“There are two things to aim at in life; first to get what you want, and after that to enjoy it. Only the wisest of mankind achieve the second.”

Logan Pearsall Smith, essayist (1865-1946)
Psychopharmacology for Sleep and Agitation

Learning Objectives
1. Understand insomnia and agitation in context; as symptoms as well as disorders.
2. Identify the situation(s) when a pharmacological intervention is required in addition to non-pharmacological approaches.
3. Integrate the clinical approach; based on best available evidence in conjunction with other resources (that are not necessarily of high quality).
4. Appreciate that insomnia and agitation are ‘moving targets’ requiring ongoing assimilation of new evidence as it emerges.

Context
• This presentation focuses on Sleep and Agitation mostly as symptoms.
• These symptoms tend to occur more often as part of specific disorders (e.g., GAD, ADHD) or in specific populations (e.g., children with neurodevelopmental disorders, ASD).
• Some of these disorders and populations will be discussed henceforth. However, for comprehensive guidelines for specific disorders or populations – you may refer to the relevant literature.

Outline
• Sleep
  – Key points in phenomenology, assessment, and diagnosis.
  – The Melatonin story.
  – Other medications.
  – Melatonin in ADHD / ASD.
• Agitation
  – Key points in phenomenology and diagnosis.
  – Experts’ opinion and guidelines.
  – Special populations: ASD and delirium.
  – Clinical Case.

SLEEP

Phenomenology, Assessment, and Diagnosis

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Sleep Problems (1)

- Sleep problems occur frequently among youth with behavioral and/or emotional disorders.
- Difficulties related to sleep often overlap with psychiatric problems.
  - Sleep difficulties are a common symptom of depression.
  - Sleep deprivation can induce irritability and difficulties with attention that mimic or exacerbate symptoms of ADHD.
- Pediatric sleep problems range from highly specific disorders such as narcolepsy (alterations in specific neural systems) to simple behavioral difficulties such as bedtime resistance and late erratic schedules.


Sleep Problems (2)

- Even simple and seemingly minor behavioral sleep problems can become a source of major distress.
- Sleep has an important role in basic aspects of learning and memory consolidation as well as impacting on the regulation of behavior and emotions.
- Four important knowledge and clinical skills:
  1. Understanding normal sleep physiology and the normal development of sleep patterns.
  2. Knowledge of common sleep disorders.
  3. Clinical skills and knowledge relevant to assessing sleep habits and symptoms and diagnosing sleep disorders.
  4. Knowledge of relevant treatment principles.

Problems Going and Staying Asleep*

- Insomnia is a common complaint among older children and adolescents, particularly sleep onset insomnia. It is defined as difficulty falling asleep or staying asleep, even when a person has the chance to do so*.
- One aspect of the difficulty is that young children often show a paradoxical reaction when obtaining insufficient or inadequate sleep.
- The three principles of treating bedtime resistance:
  1. Creating an emotional state of calmness and safety.
  2. Consistent limit setting.
  3. Establishing good bedtime habits (i.e., a wind-down period and a sequence of activities that begin 30-60 min before bedtime; sleep hygiene).

J Can Acad Child Adolesc Psychiatry, 23:3, Fall 2014

Insomnia

- Childhood insomnias are a group of sleep-related or bedtime problems involving difficulties initiating or maintaining sleep, and/or poor sleep quality. Problems may range in severity and include issues such as bedtime resistance, parent-child conflict at bedtime, and/or inappropriate sleep associations or habits. (Reid, Huntley, & Levin, 2008).
- The term inadequate Sleep hygiene applies when individuals experience insomnia or excessive sleepiness which results from poor sleep habits (or ‘sleep hygiene’). Stepanik & Wyatt, 2003. Such habits include: inconsistent wake times or bedtimes, frequent periods of extended amounts of time spent in bed, the consistent use of products containing sleep-disrupting agents before bedtime (such as caffeine), and engaging in stimulating or emotion-provoking activities close to bedtime (e.g., exercise, playing videogames, watching television), among others. To qualify for this diagnosis, a child must display only 1 habit that constitutes inadequate sleep hygiene (American Academy of Sleep Medicine [AASM], 2005).

J Can Acad Child Adolesc Psychiatry, 23:3, Fall 2014
Polysomnography (1)

- When is PSG indicated?
  1. Establishing the diagnosis of OSA.
  2. Evaluating for narcolepsy.
  3. Verifying periodic limb movement disorder.
  4. Initiating and titrating of breathing aids (CPAP, NIPPV).
  5. Neuromuscular disorders.
  6. Complex parasomnias.
  7. Epilepsy.

