

Pharmacology of Sleep



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I have no disclosures, affiliations, nor conflict in interest financial or otherwise in relation to this presentation.



Objectives

- Identify criteria for sleep disorders requiring pharmacological management
- Discuss pharmacological treatment for sleep disorders
- Recognize when a child should be referred to sleep center



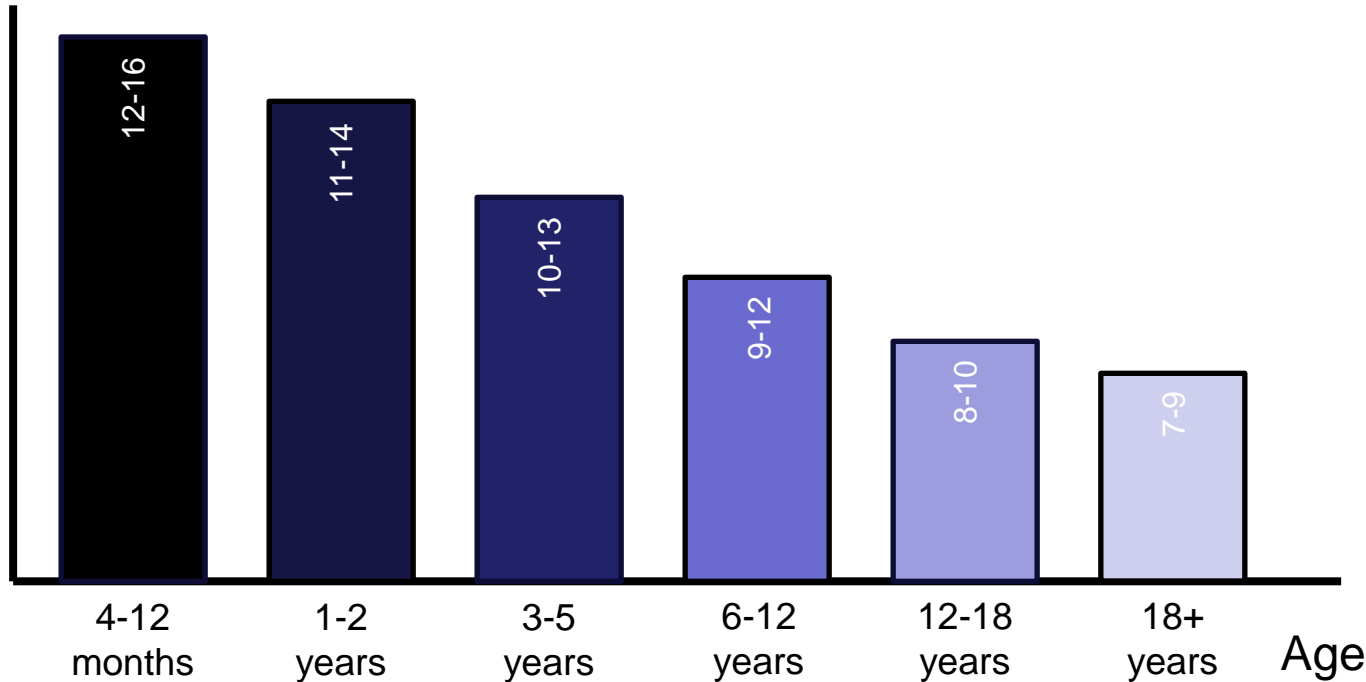
Why Sleep?

- Not 100% sure?
- Critical for Growth and Development
- Important for Healthy Immune Response
- Foundation for Recovery and Normal Body Function



How much sleep is enough?

Hours



Adapted from Sleep Foundation.org



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To know sleep is to know the brain

- Neurobiology is still an evolving field
- Very complex circuits with multiple inputs in vast network of connections

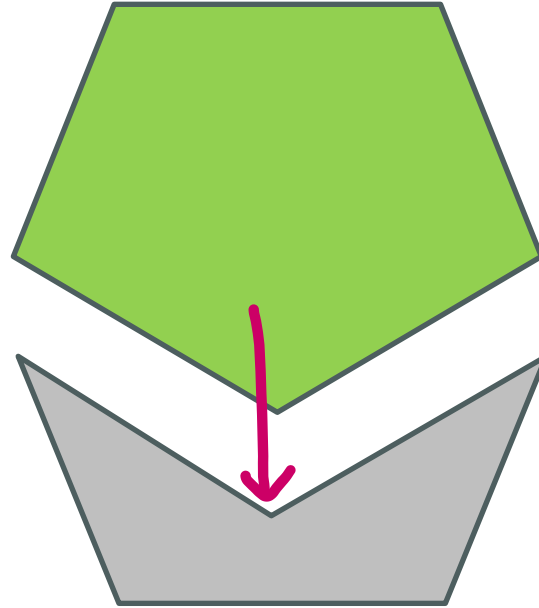


Quick Review!

