PSYCHOSTIMULANTS
AND
SUBSTANCES OF ABUSE
Classification criteria

- **Stimulants**: Cocaine, Amphetamines, Ecstasy, Nicotine, Marijuana (?)...

- **Depressive**: Opium and derivatives, Benzodiazepines ...

- **Hypnotics**: Barbiturates, Analgesics, Benzodiazepines ...

- **Psychedelics**: LSD, Mescaline, Marijuana, MDMA ...

PSYCHOSTIMULANTS
STIMOLANTI DEL SNC

STIMOLANTI PSICOMOTORI

- Amfetamina
- Atomoxetina (ADHD)
- Caffeina
- Cocaina
- Metilfenidato (ADHD)
- Modafinil
- Nicotina
- Teobromina
- Teofillina

ALLUCINOGENI

- Dietilamide dell’acido lisergico (LSD)
- Fenclclidina (PCP)
- Tetraidrocannabinolo (THC)
AMPHETAMINE AND COCAINE
AMPHETAMINE EFFECTS

• Motor activity stimulation
• Euphoria and excitement
• Psychotic behavior
• Anorexia

• Stimulatory effect is followed by depression and anxiety
• Tolerance to stimulating effects
Amphetamine (DAT > NET >> SERT)
Methamphetamine (DAT > NET >> SERT)
Methylphenidate (ritalin) (DAT/NET)
3,4-Methylenedioxy-methamphetamine (ecstasy) (NET/SERT < DAT)
Khat

**Amphetamine**
- binds to DAT for transport with the neuron
- stimulates release of intracytoplasmic DA
- interacts with VMAT (vesicular monoamine transporter) and increases non-vesicular DA
- causes reverse transport of the DA (DAT)
- stimulates TH
- MAO inhibition

Sulzer, Galli (progress Neurobiol, 2005)
PRINCIPAL EFFECTS OF AMPHETAMINE

- Vertigini
- Ipertensione
- Insomnia
- Confusione
- Potenziale di tossicodipendenza
- Nausea
- Diarrea
PSYCHOSTIMULANTS
Cocaine

Alkaloid. From coca leaves (*Erythroxylum coca*) chewed in the pre-Columbian era and still today
After the Spanish invasion largely used to alleviate fatigue and hunger
Cocaine

Pharmacological properties recognized in the second half of the 19th century (Freud and Koller)
Commercial spread: Vin Mariani (6 mg / 200 ml); Coca Cola (since 1906 no longer contains cocaine)

Preparation from coca paste; water-soluble formulations for i.v. or nasal inhalation; the free base is absorbed by inhalation (crack)
Speedball in the 60th
VIN MARIANI,

Mariani Wine, gives power to the brain, strength and elasticity to the muscles and richness to the blood. It is a promoter of good health and longevity. It makes the old young, keeps the young strong. Mariani Wine is endorsed by more than 8,000 American physicians. It is specially recommended for General Debility, Overwork, Profound Depression and Exhaustion, Throat and Lung Diseases, Consumption and Malaria.

Are You Worn Out? 

TRY

VIN MARIANI

MARIANI WINE,

The World Famous Tonic for Body and Brain.

Mariani Wine is invaluable for over-worked men, delicate women and sickly children. It stimulates, strengthens and sustains the system, and braces body and brain.

VIN MARIANI AT THE SODA FOUNTAIN.

A most refreshing, cooling, and at same time strengthening drink is Mariani taken with carbonic or soda water. Specially recommended to overworked business men, ladies when shopping, brain-workers, and all who are debilitated. It overcomes lassitude, and is helpful to the many summer complaints.

Vin Mariani taken with clipped or sweet lemon is also most refreshing, and renders beneficial aid in exhaustion during hot or debilitating weather.

SPECIAL OFFER — To those — we will kindly write, mentioning this publication, to MARIANI & Co., 41 West 41st St., New York City, will be sent, free, book containing portraits with endorsements of Emperors, Emperor, Prince Cenard, Archbishops and other distinguished personages endorsing Vin Mariani.

