Sleep Disorders and Developmental Disabilities
Rafael Pelayo, MD

Do you really want to sleep like a baby?

“He/She won’t sleep”
What goes through your mind when you hear this??

Your life is reflected in your sleep

Your sleep is a reflection of your life
Common Sleep Disorders

- Normal Sleep?
- Behavioral Insomnia of Childhood
- OSA/SDB
- Parasomnias
- PLM/RLS
- Narcolepsy
- Delayed Sleep Phase Syndrome

Sleep History: 4 Elements

- Amount
- Quality
- Timing
- State of Mind

Do you remember being tucked in?

How do we get a child to sleep in the lab?
No Need

The power of sleep

Sleep Stages

EEG Recordings

Typical Nighttime Sleep Pattern in Young Adult

Sleep Quality:

Awake
Stage 1 and REM
Stage 2
Stage 3
Stage 4

Time (hours)

1 2 3 4 5 6 7

Amount: Sleep Homeostasis

Courtesy of Dale Edgar PhD
14.5 The Retinohypothalamic Pathway in Mammals

(a) This pathway carries information about the light-dark cycle in the environment to the SCN. For clarity of synaptic connections, the SCN is shown proportionately larger than other features. (b) Axons (seen at the bottom of the image) from the left eye are labeled red, while those from the right eye green. Both eyes project so diffusely to the overlying SCN that they are outlined in yellow. (Photographs courtesy of Cynthia L. Jordan.)
Sleep Timing

- Sleep timing is influenced by homeostatic and circadian factors
- The less we sleep the more sleep we need and vice versa
- Twice a day our alertness level peaks
- Twice a day our sleepiness peaks
The need for sleep is biological
The way you sleep is learned
What wakes you up may not be what keeps you awake

What is the motivation to go to bed?
What is the motivation to get out of bed?

Kids and Sleep: What Are They On?

Trends in medication prescribing for pediatric sleep difficulties in US outpatient settings ‘07

- Cross-sectional study on pts ≤17 yrs from ‘93-‘04 NAMCS.
- 18.6 million visits occurred for sleep related difficulty in children most 6-12 yr.
- 81% of visits Rx’ed a med (only 48% of the adult patients with insomnia Rx’ed!)
- … physicians frequently prescribed medications for sleep difficulties in children in US outpatient settings. Of particular concern is prescribing of many unapproved medications for this population
The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis 2010

- Meta-analysis of RCT of melatonin in advancing DSPS pts
- 5 trials including 91 adults and 4 trials including 226 children showed that melatonin (0.3-6 mg) advanced mean endogenous melatonin onset by 1.18 hours (0.89-1.48 h) and clock hour of sleep onset by 0.67 hours (0.45-0.89 h). Melatonin decreased sleep-onset latency by 23.27 minutes (4.83-41.72 min). The wake-up time and total sleep time did not change significantly.

Potential Pharmacokinetic Basis for Zolpidem Dosing in Children With Sleep Difficulties ‘07

- Open-label, dose-escalation study in children with insomnia. 21 children, seven per age group (2-6, >6 to 12, >12 to 18 years), received a single dose of zolpidem at one of the three dose levels (0.125, 0.25, or 0.50 mg/kg (20 mg maximum dose))
- Overall, zolpidem was well tolerated and a pediatric dose of 0.25 mg/kg is recommended for future efficacy studies.

Do not to equate sedation with normal sleep!
The real issue is not the pill but the insomnia

The thought of sleeping wakes them up

**SELF Correction**

- Social
- Exercise
- Light
- Food

“...and on the box sat a fat and red-faced boy, in the state of somnolency.” C. Dickens
Sleep Disorders in Children

Correct Physiological Rest Position

Anterior portion of tongue on palate.
Lips closed and relaxed.
Teeth apart.
Nasal breathing.

Incorrect Physiological Rest Position

Tongue depressed.
Lips apart.
Teeth apart.
Mouth-breathing.
Head forward.

Thin people can have OSA too

CPAP ain’t just CPAP no more

- CPAP
- CPAP with C-Flex™/ EPR
- Bi-level
- Bi-level with Bi-Flex™
- Bi-level with a backup rate
- Automated CPAP
- Automated Bi-level
- Adaptive Servo Ventilator (SV) PAP
OSA Treatments

- PAP: autoPAP, Bi-level, autoBi-Level, ASV, AVAPS, Bi-level ST, PAP for COPD
- Surgery: Maxilomandibular advancement and expansion, nasal valves and turbinates, pharyngoplasty, genioglossus advancement, Uvulopalatal flap
- Oral appliances: dozens available
- Conservative: Weight loss, positional therapy, weight loss
- Novel treatments: Winx and Provent
- Experimental options: Hypoglossal stimulators

Can Sleepy Students Learn Anything?

School Start Times for Adolescents
AAP 2014

Insufficient sleep in adolescents as an important public health issue…the evidence strongly implicates earlier school start times (ie, before 8:30 am) as a key modifiable contributor to insufficient sleep…research has now demonstrated that delaying school start times is an effective countermeasure to chronic sleep loss. The AAP strongly supports the efforts of school districts to optimize sleep in students and urges high schools and middle schools to aim for start times that allow students the opportunity to achieve optimal levels of sleep (8.5–9.5 hours)
Sleep impacts behavior

Sleep disorders mimic attention and learning disorders

National Institutes Of Health State-of-the-Science Manifestations And Management Of Chronic Insomnia In Adults June '05

Chronic insomnia is a major public health problem affecting millions of individuals, along with their families and communities. Little is known about the mechanisms, causes, clinical course, comorbidities, and consequences of chronic insomnia. Evidence supports the efficacy of cognitive-behavioral therapy and benzodiazepine receptor agonists in the treatment of this disorder. Very little evidence supports the efficacy of other treatments, despite their widespread use. Moreover, even for those treatments that have been systematically evaluated, the panel is concerned about the mismatch between the potential lifelong nature of this illness and the longest clinical trials, which have lasted 1 year or less. A substantial public and private research effort is warranted, including the development of research tools and the conduct of longitudinal studies and randomized clinical trials. Finally, there is a major need for educational programs directed at physicians, health care providers, and the public.