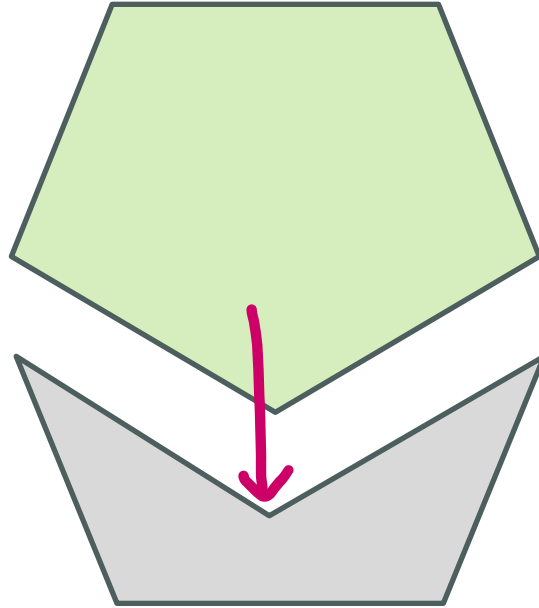
- Conceptualize as “Lock and Key”
- Agonist => **Forward Key**
- Antagonist => **Blocks Key**
- Inverse Agonist => **Emergency Shutdown/Lock breaks**
- Competitive vs Non-competitive
- Partial=>Reduced effect



