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Understanding Sleep: Anatomy, Disorders and Treatments for A Restful Night's Sleep

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ABSTRACT:

Sleep is a vital biological process essential for physical health and cognitive functioning, characterized by distinct stages including rapid eye movement (REM) and non-REM sleep. This research paper delves into the complexities of sleep anatomy, the prevalence and types of sleep disorders such as insomnia, circadian rhythm disorders, and sleep-related breathing issues, and the multifaceted impacts these disorders have on daily functioning. Emphasizing the role of melatonin—a hormone critical for regulating sleep-wake cycles—the paper examines its physiological mechanisms, pharmacological properties, and therapeutic applications in treating sleep disorders. Additionally, cognitive behavioral therapy (CBT) is discussed as an effective treatment modality for insomnia, focusing on altering detrimental sleep-related thought patterns and behaviors. Practical recommendations for fostering better sleep hygiene are presented, underscoring the importance of consistent sleep schedules and a conducive sleep environment. Overall, the study highlights the intricate interplay between sleep physiology, psychological factors, and therapeutic interventions, advocating for a comprehensive approach to sleep health management to enhance overall well-being.

KEY WORDS: Sleep, Sleep disorders, Melatonin, Cognitive behavioral therapy(CBT).

1. INTRODUCTION:

Sleep is a complicated biological process that aids in recharging, staying healthy, and processing new information. Sleep and waking cycles are a natural aspect of our biology. While you sleep, your brain is still very busy even if you are at rest. Each night, the various stages of sleep are repeated multiple times. Rapid eye movement (REM) sleep and non-REM sleep are the two different stages that the brain goes through as you sleep. Your body may experience stress if you don't get enough sleep(1). All forms of sleep-related dysfunctions, such as trouble falling asleep at night, poor sleep quality, early waking, circadian rhythm disorders, parasomnias, sleep-related movement disorders, and sleep-related breathing disorders (SBDs), are included in the broad category of sleep disorders. Fatigue during the day is frequently the result of sleep disturbances. Individuals who experience sleep problems report being less able to complete everyday tasks that require learning, memory, logical reasoning, and mathematical calculations(2). Although sleep disorders are not a natural aspect of aging, their frequency may grow as

people age. Finding the causes of sleep disturbances is therefore essential. These include substance misuse, long-term medical disorders, mental health issues, decreased physical activity, and anticipated changes in sleep patterns in older persons. Furthermore, compared to older persons without sleep issues, those who have poor sleep are more likely to experience memory loss and poorer health consequences(3). So this article discusses about the specific types of sleep disorders, treatments and methods to overcome it.

ANATOMY OF SLEEP:

