suggest that BDZ can modulate the immune system and a host of inflammatory mediators, leading to a detrimental effect on healing and tissue regeneration.

Based on this evidence, we hypothesize that inflammation of wounded tissue may not be a direct effect of midazolam but rather a consequence of sleep alterations caused by the administration of BZD.

STRESS, ANXIETY, AND THE IMMUNE SYSTEM

An important factor during the treatment of wounded patients is the stress resulting from the injury, which may affect the immune system. Another consideration is the interaction between stress and the immune system. As demonstrated by McGhee et al. (9), lesions caused by burns or other wounds are potentially stressful events and are one reason why the use of BZD among such patients has seen a rise. However, stress, anxiety, and the immune system are intimately associated, especially when dealing with inflammation and healing. Specifically, dermatologic lesions can trigger psychological alterations such as stress (10), and stressful situations may trigger alterations in the immune system as a consequence of the activation of the hypothalamic-pituitary adrenal axis (HPA) and increased glucocorticoids (11; see (16) for review), which may then impact healing.

Increased psychological stress is associated with a higher incidence of skin dermatoses (such as psoriasis and dermatitis) (12-14). This abnormality in the skin may interfere in the healing process and compromise the skin's ability to act as an immune barrier, which is one of its main functions (15). Padgett et al. (17) observed retardation in the healing process

No potential conflict of interest was reported.

in an animal model submitted to immobilization stress. In addition, immobilized mice presented increased corticosterone when compared to controls. Thus, delayed healing was correlated with higher concentrations of corticosterone, suggesting that a perturbation of neuroendocrine homeostasis may modulate the repair process of the lesion. Taken as a whole, these results suggest that alterations in the immune function are associated with stress and may exert further complications that hamper the regeneration and integrity of the skin.

EFFECTS OF SLEEP RESTRICTION ON THE IMMUNE SYSTEM

Recently, Kronholm and collaborators (18) showed that average sleep time has fallen approximately two hours per night over the past 50 years. This reduction in sleep time, which is characteristic of a modern lifestyle, may lead to repercussions upon one's health and well-being. In particular, several studies have shown that sleep deprivation (SD) causes marked and adverse alterations in the immune system (19-24). One study demonstrated that forced wakefulness in the first half of the night (from 22:00 to 3:00) and in the second half of the night (from 3:00 to 7:00) promoted a reduction in the activity of natural killer (NK) cells (25). These results suggest that a few hours of sleep deprivation is sufficient to cause adverse effects on the integrity of the immune system. Recently, Ruiz et al. (24) reported that a total of two nights of SD resulted in increased leukocytes and neutrophils in healthy men compared to their baseline values. After 24 hours of sleep recovery, those figures returned to the values observed at baseline. However, the concentrations of monocytes, eosinophils, basophiles, and cytokines (IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, and IFN-γ) remained unaltered after the SD protocol. Thus, SD may alter the immune profile. BZD also influence the immune system, affecting cytokines, neutrophils, and macrophages (26-28).

RELATIONSHIPS BETWEEN THE USE OF BZD AND SLEEP

When first administered, hypnotics and anxiolytics of the BZD class improve sleep efficiency by reducing the latency of sleep onset and arousals during the night (29). However, after chronic use, BZDs inhibit the desynchronization process, reducing REM sleep due to a decrease of the neurotransmitter GABA (30). Additionally, BZDs increase slow-wave sleep and, in the long term, lead to a condition of REM-sleep restriction (31).

The relationship between sleep deprivation, immune parameters, and skin integrity remains under investigation. Mostaghimi et al. (32) showed that rats subjected to five days of sleep deprivation by the multiple-platform method did not present a slower healing process when compared to controls. Similarly, Landis and Whitney (33) did not observe any detrimental effects on healing at the cellular level in rats that were sleep-deprived for 72 h using the single-platform method. Although these data cannot be interpreted as that the lack of sleep jeopardizes the healing process, nevertheless it is possible that those effects are mediated by other molecular mechanisms that are currently unidentified.

The wound healing process consists in a perfectly coordinated cascade of cellular and molecular events that interact to produce the reconstitution of the tissue. There are several studies in the literature showing the adverse effects, particularly stress, in wound healing in animal models and humans. It is known that sleep deprivation is an event inherent to stress and we can hypothesize that the stress caused by sleep deprivation results in negative consequences in the healing process. However, it is a challenge for researchers to investigate the effects of sleep deprivation on the healing process due to the complexity of this process.

INTEGRATION OF CONCEPTS

Recovery from skin lesions, such as burns, is intimately associated with specific inflammatory mediators, which entails a direct association with the immune system. An example of such an association can be found in the formation of granulation tissue as macrophages release a variety of pro-inflammatory cytokines (interleukin 1 and 6) and growth factors (fibroblast growth factor [FGF], epidermal growth factor EGF, transforming growth factor-beta [TGF-β], and platelet-derived growth factor [PDGF]). The formation of granulation tissue is an essential process for the synthesis, deposition, and organization of new extracellular matrix [see review, (34)]. Thus, the efficacy of the healing process is directly dependent upon the integrity of the immune system. However, particularly when the wound is of great extent, depth, or severity, symptoms such as anxiety and stress can be observed, making the relationship between stress and the immune system bidirectional; the patient is stressed by the wound, and stress can compromise the immune system, slowing healing time. Thus, stress itself is responsible for the retardation of healing time (35).

