The Role of Melatonin in Autism Spectrum Disorders

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Learning Objectives

1. Describe the diagnostic changes to Pervasive Developmental Disorders (PDD) in the Diagnostic and Statistical Manual of Mental Disorders
2. Explain the significance of regression in Autism Spectrum Disorders (ASD)
3. Explain the rationale for the use of melatonin in ASD
I. **Pervasive Developmental Disorders (PDDs)**

a. **Epidemiology**
   i. Estimated that PDDs occur in approximately 1:88 children
   ii. More common in boys than in girls
   iii. 600% increase in prevalence in last two decades

b. **Medical costs**
   i. Greater than $126 billion per year
      1. More than tripled since 2006
      2. Expected continued increase
   ii. Depending on degree of impairment, lifetime cost per affected individual is between $1.4-2.3 million
      1. Direct costs: outpatient care, home care, pharmaceuticals, lost productivity
      2. Indirect costs: special education, child daycare leading to adult placement

c. **Diagnostics**
   i. Refers to a group of five disorders characterized by delays in the development of multiple basic functions including socialization and communication
   ii. Diagnostic criteria in DSM-IV-TR and DSM-5

d. **Recognized PDDs**
   i. **Autistic disorder (classic autism)**
   ii. **Asperger’s disorder (Asperger syndrome)**
   iii. **Pervasive developmental disorder not otherwise specified (PDD-NOS)**
   iv. Rett’s disorder (Rett syndrome)
   v. Childhood disintegrative disorder (CDD)

e. Currently, the terminology autism spectrum disorder is not defined in the DSM-IV-TR

f. Currently, in practice ASD refers to Autistic disorder, Asperger’s disorder, and PDD-NOS

Figure 1. Recognized PDDs

II. **Affected Areas**

a. **Social interaction**
   i. Significant problems developing nonverbal communication skills, such as eye-to-eye gazing, facial expressions, and body posture
   ii. Failure to establish friendships with children the same age
   iii. Lack of interest in sharing enjoyment, interests, or achievements with others
   iv. Lack of empathy

b. **Communication (nonverbal and/or verbal)**
   i. Delay in, or lack of, learning to talk. As many as 40% of people with autism never speak
   ii. Problems initiating or continuing a conversation
iii. Stereotyped and repetitive use of language (echolalia)
iv. Difficulty understanding their listener’s perspective

Behaviors and interests
i. An unusual focus on pieces
ii. Preoccupation with certain topics
iii. Need for consistency and routines

III. Other problematic behaviors
a. Impairments can be mild or debilitating
   i. Aggression
   ii. Insomnia
   iii. Anxiety

<table>
<thead>
<tr>
<th>Category Name</th>
<th>Proposed Changes to DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pervasive Developmental Disorders</td>
<td>Autism Spectrum Disorder</td>
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<tr>
<td>Recognized Disorders</td>
<td></td>
</tr>
<tr>
<td>- Autistic disorder</td>
<td></td>
</tr>
<tr>
<td>- Asperger’s disorder</td>
<td></td>
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<tr>
<td>- PDD-NOS</td>
<td></td>
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<tr>
<td>- Rett’s disorder</td>
<td></td>
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<tr>
<td>- CDD</td>
<td></td>
</tr>
<tr>
<td>Three Domains</td>
<td></td>
</tr>
<tr>
<td>- Social</td>
<td></td>
</tr>
<tr>
<td>- Communication</td>
<td></td>
</tr>
<tr>
<td>- Fixated interests and repetitive behavior or activity</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Proposed Changes for DSM-5 (anticipated release date May 2013)

Mechanisms of Sleep Abnormalities in Children with ASD

IV. Sleep in ASD
a. Sleep disturbances are prevalent
   i. Estimated up to 80%
   ii. Studies have demonstrated sleep problems rarely improve over time
   iii. In a recent consensus statement, the National Sleep Foundation, in collaboration with Best Practice Project Management, Inc., identified children with ASD as one of the highest priority populations for sleep research
   iv. American Academy of Pediatrics recommends screening for insomnia after diagnosis
b. Proposed hypotheses for disturbances:
   i. Genetic abnormalities alter neuronal pathways that lead to circadian rhythm abnormalities
      1. Alterations in N-acetylserotonin O-methyltransferase (ASMT) gene
      2. Responsible for melatonin synthesis

Figure 2. Melatonin Production

3. Lower excretion rates of urinary 6-sulphatoxymelatonin (major metabolite)
   i. Normal serotonin concentrations
   ii. 50% reduction in 6-sulphatoxymelatonin excretion in children with ASD compared to typical developing controls

   ii. Sensory integration dysfunction
      1. Hypersensitive to sensory input (i.e. noises, alterations in lighting, temperature changes)
      2. Also referred to as “sensory processing disorder”

   iii. Seasonal changes

V. Definitions
   a. Sleep onset latency: time from bedtime to sleep onset
   b. Total sleep time: time from falling asleep to wakening
   c. Sleep maintenance: ability to stay asleep
   d. Night awakenings: prolonged nocturnal awakenings

Regression and the Effects of Sleep on Regression

VI. Developmental Regression

a. Symptoms of regression become apparent after a period of normal or mildly delayed development followed by the loss of previously acquired skills in up to 50% of children with ASD
   i. Language regression
   ii. Deteriorations of social behaviors
   iii. Language and/or social skills are seldom regained after loss
b. Regression typically occurs between 1 and 3 years of age (peak incidence at 2 years)
c. Regressive changes
   i. Abrupt
   ii. Insidious
d. Exact cause of regression is unknown
e. DSM-5 will include a specifier for ASD to indicate nature and severity of regression
Table 2. Affected Areas in Regressive ASD

