SUBSTANCE OF ABUSE
AND
PSYCHOSTIMULANTS

Classification criteria

- **Stimulants:** Cocaine, Amphetamines, Nicotine, methylphenidate ...
- **Depressive:** Opium and derivatives, Benzodiazepines ...
- **Hypnotics:** Barbiturates, Analgesics, Benzodiazepines ...
- **Psychedelics:** LSD, Mescaline, MDMA Marijuana…

PSYCHOSTIMULANTS

CLASSIFICATION

TABLE 4.1 Psychomotor Stimulant Drugs

Direct Sympathomimetics	Indirect Sympathomimetics	Nonsympathomimetics
Isoproterenol	Amphetamine **(ADHD)**	Caffeine
Epinephrine	Methamphetamine	Nicotine
Norepinephrine	Cocaine	Scopolamine
Phenylephrine	Methylphenidate **(ADHD)**	Strychnine
Phenylpropanolamine	Phenmetrazine	Pentylenetetrazol
Apomorphine	Pipradrol	Modafinil **(Narcolepsy)**
	Tyramine	
	Pemoline	

George F. Koob, ... Michel Le Moal, in Drugs, Addiction, and the Brain, 2014

AMPHETAMINE

AMPHETAMINE HISTORY

Methamphetamine
Nagai Nagayoshi

Amphetamines became schedule II controlled substances

1887
Germany

Amphetamine
Lazar Edeleanu

1893
Japan

1927
USA

Gordon Alles

Benzedrine
Inhaler

1935
Smith, Kline and
French pharm.

1939-1945
IIWW

methamphetamine brand
used by German soldiers

1971
USA

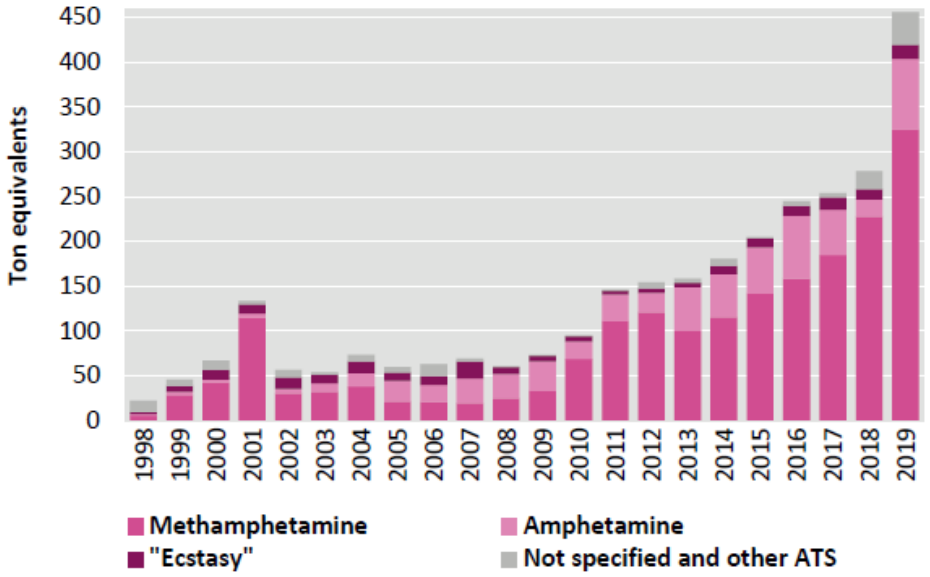
GLOBAL SEIZURES 2019

methamphetamine	amphetamine	"ecstasy"	other ATS	all ATS
325 tons	79 tons	16 tons	36 tons	456 tons
Change from previous year				
+43%	+309%	+38%	+82%	+64%

GLOBAL NUMBER OF USERS 2019

20 million
"ecstasy"

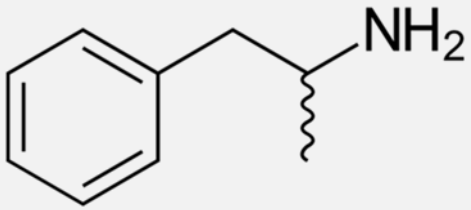
27 million
amphetamines
(methamphetamine and amphetamine)



World drug report, 2021

AMPHETAMINE EFFECTS

- Motor activity stimulation
- Euphoria, loquacity and excitement
- Reduction of fatigue
- Anorexia
- Psychotic behavior
- Stimulatory effect is followed by depression and anxiety
- Tolerance to euphoric and anorexic effects



d,l-amphetamine

toxins

MDPI

Review

Khat, a Cultural Chewing Drug: A Toxicokinetic and Toxicodynamic Summary

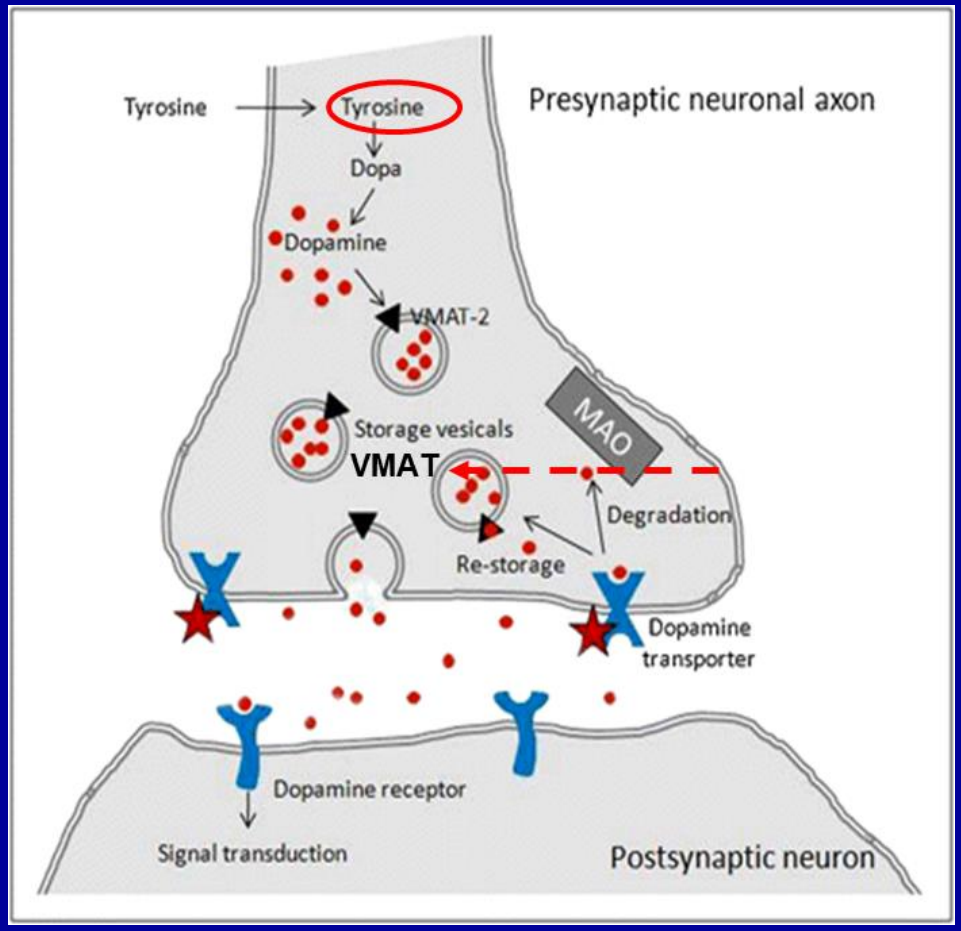
Bárbara Silva [1,2,*], Jorge Soares [1,2], Carolina Rocha-Pereira [1,2,3], Přemysl Mladěnka [4], Fernando Remião [1,2,*] and on behalf of The OEMONOM Researchers [‡]

