NICOTINE
Nicotine can do many things to the nervous system and not all of them are bad. Effects on the (+) side are considered beneficial, while those on the (-) side are considered detrimental.
Plasmatic Concentrations of Nicotine

Fig. 42.5  Nicotine concentration in plasma during smoking. The subjects were habitual smokers who smoked a cigarette, cigar or pipe according to their usual habit. (From: Bowman W C, Rand M 1980 Textbook of pharmacology. Blackwell, Oxford, ch. 4.)
NICOTINE

Ganglionic Stimulation

Ganglionic Blokade
Pharmacology of NICOTINE

- At a cellular level, nicotine acts on nicotinic acetylcholine receptors, mainly of the α4β2 subtype, to cause neuronal excitation. Its central effects are blocked by receptor antagonists such as mecamylamine.
- At the behavioural level, nicotine produces a mixture of inhibitory and excitatory effects.
- Nicotine shows reinforcing properties, associated with increased activity in the mesolimbic dopaminergic pathway, and self-administration can be elicited in animal studies.
- Electroencephalography changes show an arousal response, and subjects report increased alertness, accompanied by a reduction of anxiety and tension.
- Learning, particularly under stress, is facilitated by nicotine.
- Peripheral effects of nicotine result mainly from ganglionic stimulation: tachycardia, increased blood pressure and reduced gastrointestinal motility. Tolerance develops rapidly to these effects.
- Nicotine is metabolised, mainly in the liver, within 1–2 hours. Its inactive metabolite, cotinine, has a long plasma half-life and can be used as a measure of smoking habits.
- Nicotine gives rise to tolerance, physical dependence and psychological dependence (craving); it is highly addictive. Attempts at long-term cessation succeed in only about 20%.
- Nicotine replacement therapy (chewing gum or skin patch preparations) improves the chances of giving up smoking, but only when combined with active counselling.
Presynaptic α4β2 Nicotinic Acetylcholine Receptors Increase Glutamate Release and Serotonin Neuron Excitability in the Dorsal Raphe Nucleus
Nicotine effects on limbic areas

Nicotine binds predominantly to nicotinic acetylcholine (nACH) receptors in the CNS; the primary is the α4β2 nicotinic receptor in the Ventral Tegmental Area (VTA).

After nicotine binds to the α4β2 nicotinic receptor in the VTA, it results in a release of dopamine in the Nucleus Accumbens (nAcc) which is linked to reward.

Nicotine mimics the actions of acetylcholine at nicotinic receptors and directly activates dopamine cells.

Alcohol stimulates dopamine release indirectly at both the cell body and terminals.
Effects of Drugs on Dopamine Levels

AMPHETAMINE
- % of Basal Release vs Time After Amphetamine
- DA, DOPAC, HVA

COCAINE
- % of Basal Release vs Time After Cocaine
- DA, DOPAC, HVA

NICOTINE
- % of Basal Release vs Time After Nicotine
- Accumbens, Caudate

MORPHINE
- % of Basal Release vs Time After Morphine
- Dose (mg/kg): 0.5, 1.0, 2.5, 10
Nicotine

One cigarette 6-8 mg nicotine. Letal acute dose 60 mg

- Pharmacokinetic
  SNC and all organs
  Placenta, maternal milk
  Metabolism in lung, liver, excretion in urine
  Tollerance

- Side Effects
  Irritability, tremor
  Increase in heart rate and blood pressure, intestinal contractions, diarrhea
  Induction of CYP 450, increase in drug metabolism
  Withdrawal syndrome: irritability, anxiety, agitation, difficulty in concentration, cefalea, insomnia
Plasmatic concentration of nicotine after different supports against withdrawal

Bupropione (DAT)
Criteri diagnostici per F17.3 Astinenza da Nicotina [292.0]

A. Uso giornaliero di nicotina per almeno alcune settimane.

B. Brusca cessazione dell’uso di nicotina, o riduzione della quantità di nicotina usata, seguita entro 24 ore da quattro (o più) dei segnali seguenti:
   1) umore disforico o depresso
   2) insomnia
   3) irritabilità, frustrazione o rabbia
   4) ansia
   5) difficoltà di concentrazione
   6) irrequietezza
   7) diminuzione della frequenza cardiaca
   8) aumento dell’appetito o del peso.

C. I sintomi del Criterio B provocano disagio clinicamente significativo o menomazione del funzionamento sociale, lavorativo o di altre aree importanti.

D. I sintomi non sono dovuti a una condizione medica generale, e non sono meglio spiegati con un altro disturbo mentale.
L'ALCOOL! VOILA L'ENNEMI

DISTILLATION
DEGRADATION
DEGUSTATION
DESOLATION

Absinthe
Poison!

