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Review Article

The Role of Melatonin in the Management of Insomnia in the Elderly

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Abstract

Older people have various kinds of comorbidity that can reduce their quality of life, one of which is insomnia. The diagnosis of insomnia is established clinically through history taking and the assessment of sleep quality with PSQI (Pittsburgh Quality Sleep Index) scoring. Insomnia can be a diagnosis of exclusion if there are no signs of other sleep disturbances through polysomnography examination. However, complaints of difficulty falling asleep (Sleep onset latency) and shortened sleep duration that disrupts daily activities during the day can be classified as insomnia. The elderly population has a high prevalence of insomnia, around 60%; therefore, this issue needs to be addressed. Various factors can trigger insomnia in old age, one of which is a decrease in serum melatonin levels. Thus, it is thought that melatonin therapy can improve insomnia symptoms in the elderly and have minimal side effects.

Introduction

Indonesia is a country that has a high elderly population, approximately 27 million people (10%) based on the results of data collection from the Central Statistics Agency for 2020 [1]. This number has increased from 18 million people (7.6%) in 2010. According to the Republic of Indonesia Ministry of Health in 2019, Indonesia is entering a phase with increasing life expectancy followed by an increase in the number of elderly people, referred to as the aging population phase [2]. The increasing number of elderly population is not only happening in Indonesia but also globally. WHO (World Health Organization) data stated that in 2019 there were around 1 billion elderly population over 60 years and the number is expected to increase to 1.4 billion in 2030 and 2.1 billion in 2050 [3].

The large elderly population is a challenge for Indonesia. With old age, the risk of various metabolic diseases such as diabetes, hypertension, cardiovascular disease, and stroke tends to increase [4]. In addition to metabolic diseases in the elderly, there is also a decrease in the amount of hormones in the body, one of which is melatonin. The decrease of melatonin can play a role in sleep disturbances or insomnia in the elderly [5].

Various metabolic diseases also increase the risk of insomnia in the elderly, conversely, the condition of insomnia can also increase the risk of various metabolic diseases. In 2018, the prevalence of insomnia in the elderly is around 10% of the total population of Indonesia, around 28 million people. This figure is quite high. Therefore, the problem of insomnia in the elderly requires special attention from clinicians.

Various therapies attempt to overcome insomnia in old age. CBT (Cognitive behavior treatment) is one of the recommended first-line therapy. Whereas pharmacological therapy is recommended when CBT therapy is ineffective or unavailable. Benzodiazepines and some antidepressants are said to be effective as short-term therapy for insomnia, namely ≤4 weeks, whereas long-term use is not recommended because of possible side effects. Antihistamines, antipsychotics, melatonin, and phytotherapy are not currently recommended, even though many studies have been conducted on this matter. Research on melatonin as well as melatonin receptor agonists found that these drugs are effective for treating insomnia in the elderly.

Melatonin and melatonin receptor agonists have minimal to no side effects. A systematic review found that taking melatonin significantly increased total sleep time, sleep quality, and decrease the duration of sleep onset compared to no medication (placebo). Thus, this paper will further discuss the benefits and role of melatonin therapy in elderly insomnia patients.

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Sleep Disorders in the Elderly

In adults with old age, especially those aged more than 65 years, sleep disturbances often occur. The presence of sleep disturbances is associated with an increased risk of death, cardiovascular disease, risk of falls, and a decreased quality of life. For this reason, sleep quality in the elderly should be included in a comprehensive study of elderly patients and the presence should not be considered normal. [5]

In old age, there is a change in the structure of sleep and it continues with age, the changes that can occur are:

- Decreased slow-wave sleep
- Decreased Rapid Eye Movement (REM) sleep
- Decreased Total Sleep Time (TST)
- Decreased sleep efficiency
- Increase in sleep onset latency (duration of time in falling asleep)

Elderly people also experience an acceleration of sleep and wake cycles. So as one age, the onset of sleep tends to occur earlier in the evening, and waking time becomes earlier as well. The reason why this is happening is yet to be determined. It is thought that it occurs due to multifactorial factors that are both intrinsic and extrinsic. Intrinsic factors include changes in the structure of the aging brain, hormonal changes, lens and retinal changes, and comorbidities that occur in old age. Extrinsic factors include the presence of polypharmacy, reduced physical activities, along with social and traumatic events [5].

