



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 disturbance¹
- ²Commonly used drugs in Europe:
 - Cannabis, Cocaine, Ecstasy (MDMA), Opioids (Heroin)



¹Angarita *et al.* Addict Sci Clin Pract. 2016 Apr 26;11(1):9.

²European Drug Report 2015: Trends and Developments. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), (<http://www.emcdda.europa.eu>)

Neurotransmitters in sleep & wake



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

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

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

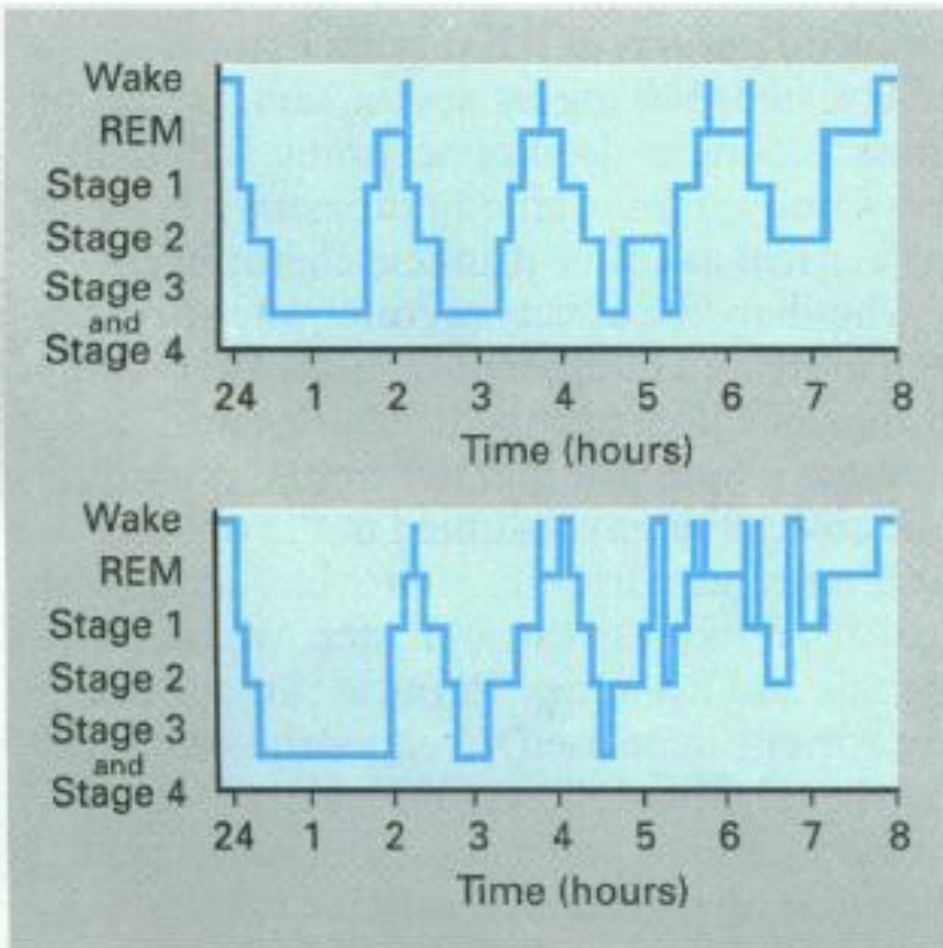
Subjective effects:

- 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



Alcohol and sleep



Hypnograms showing the effect of alcohol (bottom) on normal (top) REM and slow wave sleep.

Image taken from: Stradling JR. BMJ. 1993 Feb 27;306(6877):573-5.