Polysomnography (2)

- When is PSG not indicated?
  “PSG is not routinely indicated for the evaluation of difficulty initiating or maintaining sleep (insomnia), circadian rhythm disorders, non-epileptic parasomnias, chronic lung disease, depression, bruxism, or behavior-based sleep disorder.”

The Melatonin Story

- A total of 105 medication-free children, ages 6 to 12 years, with ADHD and chronic sleep onset insomnia participated in a randomized, double-blind, placebo-controlled trial using 3 or 6 mg Melatonin, or placebo for 4 weeks.
- There was no significant effect on behavior, cognition, and quality of life.

Sleep Onset Insomnia

- SOI was defined as:
  1. Complaints of sleep-onset problems expressed by parents and/or child.
  2. Occurrence on at least 4 days / week for longer than 1 year.
  3. Average sleep onset later than 8:30 PM for children at age 6 years and for older children 15 minutes later per year.
  4. Average sleep latency exceeding 30 minutes.

Clinical Assessment

All 204 children were assessed by a psychologist (K.B.H.) and a board-certified child and adolescent psychiatrist (W.B.G.). ADHD was diagnosed in accordance with guidelines of the American Academy of Pediatrics (2000) and American Academy of Child and Adolescent Psychiatry (1997) and included clinical history, Diagnostic Interview Schedule for Children-Parent form (Shaffer et al., 1996), Child Behavior Checklist (CBCL; Achenbach, 1991a), and Teacher’s Report Form (TRF; Achenbach, 1991b). Subtypes of ADHD were determined according to DSM-IV. A shortened IQ test (WISC-R Dutch version: Block Design, Vocabulary [De Bruin et al., 1986]) was administered when IQ had not been assessed previously and school performance had been subaverage in the past 3 years.

- What’s missing?
Melatonin (1)
- Melatonin is the primary regulatory hormone of circadian rhythm and plays an important role in initiating and maintaining sleep.
- It is synthesized from serotonin and secreted by the pineal gland.
- Levels peak around 2 am at concentrations 10 to 100 times daytime levels. Melatonin levels are regulated by exposure to light.
- Exogenous Melatonin has significant variability in pharmacokinetic and pharmacodynamic properties.

Melatonin (2)
- It is being increasingly prescribed for children with sleep disorders despite the fact that:
  - It is not registered for use in children.
  - It has not undergone the formal safety testing expected for a new drug, especially long-term safety in children.
  - It is known to have profound effects on the reproductive systems of rodents, sheep and primates, as well as effects on the cardiovascular, immune and metabolic systems.
  - Potential for important interactions with other drugs.
  - There is considerable unclarity with respect to dosage, formulation, and timing of administration.


Dosing, Formulation, Timing

Positive Bias
- This is a ‘natural’ product (it is not…), OTC, that families ask for.
- A prescription is not required.
Other Medications

Table 2 (Cont.)

- Diphenhydramine – **None specific.**
  - “Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents”. Pediatrics, 2004; 114:e85-90
- Benzodiazepines – **None.**
- Non-Benzodiazepine agonists – **Little Data.**

Data in Children (1)
Zolpidem in ADHD (1)
• An 8-week, multicenter, double-blind, placebo-controlled, parallel-group study. Patients underwent stratification according to age (6–11 years [N=111] or 12–17 years [N=90]) and were assigned randomly to receive treatment with the study drug or placebo.
• The primary efficacy variable was latency to persistent sleep between weeks 3 and 6.
• **Conclusion:** Zolpidem at a dose of 0.25 mg/kg per day to a maximum of 10 mg failed to reduce the latency to persistent sleep on PSG recordings after 4 weeks of treatment in children and adolescents 6 through 17 years of age who had ADHD-associated insomnia.

Zolpidem in ADHD (2)
• **Insomnia associated with ADHD:**
  – Sleep disorder is not a criterion of ADHD.
  – Is the medication given to counteract the side-effect of stimulants?
  – Is it that these children have some emotional problems (e.g., even subclinical anxiety or depression)?
  – Is it that these children have bedtime resistance (e.g., comorbidity with ODD)?
  – Is this truly insomnia?

