Insomnia in modern world

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ABBREVIATIONS

ACTH	Adrenocorticotropic Hormone
ARAS	Ascending reticular activation system
CBD	Cannabidiol
(d)CBT-I	(digital) Cognitive Behavioral Therapy for Insomnia
CNS	Central Nervous system
COVID-19	Coronavirus disease of 2019
DORA	Dual Orexin receptor Antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EEG	Electroencephalography
FDA	Food and Drugs Administration
GABA	γ-Aminobutyric acid
H1	Histamine H1 Receptor
HCW	Health Care Worker
Hz	Hertz
ICD-11	International Classification of Diseases, Eleven Revision
ICSD-3	International classification of sleep disorder, third edition
ipRGCs	Intrinsic photosensitive retinal ganglion cells
ISI	Insomnia Severity Index
MDD	Major Depressive Disorder
Mg	Milligram
NE	Norepinephrine
OTC	Over the counter
PTSD	Post-Traumatic Stress Disorder
REM	Rapid Eye Movement

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SUMMARY

Title: Insomnia in the modern world

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Insomnia has become a prevalent and underappreciated problem in our modern world. Characterized by the persistent difficulty in initiating or maintaining sleep, insomnia poses a significant concern for individuals from different backgrounds and age groups. The introductory chapters of this thesis provide the explanation of some relevant concepts that will set the stage for the rest of this thesis. The subsequent chapters explore the epidemiology of insomnia and its prevalence among specific risk groups. The pathophysiology of the disorder will be presented, highlighting the multifactorial nature of the disorder, and the differences observed in sleep patterns between the teenage and the elderly brain. The 3P model will investigate the specific predisposing, precipitating, and, perpetuating factors linked to insomnia.

This thesis then explores the intimacy that exists between insomnia and many other disorders. It examines the bidirectional relationship between insomnia and mental health disorders, such as anxiety and depression, as well as how certain medical conditions can contribute to the development of insomnia. The review then dives into some of the modern causes of insomnia. Nowadays, the major disrupters of our sleep patterns include technology and its associated blue light, noise pollution, daily stress, inadequate sleep hygiene, and the COVID-19 pandemic.

The lack of sleep associated with this condition comes with a cost. This paper will review the associated short- and long-term consequences that insomnia has on our bodies and emphasize the growing burden it imposes on healthcare. Prevention strategies could make a big difference but are still widely lacking. Early education and awareness of healthy sleep habits could potentially alter the prevalence of insomnia itself as well as the prevalence of other mental health disorders in the future. Additionally, this paper presents areas of future investigation regarding the remaining uncertainties surrounding insomnia.

Lastly, the management and treatment options for individuals suffering from the condition are presented, covering both pharmacological and non-pharmacological approaches with a focus on the newest treatment options including the use of Dual Orexin Receptor Antagonist and Digital Cognitive Therapy for Insomnia. Understanding how insomnia has grown into the modern world is crucial for creating a future with better sleep.

Key words: insomnia, modern world, sleep disorder, blue light, noise pollution, COVID-19

SAŽETAK

Naslov: Nesanica u modernom svijetu

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U našem modernom svijetu, nesanica je učestali i prepoznatljiv problem. Nesanicu karakterizira trajna poteškoća u iniciranju ili održavanju sna, što predstavlja značajan problem za osobe različitih karakteristika i dobnih skupina. Uvodni dijelovi ovog rada pružaju objašnjenje relevantnih pojmova u klasifikaciji nesanice, koja je temelj razrade u radu. Naknadna poglavlja istražuju epidemiologiju nesanice i njezinu prevalenciju među specifičnim skupinama rizika. Bit će prikazana patofiziologija poremećaja, uključivo multifaktorijalnu prirodu nesanice te razlike u obrascima spavanja između adolescencije, odrasle i starije životne dobi. Model 3P istražuje specifične čimbenika koji predodređuju, izazivaju i održavaju nesanicu.

Rad zatim istražuje povezanost između nesanice i drugih poremećaja te poremećaja mentalnog zdravlja, poput anksioznosti i depresije, te kako određene medicinske okolnosti mogu pridonijeti razvoju nesanice. Pregled također istražuje neke moderne uzroke nesanice. Danas, glavni čimbenici koji ometaju obrazac spavanja, uključuju tehnologiju, plavo svjetlo, buku, svakodnevni stres, neadekvatnu higijenu spavanja i pandemiju COVIDa-19.

Nedostatak sna, koji prati ovaj poremećaj, ima posljedice. Ovaj rad će pregledati kratkoročne i dugoročne posljedice nesanice na ljudski organizam te naglasiti opterećenje za zdravstveni sustav. Preventivne strategije mogle bi imati značajan utjecaj, ali još uvijek su nedovoljno razvijene. Rana edukacija o higijeni sna i podizanje svijesti o zdravim navikama spavanja mogli bi potencijalno promijeniti prevalenciju same nesanice, kao i prevalenciju drugih poremećaja mentalnog zdravlja u budućnosti. Također, ovaj rad predstavlja područja budućih istraživanja u vezi s preostalim nejasnoćama koje okružuju nesanicu.

Na kraju, prikazani su pristupi u liječenju osoba koje pate od nesanice, obuhvaćajući farmakološke i nefarmakološke pristupe s naglaskom na najnovije opcije liječenja, uključujući upor dvostrukog antagonista receptora dualnog oreksina i digitalnu kognitivnu terapiju za nesanicu. Razumijevanje kako je nesanica postala raširen problem u suvremenom svijetu ključno je za stvaranje budućnosti s boljim snom.

Ključne riječi : nesanica, suvremeni svijet, poremećaj spavanja, plava svjetlost, buka, COVID-19

1 Introduction

In today's busy world, sleep has become a luxury. Between the cacophony of noise pollution in cities, the constant blue light technology is bathing us in, and the increasing weight of everyday life stress in a slowly resolving pandemic crisis, our sleep manners have deteriorated and the consequences are significant. Indeed, 30% of the population today suffers from insomnia symptoms and insomnia disorder has made it to the top of the podium, as the most common sleep-wake disorder.

This review aims to illustrate the causes, consequences, and management of insomnia with a focus on the unique challenges and advancements brought by the modern world. Before exploring the prevalence and epidemiology of insomnia, some important concepts including, circadian rhythms, sleep architecture, sleep quality, and hygiene, as well as the classification of sleep disorders will be explained. This thesis examines the complex pathophysiology of sleep as well as insomnia, the numerous causes of insomnia as well as the short- and long-term consequences of lack of sleep. Finally, it will shortly go over some of the prevention strategies in place to manage the increasing healthcare burden insomnia has become and go over the different ways available to treat insomnia, encompassing pharmacological and non-pharmacological options.

2 Background and Definitions

2.1 The Concept of Circadian Rhythms and the Sleep-Wake Cycle

Circadian rhythms are internal biological processes that follow a roughly 24-hour cycle and are important for the regulation of various physiological and behavioral functions in living organisms, including humans. These rhythms are influenced by both internal factors, such as genetic factors but also by the body's internal clocks, as well as by external factors including light, temperature, and feeding schedules. The light-dark cycle of the environment is the largest influencer of this universal phenomenon that occurs in a wide range of organisms, including animals, plants, and microbes. The sleep-wake cycle is one of the most well-known circadian rhythms in humans, as it regulates the timing and duration of sleep and wakefulness. The release of hormones such as melatonin, prolactin, adrenocorticotropic hormone (ACTH), and norepinephrine in a rhythmic pattern throughout the day, represents another important aspect of circadian rhythms. Certain metabolic processes, such as glucose and lipid regulation are also widely influenced by these rhythms, and, their disruption can have significant impacts on one's well-being (1).

In the human brain, the suprachiasmatic nucleus, a cluster of neurons located within the hypothalamus, assume the role of the master pacemaker as it orchestrates the circadian

rhythms throughout the entire body. Indeed, its absence would result in a severe loss of synchronization among these rhythms, even in the presence of other internal clocks distributed in our bodies. (2) In the case of the sleep-wake cycle, the suprachiasmatic nucleus, which receives signals from cells of the retina, sends signals to the pineal gland to secrete melatonin in response to light levels becoming dimmer. Melatonin is a well know hormone, also sometimes called the sleep hormone, that promotes sleep. On the other hand, if light levels would increase, the suprachiasmatic nucleus would signal the pineal gland to stop the production of melatonin, promoting wakefulness instead. (3) Disruption of this precious cycle can play a significant role in the development of various sleep disorders including insomnia. The main disruptor of the sleep-wake cycle is exposure to light at night, but many more disruptors are recognized and include, irregular sleep schedules, noise, temperature, and certain medical conditions, as this thesis will explain.

2.2 Sleep Architecture: REM non-REM phases

The sleep-wake cycle can be divided into 3 main phases; wakefulness, non-REM sleep, and REM (rapid eye movement sleep). Non-REM and REM happen during sleep and together, form a cycle that lasts for about 80 to 100 minutes which will typically repeat itself 4-5 times during a full night of sleep. Non-REM sleep can further be divided into 3 stages, each is characterized by specific brain activity that can be recorded on EEG as different wave patterns and electrical activity.

- *Stage N1* consists of the transition between wakefulness and sleep. It is characterized by theta waves which have a frequency of 4-8 hertz (Hz).
- *Stage N2* shows sleep spindles, bursts of brain wave activity with a higher frequency of 12-14Hz, as well as K-complexes. The latter are sharp, high-amplitude brain waves.
- In *stage N3*, delta waves are observed and have a frequency approaching 4Hz, which is why this stage is also known as the deep sleep stage or the slow wave stage. The total amount of sleep time spent in deep sleep or N3 decreases with age and can also be reduced by the consumption of alcohol, barbiturates, benzodiazepines, and other CNS depressants. The same effect can be observed during the next phase, REM sleep. Multiple parasomnias happen in this part of the night including sleepwalking, night terrors disorders, and enuresis.

