Psychopharmacology of Sleep and Sleep Disorders

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Scope

Pharmacology of sleep and arousal
Effects of drugs on sleep and state of arousal
Therapy of primary insomnia
Circadian rhythms and insomnia
Therapy of narcolepsy
EEG

Berger (1928) recorded electrical activity from human scalp - change in amplitude noted with different states of arousal. Probable source: summation of changes in electrical potential in cortical and subcortical neurons (usually measured on the scalp).

Effect of state of arousal on EEG waveforms

- Aroused/awake: low voltage, fast, synchronized EEG
- Arousal/light sleep: slower, higher voltage, more synchronized EEG
- Deep sleep: slowest, higher voltage, unsynchronized EEG
- REM sleep: low voltage, fast, unsynchronized EEG
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Arousal Systems/Pathways

Ascending Reticular Activating System
diffuse structure from upper brain stem—intralaminar/thalamic nuclei—cortex
engaged in active control over sleep and arousal processes

main neurotransmitters associated with arousal:
- NE (locus ceruleus)
- histamine (tuberomammillary nucleus)
- orexins/hypocretins (posterior hypothalamus)
- ACh (basal nucleus of Maynertz; laterodorsal tegmental N; pedunculopontine N)

main neurotransmitters associated with sleep:
- GABA (generally inhibitory; ventrolateral preoptic N is key area)
- adenosine (inhibits cholinergic activity)

other influences on arousal
- light; melatonin; circadian clock (suprachiasmatic nucleus); social factors; physical activity; caffeine (adenosine antagonist)
- 5HT (raphe nuclei)
- DA (VTA)
- glutamate (all areas)
- 5HT (raphe nuclei)
Neurotransmitter Systems Involved in Wakefulness

- Locus Ceruleus (NE)
- Raphe N (5-HT)
- Tuberomammillary N (Histamine)
- Lateral dorsal tegmental N
- Pedunculopontine N (ACh)
- Hypothalamus (orexins)
- Ventrolateral preoptic area (dopamine)
- VTA (dopamine)

Structures/transmitters associated with arousal
Structures/transmitters associated with non-REM sleep
Structures/transmitters associated with REM sleep
Structures/transmitters associated with EEG generation

(EEG desynchronization)

(adenosine)

(Excitatory Cortical Input/ Arousal)
Neurotransmitter Systems Involved in Non-REM Sleep

- Basal forebrain (ACh, GABA)
- Locus Ceruleus (NE)
- Raphe N (5-HT)
- Tuberomammillary N (Histamine)
- Hypothalamus (orexins)
- Ventrolateral preoptic area (GABA)
- VTA (dopamine)
- Laterodorsal Tegmental N
- Pedunculopontine N (ACh)
- SCN
- Pineal (melatonin)

Structures/transmitters associated with arousal
Structures/transmitters associated with non-REM sleep
Structures/transmitters associated with REM sleep
Structures/transmitters associated with EEG generation
Structures/transmitters associated with cycle regulation
Neurotransmitter Systems Involved in REM Sleep

- Locus Ceruleus (NE)
- Raphe N (5-HT)
- Tuberomammillary N (Histamine)
- Laterodorsal Tegmental N
- Pedunculopontine N (ACh)
- Hypothalamus (orexins)
- Ventrolateral preoptic area (GABA)
- Basal forebrain (ACh, GABA)

Structures/transmitters associated with REM sleep:
- Locus Ceruleus (NE)
- Raphe N (5-HT)
- Tuberomammillary N (Histamine)

Structures/transmitters associated with non-REM sleep:
- Hypothalamus (orexins)
- Ventrolateral preoptic area (GABA)

Structures/transmitters associated with arousal:
- Basal forebrain (ACh, GABA)

Structures/transmitters associated with EEG generation:
- Lateral ventricle

(EEG desynchronization)
Pharmacological rationale for ....

