Recreational Drugs and Sleep

An overview

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Recreational Drugs

• Not all are illegal; (eg caffeine and alcohol legal)

• *Chemical substances taken to improve life in some way*
  • *Used commonly to reduce stress/ promote wake*
  • *Used parties/night clubs to improve sociability,*
  • ......*and to increase (perceived) dancing ability*
  • *Can also used to self medicate*

• All affect the neurotransmitters involved in sleep and wake

• Sleep can be affected differently depending on:
  • Dose and timing of administration
  • Occasional vs chronic use (dependence)- withdrawal of almost all leads to sleep disturbance

• ²*Commonly used drugs in Europe:*
  • Cannabis, Cocaine, Ecstasy (MDMA), Opioids (Heroin)

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Neurotransmitters in sleep & wake

Sleep and waking influenced by a wide range of neurotransmitters - drugs that affect these will potentially alter sleep.

<table>
<thead>
<tr>
<th>Endogenous transmitter</th>
<th>Increasing function maintains wakefulness</th>
<th>Increasing function promotes sleep</th>
<th>Examples of drugs promoting wakefulness</th>
<th>Examples of drugs promoting sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA</td>
<td>✓</td>
<td>(Alcohol)</td>
<td>Benzodiazepines Z drugs (Alcohol)</td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>✓</td>
<td></td>
<td>Melatonin</td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>✓</td>
<td>Antagonist: Caffeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>✓</td>
<td>Amphetamines (Cocaine/MDMA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>✓</td>
<td>SSRIs (MDMA)</td>
<td>Mirtazapine, Olanzapine</td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>✓</td>
<td></td>
<td>Promethazine</td>
<td></td>
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<tr>
<td>Acetylcholine</td>
<td>✓</td>
<td></td>
<td>Nicotine</td>
<td></td>
</tr>
<tr>
<td>Orexin</td>
<td>✓</td>
<td></td>
<td>Antagonists (suvorexant)</td>
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</tr>
</tbody>
</table>

Most recreational drugs have actions at multiple receptors.

Street preparations/ those purchased on the internet ...might not be what people think they are buying!
Alcohol and sleep

Subjective effects:
• Initial mild stimulant effects, increase in self-confidence, sociability
• As levels peak & decline, sedation, often used in insomnia (nightcap)
• Higher doses can cause nausea, confusion, sleep disturbance

• Enhances inhibitory NT (GABA), inhibits excitatory NT (glutamate)
• Effects on sleep are dose-dependent:
  • 1-2 drinks; mild, variable
  • 5-6 drinks; greater and more consistent
In healthy non-dependent good sleepers, at doses raising BAC to 0.1% (5-6 drinks) at bedtime:

**Alcohol is sleep promoting - 1\textsuperscript{st} half of the night\textsuperscript{1/2}**
- Improved sleep continuity; reduced SOL, reduced wake
- Increased SWS
- Some studies show decreased \%REM

**Alcohol is sleep disturbing- 2\textsuperscript{nd} half of the night\textsuperscript{1/2}**
- Increased wake/ Stage 1\textsuperscript{1/2}
- Secondary effects: sweating/ full bladder etc.

**Over the night as a whole\textsuperscript{2}:**
- Increased SWS
- Increased wake/sleep disturbance
- Some evidence; decreased \%REM

\textsuperscript{1}Feige B et al Alcohol Clin Exp Res. 2006 Sep;30(9):1527-37
Alcohol and sleep

- Alcohol worsens sleep disordered breathing\(^1\)
  - In the first hour of sleep after alcohol ingestion, in those with OSA:
    - Increases duration/ frequency of obstructive events
    - Increase in hypoxemia
    - Obstructive events induced in benign chronic snorers.

- Tolerance to some effects of alcohol develops
  - Higher doses needed to capture sedative effects
  - In one study\(^1\), after 9 days alcohol (3-4 drinks/night), SWS returned to baseline, but suppression of growth hormone remained.

Arterial oxyhemoglobin saturation in a patient aged 30, with obstructive apnoea. (a) control (b) after alcohol, profound increase in hypoxaemia in first hour of sleep. (apnoea only occurred in supine position)


\(^2\)Prinz J Clin Endocrinol Metab. 1980 Oct;51(4):759-64
Sleep in Alcohol Use Disorder

• In dependent drinkers while drinking
  • Sedating properties of alcohol lost, increased SOL after alcohol ingestion.
  • Sleep more chaotic, can follow a non-24 hour sleep-wake pattern, may include both insomnia and hypersomnia

• During acute withdrawal
  • severe sleep disturbance

• Sleep disturbances usually improve with continued abstinence
  • SOL may recover more quickly, followed by TST.
  • SWS may take longer to normalise (months-1/2 years)

• Sleep disturbance in patients with AUD is common and difficult to treat
  • 25% of abstinent alcoholic patients are likely to have insomnia despite abstinence for 3 months.
  • GABAergic medications (benzos/Z-drugs) not recommended as abuse potential/ risk of overdose when combined with alcohol.

