



UNA DOMANDA SENZA RISPOSTE? TOSSICOLOGIA CLINICA DEGLI PSICOSTIMOLANTI

Sarah Vecchio

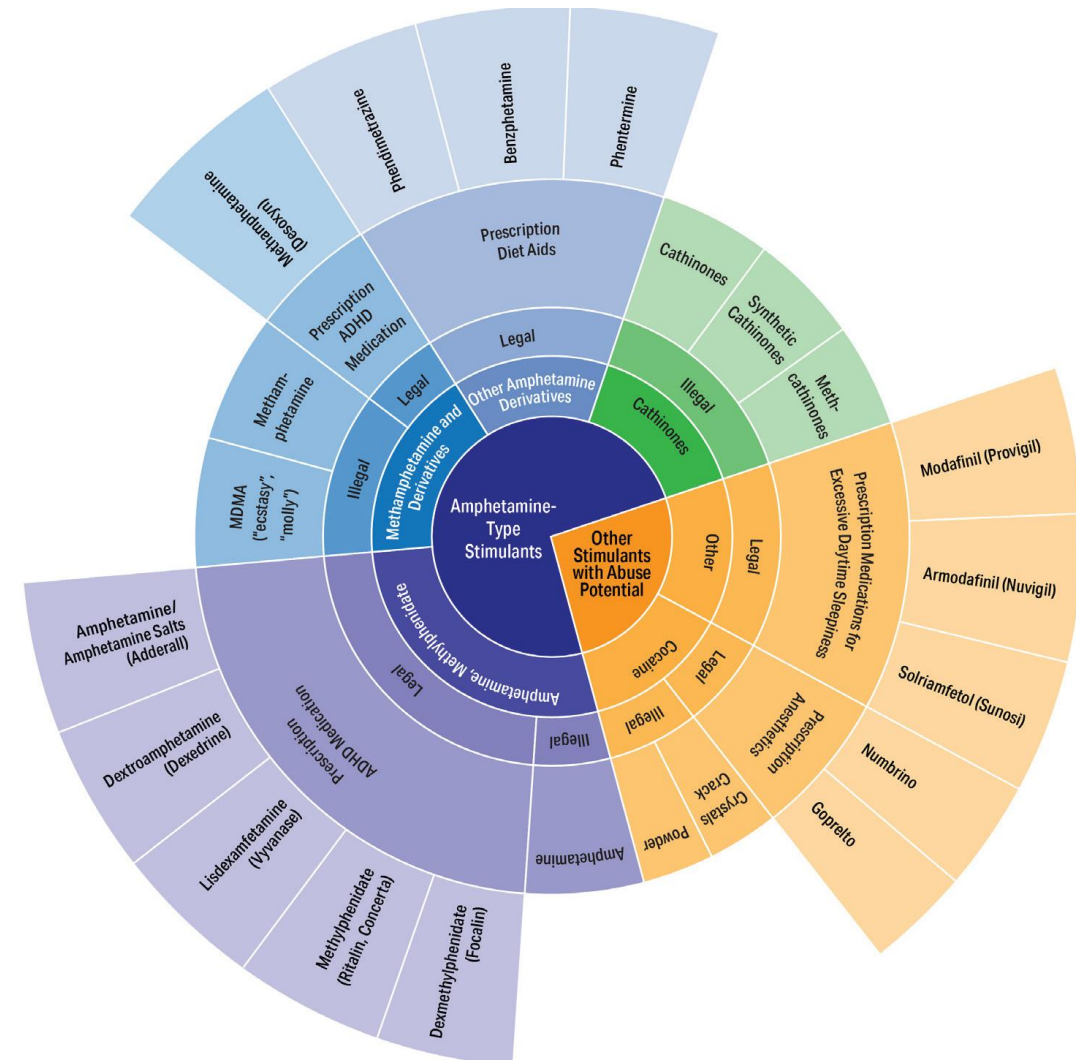
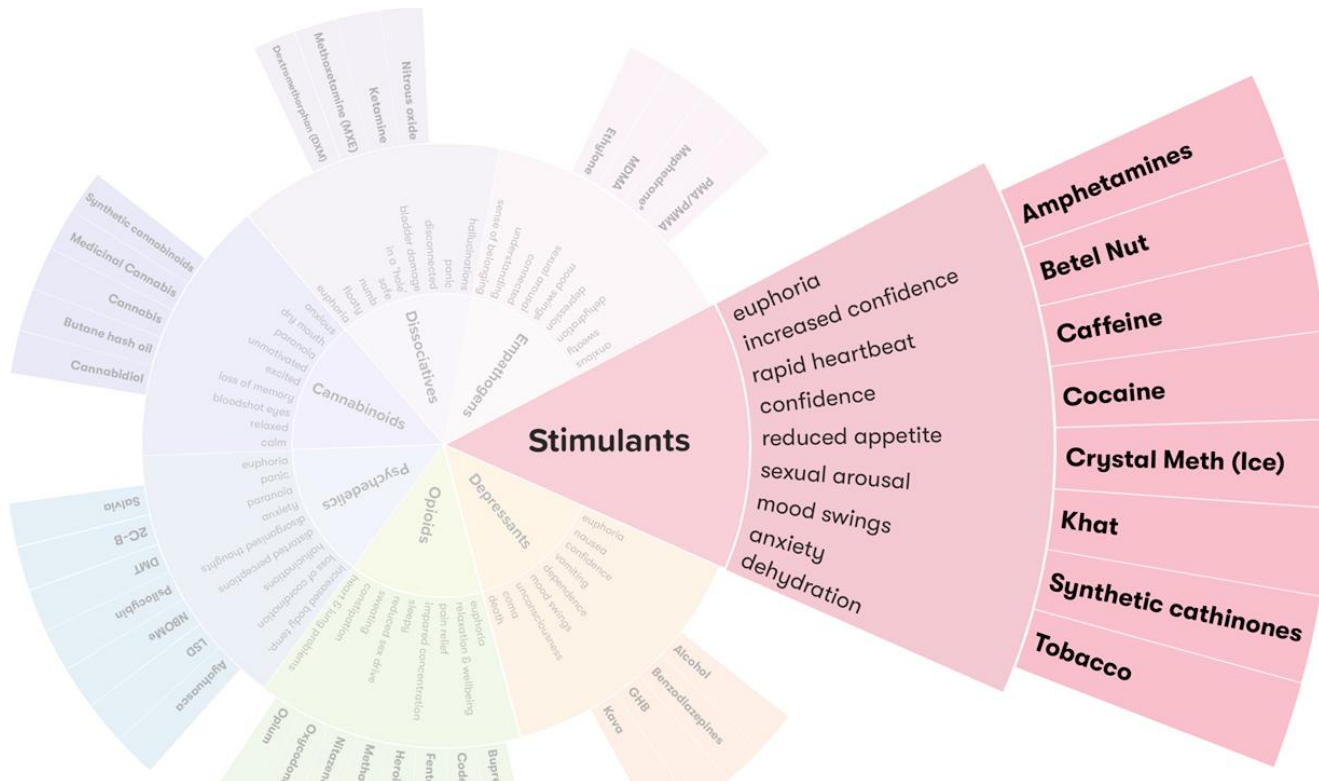
Direttore s.c. Ser.D ASL NO
Dipartimento Interaziendale Patologie da Dipendenza AA.SS.LL. BI-NO-VC-VCO