In healthy non-dependent good sleepers, at doses raising BAC to 0.1% (5-6 drinks) at bedtime:

Alcohol is sleep promoting - 1st half of the night^{1/2}

- Improved sleep continuity; reduced SOL, reduced wake
- Increased SWS
- *Some studies show decreased %REM*

Alcohol is sleep disturbing- 2nd half of the night^{1/2}

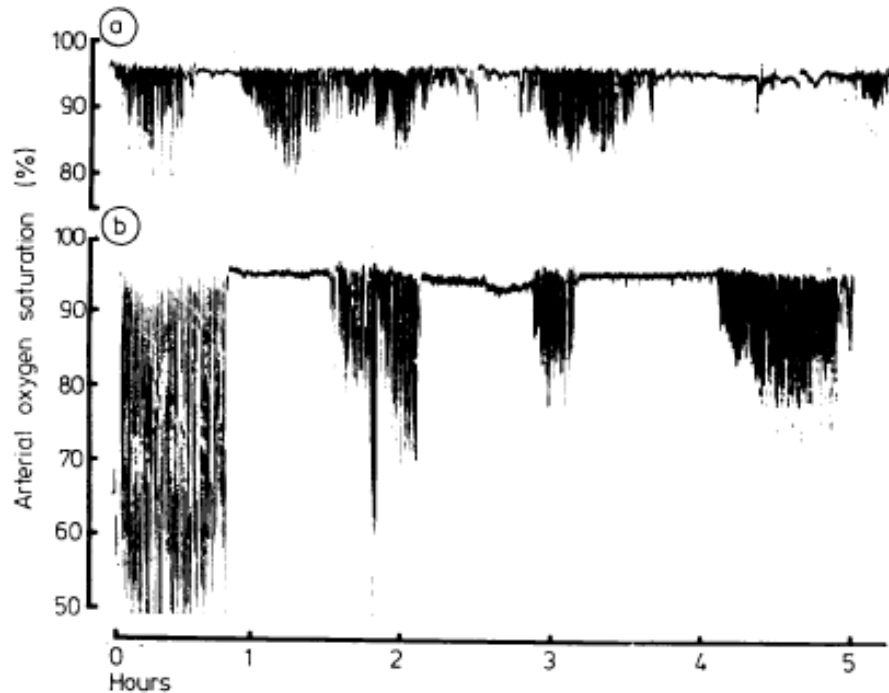
- Increased wake/ Stage 1^{1/2}
- Secondary effects: sweating/ full bladder etc.

Over the night as a whole²:

- Increased SWS
- Increased wake/sleep disturbance
- *Some evidence; decreased %REM*

¹Feige B et al Alcohol Clin Exp Res. 2006 Sep;30(9):1527-37

²Review: Ebrahim Alcohol Clin Exp Res. 2013 Apr;37(4):539-49



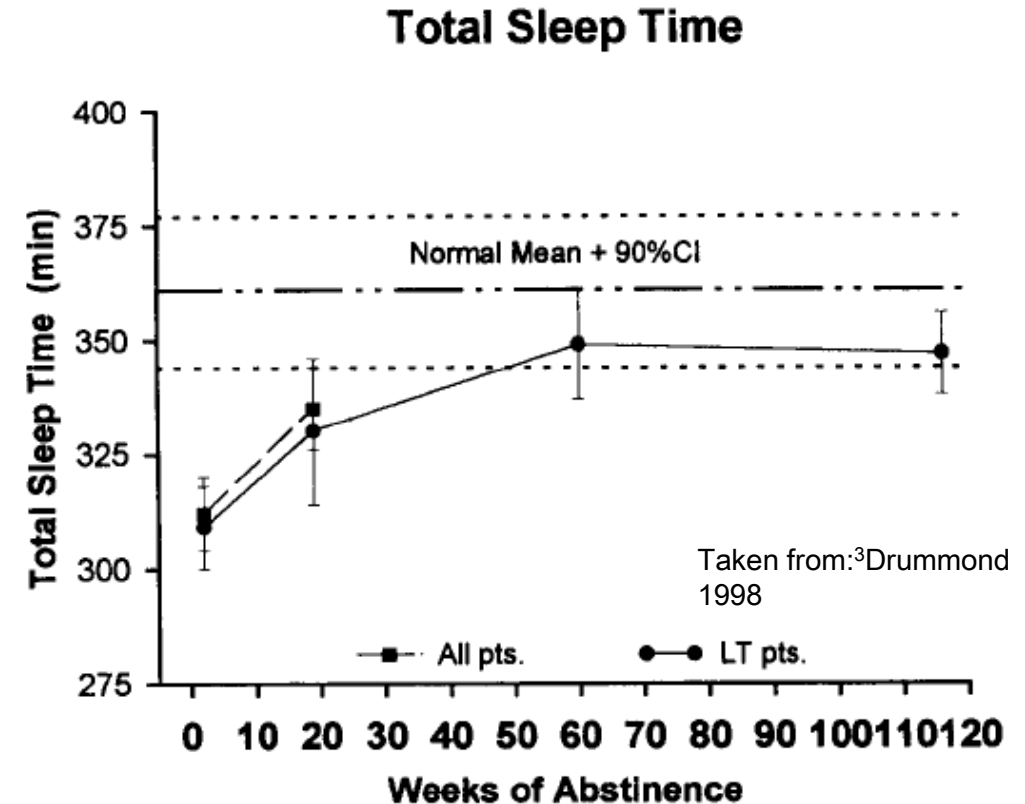
Arterial oxyhemoglobin saturation in a patient aged 30, with obstructive apnoea. (a)control (b) after alcohol, profound increase in hypoxaemia in first hour of sleep. (apnoea only occurred in supine position)