2Brower KJ. Alcohol. 2015 Jun;49(4):417-27

Taken from: 3Drummond 1998
Cannabis and Sleep

Subjective effects:
• Low doses: Sense of wellbeing, relaxation, drowsiness (analgesia).
• Higher doses: confusion, anxiety, hallucinations

• Acts on cannabinoid receptors:
  • Cannabinoid receptors abundant in the brain
  • Widespread neuromodulation, affecting many different neurotransmitter systems
• Cannabis has mild/varied effects on sleep
Cannabis and Sleep

• The cannabis plant contains >60 cannabinoids
  • Tetrahydrocannabinol (THC), most abundant and psychotropically active.
  • Cannabidiol (CBD), effects when combined with THC.
    • Over the last decade THC content has nearly doubled /CBD decreased\(^1\)

• Cannabis can be consumed in different ways:
  • When smoked (joint) ‘weed’ / skunk (more potent)
    • Peak effects fast (15-30 mins), last 2-3 hours\(^2\)
  • When orally ingested
    • Slower/more varied, peak effects delayed (2-3 hours), last 4-12 hours\(^2\)
  • Slow elimination (>12 hours) - effects can be detected the next morning when taken before bed

\(^2\) Grotenhermen F. Clin Pharmacokinet. 2003;42(4):327-60
Cannabis and Sleep

- Subjectively: reported increased ease of getting to sleep (possibly due to relaxation)

- Objectively:
  - Effects varied, possibly dependent on properties of cannabinoids.
  - Nicholson 2004: The effects of THC alone and in combination with CBD

<table>
<thead>
<tr>
<th></th>
<th>THC 15mg</th>
<th>THC 15mg + CBD 15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep architecture</td>
<td>No change</td>
<td>Slight ↓ SWS ↑ Wake</td>
</tr>
<tr>
<td>Subjective sleep</td>
<td>Increased SOL</td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>More sleepy Impaired memory</td>
<td>More sleepy</td>
</tr>
</tbody>
</table>

Cannabis and sleep

- **Chronic use:** Like alcohol, tolerance may develop to ‘sedating effects’, dose increased.

- **Very high doses of THC – sleep disturbing** (210mg 12-16 days)$^1$
  - Increased SOL
  - Withdrawal: rapid decrease SWS and increase SOL

- **Withdrawal, ‘cannabis withdrawal syndrome’**
  - Subjective reports of difficulty sleeping and strange dreams
    - (occur within 1-3 days, can persist 6-8 wks)$^2$
  - Like other substitution therapies, oral THC may attenuate sleep disturbance$^3$.

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Opiates

- Morphine named after the god of sleep, Morpheus
- Although sedating, opiates can be acutely sleep disturbing,
- ‘Dream-like state’ during opium/heroin intoxication - fluctuating light sleep/wake

Opioid receptors are found in many areas of the brain related to sleep and breathing.
- Most clinically used opiates act on the mu opioid receptor.

Subjective effect depends on speed of entry into the brain & duration of action
- Depends on the route & the opiate
- Faster brain entry > more effects > (more dependence) ‘chasing the dragon’
- Route: smoked/IV > inhaled > oral
- Opiate: Heroin (rapid/short duration) > Morphine > Methadone
  - Heroin (Diamorphine) rapidly absorption > euphoric rush, highly addictive:
  - Morphine > more slowly absorbed > can also induce euphoria > longer action
  - Methadone > longer duration of action > no euphoric effects/ blocks euphoric effects of other opiates
Morphine is sleep disturbing in healthy volunteers

- In healthy good sleepers, intravenous clinical doses of morphine (7mg) given before bed & 3am
- Causes *shift to lighter stages of sleep*: ¹⁄²
  - Reduced SWS
  - Increased stage 2 sleep
  - REM suppression (IV only)
- Replicated in larger study (15mg morphine)²
- Methadone (5mg) similar effects²

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N=7 healthy subjects, Morphine administered IV, 2 boluses; 30-60 after lights off, 03-04:00 am

