



Efficacy of Melatonin for Insomnia in Children with Autism Spectrum Disorder: A Meta-analysis

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Abstract

Aim This study aimed to evaluate the effectiveness of melatonin in treating insomnia in children with autism spectrum disorder (ASD).

Methods Comprehensive searches were conducted in the PubMed, EMBASE, and Web of Science databases from their inception to April 20, 2022. Data were extracted and assessed for quality by two researchers. Statistical analysis was performed using the Stata 15.0 software.

Results Four studies including 238 patients were included. The results showed that compared with the control group, melatonin could shorten the sleep-onset latency (standardized mean difference [SMD] = -1.34, 95% CI: -2.19 to -0.48), reduce the number of awakenings (SMD = -2.35, 95% CI: -4.62 to -0.08), and prolong the total sleep time (SMD = 1.42, 95% CI: 0.5–2.33) in children with ASD.

Conclusion Melatonin has a certain effect on relieving sleep disturbances in children with ASD, which can shorten sleep latency, reduce the number of awakenings, and prolong total sleep time. Larger studies are required to verify this hypothesis.

Keywords

- ▶ autism spectrum disorder
- ▶ melatonin
- ▶ children
- ▶ meta-analysis

Introduction

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder with a prevalence of approximately 1.7% in the general population.¹ ASD is mainly manifested as a

language disorder, social disorder, and stereotyped interest orientation and belongs to a subtype of pervasive developmental disorder.² Studies have shown that children with ASD are more likely to have sleep problems than children without

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ASD (11–37%), with a prevalence ranging from 50 to 80%.^{3–5} Sleep disturbance is often described as onset of insomnia or difficulty initiating and maintaining sleep.⁶ The severity and frequency of insomnia are associated with higher levels of maternal stress, negative attitudes toward children, and increased rates of behavioral problems and autism symptoms in children.⁷ Therefore, effective interventions are required for the treatment of insomnia.

Melatonin, also known as the pineal hormone, is an indole hormone secreted by the pineal gland and plays an important role in regulating the circadian rhythm of the body.⁸ Evidence suggests that sleep disturbances in children with ASD are associated with a disturbed melatonin secretion.^{9,10} As a result, some studies have recommended the use of melatonin to treat sleep problems in children with neurodevelopmental disorders. However, due to the results of different studies, conclusions regarding the efficacy of melatonin are varied. Therefore, this study explored the efficacy of melatonin in the treatment of insomnia in children with ASD through a meta-analysis to provide a clinical reference.

Methods

The Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines were used to conduct the meta-analysis (► **Supplementary Table S1**, available in the online version only).

Literature Search Strategy

A systematic literature search was conducted using PubMed, Embase, and Web of Science databases. The search strategies were as follows: “autism spectrum disorder,” “ASD,” “Autistic Disorder,” “melatonin,” “Rozerem,” etc. The retrieval time is April 20, 2022, and the language limit is English. In addition, this study also conducted a manual search of the paper version of the literature and screened the relevant reviews and references of the included literature, hoping to obtain more studies that can be used for meta-analysis. The detailed search strategy is described in **Supplementary Material 1** (available in the online version only).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1. The study was a randomized controlled study; 2. the subjects were children diagnosed with ASD; 3. melatonin was used in the experimental group and placebo in the control group for the intervention; and 4. at least with one reported outcome (total sleep time, sleep onset latency, and number of awakenings).

The exclusion criteria were as follows: (1) non-authoritative studies such as reviews, conference abstracts, and reviews; (2) studies that did not use melatonin; and (3) repeated publications or the same data used in multiple articles, only included studies with the most complete information, and the rest were excluded.

Study Selection and Data Extraction

Two investigators (X.M. and L.F.) independently screened the literature according to the inclusion and exclusion criteria.

