Research, Society and Development, v. 13, n. 4, e6213445540, 2024
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v13i4.45540

Melatonin versus placebo in the treatment of sleep disorders in children and adolescents with autism: Systematic review and meta-analysis

Melatonina versus placebo no tratamento de distúrbios do sono em crianças e adolescentes com autismo: Revisão sistemática com meta-análise

Melatonina versus placebo en el tratamiento de los trastornos del sueño en niños y adolescentes con autismo: Revisión sistemática y metanálisis

Received: 04/03/2024 | Revised: 04/12/2024 | Accepted: 04/13/2024 | Published: 04/16/2024

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Abstract
Objective: To systematically review the evidence on the use of melatonin in the treatment of sleep disorders in children and adolescents with autism spectrum disorder (ASD). Method: Systematic review of randomized controlled clinical trials on the use of melatonin and included children and adolescents with ASD and sleep disorders, searching MEDLINE, SCOPUS, Web of science, Cochrane Central Register Controlled Trials, in the period between September and October 2023. The selection of studies were carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Results: Changes in Total Sleep Time (TST) and Sleep Latency (SL) measurements were statistically significant. The 95% CI of 1.66 [1.10, 2.23] and 2.55 [1.02, 4.08] showed an increase in TST with the use of the intervention. ($p < 0.00001$) [18, 19]. Garstang showed a statistical difference with the use of melatonin, with the result of 95% CI of -5.96 [-8.77, -3.16], as well as Cortesi with a 95% CI of -1.23 [-1.75, -0.70] and Gringras with -1.35 [-1.79, -0.91], with reduced latency to start sleep ($p = 0.0002$). Conclusions: Larger samples are needed to evaluate the effectiveness of melatonin on other sleep patterns, such as nighttime awakenings and sleep quality.
Keywords: Insomnia; Children; Melatonin; Autism spectrum disorder; Clinical trial.

Resumo
Objetivo: Revisar sistematicamente as evidências sobre o uso da melatonina no tratamento de distúrbios do sono em crianças e adolescentes com transtorno do espectro do autismo (TEA). Método: Revisão sistemática de ensaios clínicos randomizados controlados sobre o uso de melatonina e incluídos crianças e adolescentes com TEA e distúrbios do sono, pesquisando MEDLINE, SCOPUS, Web of science, Cochrane Central Register Controlled Trials, no período entre setembro e outubro de 2023. O a seleção dos estudos foi realizada por meio do Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Resultados: As alterações nas medidas do Tempo Total de Sono (TTS) e da Latência do Sono (SL) foram estatisticamente significativas. O IC 95% de 1,66 [1,10; 2,23] e 2,55

[1,02; 4,08] mostrou aumento do PT com o uso da intervenção. (p < 0,00001) [18, 19]. Garstang apresentou diferença estatística com o uso de melatonina, com resultado de IC 95% de -5,96 [-8,77, -3,16], assim como Cortesi com IC 95% de -1,23 [-1,75, -0,70] e Gringras com -1,35 [-1,79, -0,91], com latência reduzida para iniciar o sono (p = 0,0002). Conclusões: São necessárias amostras maiores para avaliar a eficácia da melatonina em outros padrões de sono, como despertares noturnos e qualidade do sono.
Palavras-chave: Insônia; Crianças; Melatonina; Transtorno do espectro do autismo; Ensaios clínicos.

