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Efficacy and Safety of Melatonin Supplementation in Children with Autism Spectrum Disorder

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ABSTRACT

Sleep disturbance is a common symptom found in children with Autism Spectrum Disorder (ASD). Sleep disturbances contribute to decreased quality of life. In addition to pharmacological treatment, non-pharmacological options could also help sleep disturbances management in pediatric patients with ASD. Melatonin is a hormone secreted by the pineal gland and contributes to the sleep-wake cycle. The effects of melatonin supplementation on sleep disturbances have been extensively reported, but its role in children with ASD is not well known. The purpose of this study was to examine the effectiveness and safety of melatonin in the management of children with autism spectrum disorder. This systematic review research includes journals from the Google Scholar, Sciencedirect, and PubMed databases according to PRISMA which include the following requirements: last 5 years, abstract available, English language, and the research method is controlled trial. The search terms used were "Melatonin" AND "Children" AND "Autism Spectrum Disorder" AND "Sleep Disturbance". From 319 articles found, 6 journals related to melatonin were selected for further review. Melatonin supplementation is associated with reduction in symptoms of sleep disturbances in pediatric patients with ASD. Melatonin supplementation tends to be safe, where the most common symptom is temporary somnolence.

1. INTRODUCTION

Autism spectrum disorder covers a spectrum of disorder in neurodevelopment. This spectrum has characteristics in the form of behavior, interests, repetitive activities and disturbances in social interaction. ASD is a complex neurodevelopmental disorder that is often found in children. Children will experience distress when faced with the environment because of minimal adaptability. Symptoms usually appear in early childhood and affect daily functioning [26]. The prevalence of ASD is increasing every year. This can be caused by increased awareness, overdiagnosis or overinclusive diagnostic criteria. The prevalence of ASD is reported to be 1 in 68 children [2]. ASD is 3 times more common in boys than girls, and the onset begins when the child is 3 years old. ASD tends to run in families, however, the exact cause is still unknown.

Exposure to teratogens during pregnancy is thought to contribute the development of ASD, particularly in early gestation. Consumption of drugs during pregnancy such as valproic acid and beta-2-adrenergic receptor agonists are also believed to increase the risk of developing ASD [1].

Approximately 70% of children with ASD met criteria for at least one other mental illness comorbid when reviewed by structured diagnostic interviews. These comorbidities tend to persist from childhood to adolescence [22]. Patients with ASD have an increased risk for developing a common mental disorder than individuals without ASD [6]. In addition, children with ASD have a higher burden of psychiatric comorbidity than children with intellectual disabilities [18]. Study by [7] reported that comorbid psychiatric illness in ASD increases difficulty in adaptive responses and affects daily activities, decreased quality of life, social isolation, irritability and self-injury behavior.

Sleep disturbances are one of the most common mental health problems in which 40-80% of pediatric patients with ASD experience insomnia. Insomnia in children is defined as sleep onset delay (sleep latency) of more than 30 minutes per night on average, and/or frequent prolonged night waking with impaired daytime functioning. Prolonged night waking is defined as ratio of total sleep time in the episode potentially filled by sleep (time asleep/[total time in bed – time to fall asleep]) Children are said to have good sleep efficiency if > 85%. Insomnia in children with ASD is one of the main complaints reported by parents. Insomnia in children with ASD not only causes impaired function in the child itself, but can also disturb those around them. Insomnia in children could initiate over activity, disruptive behaviour, communication difficulties, repetitive behaviours and social skill deficits [21], [11].

Pathophysiology explaining the intrinsic etiology of insomnia in children with ASD include (1) brain wave organizational and maturational differences, (2) circadian-relevant genes, (3) abnormal melatonin production, and (4) arousal and sensory dysregulation. Meanwhile, external factors include: (1) environmental stresses such as changes in evening routine and sensory stimuli, (2) psychological stressors such as a difficult day at school, or (3) physiological stressors such as being sick may push a child with ASD across the threshold into insomnia [21], [16].