- **Alcohol worsens sleep disordered breathing¹**
 - 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 study¹, after 9 days alcohol (3-4 drinks/night), SWS returned to baseline, but suppression of growth hormone remained.

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 hypersomnia¹
- **During acute withdrawal**
 - severe sleep disturbance
- **Sleep disturbances usually improve with continued abstinence**²
 - SOL may recover more quickly, followed by TST.
 - SWS may take longer to normalise (months-1/2 years)²
- **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 months².
 - GABAergic medications (benzos/Z-drugs) not recommended as abuse potential/ risk of overdose when combined with alcohol.^{1/2}



¹Angarita Addict Sci Clin Pract. 2016 Apr 26;11(1):9

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

³Drummond SP, Alcohol Clin Exp Res. 1998 22:1796-8.

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



- 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 decreased¹
- Cannabis can be consumed in different ways:
 - When smoked (joint) 'weed' / skunk (more potent)
 - Peak effects fast (15-30 mins), last 2-3 hours²
 - When orally ingested
 - Slower/more varied, peak effects delayed (2-3 hours), last 4-12 hours²
 - Slow elimination (>12 hours) - effects can be detected the next morning when taken before bed

¹ European Drug Report 2015: (<http://www.emcdda.europa.eu>)

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*

	THC 15mg	THC 15mg + CBD 15 mg
Sleep architecture <i>Subjective sleep</i>	No change <i>Increased SOL</i>	Slight ↓ SWS ↑ Wake
Morning	More sleepy Impaired memory	More sleepy

THC alone- sedating
+CBD more alerting



- **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 disturbance³.

¹Feinberg I., Clin Pharmacol Ther. 1975 Apr;17(4):458-66

²Budney AJ, *et al*. Drug Alcohol Depend. 2007 Jan 5;86(1):22-9.

³Budney AJ, *et al*. Am J Psychiatry. 2004 Nov;161(11):1967-77.

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.