Figure 1: Structure of Brain

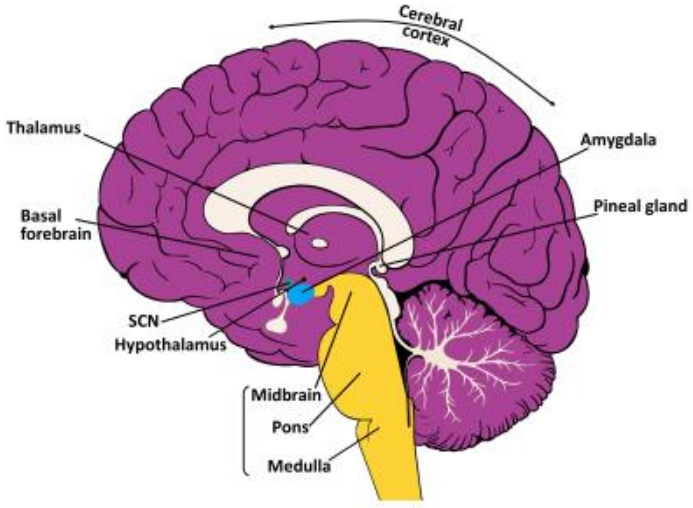
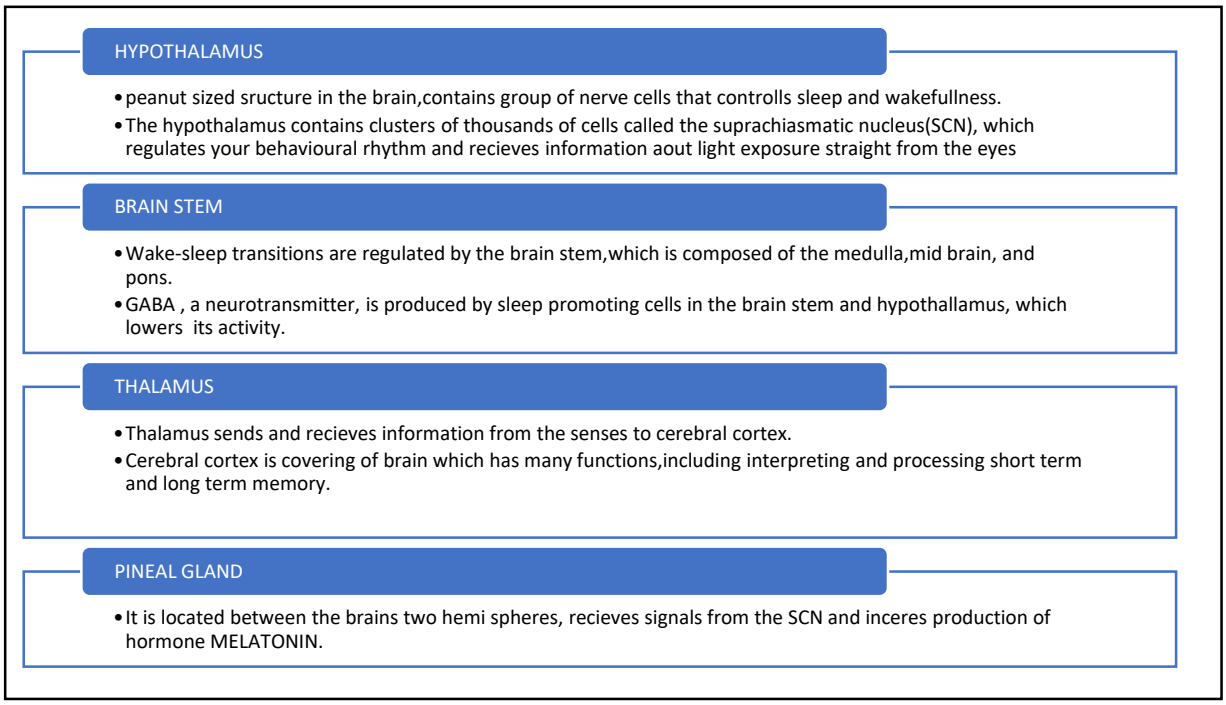
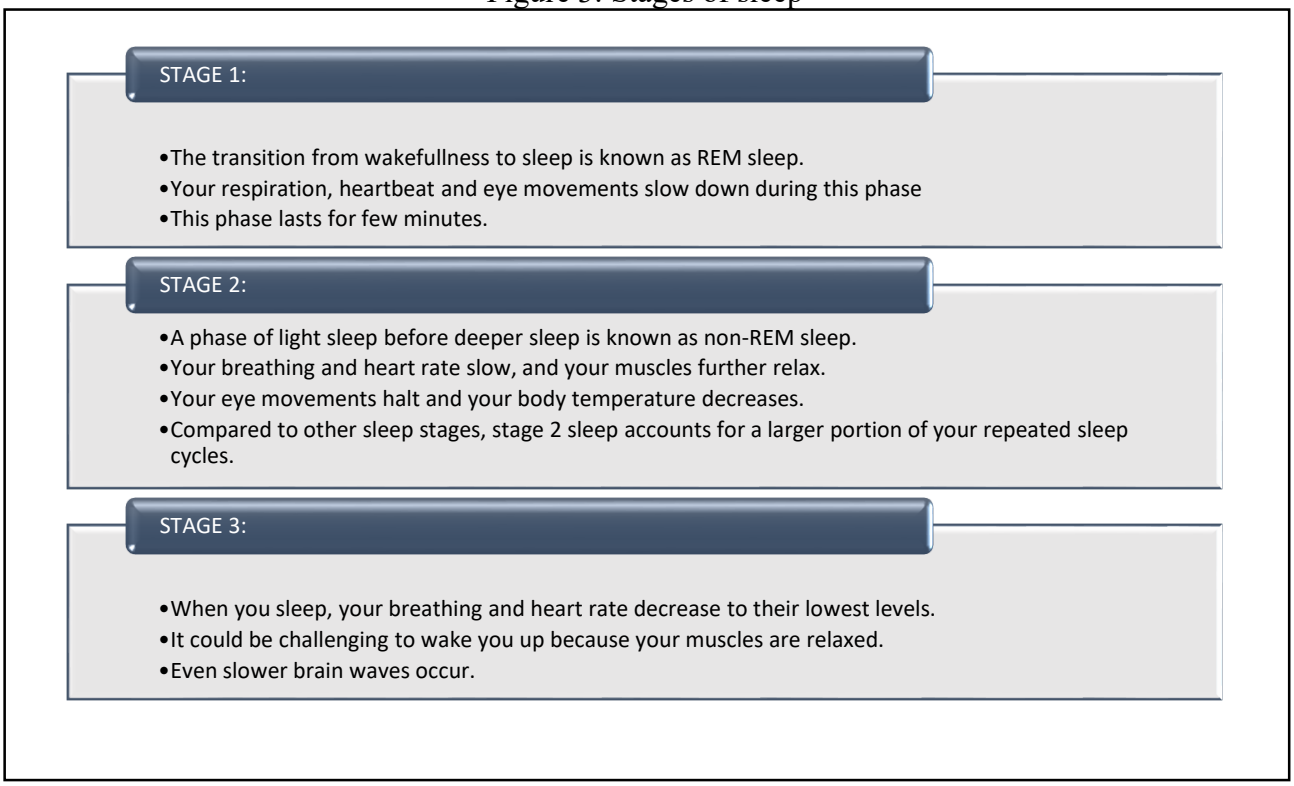


Figure 2 **:** Parts of Brain and its functions



SLEEP STAGES:

Figure 3: Stages of sleep



AVERAGE SLEEP HOURS:

