



Evaluation of drug interventions for the treatment of sleep disorders in children with autism spectrum disorders: a systematic review

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A structured review study of drug interventions on sleep disorders in patients with autism spectrum disorders (ASD) has not been published to date. This systematic review aimed to investigate drug interventions for the treatment of sleep disorders in children with ASD. The Web of Science, PubMed, and Scopus databases were searched until March 2019. Study quality was assessed using the Delphi checklist. Due to the heterogeneity of the findings, a meta-analysis was not possible. Drug interventions for the treatment of sleep disorders in patients with ASD included melatonin, atomoxetine, and risperidone. Atomoxetine had no effect on sleep disorders in patients with ASD. A total of 10 studies were reviewed. Melatonin appears to be useful for the treatment of sleep problems in patients with ASD, but further studies are needed to determine the effects of other drugs.

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Key message

Question: What drugs are used to treat sleep disorders in children with ASD?

Finding: Drug interventions for the treatment of sleep disorders in patients with ASD included melatonin, atomoxetine, and risperidone.

Meaning: Melatonin appears to be useful for the treatment of sleep problems in patients with ASD, but further studies are needed to determine the effects of other drugs.

Introduction

Autism spectrum disorders (ASD) are a heterogeneous group and lifelong neurodevelopmental disorders characterized by significantly unnatural or impaired social interaction and participation, difficulty communicating, and restricted behaviors and interests.^{1,2)} Risk factors for ASD include genetic factors, environmental factors, maternal obesity, maternal smoking, alcohol intake, and pregnancy complications such as preeclampsia and antenatal hemorrhage.^{3,4)} Pregnancy supplements such as folic acid and vitamins are associated with a 40% reduction in the risk of ASD.^{4,5)}

Sleep disorders are a common problem for children with ASD and often remain untreated. Many hypotheses regarding the cause of sleep problems among ASD patients include anxiety, related brain pathologies, and an inability to regulate the sleep hormone melatonin. Sleep disturbances among children with ASD are associated with inadequate melatonin secretion.⁶⁻⁹⁾ This problem is an important feature that affects social communication, daily life, daytime functioning and behavior, and quality of life and increases parental sleep disruption and stress.

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Increased aggression, hyperactivity, and social problems can result from sleep disorder.¹⁰

Parent-directed behavioral interventions for sleep disorders are the first-line treatment for children with ASD.¹¹ Medication use for sleep disorders is common among children with ASD.¹² Various studies have reported the useful effects of medications such as melatonin for the treatment of sleep disorders among children with ASD.^{1,6,7} To date, a structured review study of randomized controlled trials of drug interventions used to treat sleep disorders in patients with ASD. Therefore, the aim of this systematic review was to investigate drug interventions used to treat sleep disorders in children with ASD.

Methods

1. Data sources

The present systematic review aimed to identify drugs used to treat sleep disorders among children with ASD. The report based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was provided of items for reporting systematic reviews and meta-analyses.¹³ The Web of Science, PubMed, and Scopus databases were searched for studies published until March 2019.

2. Search strategy

The search strategy used the following terms: (sleep disorder or sleep disturbance or sleep problem) and (drug intervention or drug treatment) and (autism or ASD or autism spectrum disorder) and (clinical trial or controlled trial).

3. Inclusion and exclusion criteria

Inclusion criteria were all full texts that explored drug interventions for sleep disorders among children with ASD based on randomized controlled trials. Exclusion criteria were review studies, letters to the editor, observational studies, case reports, and qualitative studies.

4. Data extraction

Two authors (EJ and SA) independently screened the titles, abstracts, and full texts of the retrieved studies in EndNote X8. Disagreements were resolved by discussion. The included data were: first author, publication year, sample size, child age (range or mean), drug type, drug dose, treatment outcomes, and treatment duration.

5. Quality assessment

Study quality was evaluated using the Delphi checklist.¹⁴ The checklist includes the following: (1) Was a standard randomization performed? (2) Was the interventional allocation concealed? (3) Was the patient blinded? (4) Was the care provider blinded? (5)

Was the outcome assessed or blinded? (6) Were the 2 groups similar at baseline? (7) Were the eligibility criteria well-defined? (8) Was the variability of the outcome presented? (9) Was an intention-to-treat analysis performed? Accordingly, a maximum score of 9 was allocated to each study.