<table>
<thead>
<tr>
<th></th>
<th>Autistic Disorder (n=1305) %</th>
<th>PDD-NOS (n=435) %</th>
<th>Asperger's Syndrome (n=207) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech/Language Skills</td>
<td>77</td>
<td>81</td>
<td>44</td>
</tr>
<tr>
<td>Social Skills (eye contact/playing with others)</td>
<td>18</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Motor Skills (walking/jumping/playing with small toys)</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Daily Living Skills (feeding oneself/toileting)</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

PDD-NOS: Pervasive developmental disorder not otherwise specified

VII. Effects of Sleep on Regression

a. Over 50% of children with ASD had at least one sleep problem with a peak onset during the second year of life which coincides with the onset of regression
b. Two studies by Giannotti and Wiggins have shown:
   i. Children with regression have a more disturbed sleep pattern
   ii. Short sleep duration is associated with social skill deficits and stereotypical behavior
   iii. Children with regression have a lower concentration of melatonin

VIII. Pediatric Insomnia

a. Repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family
b. Presentation
   i. Bedtime refusal or resistance
   ii. Delayed sleep onset
   iii. Prolonged nighttime awakenings that require parental intervention
c. Background
   i. Prevalence
      1. Greater than 75% of children with neurodevelopmental disorders
      2. Approximately 6% in general pediatric population
   ii. Sleep difficulties in ASD
      1. More severe
      2. Longer duration
      3. Treatment resistant
d. Current recommendations
   i. Sleep hygiene
   ii. No FDA approved sleep medication for children
   iii. Medication must address specific problem area in sleep cycle
      1. Sleep onset: medication with short onset
      2. Sleep maintenance: medication with long duration of action

Pediatric Insomnia Guidelines
### Table 3. Medications Studied for Pediatric Insomnia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Target Sleep Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha Agonist</strong></td>
<td></td>
</tr>
<tr>
<td>• Clonidine</td>
<td>Sleep onset latency</td>
</tr>
<tr>
<td>• Guanfacine</td>
<td></td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
</tr>
<tr>
<td>• Diphenhydramine</td>
<td>Nighttime awakenings</td>
</tr>
<tr>
<td>• Hydroxyzine</td>
<td></td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
</tr>
<tr>
<td>• Clonazepam</td>
<td>Sleep onset latency</td>
</tr>
<tr>
<td><strong>Benzodiazepine Receptor Agonists</strong></td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>• Zolpidem</td>
<td>Sleep onset latency</td>
</tr>
<tr>
<td>• Zaleplon</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>• Eszopiclone</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>• Trazodone</td>
<td>Sleep onset latency</td>
</tr>
<tr>
<td>• Nortriptyline</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td>• Paroxetine</td>
<td>Sleep onset latency</td>
</tr>
<tr>
<td>• Mirtazapine</td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td><strong>Melatonin</strong></td>
<td>Sleep onset latency</td>
</tr>
<tr>
<td><strong>Melatonin</strong></td>
<td>Sleep maintenance</td>
</tr>
<tr>
<td><strong>Melatonin</strong></td>
<td>Circadian rhythm abnormalities</td>
</tr>
<tr>
<td><strong>Melatonin</strong></td>
<td>Abnormal melatonin production</td>
</tr>
</tbody>
</table>

#### Melatonin

**IX. Melatonin**

a. Natural hormone made by the pineal gland from serotonin
b. Active roles include regulation of circadian rhythm, antioxidant, anti-inflammatory, and mild immune modulator

**X. Melatonin Regulation**

a. Decreasing light stimulates the pineal gland, within the hypothalamus
   i. Melatonin production
   ii. Indirect role in cortisol production
b. Activation cycle
   i. As darkness occurs, the pineal is activated
      1. Melatonin is released into the blood starting around 9 PM
      2. Concentrations remain elevated for 8-12 hours
      3. Concentrations decrease around 6-9 AM (near undetectable)
   ii. Endogenous concentrations in children is unknown

![Figure 3. Melatonin Regulation](image-url)
XI. **Oral Melatonin Supplementation**\(^{18-20,22-25}\)

a. Non-selective binding to melatonin-1 and melatonin-2 receptors

b. Available in immediate-release (IR), controlled-release (CR), and liquid formulations
   i. Time to peak IR formulation: 0.5 to 2 hours
   ii. Time to peak CR formulation: 2 to 4 hours

c. Bioavailability
   i. Variable
   ii. Immediate release: 3% to 76%

d. Hepatic metabolism and renal elimination

e. Melatonin testing
   i. ELISA assay
   ii. Saliva and plasma options available

f. According to a study regarding psychiatrists prescribing confidence in children with neurodevelopmental disorders by Owens JA, et al.
   i. 25% of physicians are recommending the use of melatonin
   ii. 14% discourage the use
   iii. 22% did not feel knowledgeable enough to prescribe

XII. **Documented Adverse Effects with Supplementation**\(^{26,27}\)

a. Seizures
   i. Sheldon, et al. reported that melatonin increased seizure frequency in neurologically disabled children
   ii. Seizures ceased with melatonin discontinuation and reappeared with rechallenge
   iii. Mechanism behind this adverse effect is unknown

