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Review Paper: The Sleep Toll in Tinnitus: A Brief Review Based on the Neurofunctional Tinnitus Model

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ABSTRACT

Individuals suffering from tinnitus frequently report sleep disturbances. The most common sleep-related complaint among tinnitus patients, insomnia, may even remain unresolved despite adequate and specific treatments of tinnitus. The more severe the tinnitus, the more patients report impaired sleep. Given the fact that sleep disorders potentially affect physical and mental health, patients with tinnitus would require a special diagnostic and therapeutic care. Subjective (sleep questionnaires and self-rated psychometric evaluations) and objective (polysomnographic recording) assessments in Sleep-Disturbed Tinnitus Patients (SDTPs) have similar parameters compared to subjects with insomnia. However, as the elderly subjects have higher prevalence of organic sleep disorders, special care is needed regarding the differential diagnostic measures. Treatment of insomnia in SDTPs is commonly based on the use of hypnotics, with or without insomnia-specific psychotherapy. Similarly, cognitive behavior therapy for insomnia is shown to ameliorate both insomnia and tinnitus. This review article discusses sleep and insomnia based on a recently-proposed neurofunctional tinnitus model.

1. Introduction

Tinnitus is a sound perception in the absence of an external source [1]. Its prevalence has been increased considerably in epidemiological studies, so that several international scientific events and publications have been devoted to explore this subject. While a recent report has shown the prevalence of tinnitus as 25.3% among US adults [2], a similar study published 15 years before reported the prevalence of tinnitus as 15% in the same population [3, 4]. Among Brazilian children, such prevalence also reached a surprising rate of 31% [5].

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Although many people with tinnitus do not complain about their quality of life, this symptom often causes sleeping disorders [6, 7], lack of concentration, impaired social life and emotional balance, contributing to the onset or worsening of anxiety and depression [8]. Nocturnal sleep problems may be described as disturbing as the daytime tinnitus by Sleep-Disturbed Tinnitus Patients (SDTPs). SDTPs may report both nocturnal and daytime problems. The special concurrence of insomnia and tinnitus is a relatively common complaint encountered when tinnitus patients refer to sleep disorder clinics or hospital-based sleep laboratories [9-11].

Sleep is in part characterized by diminished responsiveness to the external stimuli. Interestingly, some of the earliest studies trying to investigate sleep depth were designed based on the acoustic threshold. The acoustic arousal threshold seems to increase upon wake-sleep transition and during light sleep and decrease in deep sleep [12]. As such, any undesired noise level above this threshold tends to interfere with sleep. Over the past few years, a considerable number of patients with tinnitus referring to our clinics and hospital-based sleep laboratory have complained of hard-to-tackle insomnia. Being an internally perceived acoustic stimulus, tinnitus has attracted special interest in various aspects of sleep research, mainly insomnia. However, the available literature on insomnia and tinnitus seems to be scant and mixed [7, 13, 14].

Recently, Toostani et al. proposed a Neurofunctional Tinnitus Model (NfTM) to structurally illustrate the tinnitus network through the peripheral auditory system; auditory cortex; brainstem (raphe nucleus); thalamus (reticular, medial geniculate, and dorsal nuclei); limbic system (anterior cingulate cortex, amygdala); subcallosal; and paralimbic areas including basal ganglia (ventral palladium), striatum (nucleus accumbens) and ventromedial prefrontal cortex. Over developing procedure of clinical distress stage of NfTM, the general suspicion or disease-indication of patients can turn the neutral phantom sound related cognitive-emotional interpretation into negative one that can emerge the reactions via sympathetic nervous system. This negative appraisal and evaluative conditioned learning mechanism enhance the associated cognitive-emotional value and contribute to the persistence of the perceived sound [15, 16].

