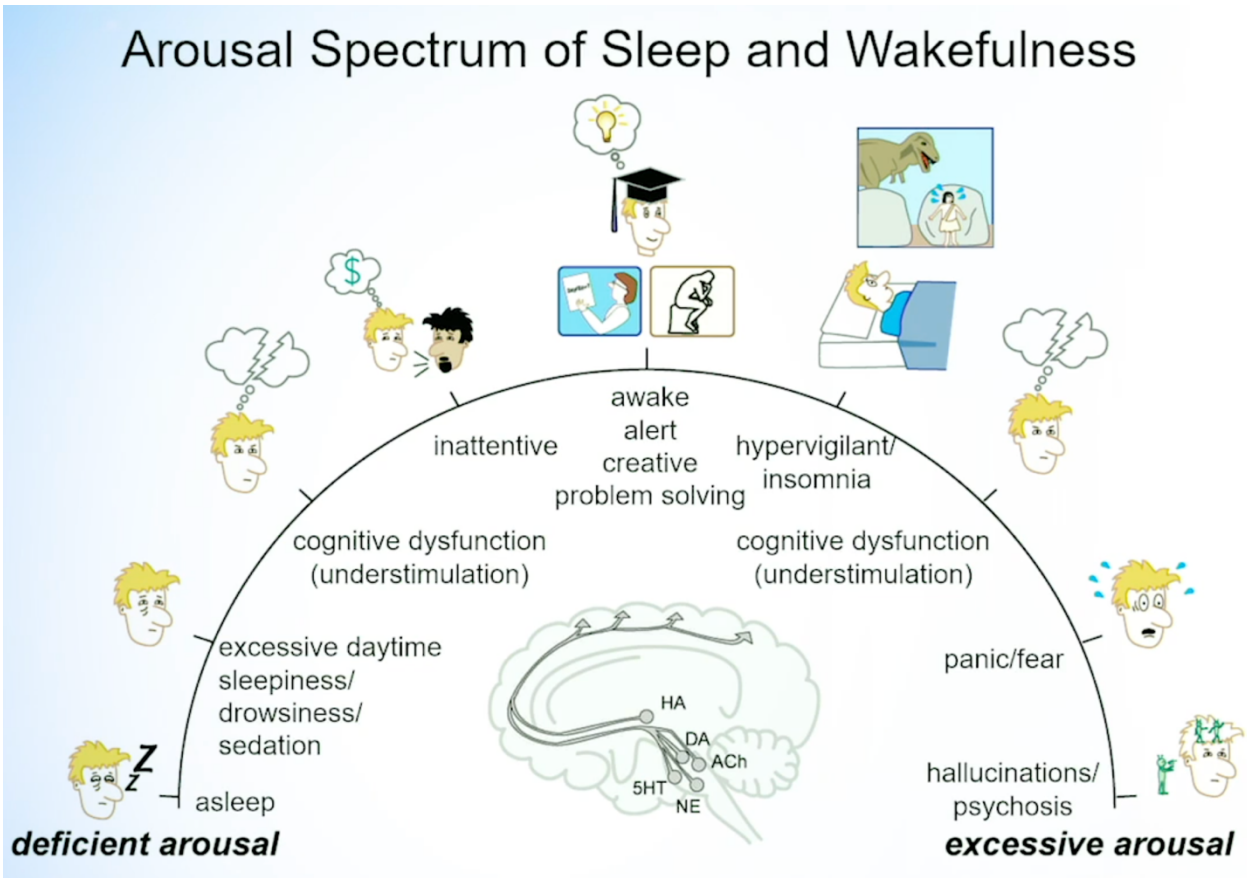
**Neurobiology of Sleep and Wakefulness**




**Histamine Neurotransmission**

- Wake promoting neurotransmitter
- Histidine is transported into the cell by histidine transporter
- Brings it into the histidine decarboxylase (HDC) turns into histamine
- Transported into synaptic vesicles for release and neurotransmission

To terminate Histamine action

- There is no reuptake pump
- It has to be converted by N-methyltransferase into N-methylindoleacetic acid
- Which is then broken down by MAO-B to N-MIAA which is inactive