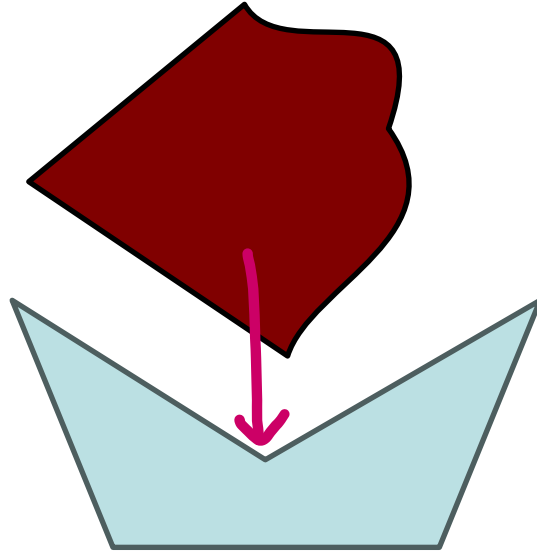
Competitive Agonist



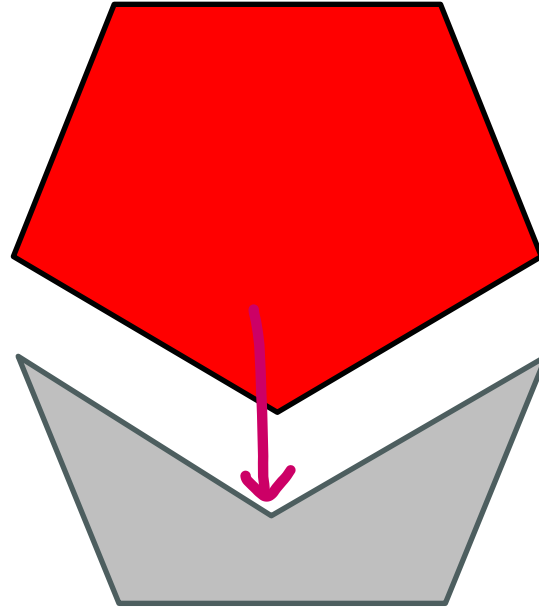
Competitive Partial Agonist



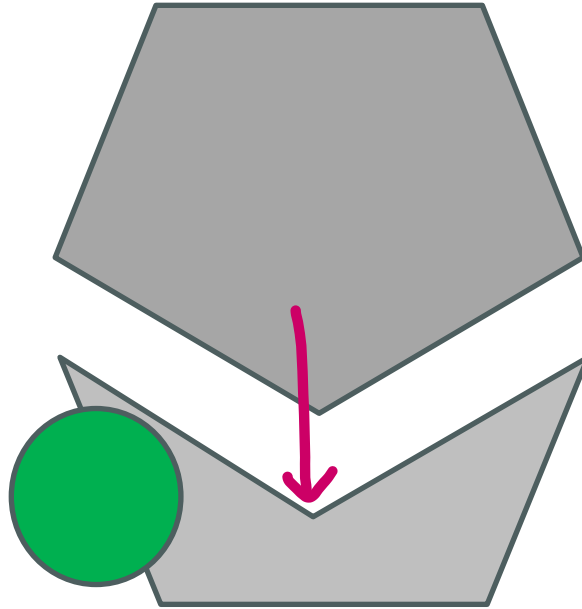
Competitive Antagonist



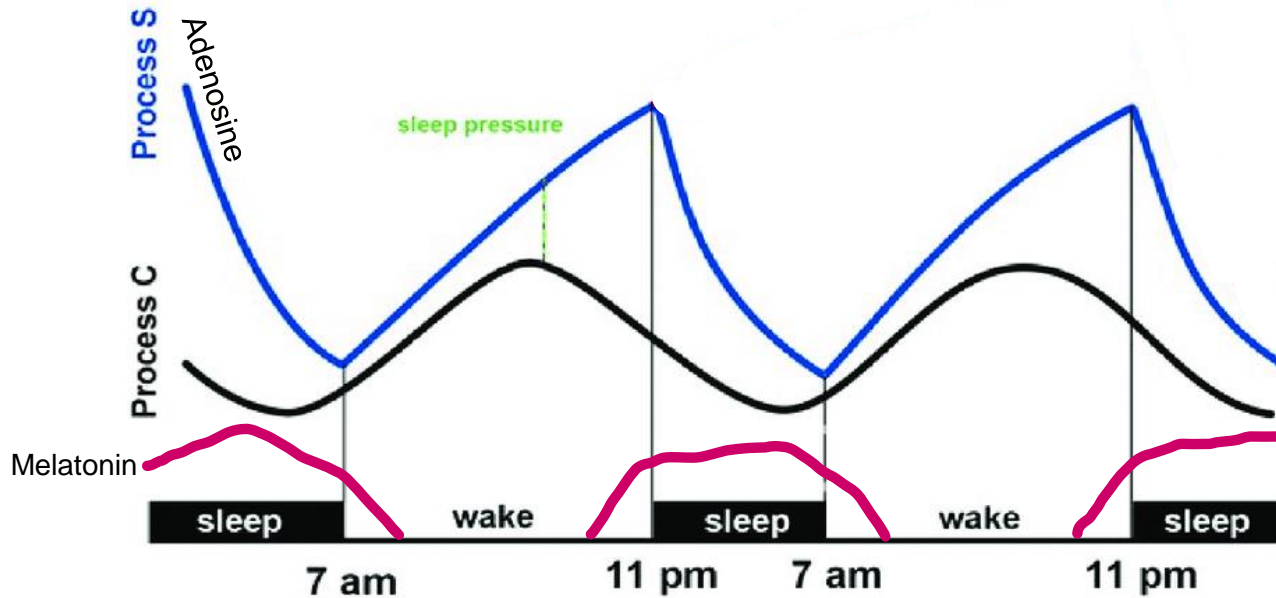
Competitive Inverse Agonist



Non-Competitive Agonist



What makes us sleep?




Adapted from: Green et al. (2020). The Possible Role of Endoepines in Sleep Regulation and Biomarker of Process S of the Borbély Sleep Model. *Chronobiology International*. 38.



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Adenosine

- Created from used ATP aka **ENERGY** 
- Builds up throughout the day
- Caffeine is a competitive antagonist

- Note to self: Slowly consume caffeine throughout the day to **STAY** alert.



Melatonin

- Made in your pineal gland
- Circadian rhythm “Body’s Natural Clock” in Suprachiasmatic Nucleus
- Positive feedback loop
- Blocked by bright lights (especially blue?)



Sleep-Wake Signals

Two main circuits:

Off/Sleep Promoter (GABA, Melatonin)

On/Wake Promoter (Histamine, Orexin)



HERE WE GO!



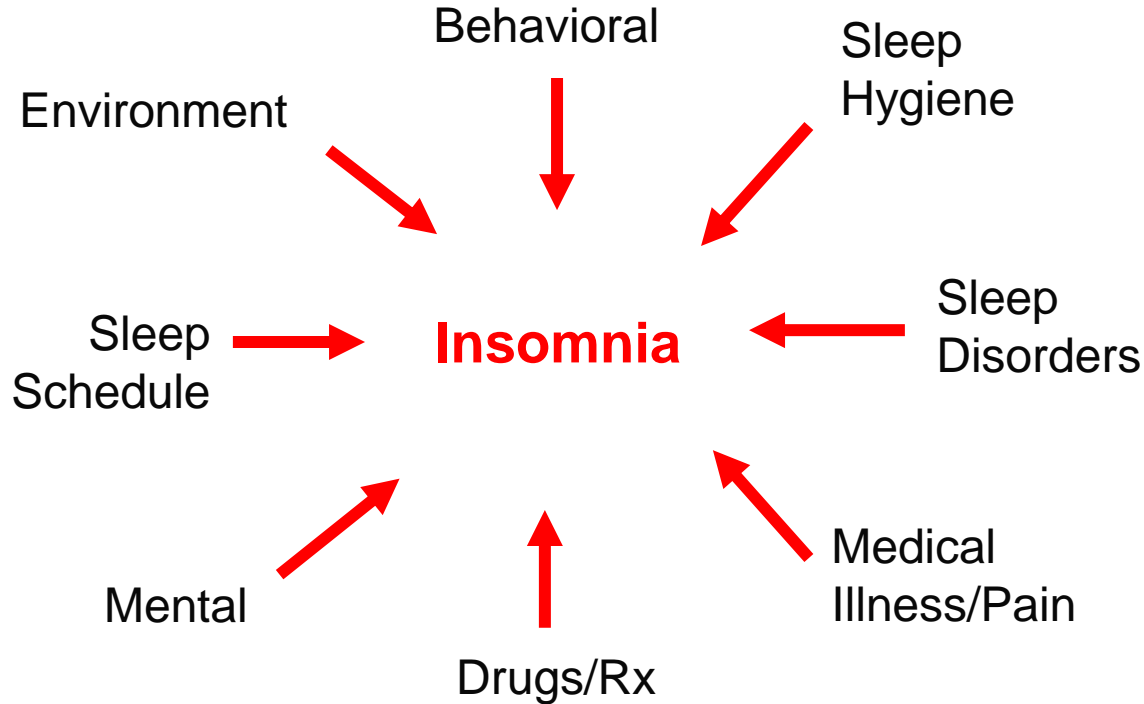
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Insomnia