Resumen
Objetivo: Revisar sistemáticamente la evidencia sobre el uso de melatonina en el tratamiento de los trastornos del sueño en niños y adolescentes con trastorno del espectro autista (TEA). Método: Revisión sistemática de ensayos clínicos controlados aleatorios sobre el uso de melatonina e incluyeron niños y adolescentes con TEA y trastornos del sueño, buscando en MEDLINE, SCOPUS, Web of science, Cochrane Central Register Controlled Trials, en el período comprendido entre septiembre y octubre de 2023. La selección de estudios se llevó a cabo utilizando los elementos de informes preferidos para revisiones sistemáticas y metanálisis (PRISMA). Resultados: Los cambios en las mediciones del tiempo total de sueño (TST) y la latencia del sueño (SL) fueron estadísticamente significativos. El IC del 95% de 1,66 [1,10, 2,23] y 2,55 [1,02, 4,08] mostró un aumento en la TST con el uso de la intervención. (p <0,00001) [18, 19]. Garstang mostró diferencia estadística con el uso de melatonina, con el resultado de IC 95% de -5.96 [-8.77, -3.16], así como Cortesi con un IC 95% de -1.23 [-1.75, - 0.70] y Gringras con -1,35 [-1,79, -0,91], con latencia reducida para iniciar el sueño (p = 0,0002). Conclusiones: Se necesitan muestras más amplias para evaluar la eficacia de la melatonina sobre otros patrones de sueño, como los despertares nocturnos y la calidad del sueño.
Palabras clave: Insomnio; Niños; Melatonina; Desorden del espectro autista; Ensayo clínico.

1. Introduction

Autism spectrum disorder (ASD) refers to a series of conditions described by some degree of impairment in social behavior, communication, and language, and by a narrow range of interests and activities that are unique to the individual and undertaken in a repetitive way (OPAS/OMS, 2023). Children and adolescents with ASD experience sleep disturbances, particularly insomnia, at rates much higher than the general population (Johnson & Zarrinnegar, 2021). Parental surveys indicate a 50-80% prevalence of sleep problems in children with ASD, compared with a 9-50% prevalence rate in age-matched, typically developing subjects (Richdale & Schreck, 2009; Allik et al., 2006).

Patients with ASD may be unable to fall asleep until late at night, despite being motivated to do (i.e., delayed sleep-phase syndrome). Other patients with ASD may exhibit irregular sleep-wake rhythms, with a lack of any fixed sleep onset and offset time, and with multiple naps scattered through the day and night (Miano et al., 2007; Zaidan et al., 1994). There is increasing evidence that sleep disorders in children with ASD are associated with disrupted melatonin (MLT) secretion (Veatch et al., 2014; Melke et al., 2007; Tordjman et al., 2005). The repercussions of sleep disturbances on quality of life and family dynamics (including siblings), as well as professional life and parental stress levels, have been widely noted by several authors (Levin & Scher, 2016; Polimeni et al., 2007).

Therefore, the use of melatonin for treating chronic sleep–wake cycle disorders of children with ASD is increasing too (Malow et al., 2012). It brings good results with its use, mostly because the prolonged release formulation which releases melatonin throughout the night appears to be effective in improving both sleep onset and sleep maintenance whereas immediate release melatonin formulations are reportedly as effective in sleep induction but less so with sleep maintenance (Schroder et al., 2019; Andersen et al., 2008). This systematic review and meta-analysis aims to update the scientific basis regarding the use of melatonin in the treatment of sleep disorders in children and adolescents with ASD.

2. Methodology

2.1 Study design

This is a systematic review with meta-analysis, carried out in accordance with the criteria and recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA, in addition to the Cochrane

Manual for Systematic Reviews of Interventions - Cochrane Manual for Systematic Reviews of Interventions (Moher, D, Liberati, A, Tetzlaff, J, Altman, DG, 2009). The PICOT approach was used to formulate the research question. Where "P" is our studied population, "I" is the intervention evaluated, "C" is the comparison measure and "O" are the outcomes found. The question is: “How are updates about the effects of melatonin in the treatment of sleep disorders in children and adolescents diagnosed with autism spectrum disorder?”. The study protocol was submitted to the International Prospective Register of Ongoing Systematic Reviews – PROSPERO (https://www.crd.york.ac.uk/pospero/) at on September 30, 2023, whose ID number is 466887.