DISCLOSURES

CT Laboratori
Molteni Farmaceutici
Indivior

PSICOSTIMOLANTI



LE DIMENSIONI

People who use drugs, 2023

316
million people

↑ 28%
over 10 years



cannabis

244
million



opioids

61
million



amphetamines

31
million



cocaine

25
million

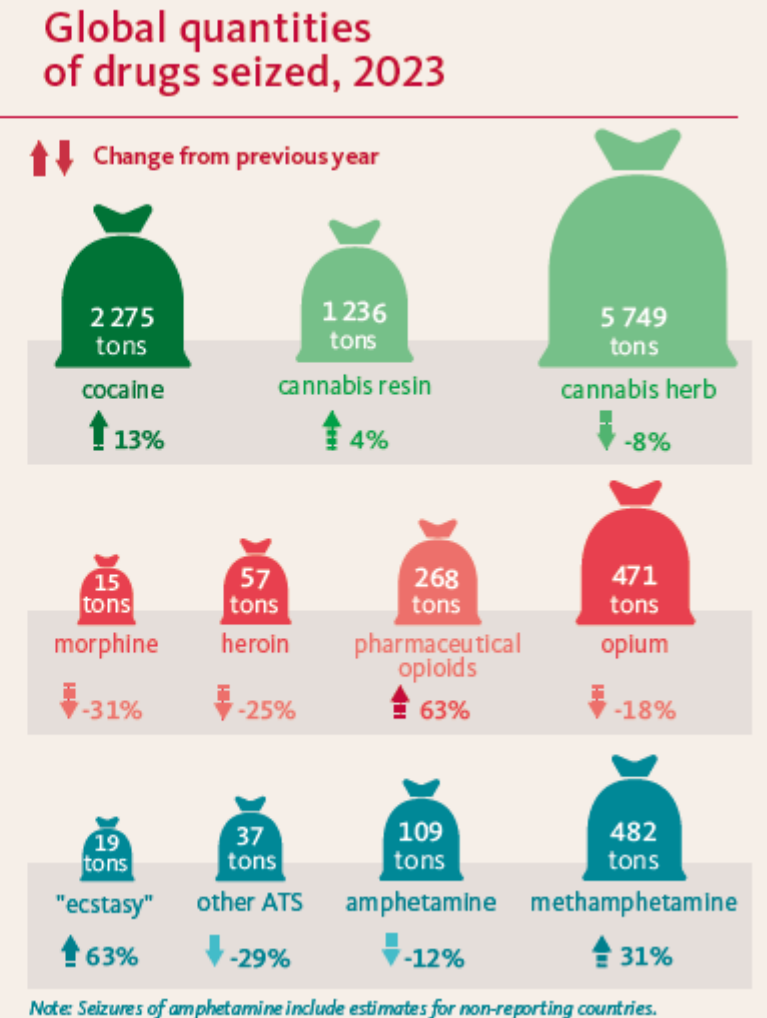
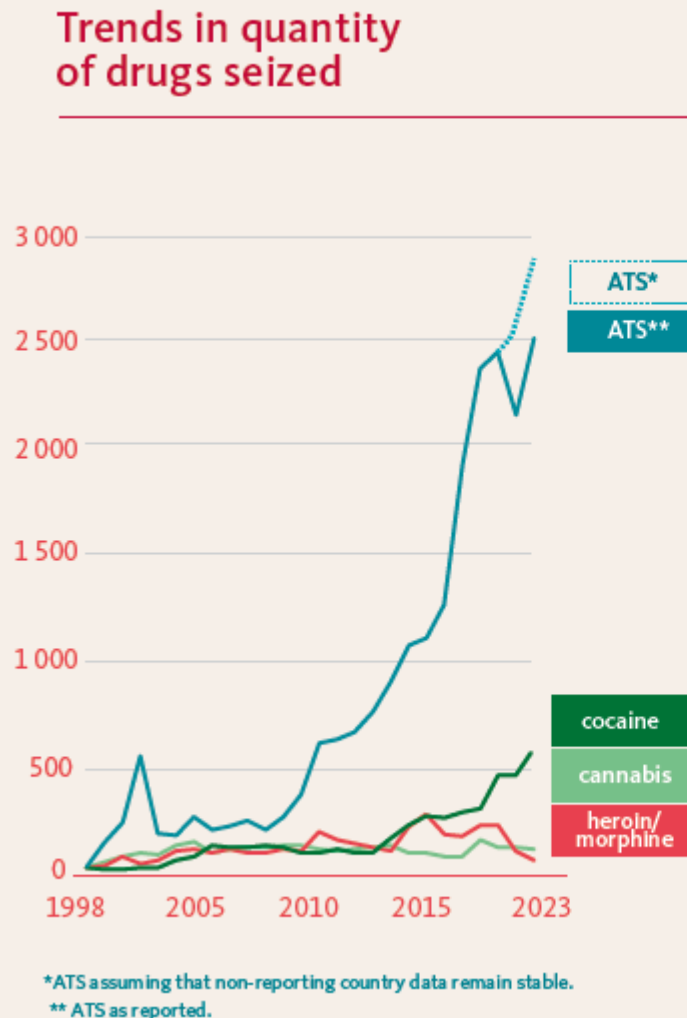


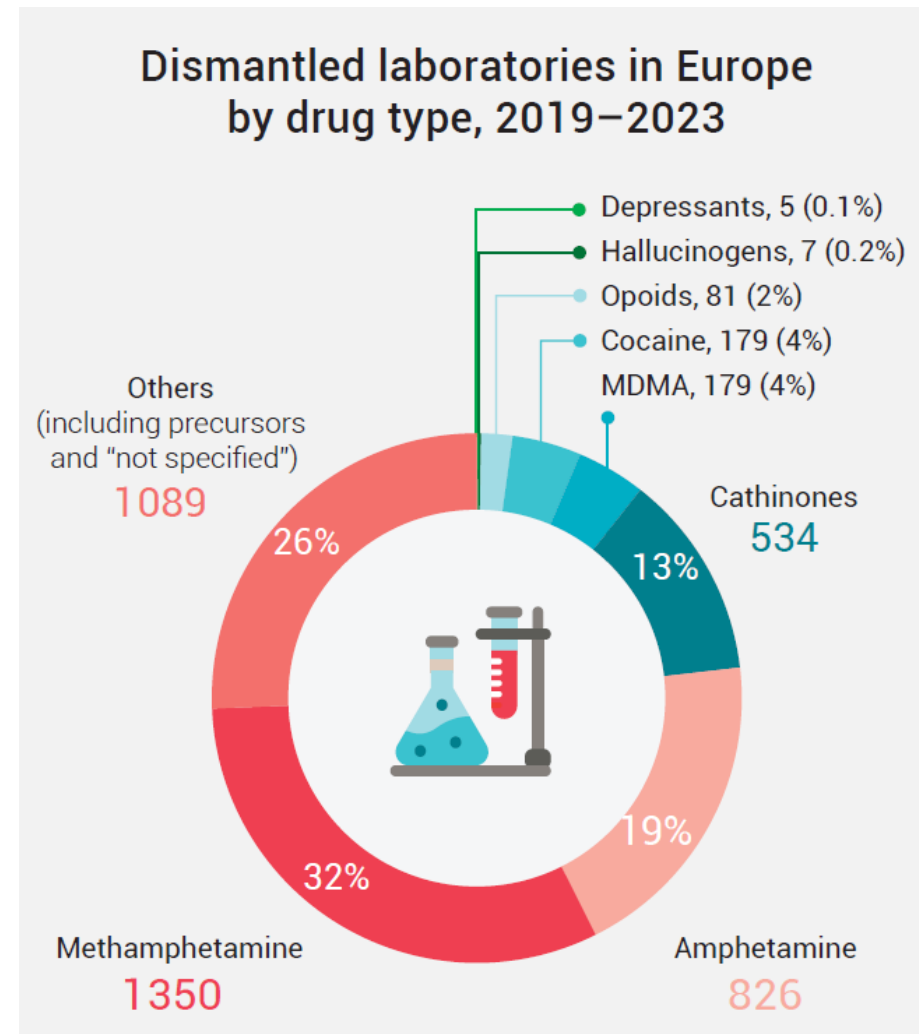
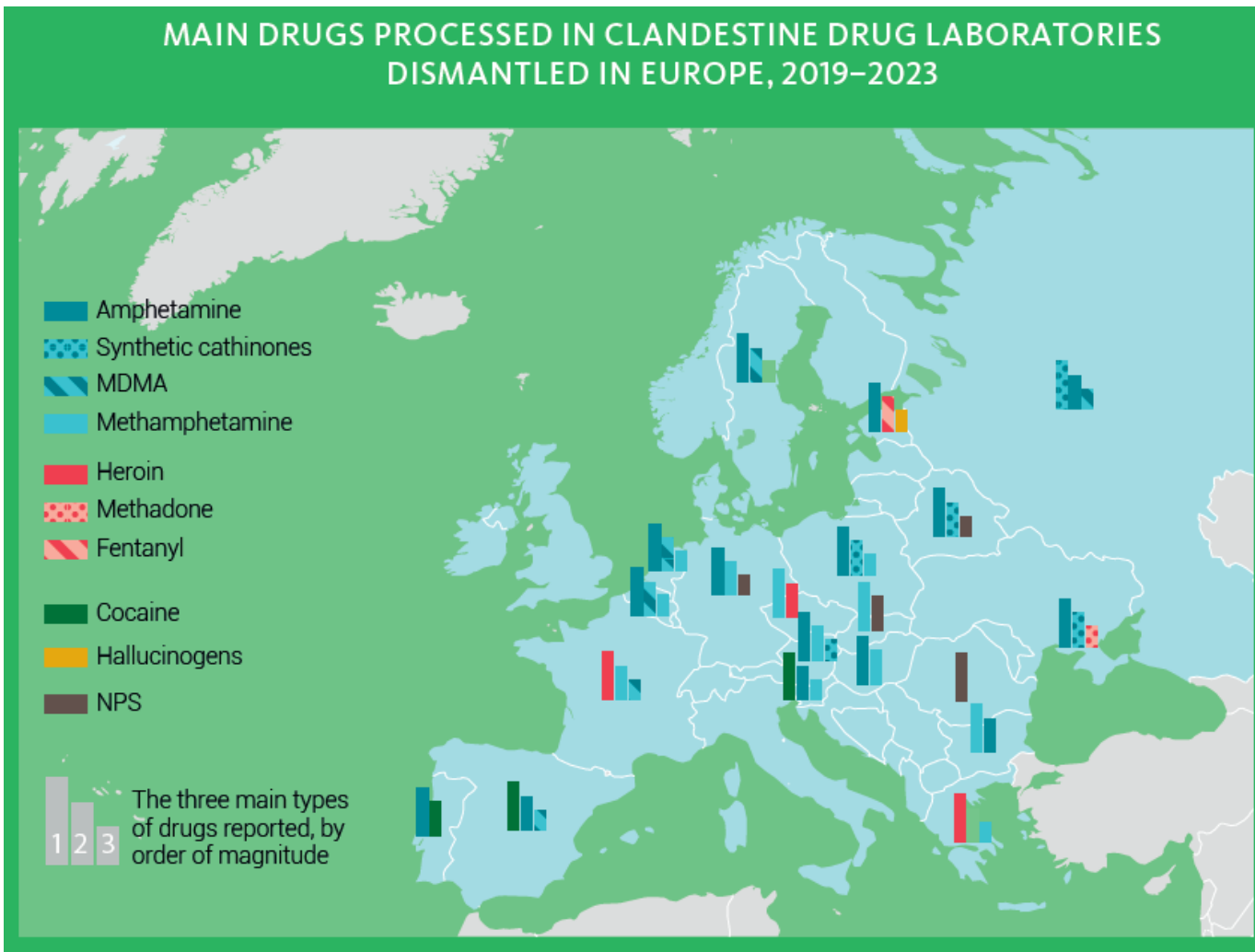
"ecstasy"

21
million

"Il tempo eccitato degli uomini
dell'ovunqueità".