Abstract: Khat (*Catha edulis*) is a recreational, chewed herbal drug that has been used as a psychostimulant for centuries in East Africa and the Arabian Peninsula, namely in Somalia, Ethiopia, and Yemen. However, the growing worldwide availability of khat has produced widespread concern. The plant comprises a large number of active substances, among which cathinone, cathine, and norephedrine are the main constituents, which can be included in the group of sympathomimetics of natural origin. In fact, these compounds are amphetamine analogues, and, as such, they have amphetamine-like nervous system stimulant effects. Chewing the leaves gives people a sensation of well-being and increases energy, alertness, and self-confidence. The chronic use of khat is, however, associated with severe cardiac, neurological, psychological, and gastrointestinal complications. The psychological dependence and withdrawal symptoms of khat are the reasons for its prolonged use. The aim of this paper is to review current knowledge on the khat plant with toxicokinetic and toxicodynamic perspectives. Namely, this review paper addresses in vitro, in vivo, and human studies. The models used, as well as the concentrations and doses with the respective biological effects, are discussed. Additionally, the main drug interactions involved with khat are described.

Comparison of Ki values of 5 psychostimulants as inhibitors of monoamine transporters in humans and mice

Drug	Cocaine	Methylphenidate	Amphetamine	Methamphetamine	MDMA
			Human		
hDAT	0.23 ± 0.03	0.06 ± 0.01	0.64 ± 0.14	0.46 ± 0.06	8.29 ± 1.67
hNET	0.48 ± 0.05	0.10 ± 0.01	0.07 ± 0.01	0.11 ± 0.01	1.19 ± 0.13
hSERT	0.74 ± 0.03	132.43 ± 10.71	38.46 ± 3.84	31.74 ± 2.40	2.41 ± 0.73
	DAT>NET>SERT	**DAT=NET>>>SERT**	**NET>DAT>>SERT**	**NET>DAT>>SERT**	**NET>SERT>>DAT**
			Mouse		
mDAT	0.49 ± 0.04 [2]	0.26 ± 0.03	0.56 ± 0.11	0.47 ± 0.08	4.87 ± 0.65
mNET	0.46 ± 0.06 [2]	0.17 ± 0.03	0.12 ± 0.02	0.19 ± 0.05	1.75 ± 0.51
mSERT	0.73 ± 0.12	114.37 ± 7.61	23.82 ± 1.71	9.28 ± 0.86	0.64 ± 0.05
	DAT=NET>SERT	**DAT=NET>>>SERT**	**NET>DAT>>SERT**	**NET>DAT>SERT**	**SERT>NET>DAT**

Han and Gu, 2006



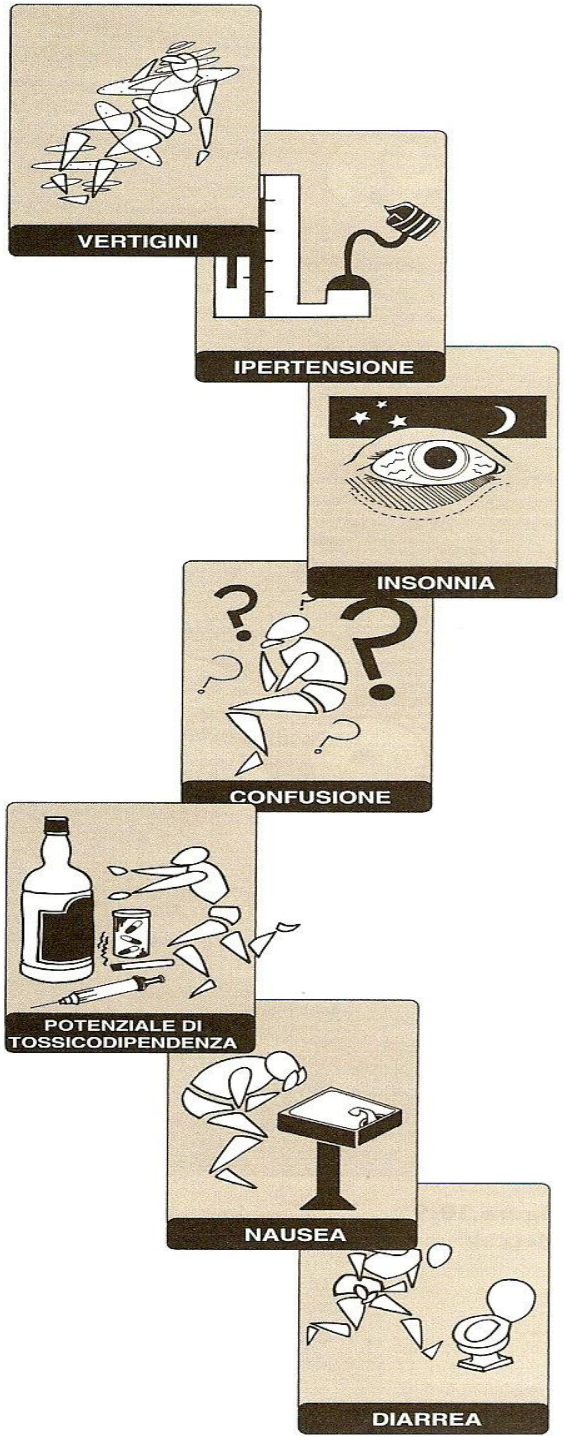
<u>Amphetamine</u>:

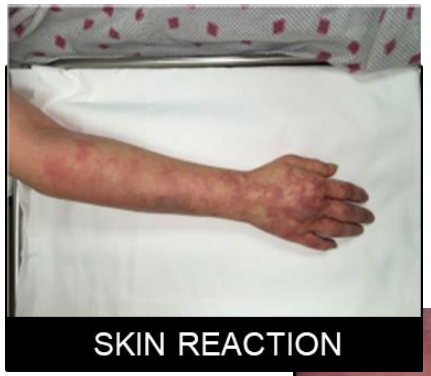
-binds to DAT for transport within the neuron