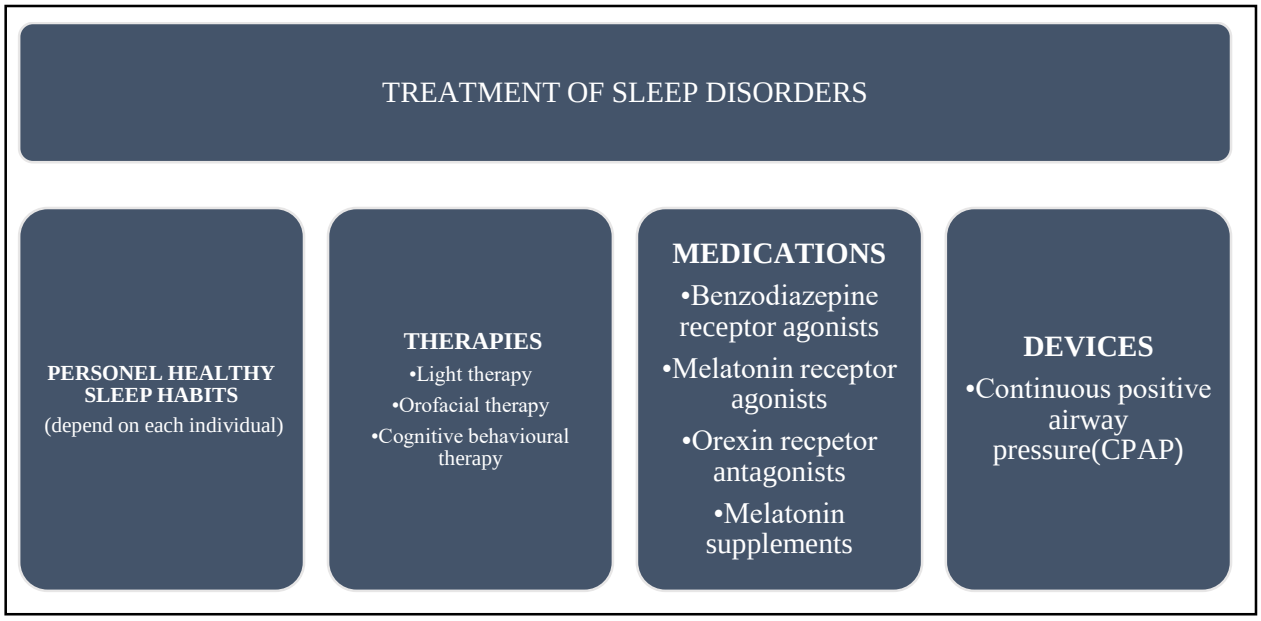
Figure 4: Average sleep hours

- No two people of the same age require the same amount of sleep.
- Babies sleep up to 16 to 18 hours a day at first, which may promote growth and development, particularly in the brain.
- On average, school-age children and teenagers require 9.5 hours of sleep every night. Even elderly persons require 7-9 hours of sleep per night.

- However, older adults are more prone to take sleep-interfering drugs and may experience more difficulties getting enough sleep.
- Due to extended workdays, the availability of 24-hour entertainment, and other activities, people are often receiving less sleep than they need.

VARIOUS TREATMENTS INVOLVED IN SLEEP DISORDERS:

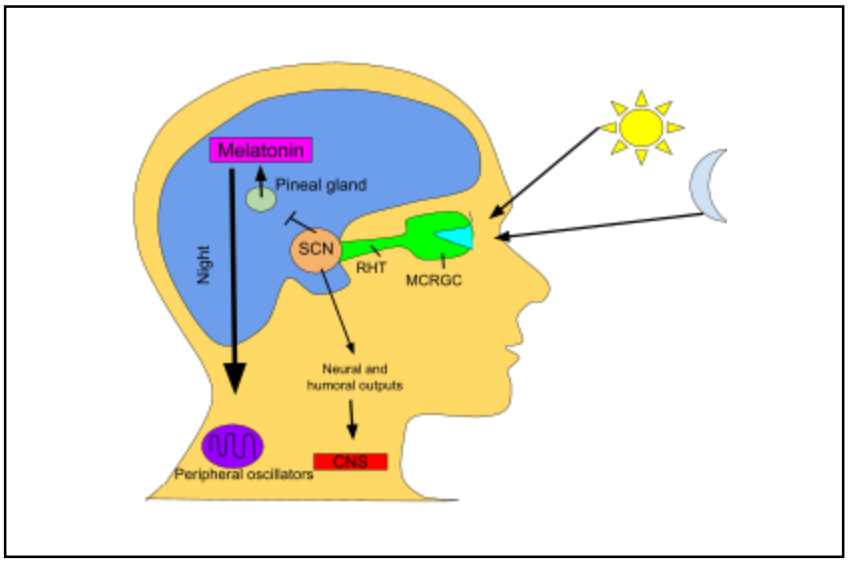
Figure 5: Treatment of sleep disorders



2. MELATONIN

Your brain releases the hormone melatonin in reaction to darkness. It facilitates sleep and the synchronization of your circadian rhythms, which are your body's 24-hour internal clock. Nighttime light exposure can inhibit the generation of melatonin. Beyond sleep, melatonin may have additional significant physiological functions, according to research. These consequences are not entirely understood, though. Although they can be derived from microbes or animals, melatonin dietary supplements are typically synthesized(4). Numerous organisms, including bacteria and eukaryotes, naturally produce the indoleamine melatonin. Aaron B. Lerner and associates discovered it in 1958 after isolating a chemical from cows' pineal glands that could cause common frogs' skin to lighten. This substance was eventually identified as a hormone released in the brain during the night, playing a critical role in regulating the sleep-wake cycle, commonly known as the circadian rhythm, in vertebrates(5).

