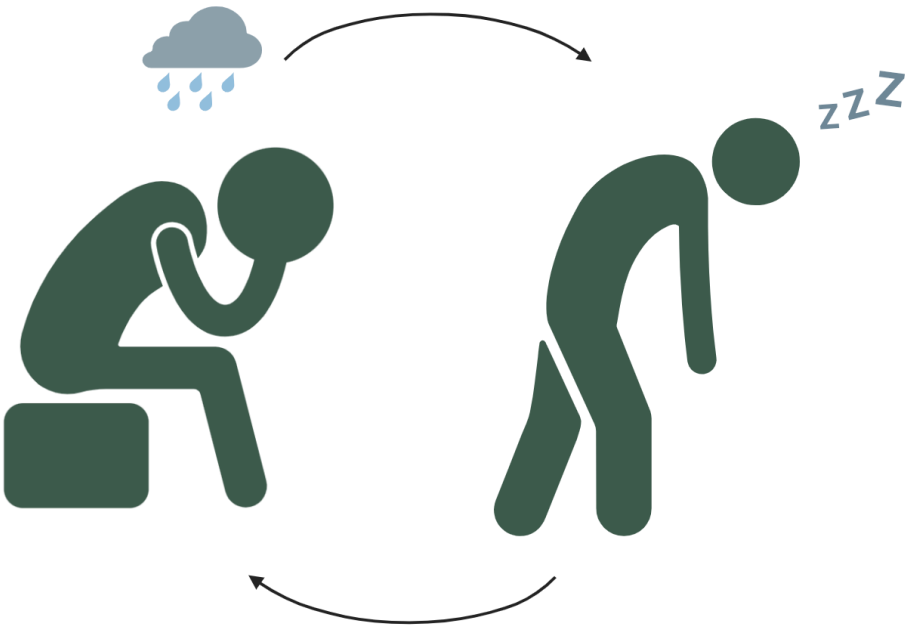
rijksuniversiteit groningen

Exploring the vicious cycle of insomnia and depression



Created in BioRender.com

Bachelor Thesis Life Sciences
WBBY901-05

Author	Eva Koeree (S4382544)
Major	Behavior & Neuroscience
Supervisor	R. Havekes
Date	Groningen, July 6, 2024

Preface

I chose this topic for my thesis because chronobiology interests me greatly. I have taken a few courses that covered sleep, and I found this to be the most enjoyable part of my biology bachelor's degree. The essay is intended for fellow enthusiasts, for people who suffer from these conditions and their families to understand them better, and for health organizations. I found writing this thesis to be very educational and helpful for my future choice of master's program. I would like to thank Mr. Havekes for supporting and helping me during the writing process.

Table of contents

List of abbreviations :

GABA = gamma-aminobutyric acid
REM = rapid eye movement
NREM = non rapid eye movement
CRF = corticotropin-releasing factor
AVP = arginine-vasopressin
HPA axis = hypothalamic-pituitary-adrenal axis
ACTH = adrenocorticotropic hormone
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition
MDD = major depressive disorder
HAM-D = Hamilton Rating Scale for Depression
MADRS = Montgomery-Asberg Depression Rating Scale
SSRI = selective serotonin re-uptake inhibitors
SNRI = selective serotonin norepinephrine re-uptake inhibitors
TCA = Tricyclic antidepressants

Abstract

Every night when you start counting sheep, it is not just to help you fall asleep quickly, it can also contribute to a brightening mood for the next day. A fulfilling life includes both good sleep and mental well-being. Despite this, many people still struggle with the disorders: insomnia and depression. Insomnia disrupts sleeping patterns by reducing REM sleep, increasing arousal during the sleep stages and impairing emotional regulation, which worsens both sleep and depressive symptoms. Individuals with depression continuously feel sadness, loss of interest and have sleep problems. The disorder leads to issues regulating the HPA axis, leading to excessive cortisol production and neurotransmitter imbalances like serotonin and norepinephrine, which further contribute to sleep problems. These disorders further worsen the impact of insomnia and depression on each other, forming a vicious cycle. Additionally, both are associated with an increased risk of suicidal thoughts, making effective treatment important. There are several treatment strategies available for these disorders, including medications and therapy. This review aims to explore the disorder insomnia and depression, by looking into their health effects, their mutual influence and the current options for treatment. Understanding both disorder and interaction is essential for developing an effective treatment that addresses both conditions. Ultimately, the goal is to enhance the overall health and well-being of individuals affected by these disorders, enabling everyone to enjoy life to the fullest once again.

Introduction

Sleep and mental well-being are important components that contribute to a good quality of life. Yet, many people continue to suffer from these disorders. In Europe, around 4.3% of the population experiences depression, while chronic insomnia affects an even higher percentage, with 10% of the population experiencing it, and these numbers continue to rise (Ellis et al., 2023; World Health Organization, 2024). Due to their high prevalence, associated healthcare costs and the reduction in quality of life, is it crucial to study these disorders and understand the interplay between insomnia and depression for developing effective interventions to improve overall mental and physical health. Previous research has shown a significant overlap between insomnia and depression, as evidenced by polysomnography studies (Riemann et al., 2019). Therefore, my central question is: To what extent can treating insomnia help with reducing depression?

Insomnia

The sleep disorder known as insomnia involves difficulty falling asleep, staying asleep, or waking up too early and being unable to return to sleep. The sleep cycle is disrupted due to these disturbances and reduces the overall sleep quality. Primary insomnia accounts for approximately 25% of chronic insomnia cases, while the majority are secondary, caused by other underlying factors or conditions. Several factors can elevate the risk of developing insomnia, such as age, sex, certain medical conditions and shift work. Insomnia can be classified into two types: transient insomnia, which persists only for a few days to a week and chronic insomnia, which persists for a longer period. Transient insomnia can eventually develop into chronic insomnia (Roth & Roehrs, 2003).

Sleep is essential for many bodily functions, including cardiovascular health, longevity, mood, immunity, learning and memory, cognitive function and overall brain health (Malhotra & Desai, 2010). It is regulated by various parts of the brain and relies on melatonin, as well as a balance of multiple neurotransmitters. Melatonin is originally a self made hormone regulated by the suprachiasmatic nucleus in the body, governing the sleep and wake cycle (Bollu & Kaur, 2019). Melatonin may become dysfunctional due to changes in receptor densities, often resulting from neurodegenerative conditions, receptor polymorphisms that disrupt signaling, and imbalances in receptor expression. All of these factors can result in sleep problems (Hardeland, 2012). Besides melatonin, neurotransmitters also play a crucial role in sleep regulation. Activating neurotransmitters, such as serotonin and norepinephrine, promote wakefulness. Serotonin, synthesized from tryptophan and produced in the raphe nuclei of the brain, is involved in regulating mood, behavior, and the sleep-wake cycle. Its levels are higher during the day and it helps inhibit REM sleep (Bamalan et al., 2023; Monti, 2011). Norepinephrine, synthesized from tyrosine and produced in the adrenal medulla, regulates arousal, alertness, and cognitive functioning (Hussain et al., 2023; Smith & Maani, 2023). In a study, it was discovered that individuals suffering from insomnia showed increased levels of norepinephrine during the night, a period when levels are normally low in healthy individuals. This high arousal activity leads in turn to difficulties with staying asleep (Irwin et al., 2003; Mitchell & Weinshenker, 2010). In contrast, inhibiting neurotransmitters like gamma-aminobutyric acid (GABA) are essential for promoting sleep. GABA is released in the hypothalamus, where it inhibits arousal promoting activities to stimulate sleep. This inhibition is crucial for initiating and maintaining sleep. In individuals with sleep disorders, the function of GABA is impaired and the receptors are reduced. This impairment disrupts the balance between excitation and inhibition in the brain, contributing to difficulties with sleep. GABA receptors are chloride channels found in the postsynaptic neurons and GABA is synthesized from glutamate by the enzyme glutamate decarboxylase (Varinthra et al., 2024).