Results

A total of 671 articles were retrieved in the primary search based on the search strategy to March 2019. We excluded 163 duplicate articles, 487 articles after the title and abstract review, and 8 after the full-text review. A total of 13 articles^{1,6,7,9,11,15-19} with 609 participants that met the criteria for inclusion was retrieved in the present systematic review. All articles were published in English. Due to heterogeneity of the findings, a meta-analysis was not possible. A flowchart of the retrieved articles and selection process is shown in Fig. 1.

The present systematic review revealed that atomoxetine had no effect on sleep disorders in patients with ASD (Table 1). It also revealed that melatonin reduced insomnia symptoms, significantly improved sleep latency, improved total sleep time and efficiency, and was a safe long-term treatment option for children with ASD and insomnia. One study reported that risperidone increased the mean sleep time by 29 minutes per day in children with ASD.

In this systematic review, 3 studies were of low quality and 7 were of high quality according to the Delphi checklist (Table 1).

Discussion

To our knowledge, this is the first systematic review to assess drug interventions for the treatment of sleep disorders in patients with ASD.

The results of this systematic review indicated that melatonin reduced insomnia symptoms, significantly improved sleep latency,

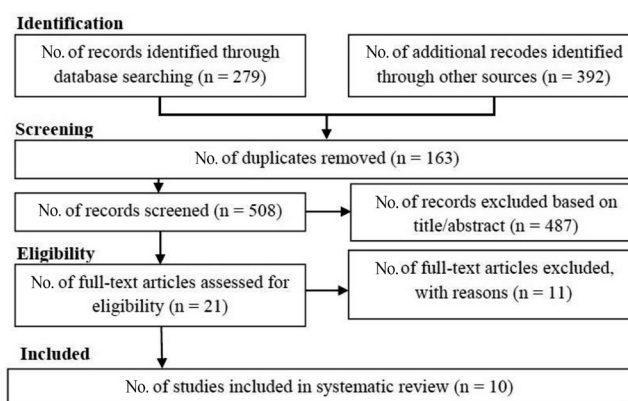


Fig. 1. Flow chart of this systematic review.

Table 1. Characteristics of the studies included in this systematic review

Study	Target	Drug name	Dose	Outcome	Treatment duration	Age average	Sample size	Study quality
Hollway et al. ⁶⁾ (2018)	ASD	Atomoxetine	The target dose was 1.2 mg/(kg/day), but if necessary this could be increased to 1.8 mg/(kg/day)	There were no significant differences between treatment groups, ATX appears sleep neutral	10 Weeks	5.0–14.11 Years	54	6
Cortesi et al. ⁷⁾ (2012)	ASD	Controlled-release melatonin	3 mg	Melatonin treatment was mainly effective in reducing insomnia symptoms, while cognitive-behavioral therapy had a light positive impact mainly on sleep latency.	12 Weeks	4–10 Years	134	7
Gringras et al. ¹¹⁾ 2017	ASD	Prolonged-Release Melatonin	dose titration: 2–5 mg/day and up to 10 mg/day	PR-M was efficacious and safe for treatment of insomnia in children and adolescents with ASD	13 Weeks	2–17.5 Years	125	7
Maras et al. ¹⁾ (2018)	ASD	Prolonged-Release Melatonin	2, 5, or 10 mg	PR-M, shown to be efficacious versus placebo, is an efficacious and safe option for long-term treatment of children with ASD who suffer from insomnia.	13 Weeks	2–17.5 Years	95	7
Wirojanan et al. ¹⁵⁾ (2009)	ASD, Fragile X syndrome	Melatonin	3 mg	The results of this study support the efficacy and tolerability of melatonin treatment for sleep problems in children with ASD	4 Weeks	2–15.3 Years	12	7
Wright et al. ⁹⁾ (2011)	ASD	Melatonin	2 mg to a maximum dose of 10 mg/day	Melatonin significantly improved sleep latency (by an average of 47 min) and total sleep (by an average of 52 min) compared to placebo. The side effect profile was low.	3 Months	3–16 Years	17	6
Garstang and Wallis ¹⁸⁾ (2006)	ASD	Melatonin	5 mg	This study provided evidence of effectiveness of melatonin in children with sleep difficulties and ASD.	4 Weeks	4 - 16 Years	11	5
Wasdell et al. ¹⁶⁾ (2008)	Mixed: neurodevelopmental disabilities, ASD	Controlled-release melatonin	5 mg	The therapy improved the sleep of 47 children and was effective in reducing family stress. Children with neurodevelopmental disabilities, who had treatment resistant chronic delayed sleep phase syndrome and impaired sleep maintenance, showed improvement in melatonin therapy.	10 Days	2–18 Years	51	7
McArthur et al. ¹⁷⁾ (1998)	ASD, Rett syndrome	Melatonin	2.5–7.5 mg	Administration of melatonin appeared to improve total sleep time and sleep efficiency. It is a safe treatment as no adverse side effects were detected.	4 Weeks	10.1 Years	9	5
Aman et al. ¹⁹⁾ (2005)	Autism	Risperidone	0.5–3.5 mg	Difficulty falling asleep appeared to decline with Risperidone. Increase in sleep time: mean increase of 29 min of sleep per day, after with risperidone therapy.	8 Weeks	5–17 Years	101	7