Slumber Parties ain’t about sleeping

Any Questions?

Benzodiazepine hypnotics

<table>
<thead>
<tr>
<th>Hypnotic Drugs</th>
<th>Half-life (hr)</th>
<th>Onset of Action (min)</th>
<th>Pharmacologically Active Metabolites</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quazepam (Doral)</td>
<td>48-120</td>
<td>30</td>
<td>N-desalkyl (flurazepam)</td>
<td>7.5-15</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>48-120</td>
<td>15-45</td>
<td>N-desalkyl (flurazepam)</td>
<td>15-30</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>2-6</td>
<td>2-30</td>
<td>None</td>
<td>0.125-0.25</td>
</tr>
<tr>
<td>Estazolam (ProSom)</td>
<td>8-24</td>
<td>Intermediate</td>
<td>None</td>
<td>1-2</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>8-20</td>
<td>45-50</td>
<td>None</td>
<td>15-30</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol)</td>
<td>10.7-20.3</td>
<td>Short</td>
<td>N-desmethyl (flunitrazepam)</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Nitrazepam (Alodorm)</td>
<td>25-35</td>
<td>Intermediate</td>
<td>None</td>
<td>5-10</td>
</tr>
</tbody>
</table>
Receptor Pharmacology of Sedating Antidepressant Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>NE Reuptake</th>
<th>5-HT Reuptake</th>
<th>5-HT Receptor Antagonism</th>
<th>Alpha Adrenergic Antagonism</th>
<th>M Adrenergic Antagonism (Anticholinergic)</th>
<th>H Antagprphic Antagonism (Antihistaminic)</th>
<th>Other Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>+</td>
<td>0+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>5-HT, 5-HT, 5HT, 5HT</td>
</tr>
<tr>
<td>Valproate</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>4HT, 4HT, 4HT</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>1+</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>4HT, 4HT, 4HT</td>
</tr>
</tbody>
</table>

Summary of Other Drugs Used to Treat Insomnia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tmax (hr)</th>
<th>Metabolism</th>
<th>Kt (hr)</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin</td>
<td>20-60 min</td>
<td>Conjugation, oxidation by CYP enzymes</td>
<td>0.5-0.6 min</td>
<td>Agonist at melatonin receptor</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>0.3 hrs</td>
<td>Extensive first pass metabolism, hepatic oxidation primarily via CYP1A2, active metabolite M-II</td>
<td>1.2 (2-5 hours for M-II)</td>
<td>Agonist at melatonin MT1 and MT2 receptors</td>
</tr>
<tr>
<td>Melatonin</td>
<td>2-2.5</td>
<td>Demethylation, oxidation</td>
<td>0-2</td>
<td>Agonist at melatonin MT1, MT2 receptors</td>
</tr>
<tr>
<td>Valproate</td>
<td>Uncertain</td>
<td>Uncertain owing to multiple constituents</td>
<td>Uncertain owing to multiple constituents</td>
<td>Uncertain owing to multiple constituents</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>2-3</td>
<td>Converted to metabolites, which undergoes conjugation</td>
<td>0-10 (in infants)</td>
<td>May act directly as neurotransmitter, increases brain dopamine levels</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1-2</td>
<td>CYP 3A4</td>
<td>6</td>
<td>Antagonizes H1, alpha1, M1, 5-HT2, D2 receptors</td>
</tr>
<tr>
<td>Gamma-Hydroxybutyrate</td>
<td>30-45 min</td>
<td>Metabolized to GABA, succinic semialdehyde, H2O and CO2</td>
<td>25-70 min</td>
<td>May act directly as neurotransmitter, increases brain dopamine levels</td>
</tr>
</tbody>
</table>

The trial of infant response to diphenhydramine: the TIRED study--a randomized, controlled, patient-oriented trial Merenstein et al 06

- Double-blind, randomized, controlled clinical trial. 44 kids aged 6 to 15 months. Placebo or diphenhydramine given for a week.
- Data safety monitoring board voted unanimously to stop the trial early because of lack of effectiveness of diphenhydramine over placebo. Only 1 of 22 children receiving diphenhydramine showed improvement compared with 3 of 22 receiving placebo.
- CONCLUSION: During 1 week of therapy and at follow-up 2 and 4 weeks later, diphenhydramine was no more effective than placebo in reducing nighttime awakening or improving overall parental happiness with sleep for infants.

Peds Sleep Pharm

- There is a need for greater information on the pharmacological management of sleep disorders in children.
- Pharmacological guidelines need to be developed specifically for sleep disorders in children.
- These guidelines should FDA approved for the specific sleep disorder or for the pediatric age range. This will avoid physicians from being forced to prescribe medications as an “off label” indication.
Peds Sleep Pharm

- Development of easy to swallow, chewable or liquid forms of these medications would be well received by parents everywhere. When these are not available, instructions for compounding these medications into a suspension by pharmacists are needed.
- Integration of behavioral and pharmacological treatments may yield better patient outcomes. This would require pediatricians to have a comprehensive understanding of clinical sleep disorders in children.
- Training programs should play lead role in enhancing pediatricians’ knowledge of the pharmacological treatment of sleep disorders in children.

Non-pharmacological management of problematic sleeping in children with developmental disabilities.

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