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May 2015 |

Clinical Pharmacology of Illicit Drugs

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Agenda

- › Clinical pharmacology of Alcohol
- › Clinical pharmacology of Cannabis
- › Clinical pharmacology of Opioids
- › Clinical pharmacology of Cocaine
- › Clinical pharmacology of Amphetamine
- › Clinical pharmacology of Ecstasy (XTC, MDMA)
- › Clinical pharmacology of Tobacco
- › Clinical pharmacology of Gamma-Hydroxybutyrate (GHB)



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Alcohol



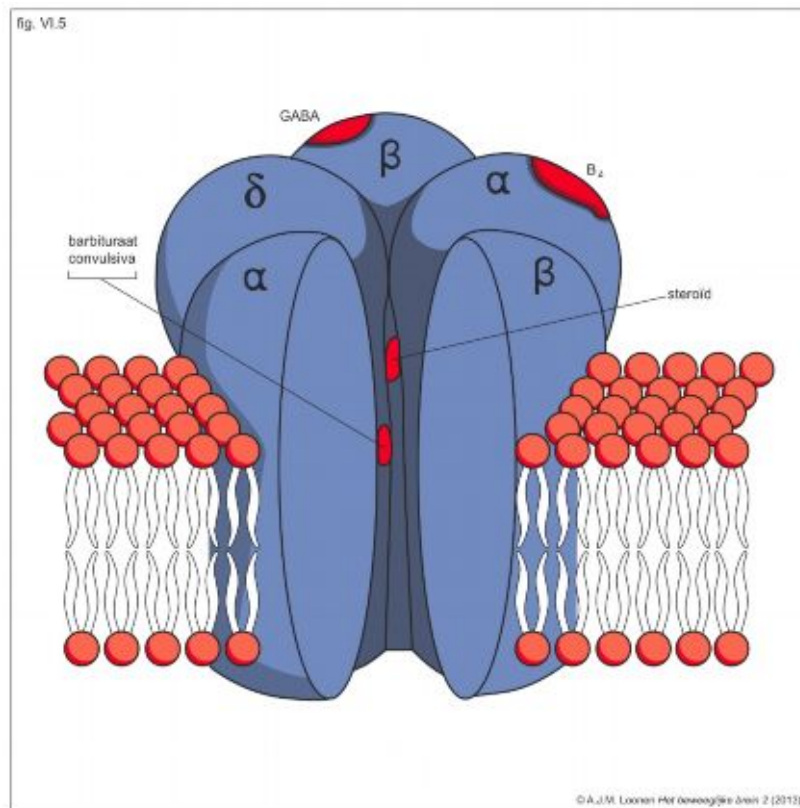


Pharmacological characteristics

- › Anaerobic synthesis by yeast of glucose: ethanol fermentation
- › Pharmacokinetics
 - Rapid absorption and distribution (0.5 L/kg)
 - Zero-order elimination (7-15 mL/hr)
 - Alcohol dehydrogenase and CYP2E1 (MEOS)
 - ADH polymorphism (Yellow race)
 - Induction of CYP2E1
- › Pharmacodynamics

