Psychopharmacology of Sleep Disorders

Matt T. Bianchi MD PhD MMSc
Assistant Professor
Director, Sleep Division
Neurology Department
Massachusetts General Hospital
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Outline

- Overview
- Insomnia and hypnotics
- Hypersomnia and stimulants
- RLS, PLMS: iron, dopamine, and others
- Parasomnia therapy
- Circadian disorders and chronotherapy
Two main sleep control systems

1. Circadian Rhythm
   - Internal clock regulating tendency to sleep
   - Dissociable from actual sleep-wake patterns

2. Homeostasis
   - Depends on recent sleep-wake behavior
   - The longer you are awake, the sleepier you get
Mono-amine control of wakefulness

Tuberomammillary nucleus (histamine)

Ventral tegmental & periaqueductal gray (dopamine)

Raphe nuclei (serotonin)

Locus coeruleus (norepinephrine)

Aston-Jones 1981; Espana 2004; Parmentier 2002; Saper 2005
Cholinergic control of wake (and REM)

Espana 2004; Saper 2005; Mesulam 2004
Sleep promoting center: VLPO

Ventrolateral preoptic area (GABA)

Fuller & Saper 2006
“Flip-Flop” model of sleep and wake

Ventrolateral preoptic area

GABA

NE, 5HT, ACh

Monoamines Acetylcholine

 orexin

Sleep

Wake

Lu 2006; Saper 2010
Remarks on melatonin

- Melatonin signals darkness: 3-5 hours before bed time
- Any light after dusk suppresses natural nocturnal rise
- In humans, melatonin has circadian and hypnotic action
- Dosing is 0.3 to 5mg in OTC formulations, but PK is highly variable even from same preparation
- The only real contraindication is warfarin
Receptor pharmacology overview

Bianchi 2014: Essentials of Sleep Pharmacology (in Therapy in Sleep Medicine, Barkoukis et al, Eds)
Drug impacts on sleep scoring

- Many drugs outside of neuro/psych suppress REM
- Most antidepressant drugs (SSRI, SNRI, and TCA) tend to suppress REM sleep
- Benzodiazepines tend to suppress REM and deep NREM (N3), while enhancing N2.
- Z-drugs have the least impact on stages
- There is no evidence that any of these changes have meaningful clinical correlate
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Insomnia

- Trouble falling asleep or staying asleep
- Purely clinical diagnosis based on self-report
- Many causes and contributors
- Spielman’s 3P model to structure approach:
  Pre-disposing, precipitating, perpetuating
The challenge of sleep perception

Many factors influence reporting sleep-wake duration:

- Demographics (Kurina, 2013)
- Who you ask (e.g., insomnia, mood, health status) (Harvey, 2011; Bliwise, 1993)
- When you ask (daily diary vs retrospective “gestalt”) (Fichten, 2005)
- How you ask (direct query or indirect via clock times) (Alameddine, 2014)
The insomnia phenotype challenge

- It seems natural to define insomnia by symptoms only
- When objective data is available in other settings, we do not follow self-report (HTN, DM, weight)
- Unclear medication risk-benefit balance
- The only large epidemiological study to measure symptoms and objective PSG showed prospective medical risk (and incident depression) only in those with both insomnia symptoms and objective short sleep
  
  (Vgontzas 2013, review)
CBT for insomnia

- A specialized subset of CBT
- Requires special training offered at some centers
- Equivalent or superior to medications in comparative effectiveness trials
- Can be primary therapy, or used in those already on chronic medication to help with weaning
- Online versions are validated (e.g., Shut-I, others)
CBT-I components

- Stimulus control
- Sleep hygiene
- Sleep restriction
- Relaxation training
- Cognitive therapy (re-focus beliefs)
Hypnotics: A last resort for insomnia

- Only after other avenues tried/failed, and candid risk-benefit discussion occurs
- Assess and Rx potential contributors (even if not “root”)
  - Psychiatric co-morbidities, OSA, RLS, pain, etc
- Subtype (phenotype) informs treatment pathways
  - Circadian delay (Rx: light, melatonin, schedule)
  - Sleep Hygiene (Rx: education)
  - Psychophysiolectric (Rx: CBT-I versus meds)
  - Paradoxical (Rx: CBT-I, reassurance)
What is the ideal sleeping pill?