b. Asthma exacerbations
   i. Maestroni, et al. reported melatonin can raise levels of inflammatory cytokines which may affect patients with immune mediated conditions
   ii. Peak melatonin levels are inversely related to respiratory function
XIII. Primary Literature Comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>Published in</th>
<th>Design</th>
<th>Intervention</th>
<th>Subjects</th>
<th>Measures</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malow, et al.</td>
<td>Journal of Autism and Developmental Disorders 2012</td>
<td>Open-label, 17-week, multi-center dose-escalation trial</td>
<td>Melatonin</td>
<td>Age 3-10 years, diagnosis of ASD, sleep onset delay of ≥30 minutes or more ≥3 nights/week, no use of psychotropics, failed sleep hygiene</td>
<td>Sleep diary, actigraphy, questionnaires</td>
<td>Sleep latency of 30 minutes or less on 5 or more nights per week</td>
</tr>
<tr>
<td>Cortesi, et al.</td>
<td>Journal of Sleep Research 2012</td>
<td>Randomized, double-blind, 12-week</td>
<td>Cognitive behavioral therapy (CBT), melatonin CR, or CBT + melatonin CR versus placebo</td>
<td>Age 4-10 years, diagnosis of ASD, sleep onset &gt;30 minutes more than 3 nights/week, normal EEG, drug free for at least 6 months prior to baseline, no use of psychotropics, had not failed sleep hygiene</td>
<td>Sleep diary, actigraphy, and questionnaires</td>
<td>mean change in group difference from baseline to endpoint, including total sleep time (TST), sleep onset latency (SOL), sleep efficiency (SE), and wake after sleep onset (WASO) as compared to placebo</td>
</tr>
<tr>
<td>Wasdell, et al.</td>
<td>Journal of Pineal Research 2008</td>
<td>Randomized, double-blind, multi-center, placebo-controlled, 4-week, crossover trial followed by 3-month open-label study</td>
<td>Melatonin CR versus placebo</td>
<td>Age 2-18 years, failed sleep hygiene, sleep difficulty, persistent nightly sleep onset delay of ≥30 minutes, more than two nighttime awakenings lasting at least 15 minutes in duration resulting in daytime insomnia symptoms, neurodevelopmental disorder, psychotropic use not assessed</td>
<td>Sleep diary, actigraphy, and questionnaires</td>
<td>Total nighttime sleep as recorded on caregiver-completed sleep diary</td>
</tr>
<tr>
<td>Wright, et al.</td>
<td>Journal of Autism and Developmental Disorders 2011</td>
<td>Randomized, double-blind, multi-center, 36-week, crossover trial</td>
<td>Melatonin versus placebo</td>
<td>Age 3-16 years, diagnosed ASD, failed behavior based sleep hygiene, sleep disorder involving excessive sleep latency, excessive night awakenings, or reduced total sleep time, no use of psychotropics</td>
<td>Sleep diary and questionnaires</td>
<td>Sleep latency, total sleep time, and number of awakenings</td>
</tr>
</tbody>
</table>

**Purpose**
- To evaluate the possible therapeutic effectiveness of melatonin in children with ASD with sleep onset insomnia

**Design**
- Open-label, 17-week, multi-center, dose-escalation trial

### Table 4. Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 3-10 years</td>
<td>Use of psychotropic medications</td>
</tr>
<tr>
<td>Diagnosis of ASD</td>
<td>Children with:</td>
</tr>
<tr>
<td>Sleep onset delay of ≥30 minutes or more ≥3 nights/week</td>
<td>o Fragile X syndrome</td>
</tr>
<tr>
<td>Allergy/constipation medications could be continued</td>
<td>o Down syndrome</td>
</tr>
<tr>
<td>o No medication changes during study</td>
<td>o Neurofibromatosis</td>
</tr>
<tr>
<td>o Unprovoked epileptic seizure in past 2 years</td>
<td>o Tuberous sclerosis complex</td>
</tr>
<tr>
<td>Use of psychotropic medications</td>
<td>Abnormal lab values at screening</td>
</tr>
<tr>
<td>Children with:</td>
<td>Sleep apnea</td>
</tr>
<tr>
<td>o Fragile X syndrome</td>
<td>Any medical of psychiatric diagnosis that could affect sleep</td>
</tr>
<tr>
<td>o Down syndrome</td>
<td></td>
</tr>
<tr>
<td>o Neurofibromatosis</td>
<td></td>
</tr>
<tr>
<td>o Tuberous sclerosis complex</td>
<td></td>
</tr>
<tr>
<td>o Unprovoked epileptic seizure in past 2 years</td>
<td></td>
</tr>
</tbody>
</table>

**Cohorts**
- Melatonin with escalating doses (liquid formulation)

**Outcomes**
- Primary outcome: sleep latency of 30 minutes or less on 5 or more nights/week
- Secondary outcome: safety, tolerability, effective dose

**Methods**
- Satisfactory response: falling asleep within 30 minutes in ≥5 nights/week
  - Actigraphy worn by all children
  - Sleep diary completed by parents to validate actigraphy data
- Two-week acclimation phase
  - Week-one: parents received 1 hour of structured sleep education
  - Week-two: placebo run in phase where all children received liquid placebo 30 minutes before bedtime
- Tier 1 dosing
  - 1 mg daily for 3 weeks
- Tier 2 dosing
  - 3 mg daily for 3 weeks
- Tier 3 dosing
  - 6 mg daily for 3 weeks
- Tier 4 dosing
  - 9 mg for 3 weeks
- Final 2 weeks, subjects remained on same dose
- Questionnaires
  - Children’s Sleep Habits Questionnaire (CSHQ), Child Behavior Checklist (CBCL), Repetitive Behavior Scale-Revised (RBS-R), Parenting Stress Index Short Form (PSI-SF)
- Adverse effects
  - Assessed weekly by telephone using the Hague Side Effects Scale

**Statistics**
- Wilcoxon signed-rank test used for within group comparison
  - Alpha=0.05

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**Figure 4. Dosing Strategies**