After identifying the literature included in the analysis, data extraction was performed independently according to a pre-designed table. The extracted information included the first author, year of publication, basic characteristics of the research participants (sample size, age, etc.), intervention measures, intervention time, and study outcomes. After both have completed the above data extraction work, they exchange and review the extraction forms.

The quality of the literature was assessed using Cochrane quality assessment criteria. Judgments were made independently by two investigators, and if disagreements occurred, a consensus was reached through discussion.

Statistical Analysis

Statistical analysis was performed using the Stata 15.0 software. A generic inverse variance method was used to calculate the estimated pooled standardized mean differences (SMD) with 95% confidence interval (CI) for the outcomes. I^2 statistic was used to assess the heterogeneity of the included RCTs. If $I^2 < 50\%$, data were analyzed using a fixed-effects model; otherwise, data were analyzed using a random-effects model. Publication bias was quantitatively assessed using Egger's test.

Results

A flow chart of literature screening is shown in ► **Fig. 1**. A total of 988 articles were searched in the PubMed, Embase, and Web of Science databases. After excluding duplicate studies, a total of 626 articles remained. After browsing titles and abstracts, 613 papers that did not meet the inclusion criteria were excluded. Nine of the remaining 13 papers were removed after reading the full text. Finally, four studies were included in the meta-analysis.^{11–14} The results of the quality evaluation of the included studies are shown in ► **Fig. 2**.

Overall, the studies involved 238 children aged 2 to 17.5 years. Children receive melatonin at doses between 1 and 10 mg. Treatment duration is 4 to 13 weeks. ► **Table 1** provides an overview of the baseline data, treatment drugs, and outcome indicators reported in the literature.

Sleep Onset Latency

Four studies reported the effects of melatonin on sleep onset latency in children with ASD. There was significant heterogeneity among the studies ($p < 0.001$, $I^2 = 83.3\%$); therefore, a random-effects model was selected. The results of the meta-analysis showed that the experimental group had a better effect on shortening the sleep onset latency of children with ASD than the control group, and the difference was statistically significant (SMD = -1.34 , 95% CI: -2.19 to -0.48 , ► **Fig. 3**).

Number of Awakenings

Data on the effect of melatonin on the number of awakenings in children with ASD were extracted from three studies. There was significant heterogeneity between the studies ($p < 0.001$, $I^2 = 94.5\%$); therefore, a random-effects model was selected. The results showed that the experimental group had a better effect in reducing the number of awakenings in children with ASD than the control group,