"Con l'avvento della droga, le mafie
hanno abbracciato le logiche del mercato
e del profitto, dando vita ad un business
che nel mondo supera i 500 miliardi di
dollari, circa 313 miliardi di euro, ovvero
un quarto del prodotto interno lordo
dell'Italia".





LABORATORI CLANDESTINI



Lo studente come “Breaking Bad”: in casa una fabbrica di droghe

di Giulia D'Aleo

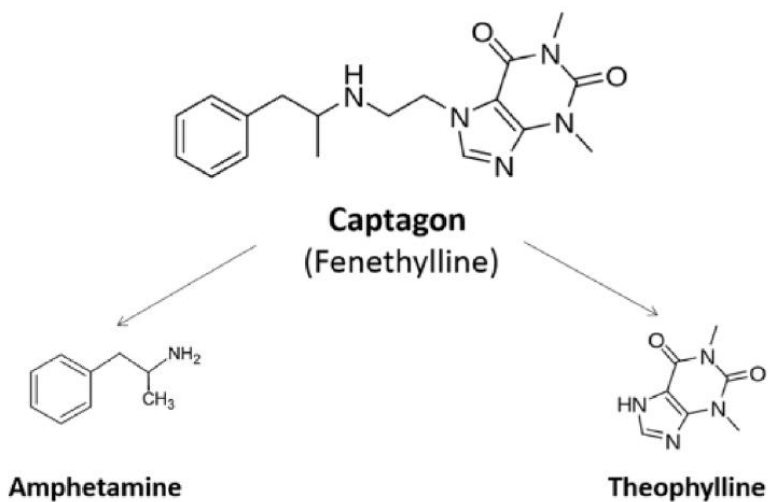
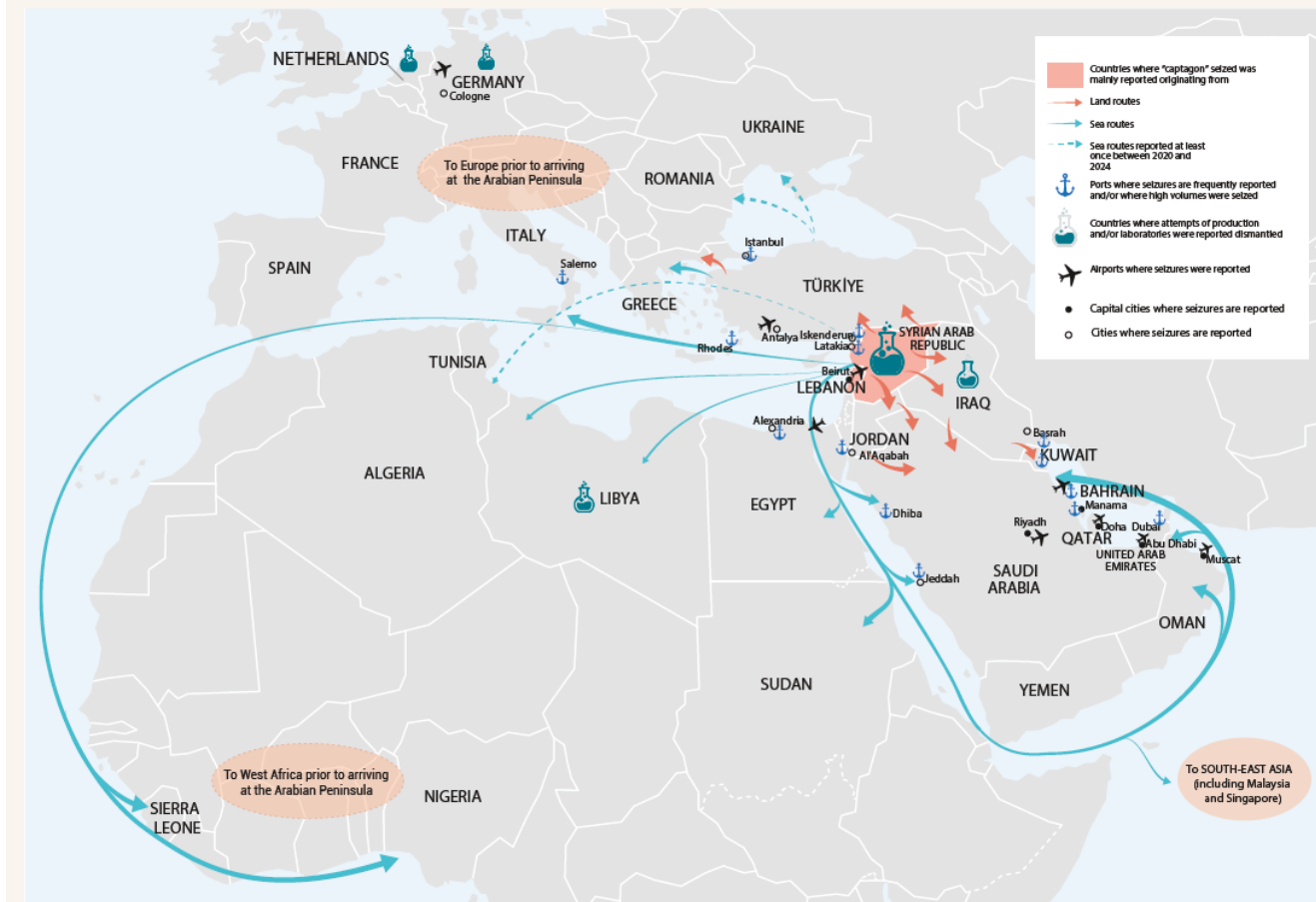


Universitario di Chimica, ventiduenne arrestato a Novara. Il suo laboratorio di metanfetamina era il più attrezzato d'Italia

"L'operazione su descritta riveste grande importanza nel panorama europeo, in quanto le **sostanze rinvenute andranno ad implementare le tabelle degli stupefacenti attualmente esistenti nei vari Paesi dell'Unione Europea**, essendo il laboratorio artigianale **tra i più grandi come diversificazione di sostanze stupefacenti prodotte**. All'operazione ha partecipato anche il Gabinetto Interregionale di Polizia Scientifica, Laboratorio di Chimica Forense, Piemonte e Valle d'Aosta la locale Polizia Scientifica".