Eszopiclone in ADHD
• A 12-week, placebo-controlled RCT evaluated efficacy and safety of Eszopiclone (1 or 2 mg in children aged 6–11 years; 2 or 3 mg in children ages 12–17 years), in 486 patients with ADHD-related insomnia.
• The primary efficacy variable was change in latency to persistent sleep from baseline to week 12, based on PSG. Key secondary measures were PSG-measured wake time after sleep onset, CGI Parent/Caregiver and Child scales, and the Conners’ ADHD rating scales.
• **Conclusion:** Eszopiclone failed to reduce latency to persistent sleep on PSG after 12 weeks in children aged 6 to 17 years with ADHD-related insomnia.

Data in Children (2)
• **Ramelteon – None.**
• **Clonidine – Limited Data** (mostly for ADHD / tics).
  – Evidence is equivocal.
• **Trazadone – None.**
• **Melatonin – Mostly for ADHD / ASD.**

Melatonin in ADHD
• Three studies looking at the effects of Melatonin on ameliorating sleep disturbances **within ADHD.**

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Effect of Melatonin on Sleep, Behavior, and Cognition in ADHD and Chronic Sleep-Onset Insomnia

- 105 medication-free children, ages 6 to 12 years, with rigorously diagnosed ADHD and chronic sleep onset insomnia participated in a randomized, double-blind, placebo-controlled trial using 3 or 6 mg melatonin (depending on body weight), or placebo for 4 weeks.
- Primary outcome parameters were actigraphy-derived sleep onset, total time asleep, and salivary dim light Melatonin onset.

Outcome Variables (1)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Melatonin</th>
<th>Placebo</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLMO</td>
<td>-0.44 ± 1.07</td>
<td>+0.13 ± 0.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Onset</td>
<td>-0.27 ± 0.48</td>
<td>+0.10 ± 0.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>-21.3 ± 33.0</td>
<td>+3.0 ± 31.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Total Time Asleep</td>
<td>+19.8 ± 61.9</td>
<td>-13.6 ± 50.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Outcome Variables (2)

- The negative placebo effect on objective sleep measures was consistent with previous results in insomniac children (Smits et al., 2001; Van der Heijden et al., 2005a), but not with positive placebo effects usually found in adult insomniacs (Perlis et al., 2005). This is an interesting phenomenon for which we do not have a clear explanation.
- CBCL, TRF, quality of life, and cognition – no difference.

Outcome Variables (3)

- Side-effects:
  - Headache, 5.7%
  - Hyperactivity, 5.7%
  - Dizziness, 3.8%
  - Abdominal pain, 3.8%
- Placebo: None

Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia

- Structured questionnaire for the parents.
- Subjects consisted of participants of the aforementioned study. Response rate was 93% (94/101). Mean time to follow up was 3.7 years.
- No serious adverse events or treatment related co-morbidities were reported.
- 65% of the children still used melatonin daily and 12% occasionally.
- Temporal discontinuation of treatment resulted in a delay of sleep onset in 92% of the children.
- 9% of the children could discontinue melatonin completely because of improvement of SOI.

"We conclude that Melatonin remains an effective therapy on the long term for the treatment of SOI in children with ADHD and has no safety concerns regarding serious adverse events or treatment related co-morbidity. Discontinuation of Melatonin treatment usually leads to a relapse of sleep onset insomnia and in resuming Melatonin treatment, even after several years of treatment".

However, Long-term questions regarding safety remain unanswered. *Lab studies not conducted, nor cognitive testing.*
Melatonin Effects in Methylphenidate Treated Children with Attention Deficit Hyperactivity Disorder: A Randomized Double Blind Clinical Trial

• 50 Children, ages of 7 to 12 years with combined-type.
• Randomly divided into 2 groups, stratified by gender.
• One group received Melatonin (3 or 6mg) **combined with Methylphenidate** (1mg/kg), and the other group received placebo combined with Methylphenidate (1mg/kg).

A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities

• A randomized double-blind, placebo-controlled crossover trial of CR Melatonin (5 mg) followed by a 3-month open-label study. Dose was gradually increased until the therapy showed optimal effects.
• Sleep characteristics were measured by caregiver who completed somnologs and wrist actigraphs. Clinician rating of severity of the sleep disorder and improvement from baseline, along with caregiver ratings of global functioning and family stress were also obtained.
• 51 children (ages 2 to 18 years) who did not respond to sleep hygiene intervention were enrolled.