Taking the proposed NfTM into accounts, some questions need to be addressed: 1. To what extent the sleep disturbance experienced by tinnitus patients is perceived as a direct consequence of tinnitus or a predisposing factor for tinnitus to appear and reinforce the previous sleep disturbance?; 2. If such an association is logical and linear, why only some patients with tinnitus report insomnia?; and 3. When tinnitus is seen as a persistent sleep-disturbing stimulus, what could be the most efficient therapeutic options based on the NfTM model?

Epidemiological insights on tinnitus and insomnia

SDTPs usually blame tinnitus for their insomnia. Studies have proposed sleep problems among the most prevalent tinnitus complaints, together with hearing loss, emotional stress and anxiety [17-21]. Several investigations have reported varied prevalence of sleep disturbances among tinnitus subjects ranging from 30% to 80% [9, 11, 13, 22, 23]. For example, one report has demonstrated that up to 60% of tinnitus sufferers experience initial insomnia [24], while a larger-sample study has contradictorily shown that nearly 15% of tinnitus patients report sleep difficulties [25].

The clear disparity in such epidemiological reports may largely depend on whether the sample comprises tinnitus sufferers [25], cases with tinnitus [13], general population [7, 17, 19, 22], or a specific subpopulation group [18, 21, 26]. Moreover, the sleep quality could vary based on the investigation time. Other contributing factors might include gender, age, medication history, psychological and neurocognitive profile as well as subjects' social history and sleep hygiene status [7].

Patients with recent onset tinnitus are generally more susceptible to insomnia [13]. In fact, nearly half of the subjects who experience tinnitus for less than 1 year tend to report sleep complaints, whereas only one fourth of the individuals with long-lasting tinnitus (10 years and more) are likely to report the same [14]. On the other hand, patients with tinnitus appear to demonstrate both acute and chronic types of insomnia. Nevertheless, whether such insomnia patterns represent distinct types or merely a variation form still needs to be elucidated. Chronic insomnia with coexisting tinnitus becomes even more debilitating since the patients suffer from both conditions for a longer duration. Follow-up studies in SDTPs have indicated that almost 25% of adequately-treated tinnitus patients may continue to have long-term sleep complaints namely insomnia.

In long-term follow-up (over 5 years), more than 60% of patients with tinnitus keep on reporting sleep problems despite treatment [27], Moreover, SDTPs generally report louder and more intense subjective sense of tinnitus [7, 11, 28]. These reports show, but do not explain, why sleep problems - mainly initial insomnia - persist

in some subjects with tinnitus. The issue which has become a difficult clinical challenge both upon diagnosis and treatment.

The clinical data of sleep-disturbed tinnitus patients

SDTPs tend to report initial insomnia due to tinnitus rather than tinnitus-induced Wakes After Sleep Onset (WASO). However, both types of sleep disturbances might coexist in up to 40% of tinnitus sufferers [9, 10]. There are contradictory reports on the association between the tinnitus loudness and sleep disturbance. The NfTM projected two different scenarios in different stages of tinnitus development. During neutral stage contingency of perceiving phantom sound and difficulty in falling sleep might be accompanied by dislike feeling of inability to sleep and stress and results in strengthening the negative cognitive-emotional value of sound by means of evaluative conditioned learning mechanism, leading to the comorbidity of tinnitus in insomnia patients.

In the second scenario, over the NfTM clinical distress stage, perceiving tinnitus in the absence of daily attentional inputs can result in reinforcement of dislike feeling which stimulates autonomic discharges (including tachycardia, perspiration, etc.) potentially leading to chronic insomnia [15, 16]. Considering the NfTM, insomnia facilitates turning tinnitus into a clinical distress while it does not generate tinnitus. The hypothesis that tinnitus can be a cause for insomnia has been tested and confirmed in several studies [29-35].