<table>
<thead>
<tr>
<th>Week of Study</th>
<th>0</th>
<th>1-2</th>
<th>3-5</th>
<th>6-8</th>
<th>9-11</th>
<th>12-14</th>
<th>15-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
<td>1 mg MEL</td>
<td>3 mg MEL</td>
<td>6 mg MEL</td>
<td>9 mg MEL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acclimation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Dose was either increased or maintained depending on child’s response.
Outcomes may not follow normal distribution
- Average sleep parameters computed for each phase (baseline, acclimation, dosing phase, satisfactory phase, and end of study dosing)

**Results**
- Enrolled: 46
  - Completed: 24
- Baseline Characteristics:
  - Average age: 5.8 years
  - Sex: 87.5% male

<table>
<thead>
<tr>
<th>Table 5. Results</th>
<th>Sleep Parameter</th>
<th>Baseline</th>
<th>Acclimation</th>
<th>Satisfactory dose (median)</th>
<th>End of Study</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency (min)</td>
<td>38.2</td>
<td>42.9</td>
<td>21.6</td>
<td>22.5</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>74.6</td>
<td>75.0</td>
<td>76.5</td>
<td>79.3</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>Wake time after sleep onset (min)</td>
<td>57.6</td>
<td>64.9</td>
<td>70.5</td>
<td>68.6</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>442.7</td>
<td>450.1</td>
<td>459.0</td>
<td>457.3</td>
<td>0.011</td>
<td></td>
</tr>
</tbody>
</table>

- Reasons for exclusion
  - 8 did not have ASD, 6 withdrew consent, 2 lost to follow-up, 1 improved with non-pharmacological techniques, 1 started psychotropic medications, 1 had elevated liver enzymes, 1 experienced seizure, 1 was unable to tolerate wrist actigraphy
- Adverse effects
  - 1 experienced loose stools
  - 1 experienced seizure; later determined not due to melatonin
- Laboratory findings
  - No alteration in CBC, BMP, renal/hepatic function, cortisol, ACTH, FSH, LH, estrogen, testosterone, or prolactin

**Author's Conclusion**
The majority of children responded to 1-3 mg dose 30 minutes before bedtime with an improvement in sleep latency which was maintained until conclusion of study. The medication was well tolerated with minimal adverse effects and no laboratory changes.

**Strengths**
- Psychotropic medication use was excluded
- Exclusion of other medical diagnosis/conditions affecting sleep
- Included only children with ASD
- Sleep diary and actigraphy used
- Multi-center

**Weaknesses**
- No placebo comparator to establish efficacy
- Primary endpoint that was stated did not match results provided
- Adherence not assessed
- Open-label study design
- Melatonin assay not used

Purpose: To determine the relative efficacy of CBT, melatonin CR, or CBT + melatonin CR versus placebo in autistic children with persistent insomnia.

Design: Randomized, single-center, 12-week, placebo-controlled trial.

Patient Population: Table 6. Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 4-10 years</td>
<td>Other neurological conditions</td>
</tr>
<tr>
<td>Diagnosis of ASD</td>
<td>Other psychiatric conditions</td>
</tr>
<tr>
<td>Sleep onset &gt;30 minutes more than 3 nights/week for at least 3 months</td>
<td>Other serious medical conditions</td>
</tr>
<tr>
<td>Normal EEG for three months prior to baseline</td>
<td>Obesity</td>
</tr>
<tr>
<td>Drug free for at least 6 months prior to baseline</td>
<td>Other breathing disturbances</td>
</tr>
<tr>
<td></td>
<td>Child Behavior Check List T score of+70 on any syndrome scale (undiagnosed psychiatric illness)</td>
</tr>
<tr>
<td></td>
<td>Currently receiving psychotherapy or psychiatric medications</td>
</tr>
<tr>
<td></td>
<td>Family receiving psychotherapy</td>
</tr>
</tbody>
</table>

Cohorts: Cognitive behavioral therapy (CBT), melatonin CR, or CBT + melatonin CR versus placebo

Outcomes: Primary: mean change in group difference from baseline to endpoint, including total sleep time (TST), sleep onset latency (SOL), and wake after sleep onset (WASO) as compared to placebo inferred from actigraphy data.

Methods: Run in period: parents recorded sleep daily

- Children’s Sleep Habits Questionnaire (CSHQ)
  - Included parameters: bedtime resistance, sleep onset latency, sleep duration, night awakenings, sleep disordered breathing, and sleep anxiety
- Actigraphy used for first 7 nights then at week 12 reassessment
- Sleep diary performed by parents
- Randomized 1:1:1:1
- 80% compliance required to be included in study

Table 7. Treatment Groups

<table>
<thead>
<tr>
<th>CBT</th>
<th>Melatonin</th>
<th>Combination</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families attended 4 weekly individual treatment sessions (50 minutes)</td>
<td>3 mg CR tablet</td>
<td>3 mg CR tablet</td>
<td>Inert tablet with melatonin CR appearance</td>
</tr>
<tr>
<td></td>
<td>• 1 mg IR</td>
<td>• 1 mg IR</td>
<td>Dose changes not permitted</td>
</tr>
<tr>
<td></td>
<td>• 2 mg CR</td>
<td>• 2 mg CR</td>
<td>Follow up every 2 weeks for pill counts and adverse effect reporting</td>
</tr>
<tr>
<td></td>
<td>Dose changes not permitted</td>
<td>Follow up every 2 weeks for pill counts and adverse effect reporting</td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>Follow up every 2 weeks for pill counts and adverse effect reporting</td>
<td>AND</td>
<td>Families attended 4 weekly individual treatment sessions (50 minutes)</td>
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</tbody>
</table>

Statistics: Power of 90% detect an effect size of 0.6667 among the four groups

Alpha=0.05
- Assumes 25% loss to follow up
- Descriptive statistics used for all continuous variables
- Pearson’s correlation was calculated to determine the baseline level of association between sleep diary and actigraphy
- Bonferroni adjustments of p-values were performed due to multiple comparisons
- Repeated-measure analysis of variance was performed to determine if there was a difference in response among treatments

