A Systematic Review of Pharmacological and Non-Pharmacological Therapeutics for Insomnia

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Sleep is an essential part of human life and is vital to immune functions, memory, and healing. Insomnia, a sleep disorder derived from differential intrinsic and extrinsic factors, has been on the rise in the last 20 years, yet technology and capabilities to aid in sleep have not grown to match this need. Although pharmacological therapies have proved effective, concerns over their addictive nature and side effects have led to a decrease in use. Due to the high-risk, high-reward nature of pharmacological treatments, many patients opt for the next competing category, cognitive behavioral therapy (CBT). In this review, we investigate the efficacies of various sleep therapeutics, including both pharmacological methods and non-pharmacological methods like behavioral therapies, and environmental therapies. Our goal is to create a comprehensive list of the most effective sleep therapeutics and critically assess their benefits and risks to reevaluate how the field is currently treating insomnia.

1 Introduction

Sleep is the fundamental basis for cellular and physiological repair in all eukaryotic organisms known to sleep.[1] Conversely when an organism is sleep deprived this leads to a decrease in cellular function. Therefore, involuntary sleep deprivation, or insomnia, in humans is linked to a decrease in health, quality of life, and socioeconomic standing.[2] An estimated 30-40% of the US adult population suffers from insomnia or insomnia-like symptoms.[3] In 2020, following the onset of the COVID-19 pandemic, Google searches for insomnia increased drastically by 58%.[4]

Scientists first began to explore the mechanisms of sleep in the early 1920s.[5] Rapid eye movement (REM) sleep was characterized by Eugene Aserinksy in 1953, the first major step forward in modern sleep science. Today scientists split the sleep cycle into two separate categories: non-rapid eye movement sleep (NREM) and REM sleep.[6] NREM sleep is initiated when an individual first falls asleep and is critical for memory processing. The current widely accepted hypothesis for sleep's role in memory transfer is that while one is conscious, memory is encoded into the hippocampus; during NREM sleep these memories are replayed and transferred to the neocortex for long-term storage.[7] The time it takes to fall into NREM sleep is classified as sleep onset latency (SOL), a factor taken into consideration when defining quality of sleep. NREM sleep is split into 4 main sequential phases: (1) defined by low frequency, mixed frequency, and sharp vertex brain waves as collected by electroencephalography machines (EEG); (2) defined by oscillations and sleep spindles; (3) defined by the presence of sleep spindles and lower frequency waves than NREM 2; and (4) defined by the presence of even lower frequency waves than NREM 3 and is the last stage of NREM sleep before entering REM sleep. NREM 3 and 4 are typically grouped together and are defined as slow-wave sleep (SWS), which is critical to progressing into REM sleep (Fig 1a).[1,8,9] REM sleep is activated following SWS and is characterized by slow and fast flicker eye movements, typically occurring in groups called clusters. REM sleep can also be characterized by several other physiological traits as defined in Fig 1a. Throughout the night the body completes an average of 6 cycles of NREM and REM sleep, with each cycle taking approximately 90 minutes.[2] To regulate the sleep cycle, there are endogenous compounds that promote sleep and those which promote wakefulness. To aid in sleep, therapies can either stimulate the production of sleep-promoting endogenous compounds or suppress wake-promoting endogenous compounds.[1] This theory was modified by Datta and MacLean (2007) which proposed that the human body is constantly regulating homeostatic balance of these endogenous compounds related to sleep. They propose that throughout the day an increase in brain activity increases metabolism. As the day progresses, these metabolites accumulate and act as the sleep-promoting endogenous compounds causing decreased brain activity, drowsiness, and finally SOL.

As sleep has become more well understood, we can define the quality of sleep and the effectiveness of sleep therapies via different tests and indexes. A widespread self-reported test known as the Pittsburgh Sleep Quality Index (PSQI) takes into consideration seven main categories: sleep quality, SOL, sleep duration or total sleep time (TST), sleep efficiency, sleep dis-

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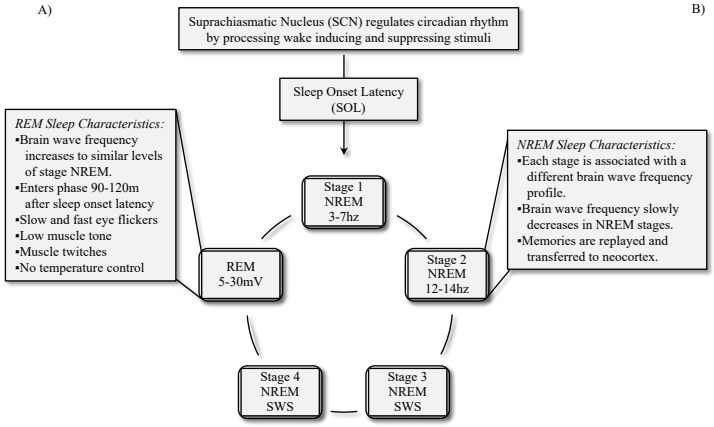
A)