Improving sleep outcomes is a priority, especially for children with ASD and their caregivers. The National Institute for Health and Care Excellence recommends behavioral interventions as first-line therapy for insomnia in ASD. Pharmacological therapy is only considered if sleep problems persist despite non-pharmacological treatment. In addition, it is important to involve parents for optimal treatment outcomes [11], [20]. One treatment which its use is increasingly is melatonin. Melatonin is produced primarily in the pineal gland and released into the bloodstream, especially at night following a circadian rhythm. Melatonin is tolerated well and has a lower risk of dependence than other sleep aids. Melatonin supplementation according to several studies is safe and effective for improving sleep onset latency, duration and sleep quality for children, adolescents and adults [25].

Formulation of the problem

How is the efficacy and safety of melatonin supplementation in children with autism spectrum disorder?

PICO

P : ASD children with insomnia
I : Melatonin supplementation
C : Placebo
O : Efficacy and Safety

2. Methods

2.1 Literature Searching Strategy

A literature search was done on the Google Scholar, Springerlink, and PubMed databases on February 10, 2021. The literature search used the keywords “melatonin”, “sleep disorder”, “autism spectrum disorder” and other related keywords. (Table 1). The results of the literature search can be seen in Figure 1.

2.2 Literature Criteria

This systematic review is carried out by limiting English or Indonesian journals and published in the last 5 years. The research method used was a randomized controlled trial with a placebo comparison. The initial search took up 319 literature. After setting the inclusion and exclusion criteria and reading the literature completely, 6 literatures were obtained.

Table 1. Search strategy in PubMed, Google Scholar and Sciencedirect conducted on 10 February 2021.

Source	Keyword	Relevant literature
Google Scholar	(((sleep disorder) AND (autism spectrum disorder)) AND (melatonin)) AND (children)) AND (randomized controlled trial))	16
PubMed	(((sleep disorder) AND (autism spectrum disorder)) AND (melatonin)) AND (children)) AND (randomized controlled trial))	128
Sciencedirect	(((sleep disorder) AND (autism spectrum disorder)) AND (melatonin)) AND (children)) AND (randomized controlled trial))	175

This systematic review includes studies by [19], [10], [15], [8], [14], [27].