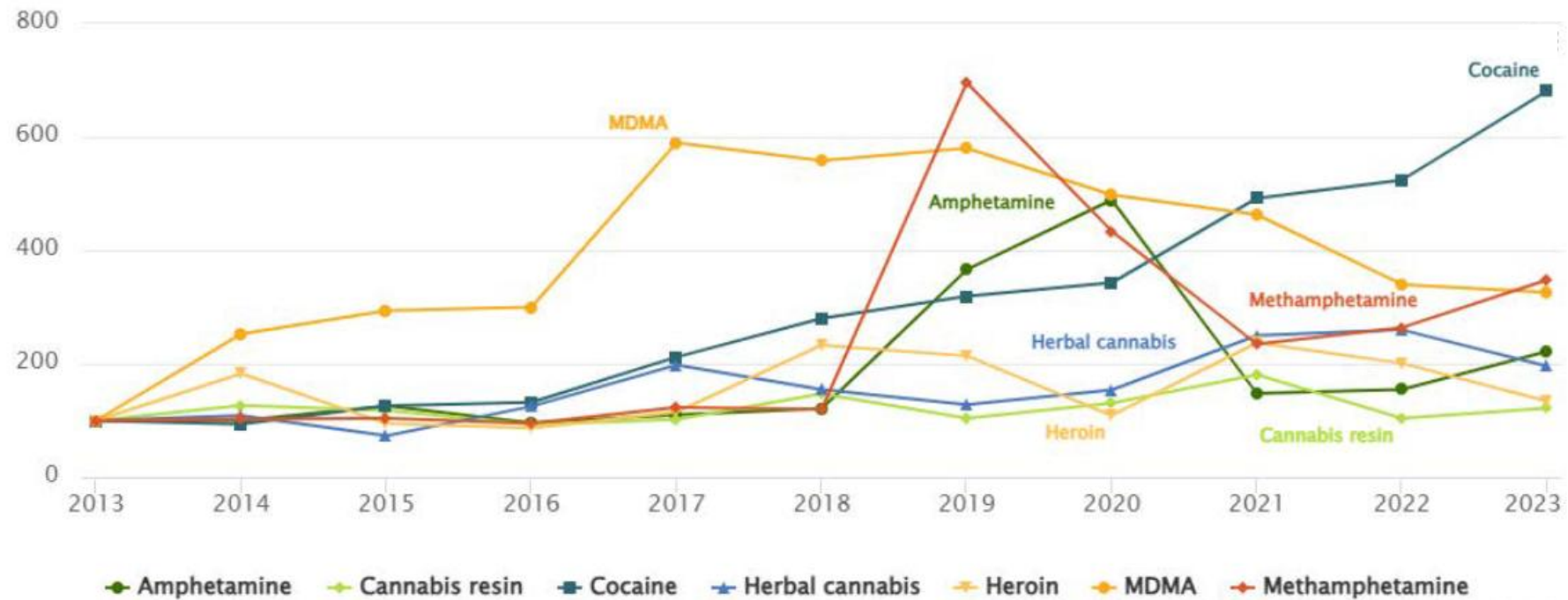
CAPTAGON

Main trafficking routes for counterfeit "captagon", 2020–2024



LE DIMENSIONI

Figure 1.5. Drug seizures in the European Union – quantity of drugs seized, indexed trends (2013 = 100)

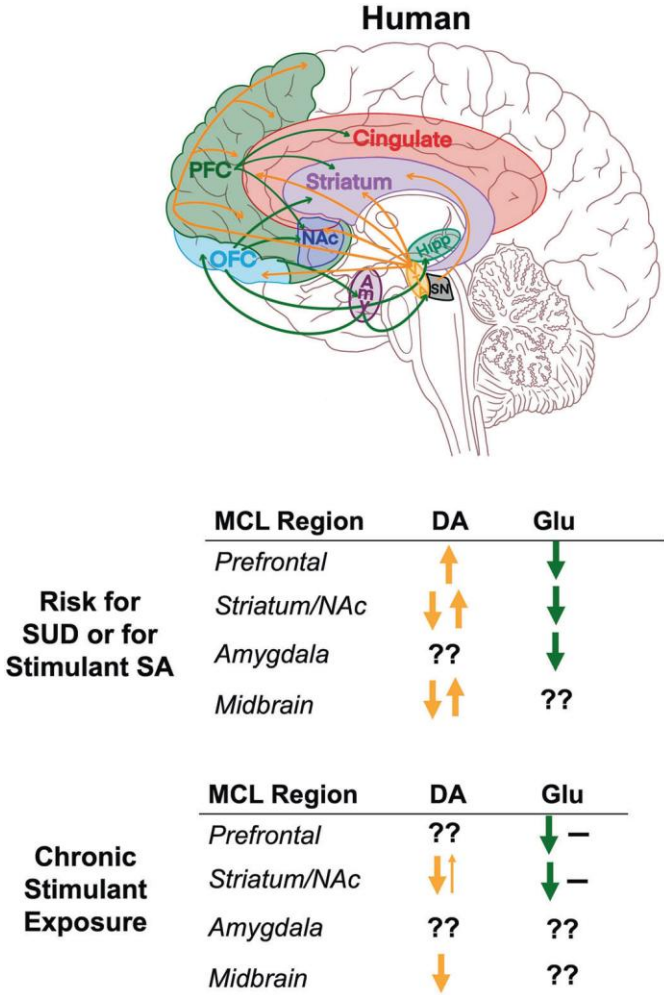
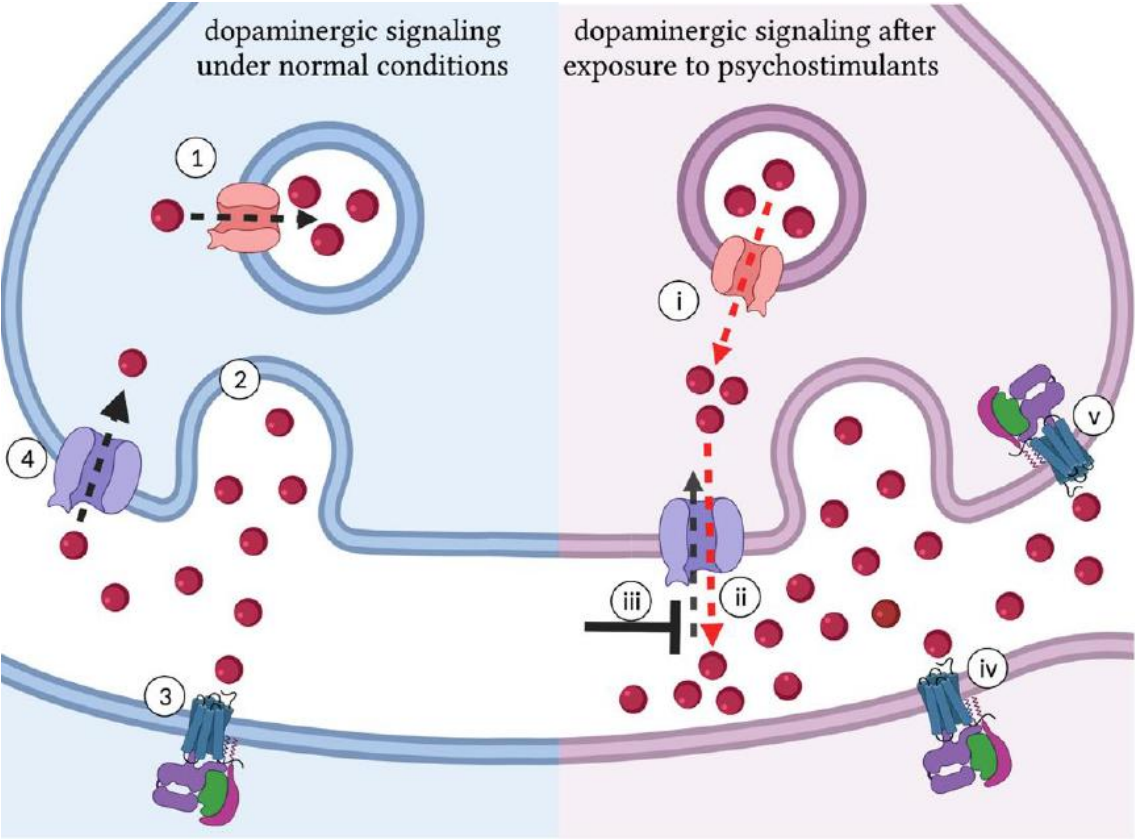


LE DIMENSIONI

Soggetti in carico presso i SerD secondo la sostanza primaria di trattamento e la sostanza di primo uso. Anno 2024

Sostanza di primo uso	Sostanza primaria in trattamento										Totale	
	Eroina		Cocaina		Cannabis*		Crack		Altro			
	n.	%	n.	%	n.	%	n.	%	n.	%	n.	%
Eroina	48.032	65,0	1.037	3,2	196	1,2	182	4,0	487	8,2	49.934	37,4
Cocaina	3.130	4,2	20.465	62,6	912	5,5	302	6,7	266	4,5	25.075	18,8
Cannabis*	15.554	21,0	6.783	20,7	13.448	81,3	779	17,3	847	14,3	37.411	28,0
Crack	159	0,2	140	0,4	108	0,7	2.804	62,2	19	0,3	3.230	2,4
Sostanze alcoliche	1.680	2,3	2.185	6,7	634	3,8	197	4,4	309	5,2	5.005	3,7
Tabacco	469	0,6	347	1,1	148	0,9	44	1,0	41	0,7	1.049	0,8
Altro	4.904	6,6	1.743	5,3	1.103	6,7	202	4,5	3.958	66,8	11.910	8,9
Totale	73.928	100,0	32.700	100,0	16.549	100,0	4.510	100,0	5.927	100,0	133.614	100,0