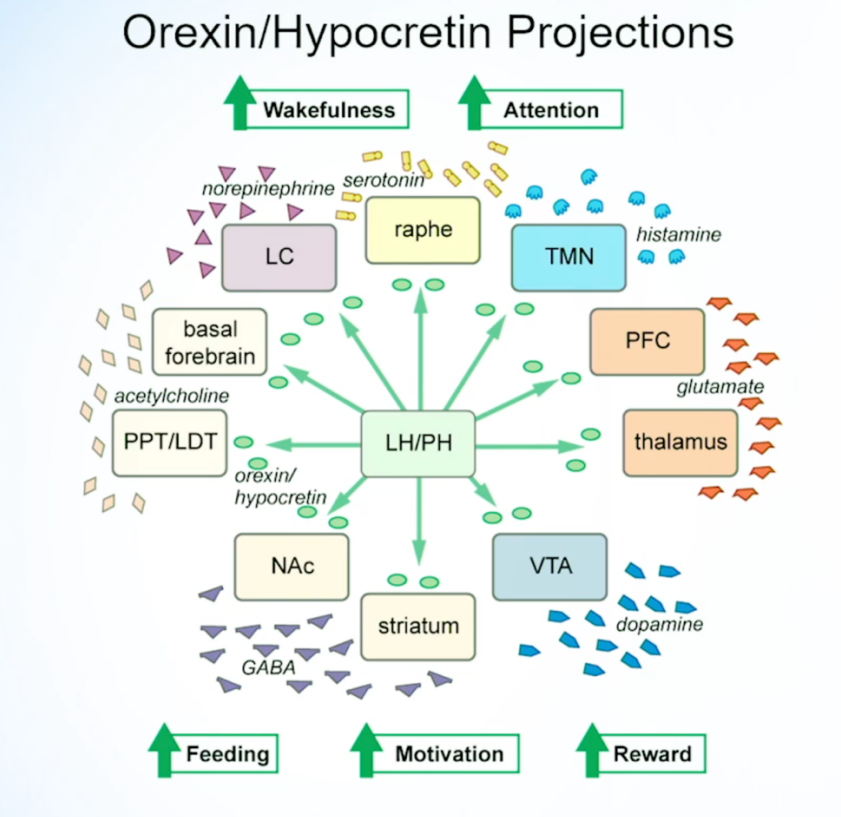
Histamine receptors

- H1 postsynaptic (promote arousal, pro-cognitive) usually blocked by antihistamines
- H2 Postsynaptic
- H3 Presynaptic (turns off histamine release)
- Can also activate NMDA receptor (polyamine site) allosteric modulator to help glutamate do its job

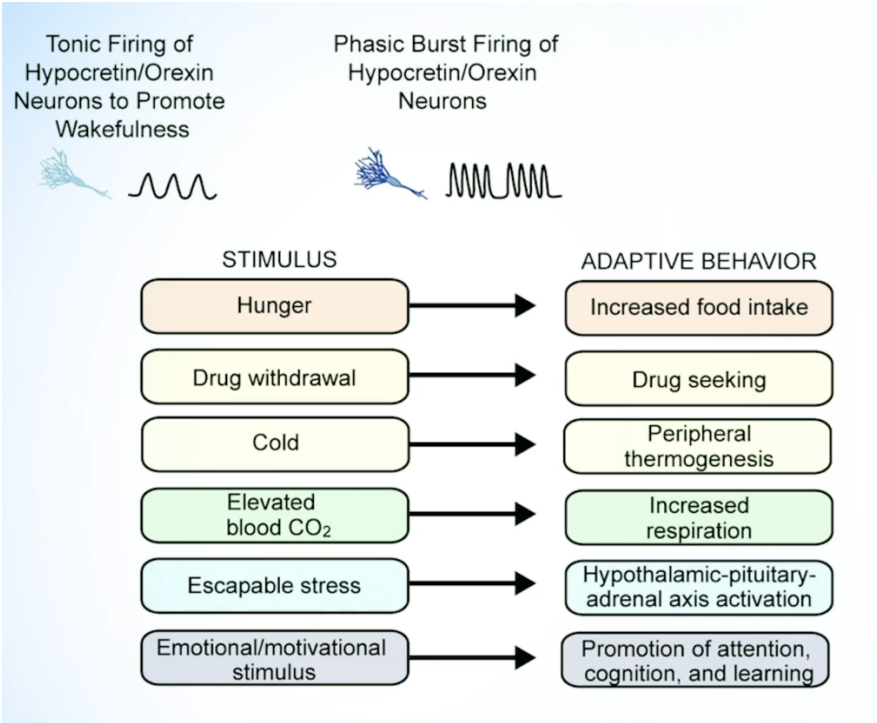
The wake circuit: Histamine

- The TMN Tuberomammillary nucleus is the house of histamine, goes lots of places in your brain (histamine on your awake)
- VLPO: is where GABA is and turns everything off
- Orexin come from lateral hypothalamus, go everywhere in the brain. Assist wakefulness by stabilizing wakefulness. If you lose this part of the brain you get narcolepsy
    - Orexin A

        - Work on receptors Orexin1R and Orexin2R
            - Orexin1R works on calcium
            - Orexin 2R works on NMDA receptors and GIRK (potassium channel)
    - Orexin B
        - Work on receptor Orexin2R