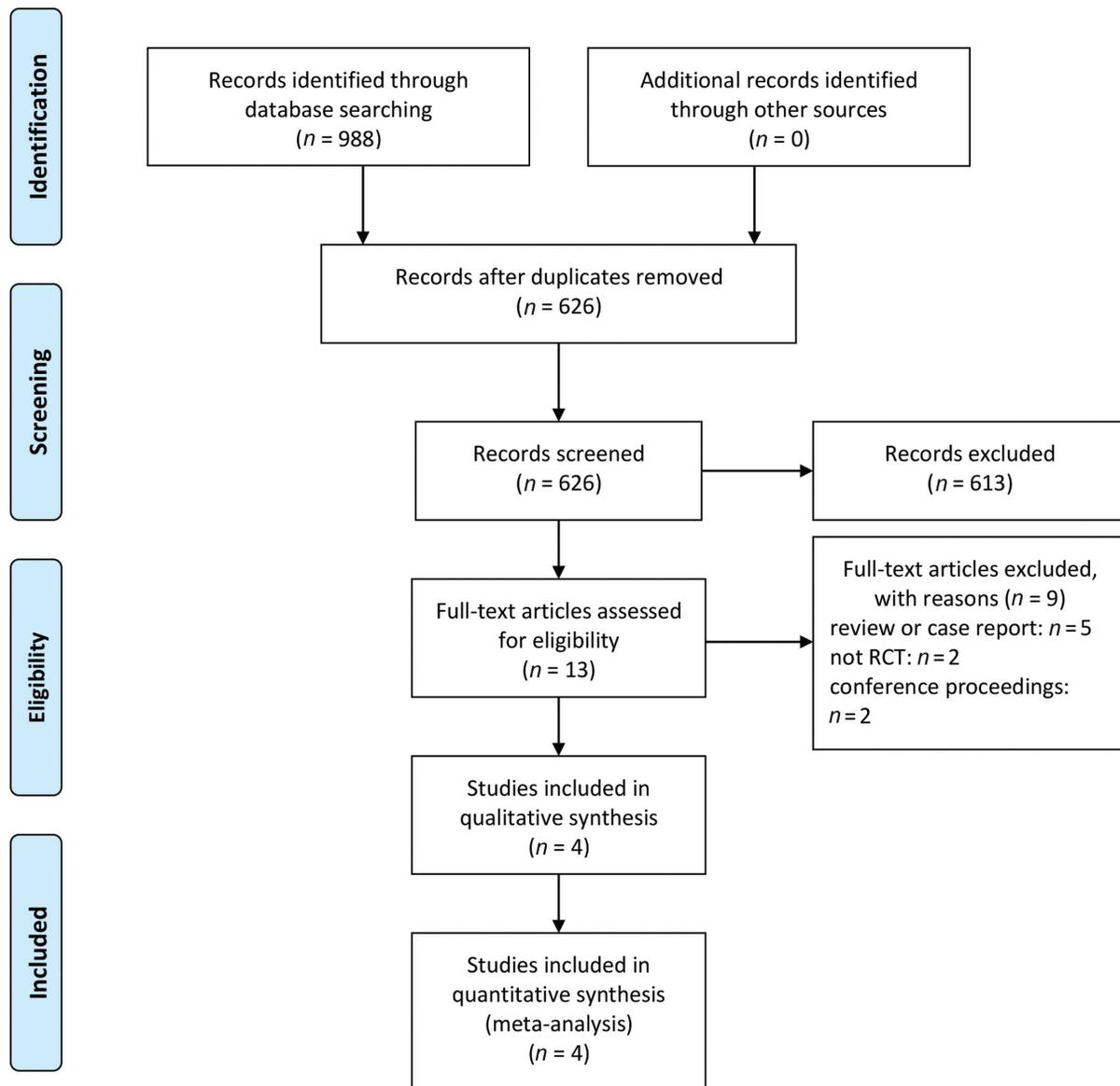


Fig. 1 Flow diagram of the systematic review selection process.

and the difference was statistically significant (SMD = -2.35 , 95% CI: -4.62 to -0.08 , ► **Fig. 4**).

Total Sleep Time

Four studies reported data on melatonin for the total sleep time in children with ASD. A random-effects model was selected because of the significant heterogeneity between studies ($p < 0.001$, $I^2 = 85.7\%$). The results showed that, compared with the control group, ASD children in the experimental group had longer total sleep time, and the difference was statistically significant (SMD = 1.42 , 95% CI: 0.5 – 2.33 , ► **Fig. 5**).

Publication Bias and Sensitivity Analysis

Egger's test showed that the p -values for each outcome measure were greater than 0.05 , suggesting that there was no significant publication bias among the included studies (► **Supplementary Fig. S1**, available in the online version

only). In addition, sensitivity analysis showed that the pooled results were stable (► **Supplementary Fig. S2**, available in the online version only).