From a neurological and endocrine perspective, various factors can affect sleep quality. These factors are changes in brain structure due to neurotoxin deposition and dysfunction of the blood-brain barrier. In addition, dysregulation of neurotransmitters will directly interfere with sleep drive or the urge to sleep, and degeneration of the Suprachiasmatic Nucleus (SCN) also affect the circadian rhythm which regulates the body's biological clock of waking and sleeping. The accumulation of pigment in the retinal ganglion cells can reduce the quality or amount of light captured by the eyes so that it could change the circadian rhythm. Changes in the amount of hormone secretion in the elderly such as cortisol could also influence the circadian rhythm [4].

Extrinsic factors such as traumatic events in life, for example losing a partner or family member, could also affect the sleep of adults with old age. In addition, low physical activity and reduced social activity are also said to be associated with sleep disturbances [4,5].

The prevalence of primary sleep disorders, such as Sleep-Disordered Breathing (SDB) also occurs in the elderly. The presence of chronic diseases and drugs consumed are also associated with sleep disturbances. This relationship is two-way in nature where sleep disturbances could be a risk factor for chronic diseases and chronic diseases could cause sleep disturbances [4,5].

Insomnia in the Elderly

Insomnia often occurs in old age. A person is diagnosed with insomnia if there is a persistent difficulty in sleeping with dysfunction of daily activities during the daytime. The diagnosis of insomnia is established clinically through history and is a diagnosis of exclusion from other sleep disorders. If other sleep disorders are suspected, such as SDB, then further tests such as polysomnography can be performed. Screening for sleep disorders such as the usage of a sleep diary can also be done, but some screenings have not been validated in elderly people with cognitive impairments [4,5].

There are several factors that contribute to insomnia in elderly people. Argyropulos found that, in people aged >65 years, sleep problems were more frequently in women, in elderly suffering from medical conditions, in poor social life, in absence of daily physical activity, in daily coffee and alcohol consumption, and in polypharmacy especially people with diuretic or antidepressants [16]. One study also found that Alzheimers diease also can contribute to insomnia in older age, odds ratio 3.32 [19]. Also, the sleep disorders will increase the risk of future cognitive decline in normal older adults [20].

In insomnia, non-pharmacological management is the first-line treatment. A systematic review study found that sleep hygiene education can improve sleep quality. In addition, cognitive and behavioral therapy for insomnia is said to be effective in improving sleep quality in elderly people. In one study, cognitive and behavioral therapy was more effective than zopiclone pharmacological therapy. However, access to cognitive and behavioral therapy is still not widely available. Other therapies such as relaxation and mindfulness therapy are also said to be effective in improving the sleep quality in the elderly [5].

Meanwhile, pharmacological therapy should be administered with caution. Statistically, it is said to be significantly beneficial, but the therapeutic effect is considered low with various risks including the risk of falling and cognitive impairment. Therefore, pharmacological therapy is recommended as adjunctive to non-pharmacological therapy, especially for patients with severe insomnia that heavily affect the quality of life and activities of daily living. Pharmacological therapy is recommended to be given in short terms with a target discontinuation time planned from the start of administration. The recommended drugs are short-acting and the choice of drug depends on the type of insomnia. Benzodiazepine drugs are not recommended to be given initially but are used as second-line therapy. Melatonin can also be given especially in patients with insomnia where the main complaint is sleep onset time [5].

Screening Evaluation and Diagnosis of Insomnia

Insomnia screening is recommended to be included in the complete assessment of geriatric patients. Various screenings can be used, but only a few have been validated for the elderly population. As a matter of fact, in elderly patients, apart from screening for sleep disorders, it is also necessary to explore comorbid diseases, regularly taken drugs, as well as environmental and psychosocial conditions. Here are some screenings that can be used: [5]

In addition to anamnesis, a complete physical examination is also needed to diagnose sleep disturbances in the elderly. Further examinations such as polysomnography can also be done.

Appropriate management according to the type of sleep disorder can be given both non-pharmacologically and pharmacologically, as listed in the following table: [4]

In addition, non-pharmacological management also plays an important role in insomnia in patients with dementia. Evidence shows a statistically significant increase in sleep efficiency in patients who are given non-pharmacological intervention com-

Table 1: Insomnia Screening [4].