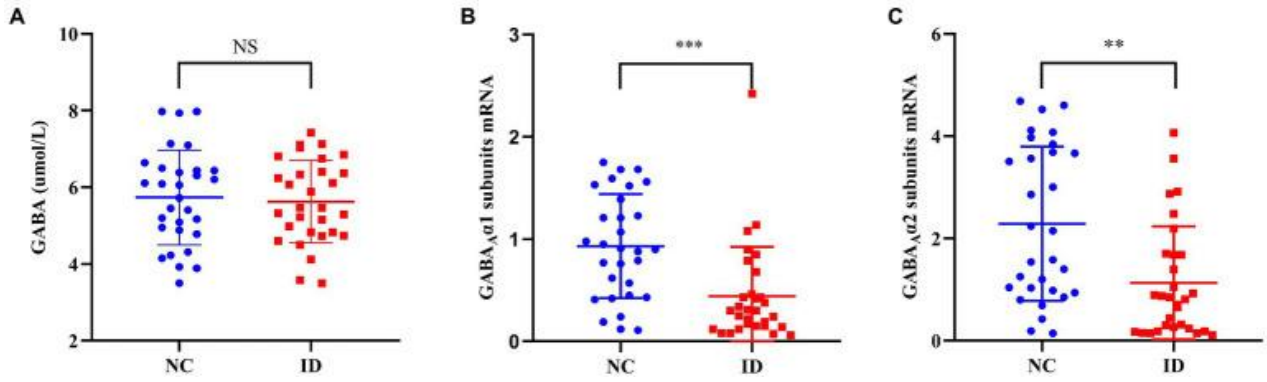


Figure 1: *Comparing GABA serum levels and GABA receptors in two groups: a control group (NC) and an insomnia group (ID). No significant difference was observed in serum GABA levels. However, the insomnia group had notably lower levels of GABA receptor alpha 1 and alpha 2 subunits compared to the control group (NS: p = 0.733, **: p < 0.01, ***: p < 0.001) (Xiang et al., 2023).*

Two types of sleep circulate during the night: non-rapid eye-movement (NREM) and rapid eye-movement (REM) sleep. Sleep begins with NREM sleep, which progresses through stages 1, 2, 3, and 4, each stage deeper than the last, before transitioning into REM sleep. This transition from NREM to REM sleep is

facilitated by the neurotransmitter GABA. The cycle repeats multiple times during the night, with REM sleep increasing in duration with each cycle (Colten & Altevogt, 2006; Varinthra et al., 2024). A study investigated the sleep differences in insomnia and found variations in REM sleep. Patients with insomnia mistook some periods of REM sleep as wakefulness with higher arousal during REM sleep. Overall, they experienced less REM sleep compared to normal sleepers. In addition, patients described feeling more awake in the morning when they had longer periods of REM sleep during the night, possibly because longer REM sleep durations increased their awareness of their sleep patterns (Feige et al., 2023).

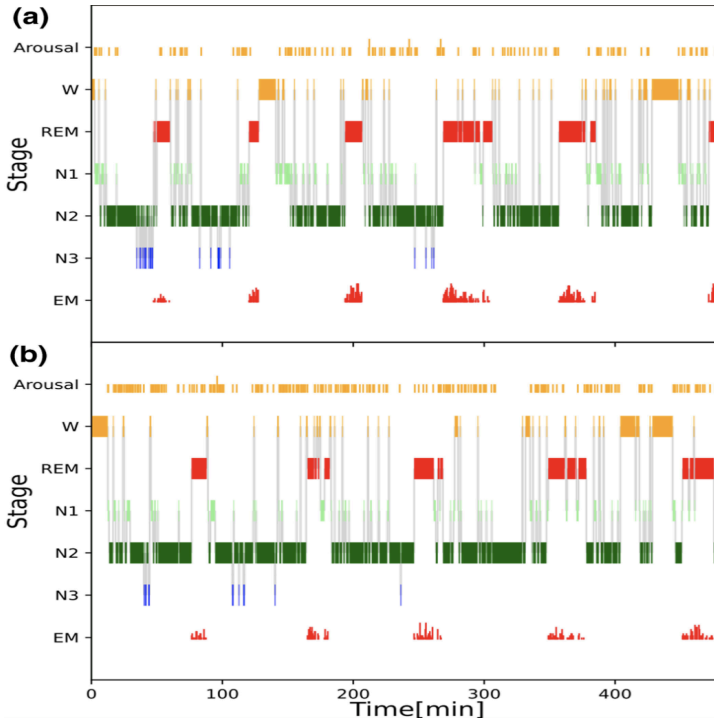


Figure 2: *The polysomnographic data shows the duration and arousal events per sleep stage, including wakefulness, with data from two individuals: a control person (Person A) who is a good sleeper and an insomnia patient (Person B). The arousal patterns differ significantly between these individuals, with the insomnia patient expressing notably higher arousal events during sleep, especially in the REM stage (Feige et al., 2023).*

The functions of REM sleep remain quite unclear, but several hypotheses have gained support through research. The first theory is that REM sleep is crucial for memory development and consolidation. This is evidenced by a study where GABA neurons responsible for activity in the hippocampus were silenced during REM and NREM sleep. Results showed that silencing during REM sleep negatively affected memory, while it had no impact during NREM sleep, indicating that GABA neurons play a crucial role in memory strengthening during REM sleep (Boyce et al., 2016). The second theory suggests that REM sleep contributes to brain development and learning. Research indicates that REM sleep strengthens and maintains new formed dendritic spines. Additionally, during REM sleep, new dendritic spines are also removed to maintain optimal spine numbers, which are essential for learning and memory formation (Li et al., 2017). The third theory proposes that REM sleep influences processing of emotions. Research

conducted by Galbiati et al. (2020) found that individuals experiencing poor REM sleep are related to experiencing emotional dysregulation linked to disturbances in the limbic and paralimbic systems, which can lead to depression. There are numerous theories, each potentially contributing to negative effects during the day or in one's overall life.

Depression

The feeling of being depressed, lack of enthusiasm, sleepless nights and increased or reduced craving for food, may all arise from the condition known as depression or major depressive disorder (MDD). There are various factors that can contribute to it, including abuse, higher likelihood among women, or genetic inheritance (Otte et al., 2016). In the COVID-19 pandemic, the prevalence even increased by 25% due to multiple stressors such as feeling lonely, worries, fear, and many more causes (World Health Organization, 2022). It affects not only the patient but their surroundings and the community as well, and it also represents an economic burden. Thereby, making it a global health problem (Pincus et al., 2001). Depression can go together with episodes of mania, resulting in continuous mood changes, a condition known as bipolar disorder (Fava & Kendler, 2000). Another alarming aspect is that the risk of committing suicide is 30 times higher among mature people with depression, reflecting concerning numbers (Stringaris, 2017). The disorder is diagnosed through various methods. Clinicians can evaluate patients using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria or laboratory test. As well as this, patients can assess and rate their own symptoms using the Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS) (Soleimani et al., 2011).

