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A review on insomnia: The sleep disorder

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Abstract
Insomnia is difficulty falling asleep or staying asleep, even when a person has the chance to do so. People with insomnia can feel dissatisfied with their sleep and usually experience one or more of the symptoms like fatigue, low energy, difficulty concentrating, mood disturbances, and decreased performance in work. Insomnia may be characterized based on its duration. Acute insomnia is brief and often happens because of life circumstances. Many people might have experienced this type of passing sleep disruption, and it tends to resolve without any treatment. Chronic insomnia is disrupted sleep that occurs at least three nights per week and lasts at least three months. Chronic insomnia disorders can have many causes. Insomnia results due to an imbalance between sleep inducing neurotransmitters. There are few methods and indexes reported to study about the sleep disorders in insomnia patients like Insomnia Severity Index, Pittsburgh Sleep Quality Index. The treatment includes many drugs like Anti-Depressants, Benzodiazepines and also intake of Melatonin rich milk was also found to be effective.

Keywords: Insomnia, insomnia severity index, melatonin, treatment

Introduction
Insomnia is the inability to get the amount of sleep we need to wake up feeling rested and refreshed. Because different people need different amounts of sleep, insomnia is defined by the quality of sleep and how we feel after sleeping not the number of hours we sleep or how quickly we doze off. Even if we are spending eight hours a night in bed, if we feel drowsy and fatigued during the day, we may be experiencing insomnia [1] Sleep problems are frequently observed among older adults. While the prevalence of sleep disorders is 20–40% for the population in general, this rate rises to 50% in people who are 65 years and older (Mathews *et al* 2004) [2]

Studies conducted on general populations report that about one third of adults suffer from insomnia symptoms, of which about 10%-15% reported accompanying daytime impairments and 6%-10% experience symptoms of insomnia disorder, which is the most common of all sleep disorders. Although insomnia may be categorized as either a symptom or an independent disorder, it is most frequently considered a co-morbid condition in relation with another medical condition or mental disorder [3].

Seligman drew attention to the possibility that a patient may believe that a particular treatment would be beneficial and that this belief may affect commitment and adherence to the treatment, therefore contributing to a better outcome. Folk theories may also impact whether patients will seek treatment and the type of treatment they seek [4].

Large-sample meta analyses have shown that patients with insomnia have mild or moderate dysfunction in attention, episodic memory, working memory, and executive function compared with healthy controls [5].

In a general sense, insomnia suggests inadequate sleep quality or quantity when one has an adequate opportunity to sleep. When defined as a sleep disorder, insomnia is characterised by a difficulty in falling asleep or remaining asleep, which may represent problems with sleep mainte nance or early morning awakening despite attempts to sleep. Sleep disorder nosologies also may include a complaint of non-refreshing sleep as an insomnia complaint. For a diagnosis of an insomnia disorder to be made, daytime consequences or functional impairment should also be present. These may include fatigue, an inability to concentrate, or irritability. Insomnia affects approximately 30% of the general population at least occasionally and is a severe or chronic problem for about 10% of the population [6].

Pathophysiology of the Disease

Insomnia results due to an imbalance between sleep inducing neurotransmitters gamma-aminobutyric acid (GABA) and adenosine present in the ventrolateral preoptic nucleus in the hypothalamus and the arousal neurotransmitters (noradrenaline, serotonin, acetylcholine, orexin and dopamine) [7]. Orexm also known as hypocretin, is a neuropeptide, which is liberated by a cluster of neurons in the lateral hypothalamus. It also appears to be involved in the control of wakefulness. Sleep impairing effect of caffeine is thought to be due to blockade of adenosine A2-receptors.

Many of the molecules involved in sleep-wake regulation are produced by specific brain structures with widespread projections throughout the brain. There is, however, mounting evidence that many sleep regulatory molecules affect neurons locally, in the regions in which they are produced. In local sleep theory proposed by Krueger *et al*, [8] sleep is defined as a fundamental emergent property of highly interconnected neurons, or cortical columns. Local sleep propensity and slow wave amplitude are posited to be dependent on accumulation of sleep-regulatory substances (tumor necrosis factor-α and IL-1β) [9, 10] resulting from prior neuronal use. Synchronous firing within cortical columns is postulated to propagate slow wave activity in adjacent regions through humoral and electric interactions, leading eventually to a "global" sleep state in the entire organism.