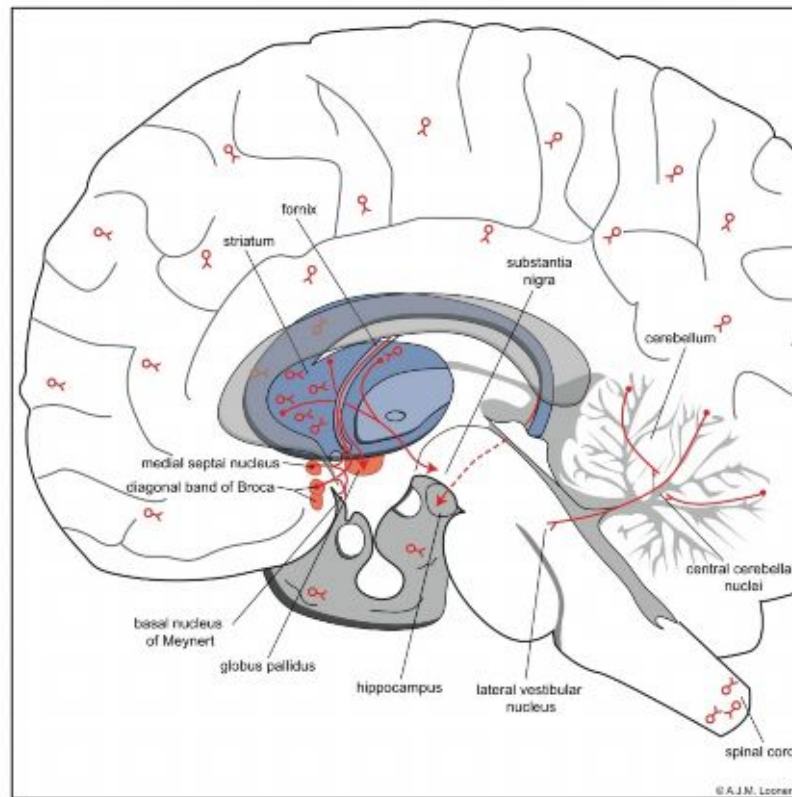
Pharmacodynamic characteristics

› GABA_A Ionotropic Receptor



- Post-synaptic chloride ion channel
- GABA binding site
- Benzodiazepine binding site
- Alcohol binding to allosteric sites

Pharmacodynamic characteristics



› Inhibitory GABA-ergic interneurons

- Cerebral cortex
- Striatum
- Spinal cord

› Distant projections



Acute alcohol intoxication

- › Symptoms:
 - Light ($< 1\%$): relaxation, talkative
 - Moderate ($1-2\%$): dysarthria, ataxia, slow, uncoordinated, disinhibited
 - Serious ($2-4\%$): amnesia, diplopia, dysarthria, hypothermia
 - Lethal ($> 4\%$): coma, respiratory arrest, death
 - Tolerance can occur: $> 8\%$ was measured
- › Differentiate from other disorders: trauma, metabolic, etc.
- › Complications: infections, delirium (withdrawal, Wernicke)



Detoxification in the Netherlands

- › Withdrawal symptoms are:
 - General: tremors, craving, vivid dreams, anxiety, hypervigilance, nausea, headache, profuse sweating
 - Specific: hallucinations, delirium, convulsions
- › Detoxification:
 - Drugs: benzodiazepines (oxazepam, lorazepam, diazepam, chlorazepate), carbamazepine, valproate
 - Dosage selections
 - Large variation due to cross-tolerance
 - Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar)
 - Assess CIWA-Ar score every 8 hrs and give Bz when score > 8.
 - Find substitution dose and taper off gradually