As individuals advance through these stages, most of our body relaxes. This includes; a decrease in muscle tone, respiratory rate, heart rate, and cortical activity. Respectively, N1, N2, and N3 make up 5-10%, 45-55%, and 10-25% of the total sleep time, making Non-REM the longest phase individuals spend in (75-80%).

- REM sleep is quite different. As its name implies, people experience rapid and irregular eye movement and an increase in brain activity. The latter is regulated by the activation of the conjugate gaze center in the paramedian pontine reticular formation, a structure found in the brainstem. Moreover, maximum muscle relaxation occurs as it is the stage

of sleep that include dreaming, preventing individuals from acting out their dreams and nightmares. REM sleep duration is typically increased in patients suffering from major depressive disorders (MDD) whereas the REM sleep latency (period of time between the onset of sleep and the first episode of REM) is typically reduced in such patients. Narcolepsy is another condition seen with shortened REM sleep latency.

Non-REM sleep predominates during the first part of the night whereas the REM stage increases in duration as the night progresses. (4,5)

2.3 Sleep Quality

According to the article "sleep quality: An evolution concept analysis" by Kathy L. Nelson, Jean E. Davis, and Cynthia F. Corbett, sleep quality is defined as "an individual's self-satisfaction with all aspects of the sleep experience." Sleep quality can be influenced by 5 main factors: sleep efficiency, sleep latency, sleep duration, wake after sleep onset, and the presence of sleep disorders or other health conditions. Sleep quality is essential to avoid poor health outcomes and good sleep quality leads to feeling rested, normal reflexes and positive family and social relationships, and many more(6).

2.4 Sleep Hygiene

Sleep hygiene is a term that was first used in the late 1970s in the context of sleep disorders, especially insomnia. Since then, its exact meaning has evolved to regroup a set of behaviors that individuals should adopt in order to have a good and restful sleep. These behaviors include, for example, establishing a constant sleep schedule, creating a relaxing sleep environment, avoiding the use of electronic devices before bedtime as well as the consumption of alcohol and/or nicotine. As this thesis will show, ignoring good sleep hygiene behaviors can have serious repercussions on one's well-being, while adopting good sleep habits could help prevent and treat insomnia (7).

2.5 Classification of Sleep-Wake Disorders

The International Classification of Diseases, Eleven Revision (ICD-11) describes sleep-wake disorders as: "sleep-wake disorders are characterized by disturbances of the quantity, quality, timing or behavior associated with sleep. This result in impaired functioning or distress and occurs despite adequate opportunity for sleep" (8).

ICD-11 classifies sleep-wake disorders in the following way (8):

1. Insomnia disorders
2. Hypersomnolence disorders
3. Sleep-related breathing disorders
4. Circadian rhythm sleep-wake disorder
5. Sleep-related movement disorders
6. Parasomnia disorders

Whereas the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), divided them into 11 diagnostic groups (9) :

1. Insomnia disorder
2. Hypersomnolence disorder
3. Narcolepsy
4. Obstructive sleep apnea
5. Central sleep apnea
6. Sleep-related hypoventilation
7. Circadian rhythm sleep-wake disorders
8. Non–rapid eye movement (NREM) sleep arousal disorders
9. Nightmare disorder
10. Rapid eye movement (REM) sleep behavior disorder
11. Restless legs syndrome and substance-/medication-induced sleep disorder

2.6 Differentiating Insomnia Symptoms from Insomnia Disorder

Insomnia disorder is described by ICD-11 in the following way: "Insomnia disorders are characterized by the complaint of persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment. Daytime symptoms typically include fatigue, depressed mood or irritability, general malaise, and cognitive impairment. Individuals who report sleep related symptoms in the absence of daytime impairment are not regarded as having an insomnia disorder"(8). ICD-11 also puts an emphasis on the nature of the sleep disturbance, which include: delayed sleep onset, trouble staying asleep, early morning awakenings and non-restorative sleep.

Insomnia disorder is a clinical diagnosis made by medical doctors. To be diagnosed with insomnia disorder, patients must meet specific diagnostic criteria's outlined by the DSM-5.

DSM-5 Diagnostic criteria for insomnia disorder (10):

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
    a. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.)
    b. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
    c. Early-morning awakening with inability to return to sleep
B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

C. The sleep difficulty occurs at least 3 nights per week.
D. The sleep difficulty is present for at least 3 months.
E. The sleep difficulty occurs despite adequate opportunity for sleep
F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).
G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Specify if:

- With non-sleep disorder mental comorbidity, including substance use disorders
- With other medical comorbidity
- With other sleep disorder

Specify if:

- Episodic: Symptoms last at least 1 month but less than 3 months.
- Persistent: Symptoms last 3 months or longer.
- Recurrent: Two (or more) episodes within the space of 1 year.

Insomnia symptoms are subjective experiences related to problems with sleep. People can experience such symptoms without being diagnosed with insomnia disorder. Common symptoms include trouble falling asleep, waking up frequently, difficulties returning to sleep, early morning awakenings, poor sleep quality, not feeling refreshed, daytime sleepiness, impaired daytime sleepiness, difficulty focusing, mood disturbances, and many more. Insomnia symptoms often arise secondary to a primary medical or mental condition or in the setting of drug/substance use and withdrawal. However, the presence of comorbidity does not exclude an independent diagnosis of insomnia disorder. Even if insomnia is initially triggered by another primary disorder it can evolve into a distinct, self-sustaining disorder. Indeed, in the older version of the Diagnostic and Statistical Manual of Mental Disorder, insomnia was classified as either primary or secondary insomnia, but this way of classification was realized wrong as it implied that, if the underlying comorbidity was treated, insomnia would automatically resolve. In 2013, as the DSM-5 replaced the DSM-IV, the differentiation between primary and secondary insomnia was dropped and replaced with the term “insomnia disorder” (11). Additionally, a person suffering from an episode of insomnia lasting a few weeks at a time but repeatedly over years that does not meet the 3 months criterion, is still warranted an insomnia disorder diagnosis (12).

3 EPIDEMIOLOGY

Insomnia is the most prevalent sleep-wake disorder with a global prevalence of 10%-30%. Around 10% of adults have a diagnosed insomnia disorder while an additional 20% report occasional symptoms of insomnia. Various studies in different countries over the last decades have shown a significant increase in the prevalence of insomnia. The most common symptom is difficulty maintaining sleep, followed by early morning awakening and difficulty initiating sleep. Insomnia has a tendency to become chronic and around 40% of people experience its persistence over a period of 5 years (13).

The prevalence of insomnia increases with age and women are more prone to experience symptoms of insomnia than men. In fact, women are 1.5 times more likely to experience insomnia than their male counterparts (14). As people age, changes in their sleep patterns and physiology, like in their circadian rhythms, typically make them fall asleep faster and wake up earlier in the morning.

Insomnia is often linked to various social and societal stressors. Individuals with a low quality of life, a low socioeconomic status as well as individuals with preexisting psychiatric or medical conditions are more easily affected by the condition. It is well known that anxiety and depression have a complex interplay with sleep and often come hand in hand. These conditions have the ability to create a hyper arousable state in the patient, making it more difficult to relax and fall asleep. Conversely, insomnia can worsen the symptoms of anxiety and depression; insomnia was found to be a significant predictor for the subsequent development of a psychiatric disorder.

Other vulnerable patient groups include military personnel and veterans due to the high likelihood of exposure to a traumatic event which could lead to subsequent PTSD and insomnia. This population also often have to deal with very irregular sleep schedule as well as noise and light pollution which are risk factors to develop insomnia. (15)

4 PATHOPHYSIOLOGY

Insomnia is a complex condition with pathophysiology involving the interplay of various factors, including psychological and cognitive arousal, as well as disruptions in the circadian rhythm and homeostatic mechanisms. A reduced capacity of the so-called “sleep-wake switch” may also play a role in the development of insomnia.

Wakefulness is regulated by ascending activity in several brainstem and hypothalamic nuclei that are all part of the ascending reticular activation system (ARAS) and which are widely connected to the cerebral cortex. Orexin A and B make up the orexin system and balance sleep and wakefulness by maintaining the state of wakefulness for longer periods. The ARAS inhibits

its “sleep analog”, known as the ventrolateral preoptic nucleus, a region found in the hypothalamus, by activation of cholinergic neurons and the release of orexin. On another hand, sleep is promoted by the ventrolateral preoptic nucleus through its inhibition of the ARAS, via the release of Gamma-Aminobutyric acid (GABA) and galanin. When photosensitive melanopsin-containing retinal ganglion cells, called intrinsic photosensitive retinal ganglion cells (ipRGCs), detect a reduction in light, they induce the stimulation of the retinohypothalamic tract which will lead to the release of norepinephrine from the suprachiasmatic nucleus in the hypothalamus. This release will eventually lead to the release of melatonin from the pineal gland and ultimately to sleep. These two interconnected systems of the sleep-wake cycle work in a way that one is switched off while the other is switched on, preventing them from occurring simultaneously (15,16).

Moreover, homeostatic factors respond to accumulated wakefulness by creating a drive to sleep. It is thought to be partly done by the accumulation of adenosine, and nitric oxide, and changes in the levels of other chemicals released in the brain throughout the day. At the end of the night, as sleep-promoting activities diminish and wakefulness is triggered, other chemicals including glutamate, norepinephrine, dopamine, serotonin, acetylcholine, histamine, and orexin A and B (11,15) begin to appear.