²Dimsdale JE. *et al* Clin Sleep Med. 2007
• Heroin - difficult to study
• Series of studies in federal prisoners in USA
• History of opiate abuse, currently abstinent.
• IM heroin before bed
• Fluctuating ‘drowsy-wake’ state, wake interrupted by S1.
• Dose-related increase in light sleep, decrease SWS/REM.
• Heroin twice as potent as morphine regarding insomnia

Sleep is also disturbed after heroin in healthy volunteers

- N=4 healthy male subjects (authors)
- Subcutaneous 7.5mg heroin 3 nights
- Increase in stage 1 sleep but delay to deeper stages of sleep.
- Increase in shifts from stage 1 to wake.
- REM suppression and rebound on withdrawal.

Caffeine

The most widely consumed psychoactive substance in the world.

Mild stimulant, taken to:
• Increase alertness
• Improve performance when fatigued
Can also lead to insomnia, sleep disturbance & anxiety
Adenosine antagonist
Caffeine content can vary hugely (70mg tea, >200mg energy drinks).

Some people are genetically more sensitive to the effects of caffeine.

Sleep effects:

- 150mg caffeine (about 2 cups cafetiere-type coffee) 1 hour before bedtime in young moderate caffeine consumers
  - Sleep onset latency increased by ~ 50%
  - Total sleep time decreased by ~ 30 minutes

2 Clark I & Landolt HP. Sleep Med Rev. 2016
Stimulants

Cocaine, amphetamines
Strong stimulants

• **Subjective effects**
  • Increased alertness & self-confidence, euphoria
  • Can also lead to paranoia, insomnia, delusions

• **Increase in monoamines - dopamine, noradrenaline, serotonin**
  • Re-uptake inhibition and neurotransmitter release lead to prolonged action of wake-promoting monoamines in the synapse
Cocaine and sleep

Acute effects in healthy volunteers\(^1\):
- Most profound effects on REM sleep
- REM decreased/ ROL increased
- **Rebound greatest on 2\(^{nd}\) recovery night**
- REM increased/ ROL reduced
- Returning to normal 3\(^{rd}\) recovery night

Inpatients after cocaine\(^2\):
- Increase in next daytime sleepiness (MSLT)

\(^1\) Johanson Exp Clin Psychopharmacol. 1999 Nov;7(4):338-46

Cocaine and sleep

- Cocaine withdrawal – ‘occult insomnia’
- In the first few weeks of withdrawal objective sleep progressively deteriorates.
- However, patients have reported unchanged or improved sleep quality

- Controlled inpatient ‘binge’ IV cocaine, days followed by abstinence.
- TST/ SOL/SWS continued to deteriorate
- Subjectively sleep quality improved; Possibly sleep better in comparison to early abstinence.
- Some evidence that sleep may improve with continued abstinence
  - Improved TST ~3 months.

\[\text{Taken from: }^1\text{Morgan et al. Drug Alcohol Depend. 2006 May }20;82(3):238-49.\]

\[\text{\cite{Angarita2014}}\]

\[\text{\cite{Schierenbeck2008}}\]
MDMA - ‘ecstasy’

- Usually taken in clubs /raves
- Stimulant: keeps people awake for dancing
- Makes people feel ‘open’, close to others ("loved-up") associated with perceptual changes

- MDMA has similar stimulant effects to amphetamines,
- Increases monoamines, however primary action is to enhance serotonergic function. (5-HT >NA> DA)

- 2 studies of sleep after acute MDMA/MDE:
- Increased wake/ potent suppression of REM sleep
Sleep and MDMA

• Eve (‘MDE’) similar to MDMA
  • Subjects dosed at 11pm, went to sleep normally, woke after 1-2 hours, then awake for 3-5 hours.
  • PSG: complete suppression of REM sleep (as expected from increased 5-HT release). Some shift of SWS to second half of night in those who slept.

Taken from: Gouzoulis et al Biol Psychiatry. 1992 Dec 15;32(12):1108-17
REM sleep suppression after MDMA

- N=7 HV, MDMA 2mg/kg, 18:00pm\(^1\)
- MDMA = decreased TST mainly due to increased SOL (~2 hours), decreased REM (3.5mins).
- **Chronic use:**
  - Evidence from semi-structured interviews suggest people report restless and troubled sleep for 48 hours after taking ecstasy\(^2\).
  - Some studies suggest ‘heavy/chronic’ MDMA use is associated with poor sleep\(^3\).
    - Possibly decreased stage 2/TST and increased stage 1.

Drugs change the sleeping brain