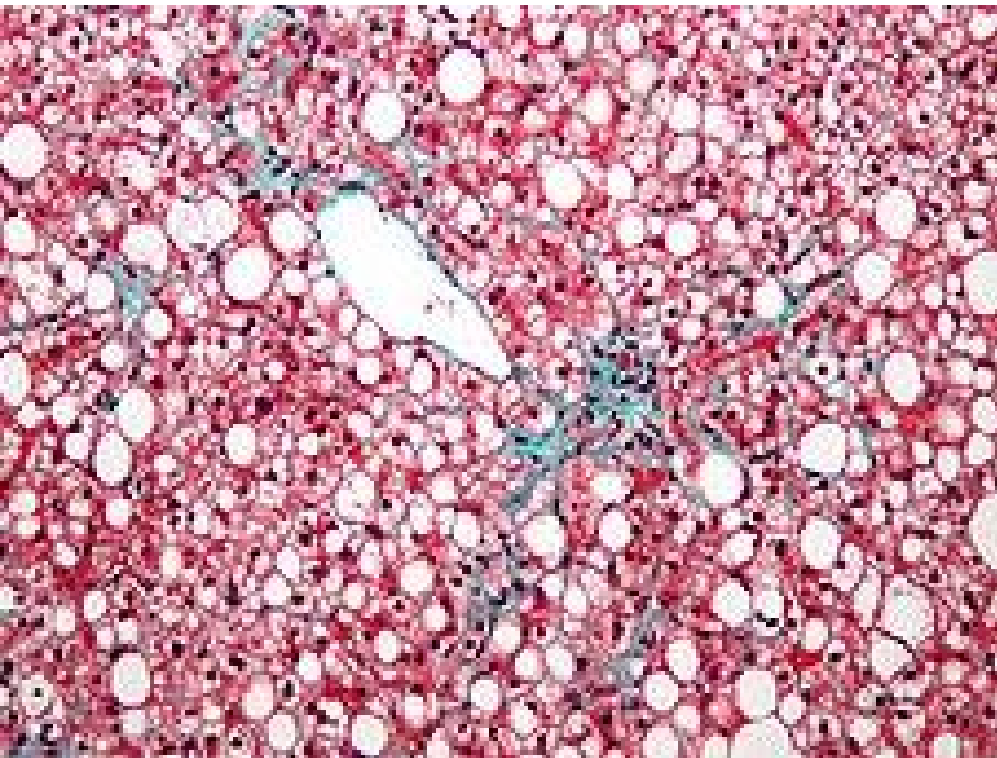


Thiamine deficiency

- › Causes of thiamine deficiency in alcoholism
 - Alcohol is a rich source of calories (inadequate diet)
 - Alcohol inhibits thiamine transporter in gastrointestinal system
- › Thiamine deficiency causes encephalopathy
 - Cerebral glucose metabolism: disturbance of TCA cycle and HMP shunt
 - Thiamine deficiency → lack of energy → Calcium release → excitotoxicity
 - Vascular reaction → haemorrhagias
 - Succinate shortage → decreased GABA levels → convulsions
- › Induction of Wernicke encephalopathy and/or Korsakoff syndrome



Liver steatosis



- › Ethanol → Acetyl-CoA
- › Acetyl-CoA → free fatty acids (FFA)
- › FFA need protein for transportation
- › Free fatty acids without protein → storage
- › Free fatty acids → CYP metabolism of
- › FFA metabolism by CYP → CYP inhibition
- › CYP inhibition → lower drug metabolism
- › Concomittant alcohol intake → first pass metabolism of many drugs is decreased



Development of hepatitis and cirrhosis

- › After 15-20 years of intensive alcohol abuse
- › Chronic exposition to acetaldehyde causes cytological damage.
- › Development of (necrotising) alcohol hepatitis
- › Haemorrhagia induces fibrotic strings and septa
- › Contractin of fibrotic tissue → micronodular cirrhosis
- › Cirrhosis → functional damage
 - Hepatic impairment → hypalbuminaemia and coagulation factor deficiency
 - Obstruction of portal system → ascitis and oesophagus varices



Maintenance drug treatment to prevent relapse

- › Acamprosate
- › Naltrexone
- › Nalmefene
- › Disulfiram
- › Other drugs



Acamprosate

- › Primarily affects glutamatergic neurons and stabilizes Glu/GABA
- › Best established treatment
- › Has small, but significant effect
 - Duration of abstinence
 - Relapse chance highest during the first few months
- › Reduces craving
- › Long halflife (about 33 hrs), no metabolism, poor absorption
- › Side effects: diarrhea, abdominal pain, nausea, pruritus, skin reactions



Naltrexone

- › Metabolite is μ -opioid > κ -opioid >> δ -opioid receptor antagonist.
- › Effective in strong craving
- › Efficacy shows conflicting results
 - Is effective after heavy drinking
 - Reduces magnitude of alcohol consumption
 - Not effective on duration of abstinence
- › Pharmacokinetics:
 - Limited bioavailability ($F = 5 - 40\%$)
 - $T_h = 4$ uur (naltrexone), 11–17 uur (6- β -naltrexole = active metabolite).
- › Side effects: sleep disorder, gastro-intestinal discomfort, anxiety



Nalmefene

- › μ , δ , and κ opioid receptor antagonist (partial for κ and δ receptors)
- › Effectiveness probably not very different from naltrexone
- › Pharmacokinetics:
 - Bioavailability better (F = about 40%)
 - No active metabolite
 - Half-life is about 12.5 hrs
- › Side effects: disturbed sleep, dizziness, headache, nausea



Disulfiram

- › Causes accumulation of acetaldehyde after alcohol intake (during about 14 days after drug intake): hot flushes, headache, nausea, tachycardia.
- › Appears not to be very effective (large placebo effect)
- › Pharmacokinetics
 - Good bioavailability ($F = 80\% - 90\%$)
 - Respiratory excretion as CS_2 (50% in 1 day, 80% in 6 days)
- › Limitation: CS_2 in beath (foetor, bad taste)
- › Side effects: gastrointestinal discomfort, sleepiness, headache, skin



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Cannabis





Characteristics of cannabis

- › *Cannabis sativa*, contains over 60 cannabinoids (mostly THC and CBD)
- › Pharmacokinetics of dronabinol (tetrahydrocannabinol, THC)
 - Very lipofylic (storage in body fat)
 - Oral bioavailability is low ($F = 10 - 20\%$)
 - Metabolized to psychoactive metabolite 11-OH-THC
 - Metabolism by CYP2C9, CYP2C19 and CYP3A4
 - Long halflife = 25-36 h
- › Pharmacodynamics