PSICOSTIMOLANTI E
DOPAMINA

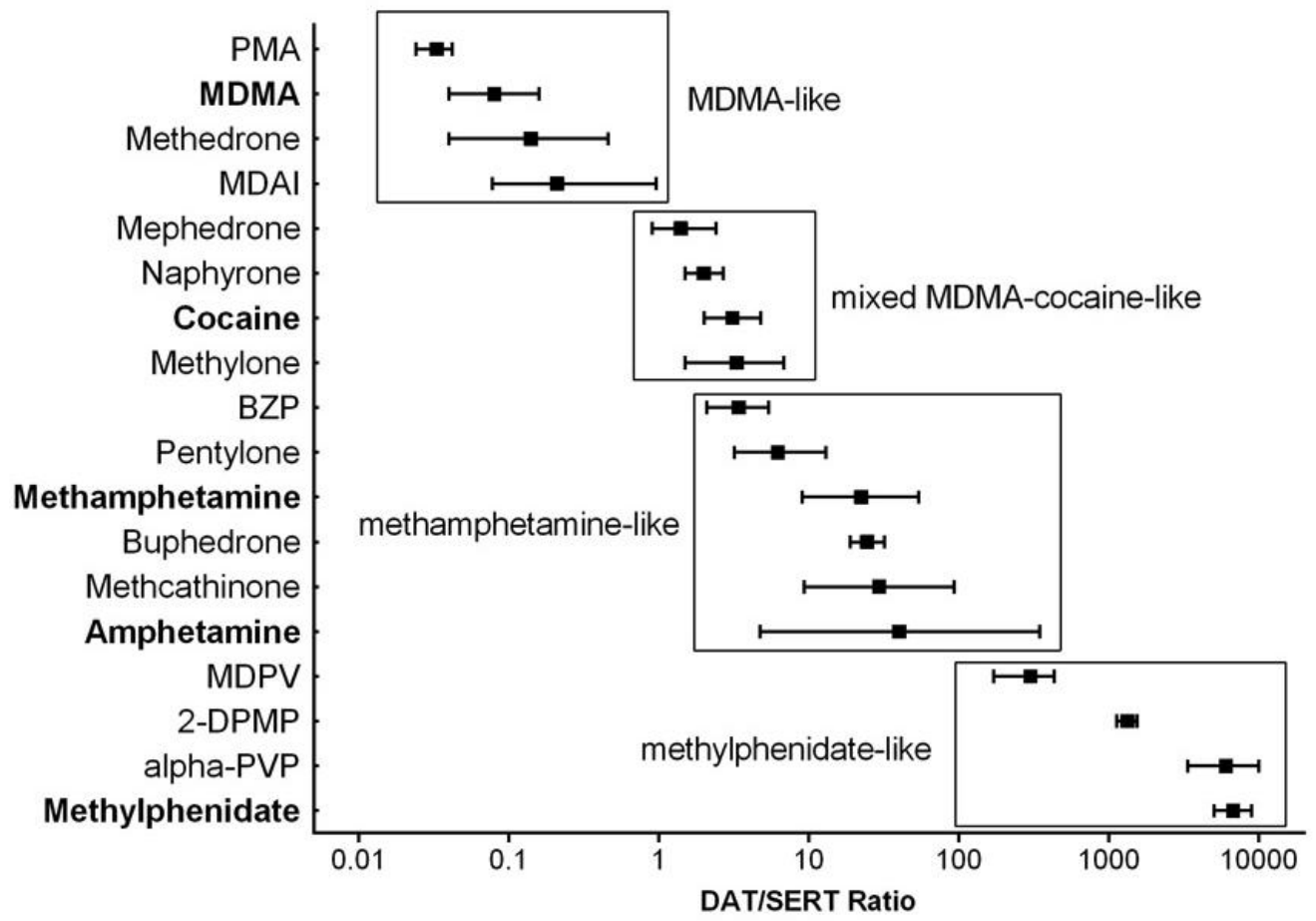
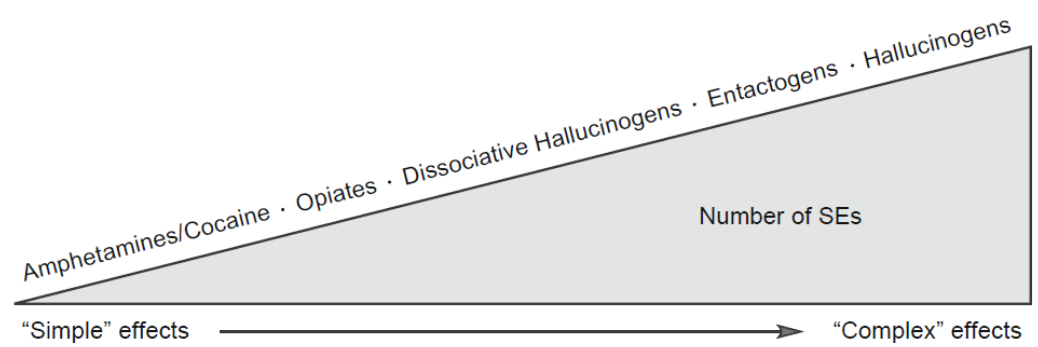




PSICOSTIMOLANTI E NEUROTRASMETTITORI

EFFECTS OF STIMULATION OF DIFFERENT MONOAMINERGIC SYSTEMS

Stimulated monoamine system	Clinical and toxic effects
Dopaminergic	Psychostimulant effects, high abuse and addiction potential, euphoria, locomotor activation, psychosis
Noradrenergic	Sympathomimetic effects, cardiostimulation and psychostimulation
Serotonergic	Entactogenic effects, hyperthermia, hyponatremia, hallucinations, seizures, reduced potential for addiction



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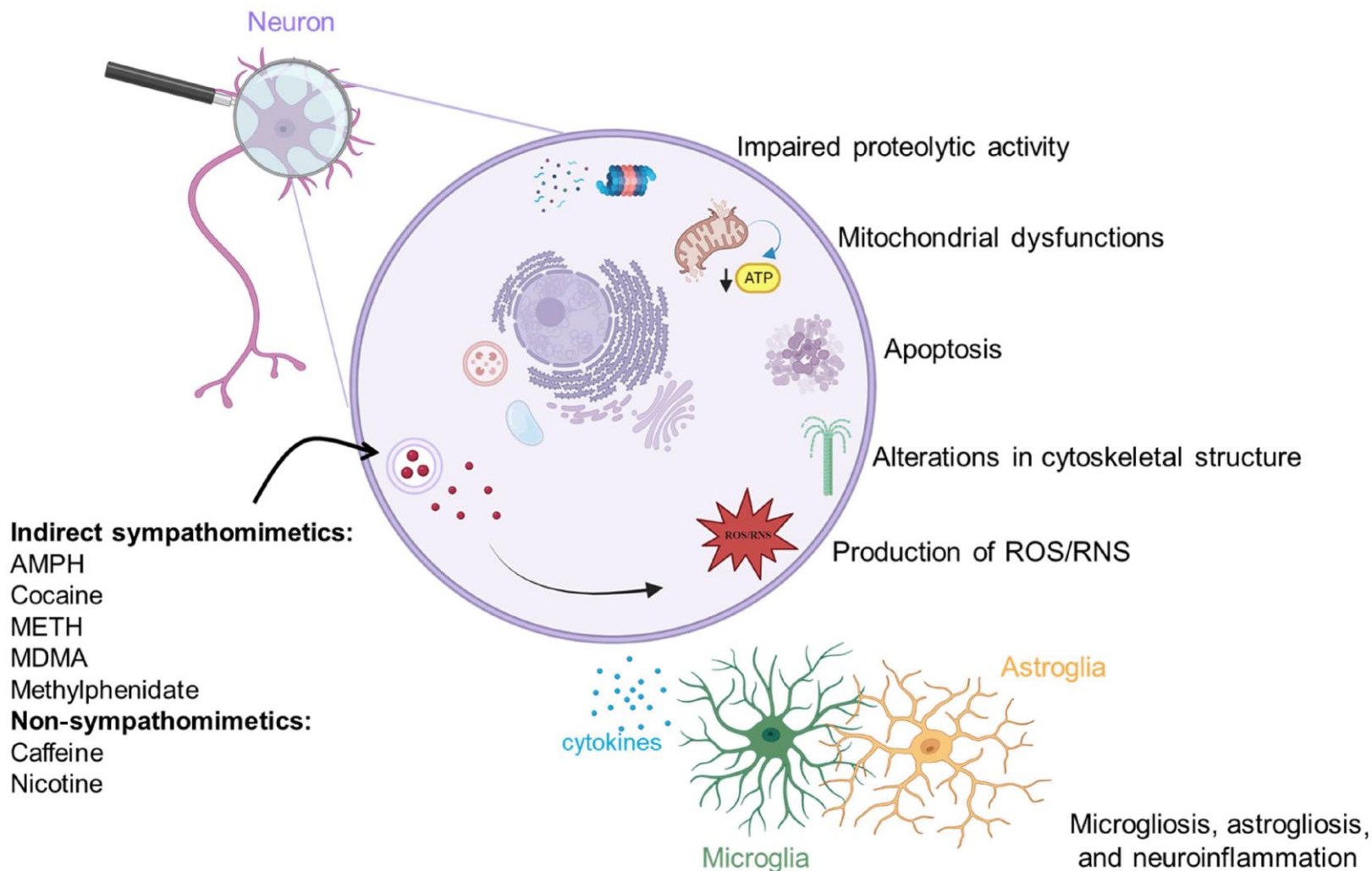
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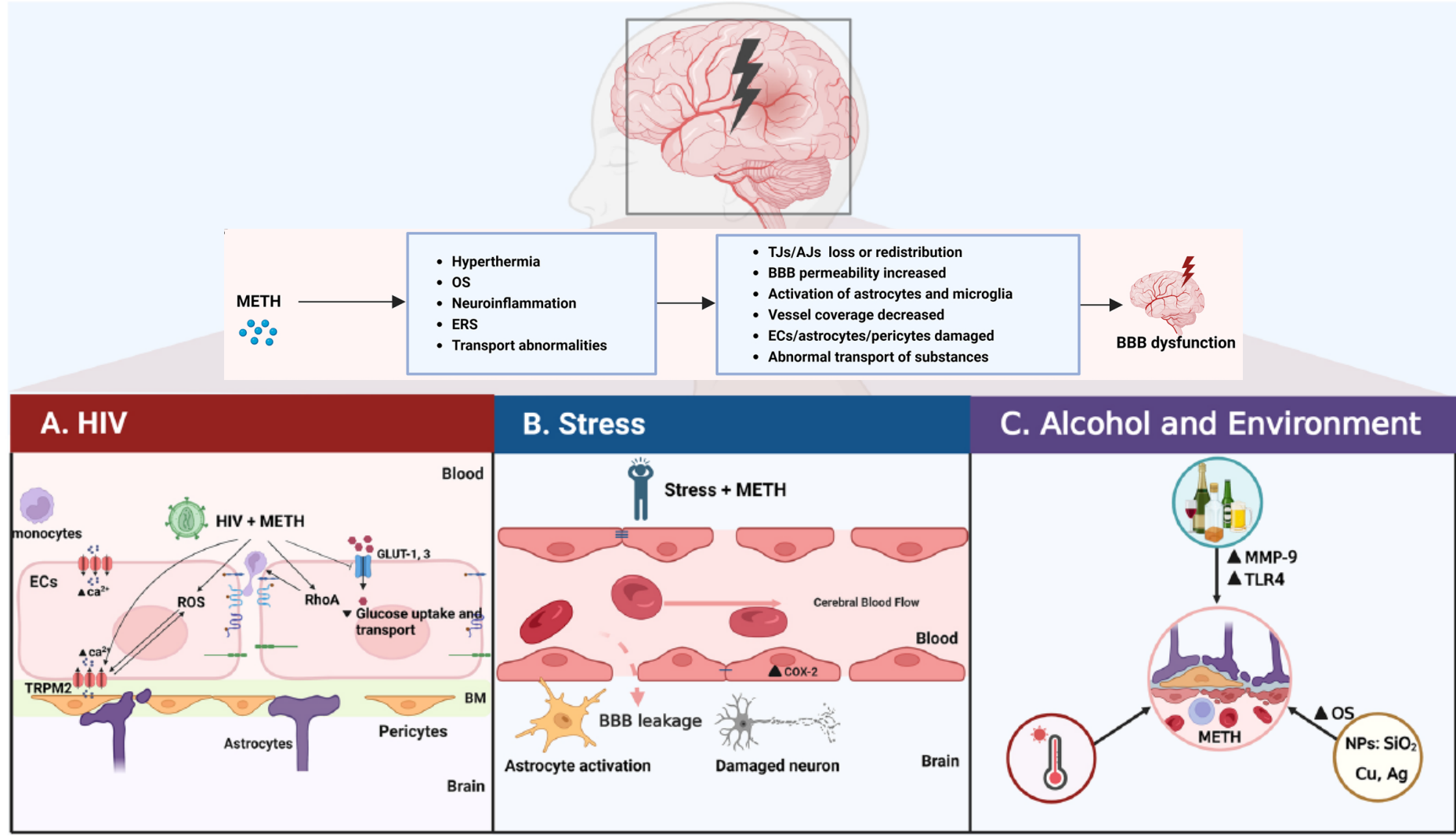
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NEUROTOSSICITA'