The pathophysiology of sleep and wakefulness is important to understand as many pharmacological treatment options have targeted and modulated the neurotransmitters involved in those processes.

4.1 Sleep Patterns of the Teenage Brain

A subject that has emerged more and more in the last decades is the sleep pattern of the teenage brain and the difficulty they have waking up and being ready to learn in early classes. As children grow older, they slowly decrease the duration of their nocturnal and daytime sleep. When they reach adolescence, they typically tend to shift their bedtime to later hours. The teenage years are a crucial stage of human development, characterized by a lot of changes, one being brain development. These changes will help adolescents prepare for their adult life and include changes in decision-making, emotional regulation, and in social behavior.

It is not surprising that during this period, adolescents have unique sleep needs. Recent studies have shown that adolescents’ sleep mechanisms change with puberty and affect both the homeostatic and circadian regulators of the sleep (17). This shift in the sleep/wake cycle will lead to a delay in sleep timing, resulting in a later start in the production of melatonin and consequently a later stop in its secretion. This explains why adolescents find it so difficult to make it to their early lectures and why going to sleep earlier would not improve their hassle. Nowadays, this is exacerbated by modern lifestyle i.e. use of technology, light exposure, to which they have an increased sensitivity, and consumption of caffeine. (18) Teenagers have a reduced ability to recover from a short night of sleep and this was found to have short- and long-term negative effects. Sleep deprivation in those years can lead to daytime sleepiness,

mood disturbances, poor academic performances, increased likelihood of substance use including cigarettes, alcohol, and drugs, obesity, and driving accidents. (19)

Researchers have come up with a few solutions to the problem of sleep deprivation during the teenage years. First of all, sleep education should be available to adolescents as well as to their surroundings—and should provide a clear explanation of sleep, its importance, and its benefits. Basic sleep hygiene should be introduced. Later school start times should be considered to realign the adolescent circadian rhythm to the school schedule and give them a chance to be fully focused during their first period of the day. Furthermore, reducing exposure to blue light and technology use before sleep could avoid an even bigger sleep delay (17,19).

4.2 Sleep Patterns in the Elderly Brain

Sleep and circadian rhythms undergo significant changes across a lifespan. Newborns typically sleep 10 to 14 per day, whereas the older population averages 5 to 7 hours of sleep. The older population was found to spend less time in slow wave sleep (N3 stage) and more time in lighter stages of sleep, such as N1 and N2 during the night and this leads to decreased sleep efficiency. Sleep efficiency is the ratio of the total time asleep versus the total time spent in bed (6) and it is known to decline with increasing age. These sleep patterns are characterized by a more shallow type of sleep and easier arousal. Sleep fragmentation with frequent awakenings during the night and early awakenings are consequently recurrent complaints of the elderly population. Interestingly, it was also found that the older population may be more tolerant of sleep deprivation than the younger population. Factors that can contribute to poor sleep and insomnia in this population are multiple and include the lack of fixed schedules and time cues, as a consequence of retirement, as well as irregular meal times, polypharmacy, comorbidities including pain, nocturnal, dyspnea, poor physical function and menopause in women (15,20). Changes in sleep patterns are by far the only consequence of aging; changes in body composition, increased fat, and decreased total water are important changes to take into account when treating insomnia and other sleep disorders in the elderly as they will impact the pharmacokinetics of drugs used. This is why, especially in this population, it is important to try to consider non-pharmacologic treatment options first.

4.3 Model of 3P

How insomnia starts and can subsequently transition from an acute condition to a chronic condition is explained by the model of 3P. This cognitive-behavioral model suggests that 3 interrelated sets of factors; “predisposing”, “precipitating” and “perpetuating” factors, when present together, can contribute to the development of insomnia.

Predisposing factors:

These are usually unmodifiable and pre-existing vulnerabilities that would predispose an individual to insomnia. They include, for example, genetic risk, prior insomnia or other sleep and non-sleep-related disorders, psychological conditions, and pain. Sleep reactivity is another

predisposing factor. It is a term used to measure how easily a person would be disturbed from their sleep by various factors. (21) A person with a high sleep reactivity experiences poorer overall sleep quality in the presence of stressors (stress or noise, for example,) than a person with a lower sleep reactivity would, in the same conditions.

Precipitating factors:

While predisposing factors alone would not necessarily lead to insomnia, the addition of a precipitating factor significantly increases the likelihood of developing the condition. These factors are usually any kind of stressful life event. Some common examples are: problems related to health, a death, family problems or divorce, and starting a new job/new school are common examples of factors that could trigger acute insomnia in a predisposed patient.

Perpetuating factors:

These factors are known to worsen and maintain insomnia even after the precipitating factor has been resolved. They include, among others, maladaptive behaviors such as spending too much time awake in bed, trying to compensate by going to bed early, or sleeping in and napping. These coping strategies typically weaken the important association of sleep with bed/bedroom, which in turn reduces the homeostatic sleep drive at bedtime. Moreover, these are often accompanied by excessive worry, especially about solving their sleep problem, which can easily turn into a vicious cycle of never-ending thoughts. These factors are believed to be the reason why some patients transition from an episode of acute insomnia to chronic insomnia. As a result, they are also of the main target of cognitive behavioral therapy for insomnia (15,22).

5 General Etiologies

5.1 Secondary Insomnia

Secondary insomnias are sleep/wake complaints that arise in the setting of a primary condition or causative condition.

5.1.1 Insomnia due to Drug or Substance

Many substances have been linked with insomnia symptoms as they have been found to have multiple mechanisms to influence sleep. For example, stimulants such as amphetamines or cocaine are known to increase arousal and have deleterious effects on sleep. A more commonly used stimulant substance is coffee. Coffee is widely consumed worldwide with the intent to decrease sleepiness. Its consumption has been linked with prolonged sleep latency, reduced total sleep time and sleep efficiency, and general poor sleep quality (23).

On another hand, alcohol, a CNS depressant with sedative properties, has a complex relationship with insomnia. While its consumption can trigger and worsen insomnia, some patients use alcohol to self-medicate and control it. Indeed, research shows that 36-91% of alcoholics report experiencing insomnia when consuming alcohol while in contrast, 15-30% of people explain using alcohol to self-medicate their sleeping problems. Unfortunately, as they develop tolerance to alcohol, individuals trying to manage their insomnia by drinking, slowly develop an addiction disorder. It can be said that alcohol and insomnia have a bidirectional connection and alcohol has a strong effect on sleep architecture. It is known to fragment sleep, to decrease REM sleep as well as the dreaming stage, leading to a worsened sleep quality. Another issue important to note is the very high insomnia rate reported (15,24) in the setting of withdrawal from alcohol consumption.

Similarly, cannabis consumers are highly susceptible to insomnia after cessation of sustained use. However, many people use cannabis, like alcohol, as a sleep aid. THC and CBD are cannabinoids that interact in the brain with other neurotransmitters and the endocannabinoid systems leading to decreased sleep latency, increased sleep maintenance, and duration. This can lead to the general perception that cannabis helps with sleep. Nowadays, this effect is a common reason for cannabis consumption in the general population. However, currently, there is ongoing research concerning the consequences of chronic use of cannabis as it has already been associated with negative sleep outcomes and other negative health outcomes (25).

5.1.2 Insomnia due to a Medical Condition

Insomnia often develops secondary to another medical condition. Cancer patients have a high prevalence of insomnia due to the psychological burden to carry such a diagnosis, often exacerbated by the tough treatments associated with cancer (26). The distress caused by the disease and its treatment can easily and significantly impact sleep. Conditions leading to chronic pain like arthritis, fibromyalgia, or back pain can make it difficult to fall asleep and maintain sleep, leading to insomnia. Patients suffering from respiratory conditions, as well as gastrointestinal conditions, also often complain of insomnia(12) as a result of the symptoms and discomfort. As many medical conditions can directly or indirectly impact sleep, it is important to recognize them and provide adequate care. This is crucial as the physiologic effects of lack of sleep can further worsen the primary condition, creating a negative cycle.

5.1.3 Insomnia due to a Mental Disorder

Here again, insomnia shares an intimate relationship with many mental disorders. 70% of patients diagnosed with a mental health disorder also complain of insomnia symptoms and more than 30% meet the criteria for an insomnia disorder diagnosis. It was found that patients having comorbid insomnia are less likely to respond well to treatment and are at higher risk of experiencing poorer outcomes compared to those who only have the mental health disorder without insomnia(27). This is why treating insomnia separately is often crucial for a better treatment outcome. Moreover, a patient suffering from insomnia is more prone to develop a

de novo mental health disorder on top of their insomnia, especially major depressive disorder. This suggests that insomnia creates the perfect foundation for the development of many mental health disorders.

Anxiety disorders, such as post-traumatic stress disorder, general anxiety disorder, or obsessive-compulsive disorder, are closely linked to poor sleep as the overwhelming anxiety feeling of these patients can easily affect and disrupt sleep patterns. Likewise, a patient suffering from a mood disorder is often affected by insomnia. Up to 90% of patients suffering from major depressive disorder (MDD) report insomnia or sleepiness. In fact, insomnia is listed as a key symptom in the criteria for diagnosis of MDD and even if its presence is not absolutely required for a definitive diagnosis, it is important to understand that insomnia almost always co-exist with major depressive disorder. The presence of insomnia in such patients was also shown to increase the risk of suicide ideation and attempts. Bipolar disorders are another prevalent group of diseases with major effects on sleep, both during manic or depressive episodes. While patients experiencing manic or hypomanic episodes may still report feeling rested after very few hours of sleep, insomnia can still be present and affect overall sleep patterns (28). In the case of schizophrenia, insomnia is also quite prevalent even if it does not appear in the criteria for diagnosis. Indeed, 80% of patient report sleeping issues related to their psychotic disorder. Multiple factors can contribute to this; the symptoms and the stress associated with the condition can easily affect sleep while some of the medications used for treatment can lead to sleep disturbance as a side effect. Moreover, that patient often suffers from a comorbid substance use disorder that can also contribute to insomnia, and finally, neurobiological factors and changes in neurotransmitters can interfere with the normal sleep cycle. It is even now believed that insomnia could be a major prodromal symptom of psychosis and if present, it can worsen it significantly (29).