Characteristics of cannabis

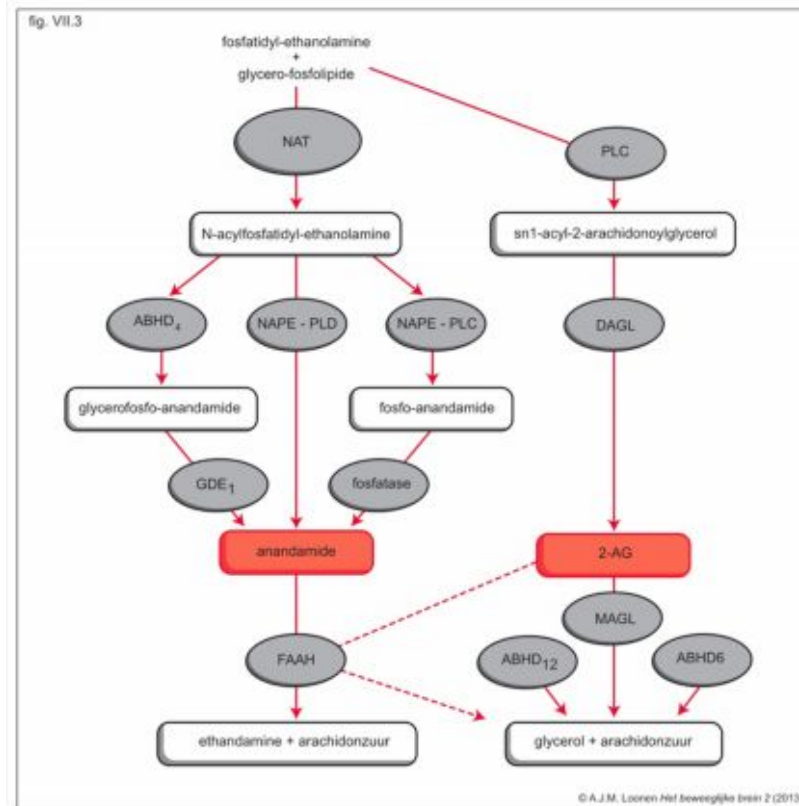
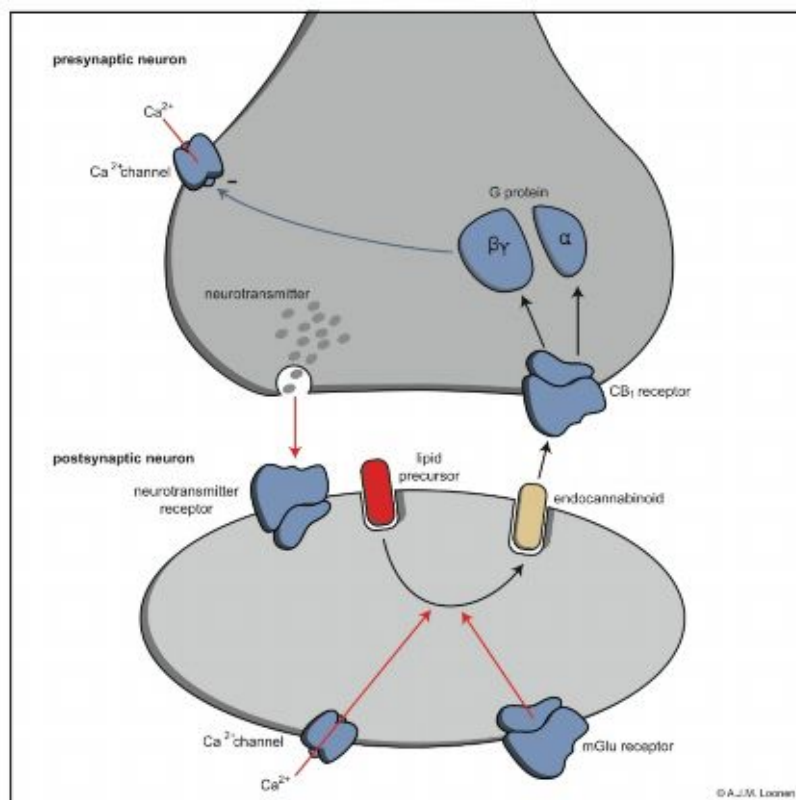
› Pharmacodynamics