- 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 EFFETS OF AMPHETAMINE




SKIN REACTION

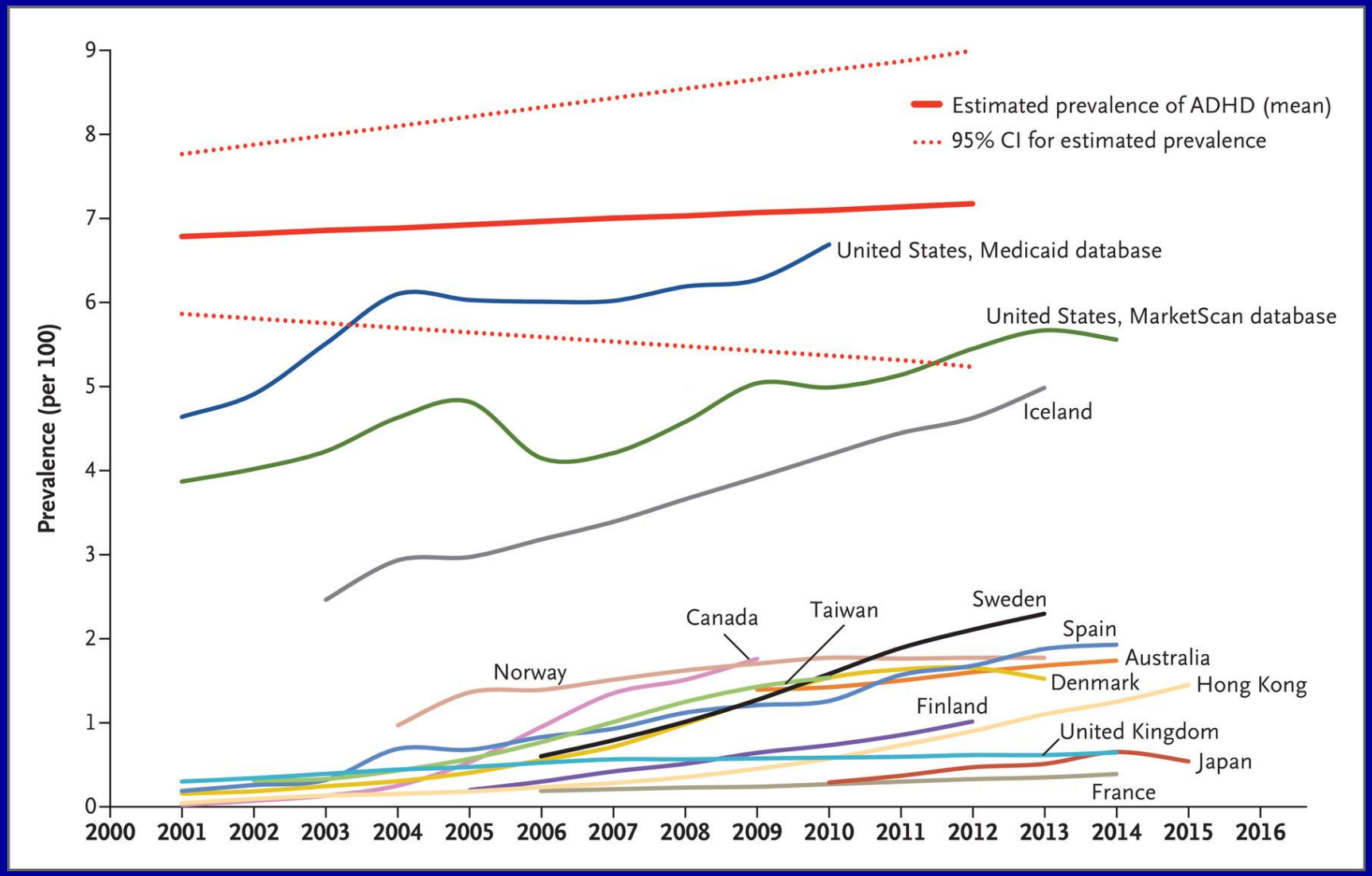

TOOTH CARIES (METH)

Attention deficit hyperactive disorder

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

www.adhd-app.com

Annual Prevalence of Medication Use for Attention Deficit–Hyperactivity Disorder (ADHD) among people having 3 to 18 Years of Age, According to Country.



Cortese, 2020

Attention Deficit Syndrome (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, go into 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

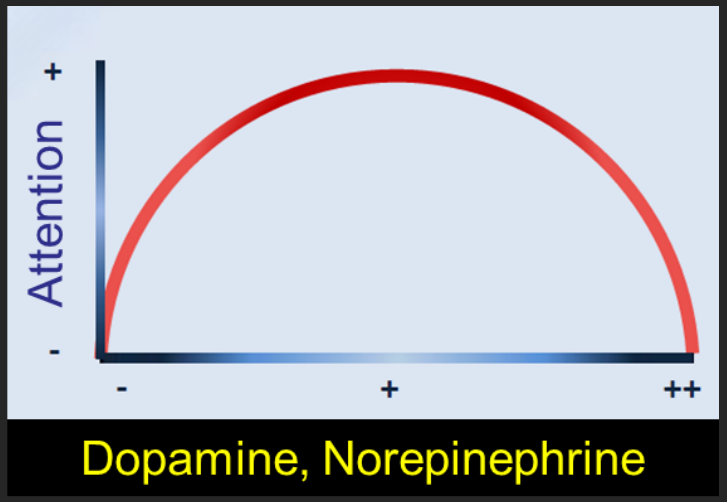


Table 2. Recommendations for ADHD Treatment from Recent Clinical Guidelines.

Organization and Patient Age	Treatment Recommendations
American Academy of Pediatrics[3]	
Preschool children (4–5 yr old)	First line: parental training in behavior management, behavioral classroom interventions, or both Second line: methylphenidate (off-label)
Children 6–11 yr old	FDA-approved medications (in descending order according to strength of evidence: stimulants, atomoxetine, extended-release guanfacine, extended-release clonidine) with parental training in behavior management, behavioral classroom interventions, or preferably both; educational interventions
Adolescents 12–17 yr old	FDA-approved medications; training or behavioral interventions, if available, or both; educational interventions
Adults	Recommendations are not included in the guideline
National Institute for Health and Care Excellence, United Kingdom[4]	
Children <5 yr old	First line: ADHD-focused group training for parents Second line: medication only after second specialist opinion
Children ≥5 yr old and young people	ADHD-focused support (e.g., education and information on the causes and effects of ADHD, advice on parenting strategies, and liaison with school) If ADHD symptoms persist in at least one area of functioning after environmental modification, start medication (in descending order of preference): methylphenidate, lisdexamfetamine (or dexamphetamine if unacceptable side effects with lisdexamfetamine), atomoxetine or guanfacine For symptoms of oppositional defiant disorder or conduct disorder: parental training Cognitive behavioral therapy for young people if symptoms still impairing at least one area of functioning after pharmacologic treatment
Adults	If ADHD symptoms persist in at least one area of functioning after environmental modification: medication (in descending order of preference): methylphenidate or lisdexamfetamine (or dexamphetamine if lisdexamfetamine associated with unacceptable side effect profile), atomoxetine Supportive psychological intervention if medication is ineffective or associated with unacceptable side effects
ADHD German Guidelines[5]	
Children <6 yr old	First line: ADHD-focused group or individual training for parents or teachers Second line: medication only after specialist advice for children >3 yr old
Children ≥6 yr old and young people	
Mild-to-moderate ADHD	After psychoeducation, first line: parental training or family-based interventions; if needed, patient-, school-, and workplace-based interventions After psychoeducation, second line: medication (in descending order of preference): stimulants, atomoxetine or guanfacine
Moderate-to-severe ADHD	After psychoeducation, first line: medication (in descending order of preference): stimulants, atomoxetine or guanfacine After psychoeducation, second line: parental training or family-based interventions; if needed, patient-based and school- or workplace-based interventions
Adults	After psychoeducation, first-line: medication; nonpharmacologic treatment if patient chooses it or if medication ineffective or associated with unacceptable side effects