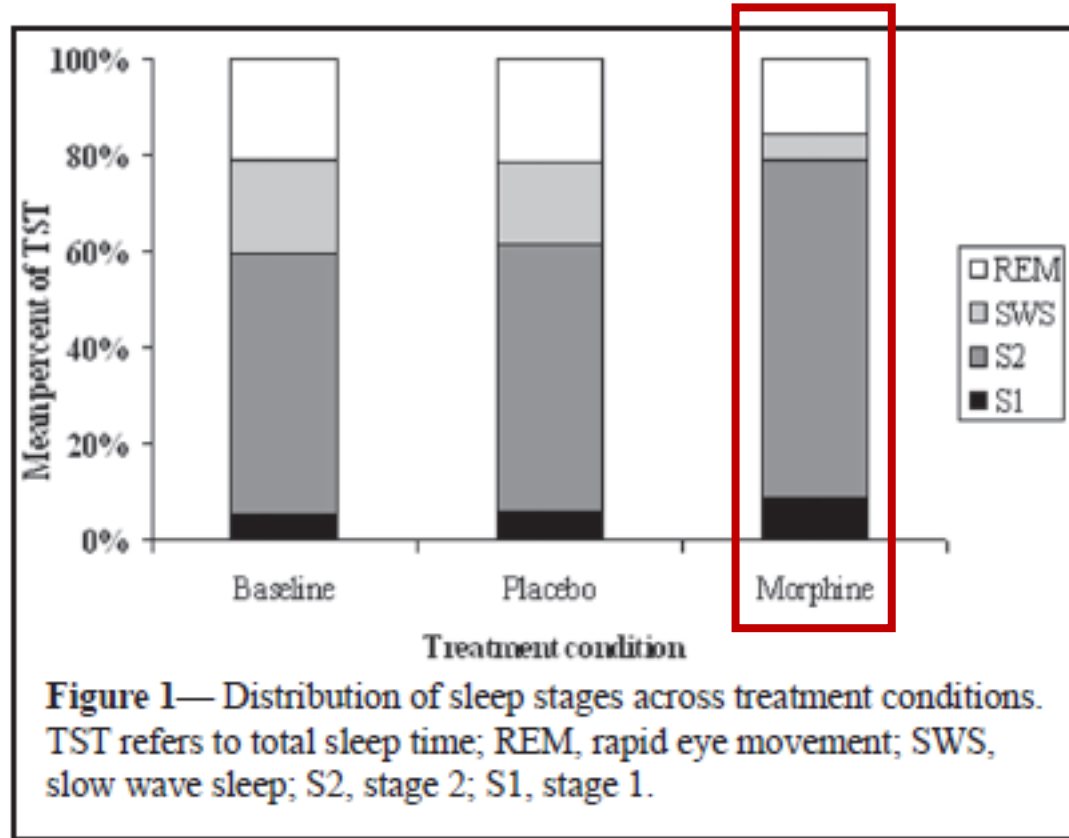
Subjective effect depends on speed of entry into the brain & duration of action