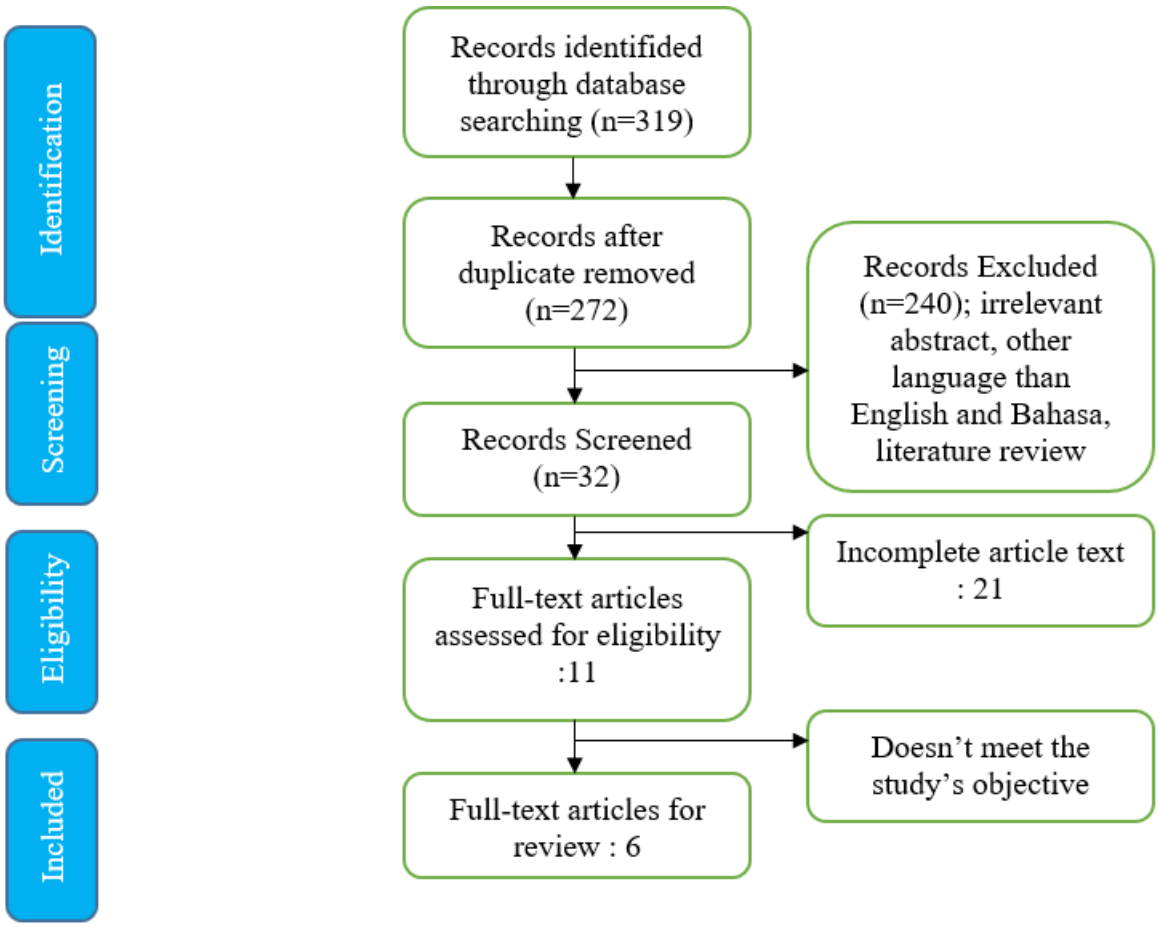

Figure 1. Literature Search Flow

3. Results

The study by [19] with a randomized placebo controlled double-blind design included 125 subjects aged 2-17.5 years with autism spectrum disorder and insomnia. This study aims to assess the efficacy and safety of prolonged release melatonin tablets. The result of this study was that prolonged release of melatonin mini tablets resulted in improvements in patient behavior and caregiver quality of life when compared to placebo. In addition, subjects who were given a placebo had an average additional sleep time of 57.5 minutes longer than the placebo, which was only 9.14 minutes. Sleep latency decreased by 39.6 min on average with prolonged release melatonin tablets compared to 12.5 min with placebo. In this study, the administration of prolonged release melatonin tablets was said to be safe because the only side effect that occurred was somnolence which occurred only in a small proportion of patients [15].

Study by [10] with a randomized placebo-controlled trial design included 196 subjects. This study divided into 3 groups, the group given melatonin 1 mg (n=65), the group given melatonin 4 mg (n=65), and the group given placebo (n=66). The primary outcomes of this study included sleep onset latency (SOL) reviewed with an electronic sleep diary. The result of this study is that the SOL tends to be shorter in the melatonin-treated group than in the placebo group [27].

Study by [15] with a double-blind randomized controlled trial design included 95 subjects (51 were given prolonged release melatonin, 44 were given placebo). Subjects given prolonged release melatonin slept (mean [SE]) 62.08 (21.5) minutes longer ($p = 0.007$); fell asleep 48.6 (10.2) minutes faster ($p < 0.001$); had 89.1 (25.5) minutes longer uninterrupted sleep episodes ($p = 0.001$); 0.41 (0.12) less nightly awakenings (>50%

decrease; p = 0.001); and better sleep quality (p < 0.001) compared with baseline. Prolonged release melatonin was generally safe; most frequent treatment-related adverse events were fatigue (5.3%) and mood swings (3.2% of patients) [19].

Study by [8] with a double blind placebo randomized controlled trial design included 125 subjects. The group of patients given prolonged release melatonin slept on average 57.5 minutes longer at night compared to 9.14 with placebo. Sleep latency (SL) decreased by 39.6 minutes on average with prolonged release melatonin and 12.5 with placebo (p=.011) without causing earlier wakeup time. Prolonged release melatonin was generally safe; somnolence was more commonly reported than placebo.

Study by [14] with a double-blind placebo controlled study design included 80 children and adolescents who were given melatonin at doses of 2 mg, 5 mg, 10 mg and placebo. The results of this study that there were improvements in child sleep disturbance and caregiver satisfaction with child sleep patterns, quality of sleep, and quality of life were maintained throughout the 104-week treatment period (p < .001 versus baseline for all). Prolonged release melatonin was generally safe; the most frequent treatment-related adverse events were fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%).