The brain undergoes changes during depression, including decreases in white matter, the frontal cortex, the frontal lobe, and parts of the limbic system, such as the hippocampus and amygdala. Many other brain areas are also affected. The partial reduction in the limbic system is likely due to glucocorticoids activating neurotoxic effects. Some connections of the hippocampus extend to regions that trigger dopamine, adrenaline, and norepinephrine and with the brain changes this can be disturbed (Ruiz et al., 2018). As shown in figure 3, the mechanism in healthy individuals begins with the secretion of corticotropin-releasing factor (CRF) and arginine-vasopressin (AVP). These peptides trigger the hypothalamic-pituitary-adrenal (HPA) axis, leading to the production of adrenocorticotropic hormone (ACTH). This process ultimately results in the secretion of glucocorticoids, such as cortisol, which help maintain balance by slowing down the release of CRF, AVP, and ACTH. However, much of the mechanism remains unclear in depressed patients. It is hypothesized that in depression, this regulatory process is disrupted with glucocorticoids failing to inhibit effectively, leading to an overly activated HPA axis and eventually excessive cortisol production (Pariante & Lightman, 2008; Ruiz et al., 2018). Normally, cortisol levels fluctuate throughout the day, peaking during the waking phase and gradually declining thereafter until they are nearly at their lowest point just before waking up again. The levels then increase again and this cycle repeats daily (Morgan et al., 2017). A continuous excessive amount of cortisol negatively affects the receptors for neurotransmitters such as serotonin, norepinephrine, and dopamine in the limbic area, leading to reduced availability of these neurotransmitters in the synaptic cleft. Cortisol increases the production of the gene responsible for the serotonin transporter, resulting in more serotonin being reabsorbed by cells. Serotonin is an important neurotransmitter that regulates mood,

sleep patterns, and many other functions (Ruiz et al., 2018). When serotonin levels are low, it can lead to symptoms such as anxiety, obsessive thoughts and compulsive behaviors. Similarly, decreased norepinephrine levels can cause issues with attention, energy, concentration and motivation. Dopamine also influences motivation and the experience of pleasure and reward. Imbalances in these neurotransmitters can reduce overall emotional well-being and negatively impact daily functioning (Briley & Chantal, 2011). Depressed patients do experience different sleeping patterns than before, which are partly due to interruptions in their REM sleep. This includes a delay in the onset of the first REM sleep, longer periods of REM sleep and overall higher recurrence of rapid eye movements in REM sleep (Palagini et al., 2013).

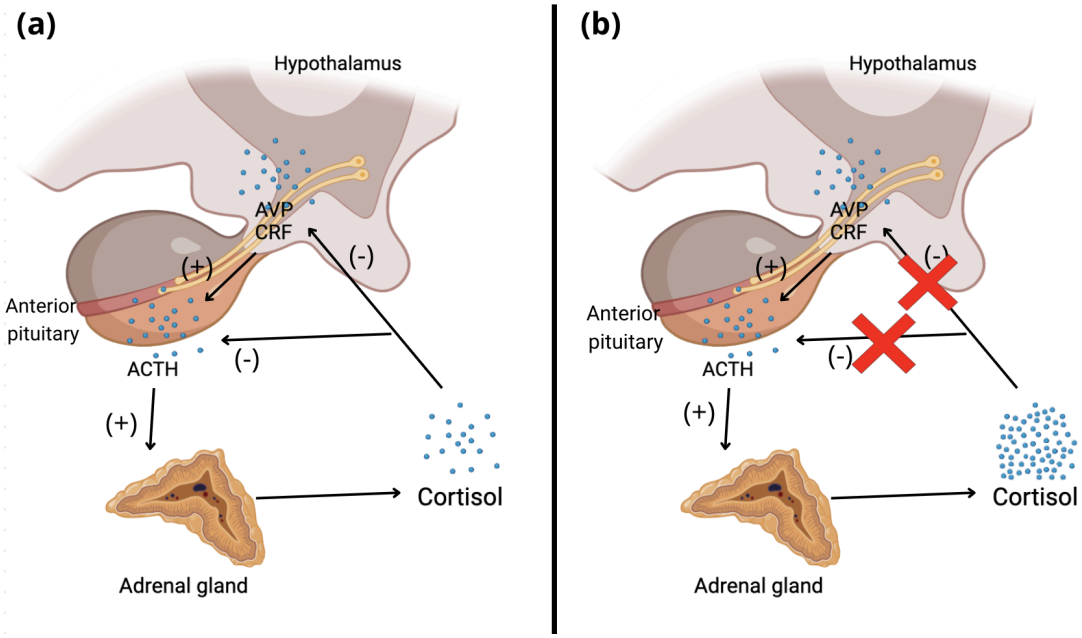


Figure 3: *Comparing the HPA axis mechanism in two individuals: a healthy person (Person A) with a normal regulatory process and a depressed patient (Person B) with a disrupted mechanism. In Person A, the process functions correctly with CRF and AVP triggering the production of ACTH in the anterior pituitary, leading to the release of cortisol from the adrenal cortex. The glucocorticoids (cortisol) then inhibit further release to maintain balance. In Person B, the inhibiting function is impaired, resulting in continuous activation of the HPA axis and excessive cortisol production (Created with BioRender.com, based on illustration by Ruiz et al., (2018)).*

This review discusses the disorders of insomnia and depression by examining their health impacts, their complex influence on each other, and the current availability of treatments. It focuses on the bidirectional relationship between insomnia and depression, pointing out how addressing one can potentially solve symptoms of the other. Additionally, the review explores current treatment options, including therapies and pharmacological interventions, assessing their effectiveness and limitations in treating both disorders simultaneously.

Health effects associated with insomnia or depression

Sleep problems can lead to numerous health complaints. Individuals may struggle with performance and functioning, experience 2.5 to 4.5 times more accidents and injuries, and suffer from higher death rates. Ultimately, these issues result in a 60% increase in healthcare costs. Sleep issues can contribute to many physical and mental problems such as depression, weight gain leading to obesity, diabetes, and cardiovascular diseases. Studies show that up to 40% of individuals with sleep problems also deal with mental problems, most commonly depression and anxiety. Patients also have a 7.5 times greater likelihood of gaining weight when their sleep is limited to six hours per night due to increased levels of the hormone ghrelin and reduced levels of leptin, which leads to increased appetite. Poor sleep also leads to problems with glucose tolerance, resulting in diabetes. Cardiovascular problems increase by 45% with only five hours of sleep or less. These problems occur with too little sleep but can also happen with too much sleep (Roth, 2007; Colten & Altevogt, 2006). The most concerning aspect is the link between short sleep and suicide. Research conducted by Liu (2004) revealed that almost 20% of the participants in the experiment had suicidal thoughts and over the 10% had even attempted suicide. These findings show the critical importance of addressing sleep duration and quality in mental health interventions.

Examining the health impacts of depression reveals numerous concerns. It diminishes the quality of life, resulting in symptoms similar to those of insomnia, such as sleep problems, appetite changes leading to weight fluctuations, diabetes, negative mood, and thinking about suicide. Additionally, individuals often experience difficulties with alertness and feelings of uselessness (Bains & Abdijadid, 2023; Chand & Arif, 2023). Depression can also manifest as physical pain in the joints, limbs, back, or gastrointestinal tract. The dysregulation of the neurotransmitter is likely associated with depression and the pain it can induce. Depending on the severity of depression, it determines the level of pain experienced. The deeper one is into depression, the harder it becomes to recover and the more symptoms one experiences (Trivedi, 2004). All these effects are very concerning, and it is important to find an effective intervention to combat this disorder.