Discussion

The study found that children with ASD had a higher prevalence of insomnia than normally developing children, ranging from 40 to 86%.^{15–18} For children with ASD, insomnia not only exacerbates some core symptoms but may also affect the effectiveness of rehabilitation training. For example, Ming found that insomnia in children with ASD was significantly associated with mood disturbances and gastrointestinal abnormalities.¹⁹ Some studies have also found an association between sleep problems and developmental regression in ASD.²⁰ Therefore, addressing insomnia in children with ASD and improving their sleep quality have become the most important issues in clinical interventions

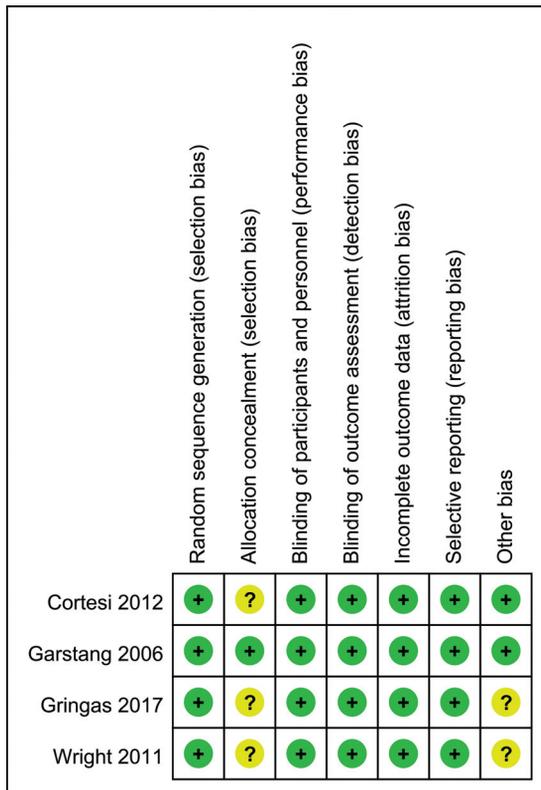


Fig. 2 Risk of bias (RoB) summary: review authors’ judgments about each RoB item for each included study.

for children with ASD. Melatonin is commonly used for insomnia in children, has favorable side effects, is cost-efficient and readily available, and is often effective for sleep disturbances.²¹ This meta-analysis systematically evaluated the efficacy of melatonin in the treatment of insomnia in children with ASD. This study found that melatonin significantly shortened sleep onset latency, reduced the number of awakenings, and prolonged the total sleep time in children with ASD.

There is growing evidence that sleep disturbances in children and adolescents with ASD are associated with

arousal dysregulation and sensory hyper-responsiveness and require a sedation strategy to improve their sleep.¹ Furthermore, insomnia in children with ASD is thought to be associated with abnormal melatonin levels.²² Melatonin is a hormone mainly secreted by the pineal gland, and its endogenous circadian rhythm is influenced by light/dark conditions.²³ Extensive research has shown that melatonin not only plays a key role in regulating the sleep/wake cycle but also has potent antioxidant and anti-inflammatory properties and is involved in immune responses and neuro-protection.^{24,25} This study confirmed the role of melatonin in the regulation of the sleep/wake cycle. In this study, we found that melatonin was effective in relieving insomnia in children with ASD, shortened sleep onset latency, reduced the number of nighttime awakenings, and prolonged the total sleep time.

There is no consensus on the optimal dose of melatonin for promoting sleep in children. Malow et al reported that 1 to 3 mg of melatonin supplementation was well tolerated and improved sleep delay in most children with ASD.²⁶ The doses of melatonin in the included studies ranged from 2 to 10 mg. In this study, melatonin doses ranging from 2 to 10 mg were included, and the results showed that at this dose range, melatonin improved sleep, children had more regular and appropriate bedtimes, children sleep for a longer period of time, and the number of nighttime awakenings was significantly reduced. Due to the small number of included studies, subgroup analysis based on dose differences could not be performed. Therefore, large-scale clinical trials are required to verify these findings.