B)

Abbreviation	Name	Definition
CBT	Cognitive Behavioral Therapy	Psychological therapy revolving around discussion from patient to therapist.
GABA	Gamma Aminobutyric Acid	Wake suppressant chemical naturally produced in the body.
NREM	Non-Rapid Eye Movement	Encompasses the first four stages of sleep including SWS.
PSQI	Pittsburgh Sleep Quality Index	Index developed to score a combination of factors and provide an overall assessment of a patients sleep.
REM	Rapid Eye Movement	Defined by clusters of movement in the eyes.
SCN	Suprachiasmatic Nucleus	Region of brain responsible for timing of sleep cycles.
SOL	Sleep Onset Latency	Measured from patients' attempted start of sleep to actual sleep onset.
SWS	Slow Wave Sleep	Occurs within stage 3-4 of NREM sleep, critical for REM sleep to occur.
TST	Total Sleep Time	Measured from sleep onset to wake.
WASO	Wake After Sleep Onset	Time patients awake

Fig. 1 Diagram of sleep functions and table of commonly used abbreviations. A) Diagram of sleep functions modeled off of Datta and MacLean (2007). Through regulation from the SCN, the body falls asleep into stage 1 NREM. This then progresses to stage 2 NREM before falling into stage 3 NREM and SWS. Stage 4 NREM leads to REM sleep and the cycle repeats. B) Common abbreviations used within the sleep science field and throughout this review.

turbances, use of medication for sleep, and daytime drowsiness. To obtain an accurate score, subjects must complete surveys over a one-month period. While there has been a decrease in the use of the PSQI with the development of sleep monitoring technology such as polysomnography, EEG spectral indexes, and actigraphy; PSQI remains as the common entry-level test to determine the general quality of sleep (Fig 1b). [10–13]

While sleep is becoming a better understood field of medicine, there is still many factors that contribute to sleep that have not been fully characterized. The goal of this paper is to create a comprehensive review on current sleep therapies to compare therapeutical efficacies and adverse side effects. The evidence presented in this paper will be a resource for clinicians, researchers, and patients in analyzing the risk-benefit ratio for different treatment options.

2 Pharmacological Therapies

In this review, pharmacological therapies are defined as any substances that are synthesized or concentrated industrially. This section will be split into two parts: hospital-used pharmaceuticals and supplements. Hospital-used pharmaceuticals have been standardized and vetted by the FDA, yielding a high efficacy in symptom relief. Gillis et al. (2014) provided a review to determine the top ten sleep-inducing pharmaceuticals in hospitalized patients. Figure 2 is a list derived from eleven different studies of the highest used sleep drugs ranging from over-the-counter medications (OTC) to Schedule 4 controlled substances. [14–24] The extremely high efficacies of the top administered pharmaceuticals for sleep therapy make them the optimal sleep therapeutic for fast and lasting results. However, clinicians must consider the extent of adverse effects experienced by patients as well as the addictive nature of these drugs. [2,25] Specifically, drugs in the benzodiazepine class that have long been prescribed for sleep but are highly addictive. Take for example the two most prescribed benzodiazepines: lorazepam and diazepam. Lorazepam comes with a long list of side effects and a heightened risk of respiratory depression which can be fatal. Diazepam has similar side effects, and a heightened risk of suicidal ideation and respiratory depression. Both drugs have been shown to be addictive due to producing dopamine responses in midbrain neurons and stimulating the mesolimbic reward system. [26] Additionally, in newer research to replace benzodiazepines, zolpidem was found to emulate the beneficial aspects of the drugs without replicating

the negative side effects, but it has been shown to be more addictive than first thought.[27] Due to benzodiazepines high adverse side effect rate and their highly addictive nature, healthcare providers now look to other pharmaceuticals for sleep therapeutics.[14,28]

While the evidence shows that pharmacological sleep aids are largely safe and effective, with the rise of the anti-modern medicine movement, many Americans have decided to avoid synthesized compounds and look for more natural alternatives, such as supplements.[2] Supplements are often concentrated forms of chemical compounds that are naturally produced. Regardless of the "natural" claims, the FDA does not approve or validate these claims.[14] While there are mechanisms to validate identity, potency, purity, and performance through United States Pharmacopeia (USP) Verification, many supplements on the market are not USP verified. Regardless of the lack of FDA backing, 1 in 5 Americans have used a sleep supplement within the last 12 months.