1863

Leone XIII
COCAINE

It has local anesthetic action (blocks voltage-gated sodium channels) which is the only current reason for its therapeutic use (obsolete): applied topically in surgery of eye, ear, nose and pharynx

Cocaine

- Cocaine acts by inhibiting catecholamine uptake (especially dopamine) by nerve terminals.
- Behavioural effects of cocaine are very similar to those of amphetamines, though psychotomimetic effects are rarer. Duration of action is shorter.
- Cocaine used in pregnancy impairs fetal development and may produce fetal malformations.
- As drugs of abuse, amphetamines and cocaine produce strong psychological dependence and carry a high risk of severe adverse reactions.
Comparison of Ki values of 5 psychostimulants as inhibitors of monoamine transporters in humans and mice

<table>
<thead>
<tr>
<th>Farmaco</th>
<th>Cocaina</th>
<th>Metilfenidato</th>
<th>Amfetamina</th>
<th>Metamfetamina</th>
<th>MDMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uomo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hDAT</td>
<td>0,23±0,03</td>
<td>0,06±0,01</td>
<td>0,64±0,14</td>
<td>0,64±0,14</td>
<td>8,29±1,67</td>
</tr>
<tr>
<td>hNET</td>
<td>0,48±0,05</td>
<td>0,10±0,01</td>
<td>0,07±0,01</td>
<td>0,11±0,01</td>
<td>1,19±0,13</td>
</tr>
<tr>
<td>hSERT</td>
<td>0,74±0,03</td>
<td>132,43±10,71</td>
<td>38,46±3,84</td>
<td>31,74±2,40</td>
<td>2,41±0,73</td>
</tr>
<tr>
<td>Rapporto</td>
<td>3,2</td>
<td>2207</td>
<td>549</td>
<td>288</td>
<td>7,0</td>
</tr>
<tr>
<td><strong>Topo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hDAT</td>
<td>0,49±0,04</td>
<td>0,26±0,03</td>
<td>0,56±0,11</td>
<td>0,47±0,08</td>
<td>4,87±0,65</td>
</tr>
<tr>
<td>hNET</td>
<td>0,46±0,06</td>
<td>0,17±0,03</td>
<td>0,12±0,02</td>
<td>0,19±0,05</td>
<td>1,75±0,51</td>
</tr>
<tr>
<td>hSERT</td>
<td>0,73±0,12</td>
<td>114,37±7,61</td>
<td>23,82±1,71</td>
<td>9,28±0,86</td>
<td>0,64±0,05</td>
</tr>
<tr>
<td>Rapporto</td>
<td>1,6</td>
<td>672</td>
<td>199</td>
<td>49</td>
<td>7,6</td>
</tr>
</tbody>
</table>

I valori delle Ki (in µM) sono espressi come medie ± l’errore standard.
Structures of the central nervous system involved in the effects of cocaine

The behavioral effects of cocaine derive from the powerful stimulation of the cortex and trunk of the brain: sensation of well-being and euphoria, hallucinations, delusional ideas and paranoia. Sense of security followed by "anxious" state, loss of appetite, reduction in perception of fatigue.

Basal Ganglia: Stimulation of motor activity, tremors and convulsions.

Respiratory and vasomotor depression.

Sympathetic nervous system

Strengthening of adrenergic stimulation, tachycardia, hypertension, pupillary dilation and peripheral vasoconstriction.
The mesolimbic system ascending from the A10 area to the striatum (nucleus accumbens, septum, olfactory tubercle), amygdala and hippocampus.

The mesocortical system connects the A10 area with the prefrontal cortex.

