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# Insomnia: Recent Advances in Genetic Aspects and Therapies

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**ABSTRACT**

Insomnia has a significant global incidence rate. Previous observational studies, general practitioner surveys, and medical trials suggest that a variety of patient and physician factors are associated with this, including low patient reporting of insomnia, limited healthcare professional training, office-based time constraints, and misconceptions about the seriousness of insomnia, treatment benefits, and the risks associated with hypnotic use. Here, we discuss the recently studied genetic aspects of insomnia pathogenesis and the orexin system and acupuncture as potential therapeutic strategies.

**Key words:** Insomnia, distortion, pathophysiology, serotonin, acupuncture, pharmacotherapy

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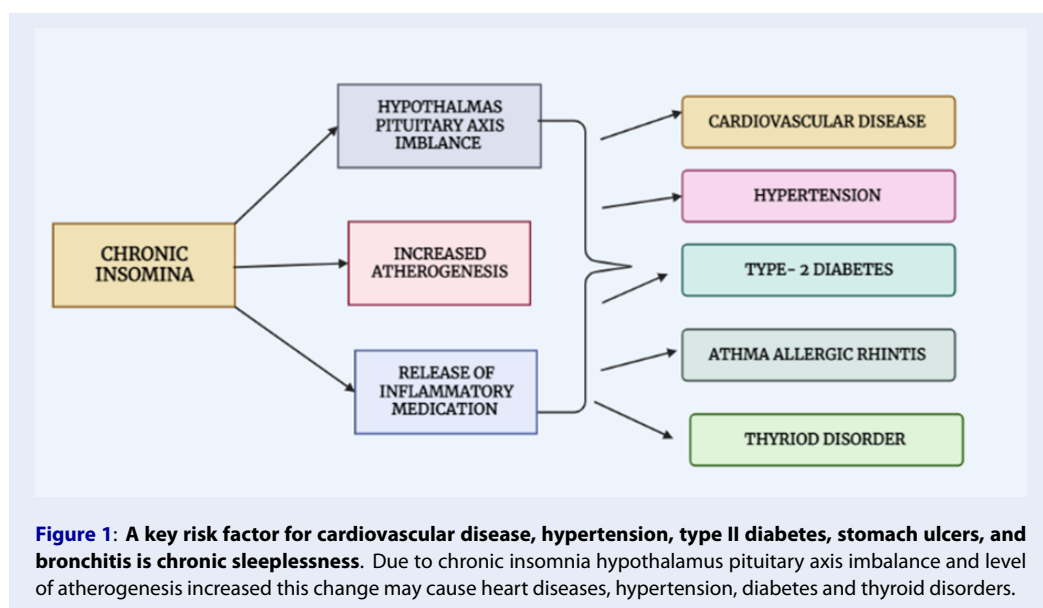Check for updates

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## INTRODUCTION

The presence of polysomnographic indication of disturbed sleep is often referred to as "insomnia." Long sleep onset times, numerous nocturnal awakenings, protracted periods of consciousness throughout the sleep phase, and several brief awakenings are all considered signs of insomnia[1]. Insomnia symptoms include difficulty falling asleep, frequent awakenings with difficulty falling back asleep, or non-restorative or poor-quality sleep, which is commonly accompanied by the feeling of getting little sleep overall[1]. Sleep-related symptoms are seen in a significant majority of epidemiological studies, with a peak incidence of 20–50%. Sleeplessness is associated with severe daytime distress, irritability, diminished focus, or weariness. Approximately 15% of adults have insomnia[2]. Insomnia is typically accompanied by a physical or psychological condition. Contrary to the long-held belief that sleeplessness was a marker of other ailments, the relationship between other illnesses and insomnia is complex and occasionally bidirectional[2]. Risk factors for sleeplessness include severe depression, mental disorders, drug and alcohol abuse, suicidality, high blood pressure, and diabetes[3,4] (**Figure 1**). As insomnia is associated with deficits in an individual's quality of life and an increased risk of accidents and falls, therapy should specifically aim to resolve insomnia, including when it occurs concurrently with other medical or mental disorders[4].

Although the vast majority of individuals with mental illnesses do not die by suicide, over 90% of those who do die by suicide have a mental disorder at the time of their death[5]. Therefore, evaluating additional risk factors besides mental illnesses may aid in identifying individuals who are most at risk of engaging in suicidal behavior[5].