**Results**
- 185 met inclusion criteria
  - 160 randomized
  - 134 eligible for analysis
- Baseline Characteristics: 
  - Mean Age: 6.5 years, sex: 82% male, white Caucasian 100%

**Table 8. Efficacy Measures**

<table>
<thead>
<tr>
<th>Sleep Measure and Time</th>
<th>Combination Mean (SD); % N=35</th>
<th>Melatonin Mean (SD); % N=34</th>
<th>CBT Mean (SD); % N=33</th>
<th>Placebo Mean (SD); % N=32</th>
<th>P value (ES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 (0.67)</td>
</tr>
<tr>
<td>Baseline 12-wk</td>
<td>414.0 (45.3); 22.0 505.01 (31.1)</td>
<td>410.3 (45.0); 17.3 484.10 (33.1)</td>
<td>408.1(49.0); 9.3 445.1 (48.3)</td>
<td>413.0 (45.1); 0.1 416.23 (43.6)</td>
<td></td>
</tr>
<tr>
<td>SOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 (0.61)</td>
</tr>
<tr>
<td>Baseline 12-wk</td>
<td>85.8 (20.0); 60.8 33.7 (14.4)</td>
<td>81.2 (32.3); 44.3 45.2 (23.2)</td>
<td>76.3 (31.7); 22.5 59.13 (27.6)</td>
<td>78.2 (33.8); 0.02 79.60 (31.8)</td>
<td></td>
</tr>
<tr>
<td>WASO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 (0.53)</td>
</tr>
<tr>
<td>Baseline 12-wk</td>
<td>69.5 (23.3); 5 7.9 29.7 (12.9)</td>
<td>73.7 (45.0); 42.5 42.2 (22.3)</td>
<td>68.7 (31.7); 10.3 61.17 (28.9)</td>
<td>69.8 (45.2); -0.07 70.15 (42.7)</td>
<td></td>
</tr>
</tbody>
</table>

%- percent improvement; (S.D): standard deviation; ES: effect size; TST: total sleep time; SOL: sleep onset latency; WASO: wake after sleep onset; CBT: cognitive behavior therapy

- Melatonin alone was more effective than CBT alone at improving bedtime resistance, sleep onset delay, night awakenings, and sleep disturbances
  - 39.29% fell asleep within 30 minutes of bedtime in the melatonin group
  - 10.34% fell asleep within 30 minutes of bedtime in the CBT group
- 84.62% fell asleep within 30 minutes of bedtime in the combination group
- Dropout rate: 10%
- No adverse effects seen in trial
- No parental reports regarding loss of response

**Author’s Conclusion**
Melatonin in combination with CBT can be considered a safe and effective treatment for the management of sleep disorders in children with ASD

**Strengths**
- Large sample size
- Actigraphy used to verify sleep diary
- Placebo comparator
- Adherence assessed
- Psychotropics, breathing disorders, and obesity excluded

**Weakness**
- Not intent-to-treat study design
- Single-center
- Non-blinded
- Melatonin assay not used
Title: Wasdell MB, Jan JE, Bomben MM. A Randomized, Placebo-Controlled Trial of Controlled Release Melatonin in the Treatment of Delayed Sleep Phase Syndrome and Impaired Sleep Maintenance in Children with Neurodevelopmental Disabilities. J Pineal 2008; 44:57-64.

Purpose: To determine the safety and efficacy of controlled released (CR) melatonin in the treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disorders including ASD.

Design: Randomized, double-blind, multi-center, placebo-controlled, 4-week, crossover trial followed by 3 month open-label study.

Patient Population:

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 2-18 years</td>
<td>Mild sleep difficulties that did not cause daytime symptoms of insomnia</td>
</tr>
<tr>
<td>Failed sleep hygiene</td>
<td>Progressive neurological disorder</td>
</tr>
<tr>
<td>Sleep difficulty</td>
<td>Life threatening illness</td>
</tr>
<tr>
<td>Persistent nightly sleep onset delay of &gt;30 minutes</td>
<td></td>
</tr>
<tr>
<td>More than two nighttime awakenings lasting at least 15 minutes in duration resulting in daytime insomnia symptoms</td>
<td></td>
</tr>
<tr>
<td>Confirmed by 7 day sleep diary</td>
<td></td>
</tr>
<tr>
<td>Neurodevelopmental disorder</td>
<td></td>
</tr>
</tbody>
</table>

Cohorts: Melatonin CR versus placebo

Outcomes: Primary: total nighttime sleep as recorded on caregiver-completed sleep diary. Secondary: sleep onset latency, longest sleep episode, number of night awakenings.

Methods:

- Phases
  - Run in period: sleep hygiene was assessed and implemented
  - Cross over: 10 days of treatment (randomized: melatonin or placebo)
  - Placebo washout: 3-5 days
  - Cross over: 10 days of alternate therapy (melatonin or placebo second)
  - Optional: 3 month open-label continuation
- Medication: melatonin CR (1 mg IR and 4 mg SR)
- Administration: given 20-30 minutes before desirable bedtime
  - Meals avoided for 2-3 hours
- Clinician and Parent Ratings
  - Clinical Global Impression-Severity ( CGI-S): measured severity of sleep difficulty
  - Clinical Global Impression-Improvement (CGI-I): measured improvement from baseline
  - Parent’s Global Assessment Scale (PGAS): measures parents’ perception of child’s impairments across several functional and health dimensions
  - Family Stress Scale: impact of stress on family

Statistics: Power and significance: 80% and alpha=0.05. T-test used to compare the means of period differences in each of the two crossover sequences (two tailed). Paired t-test used to compare groups in open-label phase (two tailed).