- Difficulty falling, maintaining, or getting back to sleep
- Impacts life
- >3 months duration



Insomnia is Multifactorial



When to start pharmacologic therapy

- QoL Burden
- Ability to implement non-pharmacologic interventions
- Adjunctive to non-pharmacologic intervention



Why should we avoid sleep medicines?

- No pediatric FDA approved sleep aid for insomnia
 - Only doxepin, benzos, Z-drugs, melatonin agonists, new orexin antagonists
- Band-aid, not building skills
- Side Effects
- Nearly all sleep aids cause habituation/tolerance
- Withdrawal



Supplemental Melatonin

- FDA Supplement, not Medicine
 - Studies have shown actual mg values vary greatly
- Often mixed with other supplements
 - St. John's Wort
 - Valerian root
 - GABA
 - L-Tryptophan
 - Magnesium
 - Herbal Extracts
 - Tart Cherry Juice



Supplemental Melatonin

- Jump starts endogenous melatonin positive feedback loop
- No tolerance, no withdrawal, etc!
- Very poor bioavailability ~15% (first pass effect)
- Quickly metabolized 15-45 minutes
 - XR formulation ~1.5-2 hours
- Parasomnias, nightmares, hangover effect, irritability, very low risk of seizure, headaches



Irritability with Sleep Medications

- Disinhibition of frontal lobe and executive functioning skills
 - “Tipsy but not passed out”
 - Increased sleep fighting/negative behaviors
- Often due to patient brain’s receptor profile and reaction to medication



Most Drugs are not Precise

- Drugs hit multiple receptors
- Drugs have different affinities to different receptors even if they are in the same “class”
- Patients have different responses to the same medication