Cortese, 2020

Table 1. Medications Approved by the Food and Drug Administration (FDA) for the Treatment of Attention Deficit–Hyperactivity Disorder (ADHD).*

Medication	Mechanism of Action	Preparation and Form†
Stimulants		
Amphetamines	Increase extracellular synaptic levels of dopamine and norepinephrine by inhibiting dopamine transporter and NE transporter; increase vesicular dopamine release by inhibiting VMAT-2 and release of cytosolic dopamine after reverse transport by dopamine transporter; inhibit monoamine oxidase; interact with ACH, 5-HT, opioid, and glutamate	Extended-release amphetamines: XR-OS liquid oral suspension, EROS liquid oral suspension (13 hr), orally disintegrating tablet (12 hr) Dextroamphetamine sulfate: tablet or solution (4–6 hr), extended-release capsule Lisdexamfetamine: capsule (13 hr), chewable tablet (13 hr) Methamphetamine: tablet Mixed amphetamine salts: tablet (4–6 hr), extended-release capsule (12 hr) Racemic amphetamine sulfate: tablet (4–6 hr), orally disintegrating tablet (10 hr) Triple-bead mixed amphetamine salts: extended-release capsule (16 hr)
Methylphenidate	Increases extracellular synaptic levels of dopamine and norepinephrine through inhibition of dopamine transporter and NE transporter and redistribution of VMAT-2; agonist activity at 5-HT_{1A} receptor	Dexmethylphenidate: tablet (4 hr), dexmethylphenidate extended-release capsule (12 hr) Methylphenidate: immediate-release tablet (4 hr), immediate-release solution, immediate-release chewable tablet, extended-release tablet (8 hr) or chewable tablet (8 hr), extended-release long-acting capsule (8 hr), controlled-delivery capsule (8 hr), transdermal patch (9 hr)‡, delayed-release and extended-release capsule (11 hr, after 10-to-12-hr delay in onset of action), osmotic-release oral system tablet (12 hr), extended-release orally disintegrating tablet (12 hr), extended-release suspension (12 hr), multilayer extended-release capsule (Aptensio XR [Rhodes Pharmaceuticals] [12 hr]; Adhansia XR [Purdue] [13–16 hr])
Nonstimulants		
Atomoxetine	Selectively inhibits NE transporter; increases extracellular synaptic levels of NE and dopamine in prefrontal cortex	Capsule (24 hr)
Extended-release clonidine	Stimulates postsynaptic α_2-adrenergic receptors	Tablet
Extended-release guanfacine	Stimulates postsynaptic α_{2A}-adrenergic receptors	Tablet (24 hr)

* Shown are medications approved for the treatment of ADHD as of April 1, 2020, under a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA). Mixed amphetamine salts (tablet), dextroamphetamine sulfate (tablet or solution), racemic amphetamine sulfate (tablet), immediate-release methylphenidate (chewable tablet), and methylphenidate extended-release tablet (8 hr) are available only under an ANDA (www.accessdata.fda.gov/scripts/cder/daf/). Additional details on the mechanisms of action and the response duration are provided in Sections S5 and S4, respectively, in the Supplementary Appendix, available with the full text of this article at NEJM.org. FDA-approved age and dose range are shown in Table S5 in the Supplementary Appendix. ACH denotes acetylcholine, 5-HT 5-hydroxytryptamine (serotonin), NE norepinephrine, and VMAT-2 vesicular monoamine transporter 2.

† The approximate response duration, if available, is in parentheses.

‡ The response to the transdermal patch may persist for 2 to 3 hours after patch removal.

Cortese, 2020

Marketed Drugs

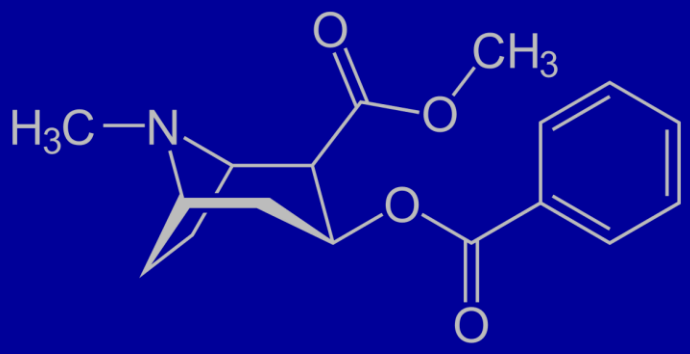
Metilfenidato	SI (Breve/Lunga durata)	SI (Breve/Lunga durata)	SI (Breve durata)
Atomoxetina	SI	SI	SI
Amfetamine	SI (Breve/Lunga durata)	SI (Breve/Lunga durata)	NO
Guanfacina	SI	NO	NO
Clonidina	SI	NO	NO

COCAINE

COCAINE

Alkaloid. From coca leaves (*Erythoxylum coca*) chewed in the pre-Columbian era and still today

After the Spanish invasion large use 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 e.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 indorsed 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.

My health and vitality I owe to Vin Mariani; when at times unable to proceed a few drops give me new life. It is delicious. I proclaim Vin Mariani the king of all tonic wines.

SARAH BERNHARDT.

Are You Worn Out?

TRY

VIN MARIANI

MARIANI WINE,

The World Famous Tonic for Body and Brain.

Mariani Wine is invaluable for overworked 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 Vin Mariani taken with carbonic or soda water. Specially recommended to overworked business men, ladies when shopping, brainworkers, and all who are debilitated. It overcomes lassitude, and is helpful in the many summer complaints.

Vin Mariani taken with chipped ice or scraped ice is also most refreshing, and renders beneficial aid in exhaustion during hot or debilitating weather.

SPECIAL OFFER.—To those ... on will kindly write, mentioning this publication, to MARIANI & CO., 52 West 15th Street, New York City, will be sent, free, book containing portraits with endorsements of Empress, Empress, Princes, Cardinals, Archbishops and other distinguished personages indorsing Vin Mariani.

Paris: 41 Boulevard Haussmann. London: 83 Mortimer Street. Montreal: 69 St. James St.

Vin Mariani is certainly unexcelled as the most effective, and at the same time, pleasant tonic.

ADA REHAN.