A drug that would make you agree to CBT
Benzos (loraz, clonaz, temaz)

Hit $\alpha_1$, $\alpha_2$, $\alpha_3$, $\alpha_5$ GABAA receptor subtypes

New Benzos (zolpidem)

Hit mainly $\alpha_1$, some $\alpha_2$ subtypes; advantages

Melatonin (often need $>1$mg)

synthetic Mel-R agonist (ramelteon)

Suvorexant: first orexin antagonist
Insomnia treatment: pharmacology (II)

- Benadryl (anti-histamine), in OTC formulations available alone or in “PM” version of analgesics
- TCAs (anti-H, anti-ACh)
  - trazodone, doxepin, mirtaz = 75% of the market
- Adrenergic blockers (clonidine, α2-agonist)
- Other (gabapentin, quetiapine / neuroleptics)
- Herbal (valerian, chamomile, hops, lavender, passion flower, skullcap, etc)
Hypnotic Choice

- Consider Co-morbidities
  - GBP: pain, RLS, HA
  - TCA: pain, HA
  - BZD: parasomnia, OSA

- Consider Pharmacokinetics
  - Onset, or hangover risk (zolpidem, zaleplon)
  - Maintenance (zolpidem CR, eszopiclone)
Risk-benefit discussion topics

- Long-term risks (falls, cognition, mortality)
- Cognitive risk especially with anti-Hist and anti-ACh
- Dependence risk
- Drug interactions
- Parasomnia (eating, texting, driving)
- Driving risk (FDA warning re: hangover effect)
Summary approach to medications

- American Academy of Sleep Medicine Recommendations:
  - If medication is used, start with short acting z-drug, benzo, or ramelteon (melatonin receptor agonist)
  - If unsuccessful, next line is sedating antidepressants, esp if comorbid depression/anxiety
  - Next: combine z-drug or ramelteon with a sedating antidepressant
  - Over-the-counter antihistamine or antihistamine/analgesic type drugs (OTC “sleep aids”) are not recommended. (AASM also says valerian, melatonin, and herbals, are not recommended)
  - Barbiturates, barbiturate-type drugs and chloral hydrate are not recommended for the treatment of insomnia.
Which insomniacs need a PSG?

- The American Academy of Sleep Medicine does not recommend PSG for routine insomnia cases.
- AASM states that PSG is indicated if a “primary” disorder requiring PSG is suspected.
- If case is refractory, unusual, or if parasomnia is part of clinical picture, consider PSG.
- NB: occult OSA and/or PLMS present in 20-50% of insomniacs, even without clinical “suspicion”!
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Hypersomnina

- Sleepiness, fatigue etc: difficult to distinguish
- Central causes, e.g. narcolepsy and idiopathic
- Minimum: PSG to rule out OSA and PLMS, followed by multiple sleep latency test (MSLT)
- MSLT: should be off stimulants for 2 weeks, and
- for narcolepsy, off all psych meds (REM suppr)
## Stimulants overview

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
<th>Half-life and metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine (coffee, pills, soda)</td>
<td>100-400 (&gt;1000 toxic)</td>
<td>5h (hepatic)</td>
</tr>
<tr>
<td>Methylphenidate (Ritalin, Metadate, Concerta)</td>
<td>60mg/day total (concerta: 72mg)</td>
<td>3-4h (renal)</td>
</tr>
<tr>
<td>Dexmethylphenidate (Focalin)</td>
<td>40mg/day total</td>
<td>2-5h (hepatic)</td>
</tr>
<tr>
<td>Dextroamphetamine (Dexedrine)</td>
<td>40mg/day total</td>
<td>4-8h (renal)</td>
</tr>
<tr>
<td>Amphet/dextroamphetamine (Adderall)</td>
<td>60mg/day total</td>
<td>4-10 (renal)</td>
</tr>
<tr>
<td>Lisdexamfetamine (Vyvanse)</td>
<td>70mg/day total</td>
<td>10-12 (hepatic)</td>
</tr>
<tr>
<td>Modafinil (Provigil)</td>
<td>400mg/day total</td>
<td>6-10 h (hepatic)</td>
</tr>
<tr>
<td>Armodafinil (Nuvigil)</td>
<td>250mg/day total</td>
<td>6-10 h (hepatic)</td>
</tr>
</tbody>
</table>

All are pregnancy class C. Also: the “vigils” lower OCP levels!
Other activating agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>Lowers seizure threshold, caution if on other 5HT re-uptake blockers</td>
</tr>
<tr>
<td>Atomoxetine (Strattera)</td>
<td>Priapism, liver function, suicidality, Insomnia</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Protriptyline (Vivactyl)</td>
<td>Cardiac conduction (consider EKG)</td>
</tr>
<tr>
<td>Sodium oxybate (Xyrem)</td>
<td>Sedation, abuse, parasomnia</td>
</tr>
</tbody>
</table>
Caffeine

- Variable sensitivity
- Benefit can desensitize
- Risks (headache, nausea, anxiety, palpitations, GERD, and of course: insomnia)

Table 1  Caffeine content of drinks and foods.