Melatonin in NDD / ASD

• Several studies looking at the effects of Melatonin on ameliorating sleep disturbances **within** NDD / ASD, of which 2 are relatively large (N>30):
  - “A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities”.
    J Pineal Res, 2008; 44:57-64.
  - “Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial”.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Melatonin-Placebo</th>
<th>Placebo-Melatonin</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Somnolog</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- night-time sleep</td>
<td>-37.00 (85.32)</td>
<td>24.54 (62.76)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>- Sleep latency</td>
<td>24.83 (38.95)</td>
<td>-41.94 (43.99)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Actigraph</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- night-time sleep</td>
<td>-26.40 (48.34)</td>
<td>20.35 (61.70)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>- Sleep latency</td>
<td>15.99 (28.46)</td>
<td>-34.68 (45.86)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial

• 161 children with ASD, aged 4–10 years, suffering from SOI and impaired sleep maintenance, were assigned randomly to either:
  1. Combination of **CR Melatonin** and CBT.
  2. CR Melatonin.
  3. Four sessions of CBT.
• Twelve weeks; 1:1:1:1 ratio. Children were studied at baseline and at endpoint.
• Treatment response was assessed with 1-week actigraphic monitoring, sleep diary and sleep questionnaire.

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Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial

- Outcome measures, derived actigraphically, were sleep latency, total sleep time, wake after sleep onset and number of awakenings.
- All active treatment groups showed improvements across all measures, with moderate-to-large effect sizes. Melatonin treatment was mainly effective in reducing insomnia symptoms, while CBT had a small positive impact mainly on sleep latency.
- The combination treatment group showed a trend to outperform other active treatment groups, with fewer dropouts and a greater proportion of treatment responders.

The Problem (1)

- Rates of off-label medication use in the pediatric population continue to increase, and are often used in the management of acute - and chronic - agitation in the pediatric population.
- Evidence to inform best practice is limited.
- An overwhelmed MH system
  - more emergency department visits
  - more prescriptions (easy way).
- Particular problem for immigrants. No access in time
  - ED referral; more likely during a crisis.
- Fewer visits occurring during the summer months, and presentations tend to occur most often in the evening.
  - Arrival time to ED is an important factor.
The Problem (2)

• Clinical practice often based on available expertise and resources, and lacks evidence base to inform best practice.
  We offer what we have, not what we should.

• **Acute agitation** is defined as a state of behavioral dyscontrol that will likely result in harm to the patient or healthcare workers without intervention.

• Agitation may be a symptom of: suicidality, NSSI, depression, anxiety, disruptive behavior, ASD, medical condition (including delirium).

• Strive to use least restrictive means possible.

The Problem (3)

• Common off-label uses of **antipsychotics** include treatment of: disruptive behaviors, aggression in both neuro-typical and neuro-atypical children, ODD, CD, PTSD, ADHD, cluster B traits, and sleep disorders. Off-label use is rising.

• Only chlorpromazine, haloperidol, droperidol, risperidone, and aripiprazole carry FDA indications for aggression and/or irritability, often for **select subsets** of the pediatric population (e.g., irritability in ASD).

• Benzodiazepines – **Limited Data**.

• Antihistamines – **None**.

Pharmacotherapy: Two Approaches

1. **Treat co-morbid / underlying disorders.**
   E.g. stimulants for ADHD, antidepressants for depression, treat sleep disorders.
   – The Center for Education and Research on Mental Health Therapeutics (CERT) developed the Treatment of Maladaptive Aggression in Youth (T-MAY) guidelines.
   – It concluded: “Initial medication treatment should target the underlying disorder(s). (Grade of evidence: A; Strength of recommendation: very strong)”.

2. **Treat maladaptive aggression as a ‘target symptom’**.

Experts’ Opinion and Guidelines

*Experts’ Recommendations for Treating Maladaptive Aggression in Youth*.

Treatment of Choice* - rated a ‘9’ by at least 50%.

Experts’ Opinion Vs. Guidelines

• “Experts’ Recommendations for Treating Maladaptive Aggression in Youth”.

Treatment of Maladaptive Aggression in Youth: CERT Guidelines II. Treatments and Ongoing Management

• Pediatrics, 2012; 129:e1577-e1586.

• **Conclusion:** “Treatment of children with maladaptive aggression is a moving target requiring ongoing assimilation of new evidence as it emerges”.