- Tonic firing of Hypocretin/Orexin neurons promote wakefulness
- Phasic Burst firing or hypocretin/Orexin Neurons may be related to behavioral cues



**The wake circuits**

- Histamines
- Acetylcholine
    - Comes from pedunculopontine and laterodorsal tegmental nuclei
- Dopamine
    - Ventral tegmental area in cortex
- Norepinephrine
    - Locus coeruleus in cortex
- Serotonin
    - Involved more in sleep
    - Raphe nucleus to basal forebrain and thalamus

**The sleep circuit**

- Affected by GABA coming out of the VLPO to the brain and shuts it down

Sleep:

- Four stages and REM
    - Stages 3 and 4 is restorative sleep
- GABA turns sleep switch on, higher during sleep
- Orexin/Hypocretin is the opposite, goes down when you sleep, high when you are awake
- Acetylcholine tracks REM sleep, up and down all night, high during REM sleep, low in other stages
- Other neurotransmitters are opposite, low during REM, high during Stage 4

**The purpose of sleep**

- Helps to maintain your brain garden. Changes synapse formation and revisions at night.
- Weakens learning memory
- Prevents psychiatric disorders
- Affects immunity, need sleep. Lack of sleep can trigger neuroinflammation by not sleeping
- Neurological disorders like Alzheimer's and chronic pain
- Economic costs, sickness absence, lost productivity, motor vehicle accidents
- HPA axis and endocrine dysfunction
- Cancer
- Cardiometabolic disorders such as diabetes, heart disease and stroke

**Sleep and Cognition**

- Sleep wake cycle disturbance
    - Impaired hippocampal neurogenesis
        - Cognitive disfunctions
    - Obesity
        - Decrease leptin, Increased ghrelin, and Gut microbiota dysbiosis
            - Increase risk of obesity, type 2 diabetes and cardiovascular disease
    - Medical conditions
    - Substance abuse
    - Psychiatric conditions: "psychiatric vital sign" 3-5 years of insomnia
        - 4x more likely to have depression, 2x more likely to have anxiety, 7x more likely to develop substance use disorder
    - Behavioral or psychological causes
    - Medication side effects
    - Sleep wake disorders

**Diagnosis and Treatment of Sleep and Wake Disorders**

**Insomnia**

- Excessive arousal at night

Biology of insomnia

- Neuroanatomical abnormalities
  - Reduced brain matter in left orbitofrontal cortex and hippocampus
- Neurobiological abnormalities
  - Decreased GABA levels in occipital and anterior cingulate cortices
  - Reduced nocturnal melatonin secretion
  - Increased glucose metabolism
  - Attenuated sleep-related reduction in glucose metabolism
  - Decreased serum BDNF (growth factor, brain derived neurotropic factor)
- Autonomic nervous system abnormalities
- HR elevations and variability
- Increase metabolic rate
- Increased body temp
- HPA axis activation
- Increased NE
- Systemic inflammation
  - Increased cytokines
- Genetic Factors
  - CLOCK gene polymorphisms
  - GABA-A receptor gene polymorphisms
  - Serotonin reuptake transporter (SERT) gene polymorphisms
  - Human leukocyte antigen (HLA) gene polymorphism
  - Epigenetic modification affecting genes involved in the response to stress

DSM-5 Diagnostic criteria

- Insomnia as a comorbidity
- Psychiatric illness can cause insomnia
- Or insomnia can cause psychiatric illness
- Suggested criteria for defining insomnia:
  - Average sleep latency .30min
  - Wakefulness after sleep onset (WASO) .30min
  - Sleep efficiency<85%
  - Total sleep time<6.5hours

To promote sleep

- Enhance
  - GABA
- Inhibit
  - Hypocretin/orexin
  - Ach
  - Dopamine
  - Norepinephrine
  - Serotonin
  - Histamines
- Benzo hypnotics