2.2 Identification and selection of studies

Searches were carried out in the following databases: MEDLINE, EMBASE, CINAHL, Web of Science, SCOPUS, Cochrane Central Register Controlled Trials. There were no language restrictions or publication data. The full texts, abstracts and titles of all articles were evaluated by two independent reviewers. In case of disagreement, the evaluation of a third reviewer was requested. The following descriptors were used: insomnia, children, melatonina, autism spectrum disorder, clinical trial.

2.3 Inclusion criteria

Only randomized controlled clinical trials were included. Studies should involve the following criteria: children and adolescents aged 2 to 18 years diagnosed with Autism Spectrum Disorder diagnosed through DSM-IV or DSM-V with non-respiratory sleep disorders.

2.4 Exclusion criteria

Trials with quasi-random allocation procedures were excluded, as were protocol registrations without publication of full texts, complete studies with missing results and no return from authors, trials involving other health conditions, interventions, outcomes or another design (bibliographical review; theses, dissertations and conference abstracts).

2.5 Types of outcomes

The primary outcomes were total sleep time, nighttime awakenings and sleep latency, while the secondary outcome corresponded to sleep quality.

2.6 Study selection and data extraction

The selection of studies was initially carried out by removing duplicates, then screening was carried out by reading eligible titles, later by reading the abstracts, and finally, by reading the complete articles, each step was carried out independently by two authors. Disagreements between authors were resolved by consensus. Data were extracted by two authors independently and entered into a data extraction form. The accuracy of data extraction was confirmed by a third author. The following data were extracted:

- Bibliometric data: authors, language and year of publication;
- Characteristics of included studies: study design, sample size, participant details, inclusion and exclusion criteria, experimental intervention characteristics, type of control used, frequency, duration of treatment interventions, duration of follow-up and primary outcomes, conflict of interest and sources of financing;
- Characteristics of the participants included: age, sex, diagnostics;
- Statistical data: mean, standard deviation (SD) and sample sizes for main results.

Information about interventions was extracted using the Template for Intervention Description and Replication – (TIDieR). The TIDieR is a 12-item checklist that was developed with the aim of improving the reporting of interventions (Hoffmann et al., 2014).

2.7 Bias risk assessment

The risk of bias of randomized controlled trials (RCTs) was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2.0) (Sterne et al., 2019), in which five domains were evaluated: Randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was assessed for risk of bias. Studies were graded as (1) "low risk of bias" when a low risk of bias was determined for all domains; (2) "some concerns" if at least one domain was assessed as raising some concerns but not at a high risk of bias for any single domain; or (3) "high risk of bias" when a high risk of bias was reached for at least one domain or the studied judgment included some concerns in multiple domains (Sterne et al., 2019).

2.8 Quality of evidence

The general quality of the evidence was classified according to the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach, according to the classification recommended in the GRADE guidelines. The GRADE approach establishes the quality of evidence as high, moderate, low and very low. Five domains that can reduce the quality of evidence are: risk of bias; inconsistency; indirect evidence; inaccuracy; publication bias. The quality of the evidence was then classified as: High-quality evidence: when there were consistent results in more than 75% of the included studies, with no known publication bias. Future research is unlikely to impact effect estimates; Moderate quality evidence: At least one of the domains was not met. Future research is likely to have an important impact on our confidence in the effect estimate. Low quality evidence: Two of the domains were not met. Future research is likely to have an important impact on our confidence in the effect estimate. Very low-quality evidence: Three of the domains were not met. There is significant uncertainty with the effect estimates.