Overall, insomnia, in the context of mental health disorder, can impact as much the disease and its course as its treatment and its outcomes and this is why it is important to recognize it and to address it as an integral part of mental health care.

5.2 Behavioral Insomnia of Childhood

Children are not spared by insomnia, indeed up to 30% of children, starting from 6 months of age, experience symptoms of insomnia. It most likely results from bad sleep training by parents or by them not establishing adequate boundaries to do so. Behavioral insomnia in childhood can be divided into 2 types. The first type is a “sleep onset” associated type and it is characterized by the child relying on a specific stimuli, object, or condition to both fall asleep and/or go back to sleep. This type is more common in children of less than 2 years of age whereas the limit-setting type is seen in older children. In the limit-setting type, the child refuses to go to sleep as a result of insufficient boundaries set by the caregivers. A mixed type is possible. These types of dexterous behaviors can have a significant impact not only on the child but also on the parents and if left untreated it can persist into adulthood (12,30).

6 Modern Causes of Insomnia

How have the recent advancements, developments, and trends, making up the modern era affected sleep? In this chapter, the causes of insomnia brought on by technology, globalization, and changing society will be discussed.

6.1 Blue Light and Technology

The use of digital technology such as computers, smartphones, and tablets can be nowadays, considered a new drug or addiction, with which people can access whatever content they want, wherever and whenever they want. Indeed, 77% of Americans owned a smartphone in 2018, but this number is believed to be closer to 95% today, with the COVID-19 pandemic partly responsible for this increase (31). Since the beginning of technology use, 3 common conceptualizations of maladaptive technology use have emerged and are even recognized as conditions for further study in the DSM-5; problematic internet use, internet gaming disorder, and social media addiction. Internet addiction does not come at no cost, psychological problems and mood disorders are reportedly more prevalent among about 65% of internet addicts, and of course sleep disorders, including insomnia, are part of the list (32,33). Naturally, addictions lead to the neglect of healthy habits i.e. sleep, but, one doesn't have to be addicted to electronic media to develop sleeping problems, and this is because of blue light.

Blue light refers to the short-wavelength light in the visible light spectrum and is known to have a very high impact on our precious circadian system which keeps most biological and psychological rhythms internally synchronized. Blue light is emitted by many sources including artificial light such as LED lamps, digital screens, but also the sun. It has the ability to induce a sustained depolarization of the ipRGCs in the retina especially if exposure is through bright and continuous light. These special cells, which are most important in the non-image-forming photoreception, transmit the information to the master pacemaker, the suprachiasmatic nucleus, which then regulates the production of melatonin by the pineal gland. Melatonin is suppressed by light exposure, with the short or blue wavelengths being much more effective at it than the longer wavelength (red to yellow). This process of suppression of melatonin is essential and helps us stay and feel awake during the day (32,34,35). This also explains how mistimed exposure to such light can disrupt the normal melatonin production and the normal sleep/wake cycle. At least 90% of young adults aged less than 30 use some kind of technological device in the hour before they go to sleep. Studies are unanimous on the subject and came up with the same conclusion; exposure to screens before sleep leads to delayed sleep time as well as a decrease in the total sleep time. In a recent investigation, 3 groups of students were examined based on the number of hours they were using their smartphones before sleep in order to find out the extent it affected their sleep quality. The study showed that there was an overall decreased sleep quality and duration with severity collating with increased hours of use. It also showed that there is a lack of awareness about the function "Night Shift mode", which reduces blue light emission when turned on (36).

In our digital world, it became more important to stay connected than to feel well-rested. This is a problem among kids, adolescents, and adults who are often not fully aware of the impact of using their digital devices daily and more importantly, in bed before sleep.

However, there are solutions or strategies that are known to reduce blue light exposure. First of all, blue light-blocking glasses have become more and more popular in recent years. They are designed in a way to filter and reduce the amount of blue light that reaches the retina and have the potential to depolarize ipRGC. They also come in the form of lenses. Studies have shown good results in their effectiveness to reduce the delayed sleep onset created by exposure to blue light and can be used in the setting of insomnia and other sleep disorders (37). Similarly, blue light filtering apps or settings, known as the night shift mode, now exist and are believed to reduce the amount of blue light emission by devices by shifting the blue light emitted by screens to a more orange light (36). Of course, limiting the use of these devices before sleep would be the best solution to avoid exposure to blue light.

In some cases, blue light can also be used as a therapy for sleeping problems, especially for delayed sleep-wake phase disorders.

6.2 Noise Pollution

Another major factor affecting sleep in our modern world is noise pollution. Noise pollution is defined as any unwanted or harmful sounds typically produced by human daily activities and living. They include, for example, transportation-related noises, such as traffic or aircraft and trains but also noise from construction sites, industrial processes, and neighborhood noises. People living in cities and in large or old apartment buildings are the most affected (38).

The article "WHO Environmental Noise Guidelines for the European Region: A systematic review on Environmental Noise and Effects on Sleep" illustrate further how noise pollution has a bad effect on sleep. As explained in the article, this can lead to sleep disturbances such as difficulties falling asleep, staying asleep, or falling back asleep after being awakened which leads to a general poor sleep quality and contributes to the development of insomnia. In the long-term, as sleep has so many vital functions, it is suggested that constant noise pollution and sleep fragmentation can lead to cardiovascular complications, mental health problems, including depression and anxiety, and the impairment of cognitive function (39). These are only a few examples of the consequences of insomnia as it will be explained later in more details.

It was found that traffic noises are the ones disturbing sleep the most. This is most likely due to their unpredictable and generally loud nature compared to indoor noises or constant noises. They can also be accompanied by vibrations, as in the case of trains, which is linked with a higher sleep disturbance (40). When it comes to disrupting someone's sleep, the nature and type of noise can be evaluated using various factors such as loudness, duration, and peak sound pressure. Typically, traffic noise is defined by its loudness and duration, whereas a louder and shorter sound like a siren is often described by its peak sound pressure. Ultimately,

the ability of noise to fragment someone's sleep could be described using those parameters. Sleep stages and sleep timing are two other crucial variables to consider when determining whether a person is going to wake up from noise. As explained, as one falls asleep, he goes through different sleep stages which have different characteristics and vulnerabilities to noise. Deep sleep is the time when the body goes through important physiological processes and our brains are less responsive to external stimuli. This is why a louder noise would be required to wake someone up from this stage. Disruption of deep sleep specifically is thought to be linked to many short and long-term negative side effects. Sleep timing refers to the time of the night when the noise would happen, for example, late nights or early mornings, and could also influence our responsiveness to the disturbances(41).

Not everyone is affected by the noise the same way. It was found that some populations are more sensitive to noise and they include individuals with a preexisting sleep condition, the elderly, and children. The notion of habituation to noise is also important. It was studied that people get used to noise with time. This is seconded by the fact that patients are more sensitive to noise disturbances during the first few nights of a sleep monitoring experiment compared to the later stages of the study. However, habituation varies from one person to another. Spontaneous rhythms of the brain, thalamocortical sleep spindles to be precise, are believed to be a good predictor of how a person asleep will react to noisy stimuli. (42) It is important to notice that the autonomic nervous system has a lower ability to habituate and this is proposed as the link between the long-term effects of noise pollution and cardiovascular diseases. It is also relevant to state that the opposite of habituation is also possible and is known as sensitization but little is known about it for now. (39)

Many countries have now regulations in place regarding noise in different settings in order to reduce the hazardous effect of noise disturbances. Noise levels are identified and reported in order to create guidelines. Noise pollution has been around humanity for quite some time but it is now more and more recognized as a problem and its impact and consequences have brought it into the spotlight in recent years. With more attention comes also more solutions, as highlighted by the article. It suggests that more rules and guidelines should be implemented based on the findings made in research. Rules should include guidelines on urban construction and planning, both within and surrounding urban areas. For example, the construction of noise barriers when necessary to protect neighborhood from traffic sounds. In addition, individuals can also take matters into their own hands by considering the use of earplugs or other more modern noise canceling devices to help mitigate the impact of noise on their sleep. Finally public awareness and education about the subject can push people to take actions and reduce noise levels and, with it, the possible negative impacts it may have on their lives.

In conclusion, environmental noise, especially unpredictable traffic noise at night has a variety of significant harmful effects on our health ranging from sleep fragmentation and daytime sleepiness to increased risk of cardiovascular diseases in the future. Whether or not a certain noise will fragment our sleep depends on individual factors (age and individual sensitivity to

noise), situational moderators (current sleep stage), and the specific characteristics of the noise. Increased awareness in recent decades has led to the need for the implementation of guidelines and regulations about how to reduce noise pollution in the affected areas and protect public health and our basic need for sleep. (39)

6.3 Stress and Psychophysiological Insomnia

Stress, although present around us throughout history, is rapidly evolving and has become a prominent part of our modern lives. Technological advancements, the fast-paced lifestyles of modern society, social pressure and expectations, overcrowding, and economic uncertainties, are just a few examples of the various forms in which stress can manifest in one's life nowadays. Other examples of stressors affecting the American population in recent years, as illustrated by the American psychological association, encompass issues such as violence and safety concerns related to guns, shootings, and other crimes, inflation, the COVID-19 pandemic, racial injustice, and politics (43). Stress is a well-known contributing factor to numerous conditions and it was found that both, major life events and everyday stressors, can affect sleep and precipitate people into insomnia.

