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REVIEW ARTICLE

Sleep disturbances in Post-Traumatic Stress Disorder

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Abstract: Introduction: Post-traumatic stress disorder (PTSD) is characterized by a set of symptoms that occur following exposure to a traumatic event. These include re-experiencing the trauma, avoidance of stimuli related to it, and persistent symptoms of hypervigilance. PTSD is also associated with major sleep disturbances and these disturbances have a significant impact on quality of life and prognosis.
Objectives: Our aim was to review the main changes in sleep pattern observed in bipolar disorder, the physiopathological mechanisms involved in those changes and their clinical impact.
Methods: A non-systematic review of the literature in English was carried out by searching PubMed with the key words "sleep disturbance", "post traumatic stress disorder" and "polysomnography".
Results: Complaints of altered sleep patterns include nightmares, insomnia, frequent nocturnal waking, poor sleep quality, a decrease in total sleep time (TST) and an increase in stage N1 of NREM sleep, with a decrease in stage N2. As regards REM sleep, previously mentioned changes previously observed on polysomnography (an increase in its density and percentage) proved inconsistent.
Discussion and conclusions: Correcting the sleep disturbances observed in PTSD should be considered a therapeutic priority, as it prevents the recurrence of symptoms of the disorder and facilitates socio-professional integration, leading to greater success in rehabilitation and improved quality of life for these patients.

Keywords: "post-traumatic stress disorder", "sleep disorder", "polysomnography", "sleep".

Introduction

Initially termed "shell shock", post-traumatic stress disorder was described for the first time in World War I in relation to the psychiatric clinical picture seen in some soldiers following exposure to an adverse environment during the war [1] . Later, in 1952, at the time of publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-1, it was referred to as "gross stress reaction". It was not until a number of years later that PTSD was defined, filling an important gap in clinical psychiatry [2] .
PTSD is currently defined as a clinical syndrome characterized by a set of core symptoms that occur following exposure to a traumatic event. These symptoms include re-experiencing the trauma, avoidance of stimuli related to the trauma, and persistent symptoms of hyperarousal [3, 4] . Sleep disturbances are also recognized as one of the core symptoms of this syndrome and are thus an integral part of the current "re-experiencing" and "arousal/reactivity" criteria of PTSD (DSM-5) [3] .

The epidemiological data available show that approximately 70-91% of patients with PTSD suffer from sleep disturbances [4, 5] . Difficulty falling asleep or remaining asleep occurs in approximately 50% of patients, and nightmares may occur in 19-71% of patients, depending on the severity of illness, exposure to trauma and subsequent concomitant physical attacks [5-8] . In addition, violent behaviors during sleep, sleep paralysis, sleep-walking and hypnagogic/hypnopompic hallucinations are prevalent in this pathology [5, 6] .

In clinical practice, complaints of sleep disturbances are recurrent: this is the second most common reason for referral of patients with PTSD to mental health departments [9] . Generally speaking, these patients report nightmares, difficulty falling asleep and, in some cases, sleep paralysis.

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If left untreated, sleep disturbances may persist for years and worse the symptoms of PTSD, as well as psychiatric comorbidities. This happens because sleep has a restorative function and affects emotional regulation [9-11] . In addition, sleep disturbances may affect emotional processing of traumatic experiences and contribute to a worse prognosis of the disorder [9] . In this case, insomnia is common and may interfere negatively with the quality of life of these patients [12, 13] . However, many patients with PTSD show alcohol abuse and dependence, which makes a more precise diagnosis of sleep disturbances problematic [14] .-

Correcting the sleep disturbances observed in PTSD should be considered a therapeutic priority given that, as well as preventing the recurrence of symptoms of the disorder; adjustment of the sleep-wake rhythm may facilitate social integration and consequently lead to greater success in rehabilitation and an improvement in the quality of life of these patients.

Objectives

The authors of this paper aim to review the main sleep disturbances observed in PTSD, the pathophysiological mechanisms involved in those disturbances, their clinical impact and the corresponding treatment.

Material and methods

A non-systematic review of the literature in English was carried out by searching PubMed (http://www.pubmed.com) with the key words “sleep disturbance”, “post traumatic stress disorder” and “polysomnography”, in the period between 1965 and 2014. The studies reviewed were selected according to their relevance to the subject. Some articles were also included from the references of the previously selected bibliography.