- Dronabinol binds to CB₁-receptor
- Anandamide is endogenous ligand for this receptor
- Retrograde inhibition
 - LTD in glutamatergic transmission
- Complex and multiphasic pharmacological effects
- Longterm and possibly structural consequences of usage

› Treatment of intoxication

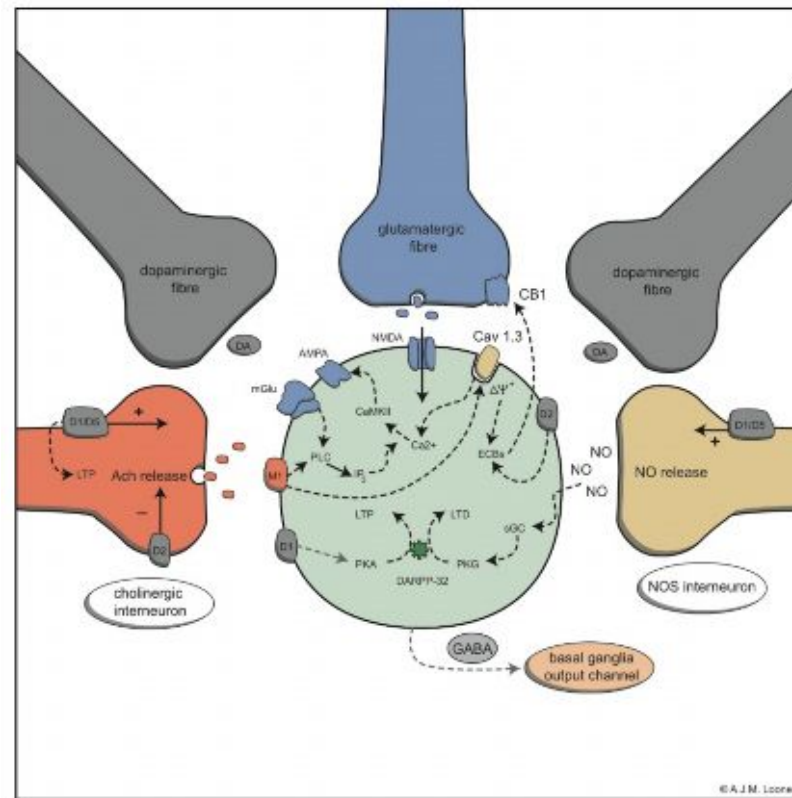
- Antipsychotics

Endocannabinoids





Example of retrograde transmission





Complex effects of cannabis

- › Two types of cannabinoid receptors
 - CB₁: presynaptic receptors
 - CB₂: immunocompetent glia cells within the CNS
- › Two major components of cannabis
 - Dronabinol: partial agonist of CB₁ and CB₂ receptors
 - Cannabidiol: antagonist of CB₁/CB₂ agonists
- › Contrasting clinical effects:
 - Dronabinol is psychotomimetic/psychodelic
 - Cannabidiol is antipsychotic



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Opioids





Characteristics of opioids

- › Opium and (half)synthetic opioids
 - Morphine and heroin
- › Pharmacokinetics of morphine
 - Modest oral bioavailability ($F = 25 - 40\%$)
 - Rapid and extensive distribution
 - Metabolism by glucuronidation
 - Short half-life ($T_{1/2} = 2 - 3 \text{ hr}$)
- › Pharmacodynamics of morphine



Characteristics of opioids

› Pharmacodynamics

- Interact with opioid receptors (μ , δ , κ)
- Endogenous ligands are endorphins en enkefalines
- Modulate dopaminergic activity in VTA and NAcb
- Modulate adrenergic activity in locus coeruleus
- Modulate activity of HPA-axis

› Clinical syndromes

- Intoxication
- Tolerance and withdrawal syndrome
- Craving and abuse



Treatment of opioid dependence

- › Acute intoxication
 - Naltrexone
- › Detoxification
 - Methadone
 - Buprenorphine
- › Maintenance treatment
 - Methadone
 - Buprenorphine/naloxone combination (Suboxone)
 - Heroin



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Cocaine





Characteristics of cocaine

- › *Erythroxylon coca*
- › Usually smoked in small pipes as basecoke (Crack)
- › Pharmacokinetics
 - Rapid absorption and distribution (gives rush)
 - Metabolism in blood by esterase enzymes (butyrylcholinesterase)
 - Concomitant use of alcohol → coca-ethylene (cardiotoxic effects)
 - Rapid elimination ($T_h = 50 - 75$ min)
- › Pharmacodynamics