Results:

- N=50
- 31 males; 19 females
- Average age: 7.38 year (range 2.05-17.81)
- Developmental condition breakdown: Severe intellectual loss (32), cerebral palsy (26), epilepsy (23), visual impairment (20), lack of mobility (18), ASD (16)
**Table 10. Efficacy Measures**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Baseline</th>
<th>Crossover Trial</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Treatment</td>
<td>Placebo</td>
<td>Melatonin</td>
</tr>
<tr>
<td><strong>Somnolog</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-NNS (m)</td>
<td>496.4 (71.1)</td>
<td>503.6 (87.7)</td>
<td>534.8 (86.2)</td>
</tr>
<tr>
<td>-SL (m)</td>
<td>72.9 (38.99)</td>
<td>65.2 (41.8)</td>
<td>32.5 (28.7)</td>
</tr>
<tr>
<td>-LSE (m)</td>
<td>415.4 (106.2)</td>
<td>434.3 (109.1)</td>
<td>453.3 (118.4)</td>
</tr>
<tr>
<td><strong>Actigraphy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-NNS (m)</td>
<td>449.3 (92.3)</td>
<td>443.1 (79.9)</td>
<td>466.8 (91.1)</td>
</tr>
<tr>
<td>-SL (m)</td>
<td>76.6 (52.10)</td>
<td>66.8 (37.3)</td>
<td>42.5 (31.8)</td>
</tr>
<tr>
<td>-LSE (m)</td>
<td>185.2 (102.6)</td>
<td>189.3 (99.9)</td>
<td>199.4 (100.5)</td>
</tr>
</tbody>
</table>

m: minute; (S.D): standard deviation; NNS: nighttime sleep; SL: sleep latency; LSE: longest sleep episode

**Table 11. Crossover Measures**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Randomization Trial (Melatonin)</th>
<th>Open-Label (Melatonin)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Diary N=50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-NNS (m)</td>
<td>539.9 (83.4)</td>
<td>540.8 (86.7)</td>
<td>0.90</td>
</tr>
<tr>
<td>-SL (m)</td>
<td>33.4 (29.5)</td>
<td>27.8 (24.9)</td>
<td>0.81</td>
</tr>
<tr>
<td>-LSE (m)</td>
<td>456.2 (120.9)</td>
<td>488.1 (122.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Actigraphy N=32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-NNS (m)</td>
<td>461.8 (86.4)</td>
<td>434.7 (96.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>-SL (m)</td>
<td>44.1 (30.1)</td>
<td>46.5 (48.4)</td>
<td>0.80</td>
</tr>
<tr>
<td>-LSE (m)</td>
<td>174.2 (75.7)</td>
<td>174.3 (78.9)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

m: minute; (S.D): standard deviation; NNS nighttime sleep; SL: sleep latency; LSE: longest sleep episode

- **Serious Effects/Side Effects from Randomization Phase:**
  - One hospitalization—Upon review, determined not to be drug related
  - 36% in melatonin CR group and 40% in placebo experiences side effects
  - Included: seizures, cold/flu/infection, gastrointestinal illness, agitation, anxiety, and headache
  - After investigation, these side effects were determined not to be drug induced and were typical of the children involved
  - No changes in vital signs between groups

- **Open-label Results:**
  - 50 children entered open-label phase
  - Final doses 5 mg (21 patients); 10 mg (25 patients); 15 mg (4 patients)
  - Somnolog data showed significant improvements in longest sleep episode and sleep efficiency
  - CGI-I showed greater improvement than in randomization phase

**Author’s Conclusion**

Controlled release melatonin is an effective treatment for delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental delays.

**Strengths**

- Actigraphy + sleep diary used
- Multi-center
- Included children 2 years and older

**Weaknesses**

- Coadministration of psychotropics was not assessed
- Results did not indicate which groups were most affected by melatonin use
- Adherence not assessed
- Short duration
- Melatonin assay not used
**Title**

**Purpose**
- To compare melatonin or placebo used alongside behavior management in children with ASD for sleep latency, multiple night awakening, and/or total sleep time

**Design**
- Randomized, double-blind, multi-center, 36-week, crossover trial

**Patient Population**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 3-16 years</td>
<td>Previous use of melatonin</td>
</tr>
<tr>
<td>Diagnosed ASD</td>
<td>Current use of melatonin</td>
</tr>
<tr>
<td>Failed behavior based sleep hygiene</td>
<td>Use of psychotropic medications</td>
</tr>
<tr>
<td>Sleep disorder involving:</td>
<td>Diagnosis of</td>
</tr>
<tr>
<td>- Excessive sleep latency</td>
<td>- Fragile X syndrome</td>
</tr>
<tr>
<td>- Excessive night-waking</td>
<td>- Rett’s syndrome</td>
</tr>
<tr>
<td>- Reduced total sleep time</td>
<td>- Other developmental disorder other than ASD</td>
</tr>
</tbody>
</table>

**Cohorts**
- Melatonin versus placebo

**Outcomes**
- Primary: Sleep latency, total sleep time, and number of night awakenings

**Methods**
- Washout Phase
  - Sleep hygiene was taught to all parents
  - Evening nutrition, relaxing environment, bedtime routine
- Sleep diaries were required for all parents to complete
  - Good sleep: 50% improvement
- Pharmacotherapy phase
  - Children had to fail sleep hygiene phase
  - Melatonin or placebo taken 1 hour before bedtime
- Dosing
  - Starting dose 2 mg
  - May increase by 2 mg every 3 nights
  - Maximum dose 10 mg
- Questionnaires
  - Included: Sleep Difficulties Questionnaire (SDQ), Developmental Behavior Checklist (DBC), General Health Questionnaire (GHQ), Side Effects Questionnaire (SEQ)