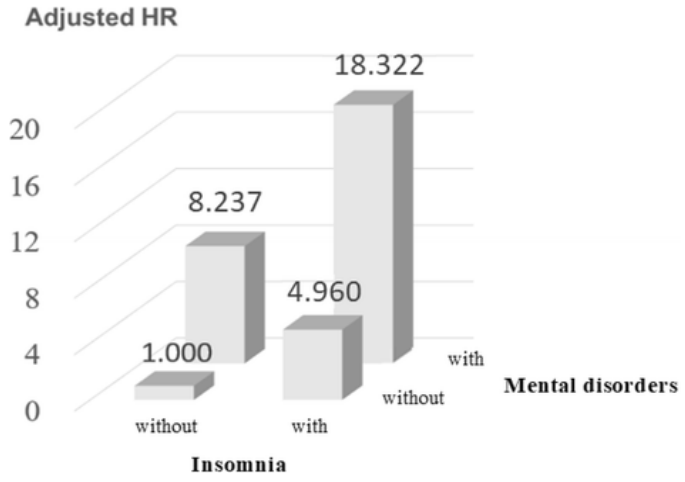


Figure 4: *The Impact of insomnia and mental disorders on suicide attempt rates. The likelihood of suicide attempts is greatest among individuals who suffer from both insomnia and mental disorders, as they are over eighteen times more likely to attempt suicide than those without either condition (P < 0.001) (Lin et al., 2018).*

The bidirectional relationship between insomnia and depression

How insomnia contributes to depression

Insomnia is frequently associated with depression. It can contribute to the onset and worsening of depression. Insomnia may occur primarily due to overactive systems, or as secondary insomnia, where it could have been initiated by psychiatric conditions, narcotics, or other influences (Riemann, 2003). Over 40% of individuals with depression reported experiencing insomnia symptoms before depression symptoms, while only 22% reported both symptoms happening simultaneously. This suggests that insomnia is in most cases the beginning of depression (Ohayon & Roth, 2003). Research, including 21 studies, indicates that depression often appears as a symptom in many cases of insomnia. An analysis of multiple studies revealed that individuals with insomnia have approximately twice the likelihood of developing depression compared to those with normal sleep patterns (Baglioni et al., 2011). In any case, sleep is crucial for your mental and physical health. Therefore, issues with sleep can affect mental well-being (Del Rio João et al., 2018).

People experiencing poor sleep caused by hyperarousal may encounter issues with the regulations of emotions, affecting how we manage, perceive, and express our emotions (Galbiati et al., 2020). Additionally, it creates negative emotions, diminishes the pleasant emotions (Kahn et al., 2013) and complicates the ability to manage stressful situations, thereby increasing susceptibility to developing depression (Vandekerckhove & Wang, 2018). When experiencing stress, the body struggles to return cognitive and physiological functions back to normal. The suspected reason is that REM sleep is causing these issues (Galbiati et al., 2020). Research done by Feige and colleagues (2023) examined differences in sleep patterns across the sleep cycle and identified differences in REM sleep, as illustrated in figure 2, showing shortened REM sleep and higher arousal events during this period. Sleep problems can result in altered cognitive activity, where individuals begin to overthink, worry excessively, or experience an overactive mind, making it harder to fall asleep (Espie, 2007). This pattern is also common in depression, where negative thought patterns continuously reappear (Wenzlaff et al., 1988).

How depression affects sleep patterns and contributes to insomnia

Depression can make alterations in sleeping patterns, often leading to the development of insomnia. Insomnia can be both a risk factor for and a symptom of depression (Palagini et al., 2013). Research indicates that a majority, approximately 90%, of individuals with depression experience poor quality of sleep (Tsuno et al., 2021). Additionally, about 38% of patients with depression have reported that their depressive symptoms appeared before the onset of insomnia (Ohayon & Roth, 2003). Depression disrupts the regulations in the HPA axis, resulting in changes in cortisol and neurotransmitters such as serotonin and norepinephrine. The disruptions lead to cortisol being overproduced (Ruiz et al., 2018). Normally, cortisol levels should peak during the waking phase and decline as the day progresses, following a daily cycle (Morgan et al., 2017). However, continuous elevation of cortisol levels can interfere with falling asleep by disrupting this normal cortisol rhythm and negatively affecting neurotransmitter receptors, which leads to reduced availability of these neurotransmitters (Ruiz et al., 2018).

Beyond cortisol, neurotransmitters such as serotonin and norepinephrine also play crucial roles in sleep regulation. Serotonin is involved in balancing wakefulness and sleep and helps manage both sleep patterns and mood by regulating arousal and inhibiting REM sleep (Monti, 2011; Varinthra et al., 2024). Disruptions or imbalances in serotonin levels can impact the sleep-wake cycle and are linked to depression (Ursin, 2002). Similarly, norepinephrine is also involved in sleep processes. This neurotransmitter, which is involved in regulating arousal (Hussain et al., 2023), can show abnormal levels in individuals with insomnia. As mentioned before, the research done by Irwin and colleagues (2003) discovered high levels of norepinephrine during the night in patients with insomnia, contributing to difficulties with staying asleep. While these activating neurotransmitters normally promote wakefulness, disruptions caused by depression can lead to sleep problems.

The cited research suggests that the relationship between depression and insomnia is bidirectional. Depression can disrupt sleep patterns, leading to insomnia, while chronic insomnia can impair emotional functioning and increase the risk of developing depression. Lack of sleep affects emotional regulation and mental health, just as mental health issues impact neurotransmitters crucial for sleep. The evidence indicates that treating insomnia may help prevent depression (Ohayon & Roth, 2003). Conversely, it is less clear whether treating depression can prevent insomnia. Research indicates that biochemical mechanisms play an important role in depression, which in turn affects the sleep cycle.

Current treatments and effectiveness

Treatments for insomnia

Many people struggle with poor sleep and want to improve their sleep quality to feel refreshed in the morning. The easiest step often involves enhancing sleep habits, focusing on improving sleep hygiene and reducing time spent in bed. This can be achieved by changing small habits and surroundings to promote better sleep, such as avoiding big meals, caffeine, tobacco, or alcohol before bedtime and exercising earlier in the day. Consistency in sleep and wake times in a dark, quiet environment is also crucial. Besides that it is beneficial to avoid snoozing in the morning and only use the bed when feeling tired (Institute for Quality and Efficiency in Health Care, 2022). This approach alone is not effective enough, so it should be done in combination with other treatments (Kaur et al., 2023).

One option to combine with is cognitive behavioral therapy for insomnia, which offers many advantages such as no adverse effects, reduced likelihood of recurrence and even after completing the therapy sessions, there is still an improvement notable in some people's sleep. This therapy focuses on long-term solutions by learning and promoting changes in the sleep mechanism to improve sleep quality. It consists of five components; sleep restriction, cognitive restructuring, relaxation techniques, stimulus control and the previously mentioned sleep hygiene.

- Sleep restrictions teach the patient to use the bed solely for sleep, so people are more tired when they finally go to bed.
- Cognitive restructuring involves replacing the beliefs and thoughts to a more positive view.
- Relaxation techniques such as meditation, breathing exercises promote relaxation before bedtime.

- Stimulus control helps reassociate the bed with sleeping, no activities besides sleeping are carried out in bed (Rossman, 2019).

Research confirmed the effectiveness of this therapy even with just three components. Individuals experienced a longer sleep of approximately 8 minutes more after the treatment, along with a 10% improvement in the actual time spent sleeping in bed (Trauer et al., 2015). However, it is still not used everywhere due to the lack of available therapists (Rossman, 2019).