Figure 6 : Melatonin production



The pineal gland's melatonin production is suppressed when the eyes are exposed to sunlight, and the resulting hormones keep people awake. The pineal gland produces melatonin when the eyes aren't exposed to light, which makes people tired(6).

MELATONIN AS A MEDICATION:

The brain naturally produces the hormone melatonin, which is also utilized as a medicine and nutritional supplement. The pineal gland releases the hormone melatonin, which plays a role in sleep-wake cycles. It is usually taken orally as a supplement to try to rectify disturbed sleep patterns, like those caused by jet lag or shift work, in the short term. Although it is not very strong, there is evidence that it is beneficial for this use. A 2017 review found that sleep onset occurred six minutes faster with use on average but found no change in total time asleep(7).

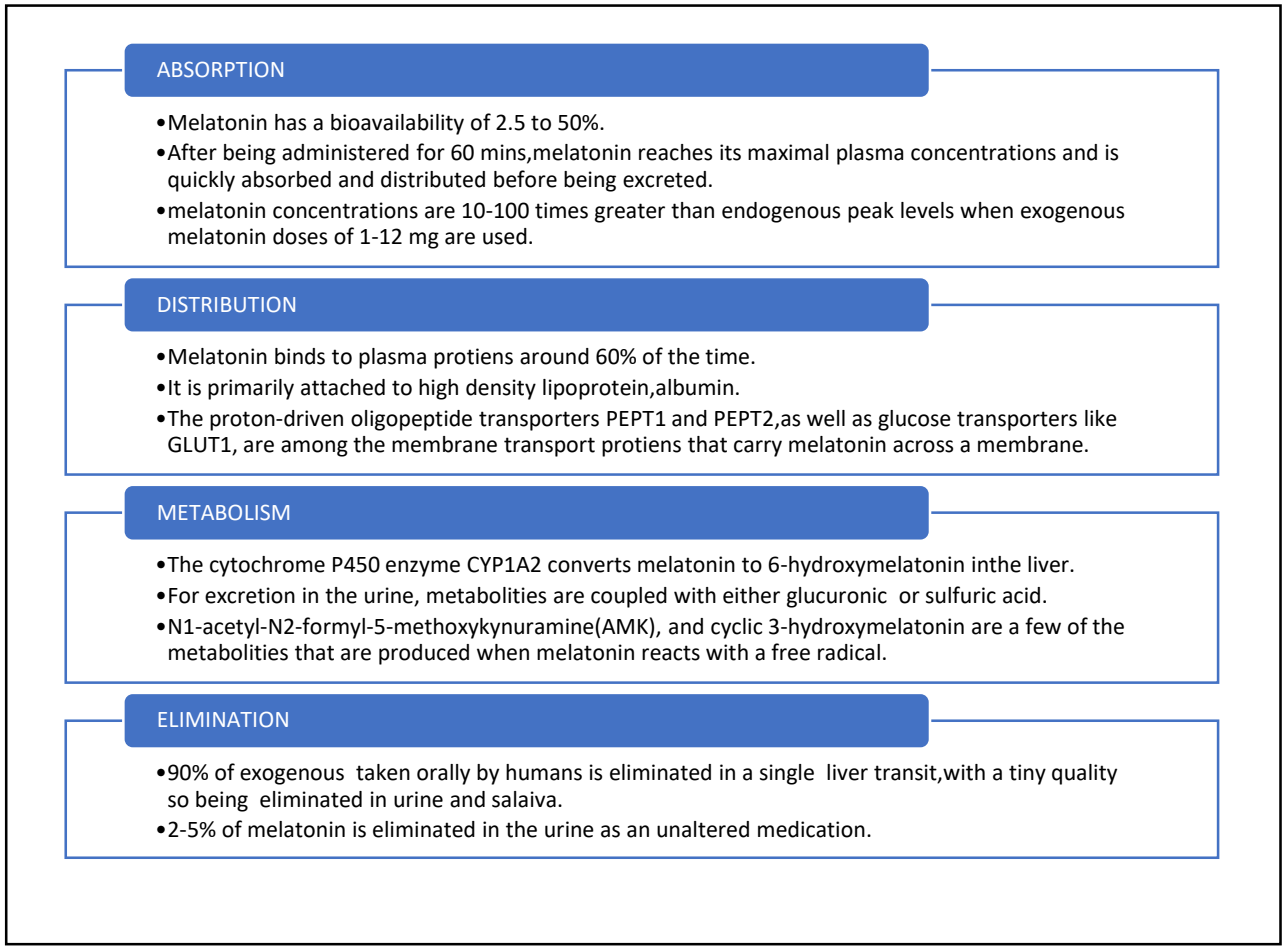
PHARMACOLOGY OF MELATONIN

- PHARMACODYAMICS

  The biological targets of endogenous melatonin, the melatonin MT1 and MT2 receptors, are agonistically acted upon by melatonin. The brain's pineal gland typically secretes endogenous melatonin. It is believed that melatonin regulates the circadian clock and sleep-wake cycles by activating melatonin receptors in the hypothalamic suprachiasmatic nucleus. Small doses (0.3 mg) of melatonin shift the circadian clock earlier, promoting an earlier sleep onset and morning awakening when taken several hours before bedtime, based on the human melatonin phase response curve.(8)