ATS E ALTERAZIONI DELLA BEE





NEUROTOSSICITA'

Stimulant actions

ACUTE MONAMINE RELEASE

- Increased synaptic dopamine and serotonin
- Sympathomimetic effects: tachycardia, hypertension, hyperthermia

ONGOING NEUROTRANSMITTER EFFECTS

- Dopamine and serotonin binding, transport and receptor changes
- Neurotoxicity and cell loss (fronto-striatum, basal ganglia)
- Reduction / kindling of seizure threshold

INDIRECT EFFECTS

- Inflammatory vasculitis, atherosclerosis, cerebral vasculitis
- Cardiomyopathy and arrhythmias
- Thromboembolism
- Hypo-natraemia
- Hyper-coagulation

Moderators

DRUG USE FACTORS

- Dose and frequency
- Route
- Duration of abstinence
- Comorbid use of cannabis and other drugs



PERSONAL FACTORS

- Age, gender
- Family history and genetic vulnerability
- Personal and social supports
- Health literacy
- Service access

Cerebral effects

Stroke

Neurocognitive impairment

Parkinson's disease

Seizures

Psychotic symptoms & illness



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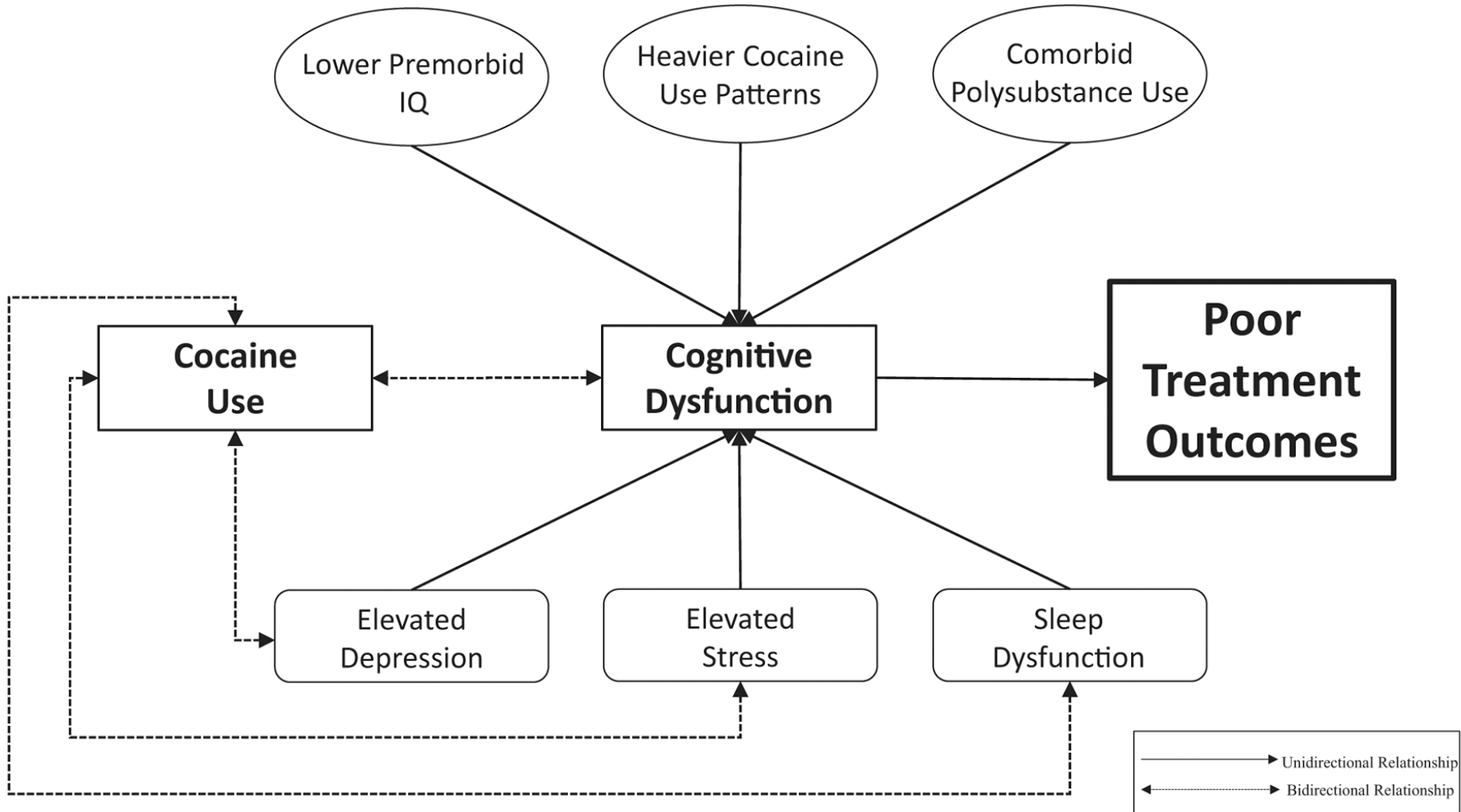
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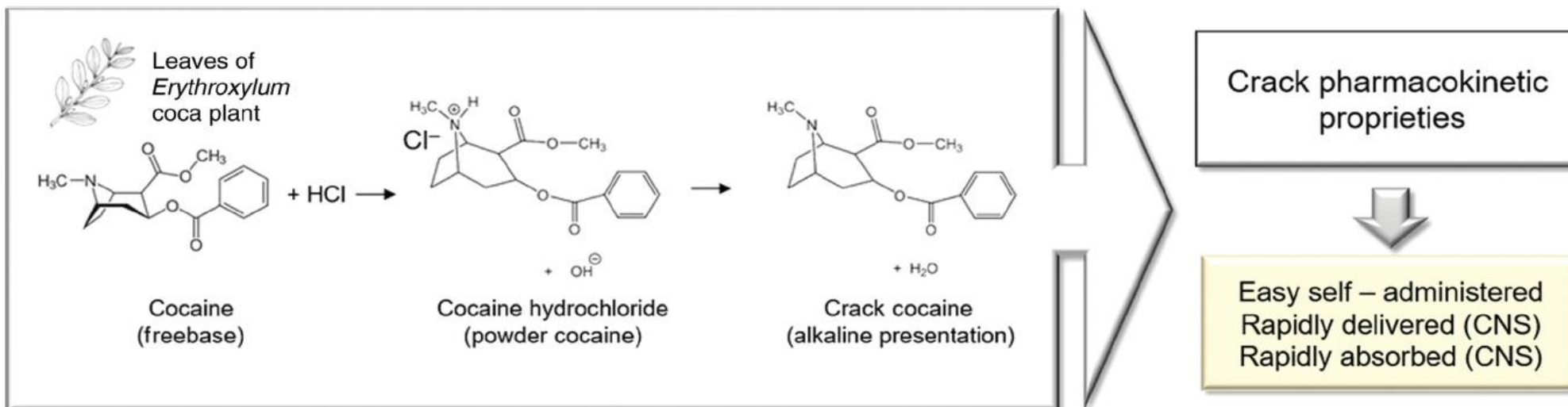
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QUALE COCAINA