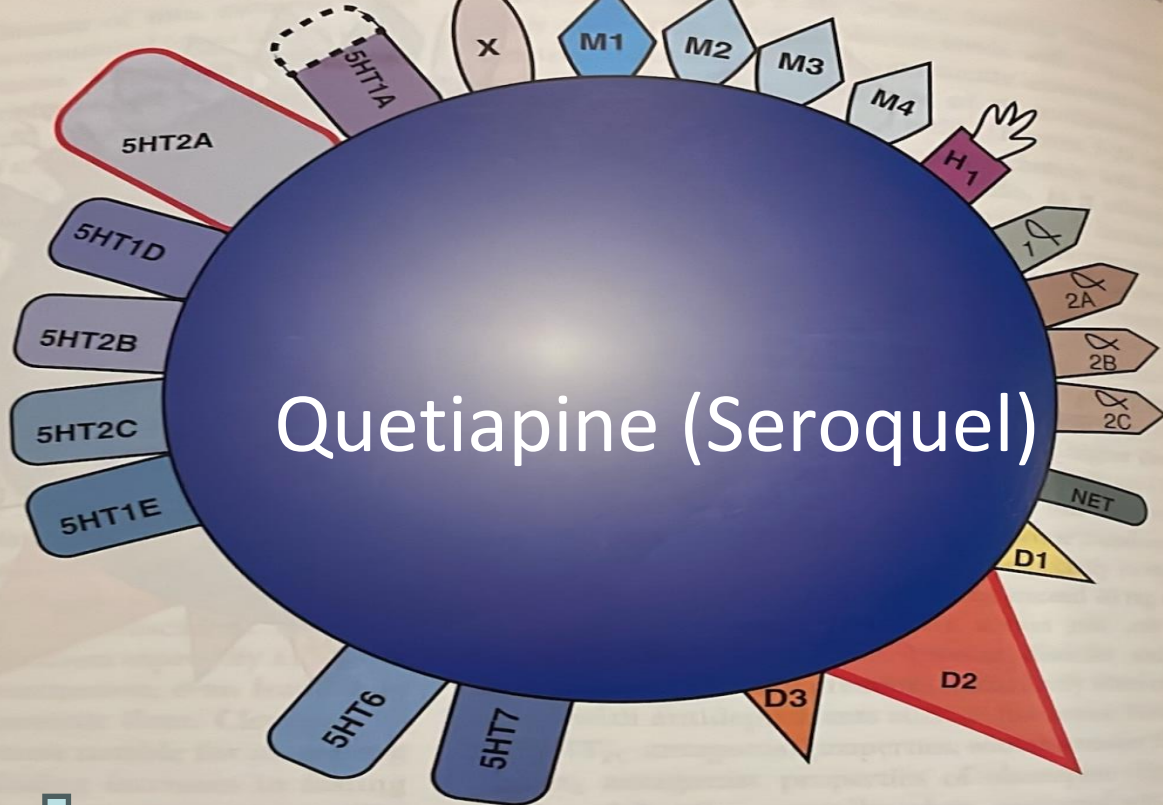


Antipsychotics

- Sedative effect driven by Histamine-1, Muscarinic-1, adrenergic- α 1 antagonism in the brain
- Ultimate sledgehammer



Quetiapine (Seroquel)



quetiapine

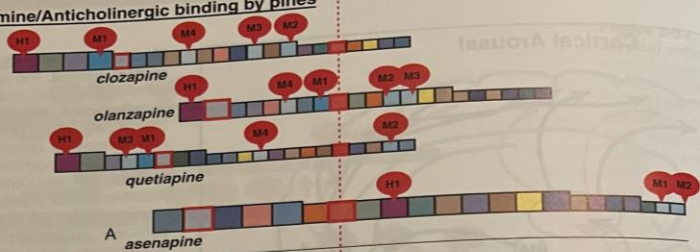


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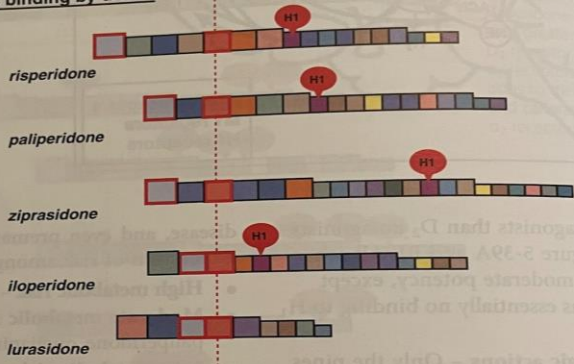


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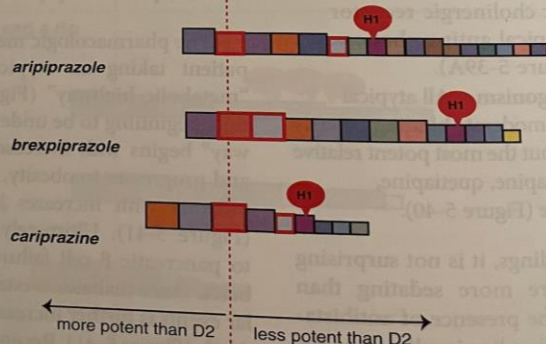
Antihistamine/Anticholinergic binding by pines



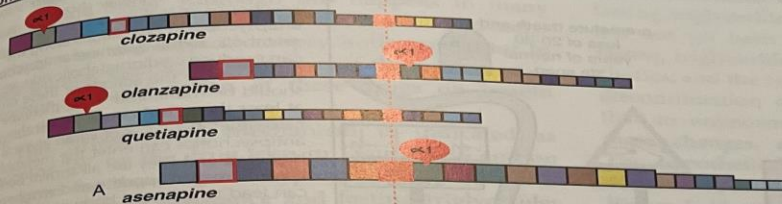
Antihistamine/Anticholinergic binding by dones



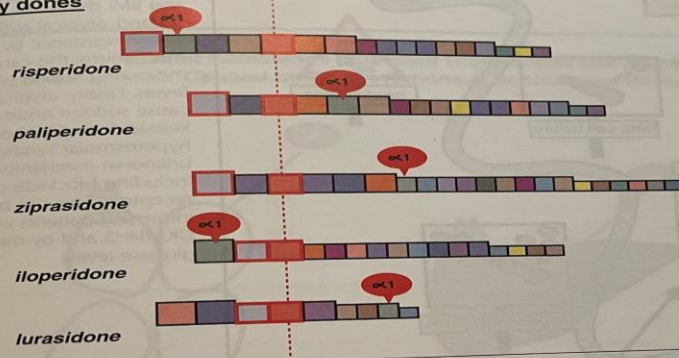
Antihistamine/Anticholinergic binding by two pips and a rip