<table>
<thead>
<tr>
<th>Product</th>
<th>Serving size</th>
<th>Caffeine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffees</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brewed-graved</td>
<td>8 oz</td>
<td>80–135</td>
</tr>
<tr>
<td>Instant</td>
<td>8 oz</td>
<td>40–108</td>
</tr>
<tr>
<td>Drip</td>
<td>7 oz</td>
<td>115–175</td>
</tr>
<tr>
<td>Espresso</td>
<td>2 oz</td>
<td>100</td>
</tr>
<tr>
<td>Starbucks regular</td>
<td>16 oz</td>
<td>259</td>
</tr>
<tr>
<td>Decaffeinated</td>
<td>8 oz</td>
<td>5–6</td>
</tr>
<tr>
<td>Teas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leaf teas</td>
<td>7 oz</td>
<td>50–60</td>
</tr>
<tr>
<td>Instant</td>
<td>7 oz</td>
<td>30</td>
</tr>
<tr>
<td>Bottles</td>
<td>8 oz</td>
<td>40–80</td>
</tr>
<tr>
<td>Soft drinks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jolt</td>
<td>12 oz</td>
<td>71</td>
</tr>
<tr>
<td>Mountain dew</td>
<td>12 oz</td>
<td>58</td>
</tr>
<tr>
<td>Mellow yellow</td>
<td>12 oz</td>
<td>53</td>
</tr>
<tr>
<td>Coca-Cola</td>
<td>12 oz</td>
<td>45</td>
</tr>
<tr>
<td>Dr. Pepper</td>
<td>12 oz</td>
<td>41</td>
</tr>
<tr>
<td>Pepsi Cola</td>
<td>12 oz</td>
<td>37</td>
</tr>
<tr>
<td>RC Cola</td>
<td>12 oz</td>
<td>36</td>
</tr>
<tr>
<td>Energy drinks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red devil</td>
<td>8.4 oz</td>
<td>42</td>
</tr>
<tr>
<td>SoBe no fear</td>
<td>16 oz</td>
<td>141</td>
</tr>
<tr>
<td>Red bull</td>
<td>8.3 oz</td>
<td>67</td>
</tr>
</tbody>
</table>

Roehrs 2008
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Restless Legs Syndrome (RLS)

- Uncomfortable sensation in legs
- Worse at night or at rest (car, plane)
- Better with movement, massage, stretching
- Diagnosed by symptoms (though most have PLMS)
- Sleep study is not needed usually
- Linked to dopamine; iron stores
Periodic Limb Movements of Sleep (PLMS)

- Most RLS patients also have PLMS
- But, only a small portion of PLMS patients have RLS
- PLMS can cause insomnia and/or sleepiness
- Bed partner may or may not notice PLMS
- Like RLS, linked to dopamine and iron stores
- Diagnosing PLMS requires sleep study (PSG)
RLS and PLMS - Treatments

- Avoid Triggers
  - smoking, alcohol, caffeine, sleep deprivation, and certain medications (anti-DA, SSRI, TCA, anti-Hist)

- Over-the-counter options
  - Iron supplements (between meals, with VitC)

- Prescriptions…
RLS and PLMS - Treatments

- First line: dopamine agonists
  - Pramipexole, ropinirole, rotigotine (patch)

- Alternatives:
  - Gabapentin enacarbil is FDA approved for RLS
  - Pregabalin has recent data supporting use
  - Benzodiazepine (off label)
  - Opiates (off label)
  - Other (amantadine, clonidine, propranolol)
RLS and augmentation

- Dopamine agents (especially sinemet) associated with idiosyncratic reaction: worsening sx, earlier in the day, migrating to trunk/arms

- Treatment: d/c agent, change to other class (or, can try other DA agent, but cross-augmentation possible)
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Parasomnia: Non-REM

- Most commonly: walking, talking, terror
  Usually benign course and Rx is conservative
- Sleep eating can be related to RLS; +/- recall of events
  Can respond to DA agents, topiramate
- DDx includes seizure, REM behavior disorder
- Behavioral management (EtOH, caffeine, schedule)
- Treat primary sleep d/o (occult sleep apnea or PLMS)
Parasomnia: REM

- REM behavior disorder (RBD): dream enactment
- Linked to Parkinson’s (may precede by decades)
- Other neurological disorders: concurrently arises
- PSG confirms REM without atonia, & rules out OSA
- Rx: melatonin (hi dose), clonazepam, or both
- Bedroom safety, as injury is not uncommon
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Circadian disorders

- Usually presents if clash with social/work schedule

- Delayed Sleep Phase (“night owl”)
  - Common in teens and young adults
  - Presents as onset insomnia – must be distinguished

- Advanced Sleep Phase (“lark”)
  - Mainly in older adults

- Other: shift work, jet lag, irregular cycle, blindness
Advanced Sleep Phase

Normal Sleep Phase

Delayed Sleep Phase
Treating Delayed Sleep Phase

- Most common circadian d/o (“night owl” type)
- Chrono-therapy: 3-pronged approach
  - Melatonin: “night-signal” 3hr before bedtime
  - Avoid light during sleep; bright light upon wake
  - Shift time in bed by 30 minutes (q.o.d.)
And if you just can’t stop snoozing...
Thank you!

www.mghsleep.com

mtbianchi@partners.org