MARIANI WINE

MARIANI WINE Quickly Restores HEALTH, STRENGTH, ENERGY & VITALITY.

MARIANI WINE FORTIFIES, STRENGTHENS, STIMULATES & REFRESHES THE BODY & BRAIN

HASTENS CONVALESCENCE especially after INFLUENZA.

His Holiness THE POPE

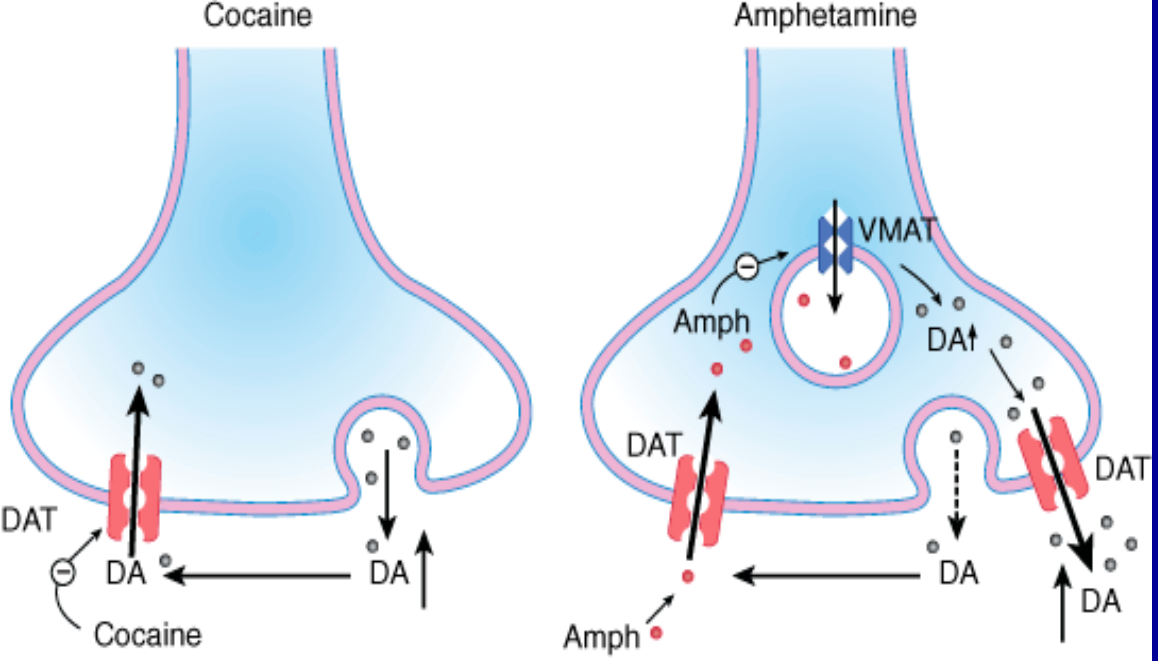
writes that he has fully appreciated the beneficent effects of this Tonic Wine and has forwarded to Mr. Mariani as a token of his gratitude a gold medal bearing his august effigy.

MARIANI WINE

is delivered free to all parts of the United Kingdom by WILCOX & CO., 83, Mortimer Street, London, W., price 4/- per Single Bottle, 22/6 half-dozen, 43/- dozen, and is sold by Chemists and Stores.

1863

Leone XIII



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.

COCAINE

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

Comparison of Ki values of 5 psychostimulants as inhibitors of monoamine transporters in humans and mice

Drug	Cocaine	Methylphenidate	Amphetamine	Methamphetamine	MDMA
			Human		
hDAT	0.23 ± 0.03	0.06 ± 0.01	0.64 ± 0.14	0.46 ± 0.06	8.29 ± 1.67
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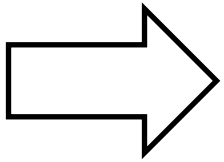
			Mouse		
mDAT	0.49 ± 0.04 [2]	0.26 ± 0.03	0.56 ± 0.11	0.47 ± 0.08	4.87 ± 0.65
mNET	0.46 ± 0.06 [2]	0.17 ± 0.03	0.12 ± 0.02	0.19 ± 0.05	1.75 ± 0.51
mSERT	0.73 ± 0.12	114.37 ± 7.61	23.82 ± 1.71	9.28 ± 0.86	0.64 ± 0.05
	DAT=NET>SERT	**DAT=NET>>>SERT**	**NET>DAT>>SERT**	**NET>DAT>SERT**	**SERT>NET>DAT**

Han and Gu, 2006

ACUTE CENTRAL EFFECTS OF COCAINE

- Increased energy;
- Increased sociability;
- Improved mood;
- Powerful rush of euphoria;
- Hunger reduction
- Heightened feelings of sexuality
- Paranoid, mania, aggressiveness (high doses)



ACUTE PERIPHERICAL EFFECTS OF COCAINE

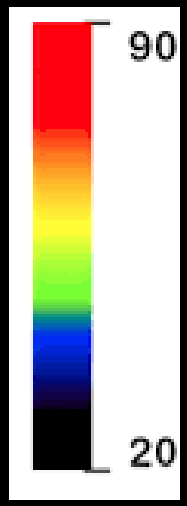
- Increased heart rate;
- Arrhythmias;
- Constriction of small blood vessels;
- Increased cortisol secretion from the adrenal gland.

CHRONIC CENTRAL EFFECTS OF COCAINE

- Extreme paranoia;
- Schizophrenic-like psychosis with delusions and hallucinations;
- Sadness and depression;
- High incidence of dependence with intense craving.

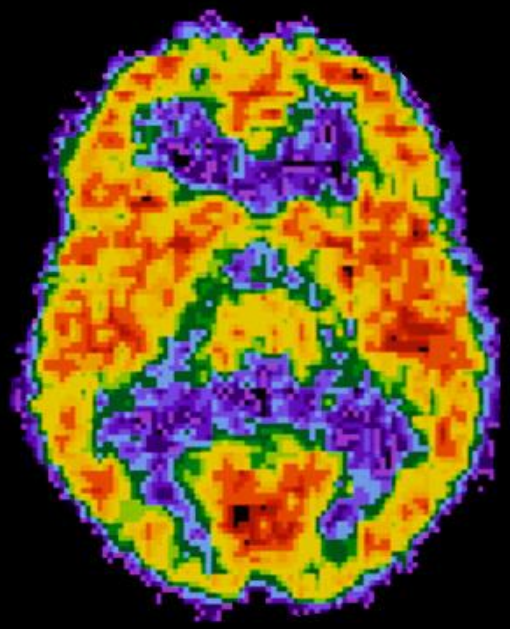
Positron emission tomography (PET)-Fluorodeoxyglucose (^{18}F) of healthy vs cocaine abuser