Method / Screening Instrument	Goal	Notes
Pittsburgh Sleep Quality Index (PSQI)	Identify the quality of sleep and sleep disorders	Analyzing sleep history for the last 1 month, takes >30 minutes to complete, not appropriate for geriatric polyclinic and patients with short-term memory impairment
Epworth Sleepiness Scale (ESS)	Identify excessive daytime sleepiness, a score of >10 is less likely to be insomnia	Difficult to use for some geriatric populations
Insomnia Severity Index (ISI)	Assess the severity of insomnia	Validation is required in elderly patients. Applies to insomnia alone and not to sleep disorders as a whole
Patient Reported Outcomes Information System (PROMIS) Sleep Disturbance Scale	Using six items to assess sleep quality and difficulty in falling asleep	Analyze sleep history for the last 7 days and assess the severity of all sleep disturbances
The Essener Questionnaire on Age and Sleepiness (EQAS)	Assess for daytime sleepiness	Does not assess all sleep disorders, but can be used for patients with cognitive or communication disorders through their caregivers
Berlin Questionnaire (BQ)	Identify patients at risk of obstructive sleep apnea (OSA)	Has limitations in elderly patients and only for OSA patient screening
STOP-BANG Questionnaire	Identify patients with OSA	Has limitations in elderly patients and only for OSA patient screening
Sleep Apnea Clinical Score (SACS)	Identify patients with OSA	Can be an option in elderly patients with COPD, but requires further study

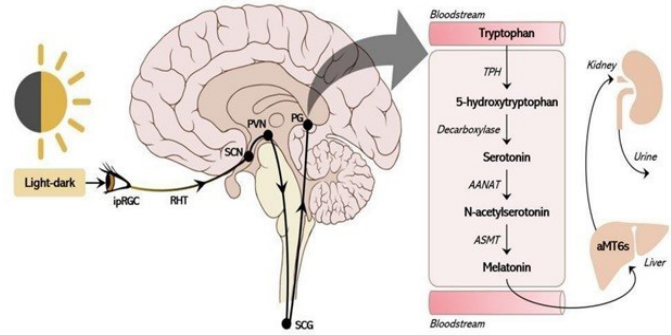

Figure 1: Melatonin Synthesis [6].

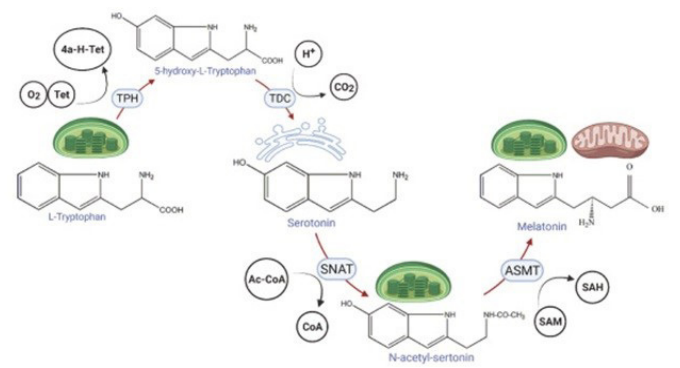

Figure 2: Melatonin Synthesis [7].

pared to those who are not. However, there was no significant difference in sleep duration and the number of awakenings during the night. There is still a small number of studies regarding Cognitive Behavioral Therapy interventions for insomnia (CBT-I) in patients with dementia. Based on studies, patients with mild cognitive impairment who are given six sessions of CBT-I can improve their sleep quality [4].

Melatonin Synthesis [6,7]

Melatonin is a hormone produced by the pineal gland and is derived from the essential amino acid tryptophan (N-acetyl-5-methoxytryptamine).

There are two types of exogenous melatonin, namely long-acting (prolonged release) and short-acting (short release). There have been no reports of dependence or adverse side effects when using oral melatonin. Minimal side effects that may arise are headaches and dizziness when consumed at low dose levels, which can slightly affect the quality of life. Various doses of melatonin can be taken without a doctor's prescription. Meanwhile, melatonin receptor agonists such as ramelteon can also be used to treat insomnia. Ramelteon is an MT1 and MT2 melatonin receptor agonist that has a specific effect on melatonin receptors in the suprachiasmatic nucleus. In clinical studies, it was found that the use of ramelteon is safe for the treatment of insomnia [7,8].