Results

Subjective complaints of sleep disturbances in post-traumatic stress disorder

The sleep-related complaints most commonly reported by patients with PTSD are: initial insomnia, difficulty maintaining sleep, and nightmares [10, 15-18] . Comparative studies in war veterans showed that patients with PTSD had a higher prevalence of initial insomnia (44% of veterans with PTSD vs 9% of veterans without PTSD vs 9% of civilians), difficulty maintaining sleep (47% of patients with PD vs 18% of patients without PTSD) and frequent nightmares (52% of veterans with PTSD vs 5% of veterans without PTSD vs 3% of civilians) [19, 20] . Other sleep disturbances, such as sleep avoidance, night terrors, nocturnal anxiety episodes, vocalizations and complex motor behaviors, vivid dreams, sleep apnea and periodic leg movements, are more frequent in patients with PTSD [10, 21, 22] .

It is worth stressing that these disturbances are independent risk factors for the worsening of day-time symptoms of PTSD, such as increased severity of depressive symptomatology, suicidal ideation, poorer quality of life, worse overall functioning and increased consumption of alcohol and drugs [16] .

Objective aspects of sleep disturbances in post-traumatic stress disorder

Assessing sleep disturbances is a challenge for health professionals, because of the subjective nature of complaints. Often patients may have erroneous perceptions of their sleep, because of sleep dissociation/fragmentation (a condition known as paradoxical/subjective insomnia) [23-25] . This subjective insomnia shows that patients tend to overestimate the time they take to fall asleep and to underestimate the time they have really slept [15] . Moreover, patients with PTSD wake up more often during the night (increased night-time waking), which leads to a more negative assessment of perceived sleep quality, compared with objective sleep assessment [15] .

This discrepancy has led some investigators to use polysomnography to investigate sleep disturbances in this group of patients [23] . However, polysomnographic data on sleep in PTSD were inconsistent [24-25] . In a significant proportion of studies, the data provided by polysomnography show an increase in sleep latency (SL), a reduction in sleep efficiency (SE), a decrease in total sleep time (TST) and an increase in stage N1, with a decrease in stage N2, of NREM sleep (table I) [4, 24-31] . Published data also show that this group of patients presents a greater number of nocturnal awakenings (reflecting a state of hyperarousal), more frequent transition to superficial sleep and a reduction in stage 4 of deep sleep (slow delta waves), which is responsible for restorative sleep [32-35] .

Table I. Sleep characteristics in PTSD, taken from Afonso P. *As alterações do sono nas doenças psiquiátricas* (Sleep changes in psychiatric disorders) in *O Sono e a Medicina do Sono* (Sleep and Sleep Medicine). Eds.: Paiva T, Andersen M, Tufik S. Editora Manole, Brazil, January, 2014.

The hypothesis that changes in REM sleep are a pathognomonic characteristic of patients with PTSD was initially proposed by Ross, in 1989, and subsequently reiterated in studies that showed there was a dysregulation of REM sleep, with an increase in the percentage and density of such sleep, in patients with PTSD [21, 24, 25, 36, 37] . Despite this, polysomnography data again proved inconsistent. While some studies corroborated the findings of Ross (1989), showing that there was an increase in the percentage of REM sleep [30, 38-44] , others found a decrease in REM sleep [31, 45-47] .

As regards density of REM sleep, once again inconsistencies are observed, with some studies reporting an increase in density of REM sleep, and others with results to the contrary [24, 25, 30] . Data on latency of REM sleep (LREMS) were also inconsistent [24, 25, 30] . Despite the disparities mentioned, a meta-analysis that assessed 20 polysomnographic studies in patients with PTSD showed that these patients present an increase in REM sleep density, an increase in stage 1 sleep and a decrease in deep, slow-wave sleep [24] . In view of these results, it is important to raise the possibility that changes in percentage of REM sleep, over time, may reflect the adaptive process essential for recovery from PTSD [48] .

Therapeutic approaches to sleep disturbances in PTSD

Nightmares and insomnia are the most common symptoms in PTSD and affect the overall mental health of patients, justifying a therapy aimed at these sleep disturbances. Imagery rehearsal therapy (IRT) is currently used for the management of nightmares in patients with PTSD. Initially developed for chronic nightmares, this therapy consists of selecting a dream, writing it down, changing it in whatever ways the patient wishes and rehearsing that imagery for 10 to 15 minutes a week (limit of two dreams per week). This therapy decreases nightmares, increases sleep quality and reduces the severity of symptoms [49-52] .