This study had some limitations. First, the included studies were few, and the source of heterogeneity could not be explored through quantitative methods, such as subgroup analysis and meta-regression. Second, the intervention measures used were inconsistent. Although the experimental groups in the included studies all used melatonin for intervention, the dose of melatonin was not strictly limited; therefore, there were certain differences in the intervention measures. Finally, although significant results were obtained, the small number of included studies may have reduced the accuracy of

Table 1 Basic information included in the study

Study	Sample size	Age (Year)	Interventions	Intervention time	Sleep diary or actigraph record	Outcomes
Garstang and Wallis 2006	11	4–16 y	5 mg melatonin	4 wk	Sleep diary	Total sleep time, sleep onset latency, number of awakenings
Wright et al 2011	22	3–16 y	2–10 mg melatonin	12 wk	Sleep diary	Total sleep time, sleep onset latency, number of awakenings
Cortesi et al 2012	80	4–10 y	1 mg fast-release and 2 mg controlled-release melatonin	12 wk	Both diary and actigraph	Total sleep time, sleep onset latency, number of awakenings
Gringras et al 2017	125	2–17.5 y	2 mg escalated to 5 mg prolonged-release melatonin	13 wk	Both diary and actigraph	Total sleep time and sleep onset latency

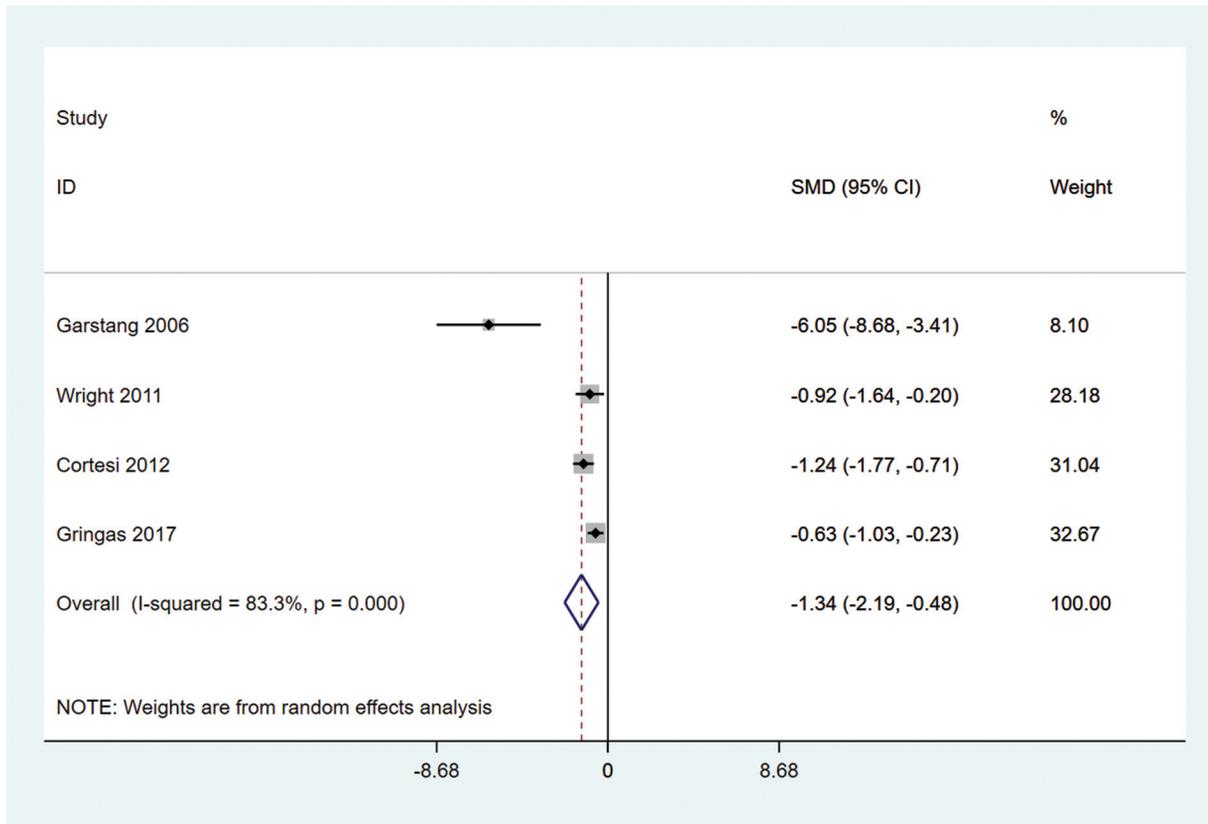


Fig. 3 Forest plot comparing efficacy of melatonin over control in sleep onset latency in children with ASD. ASD, autism spectrum disorder.