As mentioned earlier, individuals may experience sleep difficulties when faced with some stressor, but the degree to which they are affected can vary significantly, and this is explained by the concept of sleep reactivity. Highly sleep-reactive patients will experience a significant deterioration in their sleep quality even when faced with a small stressor, whereas some people will sleep through even big sleep disruptors. Studies have shown that individuals with a high sleep reactivity are at increased risk of developing insomnia disorder as described in the DSM-5. Stressors can induce a state of rumination in which the patient suffers from repetitive and intrusive thoughts that focus on negative experiences, emotions, or problems and often involve excessive worry, replaying past events while self-criticizing themselves. Such thoughts can interact with someone's sleep reactivity, potentially triggering or exacerbating insomnia symptoms by inducing a state of hyperarousal. When people engage in rumination, they unwillingly activate the sympathetic nervous system which will make it difficult for them to relax and unwind in order to fall asleep. This continuous activation of the mind keeps individuals alert and stimulated, putting them into this hyperarousal state, that often keeps feeding on thoughts about not managing to calm down to fall asleep. This often leads to sleep-interfering habits, such as spending too much time in bed while worrying instead of sleeping, undermining the important association between the bed and sleep, which should be set in our brains for maintaining good sleep hygiene (44). Moreover, people experiencing daily stress, have demanding schedules, or experience insomnia symptoms often have anxious thoughts about sleep. They may worry about their ability to fall asleep and the consequences of inadequate sleep for the next day. These worries tend to increase as bedtime approaches further exacerbating the existing difficulty in falling asleep, creating a cycle of poor sleep or insomnia.

Stress can contribute to poor sleep quality, and in turn, poor sleep quality can further contribute to more distress. During sleep, the locus coeruleus, in association with the activation of the amygdala-hippocampus-medial prefrontal cortex circuit, is essential for emotional and memory processing. During REM sleep, the noradrenergic neurons of the locus coeruleus are inactive, leading to low levels of norepinephrine (NE) release. This unique state of low NE is very important during REM sleep as it is during this time period and in these conditions memory and emotions are processed the best. A hyperarousal state created by stress can lead to an increased release of NE during REM, leading to disruption in the activation of the amygdala-hippocampus-medial prefrontal cortex circuit. This disruption can further interfere with the selective cutting and consolidation of synapses formed during learning, potentially leading to memory misprocessing and emotional dysregulation. This phenomenon is commonly referred to as restless REM sleep, which results in individuals waking up feeling unrested and experiencing a negative impact on their mood. Over time, this can have a detrimental impact on mental health, potentially leading to more stress and anxiety(45). Interestingly, a study suggests that stress occurring during a critical period of brain development in childhood could lead to "learning of being unsafe" and could have a long-term impact on the brain and sleep. Indeed, it suggests that learning of being unsafe leads to a state of hypervigilance and watchfulness that could follow us for years and into our sleep (45).

Even if our endogenous circadian rhythm is healthy and well regulated by external factors and all the necessary conditions for a good night of sleep are present, emotional distress or rumination can still significantly after sleep. Insomnia is in a way distress that presents at night.

6.4 Inadequate Sleep Hygiene

Poor sleep hygiene can contribute to the development or worsening of insomnia. Unfortunately, there is a significant lack of awareness regarding this issue, especially in the young adult population and those complaining of poor quality of sleep. In our fast-paced, technology-run, stressful world, sleep often takes a backseat on our priority list. With excessive exposure to blue light before sleep, frequent coffee consumption, and a lack of a regular sleep routine, individuals become more vulnerable to bad sleep quality and the development of insomnia.

Good sleep hygiene includes:

1. Consistent sleep schedule: going to sleep at the same time and waking up at the same time, including weekends helps regulate the body's internal clock.
2. Bedtime routine: establishing a relaxing routine before bedtime can help unwind and signal the brain that it is time to sleep.
3. Comfortable sleep environment: a cool, dark, and silent bedroom is important for falling asleep.
4. Avoiding stimulants: limit the consumption of coffee and other energy drinks already in the afternoon as they can interfere with the process of falling asleep.

5. Limit exposure to blue light: Avoid the use of electronic devices before bedtime as they are a well-known sleep disrupter, dysregulating melatonin secretion.
6. Bed is for sleep and intimacy: it is important to keep this association and avoid using the bedroom to do other things.
7. Exercise: Regular exercise promotes good sleep but it is recommended to finish working out at least a few hours before sleep to give time to the body to relax.
8. Avoid large meals and fluids before bedtime.
9. Manage stress: it is important to go to bed with a calm mind and to leave any stress and intrusive thoughts outside the bedroom. Meditation and writing down thoughts can help achieve this.
10. Avoid napping: naps can interfere with the sleep-wake cycle.

Over the years, the concept of sleep hygiene has gained popularity and has become a well-liked non-pharmacological treatment option for people suffering from sleep-related disorders including insomnia(7).

6.5 COVID-19 Pandemic Effect on Sleep

Since the onset of the global COVID-19 pandemic in late 2019, populations worldwide have been forced to drastically change their everyday lives. As a lot of efforts have been dedicated to slowing down the transmission of the virus, measures such as the lockdown of more than half of the world's population, closure of schools and universities, working from home, and social distancing has become the new reality of a large portion of the global population. A year later, more than 53,78 million confirmed cases of COVID were identified and more than 1.3 million died due to the infection. (46) It is not surprising that the stress brought about by the pandemic has led to an increased prevalence of a number of mental health disorders particularly depression, anxiety, and also insomnia.

Indeed, in Spain, a systematic review and meta-analysis of the symptoms of anxiety, depression, and insomnia during the covid-19 crisis have shown that these have increased during the pandemic compared to their pre-pandemic prevalence. The population groups that reported the highest number of symptoms included healthcare workers, students, and women. The pooled prevalence found in this study was 20% for anxiety, 22% for depression, and 57% for insomnia. (47) Another study, based on a Greek population this time, similarly found that women were more affected than men by insomnia and added that people living in urban areas were more vulnerable to sleep disorders during the pandemic. Moreover, the study revealed that depression could be considered a predictive factor for the development of insomnia. The prevalence of insomnia in the Greek population was estimated to be around 37.6% at that time (48). Now looking at a cross-sectional study done in the Chinese population, the prevalence of anxiety during the pandemic was of 35.1%, depression of 20.1%, and 18.2% for insomnia. Here, no difference in prevalence between gender was found, but the younger population (<35) was found to be more likely to experience symptoms of anxiety than the older

population (>35) but again, healthcare workers were the most affected and reported the highest rate of insomnia symptom (49).

In addition to the overall impact of the COVID-19 pandemic on daily life, the direct infection by the virus has also had a significant effect on sleep and this regardless if the patient presented with heavy symptoms or as an asymptomatic patient. A significant number of COVID-19 patients, ranging from 14-61% have reported experiencing psychiatric symptoms, including insomnia, during their illness. Furthermore, even after recovering from the acute phase of the infection, a high percentage of patients (ranging from 14.8 to 76.9%) continued to experience similar symptoms. One study found that individuals with a positive COVID test result were more likely to report frequent trouble sleeping since the start of the pandemic than those with a negative COVID test. However, there is a lack of comprehensive data on whether these sleep difficulties stem directly from the viral infection itself, or if they are influenced by the stress and changes brought in by the pandemic(11,46). The truth probably lies somewhere in between.

As proven by many studies, pandemics are associated with the increase in the prevalence of many mental health disorders as well as insomnia. What are the pandemic's specific predisposing, precipitating, and perpetuating factors in play to lead to such results?

The general predisposing factors to insomnia listed earlier (genetic predisposition, suffering from another underlying sleep or psychological condition), also apply in the scenario of the pandemic. However, studies have found that there are some pandemic-specific predisposing factors, for example, occupation during the COVID-19 crisis has been identified as a major factor. It comes as no surprise that healthcare workers have been affected the most, reflecting the high demand of their jobs during the pandemic including increased working hours, night shifts, concerns about virus exposure, and increased emotional burden. It is also important to note that many of these factors were already present prior to the pandemic, leaving healthcare workers already vulnerable to sleeping or mental health disorders. Another specific predisposing factor is gender. As highlighted by many studies, women have a higher rate of reported insomnia symptoms during this period. This is partly explained by the fact that they were more likely to lose their job and take on childcare or homeschooling than men were. Moreover, the geographic location of one's residence during the pandemic has also emerged as a predisposing factor. Indeed, studies showed that living in regions more heavily affected by the virus leads to more sleep-related complaints. For example, people living in North Italy, which was the region the most affected at that time in Italy, reported more sleep disturbances than those living in the South of the country. This is also true for urban vs rural areas. Finally, neuroticism, anxiety in general, and health anxiety are common predisposing factors to insomnia. People suffering from health anxiety (constantly anxious about their health) are prone to overthink physical signs and symptoms as signs of illness and even more so in the setting of a worldwide pandemic broadcasted constantly in the news (22).

As explained earlier, precipitating factors in addition to predisposing factors highly increase the vulnerability to insomnia. Precipitating factors are often seen as stressors and the COVID-19 pandemic has been a major stressor since its outbreak. First of all, the situation created by the virus had never been seen or experienced before. Everyone was forced to change drastically their daily routines; isolate and spend most, if it's not all, of their time at home. This new situation of uncertainty about the future and the lack of control led to a lot of stress and worry. Moreover, people feared for their health, feared for the health of their loved ones, and feared contracting the virus. Another precipitating factor recognized during the pandemic was the economy and finances. While many people worked from home, others lost their jobs or didn't have to work during the pandemic as their businesses were forced to close. This resulted in people being pushed into financial insecurity. These are only a few examples of the stress burden that came associated with the pandemic and contributed to the increased insomnia cases around the world (22).