Alpha1 binding by pines



Alpha1 binding by dones



Alpha1 binding by two pips and a rip

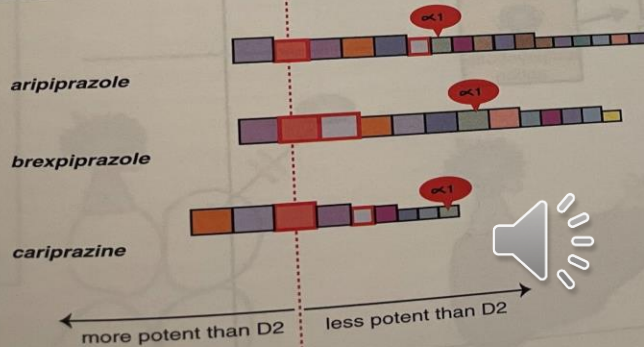
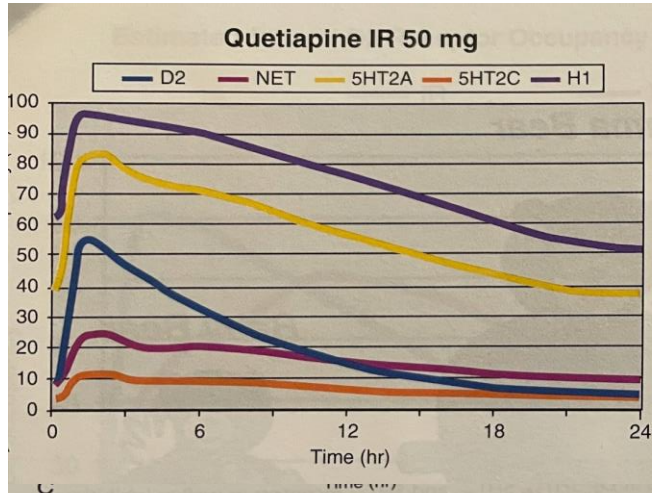
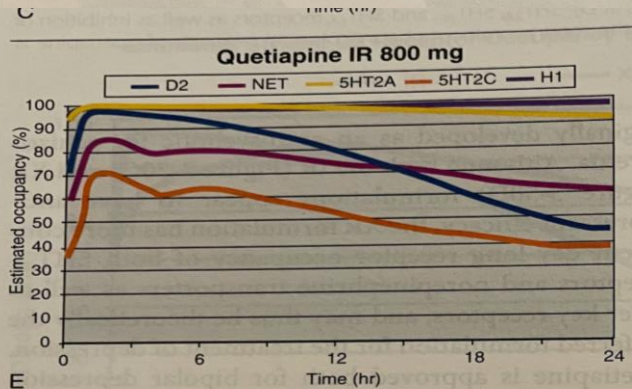
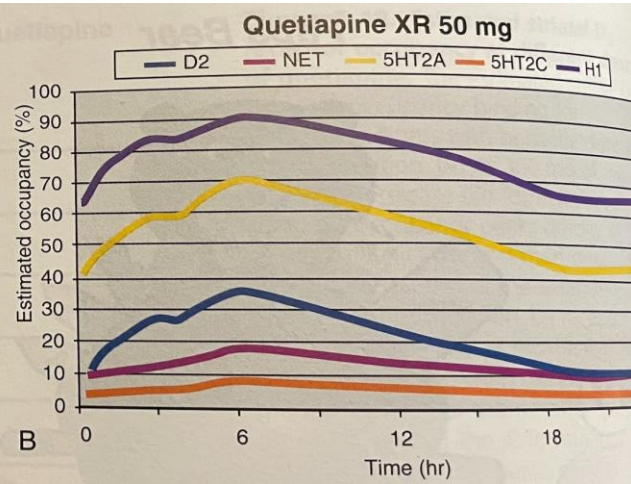


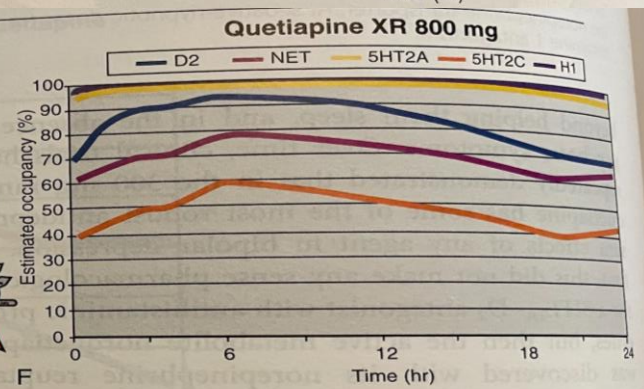
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Baby Bear



Papa Bear



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Using sleep medications

- Sedation goal (Sleep Onset or Maintenance)
- Treat other underlying issues



Quetiapine (Seroquel)

- Half life = 6-7 hours
- Time peak=2 hours for IR, 5 hours for XR
- LOW DOSE (25-100 mg)
- Weight gain, HLD, Fatty Liver, Diabetes, Dizziness, Dry Mouth, Nausea/Vomiting
- Baseline and 6 months monitoring of Glucose, HgA1c, Lipids, and CMP
- Off-label for refractive Anxiety/ADHD
- Medium Habituation Speed
- Both for sleep onset and maintenance