Several suicidal behaviors, including suicidal thoughts, suicide attempts, and suicidal behavior mortality, have been linked to insomnia symptoms in previous studies. Furthermore, several studies have reported a link between suicidal ideation and dreams[6–8]. However, a limited number of studies have investigated whether dreams or sleeplessness symptoms are linked to suicidal thoughts and conduct in the absence of psychiatric disease. Other symptoms include nightmares, depression, anxiety, and suicide ideation[9–11]. This review discusses the recently studied genetic aspects involved in insomnia pathogenesis and explores the orexin system and acupuncture as potential therapeutic strategies.

## INSOMNIA

It is crucial to characterize the various phenotypes to identify clinically significant subtypes of insomnia, as this may lessen the heterogeneity of insomnia and make it easier to identify its causes and develop specialized treatments. However, there are few standardized tools available for diagnosing insomnia that enable phenotyping[12]. Although they achieve more overall hours of sleep, insomniacs have higher mortality rates[13]. The success of cognitive-behavioral therapy (CBT), therapy outcomes, and concomitant bipolar disorder are all influenced by the 6-hour distinction in sleep duration[13]. A recent study inves-

**Figure 1**: **A key risk factor for cardiovascular disease, hypertension, type II diabetes, stomach ulcers, and bronchitis is chronic sleeplessness**. Due to chronic insomnia hypothalamus pituitary axis imbalance and level of atherogenesis increased this change may cause heart diseases, hypertension, diabetes and thyroid disorders.

tigated different types of insomnia based on psychological stress[14]. Following interviews with 2,224 volunteers, five different types were identified: extremely depressed, moderately distressed but insensitive to positive reinforcement, moderately distressed but highly reactive to their environment and life circumstances, and slightly distressed but with low reactivity. Furthermore, participants were consistently placed in the same category throughout the five-year investigation[15].

## PREVALENCE

Insomnia has several potential causes, with some being directly linked to the disease. The two demographic risk factors are age and gender, with the highest incidences seen in women and older adults. Although the reason for the age risk factor is unknown, it may be related to the older population's propensity for insomnia and the partial functional degradation of sleep regulation mechanisms associated with aging[12]. The increasing prevalence of insomnia among elderly individuals is significantly influenced by the presence of concomitant medical disorders. Furthermore, menstruation and menopause onset both increase the prevalence of sleeplessness in women[16]. Working night or rotational shifts, having comorbid medical conditions, a chronic illness, or having psychiatric conditions are all risk factors for sleeplessness[16]. Approximately 75–90% of insomniacs are considered to be at an elevated risk for other medical conditions, including those that cause hypoxemia and dyspnea, gastric reflux disease, pain syndromes, and neurodegenerative diseases. It is important to note that a range

of primary sleep disorders and circadian rhythm abnormalities frequently coexist with and contribute to insomnia[17,18].

Insomnia symptoms with the highest prevalence include early morning wakeups (2.2%), difficulties falling asleep (7.7%), and nonrestorative sleep (25.2%)[19]. The difficulty sustaining sleep symptom was the most common symptom (61%). While the incidence of insomnia among working individuals is 23.2%, women are substantially more likely to develop it[19]. This sex-based difference begins to appear during adolescence and peaks after menopause. In addition to women, individuals with sociological difficulties, poorer health, or lower standards of living are more prone to insomnia[20]. In longitudinal studies, 40–70% of patients had insomnia that persisted for up to 4 years. While some individuals' symptoms do not disappear, others may experience a waxing and waning course of insomnia[21].

To the best of our knowledge, there is no information regarding the prevalence of insomnia, the contributing variables, and the incidence of adults living in urban and semi-urban areas using sleep aids among Pakistan's general population, nor in the specific setting of Karachi[22,23]. Sleep issues were reported by one-third of our sample at the time of the survey.

This prevalence rate was comparable to those reported in other Asian nations. For instance, samples from Turkey[24] and South India both demonstrated a prevalence rate of insomnia or other sleep-related problems of 20% and 34%, respectively. However, our prevalence rate was lower than that of Japan (44.8%) and Hong Kong 19.4% and 39.4%, respectively[25].

## INSOMNIA PATHOPHYSIOLOGY

The intricate combination of altered circadian and homeostatic processes and psychological and cognitive arousal can cause insomnia[26]. Insomnia may also be caused by sleep-wake disorders and switch to work[26,27]. Stages N1–N3 are non-REM sleep stages, during which cortical activity is minimal, as REM sleep is characterized by intense brain activity[26].