The most highly used sleep supplement in the US is melatonin, with over 3 million Americans reporting usage within the last 30 days.[29] Melatonin is a critical aspect of sleep regulation in the SCN (Fig 1b). By ingesting melatonin, the SCN is stimulated which causes sleep onset.[1] Side effects of melatonin are minor with rare reports of daytime sedation.[14] Although the effectiveness of melatonin is relatively low when taken in low doses, it is a good starting treatment due to its few minor side effects.[29,30]

Gamma AminoButyric Acid (GABA) also falls into the category of natural supplements that suppress wakefulness.[1] GABA functions in suppressing wakefulness through the same mechanism by which it does in vivo. GABA binds to a GABA-A receptor, which causes chloride channels to open and influx these negative ions into neuronal cells. The negativity of the neuronal cell slows synaptic transmission, causing drowsiness.[1] A study 2015 found that the intake of 100mg of GABA decreased SOL and increased REM sleep. Side effects for this concentrated GABA were not listed. Apocynum venetum leaf extract (AVLE), is derived from an herb indigenous to Asia and is another common supplement used to help with the onset of sleep. AVLE contains flavonoids that have proven antidepressant effects. The same 2015 study found that AVLE decreases SOL and sleep outside of REM.[31] Furthermore, the authors tested to see if these two supplements would work synergistically, but their results showed that when combined the effects on SOL and sleep outside of REM were not enhanced.[32]

Theanine, a commonly occurring compound in teas, is concentrated to produce the desired calming effect. However, subjects given theanine resulted in only a slight decrease in TST and WASO (Fig 1b) and a minor increase in sleep efficiency. Furthermore, theanine users report minimal negative side effects, making this a low-risk and benefit supplement.[2,33]

Lastly, cannabidiol (CBD) and Tetrahydrocannabinol (THC) belong to the compound class of cannabinoids and are supplements. Due to the varying legality of cannabinoid products, large-scale sleep studies on their direct use are uncommon. A few studies have been done which resulted in SWS increasing in minor and infrequent usage of CBD and THC but decreasing with chronic usage. Specifically, REM sleep decreased with minor and infrequent usage of these cannabinoids but stayed relatively the same with long-term usage. Why this occurs is yet to be determined with definitive evidence, speculation points to the fact that THC and CBD bind to endocannabinoid receptors and the endocannabinoid system aids in the regulation of homeostatic mechanisms.[34]

3 Non-Pharmacological Therapies

In this review, non-pharmacological therapy is defined as any therapy that does not require the intake of a synthesized or concentrated substance. These treatments are split into two separate categories: psychological and environmental. Psychological therapies require a trained professional to guide the patient through the process, while environmental therapies include methods outside the realm of pharmacological or psychological therapeutics, encompassing the patient's sleeping environment and exposure to elements or stimuli prior to or during, sleep.[35,36]

Psychological Therapies - Cognitive-behavioral therapy (CBT) is an effective and commonly used therapy amongst non-pharmacological methods for sleep. Multiple studies have shown that CBT increases sleep duration, SOL, sleep efficacy, and decreases WASO more effectively than any other non-pharmacological therapy.[36] In summary, CBT is among the most effective for aiding in sleep, while at the same time aiding in other mental health issues.

Environmental Therapies - Blue Light Blocking is an environmental therapy that patients may complete from their own home and provides a means to improve sleep without scheduling appointments or ingesting any compound which could adversely affect other aspects of their lives. Blue light has been shown to negatively affect sleep due to the light regulation aspect of our sleep cycle. Blue light blocking glasses provide an inexpensive and effective solution to this problem. Subjects who wore blue blocking glasses throughout the day experienced a sharp decrease in SOL with few side effects minus their vision adjusting to the new coloring. Therefore, blue light blocking glasses provide an easily accessible solution for moderate sleep problems.[37]

Muscle Relaxation via psychological discussion or memorized patterns has been shown to be effective yet has not shown to be as effective in increasing the same factors as CBT.[1] Sleep Hygiene including sleep journaling, discussing sleep, learning