From this perspective, insomnia may not be a "whole-brain" event (i.e, a simple matter of imbalance between global amounts of sleep and wake). An animal model of insomnia has demonstrated simultaneous localized activation in both sleep-promoting and wake-promoting regions during global sleep. [11] In humans, spectral EEG methods have identified heightened regional electrical brain activity in patients with insomnia during non-rapid eye movement (NREM) sleep [12, 13]. Merica *et al*. [14] proposed that the lack of objective sleep disruption in many patients with insomnia may be due to isolated neuronal groups remaining active during PSG-defined sleep. This dynamic in the brain may be experienced as wakefulness by many patients with insomnia and miscategorised as "normal" sleep based on standard PSG criteria.[15]

Symptoms of Insomnia

- General tiredness
- Problems with concentration or memory
- Difficulty falling asleep at night
- Sleepiness during the day
- Waking up during the night
- Waking up too early
- Not feeling well-rested after a night's sleep
- Daytime tiredness or sleepiness
- Irritability, depression or anxiety
- Difficulty paying attention, focusing on tasks or remembering
- Increased errors or accidents
- Ongoing worries about sleep

Cause of Type –2 Diabetes

Insomnia symptoms (defined here as trouble initiating or maintaining sleep) are associated with risk of type 2 diabetes. Insomnia can be effectively treated and may be a promising avenue for interventions to reduce type 2 diabetes incidence, as there are plausible biological mechanisms linking sleep loss to the development of type 2 diabetes via increases in insulin resistance and appetite. Psychiatric distress and being overweight /obese may even have reciprocal relationships with sleeping trouble where each aggravates the other.

Methods

Patients with insomnia and volunteers were enrolled from a neurology clinic. The participants underwent a series of examinations, including a clinical interview, laboratory blood tests, and neuropsychological assessment. Consent forms were signed by the participants before the study, and the study protocol was approved by the ethics committee. All participants underwent a complete physical and neurologic examination, standard laboratory tests, and an extensive battery of neuropsychological assessments, which included the Pittsburgh Sleep Quality Index, Insomnia Severity Index, Hamilton Anxiety Scale, Hamilton Depression Rating Scale, Mini-Mental State Examination, Montreal Cognitive Assessment, and Clinical Dementia Rating. Patients with CID also underwent polysomnography [16].

MR- Imaging Acquisition

Briefly, MR imaging was performed using a 1.5T superconductor MR imaging scanner (Intera Achieva; Philips Healthcare, Best, the Netherlands). The parameters and scanning mode of the MR imaging in this study can be found in the previously published study [17].

Sleep-Related Scales

Insomnia Severity Index

The ISI includes severity of sleep onset and maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, appearance of impairment attributed to the sleep problem, and the degree of concern caused by insomnia. Each item is scored by the five-point Likert Scale (0 = not at all, 4 = extremely). Score range is 0–28, and total score is classified as follows: 0–7, no clinical significant insomnia; 8–14, sub threshold insomnia; 15–21, clinical insomnia of moderate severity; and 21–28, severe clinical insomnia.

Pittsburgh Sleep Quality Index

The PSQI measures the retrospective sleep quality and disturbances. Individual self-report items assess a broad range of domains associated with sleep quality, including usual sleep wake patterns, duration of sleep, sleep latency, the frequency and severity of specific sleep-related problems, and the perceived impact of poor sleep on daytime functioning. This index consists of item scores ranges from 0–3. The global score is classified as follows: 10-15, mild depression; 16–23, moderate depression; 24–63, severe depression. Insomnia is a frequently associated symptom of depression or other psychiatric disorders. Hence, the subject's depression symptoms were evaluated as a potential confounder [18]

They have reviewed sleep studies conducted on 106 chronic insomnia patients at the multidisciplinary sleep disorder unit (SDU) of the Singapore General Hospital from 2006 to 2010. Patients' PSG indices and diagnoses were tabulated and cross-referenced to medical records to identify the reasons the sleep studies were conducted. Pre and post-PSG diagnoses were compared to examine the utility of targeted PSG in the evaluation of chronic insomnia. Information regarding comorbid psychiatric conditions was also collected to examine how these conditions influenced the management of

insomnia. Patients who were referred for evaluation of their insomnia due to suspected primary sleep disorders or other causes were not included in this review. This allowed us to examine whether the referring doctors had missed underlying sleep disorders in chronic insomnia patients during clinical history-taking and physical examination.

The sleep studies were conducted using 12-channel attended PSG suites, and scores were given according to the criteria set by Recht schaffen and Kales. Patients undergoing PSG were asked to avoid taking any psychoactive medications or hypnotics, which may alter sleep physiology and lead to artificial findings. If the patients were not able to sleep, zolpidem was prescribed, as it is least likely to alter sleep architecture and muscular tone. The unit, which is staffed by psychiatrists, neurologists, respiratory physicians, otolaryngologists, clinical psychologists, polysomnographic technologists and respiratory therapists, receives referrals from primary care physicians in the community and other medical professionals (e.g. psychiatrists from psychiatric hospitals that are not equipped with PSG facilities); it also admits self-referred patients. As the patients involved in the present study had undergone evaluations and treatment as per usual practice, the results of this study can represent the management of insomnia patients in a real-world situation. The study was approved by the hospital's institutional review board, and consent requirements were waived, as it did not require direct patient interaction [19].