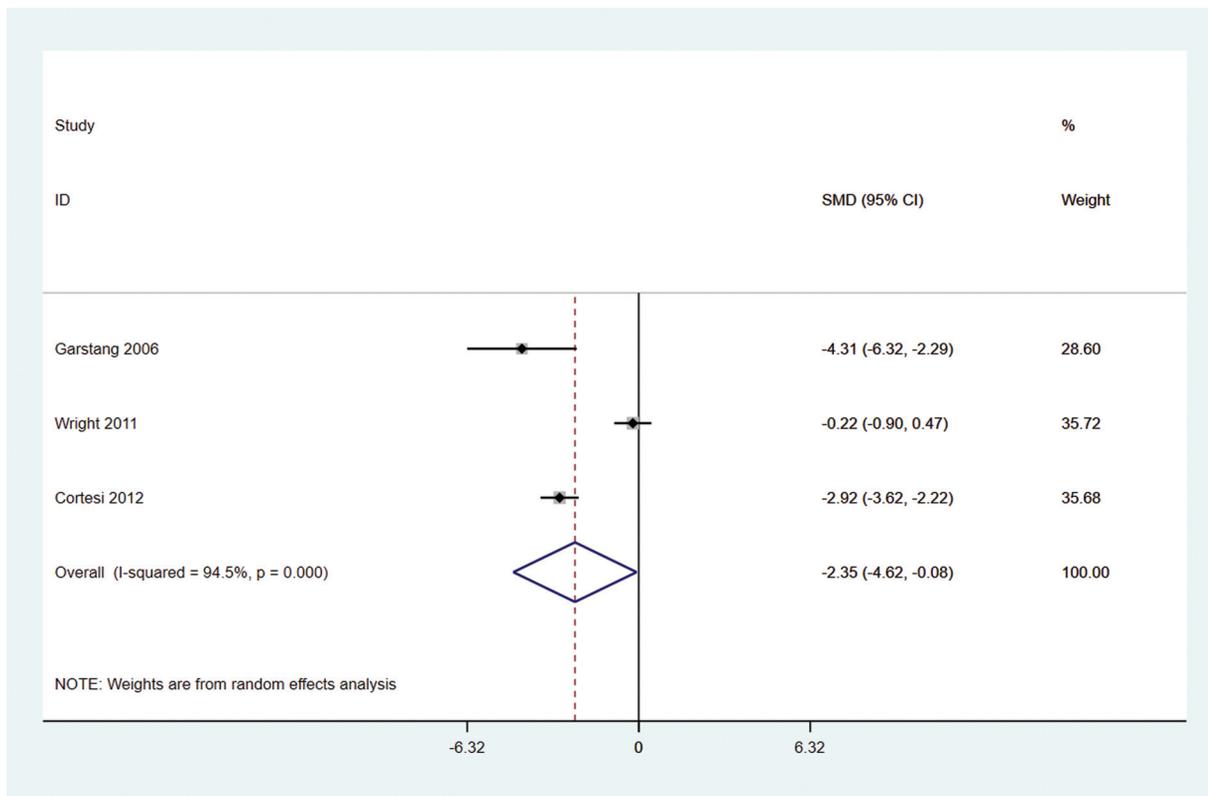


Fig. 4 Forest plot comparing efficacy of melatonin over control in number of awakenings in children with ASD. ASD, autism spectrum disorder.