- PHARMACOKINETICS

Figure 7: Pharmacokinetics of melatonin



3. MELATONIN RECEPTORS:

G protein-coupled receptors (GPCRs) that bind melatonin are known as melatonin receptors. There are three different kinds of cloned melatonin receptors. Humans and other mammals have the MT1 (also known as Mel1A or MTNR1A) and MT2 (also known as Mel1B or MTNR1B) receptor subtypes, but amphibians and birds have been shown to have the MT3 (also known as Mel1C or MTNR1C) melatonin receptor subtype. In the melatonin signal cascade, the receptors are essential. Melatonin has been identified as a crucial component in the synchronization of biological clocks in the study of chronobiology. The brain's suprachiasmatic nucleus (SCN) controls the circadian rhythmicity of the pineal gland's melatonin release. The SCN regulates melatonin's timing; melatonin then reduces SCN neuronal activation by following a feedback loop(9). This mechanism is regulated by the receptors MT1 and MT2. The brain, the retina of the eye, the cardiovascular system, the liver and gallbladder, the colon, the skin, the kidneys, and many other organs have melatonin receptors. The cryo-EM and X-ray crystal structures of MT1 and MT2 were published in 2019(10).

- **MT 1**

The activation of the MT1 receptor in the suprachiasmatic nucleus (SCN), which inhibits brain activity, has been linked to melatonin's ability to promote sleep. There is evidence that the MT1 receptor contributes to the process of entrainment to light-dark cycles, even though the MT2 receptor has been primarily associated with the phase shifting activity of melatonin. An investigation that measured the rates of entrainment in MT1 knock-out (KO) and wild-type (WT) mice after they were fed melatonin provides this evidence. The observation that entrainment accelerated in WT mice upon melatonin administration, but not in MT1 KO mice, suggests that MT1 is involved in phase-shifting activity.(11)

- **MT 2**

Numerous roles for the MT2 receptor in the body have been demonstrated. The expression of the MT2 subtype in the human retina suggests that melatonin acts on the mammalian retina via this receptor. Melatonin may decrease the Ca2+-dependent release of dopamine, according to research. Phagocytosis and photopigment disc shedding are two light-dependent processes that are thought to be impacted by melatonin's effect in the retina. This receptor is expressed on osteoblasts as well as the retina, and it increases as the cells differentiate. MT2 controls osteoblast differentiation and proliferation as well as how they contribute to bone formation(12).It appears that MT2 signaling plays a role in the etiology of type 2 diabetes. When administered during the day, activation of the MT2 receptor causes vasodilation, which reduces body temperature in the extremities. Phase shifting the internal circadian clock to synchronize with the Earth's natural light-dark cycle is the most prominent of the roles that the MT2 receptor primarily mediates. As previously mentioned, it has been demonstrated that the MT1 receptor contributes to phase shifting, albeit its function is subordinate to that of the MT2 receptor. Phase shifting activity was observed in both the WT and MT1 KO groups in trials with MT1 KO mice (and WT as a control). The inability of MT2 KO mice to phase shift, on the other hand, suggests that the MT2 receptor is required for the internal circadian clock to phase shift.(13)

- **MT 3**

Although MT3's possible function in controlling intraocular fluid pressure has been briefly discussed, it is not as relevant to important biological processes as MT1 and MT2, such as promoting sleep, controlling circadian rhythm, and promoting locomotor activity. Additionally, MT3 aids in the detoxification of the kidney, liver, heart, gut, muscle, and fat.(14)

MELATONIN IN TREATMENT OF INSOMNIA:

The most common sleep condition in children and adolescence, particularly in older teenagers, is insomnia. Among girls, the prevalence is marginally greater and varies from 19% to 24%, depending on the diagnostic criteria applied. For children and adolescents with sleep-onset insomnia, individualized cognitive behavioral therapy should be the mainstay of treatment, with occasional pharmaceutical assistance. When pharmaceutical treatment is required, melatonin ought to be the first medication prescribed. For infants and preschoolers, the suggested dosage is 1-3 mg per night; for school-age children,

it is 2.5-5 mg per night; and for teenagers, it is 1-5 mg per night. The course of treatment ought to be started gradually. It is recommended that melatonin be given 30 to 60 minutes prior to bedtime. Melatonin therapy shouldn't last longer than four weeks. There is no information available on Melatonin with extended release in kids with typical psychomotor development.(15)