- 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

Opiates and sleep - morphine



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

Opiates and sleep: heroin

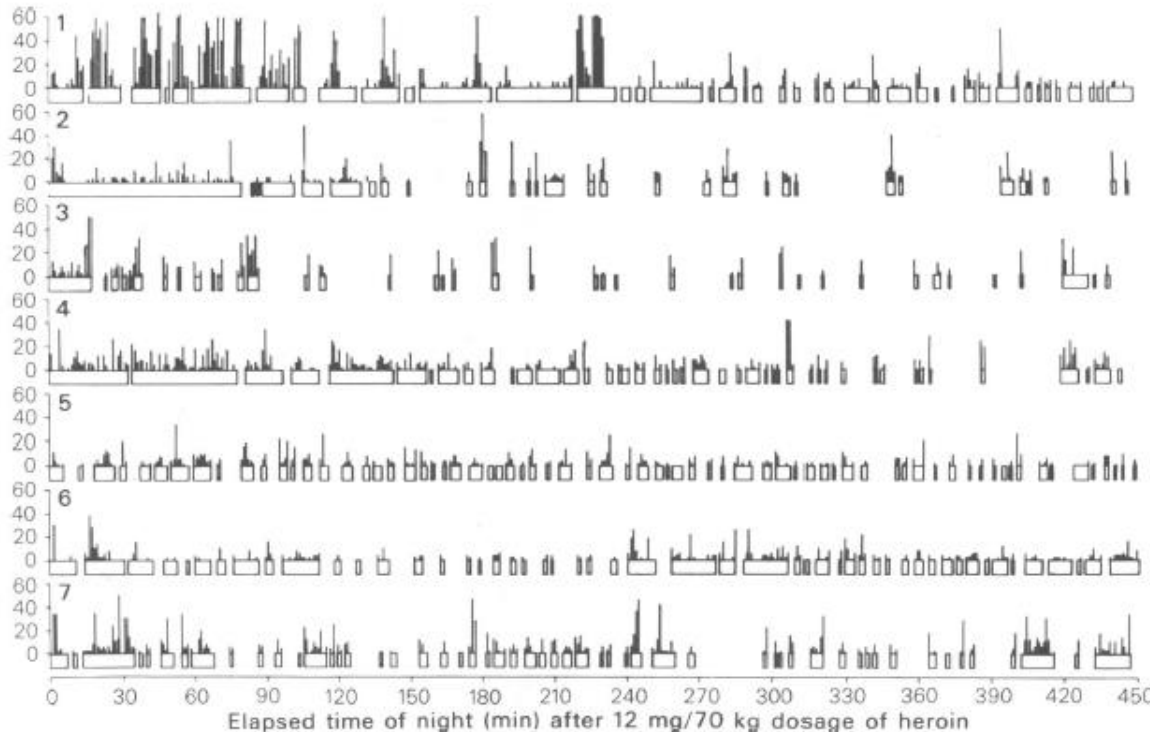


Figure 2 Wakefulness and muscle tension after heroin. For each of seven subjects, the presence of wakefulness (lower open blocks) and duration (0–60 s) of muscle tension (upper solid lines) is illustrated for each minute of the night after administration of 12 mg/70 kg of intramuscular heroin. Wakefulness is identified with each minute in which it occurs, regardless of relative proportion of the minute occupied by waking; therefore, the multiple short episodes of drowsiness which interrupted waking cannot be adequately illustrated.

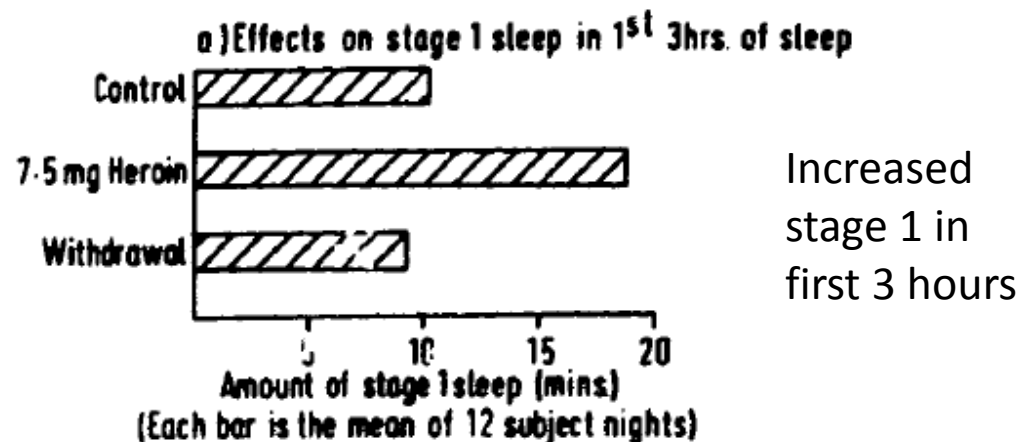
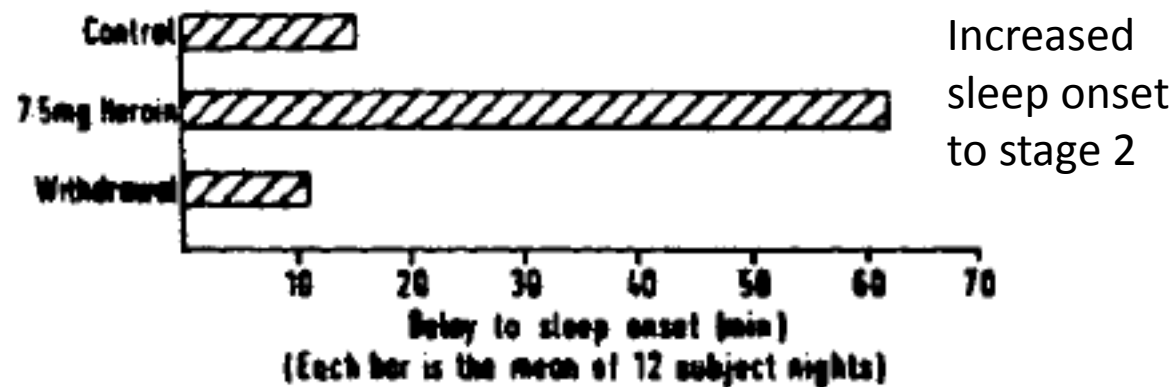
Taken from: Kay DC, *et al*/Br J Clin Pharmacol. 1981 Feb;11(2):159-69.

- 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

Opiates and sleep: heroin



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

A close-up photograph of a dark brown ceramic coffee cup filled with black coffee, sitting on a matching saucer. The cup has the word 'Café' written in a cursive script. In the foreground, a pile of dark brown coffee beans is visible. In the background, a slice of lemon is partially visible. The entire scene is set against a warm, reddish-brown background.