Finally, according to the 3P model, acute insomnia resulting from predisposing and precipitating factors are likely to resolve if not combined with a perpetuating factor. One potential pandemic-specific perpetuating factor is the disruption of zeitgebers. The latter is a German word used to refer to external factors, such as light and dark or meal times, that help synchronize our internal clock with the external world and by doing so, prevent the development of insomnia. Light has a powerful effect on our sleep-wake cycle; morning light exposure can advance sleep timing in the evening whereas evening light does the opposite. Social distancing forced people to stay indoors and prevented them from the morning exposure to natural sunlight as they go to work or school and the decrease in social activities contributed to the increased use of electronics, smartphones, and TV especially at night, delaying sleep timing. An additional behavioral Zeitgeber that has been affected by the pandemic is the ability to exercise. Sleep is positively affected by exercise; it is known to decrease sleep onset latency, wake after sleep onset, increase sleep time, and sleep quality, and increase slow wave sleep (22). Quarantine has made it difficult for people to engage in regular physical exercise, resulting in sedentary lifestyles and an increase in sleep disturbances.

Another perpetuating factor considered specific to the pandemic is the decreased association between bed/bedroom with sleep(22). Indeed, during quarantine, bedrooms were often the only place where one could find some privacy, to study or to work, while the whole family is quarantined at home. Increased time spent in the bedroom or even in bed during the day weakens this important association and leads to delayed sleep onset.

However, the pandemic also had a positive impact on sleep for some people. One of the benefits it brought us was a reduction in social jetlag. Social jetlag refers to the differences in timing between one's biological clock and obligations (social schedule, work, studies, and so on). For a lot of people, weekdays and weekends have a completely different schedule, with early morning alarms for work during the week compensated by late sleep-ins during the weekend. This change in schedule disrupts our internal circadian rhythms and leads to

difficulties in both falling asleep and waking up in the morning. The pandemic, with the drastic decrease in social obligations, blurred the distinction between weekdays and weekends attenuating the social jetlag that most people were used to living with. This is especially true for people who worked from home during the pandemic. Indeed they had more opportunities to sleep and to do so according to their natural circadian rhythms (22).

7 Consequences of Insomnia

Acute and chronic lack of sleep can have heavy consequences affecting various aspects of physical and mental health. From immediate short-term consequences after a night of bad sleep to more long-term consequences resulting from years of struggle with insomnia, the impact of sleep deprivation can extend far beyond just feeling tired. Here are some of the short-term consequences of insomnia:

1. Daytime fatigue: lack of sleep leads to daytime sleepiness that can impact cognitive functions, concentration and productivity, and various other aspects of daily functioning. Recovering from even a single night of poor sleep can disrupt our functioning for a few days as it disturbs our circadian rhythm.
2. Impaired performance: it comes as no surprise that someone who had a bad night of sleep will wake up with poor memory, attention, decision-making skills, and reaction time, which will lead to poor overall performance at work, school, or in any other activities planned for the day. Sleep plays a major role in processing all the information one has acquired during the day. Indeed, studies have shown the benefit of post-learning REM sleep on the later retrieval of this information. Here again, the silence of the locus coeruleus and the falling level of NE allows for the synaptic plasticity necessary to incorporate newly acquired knowledge into memory circuits. A sleepless night affects cognitive function, reducing the ability to process, store, and utilize information.
3. Mood disturbances: lack of sleep is linked with increased irritability, mood swings, and increased stress levels. As covered by this thesis, sleep is key for emotion processing.
4. Increased risk of accidents: coordination and reaction time are affected by lack of sleep, increasing the risk of accidents for individuals suffering from insomnia. Depending on their type of work, this could happen there, at home, or on the road leading to danger for other people as well.
5. Weak immune system: poor sleep is known to weaken our immune system making individuals more prone to develop viral illnesses such as the flu, colds, or other infections. Sleep has a significant impact on two systems: the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system. During sleep, there is an increase in activity in both the innate and the adaptive immune system and this is because, during sleep, cortisol secretion is decreased. The natural circadian rhythm of cortisol secretion

follows a diurnal rhythm where levels are the highest in the morning and then decrease throughout the day, reaching their lowest point in the evening and during the night. Cortisol is an important hormone that is known to suppress our immune system when secreted. Lack of sleep and insomnia disrupts the normal cyclic secretion of cortisol and can result in altered immune response as well as impaired function of natural killer cells and T cell, essential components of our defense against infections. It was also found that insomnia can lead to a decreased response to vaccines. This might also be explained by the fact that sleep disruption affects the release of another hormone, growth hormone, during slow-wave sleep. The disturbed secretion of growth hormones and the increase in the sympathetic outflow caused by insomnia have been linked to the weakening of the antiviral immune response field(50).

6. Dysregulation of the inflammatory response: during sleep, there is a natural decrease in inflammatory markers and cytokines, contributing to the body's overall regulation of inflammation. Sleep loss leads to the upregulation of genes associated with inflammation and an overall increase in inflammatory markers such as IL-6 and TNF primarily through the abnormal activation of toll-like receptors. Furthermore, lack of sleep activates the sympathetic nervous system which further stimulates the expression of inflammatory genes and markers. It has been observed that women may be more susceptible to these disturbances than men. Over time, chronic inflammation resulting from sleep disturbances can increase the risk of cardiovascular diseases and cancer (50) for example.

The short-term consequences of insomnia not only impact our immediate well-being but also have the potential to contribute to the long-term consequences of lack of sleep. A weakened immune system as well as a dysregulated inflammatory response can lead to heavy long-term consequences. The physical and mental impairments caused by chronic daytime fatigue, mood disturbances, and impaired general functioning can also affect our overall health over time. Here are some of the long-term consequences of insomnia:

1. Mental health disorders: as already stated, insomnia is closely intertwined with many mental health disorders. Indeed, numerous mental health disorders have insomnia as a consequence but insomnia can also lead to the subsequent development of psychiatric disorders. It was found that insomnia is a significant predictor for the subsequent onset of depression, anxiety, and alcohol abuse. Suffering from insomnia is more than double the risk of developing depression and in those patients, it increases the risk of suicide and relapses(15). Preexisting insomnia can also increase the risk of developing PTSD as a consequence of a traumatic experience as sleep is important for emotion regulation (45)and processing of the traumatic experience.
2. Chronic health consequences: chronic lack of sleep has been associated with an increased risk of developing certain chronic health conditions including cardiovascular diseases (hypertension, heart diseases, and stroke) as well as cancer and metabolic

disorders including obesity, and diabetes type 2. This can be explained by the chronic dysregulation of immune and inflammatory responses as a consequence of long-standing sleep deprivation(45,50).

3. Reduced quality of life: persistent sleep disturbances can diminish one's overall quality of life due to the accumulation of chronic fatigue, mood swings, daytime sleepiness, and so on. In the long run, this can impact personal relationships, work performance, and overall well-being.

Recognizing the extensive range of consequences can help understand the importance of healthy sleep behaviors as well as the importance of addressing and managing insomnia. Particularly when considering that insufficient sleep can be a modifiable risk factor for these conditions.

8 Prevention and Healthcare Burden

Despite its prevalence in the general population, insomnia is often overlooked and inadequately treated, resulting in a significant healthcare burden and reduced quality of life for the affected individuals. The economic costs associated with insomnia are increasing with estimates reaching billions of dollars. This is believed to be partly due to lost productivity and increased healthcare utilization. Furthermore, its common comorbidity with psychiatric conditions and ability to lead to long-term complications including cardiovascular diseases, diabetes, and obesity further increases the burden on individuals themselves and the healthcare system, increasing healthcare utilization of sick leaves and disability pensions. When considering these comorbidities and long-term consequences, insomnia could be considered a modifiable risk factor. The heterogeneity of prevalence rates across European countries shows the need for more research and the introduction of more prevention strategies. Recognizing and adequately treating insomnia can drastically improve the patient's life, preventing the long-term health consequences and mitigating the costs associated with chronic sleep deficiency (11,51). But as it will be explained in this chapter, increasing public awareness, integrating sleep education into school curricula, and ensuring healthcare providers are adequately trained to ask about sleep habits, could decrease the insomnia burden.

One highlighted issue is that people suffering from sleep problems often fail to seek help and mention their problems to their primary healthcare physician. Indeed, according to a survey conducted by the National Sleep Foundation, 50% of the population suffers from insomnia symptoms and only 30% of them end up talking about them with their physician and only 6% actively look for help from their physician. Compounding the issue, it was reported that 70% of the patients did not get asked about their sleep habits by their healthcare physicians. This shows that effort could be made to encourage patients to talk about their sleeping issues to

their physician but also to encourage primary health care doctors to actively ask their patients about it(11). Another example illustrating how prevention strategies could be successful is a study where brief cognitive-behavioral programs were given to adolescents. Adolescence is a vulnerable phase of life and during which early interventions including introducing them to behavioral and cognitive strategies such as stimulus control, sleep hygiene education, constructive worry technique, and relaxation can have significant benefits. The research has shown that a brief modified cognitive behavioral program can effectively prevent the onset of insomnia, improve vulnerability factors and enhance functional outcome (52). By increasing public awareness, integrating sleep education into school curricula, and ensuring healthcare providers are adequately trained to ask about sleep habits, the insomnia burden could slowly decrease.