Guerre à l'alcool

Ethanol
Ethanol

\[ \text{H}_3\text{C} - \text{OH} \]
GABA

Receptors

- NMDA & KA
- Nicotinic
- 5-HT3
- Ca+ activated K channel
- oxytocin, vasopressin

Goodman & Gilman
Ethanol

alcohol dehydrogenase (ADH)

Acetaldehyde

aldehyde dehydrogenase

migraine, vomiting, sweating, confusion, tachycardia

Three wine glasses: 60-90 mg / dl
Motor slowing down: 20-30 mg / dl
Intoxication: 150 mg / dl
A glass: metabolized in 60-90 min
Men-women

disulfiram
Effets of low and high doses of ethanol

**Acute EFFECTS**
- Anxiolytics, sedatives (low doses)
- Disinhibition, violent behavior
- Motor incoordination

**Long term EFFECTS**
- Tolerance
- Addiction
- Compulsive alcohol research
- Cognitive deficits, dementia, delirium tremens
- Interference with other drugs
- Gastritis (destroys mucosa), cirrhosis, teratogenesis

Alcohol withdrawal: benzodiazepines, carbamazepine
Alcohol dependence: disulfiram, acamprosate (GABA & NMDA), ondansetron (5HT3 ant.)
gamma-hydroxy-butyrate (GHB)
Ethanol Neurotoxicity

Normal 43-year-old

Alcoholic 43-year-old
Substances that interact with alcohol

Sedatives: GHB, roipnol (flunitrazepam), ketamine

Marijuana: decreases motor control, mental concentration (driving) and inhibits swallowing reflex

Opiates: inhibition of brain function and respiratory reflex

Prescription or over-the-counter medications: anxiolytics, hypnotics, antihistamines, antidepressants

Aspirin (↑bioavailability ↓ADH)
Criteri diagnostici per F10.00 Intossicazione Alcoolica [303.00]

A. Recentemente ingestione di alcool.

B. Comportamento maladattivo clinicamente significativo o modificazioni psicologiche (per es., comportamento sessuale o aggressivo inappropriato, labilità d’umore, deficit delle capacità critiche, compromissione del funzionamento sociale o lavorativo) che si sviluppano durante, o poco dopo, l’ingestione alcoolica.

C. Uno (o più) dei segni seguenti, che si sviluppano durante, o poco dopo, l’assunzione di alcool:

1) pronuncia indistinta
2) incoordinazione
3) marcia instabile
4) nistagmo
5) deficit di attenzione o di memoria
6) stupor o coma.

D. I sintomi non sono dovuti a una condizione medica generale, e non possono essere meglio spiegati con un altro disturbo mentale.
Dependency potential

- **STIMOLANTI DEL SNC**
  - Caffeina
  - Nicotina
  - Cocaïna
  - Amfetamina

- **ALLUCINOGENI**
  - LSD
  - Cannabis
  - Fenclidina

- **DEPRIMENTI DEL SNC**
  - Etanolo
  - Barbiturici
  - Benzodiazepine

- **OPPIACEI STUPEFACENTI**
  - Morfina
  - Eroina

Basso  Alto
Treatments for withdrawal and craving relapse from drug of abuse

Opioids

Alcohol

Nicotine

Cocaine
Opioids
Interventions in opioid dependence

- Methadone
  - Long half-life
  - Governmental Regulated Programs

- Buprenorphine
  - Partial agonist of $\mu$ receptor

- Naltrexone
  - Antagonist of $\mu$ receptor

- Acupuncture?

- Clonidine (Withdrawal)
  - Activates endogenous opioid system
L'ALCOOL! VOILA L'ENNEMI

Distillation
Dégénération
Dégustation
Desolation

Absinthe
Poison!

Guerre à l'alcool

Loi

Poissons de choix

Eau-de-vie de vermouth
Schnaps
Kirsch
Absinthe
Blonde
Cognac
Etc.
Interventions in alcohol withdrawal

- Hydration state
- Electrolytic state

- Vitamin B1
- Sedative drug BZ
- Anticonvulsant

From diet. Thiamine. TPP (tiamina pirofosfato) coenzyme in catabolism of sugar and amino acids. Biosynthesis of Ach, GABA. Polyneuritis

- Oxazepam
- Carbamazepine
Interventions in alcohol dependence

Support groups, psychotherapy

Disulfiram
Antagonist of acetaldehyde dehydrogenase

Naltrexone
Slow release
Antagonist of \( \mu \) receptor

Acamprosate
Antagonist of NMDA and agonist of GABA
Interventions in alcohol dependence

Support groups, psychotherapy

Disulfiram
Antagonist of acetaldehyde dehydrogenase

Naltrexone
Antagonist of $\mu$ receptor
Slow release

Acamprosate
Antagonist of NMDA and agonist of GABA
NICOTINE
Interventions in nicotine dependence

Replacement therapy
- chew gum, patch, electronic cigarettes

Bupropion
- Antidepressant (DAT > SERT > NET); VMAT

Varenicline
- Partial agonist at nicotinic α4β2 R (α3β4, α3β2, α3β4)
- Agonist at nicotinic α7R
Figure 23–3. Nicotine concentrations in blood resulting from five different nicotine delivery systems. Shaded areas (upper panel) indicate the periods of exposure to nicotine. Arrows (lower panel) indicate when the nicotine patch was put on and taken off. (From Benowitz et al., 1988, and Srivastava et al., 1991, with permission.)
Amphetamine-related drugs and cocaine
Interventions in cocaine/amphetamine dependence

Psychotherapy
For cocaine and amphetamine

Topiramate
Na⁺ channel, Glu, GABA (cocaine relapse)

Baclofen
Antagonist of GABA_B receptors (cocaine relapse)

Modafinil
NA

Vaccine?

Methylphenidate
For cocaine