The sleep-wake phase is a complex process that regulates alertness and sleep through a feedback mechanism between opposing systems[26,28].

Wakefulness is mediated by the ascending reticular activation pathway, which involves multiple brainstem and posterior hypothalamic nuclei. This process reaches deep into the cerebral brain. The brainstem and hypothalamic arousal zones receive orexin-producing neurons from the lateral hypothalamus, which functionally encourage their activity during periods of wakefulness[29] (**Figure 2**).

## INSOMNIA GENETICS

Seugnet *et al.* reported 30 isolated Drosophila flies demonstrating rest-activity traits that resembled those of people with insomnia, including shorter rest duration, longer delay to enter a resting state after turning lights off, more fragmented rest intervals, and higher activity levels[30,31]. Furthermore, 755 human homologous genes with different expression levels were found in ins-1 flies in comparison to wild-type flies following whole-genome transcription profiling. The study of insomnia genetics may benefit from analyzing the genes connected to metabolism, cell surface interaction, sensory perception, and brain activity in ins-1 flies[32].

The classification of insomnia symptom phenotypes using self-report items produces a wide range of heritability estimates. The majority of research on human genetics has focused on a small set of genes[33,34]. Family history and twin studies on insomnia that employed stricter areas to detect insomnia have produced more realistic and consistent h2 estimates ranging from 31–58% (h2 = 0–81%)[35]. The homozygous clock gene and the 5-HTTP short (s-) allele are two examples of gene variations that have been identified through candidate gene research and may be important in insomnia pathophysiology. In a genome-wide association study, several single-nucleotide polymorphisms (SNPs) were shown to be highly associated with insomnia symptoms[36]. The most significant SNPs were found in genes related to neuroplasticity, neural excitability, and mental health[37]. In 1972, Bootzin proposed that sleep-related factors (such as a quiet, dark bedroom) might act as selective triggers that encourage sleep, and a lack of these sleep-promoting cues might lead to insomnia. A phone call, reading, or tension are some triggers that prevent sleep. The goal of stimulus management treatment is to identify the cause of sleeplessness so that an individual can sleep separately from these stimuli[38].
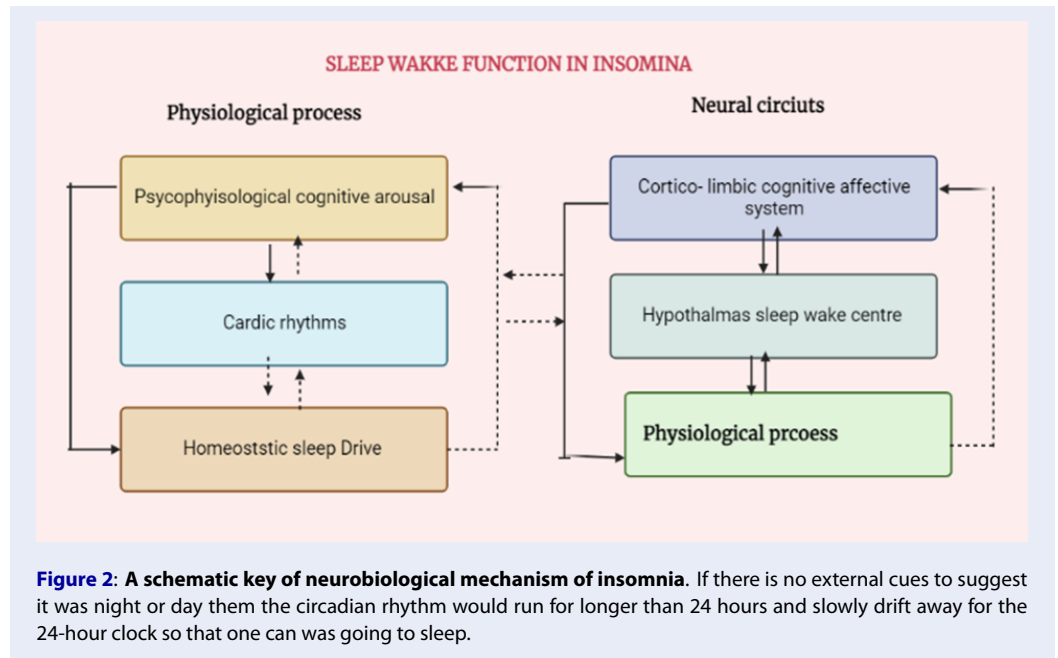
## RECENT THERAPIES FOR INSOMNIA