**Table 13. Treatment Group Assignment**

<table>
<thead>
<tr>
<th>Group</th>
<th>1 month</th>
<th>3 months</th>
<th>1 month</th>
<th>3 months</th>
<th>1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No medication</td>
<td>Melatonin</td>
<td>Washout</td>
<td>Placebo</td>
<td>No medication</td>
</tr>
<tr>
<td>B</td>
<td>Placebo</td>
<td>Washout</td>
<td>Melatonin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Statistics**
- Sleep diary data was analyzed by taking the average sleep latency, average time asleep, and average number of awakenings
  - Power: 80%; p-value=0.05
- Baseline means between randomized groups were compared using an independent groups t-test
- Melatonin and placebo scores were compared using a Wilcoxon Signed Rank test; repeated measured ANOVA was used to assess at crossover effects

**Results**
N=20 (16 male; 4 female)
- Loss to follow-up
  - 1 due to difficulties in medication administration, 1 due to inability to keep a sleep diary, 1 due to ineffectiveness of treatment assignment
- Questionnaires
Improvement in DBC with melatonin use
- No difference in side effects
  - Mean final melatonin dose = 7 mg (SD 3.01)
  - Side Effects
    - No seizures reported (no child on AED therapy)
    - No asthma attacks

### Table 14. Efficacy Measures

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (SD)</th>
<th>Mean Difference (SD) between melatonin and placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Melatonin</td>
</tr>
<tr>
<td>SL (min)</td>
<td>17</td>
<td>135 (63)</td>
<td>82.8 (50.6)</td>
</tr>
<tr>
<td>NOA (#)</td>
<td>17</td>
<td>0.50 (0.5)</td>
<td>0.43 (0.64)</td>
</tr>
<tr>
<td>TS (min)</td>
<td>17</td>
<td>499.9 (66.4)</td>
<td>556.1 (53.5)</td>
</tr>
</tbody>
</table>

SL: sleep latency; NOA: number of awakenings; TS: total sleep

### Author’s Conclusion
Melatonin (dose 2-10 mg; mean 7 mg) is safe and efficacious for the treatment of sleep disorders involving excessive sleep latency and total sleep time.

### Strengths
- Excluded psychotropic medications
- Sleep diary findings corroborated sleep difficulty questionnaire
- Long duration
- Multi-center

### Weaknesses
- Study only recruited 20 participants; did not reach 32 needed for power analysis
- Author’s conclusion is too bold because trial did not enroll enough patients to show difference between treatment groups
- Actigraphy was not used
- Adherence not assessed
- Melatonin assay not used
- Underlying sleep disorders not evaluated

### Table 15. Other Studies of Melatonin Use in Children with ASD

<table>
<thead>
<tr>
<th>Design and Treatment Groups</th>
<th>Subjects</th>
<th>Dose</th>
<th>Sleep Parameter Studied</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wirojanan^32 4-week randomized</td>
<td>ASD Fragile X ASD/Fragile X Age 2-15 Failed</td>
<td>3 mg or placebo</td>
<td>Sleep duration Sleep-onset time Sleep-onset latency time Number of night awakenings</td>
<td>- Mean night sleep duration was longer on melatonin than placebo by 21 minutes (p = 0.02)</td>
</tr>
<tr>
<td>Double-blind Placebo-controlled Crossover</td>
<td>Sleep hygiene</td>
<td></td>
<td></td>
<td>- Mean sleep-onset latency was shorter by 28 minutes (p = 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Mean sleep-onset time was earlier by 42 minutes (p = 0.02).</td>
</tr>
<tr>
<td>Garstang^33 9-week randomized</td>
<td>ASD Age 4-16 Psychotropics allowed</td>
<td>5 mg or placebo</td>
<td>Sleep latency Number of night awakenings Total sleep duration</td>
<td>- Sleep latency was 2.6 hour baseline, 1.91 hour with placebo and 1.06hr with melatonin [95% CI 2.28-2.93]</td>
</tr>
<tr>
<td>Placebo-controlled Double-blind Crossover</td>
<td></td>
<td></td>
<td></td>
<td>- Total sleep duration was 8.05 hour baseline, 8.75 hour with placebo and 9.84 hour with melatonin [95% CI 7.65-8.44]</td>
</tr>
</tbody>
</table>
### Table 16. Currently Recruiting Studies

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Study Design</th>
<th>Estimated Enrollment</th>
<th>Intervention</th>
<th>Parameter Studied</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin for Sleep in Autism</td>
<td>Randomized Single-blind</td>
<td>12</td>
<td>Melatonin 1, 3, 6, 9 mg</td>
<td>Dose response Tolerability</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td>Age 4-10 years</td>
<td></td>
<td></td>
<td>Adverse effects</td>
<td></td>
</tr>
<tr>
<td>Melatonin CR for the Treatment of Impaired</td>
<td>Open-label</td>
<td>20</td>
<td>Melatonin CR 5 mg</td>
<td>Clinical Global Impression</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Sleep Maintenance in 4-8 Year Old Children</td>
<td>Age 4-9 years</td>
<td></td>
<td></td>
<td>Improvement</td>
<td></td>
</tr>
<tr>
<td>with ASD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of Sleep Problems in Children</td>
<td>Randomized, Double-blind</td>
<td>120</td>
<td>Melatonin 3-9 mg</td>
<td>Sleep latency Aberrant Behavior</td>
<td>Recruiting</td>
</tr>
<tr>
<td>With ASD With Melatonin</td>
<td>Age 4-8 years</td>
<td></td>
<td></td>
<td>Checklist</td>
<td></td>
</tr>
</tbody>
</table>