While some reports demonstrated a linear relationship between tinnitus loudness and sleep insufficiency [19], others failed to prove the same relationship [10, 36]. In fact, evidence suggests that only some tinnitus patients report their sleep problems with tinnitus [7]. In other words, despite the fact that SDTPs are predominantly have prolonged sleep onset latency, the majority of tinnitus sufferers report sleep insufficiency regardless of tinnitus problem. Given the fact that subjective sleep assessments are based on subjects' memory, such studies may only offer limited dependable data on true influence of tinnitus on sleep. From the subjective perspective, insomniacs usually underestimate their sleep [7, 22]. There exist few published reports assessing the tinnitus sufferers' sleep using the full-polysomnographic recording setup [10].

An objective evaluation has suggested that Total Sleep Time (TST) of insomniacs with no tinnitus is significantly shorter than healthy controls [17]. However, comparing subjective and objective sleep parameters, together with clinical data on insomnia, daytime somnolence, fatigue and mood changes revealed no differences between primary insomniacs and SDTPs based on their objective sleep measures [7], subjective scores on Excessive Daytime Sleepiness (EDS) and mood changes. Meanwhile, impaired sleep efficiency and the prolonged sleep onset latency was reported as a common finding in both groups [7]. With respect to cognitive performance and sustained attention in particular, studies have yielded comparable results in sleep deprived subjects with and without tinnitus.

Findings from well-designed studies have proposed that sleep insufficiency in tinnitus patients is partially linked to their clinical distress symptoms [19, 33]. Patients whose sleep was most disturbed scored significantly greater on their tinnitus annoyance in the evening. Meanwhile, measures of mood and emotional distress did not relate to the degree of sleep disturbance. In addition, polysomnographic studies have shown that objective sleep parameters are similar in SDTPs and insomniacs [10, 12, 19]. Assuming the Tinnitus Handicap Inventory (THI) as an outcome, no correlation was found between its increased score with decreased time of REM in the tinnitus group (r=0.04). However, a mild correlation was found with the increase of light sleep time (stages 1 and 2). Therefore, patients with prolonged light sleep report a higher annoyance by THI score (r=0.4) [19].

Adjustment and psychophysiological insomnia

The fact that only some patients with tinnitus develop insomnia may be a consequence of sleep disturbance and tinnitus following different somatic covariates. Hence, the question whether insomnia in patients with tinnitus is a consequence of tinnitus or just comorbidity still remains open. Perhaps a fraction of patients with acute tinnitus suffer from adjustment insomnia, where the presence of a clear stressor is a key contributor and sleep complaints significantly improve once the stressor is removed. The clinical observation that the duration of tinnitus has an inverse correlation with the presence of insomnia could be justified by spontaneous tinnitus habituation in SDTPs [37].

On the other hand, when insomnia persists in patients with chronic tinnitus, the condition does not recount the criteria of adjustment insomnia. In some instances, although tinnitus is seen largely responsible for disturbed sleep both by the patients and physicians, no clear precipitating factor is identified. Then, one plausible condition to consider is the psychophysiological insomnia [38, 39]. In such cases, patients are preconditioned with low threshold in somatic and mental arousal where symp-

toms revolve around the urge for sleep, awareness on inability to sleep and sleep-related cues [38].

As such, several aspects of tinnitus psychology may overlap with the characteristics of psychophysiological insomnia. Classical conditioning, selective attention and tinnitus appraisal are among the measures used to ameliorate tinnitus symptoms [40]. Meanwhile, similar concepts are applied in the Cognitive Behavioral Therapy (CBT) of psychophysiological insomnia [41]. Except for the classical conditioning part, all remaining features of the above are in agreement with the NfTM [15, 16].

Emerging evidence together with NfTM [15, 16] support the notion that clinical distress stage of tinnitus and insomnia reinforce each other [26]. In acute tinnitus, many sufferers perceive the condition as sleep-preventing. Being perceived as sustainable triggers, tinnitus, obsession on sleep, selective attention toward the problem, difficulty in falling asleep and mental/somatic hyperarousal may contribute to a debilitating vicious cycle [7]. In an interim analysis of our clinical experience in a sleep disorders laboratory, a clear correlation is being noted between the severity of tinnitus and the extent of sleep disturbance (unpublished data).