Trazodone

- Serotonin 2 Antagonist/Reuptake Inhibitor
- Low Dose for Sleep (12.5-100 mg)
- Antidepressant
- Biphasic Half-life (3-6 hrs, then 5-9 hrs)
- Nausea, vomiting, blurred vision, constipation, dry mouth, dizziness, tremor, rash, easy bleeding
- Quick Habituation, Used best as PRN
- Both sleep onset and maintenance



Diphenhydramine (Benadryl)

- First Generation Anti-Histamine
- Half-Life (2-7 Hrs), Peak 2 hours
- High Habituation Rate
- Paradoxical effect, dizziness, constipation, blurred vision, dry mouth, irregular heartbeat, seizures
- Sleep onset only



Hydroxyzine

- Antihistamine
- Half-life 7 hours (in kids), peak 0.5-2 hrs
- Dose: 10-25 mg
- Dry mouth, blurred vision, urinary retention, constipation, tremor, headache, rash
- Fast Habituation, Use PRN
- Sleep onset only



Clonidine IR

- Alpha 2 agonist
- Half-life 5-13 hrs, Peak 1-3 hours
- Dose 0.03-0.4 mg
- HTN, ADHD, ODD
- Dry mouth, constipation, dizziness, irregular heartbeat, hypotension, nausea, vomiting
- Average Habituation Rate
- Sleep onset only



Clonidine XR

- Now in capsule (Kapvay) and liquid beads (Onyda XR)
- Patches rarely effective from a sleep standpoint
- Half-life 5-13 hrs, Peak 7-8 hours
- Sleep maintenance

- Can combine Clonidine XR + Clonidine IR



Gabapentin (Neurontin)

- Alpha 2 delta ligand calcium channel agonist
 - Thought to regulate dopamine indirectly
- 2-5 mg/kg QHS for Restless Leg Syndrome/Periodic Limb Movement Disorder
- Half-Life 5-7 hrs, Peak 2-3 Hrs (RENAL EXCRETION)
- Dizziness, ataxia, blurred vision, vomiting, GERD, emotional lability
- Habituation less likely if used only once a day
- Sleep maintenance primarily



Mirtazapine (Remeron)

- Dual serotonin & norepinephrine agent
- Lower doses 7.5 mg, 15 mg
- Half-life 20-40 hrs, peak time 2 hours

- Weight gain, worsened restlessness, rarely seizures
- Anxiety, Depression
- Sleep onset and maintenance



Doxepin (Silenor)

- Tricyclic Antidepressant
- Almost solely H1 antagonist at low doses
- Dose 3-10 mg, liquid formulation is generic
- Half life 8-15 hours, Peak 2 hours
- Side effects rare at low doses! Dry mouth, constipation, blurred vision
- Sleep maintenance only



Clonazepam

- Benzodiazepine (GABA Agonist)
- Half life 30 hours, Peak 1-4 hours
- Used primarily for parasomnias in extreme cases
- Can lead to addiction
- Respiratory depression, dizziness, cognitive slowing, hallucinations, dry mouth
- Sleep onset and maintenance



Eszopiclone (Lunesta), Zolpidem (Ambien), Zaleplon (Sonata)

- Non-benzodiazepine benzodiazepine receptor non-competitive agonist
- Half-life ½ as short as adults
 - Sonata ~30 minutes, Ambien 1-2 hours, Lunesta ~4 hours
- Peak times
 - Sonata 10 minutes, Ambien 1 hour, Lunesta 2 hours
- Parasomnias, amnesia, dizziness, hallucinations, headache, abdominal pain, nausea, irritability, infection risk
- Sleep onset only in children



How much is significant?

- Zolpidem
 - Improves sleep onset by 20-30 minutes
 - Improves total sleep time by 20-30 minutes
 - Improves sleep efficiency by 4-5%
- Patients report falling asleep faster, more refreshed, waking up much less than placebo
 - Amnesia?

Herrmann WM, et al. Pilot controlled double-blind study of the hypnotic effects of zolpidem in patients with chronic 'learned' insomnia: psychometric and polysomnographic evaluation. J Int Med Res. 1993 Nov-Dec;21(6):306-22.



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Restless Leg Syndrome

- Urge to move legs, unpleasant sensation in legs
- Begins or worsens during periods of rest
- Partially or totally relieved by movement
- Only during periods of rest or inactivity, worse in the evening
- Diagnosis strengthened by first degree relative with RLS or Periodic Limb Movements of Sleep on sleep study

- Associated with Dopamine!