2.9 Statistical analysis

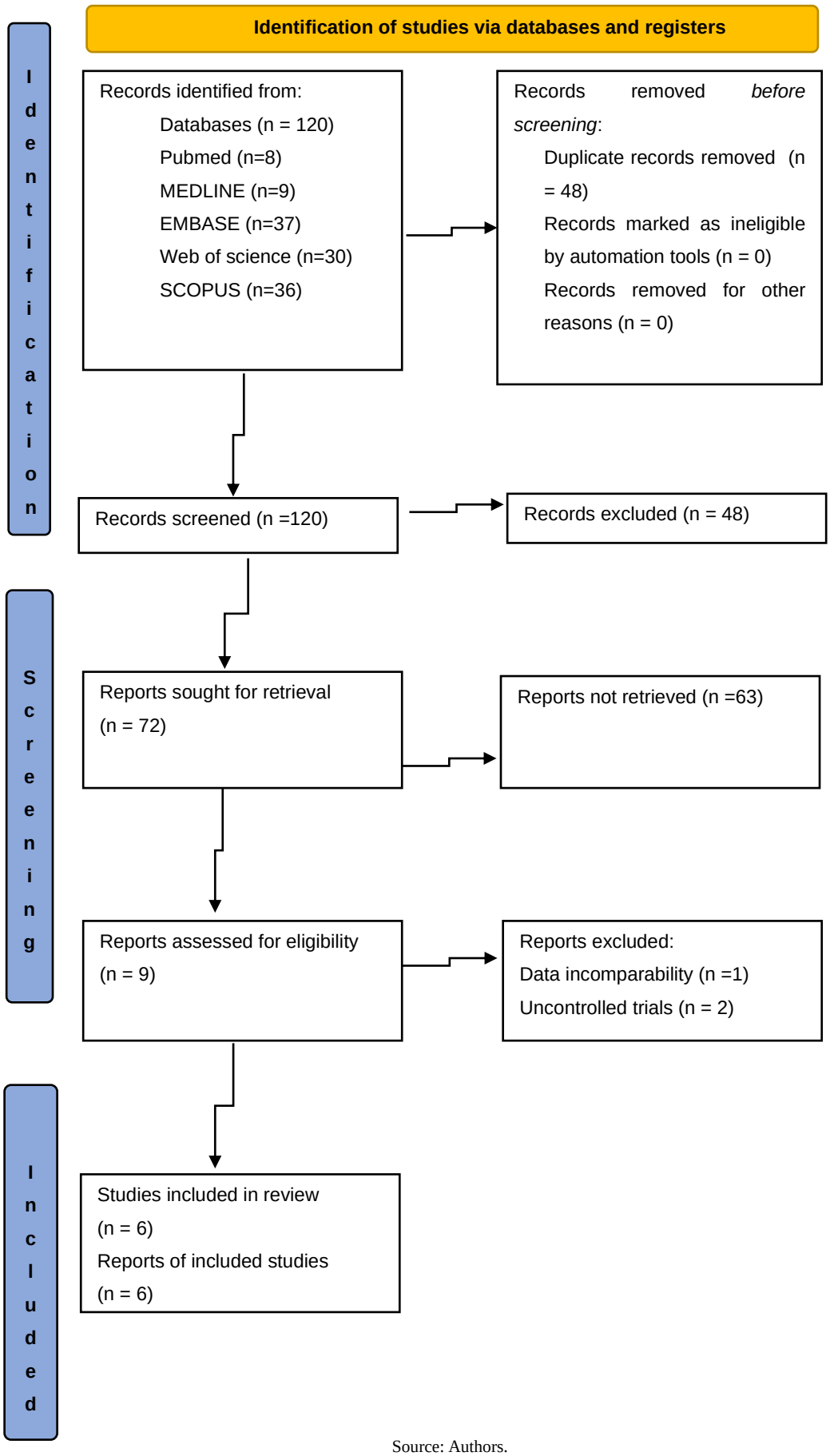
For all continuous outcomes, we estimated treatment effects using mean differences (MD) between groups and 95% confidence intervals. For effect sizes, three levels were defined: small (MD <10% of the scale), medium (MD of 10% to 20% of the scale) or large (MD>20% of the scale). We used the Chi2 and I2 test to assess the presence of heterogeneity among the studies included in this review. As a criterion for downgrading the evidence, we did so when heterogeneity was above 50% in the I2 test. We pooled treatment estimates using random effects in all meta-analyses. The IBM SPSS Statistics program, version 22 was used for the analyzes and the Review Manager – Revman version 5.4.1 was used for the meta-analysis.