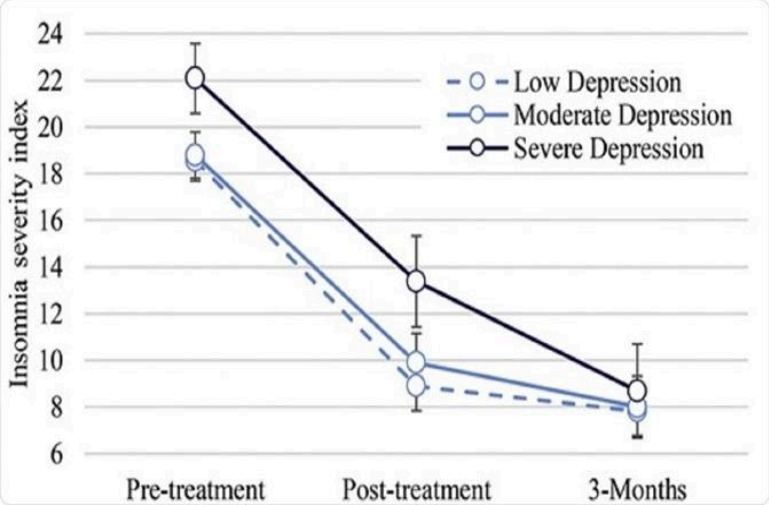


Figure 5: *The changes in insomnia severity index when treated with cognitive behavior therapy for insomnia. The figure shows a significant reduction in insomnia severity index scores from pre-treatment to post-treatment, with further improvement at the 3-month follow-up. These results show the effectiveness of cognitive behavioral therapy for insomnia in addressing insomnia symptoms across various levels of depression ($p < 0.001$) (Sweetman et al., 2020).*

Insomnia can also be treated with various medications. One medication is benzodiazepines which are used as a short-term solution that targets GABA receptors in the central nervous system. As discussed earlier, GABA plays an important role in promoting sleep by inhibiting arousal-promoting activities. Benzodiazepines enhance this inhibitory effect by binding to GABA receptors and increasing their sensitivity to GABA. When these receptors are activated, it allows chloride ions inside the neuron (Bounds & Patel, 2024; Varinthra et al., 2024), enhancing the effect of GABA, which inhibits activity throughout the central nervous system (Roehrs & Roth, 2012). This ultimately leads to a relaxing and sedating effect, which helps to stimulate and promote sleep (Edinoff et al., 2021; Varinthra et al., 2024). An analysis done by Holbrook and colleagues (2000) showed an extension in sleep periods by nearly 62 minutes. However, benzodiazepines medication stays a short-term solution because of the risky side effects of medication such as addiction or development of tolerance or other risks (Soyka et al., 2023b). Another medication can be melatonin, which targets the melatonin receptor. Melatonin dysfunction, caused by receptor density changes, receptor polymorphisms, and imbalances in receptor expression, can lead to sleep problems (Hardeland, 2012). Melatonin medication offers a targeted solution by administering a small synthetic dose to help with sleep problems (Bollu & Kaur, 2019). The research conducted by Brzezinski and colleagues (2005) confirmed that melatonin medication can enhance sleep patterns.

Treatments for depression

Dealing with depression is difficult and naturally someone wants to feel better again quickly. The recovery period can differ per individual due to the severity and type of depression. Multiple approaches, such as therapies and medication, can be tried to help individuals with depression.

Starting with cognitive therapy, this approach helps you understand how negative thoughts and beliefs impact your mood and behavior. It assists you in transforming these negative patterns into healthy, positive thoughts, which will lead to a better mood and self-concept. The depressive process probably starts with a negative thought that triggers a negative mood. The therapy session begins by helping the patient understand that their current way of thinking may not always be accurate and that this is the main cause of their problems. The patient then will identify the negative thoughts and learn a more realistic way of thinking. They should compare these negative thoughts with more realistic alternatives and determine which is more accurate. The effectiveness depends on how the patient responds to the sessions and whether they begin to acknowledge and correct their wrong way of thinking. Ultimately, the goal is for the patient to shift towards positive thoughts, leading to a better mood and self-concept. (Rupke et al., 2006). Research on this therapy, including 48 trials, has revealed that cognitive therapy is effective for treating low to moderate severities of depression and even better than medications (Gloaguen et al., 1998). Another therapy is cognitive behavioral therapy. It is almost the same as cognitive therapy, except it also includes behavioral interventions. This means that this therapy addresses both thinking patterns and behaviors to achieve a more positive outcome. The combination of cognitive therapy and behavioral therapy aims to improve both thoughts and actions (Chand et al., 2023). Research by Bogucki and colleagues (2021) found that attending this therapy significantly helped in the treatment of depression. Furthermore, it has been found that this therapy causes fewer relapses in patients (Rupke et al., 2006). There is also interpersonal psychotherapy. This therapy is designed for individuals who have recently gone through a tough time with someone or something and are struggling to cope with it. The sessions are short and focused on finding a solution to improve social functioning and eliminate depression (Mufson, 1999; Law, 2011). An analysis done by Duffy and colleagues (2019) supports its effectiveness for treating depressive patients.

Elevated cortisol levels associated with depression can negatively affect neurotransmitter receptors for serotonin and norepinephrine, reducing the availability of these neurotransmitters in the synaptic cleft (Ruiz et al., 2018). One effective approach to addressing these imbalances is through the use of antidepressants, with the most used types being selective serotonin re-uptake inhibitors (SSRIs), selective serotonin norepinephrine re-uptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs). Firstly, SSRIs are effective antidepressants and are more tolerated than other options. There are multiple types of SSRIs, but their main mechanism is to increase serotonin in the synaptic cleft for later uptake by the receptors of the post-synaptic neuron. They achieve this by blocking the serotonin transporter, preventing serotonin from being reabsorbed into the pre-synaptic neuron (Edinoff et al., 2021). This increases serotonin activity. This type of antidepressant is favored because it barely affects other neurotransmitters and has few adverse effects (Chu & Wadhwa, 2023). The other options are SNRIs and TCAs, which are as effective as SSRIs (Institute for Quality and Efficiency in Health Care, 2020). These antidepressants function similarly to SSRIs, except both serotonin and norepinephrine are increased in the synaptic cleft for later uptake by the receptors of the post-synaptic neuron (Fanelli et al., 2021). The main distinction is

that TCAs affect more neurotransmitters beyond just these two, thereby causing more side effects (Moraczewski et al., 2023). The Institute for Quality and Efficiency in Healthcare (2020) claims that these forms of medication do not lead to dependency.

Despite the availability of treatment options, stigma surrounding depression consists due to misconceptions and insufficient knowledge. Many still view depression as a sign of personal weakness, question the effectiveness of therapies, or underestimate the importance of resting. As well as some individuals prefer to solve it alone, which causes delays for seeking help. These misconceptions create barriers that prevent patients from finding treatment and support. Addressing these misconceptions through talking, education or other efforts will support and encourage people to improve their mental well-being (Yokoya et al., 2018).

Treating insomnia and depression simultaneously

Treating insomnia and depression simultaneously is crucial because they affect each other and the overall well-being. By looking at effective treatments, we explore treatment strategies that target both conditions. An overview with all the treatments is shown in table 1.

The treatment of cognitive behavioral therapy is important and effective in treating both disorders. This therapy tackles both negative thinking patterns and behaviors to eventually achieve a more realistic and positive mindset and behavior. Research shows that this therapy can help improve both conditions (Trauer et al., 2015; Bogucki et al., 2021). Using medication prescribed for insomnia, such as benzodiazepines and melatonin, to treat depression may not be ideal. Studies have found that these medications are ineffective in relieving the depressive symptoms. Although they can improve sleep, they do not effectively address depression (Birkenhäger et al., 1995; Li et al., 2022).

Regarding treatments for depression, starting with interpersonal psychotherapy, there is limited research on its effectiveness in treating insomnia. However, one study indicated some positive outcomes, offering optimistic chances for treatment (Müller-Popkes & Hajak, n.d.). Antidepressants impact neurotransmitters to enhance mood, which can either improve or disrupt sleep initially due to neurotransmitter fluctuations. Despite short-term variations, all effective antidepressants ultimately promote better sleep when given at low doses (Wichniak et al., 2017). As discussed before, elevated cortisol levels can reduce serotonin and norepinephrine availability by affecting their receptors and increasing serotonin reabsorption (Ruiz et al., 2018). Antidepressants improve sleep by boosting neurotransmitter levels in the synaptic cleft to enhance receptor uptake (Edinoff et al., 2021; Fanelli et al., 2021). Therefore, antidepressants generally improve sleep by addressing neurotransmitter imbalances.