Drugs which cause insomnia/work in narcolepsy:
   facilitate NE, DA, 5HT, ACh neurotransmission
   (inhibit adenosine (caffeine); 5HT loss (dorsal raphe))

Drugs which cause sedation/work in insomnia:
   inhibit NE, 5HT, histamine
   facilitate GABA

Drugs which inhibit REM/dreaming:
   increase NE, 5HT, GABA transmission

Drugs/states associated with vivid dreams:
   cholinesterase inhibitors; BDZ and MAOI withdrawal
Management of insomnia

History/examination/evaluations to identify and treat 20 causes for insomnia

4 major areas cover majority of 20 causes of insomnia:

- psychiatric disorders (depression, anxiety)
- level of arousal (recent stress)
- drugs (alcohol; BDZ withdrawal; others)
- circadian disturbances (recent travel; shift work)
Classification and Prevalence of Insomnia

Also: Transient and Persistent Sleep-Wake d/o’s (e.g. jet lag; shift work; etc) - very common
Pharmacological Causes of Insomnia

Non-Rx Drugs
- caffeine; nicotine; diet pills (esp. w/ pseudoephedrine/ephedrine/PPA)
- alcohol intoxication/withdrawal

Rx Drugs
- ⚡-blockers
- ⚡adrenergic agonists (albuterol)
- sympathomimetic decongestants (pseudoephedrine, phenylephrine, PPA)
- antidepressants (SSRIs - 5HT; DMI - NE; buproprion: DA and NE)
- MAOIs (DA, NE, 5HT)
- stimulants (methylphenidate, pemoline, d-amphetamine - NE, DA, 5HT)
- BDZs (short t½ rebound; longer t½ withdrawal)
- thyroid preparations
- oral/IV corticosteroids
- theophylline (adenosine antagonist)
- phenytoin
- phenytion
- quinidine
- chemotherapy
Investigation and Management of Primary Insomnia

Investigations: sleep EEG; MSLT; sleep diary
Optimal treatment combines pharmacological and behavioral approaches
  good sleep hygiene
  biofeedback
  relaxation
  sleep restriction
  drugs
Good Sleep Hygiene

Purpose: establish habits/behaviors that promote good sleep
establish regular sleep schedule (avoid fluctuations in waking time)

increase aerobic fitness; regular exercise
reduce caffeine and alcohol intake
ensure bedroom is cool, dark and quiet
wind down period (30 mins) before bed

avoid lying in bed awake and ruminating/problem solving (bedrooms are for sleep and sex) - get up and read/complete a task if not sleepy after 30 minutes in bed (stimulus control)

reduce exposure to bright light to avoid phase-delaying the circadian system (reading lights/computer screens are OK)

high tryptophan snack (milk, cookies, banana) before bed
Other Behavioral Methods

Biofeedback
for patients with insomnia associated with high arousal levels
monitoring of physiological variable (EMG, skin temp, EEG theta waves)
auditory/visual cues to monitor physiological variable
patient develops strategies to modify variables/reduce arousal level

Progressive relaxation
make patient aware of increased muscle tension/high arousal level
contract muscle groups ▼ become aware of tense state ▲ relax muscles

Sleep restriction
for patients who spend much time in bed but little of it asleep
restrict time in bed in order to consolidate sleep
aim for sleep efficiency (time asleep as % of time in bed) ~85%
patients may report initial increase in daytime sleepiness

Other non-pharmacological approaches
cognitive therapy; others….
Brief Behavioural Treatment for Chronic Insomnia in Elderly – Arch Int Med 2011.

BBTI (=2 sessions, good sleep hygiene principles, n=39) vs controls (information only, n=40)
Outcome at 4 weeks
Drug treatments for insomnia

Benzodiazepines
Chloral hydrate and ethanol derivatives
Antihistamines
Sedating Antidepressants
Melatonin/melatonin agonists/bright light
Ligands of the BDZ receptor

Positive modulators of the BDZ-binding site on the GABA-A receptor

BDZs (>40 compounds)

- benzene ring fused to (e.g. diazepam)
- 7-member *diazepine* ring

other non-BDZ structures

(still bind to BDZ-Rs)

(zolpidem)  (zopiclone)
BDZ Clinical Profile

- widely used in anxiety disorders and insomnia
  - main differentiation based on PK (short t½ for insomnia; longer t½ for anxiety)
- immediate onset of activity
- wide safety range in overdose
  - amnesia; inco-ordination; sedation; exaggerated in combination with alcohol and other sedatives
  - tolerance
  - psychological and physical dependence (less severe than for barbiturates)
  - withdrawal (less severe than for barbiturates)
    - anxiety; insomnia; arousal; minimise by long half-life BDZ and slow down-titration.
Benzodiazepines as hypnotics

all BDZs have equivalent efficacy in sleep induction

major differences: pharmacokinetics and thus side-effect liability

ideal profile: rapid absorption (rapid sleep induction)

short half-life (no hangover)

(possible increased risk of rebound insomnia)

slow absorption; delayed sleep induction

long t1/2; hangover
Recent BDZ hypnotics have:
- rapid absorption
- short half-life
- no active metabolites