**Half life**

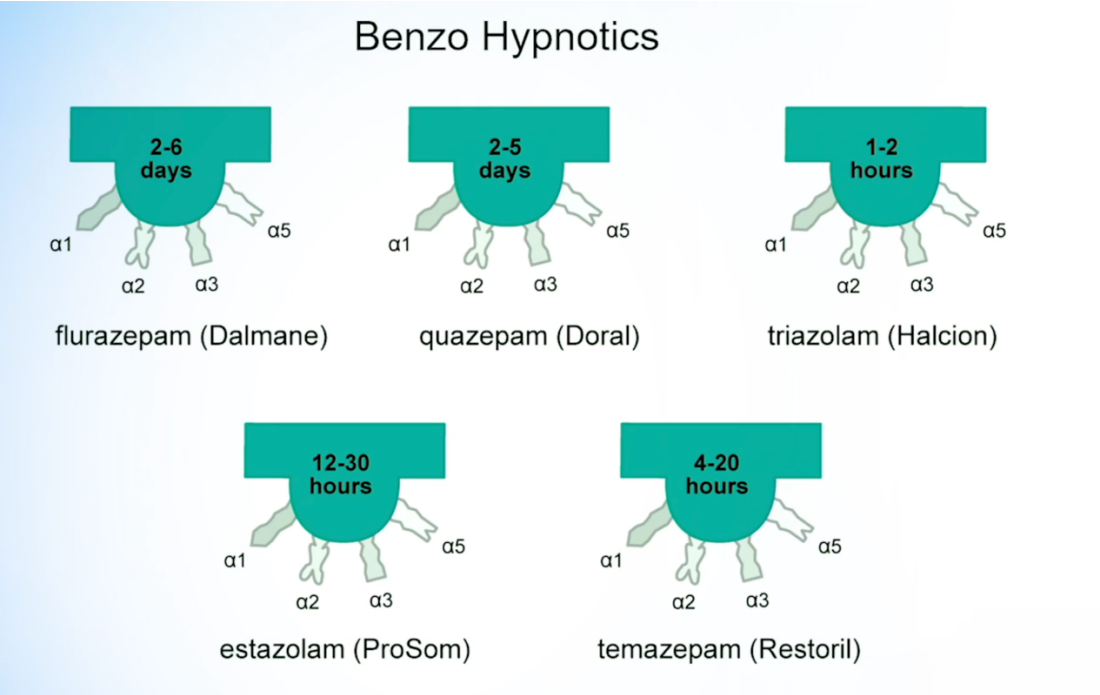
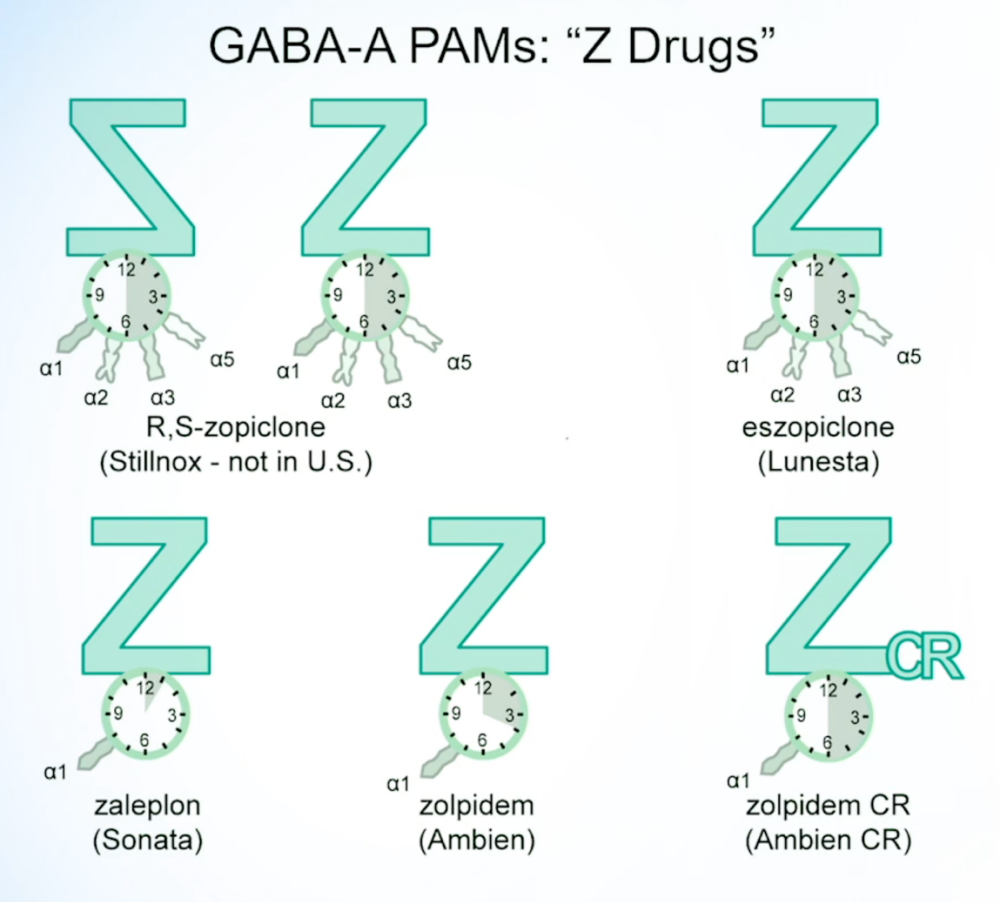