Treatment approach	Insomnia	References	Depression	References
Cognitive behavior therapy	✓	(Trauer et al., 2015)	✓	(Bogucki et al., 2021c)
Benzodiazepines	✓	(Holbrook et al., 2000)	✗	(Birkenhäger et al., 1995)
Melatonin	✓	(Brzezinski et al., 2005)	✗	(Li et al., 2022)
Cognitive therapy			✓	(Gloaguen et al., 1998)
Interpersonal psychotherapy	✓	(Müller-Popkes & Hajak, n.d.)	✓	(Duffy et al., 2019)
SSRIs	✓	(Wichniak et al., 2017)	✓	(Institute for Quality and Efficiency in Health Care, 2020)
SNRIs	✓	(Wichniak et al., 2017)	✓	(Institute for Quality and Efficiency in Health Care, 2020)
TCAs	✓	(Wichniak et al., 2017)	✓	(Institute for Quality and Efficiency in Health Care, 2020)

Table 1 Overview of treatment possibilities and their effectiveness for the disorder. ✓ indicates effectiveness, ✗ indicates ineffectiveness and an empty box indicates unclear evidence.

Discussion

The aim of this review was to evaluate the connection between insomnia and depression, along with their availability in treatments. Insomnia involves difficulties in sleeping, while depression is characterized by feelings of worthlessness. A scientific study discovered a bidirectional relationship between these two conditions. Poor sleep in insomnia caused by issues with REM sleep, contributes to difficulties in emotional regulation, managing stress situations and creating negative emotions while reducing positive ones. This all contributes to the development of depression. Conversely, depression can disrupt sleep patterns. The HPA axis is dysregulated in depressive patients, leading to imbalances in cortisol, serotonin and norepinephrine. Elevated cortisol levels cause problems with sleep onset and maintenance, while serotonin and norepinephrine, the neurotransmitters crucial for mood regulation, interfere with the sleep and wake cycle. These imbalances can ultimately lead to the sleep disorder: insomnia. The treatment strategies analyzed showed that cognitive behavior therapy is the most effective for improving sleep and depression. The therapy achieves this by changing behavior, promoting healthy sleep habits such as improved sleep hygiene, sleep restriction, relaxation techniques, stimulus control, and transforming negative thought patterns associated with depression into more realistic and positive thoughts. However, pharmacological interventions such as antidepressants can also treat the disorder. Medications like SSRIs, SNRIs and TCAs, which affect neurotransmitter imbalances, impact both depression and sleep effectiveness over the long-term. On the other hand, medications such as benzodiazepines and melatonin have not shown promising results for treating depression and are therefore not useful for addressing both disorders simultaneously.

Future research should focus on understanding the mechanisms underlying the bidirectional relationship between insomnia and depression. Investigating the roles of neurotransmitters and genetic factors will help in developing new pharmacological treatments that address both conditions simultaneously. In addition to pharmacological interventions, advancing research in this area will open the door to personalized medicine approaches. Personalized medicine aims to customize treatment strategies based on individual patient profiles, which could include genetic, neurobiological, and lifestyle factors. This approach can be promising for more effective and fitting treatment options.

While these research efforts aim to improve treatment, it is also crucial to focus on the preventive aspect of insomnia and depression. The vicious cycle between insomnia and depression can be broken by recognizing that their bidirectional relationship often flows unidirectionally from insomnia to depression. It is important to identify the underlying causes of both insomnia and depression. Research shows that insomnia often occurs before the onset of depression, (Ohayon & Roth, 2003; Baglioni et al., 2011; Del Rio João et al., 2018), with disruptions in the sleep cycle being central to both conditions. Once the causes of these disruptions are identified, effective therapies and medications can be applied to reduce the likelihood of depression developing from insomnia and vice versa. However, these are curative interventions. Preventing insomnia and depression is more beneficial than treating them after they occur. Many causes of insomnia and depression, such as stress, caffeine consumption in the evening, alcohol use, and other lifestyle factors, can be addressed through preventive strategies. A change to a healthier lifestyle can prevent insomnia, ultimately reducing the risk of developing depression.

Conclusion

Insomnia and depression are worldwide health problems that lead to high healthcare costs, reduced productivity, and decreased quality of life, making it important that a remedy is found. The review analyzed the health effects, revealed the bidirectional relationship, and examined current treatments. In most cases, the onset of the disorder begins with insomnia. Due to their mutual influence, treating one can help resolve the other. Therefore, treating insomnia helps with reducing depression. Cognitive behavior therapy is the most effective option, offering dual benefits for both insomnia and depression. Additionally, antidepressants or interpersonal therapy can also offer promising results. Further research is needed to explore this relationship for better treatment strategies. By combining all available knowledge, we can develop better strategies to break the vicious cycle of these disorders and ultimately improve the sleep, health and well-being of individuals, leading to a more fulfilling life.

References

Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., Lombardo, C., & Riemann, D. (2011). Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders*, *135*(1–3), 10–19. https://doi.org/10.1016/j.jad.2011.01.011

Bains, N., & Abdijadid, S. (2023, 10 april). *Major depressive disorder*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK559078/#:~:text=Individuals%20with%20MDD%20are%20at,disease%2C%20and%20coronary%20artery%20disease.\

Bamalan, O. A., Moore, M. J., & Khalili, Y. A. (2023, July 30). *Physiology, serotonin*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK545168/

BioRender. (2024). https://www.biorender.com

Birkenhäger, T. K., Moleman, P., & Nolen, W. A. (1995). Benzodiazepines for depression? A review of the literature. *International Clinical Psychopharmacology*, *10*(3), 181–195. https://doi.org/10.1097/00004850-199510030-00008

Bogucki, O. E., Craner, J. R., Berg, S. L., Miller, S. J., Wolsey, M. K., Smyth, K. T., Sedivy, S. J., Mack, J. D., Johnson, M. W., Burke, L. M., Williams, M. W., Katzelnick, D. J., & Sawchuk, C. N. (2021). Cognitive behavioral therapy for depressive disorders: Outcomes from a multi-state, multi-site primary care practice. *Journal of Affective Disorders*, *294*, 745–752. https://doi.org/10.1016/j.jad.2021.07.061

Bollu, P. C., & Kaur, H. (2019, February 1). *Sleep Medicine: Insomnia and sleep*. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6390785/

Bounds, C. G., & Patel, P. (2024b, January 30). *Benzodiazepines*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK470159/

Boyce, R., Glasgow, S. D., Williams, S., & Adamantidis, A. (2016). Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science*, *352*(6287), 812–816. https://doi.org/10.1126/science.aad5252

Briley, M., & Chantal, M. (2011). The importance of norepinephrine in depression. *Neuropsychiatric Disease And Treatment*, 9. https://doi.org/10.2147/ndt.s19619

Brzezinski, A., Vangel, M. G., Wurtman, R. J., Norrie, G., Zhdanova, I., Ben-Shushan, A., & Ford, I. (2005). Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Medicine Reviews*, *9*(1), 41–50. https://doi.org/10.1016/j.smrv.2004.06.004

Chand, S. P., & Arif, H. (2023, 17 juli). *Depression*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK430847/

Chand, S. P., Kuckel, D. P., & Huecker, M. R. (2023, May 23). *Cognitive Behavior Therapy*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK470241/

Chu, A., & Wadhwa, R. (2023, May 1). *Selective serotonin reuptake inhibitors*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK554406/