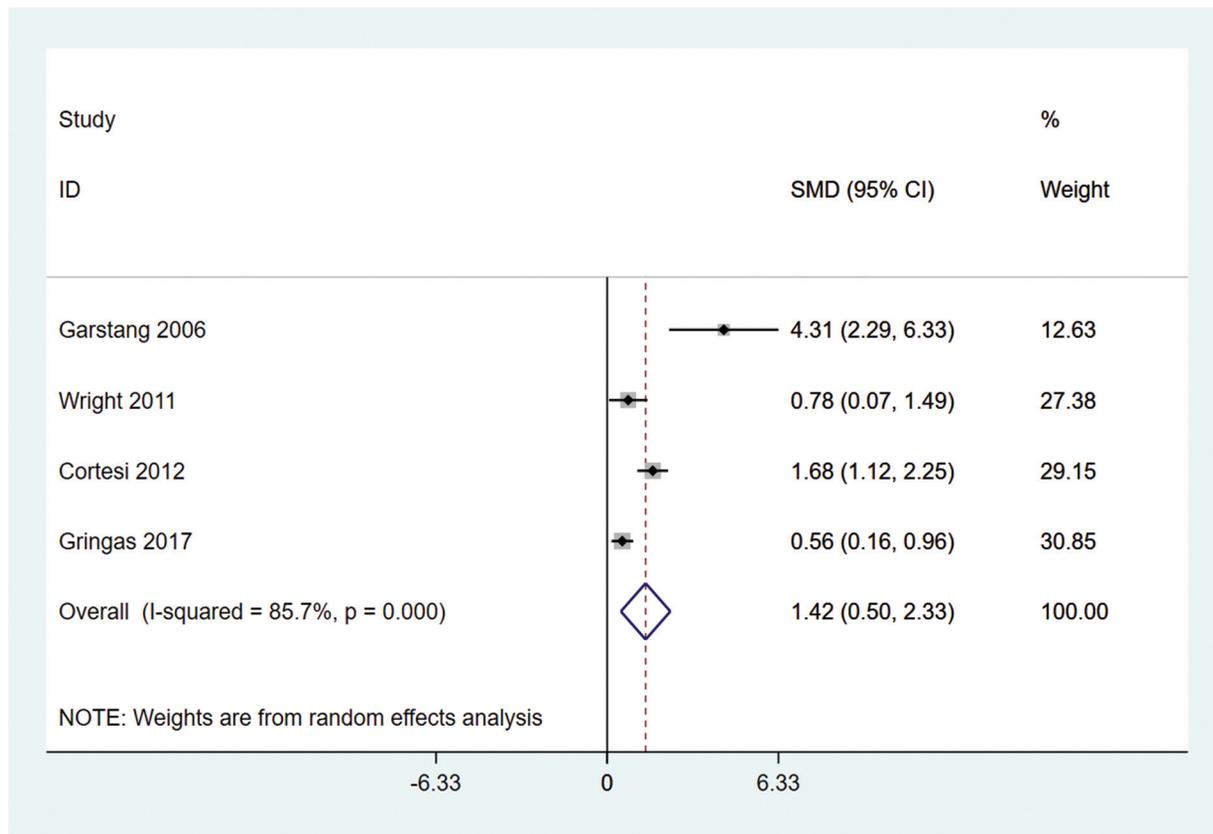


Fig. 5 Forest plot comparing efficacy of melatonin over control in total sleep time in children with ASD. ASD, autism spectrum disorder.

the results, requiring larger-sample studies to verify the results.

Conclusion

There is some evidence that melatonin is beneficial in the treatment of insomnia in children with ASD by reducing sleep onset latency, reducing the number of nighttime awakenings, and increasing total sleep time compared to controls. However, due to the limited number of studies included in this study, more and larger studies are needed to verify this.

Funding

None.

Conflict of Interest

None declared.

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