Characteristics of cocaine

› Pharmacodynamics

- Facilitates release of monoamines
- Inhibits reuptake of monoamines
- Acute stimulation of DA, NE and 5-HT
- Inhibition of GABA receptors
- Modulate activity of HPA-axis

› Clinical syndromes

- Body Packer Syndrome
- Intoxication
- Withdrawal syndrome



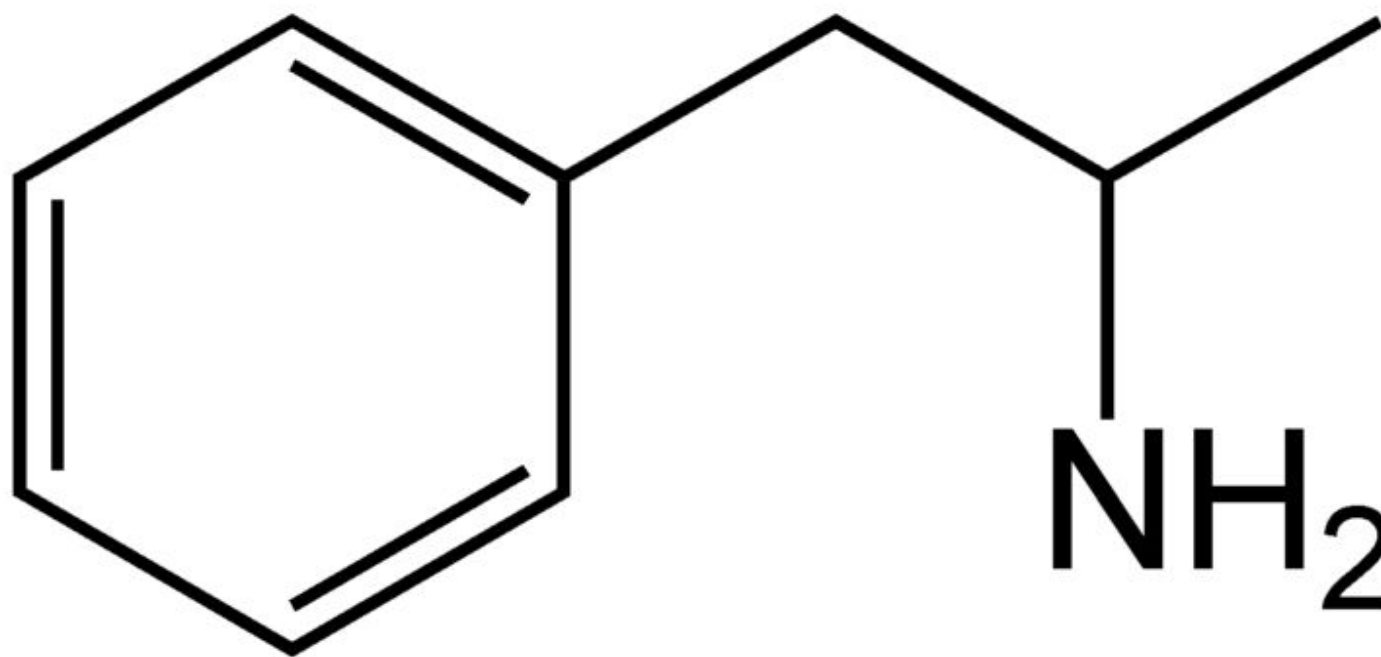
Treatment

- › (Massive) intoxication
 - Diazepam for convulsions
 - Haloperidol for hyperthermia and agitation
- › Detoxification
 - Propranolol
- › Maintenance treatment
 - No good treatment available
 - Amantadine, modafinil, propranolol
 - Anticonvulsants, disulfiram



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Psychostimulants





Characteristics of psychostimulants

- › Amphetamine, methyl-amphetamine, MDMA
- › Mescaline, ephedrine, cathinone (Khat)
- › Pharmacokinetics of amphetamine
 - Rapid and good oral absorption (within 30 min)
 - Faster and stronger after smoking (5-10 min)
 - Rapid and good tissue distribution
 - Renal excretion without metabolism (pH dependent)
 - Variable speed of elimination ($T_h = 6 - 20$ hr)
- › Pharmacodynamics of amphetamine



Characteristics of psychostimulants

› Pharmacodynamics of amphetamine

- Facilitates release of monoamines
- Inhibits reuptake of monoamines
- Inhibition of monoamine oxidase
- Increased levels of DA, NE and 5-HT (alert, active, awake)
- Acute depletion of monoamines (hangover)