ASD, autism spectrum disorders; ATX, atomoxetine; PR-M, prolonged-release melatonin.

improved total sleep time and sleep efficiency, and was a safe long-term treatment option for children with ASD and insomnia.

Hollway et al.⁶⁾ assessed the effect of atomoxetine on sleep in youth with ASD. There were no significant differences between the atomoxetine group and the manual parent training program, so atomoxetine appeared ineffective.

Rossignol and Frye²⁾ conducted a meta-analysis of 5 randomized double-blind studies to evaluate the effect of melatonin in children with ASD in 2011. They presented that melatonin use among children with ASD is associated with improved sleep parameters, better daytime behaviors, and a low incidence of side effects.

Different trials reported that melatonin has good efficacy for sleep disturbances among children with ASD. However, the effects of time

long require being thoroughly determined. Despite the widespread use of drugs to treat sleep disorders among children with ASD, the US Food and Drug Administration has not approved any for this indication.²⁰⁾

A meta-analysis was conducted by Braam et al.²¹⁾ in 2009 in which the authors searched the PubMed, MEDLINE, and Embase databases for articles published until 2008. The authors evaluated the effects of melatonin on sleep latency, total sleep time, and number of wakes per night and reported that an abnormal melatonin synthesis led to low nocturnal melatonin levels. Increasing a low melatonin level to a more physiological level may lead to less arousal that intervenes with sleep maintenance.

In 2017, Cuomo et al.²²⁾ conducted another meta-analysis to assess

the efficacy of sleep-based interventions for children with ASD. The meta-synthesis included 8 published systematic reviews based on 38 original articles assessing the efficacy of sleep interventions among children with ASD. The included reviews determined 5 major groups of sleep interventions for children with ASD: melatonin therapy, pharmacologic treatments other than melatonin, behavioral interventions, parent education programs, and alternative therapies (iron supplementation, multivitamin use, massage therapy, aromatherapy). The findings of this meta-synthesis propose that no single intervention is effective across all sleep disorders in children with ASD. However, melatonin, behavioral interventions, and parent education programs seem the most effective at improving sleep disorders.

Guénolé et al.²³⁾ performed a systematic review in 2011 on melatonin for sleep disorders in children with ASD by searching the PubMed database for studies published through November 2010. They reported evidence of the useful effects of melatonin on sleep disorders among children with ASD with a low incidence of side effects.

None of the included studies in the present systematic review compared the effects of melatonin to those of other sleep drugs. Therefore, the effectiveness of melatonin compared with other sleep drugs was not determined. However, despite this limitation, the present systematic review reviewed 10 studies and demonstrated that melatonin seems effective for the treatment of sleep problems among children with ASD. Further studies are needed to determine the effects of other drugs for these problems among children with ASD.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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