Name	Mechanism of Action	Efficacy	Side Effects	FDA or Off Label Use for Sleep
Trazodone	Blocks reuptake of serotonin and histamines.	Increases SWS, TST, and sleep efficacy.	Dizziness, drowsiness, fatigue, headache, xerostomia, nausea, and vomiting.	FDA Approved for insomnia and depression.
Lorazepam	Enhances wake suppressing effect of GABA on the nervous system.	High effectiveness due to it being a benzodiazepine. Fast onset of effects typically 1-3 minutes.	Daytime sedation, dizziness, asthenia, confusion, and hypotension. Risk of respiratory depression which in some cases can be deadly.	FDA Approved for insomnia treatment. Long term use not recommended.
Zolpidem	Enhances wake suppressing effect of GABA on the nervous system.	Emulates effectiveness of benzodiazepines. Decrease in SOL.	Headaches, dizziness, drowsiness, nausea, vomiting, anterograde amnesia, hallucinations, delirium, and unusual behavior	FDA Approved for insomnia treatment. Long term use not recommended.
Quetiapine	Stimulates serotonin receptors and blocks certain dopamine receptors.	Increased score on PSQI.	Daytime sedation, hypotension, and dizziness. In extreme cases, suicidal ideation and irrational behavior.	Off label use for insomnia.
Haloperidol	Blocks serotonin and dopamine receptors.	Blocks up to 72% of serotonin and dopamine receptors. Similar increase in PSQI as quetiapine.	Anticholinergic effects, sedation, weight gain, erectile dysfunction, and oligomenorrhea.	Off label use for insomnia.
Diphenhydramine	Blocks the immune system's histamine response.	Low effectiveness with only 4.6% of patients reporting improved sleep.	Daytime sedation and anticholinergic effects, such as dry mouth and bowel issues.	FDA Approved as a sleep aid.
Mirtazapine	Antagonizes presynaptic receptors.	Increases TST and sleep quality. Decreases SOL.	Daytime sedation, weight gain, and anticholinergic effects such as dry mouth and bowel issues.	Off label use for insomnia.
Olanzapine	Blocks dopamine and serotonin receptors	Similar effectiveness as quetiapine.	Increased appetite, increased insulin sensitivity, and metabolic change.	Off label use as a sleep aid.
Amitriptyline	Blocks the reuptake of serotonin in the nervous system	Similar effectiveness as trazodone, and mirtazapine.	Anticholinergic effects such as dry mouth and bowel issues, as well as decreased cognition, and delirium.	Off label use for insomnia.
Diazepam	Boosts GABAs efficacy on certain receptors and increases the body's absorption of GABA.	High effectiveness due to it being a benzodiazepine.	Daytime sedation, confusion, headaches, and possible depression.	FDA Approved for insomnia.

Fig. 2 Table detailing the mechanism of action, efficacy, side effects, and FDA or off-label uses for the 10 most used sleep drugs.

about sleep, and establishing a regular sleep schedule, is less effective than CBT or muscle relaxation.[35]

Regulatory Devices have become a hot topic in sleep science due to the body's inability to regulate temperature during REM sleep.[1,38] Researchers investigated the effectiveness of devices placed on the forehead or inner ear that can help to increase or decrease body temperature. The forehead regulatory device yielded better polysomnographic measures in the areas of SOL, WASO, and awakenings, while inner ear regulatory device yielded improved sleep efficiency and TST. Subjective feedback gathered by questioning subjects showed that the forehead device brought improvements in sleep latency, sleep quality, alertness, and mood, with only minimal side effects, including headaches, right knee bruising, and leg cramps. Whereas the inner ear device yielded more severe side effects such as strep throat and pain where the electrodes were placed. Altogether, temperature regulation devices have validated high efficacy, but more research and development is required to maintain the high efficacy while decreasing their current negative side effects.[39]

Aromatherapy is another easily accessible option for an environmental sleep aid. Scents used in aromatherapy studies include lavender, peppermint, bergamot, chamomile, clary sage, rosewood, lemon, marjoram, ylang ylang, eucalyptus, and rosemary. The methods of application include massage, direct inhalation via a piece of cloth, inhalation via the scent stored in a necklace, and administration via a poultice. Currently there are five studies that reported positive change in mean PSQI score and one study that reported negative change in mean PSQI score. Therefore, due to the lack of sample size and their variability, more research is required to consider aromatherapy as a sustainable sleep therapy and current usage is not practical for a long-term solution.[40,41]

Diet Analysis. Diet is critical for all aspects of life, including metabolism and sleep. In this review, diet is considered an environmental therapy due socioeconomic standing and living conditions being the primary factor that determines quality of diet. In a review of 32 studies focused on different aspects of diet, including tryptophan consumption/depletion, minerals/vitamin consumption, and chlorogenic aids, the evidence

is indisputable that diet is correlated to sleep quality. In studies conducted on tryptophan consumption, subjects showed an increase in TST and a decrease in SOL. When subjects were acutely depleted of tryptophan, both the subjects' proportion of REM to total sleep and their amount of time in REM sleep increased. However, these subjects also experienced an increase in SOL, awakenings, and WASO. Decreases in TST were also observed in subjects.[42]

An increase in minerals and vitamins also affects sleep quality in patients as follows[42]:

1. Increase of zinc intake resulted in improvements in PSQI, SOL, and self-reported sleep quality.

2. Polyphenols, a compound derived from plants, has shown to decrease sleep disturbances and increase TST and sleep quality.