A meta-analysis by Kuriyama found that ramelteon is associated with an increase in the amount of total sleep time and sleep efficiency. Another meta-analysis found that melatonin can reduce sleep onset latency and increase total sleep time and overall sleep quality. However, because the diagnosis of insomnia is a subjective complaint, objective measurements are needed to properly evaluate the therapy.

E. Melatonin Receptors [7,8]

Melatonin secretion from the pineal gland activates the paired G protein MT1 and MT2 receptors. The production of melatonin in the pineal gland is controlled by the SCN and is affected by the changes in weather and environmental light-dark cycles. Endogenous melatonin produced by the pineal gland at night will signal the SCN and activate MT1 and MT2 receptors to regulate circadian rhythms.

Melatonin acts on the MT1 and MT2 receptors. There are differences between MT1 and MT2 in terms of structure, pharmacological characteristics, and chromosome location. MT1 increases the phosphorylation of mitogen-activated protein kinase, inhibits forskolin-stimulated cAMP, and increases potassium conduction through Kir channels. The MT2 receptor inhibits forskolin-stimulated cAMP and activates the Protein Kinase C (PKC) in the SCN and decreases calcium-dependent dopamine production in the retina.

Simultaneous activation of MT1 and MT2 receptors either on the same or different cells can create addiction, synergy, or even opposite effects that can even eliminate the effects of each other. The rate of MT1/MT2 heterodimer formation is 3 to 4 times lower than that of MT1/MT2 homodimers. MT1 or MT2 receptor monomers desensitize differently with exposure to melatonin depending on the concentration, exposure time, cellular background, and whether the receptor is active or not. Ligands that have high affinity and high selectivity can make heterodimer MT1/M2 receptors give higher effects than melatonin or synthetic non-selective ligands [8].

MT1/MT2 can also form a heterodimer with the serotonin receptor (5-HT2c). Thus, antidepressant mechanisms such as agomelatine could have effects as both melatonin receptor agonists and 5-HT2c receptor antagonists [8].

Table 2: Diagnosis and Management of Sleep Disorders in The Elderly [4].

Sleep Disorder	Diagnosis	Non-pharmacological Management	Pharmacological Management
Insomnia	History, screening questionnaires, and polysomnograph as supportive diagnostic measure	Insomnia CBT or digital CBT-I, sleep hygiene education, relaxation and mindfulness exercises	Second-line and short-term
Sleep-disordered Breathing	Polysomnograph or portable home-based device	Positive airway pressure (PAP) and patient weight reduction	Consider decreasing the use of sedatives
Restless Leg Syndrome	History, screening questionnaires may help	None, lack of evidence	Iron supplementation, dopamine agonists, alpha-2 calcium channel ligands, levodopa, benzodiazepines, and opioids (usage with caution)
REM Sleep Disorder	Polysomnograph, screening questionnaires may help	Sleep environment modification	Identification of drugs causing exacerbation. There is not much evidence on the use of melatonin and clonazepam.

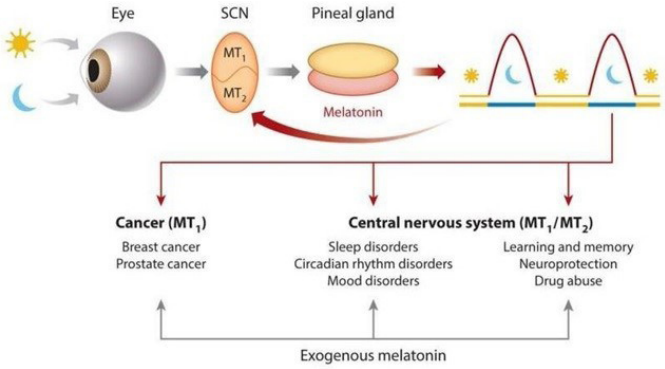

Figure 3: Melatonin Receptors [8].

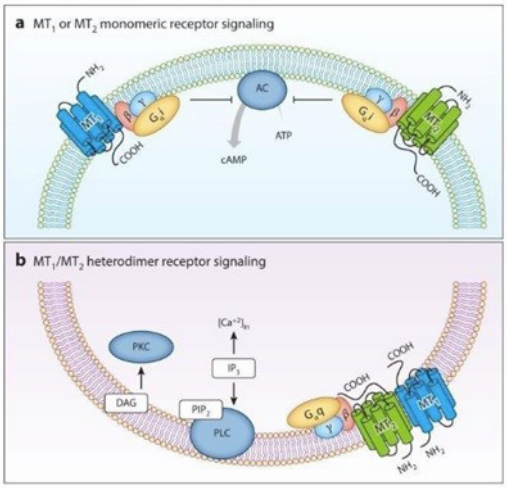

Figure 4: MT1-MT2 Homodimer and Heterodimer Receptors [6,8].