**Table 1. Common Benzodiazepines, Their Half-lives, and Speeds of Onset**

| Drug (Brand) | Half-life, h | Speed of Onset |
|---|---|---|
| **Alprazolam (Niravam, Xanax, Xanax XR, generic)** | 12-15 | Intermediate |
| **Lorazepam (Ativan, Lorazepam Intensol, generic)** | 10-20 | Intermediate |
| **Diazepam (Diastat, Diazepam Intensol, Valium generic)** | 20-80 | Fast |
| **Nordiazepam[a]** | 31-97 | N/A |
| **Oxazepam (Generic)** | 5-10 | Slow |
| **Temazepam (Restoril, generic)** | 3-13 | Fast |
| **Clonazepam (Klonopin, generic)** | 18-50 | Slow |

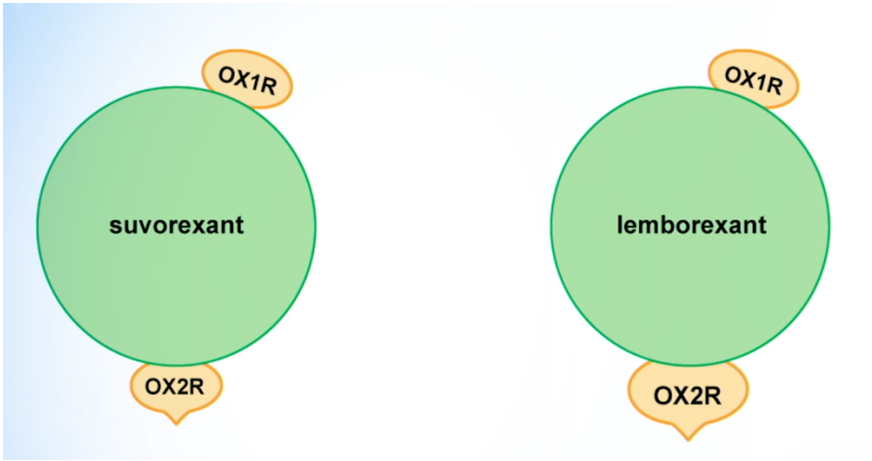
[a]Nordiazepam is not a prescribed drug in the US. It is, however, a metabolite of the following drugs: chlordiazepoxide (Librium), clorazepate (Tranxene), diazepam, halazepam (not available in the US), medazepam, prazepam and tetraprazepam. Based on reference 6.

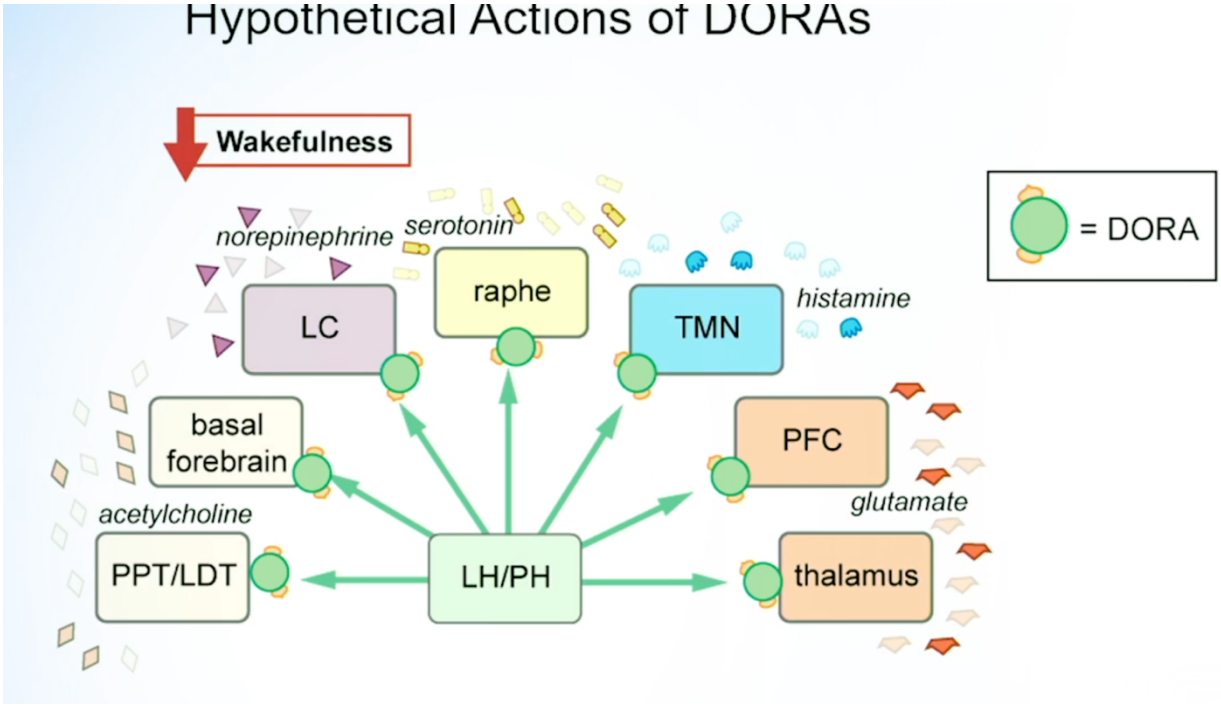
Chlordiazepoxide (Librium) 6-30 hours
Benzo withdrawal:



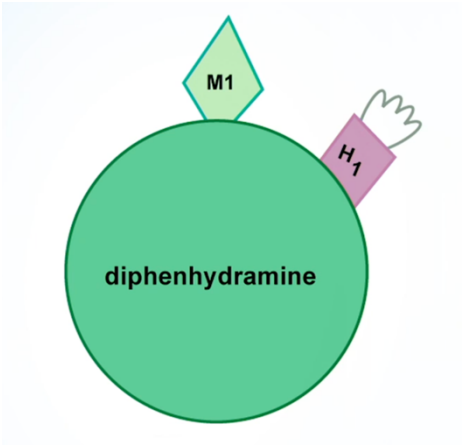

**Dual orexin receptor antagonists**

**Suvorexant** **Lemborexant**



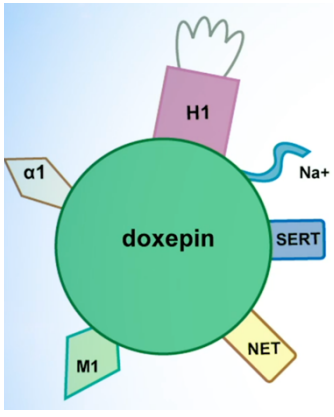



**Diphenhydramine (Benadryl)**




- Blocks H1 and M1

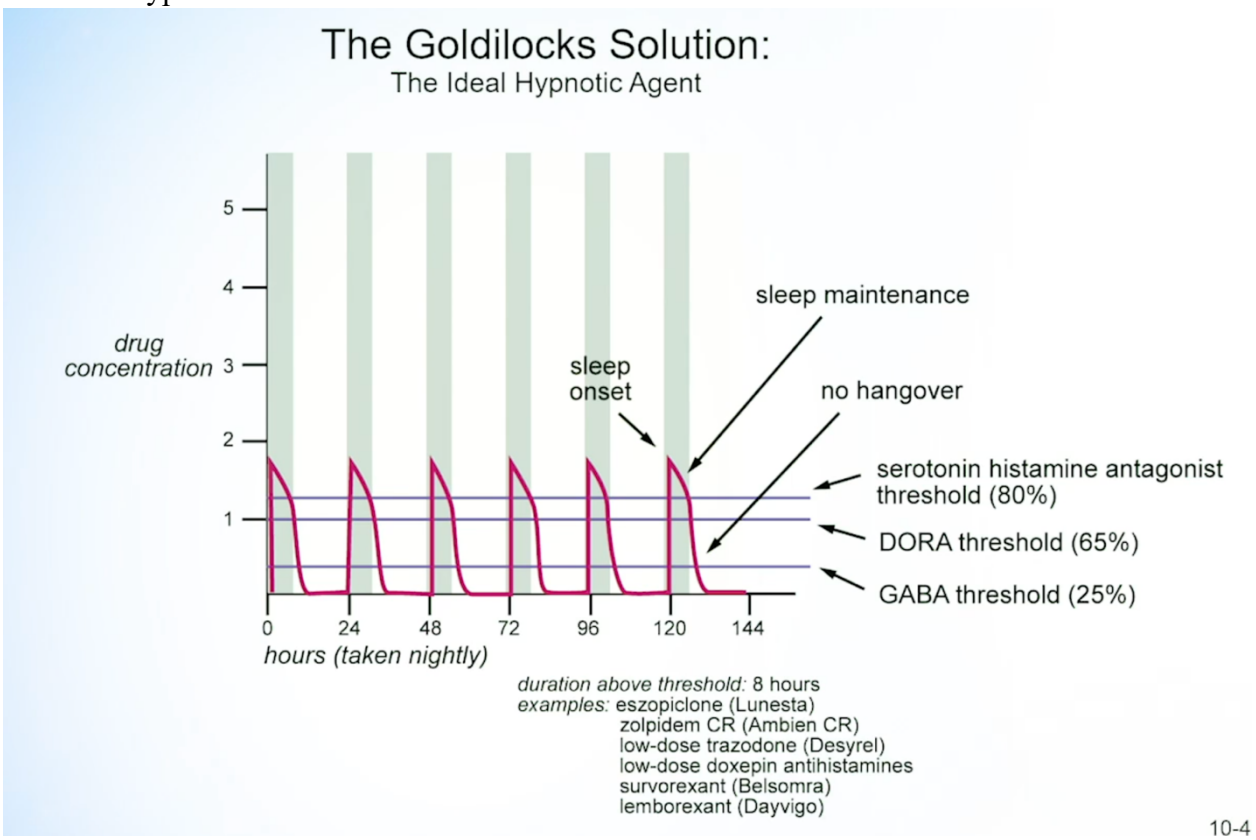
**Doxepin**




- Tricyclic antidepressant
- At low doses only works on H1 antagonist

H1 Antagonist: When you block H1 causes you to sleep

The Ideal hypnotic solution




- Ultra long half-life hypnotics can cause drug accumulation (toxicity)
  - Duration above threshold 24-150 hours
  - Flurazepam (Dalmane)
  - Quazepam (Doral)
- Moderately long half-life hypnotics do not wear off unit after time to waken (hang over)
  - Duration above threshold 15-30 hours
  - Estazolam (ProSom)
  - Temazepam (Restoril)
  - Most TCA's
  - Mirtazapine (Remeron)
  - Chlorpromazine (Thorazine)
- Short half-life hypnotic wears off before time to awaken (loss of sleep maintenance)
  - Half-life 1-3 hours
  - Examples
    - Triazolam (Halcion)
    - Zaleplon (sonata)
    - Zolpidem (Ambien)
    - Melatonin
    - Ramelteon (rozerem)

Sleep Hygiene

- Sleep time
  - No stimulants before bed
  - Cool environment
  - Dark room
  - No smoking
  - No TV
  - Dark room
  - No disturbances

- Wake time
    - Activity
    - Bright lights

Nonpharmacological treatments

- Relaxation training
    - Aimed to reduce somatic tension and intrusive thoughts that interfere with sleep
- Stimulus control therapy
    - Get out of bend if not sleepy, only use bed for sleeping, no nappy
- Sleep restrictive therapy
    - Limit time spent in bed to produce mild sleep deprivation, results in more consolidated sleep