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

Sleep effects:

- **150mg caffeine (about 2 cups cafetiere-type coffee) 1 hour before bedtime in young moderate caffeine consumers¹**
 - Sleep onset latency increased by ~ 50%
 - Total sleep time decreased by ~ 30 minutes

- Caffeine content can vary hugely (70mg tea, **>200mg** energy drinks).
- Some people are genetically more sensitive to the effects of caffeine²

¹ Paterson *et al* J Psychopharmacol. 2009 Jul;23(5):487-94.

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



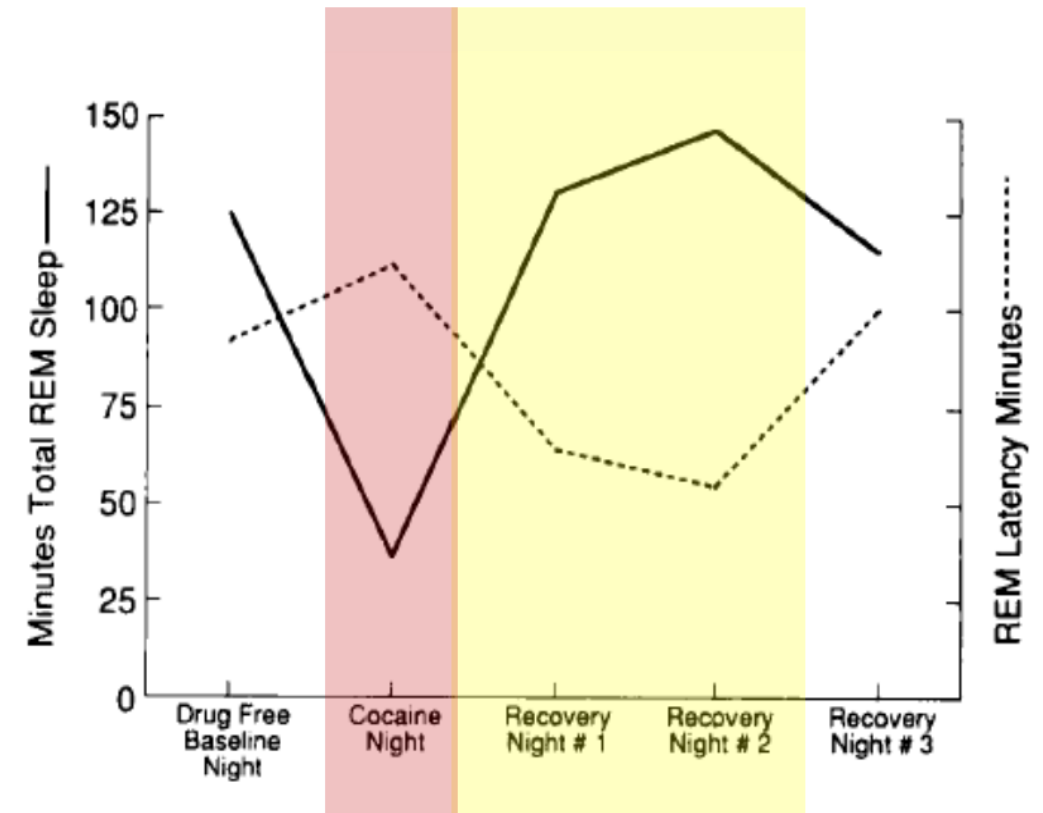
Acute effects in healthy volunteers¹

- Most profound effects on REM sleep
- REM decreased/ ROL increased
- **Rebound greatest on 2nd recovery night**
- REM increased/ ROL reduced
- Returning to normal 3rd recovery night

Inpatients after cocaine²:

- Increase in next daytime sleepiness (MSLT)

REM sleep after cocaine (1-1.5g) n=3
Watson (1992)