3. Results and Discussion

Results

Regarding the search in the databases, 120 articles were found, without restrictions on periods and language. The 48 duplicate articles were excluded and 72 were separated for reading the title and abstracts. Based on the analysis of inclusion criteria, 27 articles were read in full. Due to the exclusion criteria, 23 articles were excluded and 6 were added to the meta-analysis (Figure 1).

Figure 1 - Prisma flowchart of the study selection process.

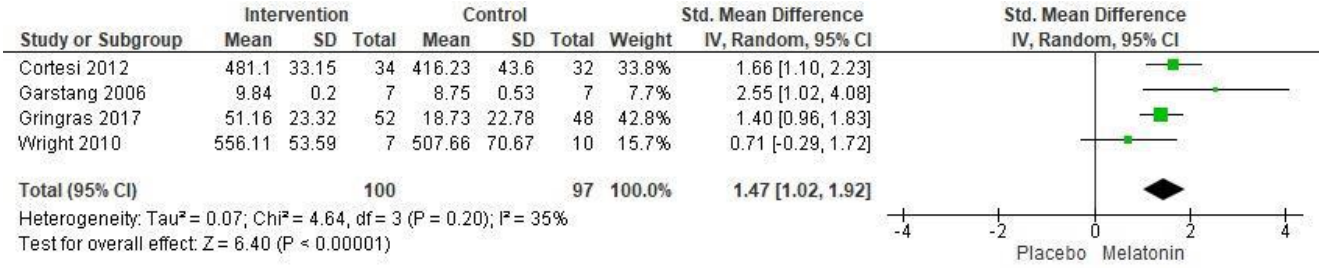


Source: Authors.

Total Sleep Time (TST)

The studies that compared the use of melatonin with placebo were statistically significant. Favorable for the use of melatonin, the 95% CI of 1.66 [1.10, 2.23] and 2.55 [1.02, 4.08] showed an increase in TST with the use of the intervention (p < 0.00001) (Figure 2) (Cortesi et al., 2012; Garstang, & Wallis, 2006).

Figure 2 - Forest Plot of comparison: Melatonin versus Placebo, outcome: Total Sleep Time (TST).

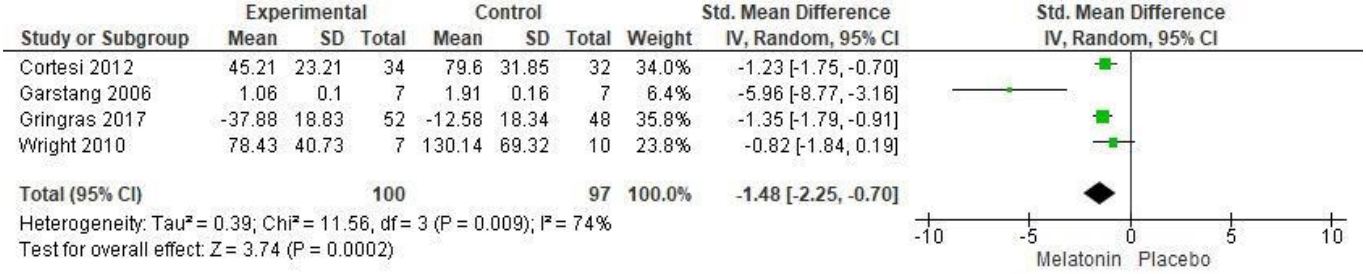


Source: Review Manager (RevMan).