A study conducted by [27] that included 99 given prolonged release melatonin showed improvement. SOL (Sleep onset latency) recorded with the electronic sleep diary shortened significantly. Temper upon wakening and sleepiness after awakening improved significantly ($P <$ 0.0001 each) from baseline. The following subscales of the ABC-J improved significantly: stereotypic behavior ($P = 0.0322$) in the medication phase I; and irritability, hyperactivity, and inappropriate speech ($P <$ 0.0001) in the medication phase II. Treatment-emergent adverse events did not occur subsequent to week 16 after medication onset.

4. Discussion

ASD can comorbid with other diseases such as genetic disease (fragile X syndrome) and other neuropsychiatric disorders such as intellectual disability, attention-deficit/hyperactivity disorder (ADHD), anxiety disorders and mood disorders and with impairing symptoms such as high level of irritability [13]. Sleep disturbance is one of the symptoms that are often found in pediatric patients with ASD. Prompt diagnosis and treatment of ASD-related sleep disorders can help manage symptoms such as inattention and irritability [4]. Sleep disturbances in ASD can occur as a result of the interaction of several factors such as biological, psychological, medical, social and environmental. Irregular melatonin levels and secretion patterns as well as abnormalities in clock-related genes are believed to be intrinsic factors that cause sleep disturbances in ASD. Sleep disturbances in ASD can cause secondary behavioral disorders such as hyperactivity, mood disorders, irritability and worsening of autism symptoms [9], [23]. In addition to having an impact on children, sleep problems can also have an impact on the health and well-being of caregivers. Studies have reported that sleep disturbances can affect caregivers' daily life and cause several comorbidities [12].

Treatment approaches for sleep disorders vary. For insomnia, treatment includes behavioral interventions, lifestyle modifications, and pharmacological treatments [17]. [5] suggest that there are 5 main treatments in the management of sleep disorders in pediatric patients with ASD including pharmacological treatment, melatonin supplementation, psychological and behavioral treatment, parent education and training; and complementary and alternative therapies.

Melatonin can safely and effectively treat primary sleep disorders and sleep disorders associated with various neurological conditions [17]. Of the six studies that we reviewed, all of them showed good efficacy in

improving the outcome of sleep disturbances in pediatric patients with ASD. Parameters assessed in efficacy in some of these studies include longer sleep duration and sleep latency or the time it takes a person to start falling asleep and overall sleep disturbance. Sleep latency is measured by electronic records. In the study of [10], [15], [8], it was found that sleep latency decreased by 22 minutes to 48.6 minutes (Figure 2). Only the study by [15] and Schroder attached the variable sleep duration to their study. There was an increase in sleep duration of 57.5 minutes and 62 minutes longer in the group given melatonin compared to placebo. This is because ASD is reported to have decreased levels of melatonin. Melatonin is synthesized in the pineal gland and is received in the suprachiasmatic nucleus, the master clock in the brain, by receptors MTNR1A and MTNR1B which are involved with multiple functions including sleep induction, circadian and seasonal rhythm regulation, and immune function. It is hypothesized that low melatonin levels and sleep onset delay in children with ASD may be related to mutations in melatonin synthesis pathway genes or changes to regulatory regions of melatonin receptor sites [21], [24]. Similarly, the study by [14] also reported improvements in sleep disturbances as measured by the CSDI (Composite Sleep Disturbance Index) which scores the frequency and duration of the participant's sleep habits over the previous month. This study found a significant improvement over placebo. Changes in CSDI are related to total sleeping time (TST) [14]. Research by [10], [15], [8], [14] recommends a dose of melatonin for children of 2 mg which can be increased gradually to 10 mg once at night. Dosage increases can be done if for 3 weeks there is no significant clinical improvement.