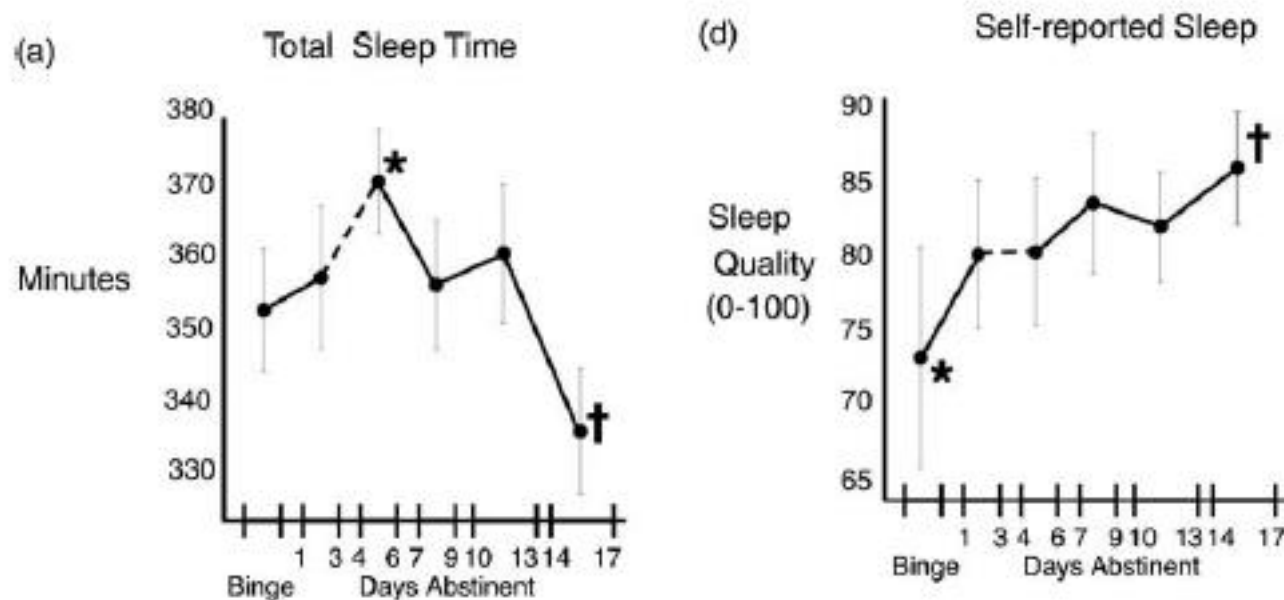
² Johanson *Exp Clin Psychopharmacol.* 1999 Nov;7(4):338-46

Taken from:¹ Watson et al *Am J Drug Alcohol Abuse.* 1992;18(1):21-8.

Cocaine and sleep



- Cocaine withdrawal – ‘occult insomnia’¹
- In the first few weeks of withdrawal objective sleep progressively deteriorates.
- However, patients have reported unchanged or improved sleep quality^{1/2}



- ¹Controlled 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 abstinence³
 - Improved TST ~3 months.

Taken from: ¹Morgan et al. *Drug Alcohol Depend.* 2006 May 20;82(3):238-49.