Despite various criteria employed across research, a considerable amount of identical twin and family literature demonstrates that sleeping problems are somewhat heritable[39]. Many studies have focused on insomnia features rather than strict insomnia disease characteristics[39]. Overall, these studies are consistent with the idea that insomnia runs in a family's genes; however, they have not distinguished between shared genetic and environmental factors[40,41]. Twin studies allow for the simultaneous analysis of both genes and shared environments, as twins are presumed to share similar environments. There is a substantially greater body of literature on twins, with over 20 twin studies to date involving insomnia phenotypes. Estimates of insomnia heritability range from 22–59% in adults and 14–71% in children[39].

## INSOMNIA-RELATED GENES

Laposky et al. investigated mice lacking the essential circadian clock gene, BMAL1/Mop3, which is also known as mop3[42,43]. These mice displayed altered sleep-wake patterns, including more fragmented sleep, fewer sleep episodes, and changes in overall sleep duration. In a human study, Viola et al. studied the PER3 gene, comparing individuals homozygous for either the short (PER34/4) or long (PER35/5) alleles. Individuals with the long alleles had reduced sleep latency and spent more of the night in slow-wave sleep compared to individuals with the short allele[43,44].

Numerous studies have investigated the links between circadian genes and the sleep-wake cycles of individuals with mood disorders. For example, Serretti *et al.* discovered a link between sleeplessness symptoms in individuals with severe depression and 3111T/C CLOCK gene allele frequencies. Similarly, Urge *et al.* studied the correlations between 113 unique SNPs in clock genes and sleep disturbance in patients with depression and control patients in a large cohort study in Finland[45,46]. They observed that the classic gene was associated with early morning awakenings in the depressed group; however, its effect varied between men and women[46,47].

**Figure 2**: **A schematic key of neurobiological mechanism of insomnia**. If there is no external cues to suggest it was night or day them the circadian rhythm would run for longer than 24 hours and slowly drift away for the 24-hour clock so that one can was going to sleep.

## THE ROLE OF SEROTONIN

Serotonin is a well-known neurotransmitter that has a significant impact on the immune system and peripheral tissues. An increasing body of research suggests that several immune cell types, such as T cells, macrophages, mast cells, dendritic cells, and platelets, express the machinery needed to produce, store, react to, and/or transport serotonin[48]. Brummett et al. investigated the link between sleep patterns and the serotonin gene in dementia caregivers. They discovered a strong gene X environment correlation with caregivers, whereby caregivers with the short allele were more to report poor sleep quality. However, there was no link between caregivers who did not show concern for others[49]. Monoamine oxidase A (MAO-A) influences serotonin availability in the brain. Two studies have revealed links between MAO-A polymorphisms and insomnia characteristics[50].

## THE ROLE OF ADENOSINE

Adenosine receptors have been linked to a variety of diseases, including cancer, immunological and inflammatory disorders, cerebral and heart ischemia, and immune and inflammatory disorders. They minimize overexcitation that could harm the brain and control sleep- and psychiatric-disorder-related systems. Adenosine is assumed to play a role in sleep regulation, and genes that affect adenosine activity may influence sleep/wake phase patterns and, therefore, sleeplessness[51]. Adenosine deaminase (ADA)

gene G/A allele carriers spend longer in slow-wave sleep, wake up less at night, and demonstrate higher strength than G/G variation carriers. Gass et al. examined 117 SNPs from 13 genes associated with adenosine transporters, receptors, and metabolic enzymes in depressed people and a control group[52]. Polymorphisms in the SLC29A3 gene, which is associated with adenosine metabolism, were only seen in women[52].

## RECENT THERAPIES FOR INSOMNIA

The present guidelines for insomnia treatment include both pharmacological and non-pharmacological therapies[53,54]. Numerous approaches are used for non-pharmacological therapy, including CBT, managing external disturbances, and relaxation training, representing both psychological and behavioral treatments for insomnia. Typically, therapy for good sleep hygiene is combined with these therapeutic techniques[54].

Benzodiazepines, non-benzodiazepines GABAA receptor stimulators (Z-drugs), melatonin receptor activators, ORAs (suvorexant and Lemborexant), and antidepressants are examples of sleep aids (hypnotics) prescribed to treat insomnia (low-dose doxepin). Benzodiazepines belong to a family of drugs that target several GABAA receptor subtypes[54,55]. In the past, prescriptions for benzodiazepines, such as flurazepam, brotizolam, temazepam, triazolam, estazolam, and quazepam, were often given for insomnia[54]. Although the effectiveness of these drugs has been

well established, their usefulness is constrained by side effects, like daytime sedation (such as hangover in the morning or the following day), cognitive impairment (including anterograde amnesia), motor incoordination, abuse potential, and dependence[56].