Treatment

Drugs Used To Treat Insomnia

- **Anti-depressants:** Some antidepressant drugs, such as Trazodone (Desyrel), are very good at treating sleeplessness and anxiety.
- **Benzodiazepines:** These older sleeping pills- Emazepam (Restoril), Triazolam (Halcion), and others may be useful when you want an insomnia medication that stays in the system longer. For instance, they have been effectively used to treat sleep problems such as sleepwalking and night terrors. But these drugs may cause you to feel sleepy during the day and can also cause dependence, meaning you may always need to be on the drug to be able to sleep.
- **Doxepine (Silenor):** This sleep drug is approved for use in people who have trouble staying asleep. Silenor may help with sleep maintenance by blocking histamine receptors. Do not take this drug unless you are able to get a full 7 or 8 hours of sleep.
- **Eszopiclone (Lunesta):** Lunesta also helps you fall asleep quickly, and studies show people sleep an average of 7 to 8 hours. Don't take Lunesta unless you are able to get a full night's sleep as it could cause grogginess. Because of the risk of impairment the next day, the FDA recommends the starting dose of Lunesta be no more than 1 milligram.
- **Ramelteon (Rozerem):** This sleep medication works differently than the others. It works by targeting the sleep-wake cycle, not by depressing the central nervous system. It is prescribed for people who have trouble falling asleep. Rozerem can be prescribed for long-term use, and the drug has shown no evidence of abuse or dependence.
- **Suvorexant (Belsomra):** It works by blocking a hormone that promotes wakefulness and causes insomnia. It is approved by the FDA to treat people that have insomnia due to an inability to fall asleep or to stay asleep. The drug may cause you to feel sleepy the following day.
- **Zaleplon (Sonata):** Of all the newer sleeping pills, Sonata stays active in the body for the shortest amount of time. That means you can try to fall asleep on your own. Then, if you're still staring at the clock at 2 a.m., you can take it without feeling drowsy in the morning. But if you tend to wake during the night, this might not be the best choice for you.
- **Zolpidem (Ambien, Edluar):** These medicines work well at helping you get to sleep, but some people tend to wake up in the middle of the night. Zolpidem is now available in an extended release version, Ambien CR. This may help you go to sleep and stay asleep longer. The FDA warns that you should not drive or do anything that requires you to be alert the day after taking Ambien CR because it stays in the body a long time. You should not take zolpidem unless you are able to get a full night's sleep at least 7 to 8 hours. The FDA has approved a prescription oral spray called Zolpimist, which contains zolpidem, for the short-term treatment of insomnia brought on by trouble falling asleep.
- **Over-the-counter sleep aids:** Most of these sleeping pills are anti-histamines. There is no proof that they work well for insomnia, and they can cause some drowsiness the next day. They're safe enough to be sold without a prescription. But if you're taking other drugs that also contain antihistamines like cold or allergy medications you could inadvertently take too much.

Insomnia Treatment with Melatonin Rich Milk

Melatonin is a non-sedating hormone secreted from the pineal gland in the brain and has an important role in regulating the sleep-wake cycle. It is synthesized and released only during the period of darkness, from sundown to sunrise. Melatonin in serum prevents awakening, by maintaining a low body temperature and inducing sleep onset. In a study among the elderly population who presented low efficacy of sleep because of low serum melatonin levels, the group consuming 0.3 mg melatonin resulted in normalized serum melatonin levels, and significantly improved sleep efficacy. However, no significant difference was observed between groups consuming 0.3 mg melatonin and 3.0 mg melatonin, which is known to be the inducing pharmacological serum level. Higher serum melatonin levels were reported in the group who took 3.0 mg melatonin. Thus, consuming higher doses of melatonin than required would induce undesirable side effects. Another study, reported that in an elderly population who consumed melatonin-rich milk containing 10 times higher melatonin (10–40 ng/L, 0.5 L) than usual milk, there was a significant improvement in daytime activity without corresponding increase in serum melatonin or decreased core body temperature. Thus, it was concluded that improved sleep quality due to consumption of melatonin-rich milk induced improved daytime activity.

Contraindications

- Paediatric patients under the age of 18
- Patients with comorbid medical conditions
- Moderate to severe pulmonary disease
- Neuromuscular disease
- Congestive heart failure
- Patients suspected of having sleep disorders other than

obstructive sleep apnea including central sleep apnea
- Periodic limb movement disorder (PLMD)
- Circadian rhythm disorders
- Narcolepsy
- Patients with medical or cognitive issues that impact the safety of a patient using the home sleep test device unattended.

Conclusion

Insomnia impairs cognitive and physical functioning and is associated with a wide range of impaired daytime functions across a number of emotional, social, and physical domains. Compared with good sleepers, people with persistent sleep disturbances are more prone to accidents, have higher rates of work absenteeism, diminished job performance, decreased quality of life, and increased health care utilization. Studies that improve the knowledge of the neurobiological mechanisms controlling regulation of sleep homeostasis, circadian rhythms, physiological hyperarousal, genetics, stress, and cognition are needed to adequately evaluate the causes and mechanisms of insomnia. Effective pharmacological and behavioural interventions to treat insomnia rely on accurate neurobehavioral and neurobiological information. As we have different methods to identify insomnia, there is a possibility to understand better about the patient symptoms and find possible alternatives to treat the disease. There are pharmacological medications and intake of melatonin rich milk before sleep may help the patients to get relieved from the disease.

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