Regardless of the therapeutic strategy used to treat insomnia in this patient group, the main goal of therapy is to improve the quantity/quality of sleep and minimize the negative impact of insomnia on day-to-day activities [49] . There are various therapeutic strategies (pharmacological and non-pharmacological) that should be used, singly or in combination, according to the patient's profile [49] . As far as "non-pharmacological" therapies are concerned, relaxation techniques, stimulus control therapy, cognitive behavioral psychotherapy and sleep hygiene measures are of particular note [49] .

Cognitive behavioral therapy is the first-line treatment for insomnia in this patient group [53, 54] ; this therapeutic approach is of particular benefit in the treatment of long-term [55-57] insomnia. Cognitive behavioral therapy for insomnia (CBT-I) in patients with PTSD has shown to reduce sleep latency, decrease nocturnal awakenings, increase TST and (subjectively) improve sleep quality [58] . CBT-I also improves other symptoms of PTSD, in particular intrusive memories, avoidance (of the traumatic situation) and excessive emotional arousal [59] .

As regards pharmacological therapy for PTSD, selective serotonin reuptake inhibitors (SSRIs) are currently the drugs most widely used, and have been approved by the FDA (Food and Drug Administration). Selective serotonin reuptake inhibitors (SSRIs), in particular sertraline and fluoxetine, are associated with an improvement in PTSD symptoms, but are not effective in improving the frequency of nightmares [60-63] . For its part, paroxetine shows inconclusive results. Although a decrease in the severity of PTSD symptoms and an improvement in sleep disturbances are seen in patients treated electively with paroxetine, unfortunately this SSRI is a significant inducer of nightmares [63] . For its part, fluvoxamine is also not recommended because of its profile of side effects (nausea, diarrhea and headaches) and drug interactions (cytochrome P450) [64] .

The use of benzodiazepines in the treatment of insomnia and nightmares is controversial. Clonazepam did not show significant benefits, and alprazolam, on the other hand, proved to be effective only in the treatment of insomnia [63] . Temazepam improved some sleep parameters, assessed by sleep diaries. However, these improvements were not maintained after the treatment was discontinued [12, 16, 64] .

Lastly, atypical anti-psychotic agents are frequently used as adjuvant treatment of insomnia in PTSD. In this case, these drugs may also be used in patients refractory to the treatments described above. Olanzapine, combined with an SSRI, was shown to decrease the incidence of insomnia, the incidence of nightmares and depressive symptoms [64, 65] . Despite this, because of their potential secondary effects, these drugs should be reserved for the most severely ill patients or for those who present other associated symptoms, in particular psychotic symptoms and psychomotor agitation [64, 65] .

Discussion

Sleep is an essential mechanism for adapting to fear situations, as it promotes memory consolidation mechanisms, particularly fear extinction (which occurs, for the most part, in REM sleep) [66, 67] . In 2013, Menz et al. showed that a night of consolidated sleep, without interruptions of REM sleep, is essential to strengthen fear memories so that the brain can distinguish an adverse stimulus from a non-adverse one [68-70] . Thus subjective complaints of insomnia, nightmares and sleep fragmentation immediately after the traumatic event are associated with the development of PTSD, as these sleep disturbances prevent emotional processing of memories related to the trauma [10, 71-77] .

The mechanisms by which both sleep and extinction memory are gradually altered in PTSD are not fully clarified. Despite this, Pavlov's paradigms (classical conditioning) have been studied and proposed to explain the pathophysiology of PTSD.

The most recent studies have shown that "fear conditioning" (activated when a neutral stimulus is present in conjunction with the occurrence of an adverse event) and fear extinction are mediated by the amygdala and the prefrontal cortex (with the amygdala being inhibited by the medial prefrontal cortex). This mechanism is essential for adapting to fear situations, in particular for making the correct distinction between maintenance of the fear response in the presence of a harmful stimulus and inhibition of the response in the presence of a harmless stimulus.

Thus reducing consolidation of "fear extinction" by reducing functional connectivity between the amygdala and the ventromedial prefrontal cortex leads to hyperactivity of the amygdala which is in turn associated with dysregulation of REM sleep. Such dysregulation is one of the first symptoms to occur after the traumatic event and increases individuals' proneness to developing inappropriate stress responses [77-82] .