## THE OREXIN SYSTEM AS A POTENTIAL THERAPEUTIC TARGET

The neuropeptides orexin A and orexin B, which are essential for the regulation of the brain's reward and aversion systems, energy balance, and wakefulness, are produced by a limited number of neurons in the lateral hypothalamic area (LHA)[57]. Prepro-orexin, a common precursor polypeptide, is the source of orexin A and B. Prohormone convertases are thought to be responsible for the proteolytic processing of prepro-orexin[58]. In projection neurons expressing orexin receptors, endogenous orexins activate the orexin-1 (OX1R) and orexin-2 (OX2R) receptors, two closely linked G protein-coupled receptors (GPCRs). While both OX1R and OX2R bind orexin A and B, OX2R binds with less selective affinity[57].

The neurostructural distribution of OX1R and OXR2 supports their crucial functions of boosting alertness and sustaining wakefulness in conditions of high motivational importance, such as physiological stress[59]. The orexin peptides and their receptors are largely conserved throughout vertebrate species. States of general need, such as hunger, reward possibility, and threat exposure. Regions important for emotion regulation, circadian rhythm, and numerous afferent inputs are all received by orexin neurons in the LHA[59,60] autonomic tone, rhythms, and hunger.

The basal forebrain, corticolimbic structures, and brainstem receive extensive and dense projections of nerve fibers from orexin immunoreactive neurons of the LHA, particularly in areas involved in wake and sleep control[61]. Orexin-producing neurons are active during wakefulness and dormant during sleep[60]. Orexin A levels vary according to circadian cycles in the cerebrospinal fluid of several animals, peaking during active waking periods. An imbalance in sleep-wake regulation, consisting of either overactivity of the arousal systems or hypoactivity of the sleep-inducing systems, is thought to be the last common route of insomnia pathophysiology[62].

## CHINESE HEMOPATHY ACUPUNCTURE AS A POTENTIAL TREATMENT

Traditional Chinese treatments, modern medicine therapies, and other approaches have demonstrated success in insomnia treatment[63]. The primary medications prescribed for insomnia treatment are diazepam, estazolam, and alprazolam[64]. Although pharmaceutical treatments for insomnia are effective, their use has been reduced due to concerns about misuse, addiction, dependency, breathing restrictions, and unpleasant reactions. Consequently, many patients try complementary and alternative therapies to treat their insomnia[64]. Using pins is one of the most successful insomnia therapies[64]. The ancient Chinese therapy known as acupuncture involves inserting small, solid, metal needles into the skin either manually or using electrical stimulation[65]. The China Sleep Research Association's most recent recommendations for the identification and treatment of insomnia in China now include acupuncture as a secure and reliable natural therapy[65].

## CONCLUSION

This review highlights the complex nature of insomnia and the need for further research on various aspects of this condition. The findings suggest that the pathophysiology of insomnia involves both environmental and genetic factors. Human genetic studies using better sleep metrics could provide a deeper understanding of the genetic aspect of insomnia pathophysiology. Furthermore, research investigating the relationship between nightmares and suicidal ideation is needed, particularly among different age groups. Prospective studies could be useful for predicting changes in suicidal ideation based on changes in insomnia symptoms or dreams. Diagnoses should be included in future research, as evaluating symptoms alone may not provide a complete picture of insomnia. Future studies could explore the use of emerging techniques, such as diaries, actigraphy, and PSG, to investigate the circuit and local level thalamic dysregulation that contributes to insomnia. Such studies may also help to determine the efficacy of potential therapeutic strategies, such as targeting the orexin system and using acupuncture.

## ABBREVIATIONS

**GABBA**: Gamma aminobutyric acid, **LHA**: lateral hypothalamic areas, **MAO A**: Monoamine oxidase, **OXIR**: orexins activate the orexin- 1 receptor, **REM**: Rapid eye movement

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## AUTHOR'S CONTRIBUTIONS

All authors significantly contributed this work, read and approved the final manuscript.

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## CONSENT FOR PUBLICATION

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## COMPETING INTERESTS

The authors declare that they have no competing interests.

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