Melatonin and the Circadian Rhythm [6]

Melatonin acts as a diurnal regulator in humans. A sharp increase in the amount of melatonin in the body occurs 2 hours after endogenous production. Circadian rhythms are caused by the rhythms of melatonin production and are related to sleep rhythms. In elderly people, autonomic nerve degeneration, diabetic neuropathy, Alzheimer's disease, and various drugs (such as β-blockers, clonidine, naloxone, and NSAIDs) can interfere with melatonin production and are associated with sleep disturbances. For this reason, people who are given melatonin during the day will have symptoms of drowsiness and fatigue. However, melatonin is not a sedative, in nocturnal (active at night) animals, melatonin is associated with wakefulness, not sleep.

The effect of exogenous melatonin can be seen significantly when the endogenous melatonin production rate is at its lowest but difficult to see when it is at its highest. Melatonin acts on the SCN to interfere with the wake signal of the circadian rhythm, causing a person to fall asleep. Melatonin also works on the Default Mode Network (DMN) area of the brain which causes fatigue and sleepiness by activating the precuneus. The DMN is an area of the brain that is active during rest. The DMN is composed of the medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal lobes, lateral temporal cortex, and hippocampus.

The precuneus itself has a multitude of functions including memory consolidation, integration of perceptual information, mental strategies, and affective responses to pain. When sleeping, the connection at the DMN will decrease and be interrupted during the Slow Wave Sleep (SWS) phase. Melatonin when given during the day to a healthy young person will interfere with the activation of the precuneus and cause fatigue. If given at night, when endogenous melatonin production increases, the effect of exogenous melatonin is unclear. Melatonin is said to not increase the duration of SWS, so melatonin's effect is primarily on circadian rhythms in sleep regulation. For this reason, research on melatonin, which can increase and improve sleep cycles, continues to be carried out, especially in people with sleep and circadian rhythm disorders.

Melatonin acts as a marker in the absence of light or dark responses. Melatonin and several current melatonin analogues, such as ramelteon, agomelatine, and tasimelteon, are used clinically to modulate circadian rhythms and neuroendocrine function in both humans and animals. However, these are all non-selective agonists and have the same affinity for MT1 and MT2. Ramelteon has a 10 times higher affinity for MT1 than MT2, and 17 times higher than endogenous melatonin. Agomelatine and tasimelteon have a slightly higher affinity for the MT2 receptor. However, all melatonin analogues (ramelteon, agomelatine, and tasimelteon) are selective and specific to melatonin receptors and have no affinity for other G protein receptors [7,8].

Melatonin as Supplementation for Insomnia in the Elderly [9]

Melatonin can make a person sleep and to maintain it, melatonin therapy can also be used to help improve sleep quality. In the 2015 study by Roth et al, giving 0.5 – 1 mg of melatonin once a day in the evening for several months can improve circadian rhythms for 24 hours [10-12]. There are two forms of oral melatonin, simple melatonin with short half life and prolonged release melatonin with longer half-life but neither have been found to be superior for the treatment of insomnia [13]. The use of exogenous melatonin has not been reported to be associated with tolerance, dependence, or a hangover effect but, minimal side effect (headache, dizziness, nausea) can be found [14]. One study also reported no effect of melatonin on cognition or activities of daily living, and no serious side effects [24]. Melatonin is absorbed rapidly following oral administration and undergoes first pass hepatic metabolism with peak plasma levels occuring between 20 min and 2 h, and levels persist for up to 1.5h, depending on the dose [18]. In the United States, the most recent National Health Interview Survey showed that the overall use of melatonin among adults more than doubled be-

tween 2007 and 2012, to an estimated 3.1 million users [21]. For chronic insomnia, melatonin has a statistically significant but relatively smalleffect on sleep latency, with a mean reduction of 9min relativeto placebo [22]. the British Association for Psychopharmacology consensus statement recommends prolonged-release melatonin as a first-line option for older patients when a hypnotic is indicated [23]. But, before giving a melatonin, first-line therapy for insomnia, cognitive behavioural therapy should be recommended like eduction on sleeping hygiene [25].