The mechanisms "central stress response", "sympathetic activation" and "changes in the hypothalamic-pituitary-adrenal axis" are associated with changes in REM sleep in PTSD. In effect, within these systems there are positive feedback mechanisms by which neuroendocrine responses triggered by a traumatic event aggravate arousal, as well as processing of its memory [82-84] . This fragmentation of REM sleep also supposes incorrect regulation of adrenergic centers and an increase in the sympathetic tonus of the autonomous nervous system (intense adrenergic activity) in this patient group [20, 85] . Recent neuro-imaging data have shown a pattern of intense adrenergic activity in the locus coeruleus during REM sleep (compared with control groups), suggesting a perpetuation of neuroadrenergic influx during this period of sleep [37] . In fact, patients who show this trauma response abnormality do not show the normal night-time decrease in norepinephrine (NA). This abnormality has a direct consequence in the disruptions seen in REM sleep and is one of the main causes of poor sleep quality [37, 86-88] . Moreover, these raised NA concentrations are also a direct consequence of disruptions in REM sleep (seen in sleep deprivation and in PTSD), giving weight to the theory that there is a two-way relationship between PTSD and sleep disturbances [86, 88] .

Although patients with PTSD often report problems with their sleep pattern, the objective data obtained by polysomnography have been inconsistent. This discrepancy may be explained by a demographic heterogeneity, (gender, age, age of trauma, etc.), or be due to the psychiatric comorbidities often observed in this patient group (for example, major depressive disorder, substance abuse, etc.) [24, 25, 89] .

Polysomnographic sleep studies show that significant changes in sleep pattern occur in major depressive disorder also, namely: changes in sleep continuity, increased SL, decreased REMSL and increased density of REM sleep [90-94] . When patients with PTSD/MDD comorbidity and patients with PTSD were compared, it was found that the first group showed differences only in the duration and percentage of deep, slow-wave sleep [95] . Although the impact of comorbid depression on sleep appears to be relatively minor (being differentiated only in terms of SLP), the high comorbidity of these disorders may be an important risk factor for the development of sleep disturbances in patients with PTSD [95] .

Another clinical aspect that may bias results of sleep studies in this patient population has to do with disorders arising from substance use (SUDs), which are also fairly common in PTSD (52% of men and 28% of women with PTSD also suffer from alcohol abuse/dependence, and 35% of men and 27% of women reported drug abuse/dependence) [96] . Sleep disturbances are common in people with alcohol dependence, who present a decrease in sleep efficiency, a decrease in deep, slow-wave sleep, a decrease in REM sleep latency and an increase in REM sleep density [97, 98] . However comorbidity with the disorder that arises from substance use may be either a consequence or a potential cause. In effect, individuals with sleep disturbances were more likely to develop SUDs than individuals without sleep disturbances. Likewise, persons with PTSD and SUD comorbidity report more sleep problems than persons with PTSD alone [99, 100] .

There are various therapeutic strategies for sleep disturbances in PTSD. However, for a more effective and targeted treatment, it is important that we be familiar with the pathophysiological mechanisms that underlie these disturbances. There is a two-way relationship between sleep disturbances and PTSD. That is to say, while on the one hand sleep disturbances in patients with PTSD are often associated with worsening of symptoms, on the other, studies suggest that sleep disturbances may be an early marker of vulnerability to PTSD [71, 72, 85] .

Lastly, it is important to mention that a large proportion of individuals do not develop PTSD or any other spectrum disorder following exposure to a traumatic event. The likelihood of developing PTSD depends on individual risk, as well as on resilience mechanisms, which increase with the number of traumatic events experienced and their intensity. Thus sleep disturbances that occur either prior to the trauma or immediately after it are considered an important risk factor to take into account and should deserve clinical attention and the necessary therapeutic measures.

Conclusion

PTSD is a chronic psychiatric disease characterized by significant compromise of quality of life. In clinical prac-

tice, nightmares and insomnia are frequent complaints in PTSD and affect the overall mental health of these patients, contributing to the chronicity of the disorder.

Polysomnography studies conducted have shown that significant changes in sleep architecture occur in this patient group, namely an increase in SL, a decrease in SE, a reduction in TST and an increase in stage N1 of NREM sleep, with a decrease in stage N2. These data point to the possibility that there is a two-way relationship between sleep disturbances and PTSD.

The mechanisms that underlie the pathophysiology of the aforementioned changes are not entirely clarified. Despite this, the hypothesis of a state of excessive arousal (associated with an increase in adrenergic activity), perpetuated by a decrease in the amount of REM sleep, has been gaining particular weight. Accordingly, more studies are required in order to establish a more comprehensive understanding of the impact of sleep on PTSD. Such clarification will provide a more specific and effective approach in the treatment of sleep disturbances in PTSD, contributing to a better prognosis in this illness.

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