Highest ^{18F}FDG utilization

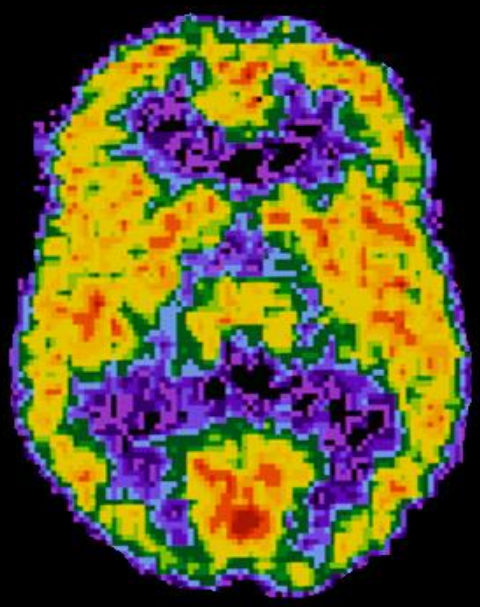


Lowest ^{18F}FDG utilization

Normal



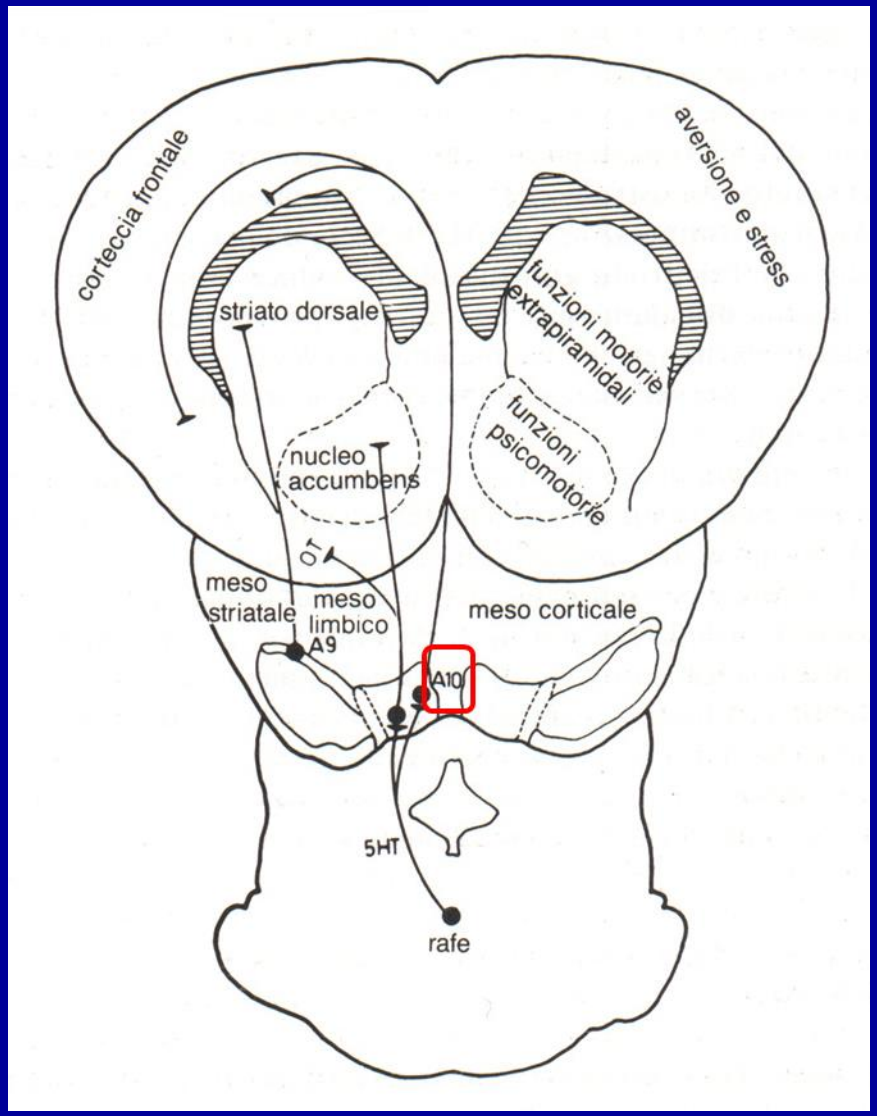
Cocaine



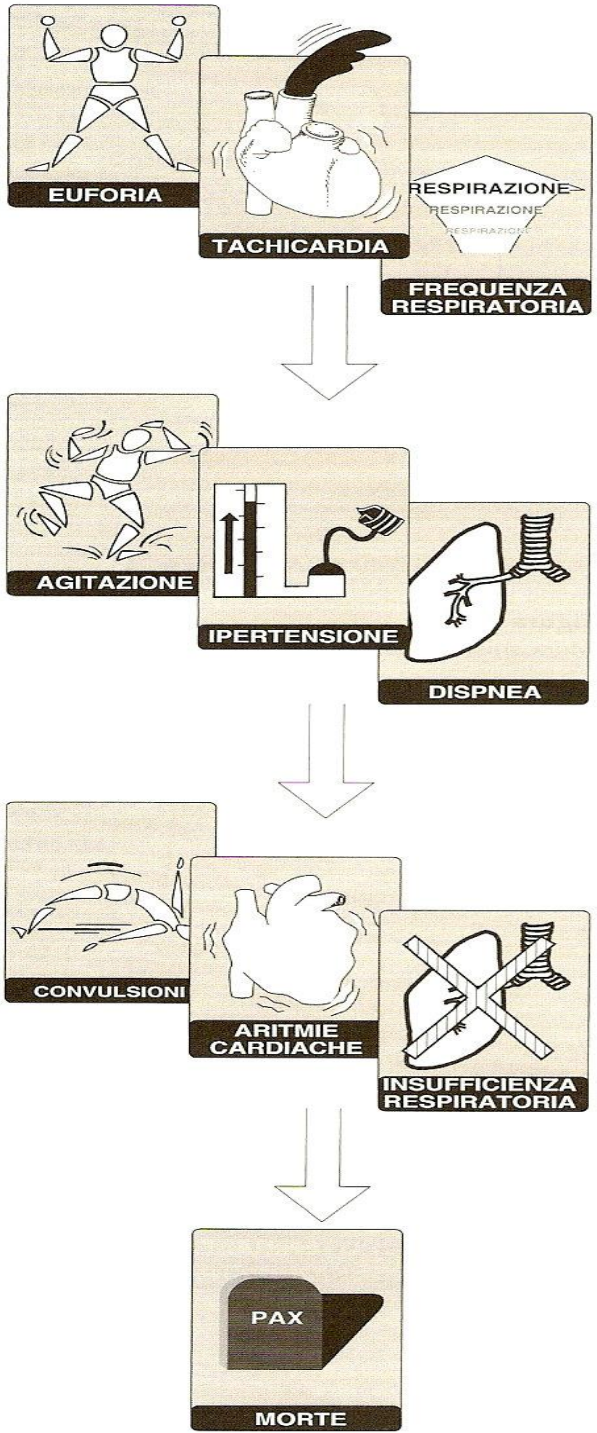
The **mesolimbic** system ascending from the A10 area to the striatum (nucleus accumbens, septum, olfactory turbercole), amygdala and hippocampus