• Apps:
**Methods:** Systematic reviews of published literature, expert survey of recommended practices, consensus conference of researchers, policymakers, clinicians, and family advocates. "synthesis of the available evidence"

- Eleven recommendations.
- Pharmacotherapy recommendation based on:
  - 29 RCTs for aggressive youth.
  - Mean age 9.5 years.
  - 81.6% of subjects boys.
  - 66.4% were white.

**First two recommendations pertain to psychosocial interventions, which should be the first-line of treatment.**

1. “Provide or assist the family in obtaining evidence-based parent and child skills training during all phases of care”. (Grade of evidence: A; Strength of recommendation: very strong).
2. “Engage the child and family in taking an active role in implementing psychosocial strategies and help them to maintain consistency”. (Grade of evidence: B; Strength of recommendation: very strong).

**Initial medication treatment should target the underlying disorder**.

4. “Consider adding an antipsychotic medication […]. If severe aggression persists after an adequate trial of treatments for the underlying disorder (including psychosocial treatments)”.  
5. “If Insufficient response, try a different antipsychotic medication”. (Grade of evidence: D; Strength of recommendation: Strong).  
6. “For a partial response to an initial first-line antipsychotic, consider augmentation with a mood stabilizer”.

7. “Avoid using more than 2 psychotropic medications simultaneously”.
8. “Conduct side-effect and metabolic assessments and laboratory tests that are clinically relevant, comprehensive, and based on established guidelines”. (Grade of evidence: A; Strength of recommendation: very strong).

**Dosages for ‘Chemical Restraint’**

- Variable by age, weight, diagnosis, availability, site, and local practice.

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**Methods:** Systematic review and meta-analysis of RCTs of antipsychotics, lithium, and anticonvulsants for aggression and conduct problems in youth with ADHD, ODD, and CD. Each medication was given an overall quality of evidence rating based on the Grading of Recommendations Assessment, Development and Evaluation approach (i.e., GRADE).

**Results:** Eleven RCTs of antipsychotics and 7 RCTs of lithium and anticonvulsants were included.

**Conclusion:** With the exception of Risperidone, the evidence to support the use of antipsychotics and mood stabilizers is of low quality.

Risperidone in youth with subaverage IQ and ODD, CD, or DBD-NOS: Cohen’s $d$ vs. placebo is 0.72

Risperidone in youth with average IQ and ODD or CD, with and without ADHD: Cohen’s $d$ vs. placebo is 0.60.

**Special Populations:** ASD and Delirium

**Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis**

**Results:** Forty-six RCTs were identified, looking at irritability and aggression in the context of ASD.

**Risperidone** and Aripiprazole were found to be the most effective, with the largest effect sizes.

Based on reduction in the Aberrant Behavioral Checklist–Irritability (ABC-I) scores.

- Cohen’s $d$ for Risperidone: 0.86.
- Cohen’s $d$ for Aripiprazole: 0.78.
Cont.
• Side-effects: Sedation, extrapyramidal sides effects, and weight gain.
• Other effective medications (low quality data):
  – Methylphenidate.
  – Clonidine.
  – Tianeptine (new antidepressant; glutamatergic).
  – NAC (N-acetylcysteine).

The Pharmacologic Management of Delirium in Children and Adolescents

• The management of delirium is predicated on treatment of the underlying condition and non-pharmacologic supportive care.
• Antipsychotic medications have not been approved by the FDA to manage delirium in children.
• No RCTs in children.
  We are left with experts’ opinion.

Cont.
• Olanzapine – Sedating and has ODT. Useful for agitation.
• Risperidone – Has liquid form which is useful for young children (low dosages).
• Quetiapine - Useful in low doses at bedtime to assist with insomnia associated with delirium. Less hepatic side-effects.
• Fluphenazine - Appears least likely to result in arrhythmia (congenital heart disease).
• Melatonin - Well tolerated with minimal side effects.
• Clonidine and Dexmedetomidine – Dexmedetomidine is very effective, but very risky (IV only).

Clinical Case
• A 14 year-old young man, undergoing several consecutive cycles of chemotherapy for sarcoma.
• Prognosis at this time is guarded, but cure is still “attainable”.
• Family and boy are increasingly anxious because of the vagueness of the situation.
• Three weeks prior, d/t anxiety and insomnia, Clonazepam was started (0.5 mg TID). Very good effect thus far; no apparent side-effects.
• Yesterday, developed delirium. Cause unknown for now.
• What do you do with the Clonazepam?