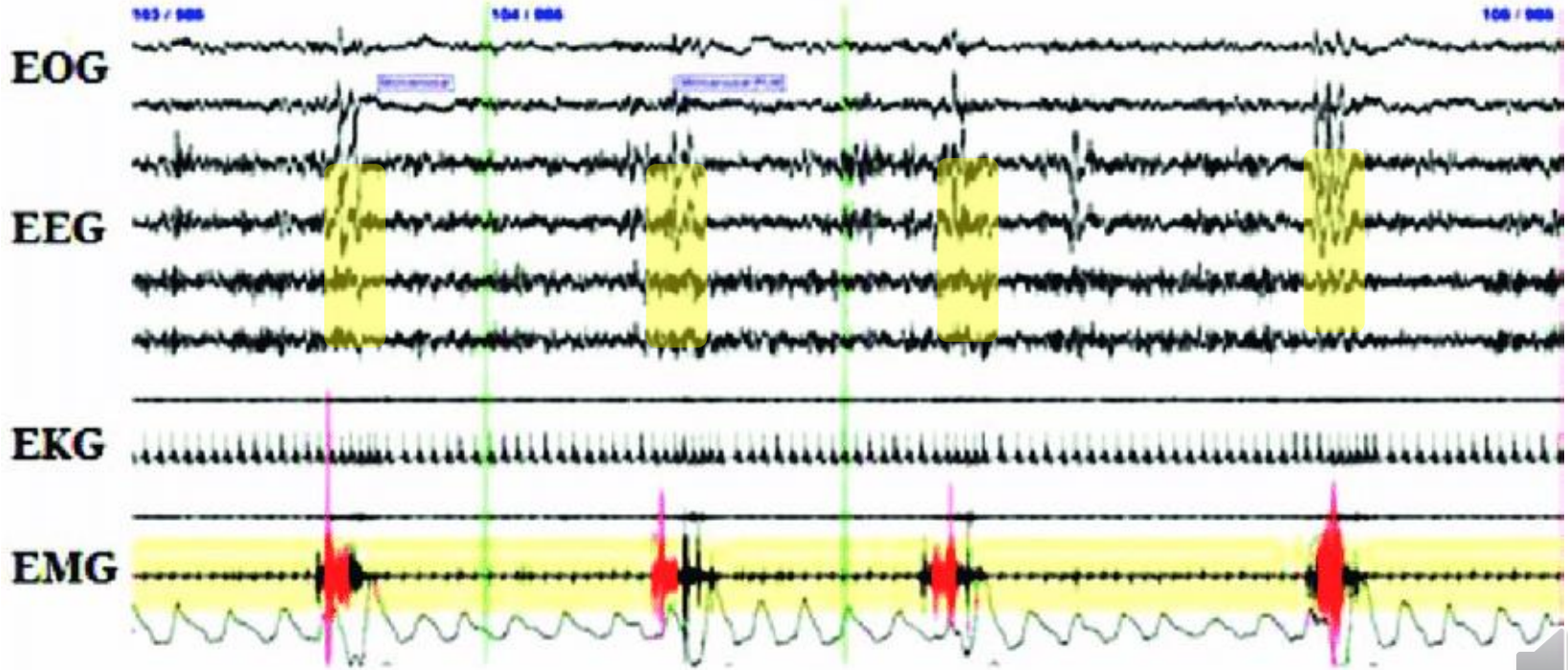
Allen RP, Picchiatti DL, et al; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. *Sleep Med.* 2014 Aug;15(8):860-73.



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Periodic Limb Movements of Sleep



Koo, Brian. (2015). Restless Legs Syndrome: Would You Like That with Movements or Without?. Tremor and other hyperkinetic movements (New York, N.Y.). 5. 316. 10.7916/D80P0Z0H.



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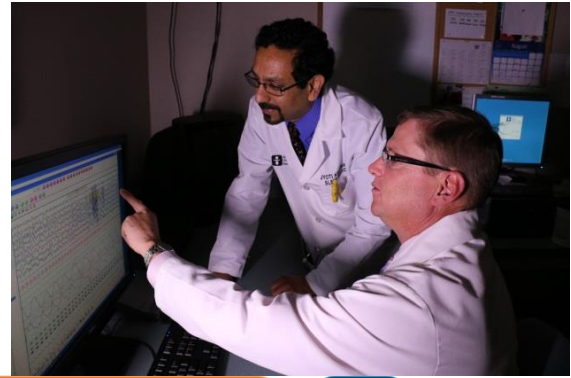
Iron

- Iron co-factor for tyrosine hydroxylase (rate limiting step of release of dopamine)
- Serum iron levels poorly correlate with CSF
- For Restlessness, Ferritin > 75 ng/ml
- Avoid dairy
- 2 mg/kg elemental iron daily orally
- May consider IV iron infusion
- Closely regulated by body



Sleep Studies

- Done at Night from 8p-6a, Sun-Fri
- Akron & Mahoning Valley/Boardman Locations
- 2-4 month wait
- Results available ~2 weeks after test



Sleep Clinic or Sleep Study

- Sleep study for Sleep Apnea or Restless Sleep
 - Snoring + 1
 - Witnessed apneas
 - Hypersomnia
 - Sleep disruption
 - Large Tonsils
 - Obese
 - “Wild” Sleeper, Sheets/Blankets tossed about in AM



Sleep Clinic

- Insomnia
- Circadian Rhythm Disorders
- PAP management
- Parasomnias
- Hypersomnia/Excessive Daytime Sleepiness
- Sleep Training



Contact

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