The mesostriatal (or nigrostriatal) system starts from the substantia nigra (area A9) and reaches the dorsal striatum.
Positron emission tomography (PET) scan of a cocaine abuser
PRINCIPAL EFFECTS OF COCAINE USE

- Euforia
- Tachicardia
- Frequentia respiratoria
- Agitazione
- Iperpressione
- Dispnnea
- Convulsioni
- Aritmie cardiache
- Insufficienza respiratoria
- Mortalità
Neuronal substrates and neurochemical mechanisms

1) The rewarding effect is based on the mesolimbic dopaminergic system that originates in the midbrain and innervates different areas of the limbic system: nucleus accumbens, amygdala, etc. (areas of primary gratification)

2) The mesolimbic system controls emotion and behavior for species survival (food, sex)

3) The rewarding effect of drugs is supported by their ability to reproduce the stimulation of the mesolimbic system
Data on utilization

Samples analyzed: 82,317

- Cocaina: 24.6%
- Eroina: 7.4%
- MDMA: 1.3%
- Hashish: 31.6%
- Marijuana: 35.1%
% of Consumers

Trend of use in students

Figura 3.1.22 - Trend dei consumi di cocaina nella popolazione studentesca
Time-course of utilization in students from 2010-2019
<table>
<thead>
<tr>
<th>Substance</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabinoids</td>
<td>97.2</td>
<td>92.9</td>
<td>95.4</td>
<td>89.3</td>
<td>90.5</td>
<td>80.3</td>
<td>80.2</td>
<td>61.4</td>
<td>65.4</td>
<td>52.9</td>
<td>45.9</td>
<td>48.7</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.7</td>
<td>2.9</td>
<td>3.1</td>
<td>4.7</td>
<td>6.9</td>
<td>11.6</td>
<td>15.0</td>
<td>27.0</td>
<td>32.5</td>
<td>38.5</td>
<td>35.9</td>
<td>37.7</td>
</tr>
<tr>
<td>Opioids/opiates</td>
<td>0.4</td>
<td>3.7</td>
<td>0.9</td>
<td>4.7</td>
<td>1.7</td>
<td>7.1</td>
<td>3.9</td>
<td>9.9</td>
<td>7.6</td>
<td>9.9</td>
<td>12.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Other substances</td>
<td>0.7</td>
<td>0.5</td>
<td>0.7</td>
<td>1.3</td>
<td>0.8</td>
<td>1.0</td>
<td>0.8</td>
<td>1.7</td>
<td>0.9</td>
<td>1.3</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Total</td>
<td>3.998</td>
<td>380</td>
<td>5.379</td>
<td>300</td>
<td>10.499</td>
<td>519</td>
<td>5.636</td>
<td>293</td>
<td>2.739</td>
<td>234</td>
<td>3.519</td>
<td>209</td>
</tr>
</tbody>
</table>

Fonte: Ministero dell’Interno – Ufficio IV – Anno 2019
ADHD
Attention deficit hyperactivity disorder

"Thoughts fly lightning fast... Can you control them?"

www.adhd-app.com
Attention Deficit Hyperactivity Disorder (ADHD)

- Characterized by inattention, impulsivity and motor hyperactivity which makes it difficult and in some cases prevents the normal development and social integration of children. Distractibility, forgetting things, moving from one activity to another, difficulty in concentration, bored with a task after a few minutes, difficulty in focusing attention on the organization and completion of a task or learning something new, having difficulty in completing or performing tasks, does not seem to listen when other people talk to them, confusion, difficulties in processing information, difficulty in following instructions

- Heterogeneous and complex, multifactorial disorder that in 70-80% of cases coexists with one or more other disorders

- Genetic causes, cerebral morphology, prenatal and perinatal factors, traumatic factors, environmental factors

- Behavioral therapies, lifestyle changes, psychotherapy, drugs
Attention Deficit Hyperactivity Disorder (ADHD)

ADHD (3-5%)

Methylphenidate
DA uptake
DA D$_2$ receptors pre & D$_1$ post
NA alpha$_2$

Atomoxetine
NA uptake