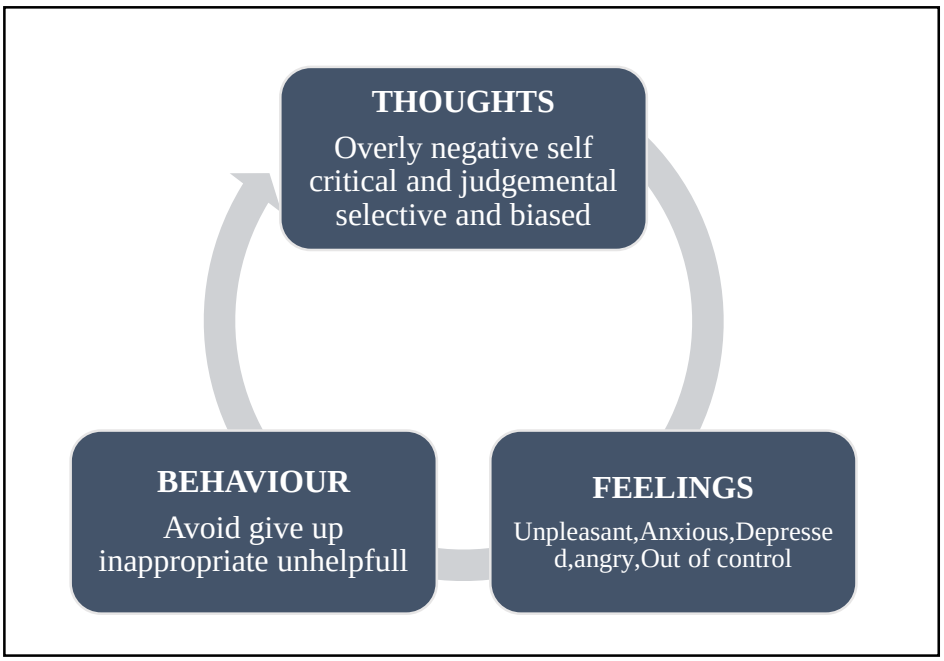
There are some kids with Circadian pacemaker failure, which manifests as delayed melatonin release in low light, is a contributing factor to chronic sleep-onset insomnia. The phrase "chronic sleep-onset insomnia with late melatonin onset" has been developed because the diagnosis of delayed sleep phase syndrome in children is not well defined or recognized. It is possible to cure these symptoms, accelerate the commencement of melatonin secretion, and regulate the sleep-wake cycle with exogenous melatonin when taken at the right time and dosage. It is advised that these individuals take smaller doses (such as 1 mg) because high doses are metabolized more slowly, which leads to decreased efficacy and longer wake times after sleep start.(16)

COGNITIVE BEHAVIOURAL THERAPY IN TREATMENT OF INSOMNIA:

A family of psychotherapy approaches that emphasize the connection between our thoughts, feelings, and behaviors are collectively referred to as cognitive behavioral therapy (CBT). Early in the 1990s, the first randomized trials assessing cognitive behavioral therapy (CBT) in children were published. As the body of data supporting CBT rapidly grew, the National Institute for Health and Clinical Excellence (NICE) approved it in 2005 for the treatment of depression. By acknowledging the significance of the individual meanings and interpretations that are created about events, CBT improved on previously used techniques, which were mostly based on behavior therapy. As a result, behavioral and cognitive theories inform CBT(17). CBT assumes that how events are interpreted, not the event itself, is what causes psychological issues and emotional suffering. These constructions may become unduly stiff and negatively biased, which could result in erroneous and dysfunctional perceptions, processing, and interpretations of events. Unpleasant emotions (such as anxiety, depression, or rage) and unhelpful behaviors (such as avoidance or withdrawal) are linked to these detrimental cognitive processes (18). Understanding and combating these skewed and prejudiced thoughts is the goal of cognitive behavioral therapy. This leads to the development of different, more balanced, and useful modes of thinking that promote more acceptable behaviors, lessen emotional pain, and enable more successful coping(19).

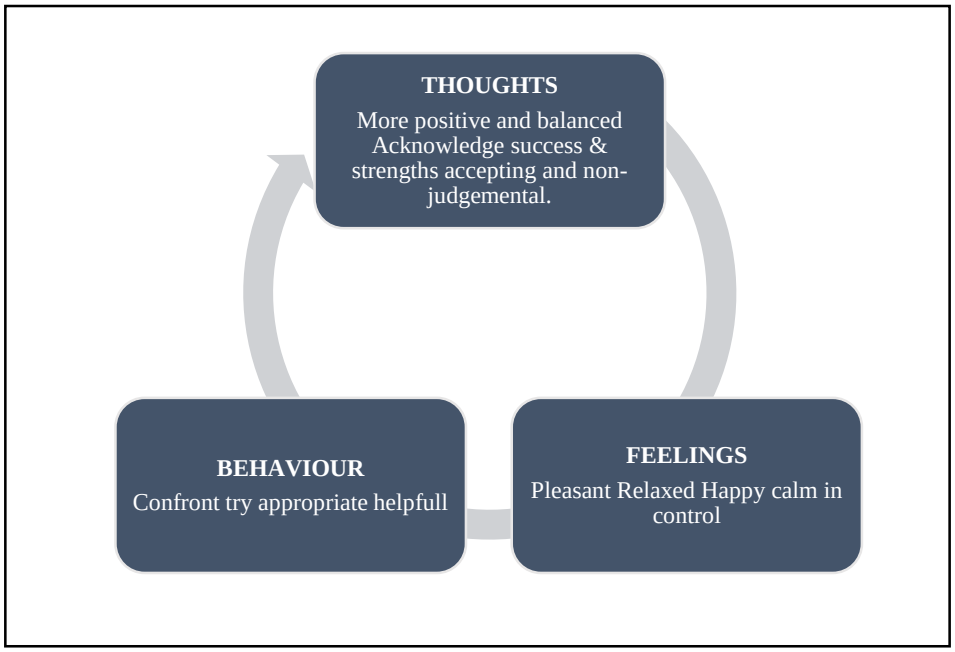
DYSFUNCTIONAL CYCLE:

Figure 8 :Dysfunctional cycle of CBT



FUNCTIONAL CYCLE:

Figure 9: Functional Cycle of CBT



CIRCADIAN RHYTHM DISORDERS:

No study has made a substantial contribution to the treatment of intrinsic circadian rhythm sleep-wake disturbances since the American Academy of Sleep Medicine released their clinical practice guidelines for their treatment in 2015(20).The American Academy of Sleep Medicine's guidelines for the use of melatonin in individuals with circadian rhythm disturbances are outlined below.