Colten, H. R., & Altevogt, B. M. (2006). *Extent and Health Consequences of Chronic Sleep Loss and Sleep Disorders*. Sleep Disorders And Sleep Deprivation - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK19961/

Colten, H. R., & Altevogt, B. M. (2006). *Sleep physiology*. Sleep Disorders and Sleep Deprivation - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK19956/

Del Rio João, K. A., De Jesus, S. N., Carmo, C., & Pinto, P. (2018). The impact of sleep quality on the mental health of a non-clinical population. *Sleep Medicine*, *46*, 69–73. https://doi.org/10.1016/j.sleep.2018.02.010

Duffy, F., Sharpe, H., & Schwannauer, M. (2019). Review: The effectiveness of interpersonal psychotherapy for adolescents with depression – a systematic review and meta‐analysis. *Child and Adolescent Mental Health*, *24*(4), 307–317. https://doi.org/10.1111/camh.12342

Edinoff, A. N., Akuly, H. A., Hanna, T. A., Ochoa, C. O., Patti, S. J., Ghaffar, Y. A., Kaye, A. D., Viswanath, O., Urits, I., Boyer, A. G., Cornett, E. M., & Kaye, A. M. (2021). Selective serotonin reuptake inhibitors and Adverse Effects: A Narrative review. *Neurology International*, *13*(3), 387–401. https://doi.org/10.3390/neurolint13030038

Edinoff, A. N., Nix, C. A., Hollier, J., Sagrera, C. E., Delacroix, B. M., Abubakar, T., Cornett, E. M., Kaye, A. M., & Kaye, A. D. (2021). Benzodiazepines: uses, dangers, and clinical considerations. *Neurology International*, *13*(4), 594–607. https://doi.org/10.3390/neurolint13040059

Ellis, J., Ferini-Strambi, L., García-Borreguero, D., Heidbreder, A., O'Regan, D., Parrino, L., Selsick, H., & Penzel, T. (2023, February 28). *Chronic Insomnia Disorder across Europe: Expert Opinion on Challenges and Opportunities to Improve Care*. NCBI. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10001099/#:~:text=Approximately%20one%20in%20ten%20adults,prevalence%20is%20increasing%20%5B2%5D.

Espie, C. A. (2007). Understanding insomnia through cognitive modelling. *Sleep Medicine*, *8*, S3–S8. https://doi.org/10.1016/s1389-9457(08)70002-9

Fanelli, D., Weller, G., & Liu, H. (2021). New Serotonin-Norepinephrine reuptake inhibitors and their anesthetic and analgesic considerations. *Neurology International*, *13*(4), 497–509. https://doi.org/10.3390/neurolint13040049

Fava, M., & Kendler, K. S. (2000). Major depressive disorder. *Neuron*, *28*(2), 335–341. https://doi.org/10.1016/s0896-6273(00)00112-4

Feige, B., Benz, F., Dressle, R. J., & Riemann, D. (2023). Insomnia and REM sleep instability. *Journal of Sleep Research*, *32*(6). https://doi.org/10.1111/jsr.14032

Galbiati, A., Sforza, M., Fasiello, E., Casoni, F., Marrella, N., Leitner, C., Zucconi, M., & Ferini-Strambi, L. (2020). The association between emotional dysregulation and REM sleep features in insomnia disorder. *Brain and Cognition*, *146*, 105642. https://doi.org/10.1016/j.bandc.2020.105642

Gloaguen, V., Cottraux, J., Cucherat, M., & Blackburn, N. I. (1998). A meta-analysis of the effects of cognitive therapy in depressed patients. *Journal of Affective Disorders*, *49*(1), 59–72. https://doi.org/10.1016/s0165-0327(97)00199-7

Hardeland, R. (2012). Neurobiology, pathophysiology, and treatment of melatonin deficiency and dysfunction. *˜the œScientific World Journal/TheScientificWorldjournal*, *2012*, 1–18. https://doi.org/10.1100/2012/640389

Holbrook, A. M., Crowther, R., Lotter, A., Cheng, C., & King, D. (2000, January 1). *Meta-analysis of benzodiazepine use in the treatment of insomnia*. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1232276/#:~:text=DATA%20SYNTHESIS%3A%20The%20meta%2Danalyses,%25%20CI%2037.4%20to%2086.2).

Hussain, L. S., Reddy, V., & Maani, C. V. (2023, May 1). *Physiology, noradrenergic synapse*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK540977/

Institute for Quality and Efficiency in Health Care (IQWiG). (2020c, June 18). *Depression: Learn More – How effective are antidepressants?* InformedHealth.org - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK361016/

Institute for Quality and Efficiency in Health Care (IQWiG). (2022, March 3). *Sleep disorders and problems (insomnia): Learn More – What can you do if you have trouble sleeping?* InformedHealth.org - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK279320/

Irwin, M., Clark, C., Kennedy, B., Gillin, J. C., & Ziegler, M. (2003). Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. *Brain, Behavior, and Immunity*, *17*(5), 365–372. https://doi.org/10.1016/s0889-1591(03)00031-x

Kahn, M., Sheppes, G., & Sadeh, A. (2013). Sleep and emotions: Bidirectional links and underlying mechanisms. *International Journal of Psychophysiology*, *89*(2), 218–228. https://doi.org/10.1016/j.ijpsycho.2013.05.010

Kaur, H., Spurling, B. C., & Bollu, P. C. (2023, July 10). *Chronic insomnia*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK526136/

Law, R. (2011). Interpersonal psychotherapy for depression. *Advances in Psychiatric Treatment*, *17*(1), 23–31. https://doi.org/10.1192/apt.bp.109.007641

Li, C., Ma, D., Li, M., Wei, T., Zhao, X., Heng, Y., Ma, D., Anto, E. O., Zhang, Y., Niu, M., & Zhang, W. (2022). The Therapeutic Effect of exogenous melatonin on depressive Symptoms: A Systematic Review and Meta-Analysis. *Frontiers in Psychiatry*, *13*. https://doi.org/10.3389/fpsyt.2022.737972

Li, W., Ma, L., Yang, G., & Gan, W. (2017). REM sleep selectively prunes and maintains new synapses in development and learning. *Nature Neuroscience*, *20*(3), 427–437. https://doi.org/10.1038/nn.4479

Lin, H., Lai, C., Perng, H., Chung, C., Wang, C., Chen, W., & Chien, W. (2018). Insomnia as an independent predictor of suicide attempts: a nationwide population-based retrospective cohort study. *BMC Psychiatry*, *18*(1). https://doi.org/10.1186/s12888-018-1702-2

Liu, X. (2004). Sleep and Adolescent Suicidal Behavior. *Sleep*, *27*(7), 1351–1358. https://doi.org/10.1093/sleep/27.7.1351

Malhotra, R. K., & Desai, A. K. (2010). Healthy brain aging: What has sleep got to do with it? *Clinics in Geriatric Medicine*, *26*(1), 45–56. https://doi.org/10.1016/j.cger.2009.11.001

Mitchell, H. A., & Weinshenker, D. (2010). Good night and good luck: Norepinephrine in sleep pharmacology. *Biochemical Pharmacology*, *79*(6), 801–809. https://doi.org/10.1016/j.bcp.2009.10.004

Monti, J. M. (2011). Serotonin control of sleep-wake behavior. *Sleep Medicine Reviews*, *15*(4), 269–281. https://doi.org/10.1016/j.smrv.2010.11.003

Moraczewski, J., Awosika, A. O., & Aedma, K. K. (2023, August 17). *Tricyclic antidepressants*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK557791/#:~:text=Mechanism%20of%20Action,-TCAs%20exert%20their&text=These%20medications%20function%20by%20inhibiting%20serotonin%20and%20norepinephrine%20reuptake%20within,neurotransmitters%20within%20the%20synaptic%20cleft.

