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.
Plasma 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

Dosi basse di nicotina
ATTIVAZIONE E RILASSAMENTO

Dosi alte di nicotina
PARALISI RESPIRATORIA Ipotensione

Ganglionic Stimulation
Ganglionic Blockade

POTENZIALE DI TOSSICODIPENDENZA
Nicotina
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 $\alpha 4\beta 2$ 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).

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.

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.
Effects of Drugs on Dopamine Release

Amphetamine

% of Basal Release

Accumbens

DA
DOPAC
HVA

Time After Drug

0 1 2 3 4 5 hr

Cocaine

% of Basal Release

Accumbens

DA
DOPAC
HVA

Time After Drug

0 1 2 3 4 5 hr

Nicotine

% of Basal Release

Accumbens
Caudate

Time After Drug

0 1 2 3 3 hr

Morphine

% of Basal Release

Accumbens

Dose
0.5 mg/kg
1.0 mg/kg
2.5 mg/kg
10 mg/kg

Time After Drug

0 1 2 3 4 5 hr

Di Chiara and Imperato, PNAS, 1988
Nicotine

One cigarette has 6-8 mg nicotine. Lethal acute dose is 60 mg

- **Pharmacokinetic**
  CNS and all organs
  Placenta, maternal milk
  Metabolism in lung, liver, excretion in urine
  Tolerance

- **Side Effects**
  Irritability, tremor
  Increase in hearth rate and blood pressure, intestinal contractions, diarrhea
  Induction of CYP 450, increase in drug metabolism
  Withdrawal syndrome: irritability, anxiety, agitation, difficulty in concentration, headache, insomnia
Plasma concentration of nicotine after different modes of administration lessens/prevents withdrawal
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! Voilà l'ennemi

Distillation
Dégénération
Dégustation
Désolation

Absinthe
Poison!

Guerre à l'alcool

Ethanol
Ethanol
**GABA**

**Receptors**

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

*Goodman & Gilman*
Ethanol

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
Effects 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 search
- 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)
Substances that interact with alcohol

**Sedatives**: GHB, rohypnol (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. Recente 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

<table>
<thead>
<tr>
<th>STIMOLANTI DEL SNC</th>
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<tr>
<td>Caffeina</td>
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<td>Nicotina</td>
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<tr>
<td>Cocaína</td>
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<td>Amfetamina</td>
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<td>LSD</td>
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<td>Cannabis</td>
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<td>Fenciclidina</td>
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<th>DEPRIMENTI DEL SNC</th>
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<td>Etanolo</td>
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<td>Barbiturici</td>
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<td>Benzodiazepine</td>
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Treatments for withdrawal and craving relapse from drug of abuse

Opioids

Alcohol

Nicotine

Cocaine

Amphetamine
Opioids
Interventions in opioid dependence

- **Methadone**
  - Long half-life
  - Governmental Regulated Programs

- **Buprenorphine**
  - Partial agonist of $\mu$ receptor

- **Naltrexone**
  - Antagonist of $\mu$ receptor

- **Acupuncture?**
  - Activates endogenous opioid system

- **Clonidine**
  - Alpha2 agonist; NA transmission in LC
  - (Withdrawal)
L’Alcool! Voilà l’ennemi

Guerre à l’alcool
Interventions in alcohol withdrawal

**Hydration state**

**Electrolytic state**

From diet. Thiamine. TPP (thiamine pyrophosphate) coenzyme in catabolism of sugar and amino acids. Biosynthesis of ACh, GABA. Polyneuritis.

**Vitamin B1**

**Sedative drug**

**BZ**

Oxazepam

**Anticonvulsant**

Carbamazepine
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 $\text{GABA}_A$ R


NICOTINE
Interventions in nicotine dependence

- **Replacement therapy**: Chewing gum, patch, electronic cigarettes
- **Bupropion**: Antidepressant (DAT > SERT > NET); VMAT
- **Varenicline**: Partial agonist at nicotinic α4β2 R (α3β4, α3β2, α6) 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**
- $\downarrow$ Na$^+$ channel, Glu, $\uparrow$ GABA (cocaine relapse)

**Baclofen**
- Agonist of GABA$_B$R (cocaine relapse)

**Modafinil**
- $\uparrow$ NA

**Vaccine?**
- For cocaine

**Methylphenidate**
- MET, cocaine