Sleep latency (SL)

Regarding sleep latency, Garstang showed a statistical difference with the use of melatonin, with a 95% CI of -5.96 [-8.77, -3.16], as well as Cortesi with a 95% CI of -1.23 [-1.75, - 0.70] and Gringras with -1.35 [-1.79, -0.91], with reduced latency to start sleep (p = 0.0002) (Figure 3) (Cortesi et al., 2012; Gringras et al., 2017).

Figure 3 - Forest Plot of comparison: Melatonin versus Placebo, outcome: Sleep Latency (SL).

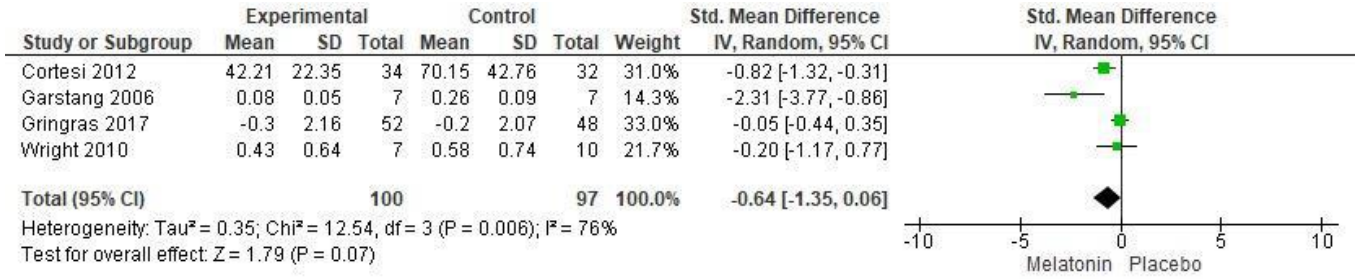


Source: Review Manager (RevMan).

Number of Awakenings (NOA)

The results related to NOA did not show statistical significance. (p = 0.07) However, the studies by Cortesi with 95% CI -0.82 [-1.32, -0.31] and Garstang with 95% CI -2.31 [-3.77, 0.86] brought favorable values to the use of melatonin, with a reduction in NOA in tested patients (Figure 4) (Cortesi et al., 2012; Garstang & Wallis, 2006).

Figure 4 - Forest Plot of comparison: Melatonin versus Placebo, outcome: Number of Awakenings (NOA).

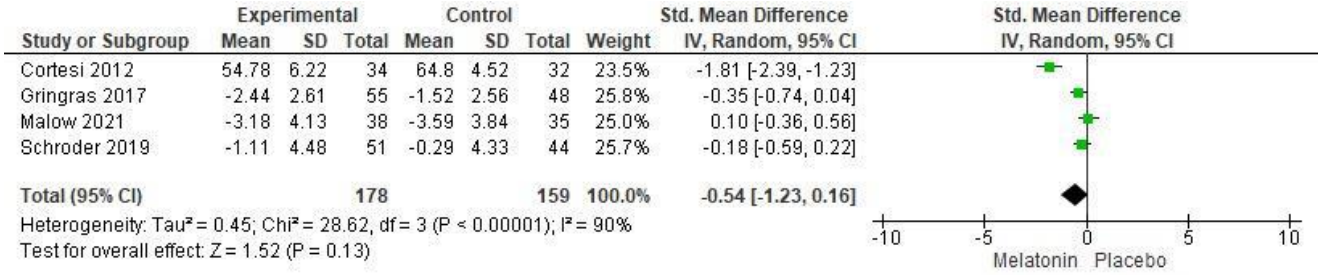


Source: Review Manager (RevMan).

Sleep Quality (SQ)

Regarding sleep quality, despite being favorable to the use of melatonin, they were not statistically significant (p = 0.13) (Figure 5) (Schroder et al., 2019; Cortesi et al., 2012; Garstang, & Wallis, 2006; Malow et al., 2021).

Figure 5 - Forest Plot of comparison: Melatonin versus Placebo, outcome: Sleep quality (SQ).