Phase of advanced sleep syndrome

Individuals who suffer from advanced sleep phase syndrome go to sleep and get up several hours before the required or preferred time. In the late evening, they exhibit somnolence, and in the early morning, they awaken on their own. Melatonin and melatonin agonists are not advised for people with the disorder since there are no systematic studies that have considered the use of melatonin in these patients. With children and adolescents who have advanced sleep phase disorders, the risk-benefit ratio is unclear.(21)

Delayed period of sleep syndrome

Individuals who suffer from delayed sleep phase syndrome go to bed two or more hours later than the customary or socially acceptable bedtime.

Patients report having trouble falling asleep and waking up at the appropriate times.

- Sleeping later phase syndrome in grownups. Two open-label trials and one double-blind research were reviewed by the guideline. For a brief period of time (≤ 29 days), all three trials used small samples (≤ 20 patients) and melatonin dosages ranging from 0.3 to 5 mg, given at various periods during the evening or night. It was discovered that melatonin increased sleep latency but not overall sleep duration or the ability to be aware at night. Because there is little data on the effectiveness of melatonin, adults with delayed sleep phase syndrome are not recommended to take it high.

- Sleeping later phase syndrome in kids and teens who don't have any concomitant conditions. Only one trial, comprising 64 participants ages 6 to 12, was assessed by the recommendation; melatonin at a dose of 0.05–0.15 mg/kg was given 1.5–2 hours prior to bedtime for six nights in straight. The highest outcomes were seen with doses of 0.15 mg/kg melatonin, which improved sleep latency by -43 minutes (CI, -24.06 to -63.54).

- Sleeping later phase syndrome among children and adolescents suffering from mental illnesses. The guidelines examined two studies where patients were given 3-5 mg of immediate-release melatonin for four weeks between the hours of 18:00 and 19:00.The findings point to an improvement in the time at which sleep begins. In any event, the low-to-moderate level of evidence currently available indicates that adults, children, and adolescents with delayed sleep phase syndrome have low levels of melatonin recommendation.(22)

Running in a free-running circadian cycle.

A problem known as free-running circadian rhythm occurs when the sleep cycle is not synchronized with the 24-hour cycle, typically lasting longer. This results from a misalignment between the light-dark cycle and the SCN; in these patients, the sleep cycle adapts to the endogenous circadian rhythm, which lasts roughly twenty-five hours. The majority of those who suffer from the condition are totally blind. The recommendation examined three observational studies with small sample sizes (a total of 24 patients), employing melatonin dosages ranging from 0.5 to 10 mg; the medication was given for 26–81 days, either an hour before bedtime or at a set time (21:00).The findings show that melatonin is useful in treating blind people's free-running circadian rhythm.(23)

Unpredictable sleep-wake cycles

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Individuals with the disorder have a disordered, unpredictable rhythm of sleep and wakefulness. Depending on the time of day, these patients may also exhibit somnolence and sleeplessness. Frequent napping is another issue.

- Unusual sleep-wake cycles among senior citizens suffering from dementia. Based on a single study of 25 patients who received 6 mg of prolonged-release melatonin at bedtime and who reported no increase in total sleep time, the American Academy of Sleep Medicine does not recommend melatonin for elderly people with dementia and irregular sleep-wake cycles.The experts also hypothesized that, because it may influence mood and daytime activity, melatonin may have more hazards than benefits for this patient population.
- Unusual sleep-wake cycles in kids and teenagers suffering from neurological conditions. The guidelines discuss a study where participants were given 2–10 mg of melatonin an hour before bed. The amount of evidence is modest, and the recommendation grade for the treatment is low.(24)

HABITS FOR BETTER SLEEP:

- Have bed time and wake up time same for every day.
- Avoid nicotine and caffeine, especially in afternoon and evening
- Exercise regularly, but don’t exercise too late in the day.
- Avoid large meals and beverages at late night.
- Avoid taking a nap after 3 PM
- Relax before going to bed, by taking bath, reading ,listening to good music.
- Keep the temperature in your bedroom cool.
- Get rid of distractions such as noises, bright lights and a TV or computer in the bedroom.
- Don’t get tempted to go on your phone or tablet just before bed.
- Get enough sunlight exposure during the day.

4. CONCLUSION:

In conclusion, sleep is a complex and multifaceted phenomenon that plays a critical role in maintaining our physical and mental health. Understanding the anatomy of sleep, including the various stages and cycles, is essential for appreciating the intricate mechanisms that govern our sleep-wake cycles. Sleep disorders, such as insomnia, can have a significant impact on quality of life, and various treatments, including melatonin, CBT, and circadian rhythm regulation, can be effective in managing these conditions.Melatonin, a hormone produced by the pineal gland, plays a crucial role in regulating sleep-wake cycles. Its receptors, MT1 and MT2, are involved in promoting sleep and synchronizing the body's internal clock. Melatonin supplementation has been shown to be effective in treating insomnia, particularly in individuals with low melatonin levels. However, it is essential to use melatonin judiciously and under medical supervision, as it can interact with other medications and have side effects.Cognitive Behavioral Therapy (CBT) is another effective treatment for insomnia and other sleep disorders. CBT helps individuals identify and change negative sleep habits and thought patterns, leading to improved sleep quality and duration. Circadian rhythm disorders, such as delayed sleep phase syndrome, can also be treated with CBT and other interventions, such as light therapy.Good sleep habits are essential for maintaining healthy sleep patterns. Establishing a consistent sleep schedule, creating a sleep-conducive environment, and avoiding stimulating activities before bedtime can all contribute to improved sleep quality. Additionally, avoiding caffeine, nicotine, and electronics before bedtime can also help promote better sleep. In summary, sleep is a vital aspect of our overall health and well-being. Understanding the anatomy of sleep, sleep stages, and various treatments involved in sleep disorders can help individuals take control of their sleep health. By promoting good sleep habits, using melatonin and other treatments judiciously, and seeking professional help when needed, individuals can improve their sleep quality and overall quality of life.