Research by [19], [27] reported an improvement in the behavior of ASD patients after melatonin administration. [19] reported that melatonin treatment mainly improved externalizing behaviors (hyperactivity-inattention and conduct) in children and adolescents with ASD or NGD compared to placebo. Furthermore, when taking into account only those children and adolescents displaying abnormal hyperactivity/inattention scores at baseline, the total SDQ (Strengths and Difficulties questionnaire) improved significantly in the melatonin group compared to placebo. In the subpopulation with abnormal conduct scores, conduct improved significantly in the melatonin-treated group compared to placebo. Likewise with the research conducted by [27] where temper upon wakening improved significantly. In addition, the group given melatonin showed improvements in hyperactivity, inappropriate speech and stereotypic behavior compared to placebo. This is explained by [24] where disturbances in melatonin secretion and rhythm not only have implications for sleep disorders but also other symptoms. (Figure 3).

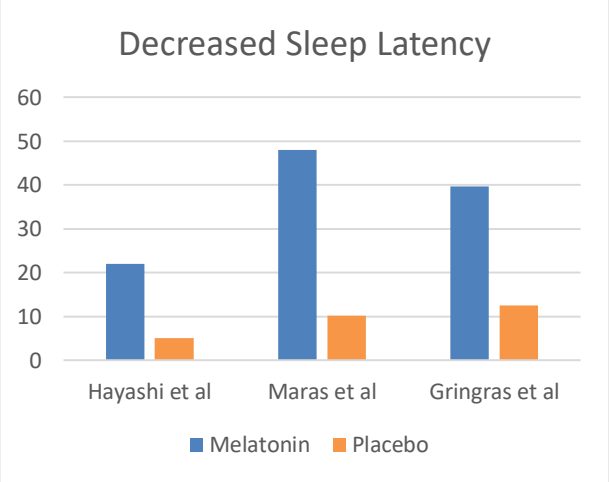

Figure 2. Decreased sleep latency according to research

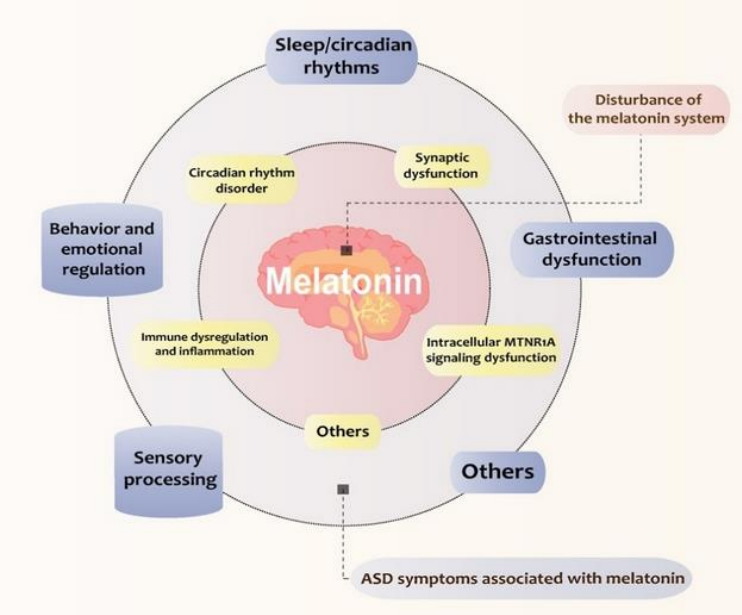

Figure 3. Disturbance of the melatonin system and its implication

To assess safety, we looked at the side effects that occurred after giving melatonin supplements. In a study conducted by [27], it was found that there were no side effects at all in the group given melatonin supplementation. Meanwhile, according to [14], [8], [10], the most common side effect found was somnolence ranging from 4.5%-6.3%. Other side effects reported include mood changes (4.2%-6%) and fatigue (4%-6.3%). However, no severe side effects were reported in all studies.

There are several advantages in giving melatonin supplementation in treating sleep disorders in children with ASD including easy to digest, cheap and easy to obtain. In contrast to the usual difficulties with tablet formulations experienced by children with ASD, compliance was excellent without the need to crush or dissolve melatonin supplementation. In addition, melatonin also does not cause symptoms of intoxication or withdrawal like benzodiazepines [3].

5. Summary

Melatonin supplementation is associated with reduction in symptoms of sleep disturbances in pediatric patients with ASD. Efficacy was demonstrated in terms of increased total sleep time, reduced SL, and improved longest continuous sleep period. Melatonin supplementation tends to be safe, where the most common symptom is temporary somnolence.

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