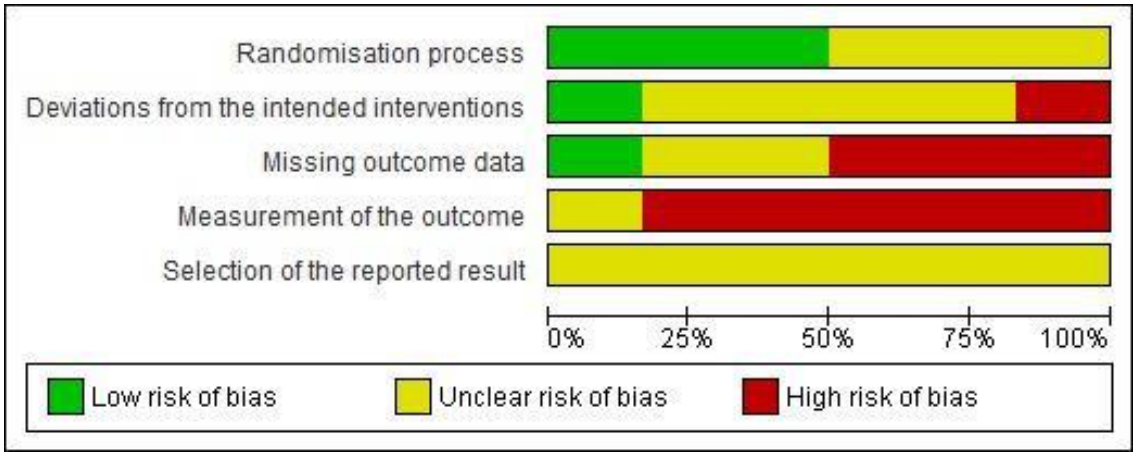
Source: Review Manager (RevMan).

Discussion

The main objective of this meta-analysis was to evaluate total sleep time, nighttime awakenings, sleep onset latency in children and adolescents with autism spectrum disorder and sleep disorders using melatonin. As a secondary outcome, sleep quality can be assessed.

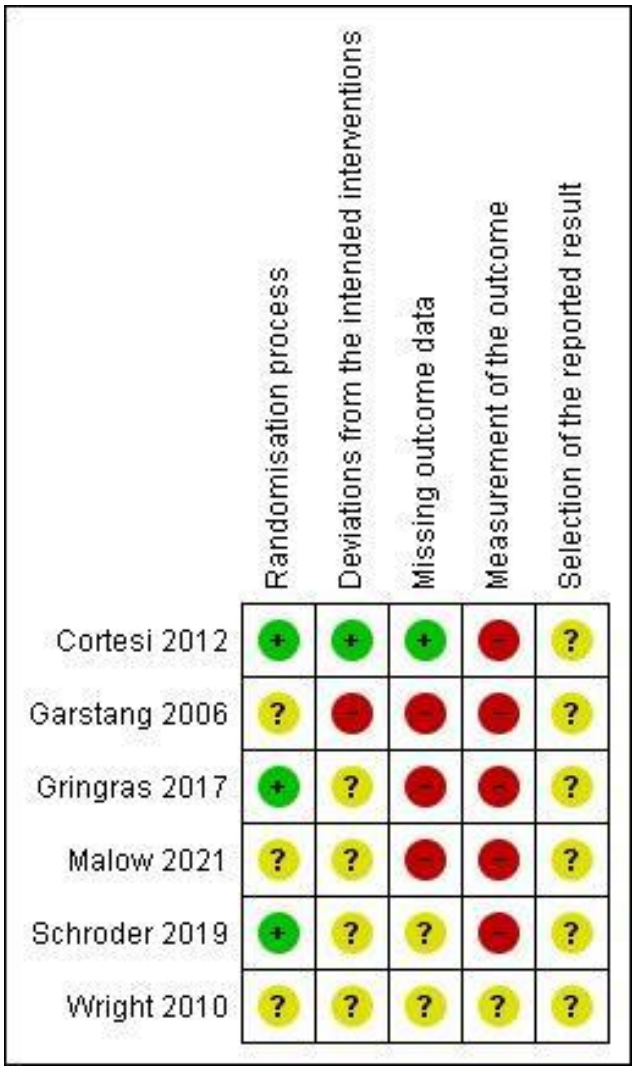
Regarding the risk of bias, it is understood that most of the criteria were characterized as having an indeterminate risk, which reduces the reliability of the results presented. Therefore, it is not possible to recommend the use of melatonin for children with ASD and sleep disorders (Tables 1 and 2).