### XIV. Summary

a. Children with ASD sleep poorly due to numerous reasons; however, an endogenous deficiency of melatonin is considered to be a primary cause
b. Recent data has shown a correlation between insomnia and regression in ASD
c. Regression is serious and devastating- vital skill sets are often lost permanently
d. Melatonin significantly improves sleep parameters, but it is still unknown if this has clinical impact on regression in children with or without regression
e. The benefits of melatonin seem to outweigh the risks and may be considered first line pharmacotherapy in children with ASD without psychiatric and neurologic disabilities for sleep disturbance
f. In earlier studies, melatonin use was associated with increased seizure risk and asthma exacerbation; however, this has not been supported in recent studies in children with only ASD
g. Although available over-the-counter, melatonin should be administered under the supervision of a physician due to the complexity of children involved
h. Doses of melatonin should range from 1-10 mg based on clinical trial data

### XV. Future Research

a. Consideration should be given to children with ASD age 1-3 years with insomnia because regression may occur at this age
b. Melatonin for primary prevention of insomnia in ASD (using the assay kit)
c. Studies with melatonin should include endpoints that include validated scales for behavior improvement
   i. Two studies currently recruiting
   ii. Aberrant Behavior Checklist and Clinical Global Impression-Improvement

### XVI. Conclusion

a. All patients with ASD should be screened for insomnia
b. Sleep disturbances may lead to regression in ASD
c. Melatonin has not been proven to prevent or treat regression in ASD
d. Melatonin may be initiated in children with ASD without other psychiatric or neurologic co-morbidities who suffer from insomnia and do not have adequate response to appropriate sleep hygiene
e. Dosage ranges between 1-10 mg/night, with 1-3 mg/night as a starting dose
## XVII. Appendix A: Full Justification for DSM-5 Updates in ASD

### Category Name

1. Delete the term “Pervasive Developmental Disorders”

<table>
<thead>
<tr>
<th>Category Name</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Delete the term “Pervasive Developmental Disorders”</td>
<td>Symptoms are not pervasive; they are specific to social-communication domain plus restricted, repetitive behaviors/fixated interests</td>
</tr>
<tr>
<td>2. Recommend new diagnostic category: “Autism Spectrum Disorder”</td>
<td>Overuse of PDD-NOS leads to diagnostic confusion</td>
</tr>
<tr>
<td></td>
<td>Lack of distinction between PDD-NOS and Asperger’s disorder</td>
</tr>
</tbody>
</table>

### Symptom Domains

THREE will become TWO

1. Social Communication domain will be created by merger of key symptoms from the DSM-IV Social and Communication domains
2. Fixated interests and repetitive behavior or activity

<table>
<thead>
<tr>
<th>Symptom Domains</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>THREE will become TWO</td>
<td>Deficits in communication are intimately related to social deficits. The two are “manifestations” of a single set of symptoms that are often present in differing contexts.</td>
</tr>
<tr>
<td></td>
<td>This de-emphasizes language skills not employed in the context of social communication.</td>
</tr>
</tbody>
</table>

### Merging of the ASD’s into a Single Diagnosis

AUTISM, ASPERGER’s and PDD-NOS will be collapsed into a single diagnosis: AUTISM SPECTRUM DISORDER

<table>
<thead>
<tr>
<th>Merging of the ASD’s into a Single Diagnosis</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTISM, ASPERGER’s and PDD-NOS will be collapsed into a single diagnosis: AUTISM SPECTRUM DISORDER</td>
<td>A single spectrum better reflects the clinical presentation, time-course and interventions.</td>
</tr>
<tr>
<td></td>
<td>Separation of ASD from typical development is reliable &amp; valid while separation of disorders within the spectrum is inconsistent (e.g. Asperger’s and PDD-NOS used interchangeably)</td>
</tr>
<tr>
<td></td>
<td>Severity is often used to differentiate autism, Asperger’s and PDD-NOS –but not consistently across centers.</td>
</tr>
</tbody>
</table>

### Diagnostic Deletion

Deletion of Rett Syndrome

<table>
<thead>
<tr>
<th>Diagnostic Deletion</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion of Rett Syndrome</td>
<td>ASD behaviors are not particularly salient in Rett Syndrome patients except for brief period during development.</td>
</tr>
<tr>
<td></td>
<td>Patients with Rett Syndrome who have autistic symptoms can still be described as having ASD, and clinicians should use the specifier “with known genetic or medical condition” to indicate symptoms are related to Rett</td>
</tr>
</tbody>
</table>

### Diagnostic Deletion

Delete Childhood Disintegrative Disorder (CDD)

<table>
<thead>
<tr>
<th>Diagnostic Deletion</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delete Childhood Disintegrative Disorder (CDD)</td>
<td>New knowledge that developmental regression in ASD is a continuous variable, with wide range in the timing and nature of the loss of skills, as well as the developmental milestones that are reached prior to regression. Rarity of CDD diagnosis makes systematic evaluation difficult, but review of accumulated world’s literature shows that CDD has important differences from other ASD’s, including the acuity and severity of regression, as well as co-occurring physical symptoms, such as loss of bowel and bladder control. DSM-5 will include a specifier for ASD to indicate nature of regression (if present)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
XVIII. **Sources**


“I have had enormous problems both getting to and staying asleep ever since the day I was born. It is a real pain I can tell you. You just cannot imagine what it feels like to lie there bored senseless, awaiting daylight and the time when it is deemed OK to get up... I didn’t used to like the dark either. My room and my things are familiar, my security. The dark creeps in and steals that familiarity and security away.” (Luke Jackson, ASD, 2002)