Evaluation of drug interventions for the treatment of sleep disorders among children with ASD: a systematic review

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Abstract

**Background:** So far, a structured review study that has drug interactions on sleep disorders in autistic patients is not done.

**Purpose:** The aim of this systematic review was to investigate drug interventions for the treatment of sleep disorders in children with Autism spectrum disorders (ASD).

**Methods:** The search in databases of Web of Science, PubMed and Scopus was carried out to March 2019. The quality assessment of the studies was performed by the Delphi checklist. Due to heterogeneity in the findings, perform of meta-analysis was not possible.

**Results:** The findings of the drug interventions for the treatment of sleep disorders in patients with autism disorders in the present systematic review were drugs of Melatonin, Atomoxetine and Risperidone that Atomoxetine had not effect on sleep disorders in patients with autism disorders.

**Conclusion:** In present systematic review, 10 studies were reviewed and demonstrated that Melatonin appears to be useful for the treatment of sleep problems in ASD. Further studies are needed to determine the effects of other drugs for these problems in Autistic patients.

**Key words:** Drug; Sleep disorders, Autism spectrum disorders, Meta-analysis
Introduction

Autism spectrum disorders (ASD) are heterogeneous group and lifelong neurodevelopmental disorders, describe by significant unnatural or impaired social interaction and participation, difficulties in relations, limitation in successful communication, restricted behavior and interests. 1, 2) Some of the risk factors for ASD are included genetic factors, environmental factors, maternal obesity, maternal smoking, alcohol intake and pregnancy complications such as preeclampsia and hemorrhage antenatal. 3, 4) The pregnancy supplements such as folic acid and vitamins were associated with 40% reduction in risk of ASD. 4, 5) Sleep disorder is mostly a common problem for children with autism spectrum disorder (ASD), High rates of sleep problems, and often stay untreated among ASD.

Many hypotheses is for sleep problems among ASD patients, including anxiety, related brain pathology and not good enough in regulation of the sleep hormone melatonin. Sleep disturbance among ASD children is associated with distracted melatonin secretion. 6-9) This problem is an important feature that has an effect on social communication, daily life, the daytime functioning of the child, child's daytime behavior, quality of life and increased parental sleep disruption and stress. Increased aggression, hyperactivity, and social problems can be as a result of sleep disorder. 10)

Parent-directed behavioral interventions for sleep disorders are first-line treatment among ASD children. 11) Also, Medication use for sleep disorders is common among ASD children. 12) Various studies have reported the useful effects of the some medications such as Melatonin for treatment of sleep disorders among ASD children. 1, 6, 7) So far, a structured review study that has drug interactions on sleep disorders in autistic patients in randomized controlled trials (RCT) is
not done. Therefore, the aim of this systematic review was to investigate drug interventions for the treatment of sleep disorders in children with ASD.

**Methods**

Data Sources

The present systematic review was performed in order to identify of drugs intervention for sleep disorders among ASD children. The report based on the PRISMA checklist was provided of Items for reporting systematic reviews and meta-analyses. The search in databases of Web of Science, PubMed and Scopus was carried out to March 2019.

Search strategy

The search strategy was carried out by terms following: (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).

Inclusion and exclusion criteria

Inclusion criteria were all full texts that explored drugs interventions for sleep disorders among ASD children based on RCT. Exclusion criteria were review studies, letter to the Editor, observational studies, case report and qualitative studies.

Data Extraction

Two authors (EJ and SA) independently determined title, abstract and full text of studies in EndNote X8. The disagreements were resolved by discussion among authors. The included data in datasheet were; first author, publications year, sample size, child age (range or mean), type of drug, drug dose, outcomes of drugs and treatment duration.
Quality assessment

The studies quality included was evaluated by the Delphi checklist. The check list has the items following. (a) Was a standard randomization performed? (b) Was the allocation of intervention concealed? (c) Was the patient blinded? (d) Was the care provider blinded? (e) Was the outcome assess or blinded? (f) Were the two groups similar at baseline? (g) Were the eligibility criteria well-defined? (h) Was the variability of the outcome presented? (i) Was an intention-to-treat analysis performed? According to, a maximum score of nine was allocated to each study.