Medical, neurocognitive, and social consequences of chronic insomnia

Chronic insomnia is deemed as a true health issue and inefficient sleep. As a direct consequence, Excessive Daytime Sleepiness (EDS) and impaired diurnal functioning are common symptoms and help defining the criteria of insomnia [42]. A considerable body of evidence has substantiated that insomnia potentially influences physical and mental health [43], hence needs to be addressed as a potential medical problem. Other secondary risks of chronic insomnia include arterial hypertension [44], ischemic heart diseases, depression, impaired professional productiveness [45], and motor vehicle accidents [46]. It has been documented that nearly 25%-30% of automobile collisions are potentially associated with driving fatigue. Drowsy driving is not only a personal but also a public hazard and commercial drivers with alternate shifts are critically at risk [47].

Furthermore, the appropriate treatment of insomnia is shown to improve patients' daytime vigilance and neurocognitive agility parameters such as attention, memory, and executive function represented by reduced reaction time upon driving. Current sleep research findings indicate that many people with untreated sleep disorders such as insomnia still involve in high-risk jobs including public transportation [46]. Therefore, in SDTPs, drowsy-driving issue, and the underlying medical factors should be taken into consideration. Well-designed studies seem to be needed to address the prevalence of this syndrome among the population and the public transport drivers in particular.

2. Therapy

Insomnia is treated through pharmacological and non-pharmacological (cognitive behavior therapy for insomnia or CBT-I) approaches [48, 49]. Benzodiazepines and sedative antidepressants are shown to retain not only limited benefits but also potential drawbacks in long-term use [50-54]. This holds true for γ-aminobutyric acid (GABA)-A receptor agonists (Z-class medications), including zolpidem, zopiclone, and zaleplon [49]. Besides the issue of tolerance, the chronic use of hypnotics is subject to precautions [53].

However, some reports have demonstrated that 6 months use of Z-class hypnotics may be well-tolerated with no potential harm [55]. Either way, given the fact that SDTPs commonly require treatments for an even longer duration, it seems that in many instances, CBT-I is the preferred approach to target the symptoms and modulate distress [56, 57]. Evidence has supported the fact that CBT-I components, including stimulus control, bed time restriction, meditative therapy, and sleep hygiene can provide positive and sustainable effects on primary insomnia [49, 58]. Studies have substantiated that neurotransmitters including glutamate, GABA, serotonin, dopamine and Acetylcholine (ACh) are contributing in tinnitus generation.

The crucial role of serotonin (5-HT) was established in sleep-wake cycles [59, 60] and its deficit causes insomnia. Considering the anatomy of central auditory pathways, the distribution of neurotransmitters may be as follows: serotonergic neurons of brainstem are mainly originated from Dorsal Raphe Nucleus (DRN) [61-63]. Thalamus reticular nucleus and dorsal thalamus trigger by serotonergic neurons which receive projects from DRN, Nucleus Accumbens (NAc) and paralimbic area [64, 65]. GABAergic neurons of TRN stimulate by serotonin [66, 67] that results in inhibiting of thalamic relay in sensory sectors [68]. The TRN inhibition may shift between tonic and burst firing mode of thalamocortical relay [69, 70]. Recently, DRN was also proposed as taking part of tinnitus connectivity network within the NfTM [15, 16].

Psychologically-stressed subjects are shown to have lower levels of serotonin concentration in their blood

samples, hence the use of serotonin reuptake inhibitors is expected to ameliorate symptoms in some patients [71]. Assessment of the blood serotonin level in tinnitus sufferers versus controls revealed that patients with tinnitus have significantly higher levels of serotonin concentration [72]. Similarly, some preclinical studies have found that increased serotonin levels induced by salicylate may be attributed to changes in neuronal activity and tinnitus [73]. Clinical experience has also confirmed that the use of Selective Serotonin Reuptake Inhibitors (SSRI) may provoke or aggravate tinnitus rather than ameliorating it [74]. The association between stress and tinnitus and the possible role of serotonin in such association need further explanation.