Given the detrimental effects of stress in these situations, BZDs are commonly administered as a means of attenuating anxiety and stress symptoms (36). However, chronic consumption of BZD also provokes significant immunological disorders in humans (37) and alterations in sleep that may also affect immune function.

Therefore, we propose that the effects of BZD on healing are not direct, but rather are modulated by alterations of sleep, which then affect the immune system (Figure 1). This hypothesis is supported by studies that demonstrate the effects of BZD on the characteristics of the immune system and the inflammatory profile in normal sleep and sleep deprivation, particularly in REM sleep deprivation.

PRACTICAL IMPLICATIONS

The potential damage caused by BZD to the healing process in patients who have skin wounds contradicts the use of these compounds in such cases (6). BZDs are used in such cases to improve the mental state of the patient and, as a consequence, promote better tissue regeneration; however, that advantage is offset by these potentially detrimental effects.

There are two important considerations that follow from our hypothesis. The first is that the hypothesis presents a novel manner of approaching the clinical condition in a patient with skin lesions. In this scenario, sleep becomes an important factor for that patient's improvement. The second is that this investigation opens a debate on the use of BZD for patients with skin lesions. BZDs are not the only drugs

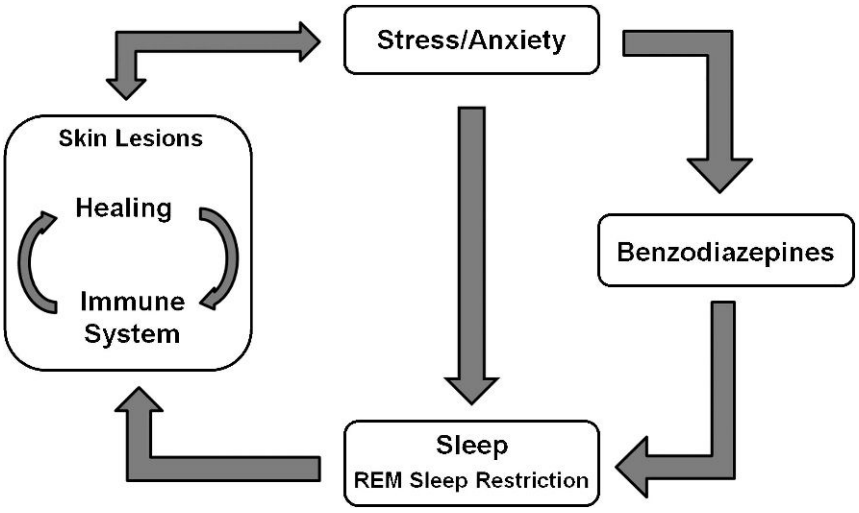

Figure 1 - The proposed model for the interplay between the use of BZD and healing in patients with skin lesions. In this case, the immune system and healing continue to be mutually dependent and are presented in relation to the bidirectional immune profile and psychological profile of the patient because large lesions cause anxiety and stress, and these effects directly affect healing and inflammatory capacity. Finally, BZD compounds are ultimately responsible for alterations in healing and tissue regeneration.

available as a therapeutic option for patients with anxiety. Medications such as buspirone, tricyclic antidepressants, and beta-blockers may be employed. Additionally, the effects of these medications on sleep differ from the effects of BZD; thus, they may reduce the negative effects on healing. This difference is particularly important when considering sleep deprivation and especially REM sleep deprivation. In these cases, the use of non-BZD hypnotics may be an option.

The physiological integrity of the skin is essential for the health of living creatures. Sleep is also a biological process that is fundamental for the quality of an individual's mental, emotional and physical life. Thus, our hypothesis combines the interaction of BZD with sleep and the possible influence on the healing process. However, additional studies, conducted in animals and humans, are necessary to test this hypothesis. This hypothesis opens opportunities for new discussions regarding this theme.

ACKNOWLEDGEMENTS

This work was supported by grants from Associação Fundo de Incentivo à Pesquisa (AFIP), CNPq, and Fundação de Amparo à Pesquisa do Estado de Sao Paulo-FAPESP (No. 2011/14462-0 to F.E., No. #2010/14768-0 to G.N.P and CEPID #98/14303-3 to S.T.). M.L.A. and S.T. are recipients of CNPq fellowships.

AUTHOR CONTRIBUTIONS

Egydio F contributed to the idea conception, the bibliographic review, the writing, and the final approval. Pires GN contributed to the idea conception, the writing, and the final approval. Tufik S contributed to the idea conception and the final approval. Andersen ML contributed to the idea conception, the writing, and the final approval.

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