What about sleep education? A study done in 2015 highlights chronic sleep deprivation among teenagers and emphasizes the lack of awareness regarding the issue. It suggested various interventions such as assessing school start times, reducing homework, and incorporating sleep education programs in the curriculum, and encouraging healthcare providers to educate both, parents and children, about sleep in order to tackle the problem. The study concluded by urging for changes and conducting research to bring long-lasting change in sleep knowledge and behavior among children and adolescent(53). Has anything changed in the last 8 years? Well, the answer was not easy to find and varied but a systematic review, including Australian sleep studies, aiming to identify school-based sleep education programs, conducted from 2007 to 2020, states that since 2016 there has been a significant increase in school sleep education. However, the study also explained that exposure to sleep education does increase sleep knowledge, but the impact on sleep behavior and secondary outcome varied. Even if sleep education seems to have increased, longer-term follow-ups and innovative delivery methods should be incorporated in future studies (53).

Considering awareness of insomnia and healthy sleep, organizations have been trying to increase it by putting together projects. Insomnia Awareness Night, is an effort organized by the American Academy of Sleep Medicine, the Society of Behavioral Sleep medicine, and the American Alliance for Healthy Sleep, to raise awareness of the disease and its sometimes severe consequences. It is organized in June, a month characterized by long days and short nights, in order to illustrate that even the shortest nights are very long for insomniacs(54). Student Sleep Health Week is another project by the American Academy of Sleep Medicine to raise awareness about good sleep during this period of life. They shed light on how students can improve their sleep but also help them understand why they might feel like night owls having difficulties waking up in the morning (55).

Primary prevention strategies for insomnia could play a crucial role in promoting healthy sleep habits and preventing severe mental health disorders as well as addressing associated health and costs burden. By raising awareness, educating the public, and ensuring healthcare providers are equipped to address sleep disorders, well-being can be improved and the long-

term impacts of insomnia, including mental health disorders, can be decreased. Indeed, maybe insomnia prevention will be part of the primary prevention of mental disorders (51) in the future.

9 MANAGEMENT AND TREATMENT

Before choosing and starting a specific treatment for insomnia, it is important to manage and assess the condition properly. This should include the evaluation of symptoms experienced by the patient including difficulties with sleep onset, maintenance, early morning awakenings, and non-restorative as well as the duration and frequency of these symptoms. This can be eased by the patient keeping a sleep diary to track their sleep patterns. The patient's medical and psychiatric history should be assessed to identify any conditions or medications that may contribute to their sleeping difficulties as well as screening for comorbidities commonly associated with insomnia such as depression, anxiety, substance use, or chronic pain. A physical examination could help identify sleep-related disorders that could be contributing to insomnia such as signs of sleep apnea or restless leg syndromes. Furthermore, assessing the patient's sleep habits and environment is important as many patients adopt bad sleep hygiene without knowing it finally determining the impact of the symptoms on the patient's daytime functioning could help shed light on the severity of the problem. The Insomnia Severity Index (ISI) is a questionnaire taken by the patient that could help assess the symptom's severity and monitor the patient's response to treatment (11). Treatment often starts with a nonpharmacological approach but sometimes it is not enough and an adequate pharmacological treatment is needed in addition. Guidelines highlight the importance of a shared decision-making approach when deciding on a treatment approach. This involves the physician discussing the risks, benefits, and costs of treatment with his patients and considering their specific needs, values, and preferences.

9.1 NON-PHARMACOLOGICAL TREATMENT OPTIONS

Non-pharmacological treatment options, also known as behavioral interventions, are recommended as the first-line treatment for managing insomnia. In general, these interventions aim to improve sleep habits, promote relaxation and address the underlying cause of sleep difficulties. These options are often preferred as the patient often fears the side effects of the pharmacological option, especially becoming dependent on a drug to manage to fall asleep.

1. Sleep Hygiene Education:
   As stated earlier, sleep hygiene in our modern world can easily be neglected and many people suffering from sleep problems often don't realize the impact their behavior can have on their sleep quality. Teaching patients about behavioral and environmental factors that could promote good sleep hygiene should be part of every treatment

regimen for insomnia. This includes recommendations about maintaining a regular sleep schedule, creating a sleep-friendly bedroom environment, and avoiding stimulating actives or substances before bedtime. Sleep hygiene education includes safe and easy steps to improve sleep quality and should always be part of the treatment regimen for insomnia. Unfortunately, sleep hygiene education is often inadequate in itself (7,11) for a full treatment of insomnia.

2. Stimulus Control and Sleep Restriction:
   Stimulus control is a behavioral strategy that aims to break the association between being in bed and the negative aspects of insomnia, such as wakefulness, frustration, and worry. It involves re-association between the bed/bedroom with sleep rather than arousal and it involves the establishment of a consistent sleep/wake schedule (waking up at the same time every day and avoiding naps). The patient is discouraged to engage in other activities in bed and to go to bed before feeling sleepy. Sleep restriction therapy aims to increase sleep drive by reducing or limiting the time spent awake in bed. It involves limiting the time spent in bed in order to match the individual actual sleep duration, which can help consolidate sleep and improve sleep efficiency. Even if both strategies may increase daytime sleepiness in the short term, in the long run, it was found that stimulus control and sleep restriction as behavioral treatment were effective in improving sleep onset and reducing awakenings during the night. However, sleep restriction should be avoided in patients with seizure disorders or bipolar disorders as it can lower the threshold for seizures or precipitate a manic episode. Patients using sleep restrictions are also advised to avoid driving and operating heavy and potentially dangerous machines(11,15) during this type of treatment option.

3. Relaxation Technique and Training:
   Relaxation techniques such as progressive muscle relaxation, deep breathing exercises, mindfulness meditation, and even yoga can help promote relaxation and reduce anxiety and arousal before sleep (11).

4. Cognitive Behavioral Therapy for Insomnia (CBT-I):
   CBT-I emerged as a non-pharmacological treatment approach for insomnia and has been the subject of many clinical trials. Nowadays, CBT-I is recommended as the first-line treatment and offers a unique combination of nonpharmacologic interventions combining cognitive therapy, stimulus control, and sleep restriction therapy with the addition of relaxation training. Cognitive therapy consists in counseling the patient, and identifying and challenging negative beliefs and thoughts in order to improve insomnia. It aims to replace these beliefs with realistic thoughts and execrations about sleep and to improve habits and anxiety. If successful, the patient should develop skills and strategies to alter abnormal behaviors and develop healthy coping mechanisms. CBT-I was proven to offer great efficacy and fewer adverse effects compared to drug therapy.

More recently the concept of Digital Cognitive Behavioral Therapy for Insomnia (dCBT-I) has emerged as a promising solution within the consumer sleep technology landscape. Today, a wide range of technological devices, applications, and tools are available to the public to track and improve sleep. The focus of those devices has primarily been on relaxation, mindfulness, and meditation. However, dCBT-I products are changing the game by seeking FDA approval as prescription digital therapeutics for treating chronic insomnia and even comorbid depression. Somryst is the first software-based program for CBT-I available as a prescription digital therapeutic and FDA-approved. An advantage of using dCBT-I is its availability and access from anywhere eliminating the in-person visit to a therapist. It provides greater convenience and flexibility in terms of scheduling and session frequency as traditional CBT-I requires a course of 6 to 8 weeks and is not widely available. Moreover, in-person CBT-I can be costly due to the expenses associated with the therapist, dCBT-I offers a potentially more cost-effective alternative. It represents a significant leap forward in the field. It not only holds the potential to revolutionize insomnia treatment but also demonstrates the growing recognition of software-based interventions in the healthcare industry. However, it is important to note that, while dCBT-I offers advantages, it may not be suitable for everyone, and face-to-face contact is an undeniable advantage in certain situations and for some patients (11,15,56).

5. Brief Therapies for Insomnia (BTIs)
   BTIs are a shorter and more focused type of CBT-I. Instead of 6-8 sessions, they typically involve only 1 to 4 sessions and place a greater emphasis on the behavioral aspect of sleep (57).

6. Biofeedback:
   Biofeedback is a technique used in relaxation training that involves using a device to monitor and provide feedback on a patient's specific physiological responses. One approach consists of the monitoring of frontalis electromyography activity, which measures muscle tension in the forehead. The device generates an auditory tone that is adjusted based on the patient's muscle tension levels, aiming to teach the patient how to relax by modifying the tone in the desired direction. This technique is good in the sense that it helps the patient gain awareness and control over their physiological responses(57).

7. Over the Counter (OTC) Remedies:
   OTC options for insomnia, such as antihistamines (like diphenhydramine and doxylamine), should be used with caution due to their potential cognitive impairment, especially in the older population, and other side effects. Valerian root, another OTC sometimes recommended for the treatment of insomnia symptoms was found to have

inconsistent effectiveness. The use of CBD and medical marijuana products for sleep is increasing. There is evidence supporting the benefits of such use for conditions like anxiety and pain which, as explained in this thesis, often coexist with insomnia. However, it is important to note that insomnia can occur due to cannabis withdrawal and this is why clinicians should stay informed about their patient's use of such products.

9.2 Pharmacological Treatment Options

While non-pharmacological treatment options are often preferred by the population and considered first-line by scientists, there are situations where prescription drugs have to be initiated. A wide range of pharmacological options exist nowadays for the treatment of insomnia and the ongoing research and advancements in the neuroscience surrounding the sleep-wake cycle and transition to sleep may even soon bring us even more. The understanding of neural pathways and neurotransmitters involved in those processes is crucial for understanding the mechanism of many of these medications but also their often multiple side effects.

GABAergic agents like benzodiazepine (temazepam and lorazepam) and nonbenzodiazepine sedative-hypnotics (such as zolpidem and Eszopiclone) are widely prescribed for short-term use but carry a risk for dependence and potential side effects. Melatonin receptor agonists (such as Ramelteon), are generally considered safer and have less risk of dependency. Other medications, such as trazodone and other sedating antidepressants (mirtazapine, doxepin, and amitriptyline), may also be prescribed off-label for insomnia as they are not FDA-approved for the treatment of insomnia (they are approved for the treatment of MDD). Interestingly, nowadays, trazodone is the most commonly prescribed drug for insomnia in the United States with 34% more prescriptions than the most common FDA-approved drug prescribed for insomnia(11).