Apart from the pharmacological approach, technological advances in sound-based and cortical stimulation have contributed to tinnitus treatment. Sound stimulation during sleep is a new strategy towards the treatment of idiopathic subjective tinnitus. This treatment is based on the notion that the auditory system keeps working during sleep by processing the incoming information. Empirical evidence with such therapy has substantiated that tinnitus intensity continues to decrease within weeks, with some SDTPs experiencing periods of complete silence [23]. This method of treatment is against the NfTM fundamental assumption in which conscious perception and attention play an important role in tinnitus development [15, 16].

Tinnitus retraining therapy and CBT-I have demonstrated acceptable and comparable efficacy in the treatment of subjective tinnitus. However, further research using objective measurements (i.e. polysomnography) would help to evaluate the effect of both approaches in SDTPs [75]. Additionally, remediating the unfavorable behavioral patterns and dysfunctional attitudes are expected to help SDTPs regaining pre-sleep ease when psychological insomnia is suspected [76].

With regard to the assessment of results following the treatments, the Pittsburgher Sleep Quality Index (PSQI) is among the most preferred validated sleep questionnaires used in the practice of sleep medicine [77]. This questionnaire is a self-rated 19-item tool used to assess the subjects' sleep quality over the past month. Its subscales comprise sleep duration (PSQIDURAT), sleep latency (PSQILATEN), sleep disturbances (PSQIDISTB), subjective sleep quality (PSQIQUAL), use of sleeping medication (PSQIMEDS) and day-time dysfunction (PSQIDAYDYS) [78].

Items are scored from 0 (without difficulty) to 3 (maximal difficulty). The total scores of all components yields the global PSQI score (ranging from 0 to 21). The higher the total PSQI score, the sleep quality will be poorer. This subjective assessment tool is recommended to evaluate the efficacy and safety of the treatments for the management of sleep disturbances in patients with tinnitus , too [79].

Other sleep disturbances in patients with tinnitus Sleep Apnea Syndrome (SAS) (obstructive or central type) and Periodic Leg Movements during Sleep (PLMS) may be concurrently observed in up to 40% of SDTPs [80]. Diagnosing primary sleep disorders in SDTPs becomes particularly important since mild sleep insufficiencies due to SAS or PLMS might result in sleep fragmentation and synergize the sleep disturbance caused by insomnia in SDTPs. Such patients generally report difficulty falling back asleep upon WASO.

To our knowledge, there is no report on the prevalence of sleep-related breathing disorders in patients with tinnitus, nor on the impact of Continuous Positive Airway Pressure (CPAP) therapy on the severity of sleep disturbance in tinnitus sufferers with SAS. The fact that benzodiazepines and other sedative agents which are used to control tinnitus symptoms may aggravate sleep-related breathing disorders should be considered in treating the patients [81].

In addition, PLMS may also exert further impairing effects in the sleep efficiency of SDTPs. The condition is characterized by stereotyped and repetitive leg movements during sleep. Studies have proposed that PLMS occurs in up to 20% of insomniacs and its prevalence increases by age [17, 19, 79]. Likewise, some sedative drugs used to treat insomnia may worsen PLMS symptoms [22].

3. Conclusion

Insomnia and tinnitus which may coexist or contribute to each other are chronically-debilitating conditions affecting the quality of life. When sleep disturbances (particularly insomnia) are being addressed in tinnitus sufferers, it is essential to consider organic sleep disorders. The NfTM may be used to develop specific treatment measures to help SDTPs.

Ethical Considerations

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Conflict of interest

Authors declared no conflict of interest.

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