- Intrusive sleep retraining
    - 25hour sleep deprivation period in which the patient is given 50 sleep onset trails but awoken following 3 minutes of sleep
- Cognitive behavioral therapy
    - Reduce negative attitudes and misconceptions about sleep

**Excessive daytime sleepiness**

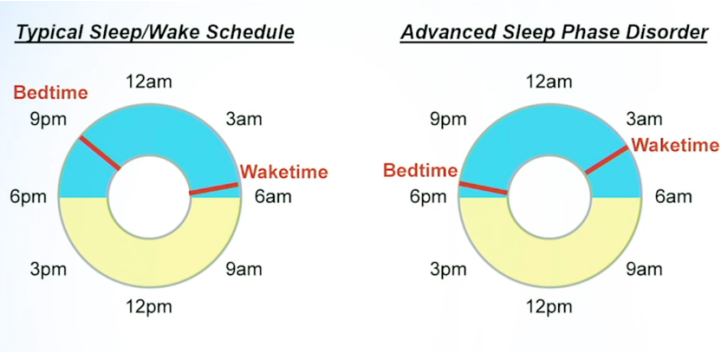
**Hypersomnia (too much sleepiness)**

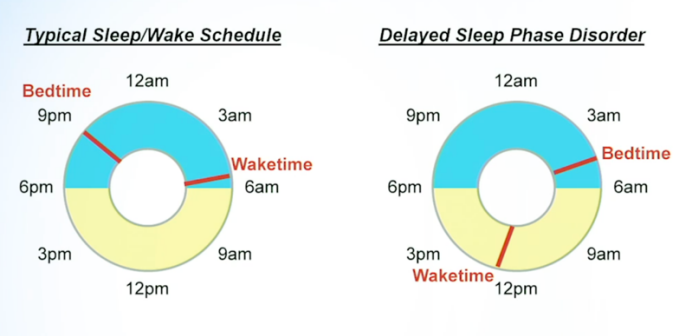
- Central disorders of hypersomnolence
    - Idiopathy hypersomnia
        - Do not know the cause
        - Long >10 hours or normal sleep duration
        - Non-refreshing sleep
        - Tx: medication that increases sleep to get deeper sleep for delta sleep
    - Recurrent hypersomnia
    - Narcolepsy
        - With or without cataplexy
        - Abnormal REM manifestations
        - Intrusion of sleep during wake times
        - Causes the death of the lateral hypothalamus (orexin neurons)
            - Don’t stabilize wakefulness so you have sleep attacks.
            - Possible immune system abnormalities. Unknown cause.
- Other causes
    - Medical conditions
        - Obstructive sleep apnea
            - Clinical features:
                - Loud snoring
                - Obesity
                - HTN
                - Neck>17”
                - Enlarged tonsils
                - Loss of interest
                - Excessive daytime sleepiness
                - Fatigue
                - Depression
            - Pathophysiology
                - Partial or full collapse of upper airway
                - Narrowing may occur at different levels