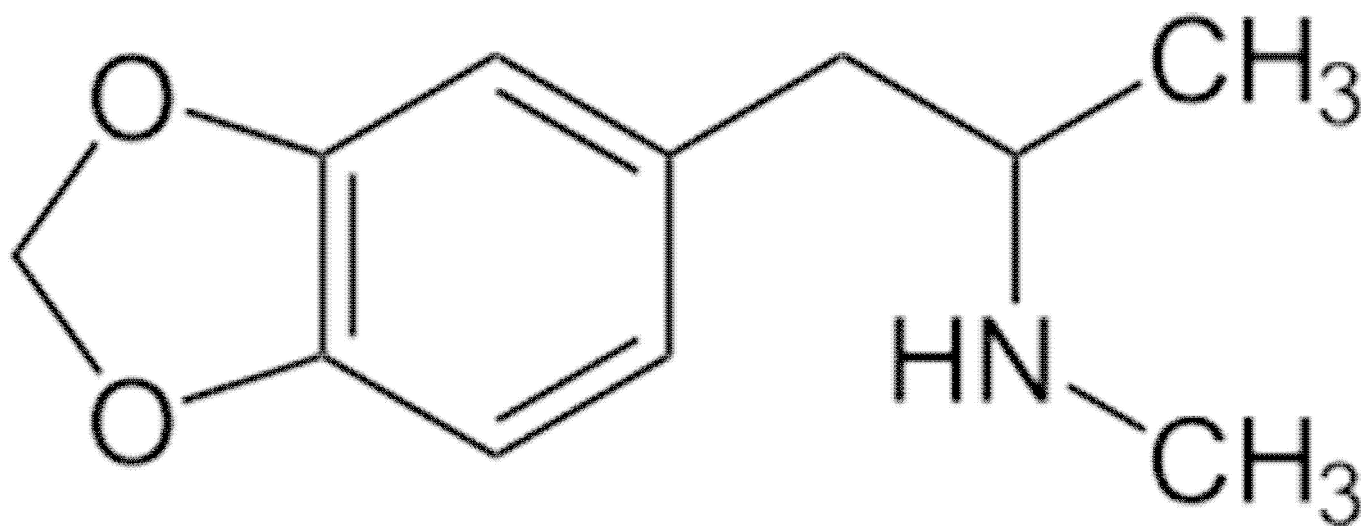
› Toxic effects

- Acute overdose: psychosis, delirium, hypertension
- Neurotoxic effects (however not firmly established)
- Neuroplastic effects (by modulating LTP/LTD)



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Ecstasy (MDMA)





Characteristics of ecstasy

- › 3,4-Methylenedioxymethamphetamine (MDMA)
- › Psychostimulant with love-drug effects
- › Pharmacokinetics
 - Disproportional absorption (non-linear pharmacokinetics)
 - Metabolized by CYP2D6 and CYP2B6 (with polymorphisms)
 - Disproportional duration ($T_h = 6 - 8$ hrs, but effects last for only 2 – 4 hrs)
 - Risk of cumulation due to repeated use
- › Pharmacodynamics



Characteristics of ecstasy

› Pharmacodynamics

- Reverses activity of monoamine reuptake transporter
- DA, NE → psychostimulation (awake, energetic)
- Larger influence on 5-HT levels (love effects)
- 5-HT_{1a} receptors → promote release of oxytocin by SON neurones
- 5-HT₂ receptors → hallucinations, serotonin syndrome

› Clinical syndromes

- Panic attack
- Hyperpyrexia, rhabdomyolysis, Multi Organ Failure
- Serotonin syndrome
- Hyponatraemia and cerebral oedema



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Tobacco





Characteristics of tobacco

- › *Nicotiana tabacum*
- › Contains numerous alkaloids (nicotine, harman, norharman, etc.)
- › Pharmacokinetics of nicotine
 - Rapid and almost complete absorption after smoking ($F = 90\%$)
 - Rapid penetration into the CNS (within 7-10 sec)
 - Metabolism by CYP2A6, also CYP2B6 and CYP2E1
 - Metabolite is cotinine ($t_h = 16-20$ uur)
 - Rapid elimination ($T_h = 2$ hr)
- › Pharmacodynamics of nicotine