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



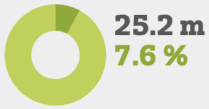
PRINCIPAL EFFECTS OF COCAINE USE



Cannabis

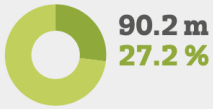
Adults (15-64)

Last year use



25.2 m
7.6 %

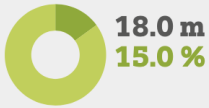
Lifetime use



90.2 m
27.2 %

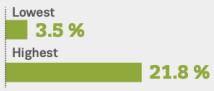
Young adults (15-34)

Last year use



18.0 m
15.0 %

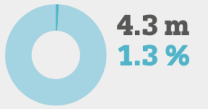
National estimates of use in last year



Cocaine

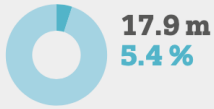
Adults (15-64)

Last year use



4.3 m
1.3 %

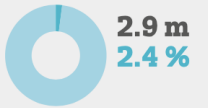
Lifetime use



17.9 m
5.4 %

Young adults (15-34)

Last year use



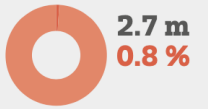
2.9 m
2.4 %

National estimates of use in last year

MDMA

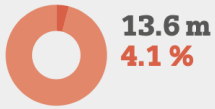
Adults (15-64)

Last year use



2.7 m
0.8 %

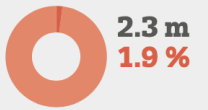
Lifetime use



13.6 m
4.1 %

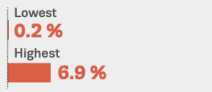
Young adults (15-34)

Last year use



2.3 m
1.9 %

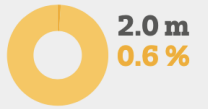
National estimates of use in last year



Amphetamines

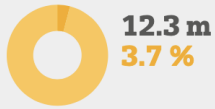
Adults (15-64)

Last year use



2.0 m
0.6 %

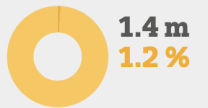
Lifetime use



12.3 m
3.7 %

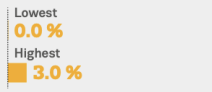
Young adults (15-34)

Last year use



1.4 m
1.2 %

National estimates of use in last year



Heroin and other opioids

High-risk opioid users

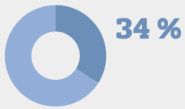
1.3 million

660 000

opioid users received substitution treatment in 2018

Drug treatment requests

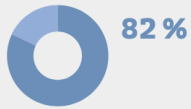
Principal drug in about 34 % of all drug treatment requests in the European Union