Results

In beginning, 671 articles were included in the primary search based on search strategy to March 2019. We excluded 163 articles due to duplicate. Then, 487 articles were excluded after reviewing titles and abstracts and eight articles were excluded after checking full texts. In total, 13 articles with 609 participants that met the criteria for inclusion was retrieved in the present systematic review. All articles were published to English. Due to heterogeneity in the findings, perform of meta-analysis was not possible. The flowchart of retrieved articles and selection process are presented in figure 1.

The findings of the drug interventions for the treatment of sleep disorders in patients with autism disorders in the present systematic review were drugs of Melatonin, Atomoxetine and Risperidone that Atomoxetine had not effect on sleep disorders in patients with autism disorders (table 1). The results of the present systematic review indicated that Melatonin mainly effective in reducing insomnia symptoms, Significantly improved sleep latency, improve total sleep time and sleep efficiency and safe option for long-term treatment of children with ASD who suffer
from insomnia. Also, in one study was used from Risperidone drug that this drug could increase the mean of sleep time (29 minutes per day) in children with autism.

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

Discussion

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

The results of this systematic review indicated that Melatonin mainly effective in reducing insomnia symptoms, Significantly improved sleep latency, improve total sleep time and sleep efficiency and safe option for long-term treatment of children with ASD who suffer from insomnia.

Hollway et al. in 2018 conducted an analysis in order to assess the effect of Atomoxetine on Sleep in Youth with Autism Spectrum Disorder. There were no significant differences between Atomoxetine group and manualized parent training program, so Atomoxetine appeared sleep neutral. 6)

Rossignol et al. conducted a meta-analysis study to evaluate the effect of Melatonin among ASD children in 2011. This study included five studies of randomized double-blind. They presented that Melatonin prescription among ASD children is associated with improved sleep parameters, better day time behavior and low side effects. 2)

The different trials reported that Melatonin has good efficacy for sleep disturbances among ASD children. However, effects of time long require being thoroughly determined. Despite the
widespread use of drugs to treat sleep disorders among ASD children, FDA has not approved these drugs for this disturbance. 21)

A meta-analysis was conducted by Braam et al. in 2009. 22) The search was performed in major databases of PubMed, Medline, and Embase until 2008. It determined the effect of melatonin on sleep latency, total sleep time, and number of wakes per night. They reported that an abnormal melatonin synthesis wad leaded to levels of low nocturnal melatonin. Increase in level of low melatonin to a level of more physiological may be leads to less arousal that intervene with sleep maintenance.

Cuomo et al. in 2017 conducted another meta-analysis for assess the effectiveness of sleep-based interventions for ASD children. The meta-synthesis included eight published systematic reviews based on 38 original articles assessing the efficacy of sleep interventions among ASD children. 23) The included reviews had determined five major groups of sleep interventions for ASD children: melatonin therapy, pharmacologic treatments except melatonin, behavioral interventions, education programs for parent, and alternative therapies (iron supplementation, multivitamin, massage therapy, and aromatherapy). The findings of this meta-synthesis propose that no single intervention is effective across all sleep disorders among ASD children. However, melatonin, behavioral interventions, and education programs for parent treatments seem the most effective at improving of sleep disorders compared with other treatments.

A Systematic review was conducted by Guéolé et al. in 2011. They determined Melatonin for sleep disorders in ASD children by searching in PubMed Database. 24) This search was performed to November 2010. They reported that there are evidences of useful effects of melatonin on sleep disorders among ASD children with low side effects.
In none of included studies in the present systematic review, the effects of melatonin with other sleep drugs were not compared. Therefore, findings about the effectiveness of melatonin compared with other sleep drugs cannot be determined. However, despite this limitation, in the present systematic review, 10 studies were reviewed and demonstrated that Melatonin seems to be effective for the treatment of sleep problems among ASD children. Further studies are needed to determine the effects of other drugs for these problems among ASD children.

In this study, 10 studies were reviewed and demonstrated that Melatonin seems to be effective for the treatment of sleep problems among ASD. Further studies are needed to determine the effects of other drugs for these problems among ASD children.