Characteristics of tobacco

› Pharmacodynamics of nicotine

- Stimuleert AChN-receptoren (promote release of DA, 5-HT, Glu, etc.)
- (Tobacco smoke also inhibits monoamine metabolism by MAOI: harman)
- Increased release of epinephrine by adrenal medulla
- Modulation of HPA-axis

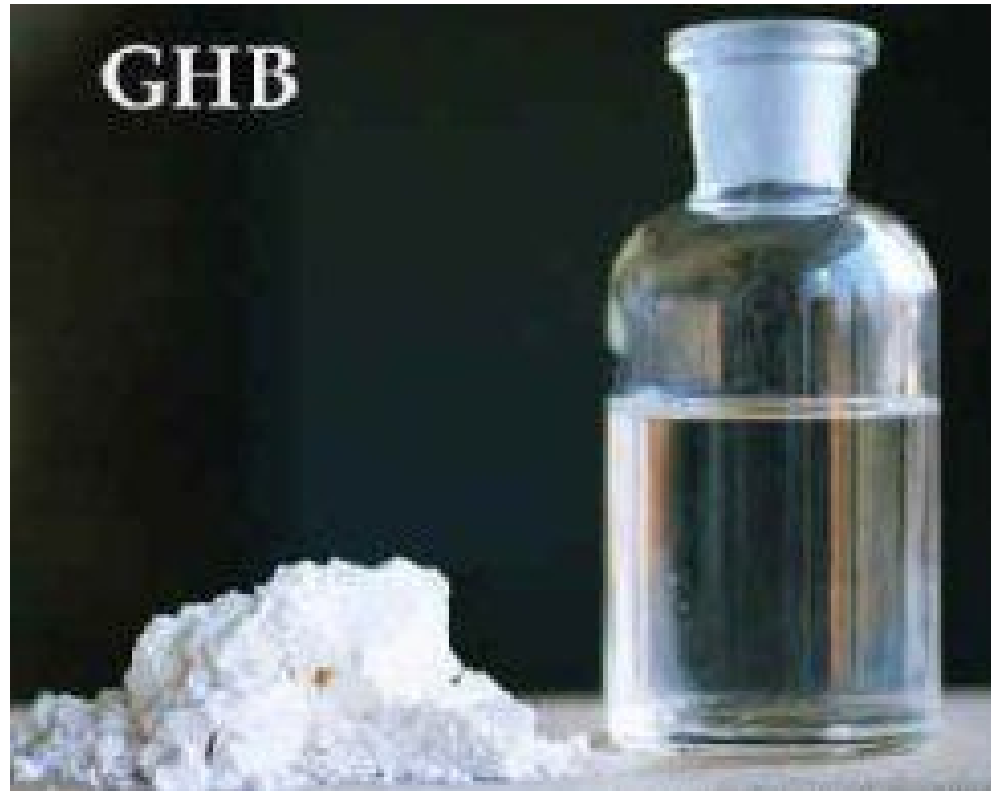
› Treatment (caution of predisposed depression)

- Nicotine substitution
- Nicotine agonist (varenicline)
- Dopaminergic antidepressant (Bupropion, MAO_B Inhibitor)



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GHB





Characteristics of GHB

- › γ -Hydroxybutyric acid (GHB), also known as 4-hydroxybutanoic acid
- › Heating of γ -butyrolactone or 1,4-butanediol with NaOH in alcohol or water (sodium oxybate solution)
- › Pharmacokinetics
 - Rapid absorption and distribution
 - Metabolism by alcohol dehydrogenase to succinate (enters Krebs cycle)
 - Rapid elimination ($T_{1/2}$ = 20 – 60 min)
- › Pharmacodynamics



Characteristics of GHB

› Pharmacodynamics

- GHB is putative neurotransmitter
- Precursor and metabolite of GABA
- Binds to GABA_B- and GHB-receptors
- Modulates neurotransmitter release (e.g. DA, endorphine)
- Stimulates growth hormone release (used by body builders)
- Repeated use induces down-regulation of GABA_B receptors
- Rapid dependence and unpredictable, severe withdrawal reactions



Treatment GHB dependence

› Detoxification

- Substitution with medicinal sodium oxybate solution
- (Substitution with benzodiazepines has lower efficacy)
- In severe cases propofol (needs intensive care treatment)
- In delirium haloperidol

› Relapse prevention (Kamal et al., J Clin Psychopharmacol 2015;35:313-8)

- Untreated relapse rate is high (65% in 3 months)
- Case series (ITT: no relapse in 9/11 patients in 12 weeks)



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Thank you for your attention