34 %

Fatal overdoses

Opioids are found in 82 % of fatal overdoses

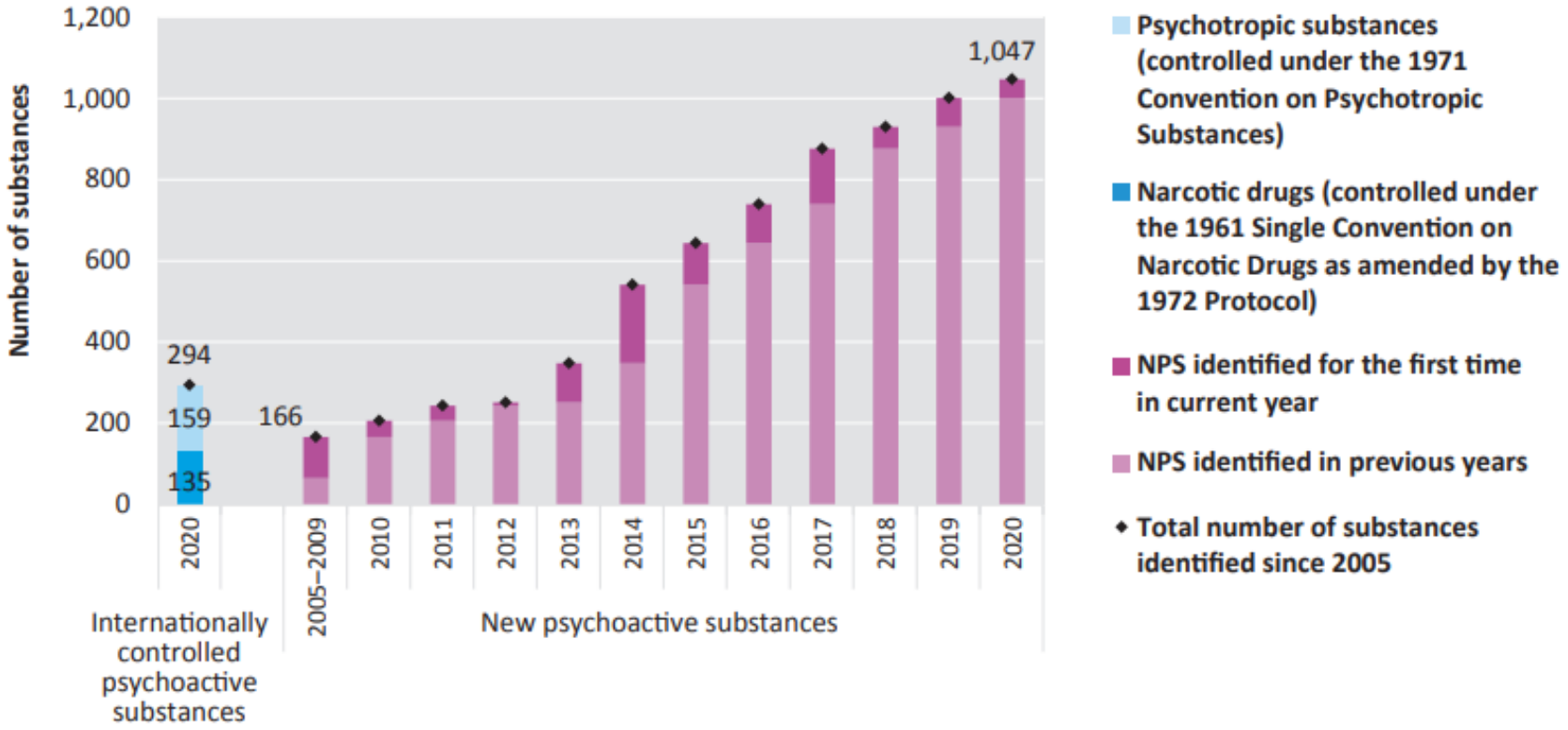


82 %

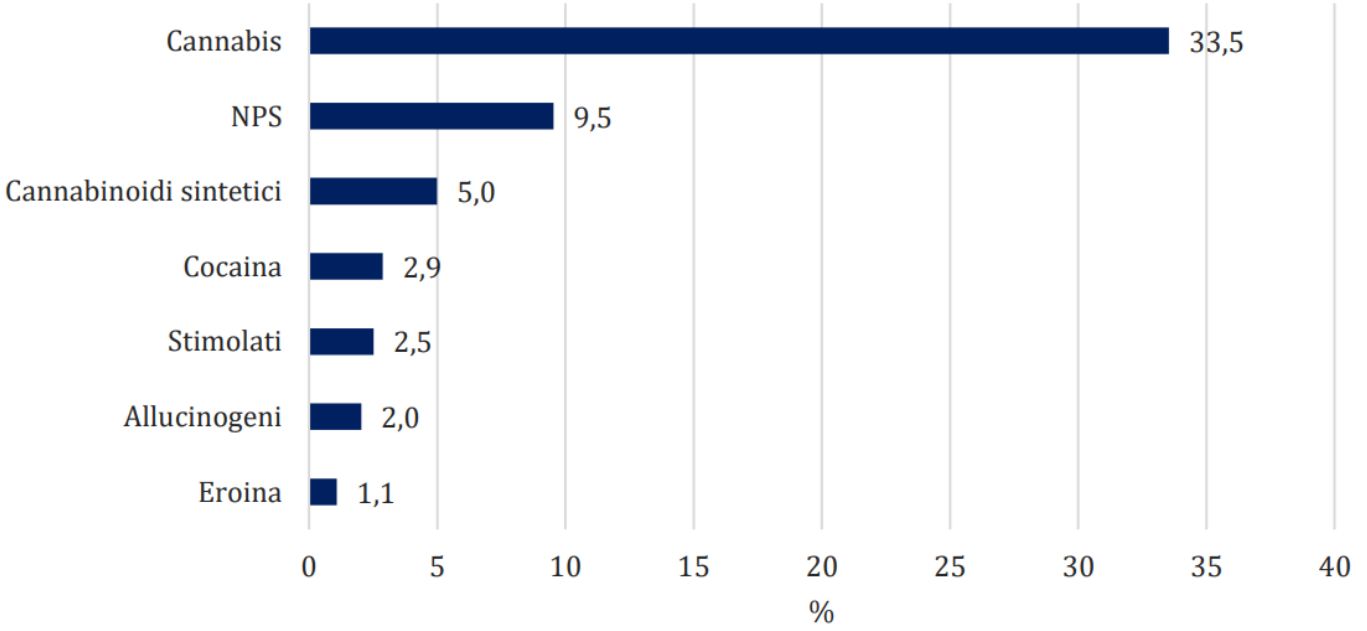
For the complete set of data and information on the methodology, see the accompanying online Statistical Bulletin.

Source: European monitor center for Drugs and Drug addiction

FIG. 38 Number of internationally controlled drugs in 2020 and new psychoactive substances identified at the global level, 2005–2020 (cumulative figures)



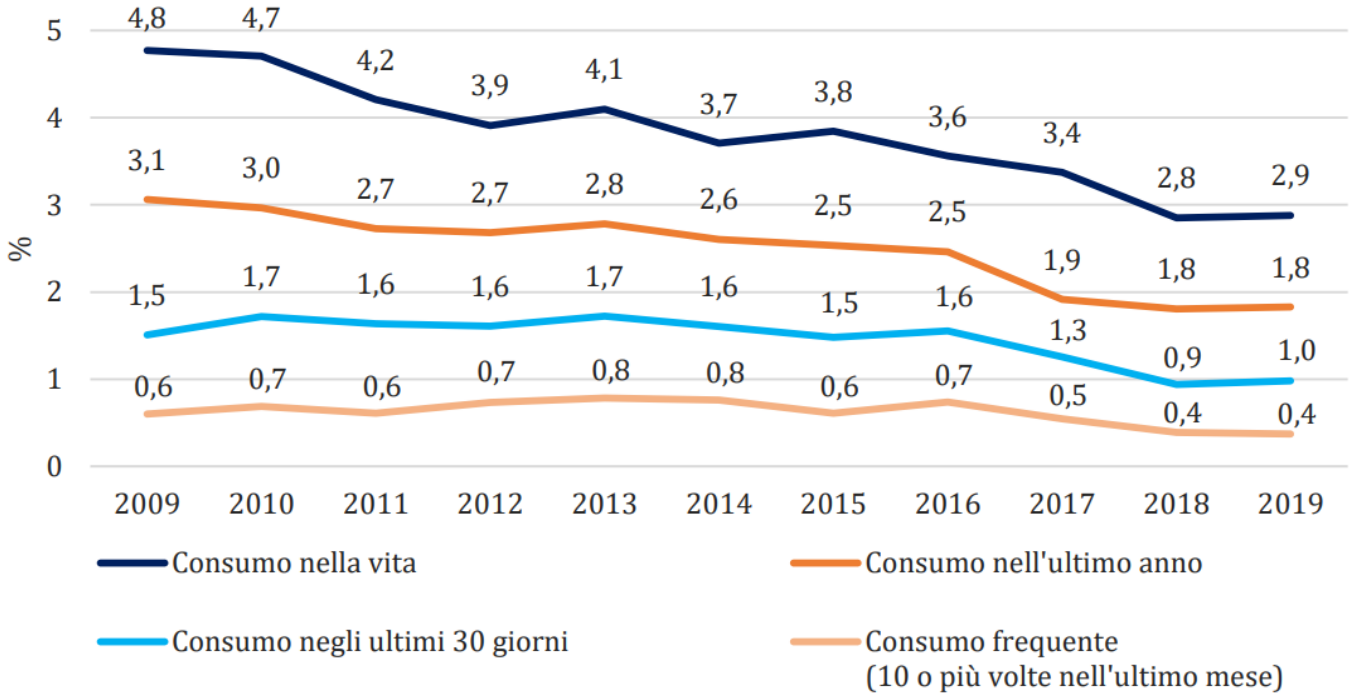
World drug report, 2021



% of Consumers

Trend of use in students

Figura 3.1.22 - *Trend* dei consumi di cocaina nella popolazione studentesca



Male and female distribution

		≤ 17 anni	18-19 anni	20-24 anni	25-29 anni	30-34 anni	35-39 anni	≥ 40 anni
Cannabinoidi	Maschi	97,2	95,4	90,5	80,2	65,4	52,9	49,0
	Femmine	92,9	89,3	80,3	61,4	45,9	48,7	47,3
Cocaina	Maschi	1,7	3,1	6,9	15,0	26,0	35,9	37,7
	Femmine	2,9	4,7	11,6	27,0	32,5	38,5	40,2
Eroina/oppiacei	Maschi	0,4	0,9	1,7	3,9	7,6	9,9	12,3
	Femmine	3,7	4,7	7,1	9,9	20,6	12,8	10,9
Altre sostanze	Maschi	0,7	0,7	0,8	0,8	0,9	1,3	0,9
	Femmine	0,5	1,3	1,0	1,7	1,0	0,0	1,5
TOTALE (n.)	**Maschi**	**3.998**	**5.379**	**10.499**	**5.636**	**3.519**	**2.739**	**5.452**
	Femmine	**380**	**300**	**519**	**293**	**209**	**234**	**338**

Fonte: Ministero dell'Interno – Ufficio IV – Anno 2019