        - Muscle tone, airway reflexes
        - Metabolic abnormalities in frontal love white matter of hippocampus due to hypoxia
    - medication side effects
    - Substance use
    - Psychiatric conditions
        - Depression

Circadian rhythm disorders

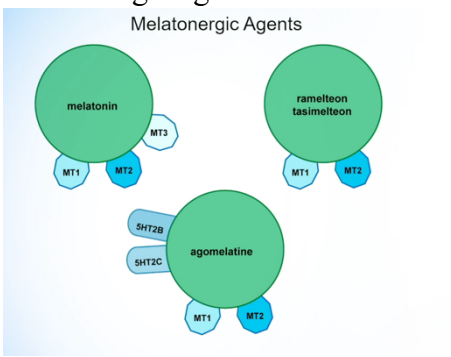
- Persistent or recurrent patterns of sleep disruption primary attributed to circadian disruptions and circadian misalignment
- Circadian related sleep disruption resulting in insomnia excessive daytime sleepiness or both
- Sleep disturbance that is associated with impairment in social, occupational, or other areas of function
- Disorders
    - Delayed sleep phase disorder
        - Wake up late, wake up late
        - Seen in teens and elderly
    - Non-24
        - Rhythm is set by the sun and light (turns off SCN, light inhibits)
    - Shift work disorder
        - Insomnia or excessive sleepiness temporarily associated with a recurring work schedule that overlaps with the usual time for sleep
        - Symptoms associated with shift work schedule are present for at least 1 month
        - Sleep log or actigraphy monitoring (with sleep diaries) for at least 7 days demonstrates disturbed sleep (insomnia) or circadian and sleep time misalignment
        - Sleep disturbances is not due to another current sleep disorder, medical disorder, mental disorder, substance use disorder, or medication
    - Advanced sleep phase disorder
        - Wake up to early and go to bed to early






- Can manipulate this with a combination of light and melatonin
    - Light therapy early in the day can readjust the circadian rhythm
        - Early morning light

Melatonergic agents




- agomelatine not approved in US

**Promote wakefulness**

- Inhibit
    - Gaba
- Enhance
    - Hypocretin/orexin
    - Ach
    - Dopamine
    - Norepinephrine
    - Serotonin
    - Histamine

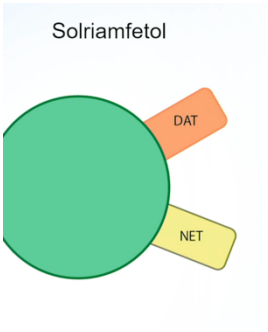
**Caffeine**

- Dopamine is next to a purine receptor,
- Dopamine fills the dopamine receptor
- Adenosine goes into the purine receptor
    - This inhibits dopamine actions
- Caffeine blocks the adenosine at the purine receptor
    - Cannot inhibit dopamine
    - Which means dopamine will work better

**Amphetamine and Methylphenidate**

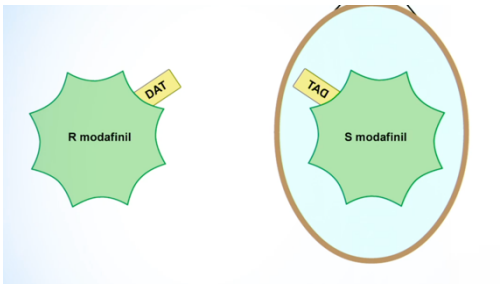
- Blocks norepinephrine and dopamine reuptake
- Used for narcolepsy and obstructive sleep apnea

**Solriamfetol**




- used for obstructive sleep apnea and narcolepsy

**Modafinil or Armodafinil**




- block dopamine reuptake and enhance dopamine action
- Once dopamine is triggered it triggers more neurotransmitters
- keeps GABA down

**Treating sleep apnea**

- CPAP: opens airway
- Oral appliances
- Weight loss
- Surgery of tonsils

**Pitolisant**

- Stops histamine from being able to turn its self-off. Releases histamine from receptor

**Gamma hydroxybutyrate**

- Occurs at a GABA receptors A, B and GHB
- Approved for narcolepsy, improves nighttime sleep
- Approved for idiopathic hypersomnia better sleep