REFERENCES:

1. National Institute of Neurological Disorders and Stroke. (n.d.). Brain basics: Understanding sleep. Retrieved June 7, 2017, from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Understanding-Sleep
2. Amihaesei IC, Mungiu OC. Main neuroendocrine features and therapy in primary sleep troubles. Rev Med Chir Soc Med Nat Iasi. 2012;116:862–866.
3. Cross NE, Carrier J, Postuma RB, et al. Association between insomnia disorder and cognitive function in middle- aged and older adults: A cross- sectional analysis of the Canadian Longitudinal Study on Aging. Sleep. 2019;42(8). DOI: https://doi.org/10.1093/sleep/zsz114.
4. Andersen LP, Gögenur I, Rosenberg J, et al. The safety of melatonin in humans. Clinical Drug Investigation. 2016;36(3):169-175.
5. Amaral FG, Cipolla-Neto J (2018). "A brief review about melatonin, a pineal hormone". Archives of Endocrinology and Metabolism. **62** (4): 472–479. doi:10.20945/2359-3997000000066
6. Duffy JF, Wright KP (August 2005). "Entrainment of the human circadian system by light". Journal of Biological Rhythms. **20** (4): 326–38. doi:10.1177/0748730405277983
7. Auld F, Maschauer EL, Morrison I, Skene DJ, Riha RL (August 2017). "Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders" . Sleep Medicine Reviews. **34**: 10–22. doi:10.1016/j.smrv.2016.06.005

8. "Melatonin and the circadian system: Keys for health with a focus on sleep". The Human Hypothalamus: Anterior Region. Handbook of Clinical Neurology. Vol. 179. pp. 331–343. doi:10.1016/B978-0-12-819975-6.00021-2.
9. "Melatonin receptors: molecular biology of a new family of G protein-coupled receptors". Journal of Biological Rhythms. **12** (6): 528–531. doi:10.1177/074873049701200606.
10. "Melatonin and its receptors: a new class of sleep-promoting agents". Journal of Clinical Sleep Medicine. **3** (5 Suppl): S17 – S23. doi:10.5664/jcsm.26932.
11. "Melatonin receptors: role on sleep and circadian rhythm regulation". Sleep Medicine. **8** (Suppl 3): 34–42. doi:10.1016/j.sleep.2007.10.007
12. "Melatonin receptors: localization, molecular pharmacology and physiological significance". Neurochemistry International. **24** (2): 101–146. doi:10.1016/0197-0186(94)90100-7
13. "Methoxyindoles and photoreceptor metabolism: activation of rod shedding". Science. **219** (4590): 1341–1343. Bibcode:1983Sci...219.1341B
14. "Melatonin receptors as therapeutic targets in the suprachiasmatic nucleus". Expert Opinion on Therapeutic Targets. **20** (10): 1209–1218. doi:10.1080/14728222.2016.1179284.
15. Pin Arboledas G, Soto Insuga V, Jurado Luque MJ, Fer nandez Gomariz C, Hidalgo Vicario I, Lluch Rosello A, et al. Insomnio en ni˜ nos y adolescentes. Documento de consenso. An Pediatr (Barc). 2017;86:165.e1—11, http://dx.doi.org/10.1016/j.anpedi.2016.06.005.
16. Van Maanen A, Meijer AM, Smits MG, van der Heijden KB, Oort FJ. Effects of melatonin and bright light treatment in child hood chronic sleep onset insomnia with late melatonin onset: a randomized controlled study. Sleep. 2017;40:1—11.
17. Stallard P, Good T. Feel good: a cognitive behavioural therapy workbook for children and young people. 2nd Edn. John Wiley & Sons, 2019.
18. Wolpe J. Psychotherapy by reciprocal inhibition. Stanford, CA: Stanford University Press, 1958.
19. Beck AT. Cognitive therapy and the emotional disorders. New York: International Universities Press, 1976.
20. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017, http://dx.doi.org/10.1111/jsr.12594.
21. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. The efficacy and safety of exogenous mela tonin for primary sleep disorders. A metaanalysis. J Gen Intern Med. 2005;20:1151—8.
22. Posa L, de Gregorio D, Gobbi G, Comai S. Targeting mela tonin MT2 receptors: a novel pharmacological avenue for inflammatory and neuropathic pain. Curr Med Chem. 2017, http://dx.doi.org/10.2174/0929867324666170209104926
23. Andersen LP. The analgesic effects of exogenous melatonin in humans. Dan Med J. 2016;63, pii: B5289.
24. Meng L, Zheng Y, Hui R. The relationship of sleep duration and insomnia to risk of hypertension incidence: a meta-analysis of prospective cohort studies. Hypertens Res. 2013;36:985—95.