Table 1 - Risk of bias graph.



Source: Review Manager (RevMan).

Table 2 - Risk of bias summary.



Source: Review Manager (RevMan).

Analytical data on TST, SL and NOA patterns showed that melatonin is superior to placebo when evaluating TST and SL, however, not statistically significant in relation to NOA and SQ (Schroder et al., 2019; Cortesi et al., 2012; Garstang, & Wallis, 2006; Malow et al., 2021; Gringras et al. 2017; Wright et al., 2010; Malow et al., 2021).

Through questionnaires relating to sleep quality, it can be said that with the use of melatonin, only the Cortesi trial showed an improvement in sleep quality in the treated sample (Schroder et al., 2019; Cortesi et al., 2012; Gringras et al., 2017).

Due to the lack of data in the studies by Malow 2021 (Malow et al., 2021) and Garstang 2006 (Garstang, & Wallis, 2006), a calculation was necessary to find the standard deviation, so that they can be comparable with other studies. Additionally, for reasons of data incomparability and statistical differences, the studies by Paavonen 2003 (Paavonen et al., 2003), Malow 2012 (Malow et al., 2012) and Maras 2018 (Maras et al., 2018) could not be included in this review.

As known that melatonin concentration is low in some individuals with ASD, and because some individuals with ASD have abnormalities in genes involved in melatonin synthesis, the use of melatonin may work to replace a deficiency. (Rossignol, & Frye, 2011) Numerous biochemical studies have confirmed this hypothesis, demonstrating abnormally low levels of 6-sulfatoxymelatonin (the main metabolite of melatonin) in autism, particularly in prepubertal children (Lalanne et al., 2021; Tordjman et al., 2012; Tordjman et al., 2005).

Current evidence explains that melatonin is beneficial in the treatment of insomnia in children with ASD, reducing sleep onset latency, reducing the number of nighttime awakenings and increasing total sleep time (Xiong et al., 2023; Cuomo et al., 2017). Therefore, in September 2018, the marketing of a sustained-release pediatric melatonin molecule was authorized by the European Medicines Agency (EMA) (European Medicines Agency, 2023). However, we found limitations regarding the sample size of the clinical trials carried out to date, which may reduce the success rate of the studies. The Xiong 2023 review, despite being recently launched, did not include the Schroder 2019 and Malow 2021 clinical trials, which could influence its final results (Schroder et al., 2019; Malow et al., 2021; Xiong et al., 2023).

It is important to emphasize that non-pharmacological treatment is also very important in the management of these patients. This treatment generally combines parental education about sleep development, a sleep hygiene approach adapted to the child's age and particularities, and more specific behavioral approaches (Schroder et al., 2022).

Furthermore, studies described analyzes carried out with heterogeneous doses of melatonin - doses of 2 to 10 mg were tested, as well as considerable differences in terms of intervention time. In view of this, new randomized clinical trials are necessary to develop a new meta-analysis.

4. Conclusion

The study demonstrated the need to reduce methodological errors in the production of new research. It is concluded that due to the indeterminacy of the risks of bias, as well as the high risk of bias declared, the formal recommendation of the use of melatonin by children and adolescents with Autism and sleep disorders is not justified, even with positive results regarding the total time of sleep and latency to initiate sleep.

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