**Conflict of interest**

None

**Acknowledgement**

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References


Figure and table Legend

**Figure 1:** Diagram of studies through the different phases of the systematic review

**Table 1:** Characteristics of included studies in the present systematic review
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Target</th>
<th>Drug name</th>
<th>Dose</th>
<th>Outcome</th>
<th>Treatment duration</th>
<th>Age average</th>
<th>Sample size</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hollway, 2018 (6)</td>
<td>ASD</td>
<td>Atomoxetine</td>
<td>The target dose was 1.2mg/ (kg/d), but if necessary this could be increased to 1.8mg/(kg/d)</td>
<td>There were no significant differences between treatment groups, ATX appears sleep neutral</td>
<td>10 weeks</td>
<td>5.0–14.11 years</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>Cortesi , 2012 (7)</td>
<td>ASD</td>
<td>Controlled-release melatonin</td>
<td>3-mg</td>
<td>Melatonin treatment was mainly effective in reducing insomnia symptoms, while cognitive–behavioral therapy had a light positive impact mainly on sleep latency.</td>
<td>12 weeks</td>
<td>4–10 years</td>
<td>134</td>
<td>7</td>
</tr>
<tr>
<td>Gringras , 2017 (11)</td>
<td>ASD</td>
<td>Prolonged-Release Melatonin</td>
<td>dose titration:2-5 mg/day and up to 10 mg/day</td>
<td>PR-M was efficacious and safe for treatment of insomnia in children and adolescents with ASD</td>
<td>13 weeks</td>
<td>2-17.5 years</td>
<td>125</td>
<td>7</td>
</tr>
<tr>
<td>Maras, 2018 (1)</td>
<td>ASD</td>
<td>Prolonged-Release Melatonin</td>
<td>2, 5, or 10 mg</td>
<td>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</td>
<td>13 weeks</td>
<td>2–17.5 years</td>
<td>95</td>
<td>7</td>
</tr>
<tr>
<td>Wirojanan, 2009 (15)</td>
<td>ASD, Fragile X syndrome</td>
<td>Melatonin</td>
<td>3 mg</td>
<td>The results of this study support the efficacy and tolerability of melatonin treatment for sleep problems in children with ASD</td>
<td>4 weeks</td>
<td>2-15.3 years</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Researcher, Year</td>
<td>Condition</td>
<td>Treatment</td>
<td>Dose</td>
<td>Description</td>
<td>Duration</td>
<td>Age</td>
<td>Participants</td>
<td>Side Effect Profile</td>
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<tr>
<td>Wright, 2011 (9)</td>
<td>ASD</td>
<td>Melatonin</td>
<td>2 mg to a maximum dose of 10 mg/d</td>
<td>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.</td>
<td>3 months</td>
<td>3–16 years</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Garstang, 2006 (18)</td>
<td>ASD</td>
<td>Melatonin</td>
<td>5 mg</td>
<td>This study provided evidence of effectiveness of melatonin in children with sleep difficulties and ASD.</td>
<td>4 weeks</td>
<td>4 - 16 years</td>
<td>11</td>
<td>5</td>
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<tr>
<td>Wasdell, 2008 (16)</td>
<td>Mixed: Neurodevelopmental disabilities, ASD</td>
<td>Controlled-release (CR) melatonin</td>
<td>5 mg</td>
<td>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.</td>
<td>10 day</td>
<td>2–18 years</td>
<td>51</td>
<td>7</td>
</tr>
<tr>
<td>McArthur, 1998 (17)</td>
<td>ASD, Rett syndrome</td>
<td>Melatonin</td>
<td>2.5 to 7.5 mg</td>
<td>Administration of melatonin appeared to improve total sleep time and sleep efficiency. It was a safe treatment as no adverse side effects were detected.</td>
<td>4 weeks</td>
<td>10.1 years</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Aman, 2005 (20)</td>
<td>Autism</td>
<td>Risperidone</td>
<td>0.5–3.5 mg</td>
<td>Difficulty falling asleep appeared to decline with Risperidone. Increase in sleep time: mean increase of 29 minutes of sleep per day, after with risperidone therapy.</td>
<td>8 weeks</td>
<td>5–17 years</td>
<td>101</td>
<td>7</td>
</tr>
</tbody>
</table>
Identification
No of records identified through database searching (n = 279)
No of additional recodes identified through other sources (n = 392)

Screening
No of duplicates removed (n = 163)
No of records screened (n = 508)
No of records excluded based on title/abstract (n = 487)

Eligibility
No of full-text articles assessed for eligibility (n = 21)
No of full-text articles excluded, with reasons (n = 11)

Included
No of studies included in systematic review (n = 10)