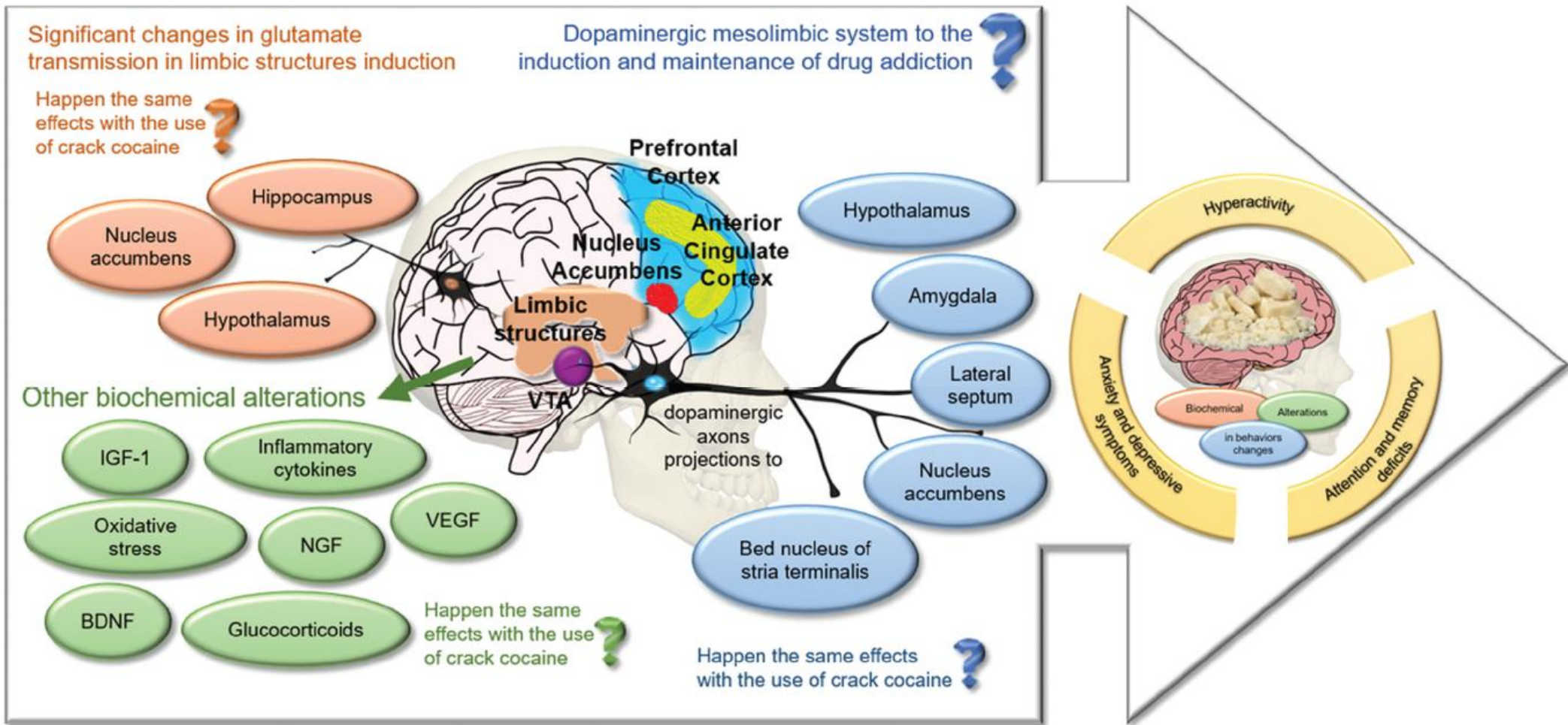
Cocaine Form	Cocaine Hydrochloride	Cocaine Free Base
Other names it is known by	'coke', 'snow', 'blow'	'crack'
CAS	53-21-4	50-36-2
Molecular formula	$C_{17}H_{22}ClNO_4$	$C_{17}H_{21}NO_4$
Molecular weight	339.8 g mol^{-1}	$303.35 \text{ g mol}^{-1}$
Boiling point	-	187°C
Melting point	195°C	98°C
Solubility in water	2 g/mL	$1.7 \times 10^{-3} \text{ g/mL}$
pKa; pKb (at 15°C)	-	8.61; 5.59
Log P	-	2.3