3. Additional crocetin resulted in fewer waking episodes and patients reported feeling more refreshed. Researchers observed an increase in delta power, which typically is associated with more waking episodes.

4. Chlorogenic acids from green coffee showed a decrease in SOL.

5. Chlorophytum borivilianum and velvet beans cause a decrease in SOL, as well as an increase in PSQI scores. Patients reported better sleep quality, sleep efficacy, and sleep disturbances.

6. Consumption of Jerte Valley cherries, which have high concentrations of melatonin and serotonin, led to an increase in TST and a decrease in waking episodes and SOL.

7. Changes to carbohydrates (CHO), protein, and fat in diets also yield changes in subjects' sleep. In diets in which CHO, protein, or fat consumption were increased, patients experienced a decrease in SOL, sleep disturbances, and increases in PSQI and in stage 3 NREM. In diets in which CHO, protein, or fat consumption were decreased, subjects experienced an increase in NREM, and a reduction in proportion of REM to total sleep time.

Exercise is essential to human health due to cardiovascular, muscular, and neuronal benefits. Exercise is an excellent regulator of sleep due to exercise increasing metabolic rate, therefore increasing accumulation of metabolites that contribute to drowsiness. Exercise on a constant basis has been shown to increase SWS and TST, while decreasing REM, SOL, and WASO.[43] One aspect to consider is that exercising within four hours before sleep can adversely affect the patient, therefore timing of exercise is crucial to see improvements.

4 Discussion

When evaluating therapies for sleep it is important to take into consideration not just the efficacy, but also the potential side effects. Pharmacological therapies are associated with much higher rates of potentially fatal side effects, however in some cases, patients may be willing to endure the side effects to sleep rather than continuing to suffer from the effects of sleep deprivation. A recommendation that can be derived from our analyzed data is the discontinuation of benzodiazepine use for sleep and substituting zolpidem instead due to its high efficacy, mild side effects, and low addictive nature. An additional option health care providers should consider is the use of off-label drugs such as mirtazapine and amitriptyline. The side effects of mirtazapine are comparable with other sleep drugs, with one abnormality being an increase in appetite. Furthermore, mirtazapine has been shown to aid in patients' recoveries in addictions to other substances, so it is beneficial when transitioning off benzodiazapines.[44] Amitriptyline has a similar side effect profile as mirtazapine, without an increased appetite. Amitriptyline is generally considered to be non-addictive. However, one case study reported addictive behavior, so it is imperative to conduct more research on this drug.[45] Supplements are generally well tolerated and come with few side effects. Because supplements affect different receptors in the brain, theoretically multiple can be used at once to produce a combined effect, but there is very little research that supports this. Further studies into the ideal dosage for each of these supplements is necessary for the progression of supplements as a sustainable sleep therapy.

Psychological and non-pharmacological therapies, often preferred as an alternative to pharmacological drugs, may aid in other pre-existing conditions. Psychological and other non-pharmacological therapies may aid patients whose sleep condition is mild, offering a means to improve sleep without the risk of side effects or addiction. Further studies into more niche forms of therapy, such as Gestalt Therapy, is necessary to gain a bigger picture into the potential benefits of psychological therapies for sleep.

Finally, environmental therapies are the most inexpensive and effective methods for aiding in sleep and can safely be combined with any other therapies without the requirement of professional guidance.

With the increasing rate of insomnia in the US due to the increase in mental health conditions associated with the COVID-19 pandemic, the sleep industry is undergoing a time of exponential growth to accommodate this need. Therefore, it is essential for varying sleep therapy efficacies to be researched to provide a wide scope of therapies for patients.

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6 Biography

Andrew is a sophomore in high school out in Southern California. On the academic front, he is interested in biochemistry and discovering the mechanisms of how the world interacts. Andrew had the opportunity to conduct research with Arianna Broad, a Ph.D. student at the Weill Institute for Cell and Molecular Biology at Cornell University, through the Lumiere Research Program. During this time, he sought to produce a comprehensive paper on the current methodologies and treatments for sleep issues. He desired to create a source that scientists and non-scientists alike could appreciate and learn from.

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