*not approved for anxiety disorders; no licensed dose
Use of BDZs for insomnia

Short courses associated with periodic worsening of symptoms/e.g. associated with stress
  there are virtually no studies to assess efficacy if used for >5wks

Shorter t½ compound to avoid a.m. hangover
Longer t½ compound if significant residual anxiety
  although risk of daytime psychomotor impairment

Reassess need for BDZ regularly
  Is insomnia still present?
  Is the patient escalating the dose?
  Are there changes in psych./medical diagnoses?
Withdrawal from BDZs

Complaints: recurrence or worsening of original symptoms (insomnia, anxiety) upon dose reduction or cessation

Risk factors: patients with worst sleep at baseline; longer duration of treatment; higher BDZ dose

Management:
- prevention (try to limit duration of BDZ course; avoid dose escalation)
- switch to longer t½ compound (e.g. diazepam)
- dose reduce gradually over several weeks/months
Comparison of BDZs vs CBT in insomnia

78 patients randomized to CBT, temazepam 7.5-30mg, combined CBT + temazepam, or placebo (JAMA 1999, 281:991)
Treatment for 8 weeks; f/u at 3, 12 and 24 months

Conclusion: short-term: CBT≈BDZs; long-term: CBT > BDZs;
no obvious additive effects on sleep variables
Alcohol-type hypnotics

Chloral derivatives - e.g. chloral hydrate
  pharmacology: act at site(s) on GABA-A receptor
  short t1/2 (4-6 hours)
  decrease sleep latency and reduce number of awakenings; little effect on SWS or REM sleep

Acute side effects:
  unpleasant taste; epigastric distress and nausea; lightheadedness, ataxia and nightmares; skin irritation; risk of respiratory/CV depression in overdose

Chronic side effects:
  tolerance to hypnotic effects; potential physical dependence

Conclusion:
  No efficacy advantages over BDZs
  Substantially higher risk than BDZs in overdose
  Rationale for use of these compounds marginal at best
Antihistamines

Nonselective H-antagonists (e.g. promethazine, diphenhydramine, hydroxyzine)

Effects on arousal

Nonselective antagonists are effective hypnotics; no abuse potential; no tolerance reported (although not carefully studied)

Problems:
- long t1/2 (hangover)
- dry mouth, constipation, confusion from anticholinergic effects
Sedating Antidepressants

Examples:
Mirtazapine, maprotiline, amitriptyline

Different antidepressant pharmacologies; sedation due to antihistaminergic +/- antiadrenergic effects

no controlled clinical data to support their use (one study showed worsening of sleep EEG profile with AMI)

not recommended for primary insomnia

may be useful for depressed patients with prominent insomnia symptoms
Melatonin

Neurohormone produced by pineal during dark phase
One of several circadian rhythms driven by biological clock
(suprachiasmatic nucleus) and synchronised by environmental clues

Involved in circadian regulation of sleep and seasonal reproduction control
Melatonin in insomnia

Implicated in disturbances of circadian rhythm (jet lag, shift work); non-24h-sleep/wake cycle in blind subjects; ?delayed sleep phase insomnia
Low doses at bedtime (0.5-3mg) may be useful in such cases.

No evidence of melatonin disturbances in 10 insomnia
Low dose melatonin (<3mg) or ramelteon (synthetic MT1 agonist) may reduce sleep latency; high doses (>3mg) may have hypnotic effects; overall effects modest
Generally well tolerated

Issues: OTC; short half-life (~40min); little controlled data; overall efficacy <BDZs and H-antags; may have effects on reproductive function.
Bright light for circadian rhythm disturbances

Use bright light (5000 lux; 3-4h) to phase advance or phase delay circadian system for sleep disturbance associated with jet lag; shift work
Bright light exposure given **before** temperature nadir (equivalent of 11PM-3AM) will **phase delay**
Bright light exposure given **after** temperature nadir (equivalent of 4AM-7AM) will **phase advance**
Narcolepsy

Clinical Features

Daytime sleepiness

“irresistable attacks of refreshing sleep”; MSLT <5min + early REM appearance

disturbed nocturnal sleep may also contribute to daytime sleepiness

Cataplexy (~70% of narcoleptics)

loss of muscle tone associated with strong emotion

Sleep paralysis (~30-50%)

Hypnagogic hallucinations (~30%)

REM sleep at sleep onset

normally occurs ~90min after sleep onset

Epidemiology

onset 10-20y; rare after 40y; normal sleep/wake cycles earlier in life

prevalence ~1/2000; M=F

1st degree relatives: narcolepsy in 5-15%; 1o hypersomnia in 25-50%
Pathophysiology:

HLA-DQB1*0602 in 85-95% of NL patients with severe cataplexy, 40% in NL patients without cataplexy (~25% of general population)

nonfunctional orexin 2 receptors or loss of orexin production in animal narcolepsy models (dobermans, labradors and mice)

loss of orexin-producing neurons in hypothalamus of human narcoleptics (>90%)

Orexin A and B (also known as hypocretin 1 and 2) are hypothalamic peptides which influence feeding and sleep

ICV orexins increase arousal (++) and increase feeding (+) in animals

Orexin B knockout mice have more severe symptoms (cataplexy, REM onset sleep) than Orexin A k/o mice

loss of neurons in man may be ?early onset neurodegenerative disorder or ?autoimmune (mixed evidence of inflammation or gliosis)

no evidence of orexin or orexin receptor gene deletion/mutation in man
Neurotransmitter Alterations in Narcolepsy

Structures/transmitters associated with arousal
- Locus Ceruleus (NE)
- Raphe N (5-HT)
- Tuberomammillary N (Histamine)

Structures/transmitters associated with non-REM sleep
- Basal forebrain (ACh, GABA)
- Ventrolateral preoptic area (ACh, GABA)
- VTA (dopamine)

Structures/transmitters associated with REM sleep
- Hypothalamus (orexins)

Structures/transmitters associated with EEG generation
- Laterodorsal Tegmental N
- Pedunculopontine N (ACh)

(EEG desynchronization)

(REM sleep)

(Reduced arousal; Reduced inhibition of ACh/REM)
Treatments For Narcolepsy

Psychostimulants

d-amphetamine, methamphetamine, methylphenidate, pemoline

release DA, NE

modafinil

Increased synaptic DA due to blocking transporter

all decrease daytime sleepiness; increase duration of MSLT

little effect on other symptoms of narcolepsy
# Treatments For Excessive Daytime Sleepiness in Narcolepsy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/day)</th>
<th>Half-life (h)</th>
<th>Tolerability Profile</th>
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<tbody>
<tr>
<td>d-amphetamine</td>
<td>5-60</td>
<td>10-12*</td>
<td>Irritability; mood changes; headaches; palpitations; sweating; tremors; insomnia; anorexia; ↑BP</td>
</tr>
<tr>
<td>Methamphetamine (AMP)</td>
<td>5-60</td>
<td>4-5*</td>
<td>Irritability; mood changes; headaches; palpitations; sweating; tremors; insomnia; anorexia; ↑BP</td>
</tr>
<tr>
<td>Methylphenidate (MPH)</td>
<td>10-60</td>
<td>3-4**</td>
<td>Similar to amphetamine with less anorexia and less ↑BP</td>
</tr>
<tr>
<td>Pemoline</td>
<td>20-115</td>
<td>16-18</td>
<td>Milder stimulant; slow onset of action; potential for liver toxicity (need regular LFT assessments)</td>
</tr>
<tr>
<td>Modafinil</td>
<td>100-400</td>
<td>9-14</td>
<td>Headache, nausea, nervousness; little sympathomimetic activity; overall magnitude of efficacy may be less than for MPH or AMP; lower abuse and dependence liability than AMP or MPH.</td>
</tr>
<tr>
<td>Caffeine</td>
<td>100-200</td>
<td>3-5</td>
<td>Weak stimulant effect; palpitations and ↑BP</td>
</tr>
</tbody>
</table>

*: dependent on urinary pH; **: new once daily formulations available
Treatments For Other Symptoms of Narcolepsy

Cataplexy:
- monoamine reuptake inhibitors (tricyclic antidepressants; venlafaxine; SSRIs) - NE component probably most important
- generally anecdotal evidence

Hypnagogic Hallucinations and Sleep Paralysis:
- TCAs (anecdotal evidence)

Nonpharmacological Management:
- good sleep hygiene
- avoid shift work
- daytime naps may be useful
- warn about driving risks if undertreated
The Future

Insomnia Rx: selective H3 agonists; orexin antagonists?
Narcolepsy Rx: Orexin agonists; H3 antagonists?
Other treatments based on more detailed understanding of control of sleep and arousal
Dual OX-1/-2 antagonist ACT-078573

Dose-response relationship for change in alertness (expressed as AUC) for ACT 1-1000mg and zolpidem 10mg.

Time course of change in alertness for ACT 400mg, Z 10mg and placebo