The newest class of drugs for the treatment of insomnia are the Dual Orexin Receptor Antagonists (DORAs). DORAs, as their name suggests, block orexin receptors involved in arousal behavior, promoting sleep induction and maintenance. They act during the first part of our sleep and this is why patients struggling with falling asleep or staying asleep can really benefit from these drugs. Since the discovery of the orexin system and its role in sleep-wake regulation in the late 1990 and early 2000, scientists have made major advances and come up with the first FDA-approved DORAs, Suvorexant in 2014 which was followed by Lemborexant in 2019 and finally by Daridorexant in 2022(11,58). Daridorexant was discovered through an intensive drug discovery program aimed at developing a sleep-promoting agent with improved efficacy and pharmacokinetics. Indeed, trials showed that it improves both sleep and daytime functioning with a favorable safety profile making it a good option for the elderly as well. Currently, Seltorexant is being studied for its potential use in both MDD and insomnia disorders. It is characterized by being a selective orexin type 2 receptor antagonist and by its short half-life of 2 to 3 hours (compared to 8 hours, 12 hours, and 17-19 hours for

Daridorexant, Suvorexant, and Lemborexant respectively). The selectivity for one type of orexin receptor may potentially offer advantages in terms of efficacy and safety, but further research is needed to establish its benefits compared to the dual inhibition of type 1 and type 2 receptors(11,58).

In conclusion, pharmacological treatment options for insomnia play a big role in managing the condition. However, most options are far from perfect. Most are coming with heavy luggage of adverse effects and have variable efficacy and safety with the limited available evidence. The discovery of Dual Orexin Receptor Antagonists offers promising alternatives with the potential to not only promote sleep but also to preserve cognitive function. As DORAs are quite new, further research and clinical trials are needed to fully understand the benefits and long-term effects. Ultimately the choice of pharmacological treatment should be based on the patient's own needs, considering factors such as response to previous treatments, potential adverse effects, and the patient's preferences.

Summary of the drugs commonly prescribed for insomnia (11)

Class/drug	Mechanism	Dosage in mg
Antidepressants		
Doxepine	- Serotonin-norepinephrine reuptake inhibitor - H1 blocker	3-6
Amitriptilyline		10-25
Trazodone	- Serotonin antagonist and uptake inhibitor - H1 receptor blocker	25-100
Mitrazepine	- Serotonin-norepinephrine transmission blocker - H1 receptor blocker	3.75-7.5
Benzodiazepines		
Alprazolam	- $GABA_A$-receptor agonists	0.25-0.5
clonazepam		0.25-2
Estazolam		1-2
Flurazepam		15-30
Lorazepam		1-2
Quazepam		7.5-15
Benzodiazepine receptor agonists		
Eszoplicone	- $GABA_A$-receptor agonists	1-3
Zaleplon		5-20
Zolpidem		5-10
Melatonin agonist		
Ramelteon	- Highly selective melatonin-receptor agonist	8
Dual orexin Receptor antagonists		
Daridorexant	- Dual orexin Receptor antagonists	25-50

lemborexant		5-10
Suvorexant		10-20

10 In the Future

30 years after Allison G Harvey and Nicole K.Y Tang raised the question, "Can we rest yet?"(59), in one article, it is still hard to address that question properly even with the knowledge that the last 3 decades have brought us. Indeed, the future could still shed some light on some of the concepts surrounding insomnia. The article "Insomnia disorder: State of the science and challenges for the future" helps to highlight some of the still evolving facets of insomnia(51).

While major diagnostic systems (DSM-5, ICSD-3, ICD-11) have finally converged to define insomnia disorder in a similar way, it is crucial that from now on insomnia use a consistent diagnostic criterion in order to be able to compare worldwide data more easily. Furthermore, the future should put importance on the concept of insomnia phenotypes. Insomnia phenotypes, for example, sleep onset insomnia vs sleep maintenance insomnia, categorize individuals with insomnia into distinct groups, allowing for a better understanding of the heterogeneity of insomnia disorder. Ultimately, it will allow better management of patients with a more personalized treatment approach (51).

The same article also suggests that, as the concept of hyperarousal plays an important role in insomnia, further research could be beneficial in this area. The development of a new hyperarousal test, capable of objectively assessing the level of hyperarousal in individuals with insomnia, could lead to significant progress in the domain. This could simply be done by analyzing stress response through measuring heart rate, cortisol levels, and EEG activity, for example, providing insight into the individual's autonomic nervous system activity. By combining the findings with neuroimaging techniques like functional magnetic resonance imaging, important advances in our understanding of the condition could be done, diagnosis and treatment approaches could be improved, and potentially novel therapeutic targets (51) could be identified.

Another aspect of insomnia that should be subject to further research is its treatment, more precisely, Cognitive Behavioral Therapy for Insomnia. This non-pharmacologic treatment approach has widely replaced hypnotic drugs as the first-line treatment of insomnia, as more and more evidence supports its effectiveness. However, more research is needed to solidify this evidence and address the significant lack of objective measurements to show the impact of CBT-I on insomnia. Indeed, so far, most proof showing CBT-I as a good treatment relies on subjective measurements, such as self-report questionnaires. Furthermore, there is a lack of evidence of the long-term benefits of this treatment option. Finally, the integration of CBT-I in the care of mental health could potentially lead to better outcomes and should be considered.

Furthermore, educating the population about this therapy should also be considered as it could be used in the prevention of insomnia and mental health disorder (51).

In summary, future research in the phenotyping, diagnosis, and treatment of insomnia, could hold new insight on the condition that could greatly help our understanding and management of this disorder. However, the future could also bring us new challenges to face, more reasons for sleepless nights, and maybe, yet unknown more long-term consequences of COVID-19's effect on sleep. So will we ever rest? The future will tell us.

11 Conclusion

In conclusion, this thesis has explored the multifaceted phenomenon of insomnia in our modern world. By first examining various aspects related to sleep, including circadian rhythms, sleep architecture, sleep quality, and sleep hygiene, the necessary knowledge has been acquired to understand the complexity surrounding insomnia and its impact on people. The thesis has given an understanding of the increasing prevalence of insomnia and has provided examples of the more vulnerable groups of people who have a higher tendency to suffer from insomnia.

Furthermore, the thesis shed some light on the complexity of the pathways involved in the pathophysiology of insomnia and sleep as well as on the differences in different populations such as teenagers and the elderly. The 3P model has provided a framework for understanding the interplay of predisposing, precipitating, and perpetuating factors that contribute to insomnia and its chronicity.

Then, the thesis proceeded to highlight some of the general causes of insomnia, including secondary insomnia in the setting of another medical condition or psychiatric condition. The bidirectional relationship between insomnia and some mental health disorders such as major depressive disorder has been discussed, highlighting the importance of insomnia as a predisposing factor to such conditions but also emphasizing the importance of acknowledging it as a separate condition. The thesis also highlighted some of the more modern challenges to sleep that can lead to insomnia. These include the widespread use of electronics and their subsequent exposure to blue light affecting our circadian rhythms, the constant noise pollution interfering with sleep architecture, the decreased importance the population puts on their sleep hygiene, the increasing stress load from daily life making it hard to relax and drift into sleep, and the multiple ways in which the COVID-19 pandemic has affected our sleep.

This thesis has shown that insomnia does not only lead to short-term consequences such as daytime fatigue and decreased performance but also to long-term consequences ranging from increased risk of infections to chronic diseases such as diabetes and hypertension. Another consequence of the prevalence of insomnia nowadays is the heavy burden it imposes on the

healthcare system, reaching billions of dollars. Some preventive strategies have been discussed to alleviate some of these consequences.

Regarding the management and treatment of insomnia, both pharmacological and non-pharmacological options have been explored with an emphasis on the more recent concept of digital cognitive therapy for insomnia as well as on the newest drugs known as dual orexin receptor antagonists.

In conclusion, this thesis has helped us understand the importance of sleep, in a modern world that has a tendency to neglect it, as well as the profound effect of its counterpart, insomnia. It is imperative that the significant impact of insomnia on individuals and on society is recognized. By promoting greater awareness, education, prevention strategies, support for the population, and continued research on the subject, it is possible to mitigate the burden of insomnia and move towards a well-rested future world.

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13 BIOGRAPHY

Audrey Nina Strähl was born in December 1996 in Neuchâtel, Switzerland, where she grew up bilingual in French and German. In 2012, she enrolled in “High School Denis de Rougemont” in Neuchatel with biology and chemistry as specialties, as part of a bilingual French-English program. During this time, she seized the opportunity to enhance her English skills by participating in a two-month exchange program with Australian students.

To enhance her chances of getting into medical school, Audrey Nina Strähl completed a three-month premedical course in early 2017. Subsequently, in September 2017, she began her medical studies at the School of Medicine, University of Zagreb in the English program. During these six years, she volunteered as a mentor for new students embarking on their first year at the same university. Her final year of study was marked by her successful completion of the USMLE Step 1 and the completion of her graduate thesis titled “Insomnia in the Modern World”. Finally, she concluded her studies with a first clinical rotation at Norfolk and Norwich University Hospital in England in the Department of Gynecology. Following this, she completed two additional rotations in Zagreb, one at the University Hospital for Infectious Diseases Dr. Fran Mihaljevic and another at the Pediatric Endocrinology department at the University Hospital KBC Zagreb. She is set to graduate in the summer of 2023.

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