Circadian rhythm disturbances such as Delayed Sleep Phase Syndrome (DSPS) or Advanced Sleep Phase Syndrome (ASPS) are said to be related to the pacemaker in the heart. DSPS is a disorder in which there are sleep onset insomnia and difficulty waking up. Meanwhile, ASPS is a disorder in which there are early or rapid onset of sleep and early awakening. In DSPS, endogenous melatonin rhythms are slower than normal. Melatonin therapy for these conditions is said to be able to improve sleep onset and wake time compared to placebo controls and can improve the patient's cognitive function.

Melatonin serves as a time cue (signal of darkness) to various organs including the SCN itself and in the absence of light, may entrain the sleep-wake and neuroendocrine rythms to the 24h cycle [17]. Activation of melatonin receptors in the Suprachiasmatic Nucleus (SCN) plays an important role in regulating circadian rhythms. Phase shifting of the circadian rhythm by melatonin is mediated by MT1 receptor activation. Thus, therapy using melatonin receptor agonists can be used to treat primary insomnia and circadian rhythm disorders. Some of the widely available melatonin receptor agonists are ramelteon and tasimelteon.

Ramelteon is a melatonin receptor agonist that has a high affinity for MT1 and MT2. It is said ramelteon can help patients fall asleep without causing impairment of memory, learning, or motor function. In subjects with chronic primary insomnia, ramelteon can be used to decrease sleep onset latency and increase total sleep time without causing side effects the next day. Repeated use of ramelteon before going to bed is said to improve circadian rhythms through the activation of the MT1 receptor. Kuriyama et al, found in 13 studies involving 5812 subjects concluded that ramelteon was associated with improvement in TST (total sleep time) and sleep efficiency [15].

Tasimelteon is also used to treat insomnia, especially in non-24-hour sleep-wake disorder (N24HSWD) which usually occurs in people with blindness. Tasimelteon is said to have a high but non-selective affinity for MT1 and MT2 receptors and no affinity for other G protein receptors. In phase III clinical trials, it is said that tasimelteon can have a better effect compared to placebo in 5 hours of wake and sleep cycles. In addition, tasimelteon usage could significantly replace the endogenous melatonin rhythms, reduce sleep onset latency, and improve sleep efficiency without causing side effects.

Currently, melatonin agonists are being developed which are more selective for MT1 or MT2 receptors. UCM765 is a selective preparation for MT2 which can reduce sleep latency and increase the amount of Non-Rapid Eye Movement (NREM) sleep. IIK7 is also a selective MT2 receptor agonist that can improve sleep onset latency and NREM count. Thus, it is said that MT2 receptors agonist could improve sleep structure. In an experiment on rats, it was found that MT2 is responsible for NREM, whereas MT1 is for REM [9].

In addition to melatonin receptor agonists, there are also exogenous melatonin preparations. Circadin is a prolonged-release melatonin that mimics endogenous melatonin secretion. It is said that circadin can improve sleep quality and sleep onset latency in elderly insomnia patients. Circadin may also improve sleep quality in adults with non-24-hour sleep-wake disorder (N24HSWD). The use of circadin has not been associated with memory impairment and has no withdrawal symptoms.

Conclusion

The number of people with old age in Indonesia is moderately high. Older people have various comorbidities, one of which is sleep disturbance or insomnia. Insomnia can be triggered by various factors, both internal and external. Possible complications caused by insomnia can also vary, including depression and increased cardiovascular risk. Therefore, insomnia is a problem that needs proper attention when treating elderly patients. A variety of diagnostic methods can be used to diagnose insomnia in the elderly. The main recommended therapy is Cognitive Behavior Therapy (CBT). However, various pharmacological agents can also be administered if CBT therapy is ineffective or unavailable, including melatonin and melatonin receptor agonists. These therapies can improve sleep quality, reduce sleep onset latency, and increase the amount of total sleep time. Melatonin and melatonin receptor agonists can be taken without a doctor's prescription. However, melatonin usage is better to be monitored by a doctor to ensure the insomnia has been completely resolved. Thus, the use of melatonin and melatonin receptor agonists can be an alternative therapy in elderly insomnia cases in Indonesia.

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