Morgan, E., Schumm, L. P., McClintock, M., Waite, L., & Lauderdale, D. S. (2017). Sleep characteristics and daytime cortisol levels in older adults. *Sleep*. https://doi.org/10.1093/sleep/zsx043

Mufson, L., PhD. (1999, June 1). *Efficacy of interpersonal psychotherapy for depressed Adolescents*. Adolescent Medicine | JAMA Psychiatry | JAMA Network. https://jamanetwork.com/journals/jamapsychiatry/article-abstract/1673771

Müller-Popkes, K., & Hajak, G. (n.d.). [Interpersonal psychotherapy in treatment of patients with primary insomnia--preliminary data of polysomnographic macro-analysis]. PubMed. https://pubmed.ncbi.nlm.nih.gov/9012161/

Ohayon, M. M., & Roth, T. (2003). Place of chronic insomnia in the course of depressive and anxiety disorders. *Journal of Psychiatric Research*, *37*(1), 9–15. https://doi.org/10.1016/s0022-3956(02)00052-3

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews. Disease Primers*, *2*(1). https://doi.org/10.1038/nrdp.2016.65

Palagini, L., Baglioni, C., Ciapparelli, A., Gemignani, A., & Riemann, D. (2013). REM sleep dysregulation in depression: State of the art. *Sleep Medicine Reviews*, *17*(5), 377–390. https://doi.org/10.1016/j.smrv.2012.11.001

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences*, *31*(9), 464–468. https://doi.org/10.1016/j.tins.2008.06.006

Pincus, H. A., Pettit, A. R., & Physicians Postgraduate Press, Inc. (2001). Societal costs of chronic depression. In *J Clin Psychiatry* (Vols. 62–62, Issue suppl 6). https://www.psychiatrist.com/wp-content/uploads/2021/02/17810_societal-costs-chronic-major-depression.pdf

Riemann, D. (2003). Primary insomnia: a risk factor to develop depression? *Journal of Affective Disorders*, *76*(1–3), 255–259. https://doi.org/10.1016/s0165-0327(02)00072-1

Riemann, D., Krone, L. B., Wulff, K., & Nissen, C. (2019). Sleep, insomnia, and depression. *Neuropsychopharmacology*, *45*(1), 74–89. https://doi.org/10.1038/s41386-019-0411-y

Roehrs, T., & Roth, T. (2012). Insomnia Pharmacotherapy. *Neurotherapeutics*, *9*(4), 728–738. https://doi.org/10.1007/s13311-012-0148-3

Rossman, J. (2019). Cognitive-Behavioral therapy for Insomnia: An effective and underutilized treatment for insomnia. *American Journal of Lifestyle Medicine*, *13*(6), 544–547. https://doi.org/10.1177/1559827619867677

Roth, T. (2007, 8 augustus). *Insomnia: Definition, Prevalence, Etiology, and Consequences*. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1978319/#B21

Roth, T., & Roehrs, T. (2003). Insomnia: Epidemiology, characteristics, and consequences. *Clinical Cornerstone*, *5*(3), 5–15. https://doi.org/10.1016/s1098-3597(03)90031-7

Ruiz, N. a. L., Del Ángel, D. S., Olguín, H. J., & Silva, M. L. (2018). Neuroprogression: the hidden mechanism of depression. *Neuropsychiatric Disease and Treatment*, *Volume 14*, 2837–2845. https://doi.org/10.2147/ndt.s177973

Rupke, S. J., Blecke, D., & Renfrow, M. (2006, January 1). *Cognitive therapy for Depression*. AAFP. https://www.aafp.org/pubs/afp/issues/2006/0101/p83.html

Smith, M. D., & Maani, C. V. (2023, 8 mei). *Norepinephrine*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK537259/

Soleimani, L., Lapidus, K. A., & Iosifescu, D. V. (2011). Diagnosis and treatment of major depressive disorder. *Neurologic Clinics*, *29*(1), 177–193. https://doi.org/10.1016/j.ncl.2010.10.010

Soyka, M., Wild, I., Caulet, B., Leontiou, C., Lugoboni, F., & Hajak, G. (2023b). Long-term use of benzodiazepines in chronic insomnia: a European perspective. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1212028

Stringaris, A. (2017). Editorial: What is depression? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *58*(12), 1287–1289. https://doi.org/10.1111/jcpp.12844

Sweetman, A., Lovato, N., Micic, G., Scott, H., Bickley, K., Haycock, J., Harris, J., Gradisar, M., & Lack, L. (2020). Do symptoms of depression, anxiety or stress impair the effectiveness of cognitive behavioural therapy for insomnia? A chart-review of 455 patients with chronic insomnia. *Sleep Medicine*, *75*, 401–410. https://doi.org/10.1016/j.sleep.2020.08.023

Trauer, J. M., Qian, M. Y., Doyle, J. S., Rajaratnam, S. M., & Cunnington, D. (2015). Cognitive Behavioral therapy for chronic insomnia. *Annals of Internal Medicine*, *163*(3), 191–204. https://doi.org/10.7326/m14-2841

Trivedi, M. H. (2004). *The Link Between Depression and Physical Symptoms*. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC486942/

Tsuno, N., Besset, A., & Ritchie, K. (2021, July 13). Sleep and depression. *Psychiatrist.com*. https://www.psychiatrist.com/jcp/sleep-depression/

Ursin, R. (2002). Serotonin and sleep. *Sleep Medicine Reviews*, *6*(1), 55–67. https://doi.org/10.1053/smrv.2001.0174

Vandekerckhove, M., & Wang, Y. (2018). Emotion, emotion regulation and sleep: an intimate relationship. *AIMS Neuroscience*, *1*(1), 1–22. https://doi.org/10.3934/neuroscience.2018.1.1

Varinthra, P., Anwar, S. N. M. N., Shih, S., & Liu, I. Y. (2024). The role of the GABAergic system on insomnia. *Tzu-chi Medical Journal/Cí-jì Yīxué*, *36*(2), 103–109. https://doi.org/10.4103/tcmj.tcmj_243_23

Wenzlaff, R. M., Wegner, D. M., & Roper, D. W. (1988). Depression and mental control: The resurgence of unwanted negative thoughts. *Journal of Personality and Social Psychology*, *55*(6), 882–892. https://doi.org/10.1037/0022-3514.55.6.882

Wichniak, A., Wierzbicka, A., Walęcka, M., & Jernajczyk, W. (2017). Effects of antidepressants on sleep. *Current Psycchiatry Reports/Current Psychiatry Reports*, *19*(9). https://doi.org/10.1007/s11920-017-0816-4

World Health Organization: WHO. (2022, March 2). COVID-19 pandemic triggers 25% increase in prevalence of anxiety and depression worldwide. *WHO*. https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide

World Health Organization. (2024, June 3). *Supporting country work around mental health*. https://www.who.int/europe/activities/supporting-country-work-around-mental-health/raising-awareness-of-depression#:~:text=In%20the%20WHO%20European%20Region,it%20can%20lead%20to%20suicide.

Xiang, T., Liao, J., Cai, Y., Fan, M., Li, C., Zhang, X., Li, H., Chen, Y., & Pan, J. (2023). Impairment of GABA inhibition in insomnia disorders: Evidence from the peripheral blood system. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1134434

Yokoya, S., Maeno, T., Sakamoto, N., Goto, R., & Maeno, T. (2018). A brief survey of public knowledge and stigma towards depression. *Journal of Clinical Medicine Research*, *10*(3), 202–209. https://doi.org/10.14740/jocmr3282w