²Angarita GA, et al. *Drug Alcohol Depend.* 2014 Jan 1;134:343-7

³Schierenbeck T et al. *Sleep Med Rev.* 2008 Oct;12(5):381-9

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

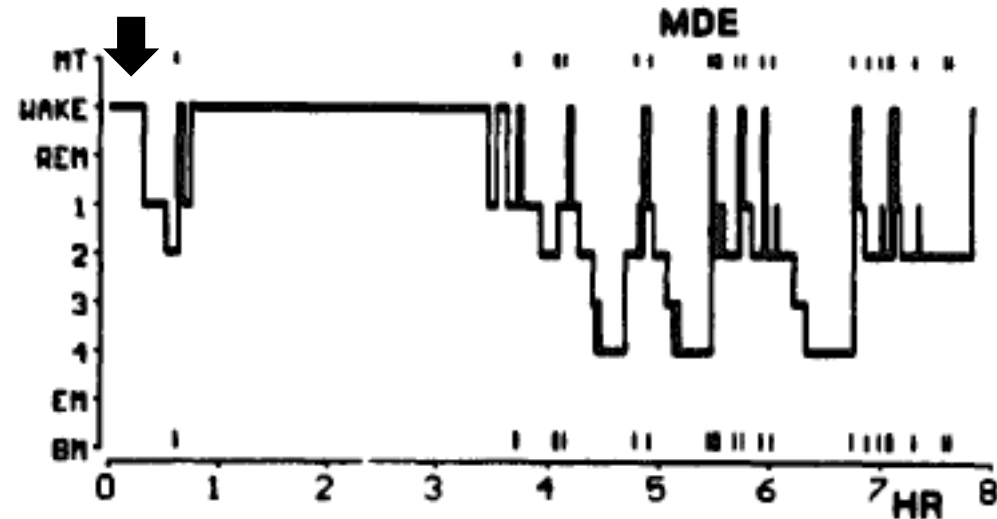
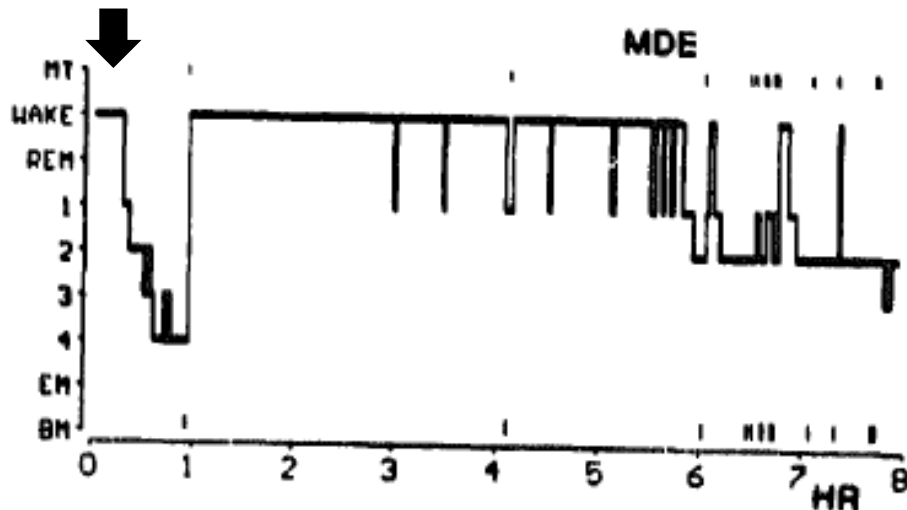
Sleep and MDMA



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Centre for
Neuropsychopharmacology

- 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.

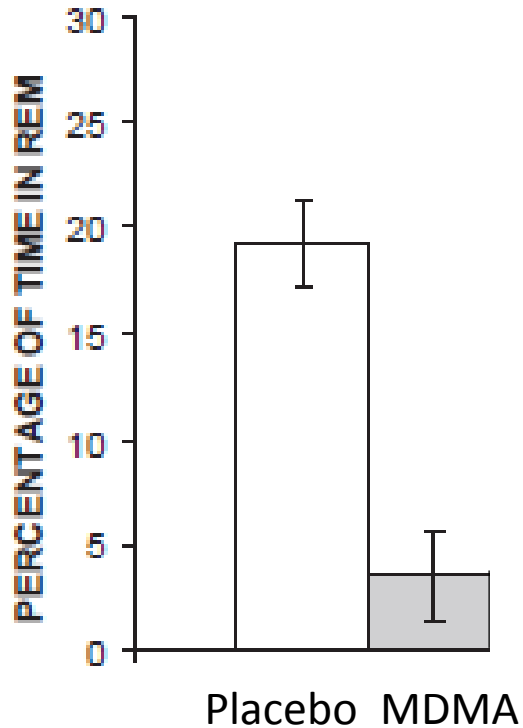


Taken from: Gouzoulis *et al* Biol Psychiatry. 1992 Dec 15;32(12):1108-17

Sleep and MDMA



REM sleep suppression after MDMA



- N=7 HV, MDMA 2mg/kg, 18:00pm¹
- 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 ecstasy².
- Some studies suggest 'heavy/chronic' MDMA use is associated with poor sleep³.
 - Possibly decreased stage 2/TST and increased stage 1.



Drugs change the sleeping brain

Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med Rev.* 2008 2(5):381-9.

Angarita GA, Emadi N, Hodges S, Morgan PT. Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review. *Addict Sci Clin Pract.* 2016 26;11(1):9.