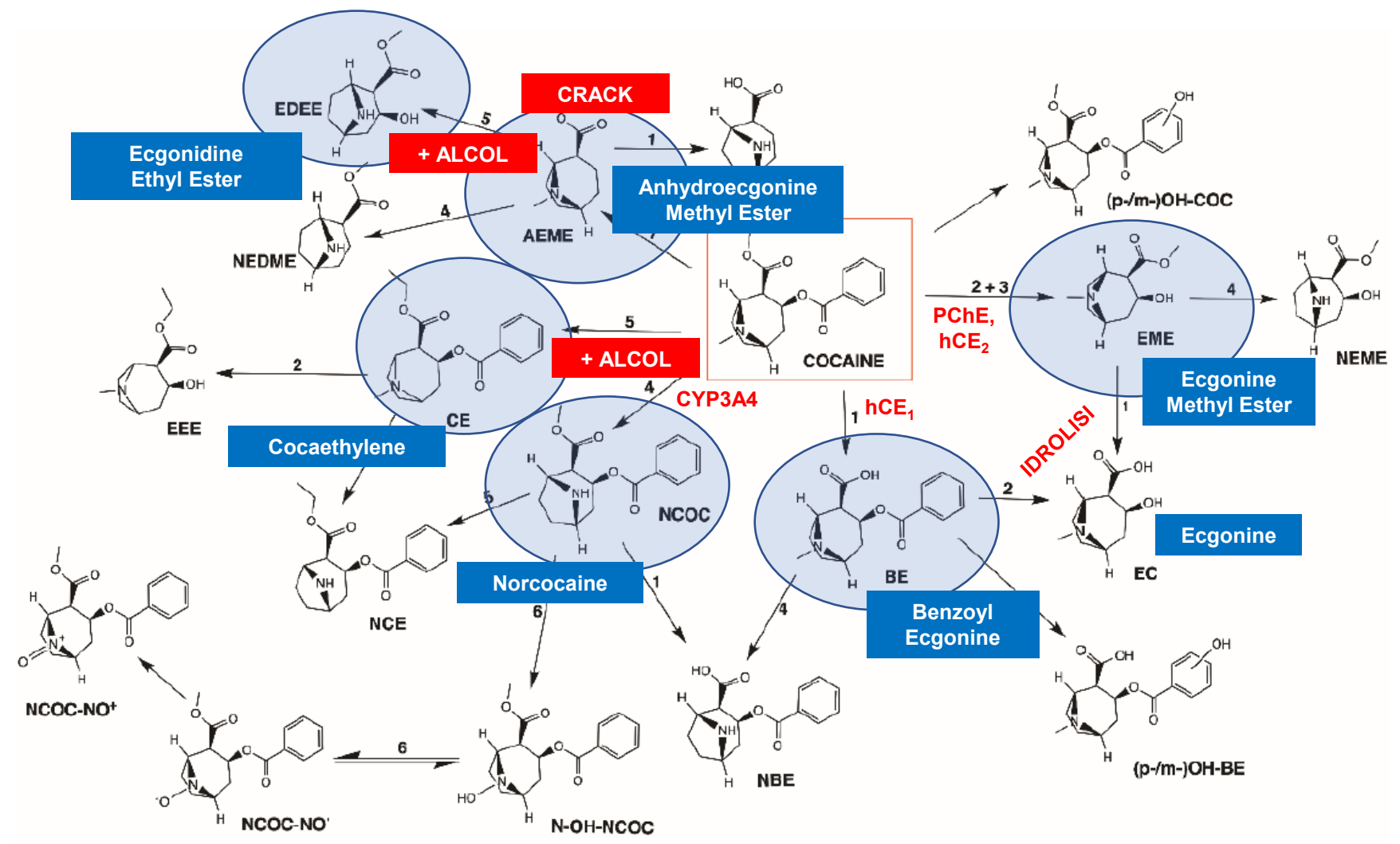
COCAINA vs CRACK

Cocaine neuroanatomical, biochemical and behavior alterations



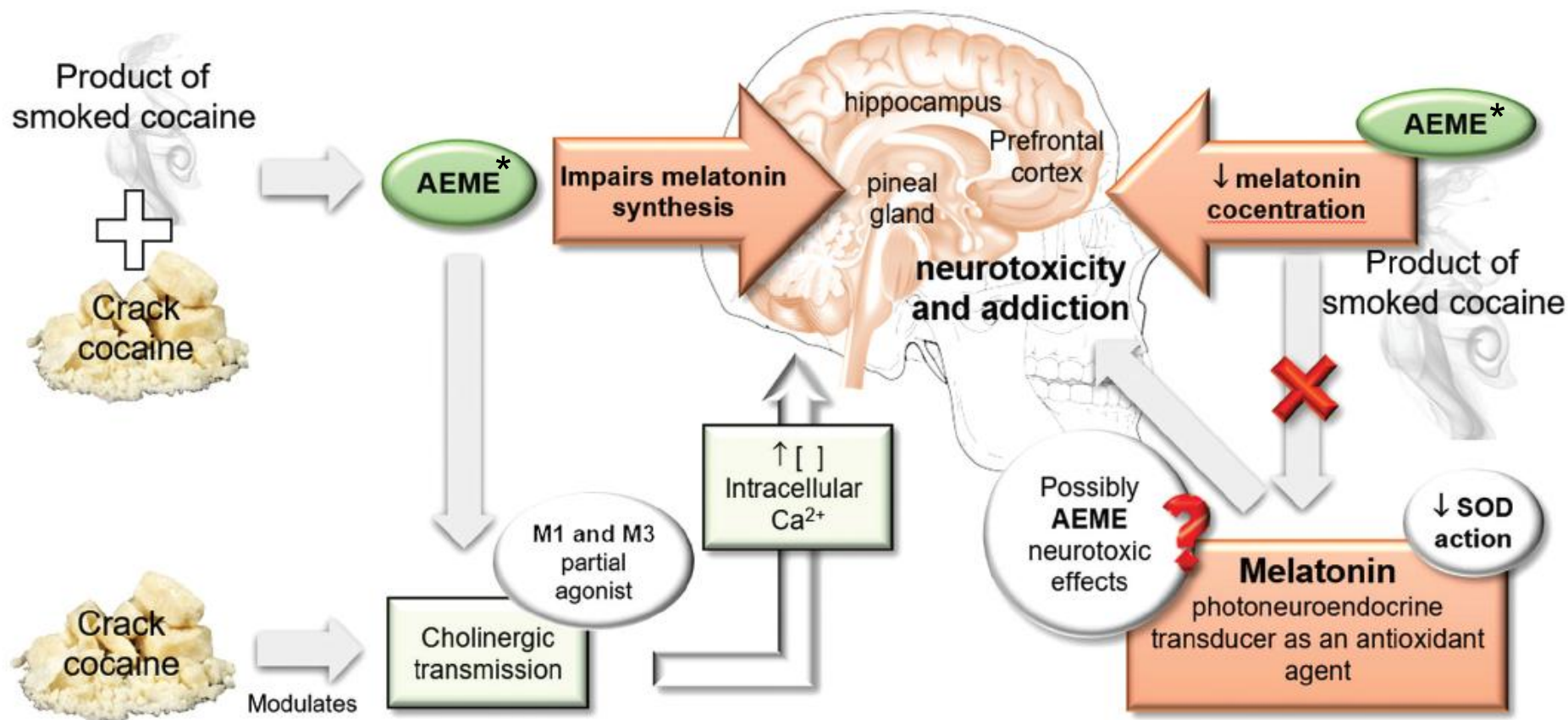


COCAINA E METABOLITI



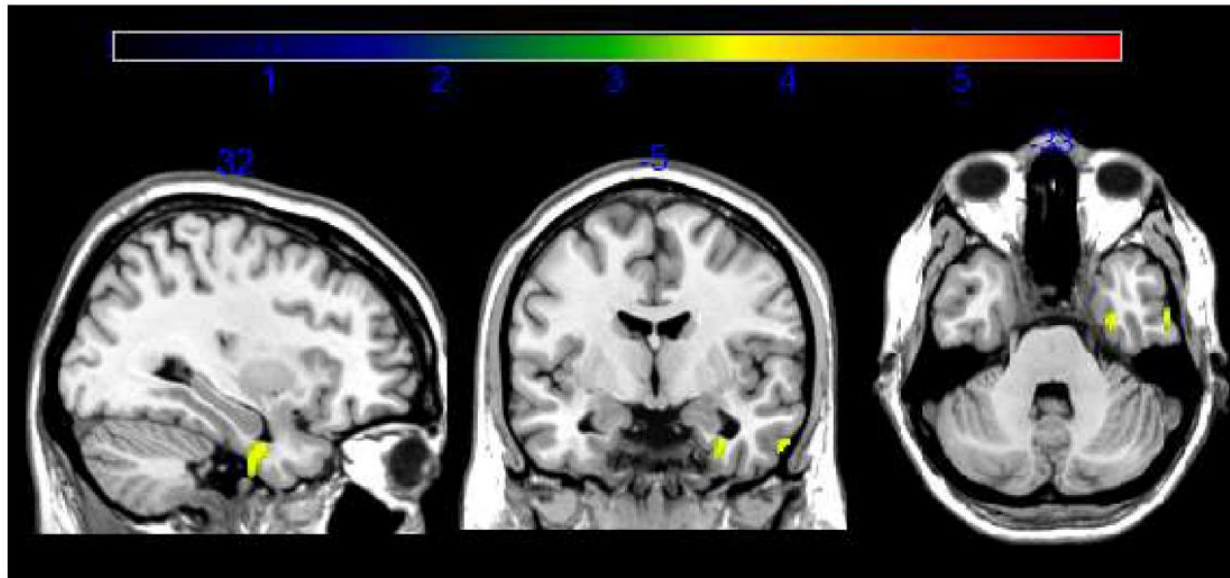
COCAINA vs CRACK

*Anhydroecgonine Methyl Ester

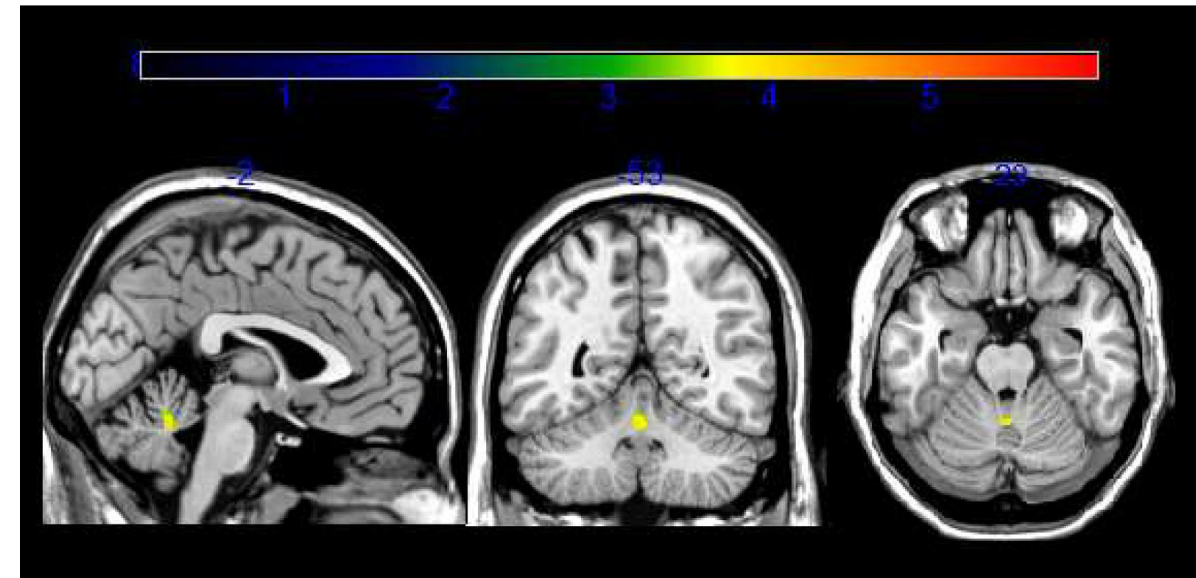


COCAINA vs CRACK

Patients with CUD display widespread cortical and subcortical brain shrinkage. Patients with preferential crack-cocaine use and subsequent relapsers showed **specific gray matter volume deficits**, suggesting that different patterns of cocaine use and different clinical outcome are associated with different brain macrostructure.



GRAY MATTER BRAIN ABNORMALITIES IN CUD-CRACK COMPARED TO CUD-HYDRO



GRAY MATTER BRAIN ABNORMALITIES IN RELAPERS COMPARED TO ABSTAINERS

COCAINA E NEUROGENESI

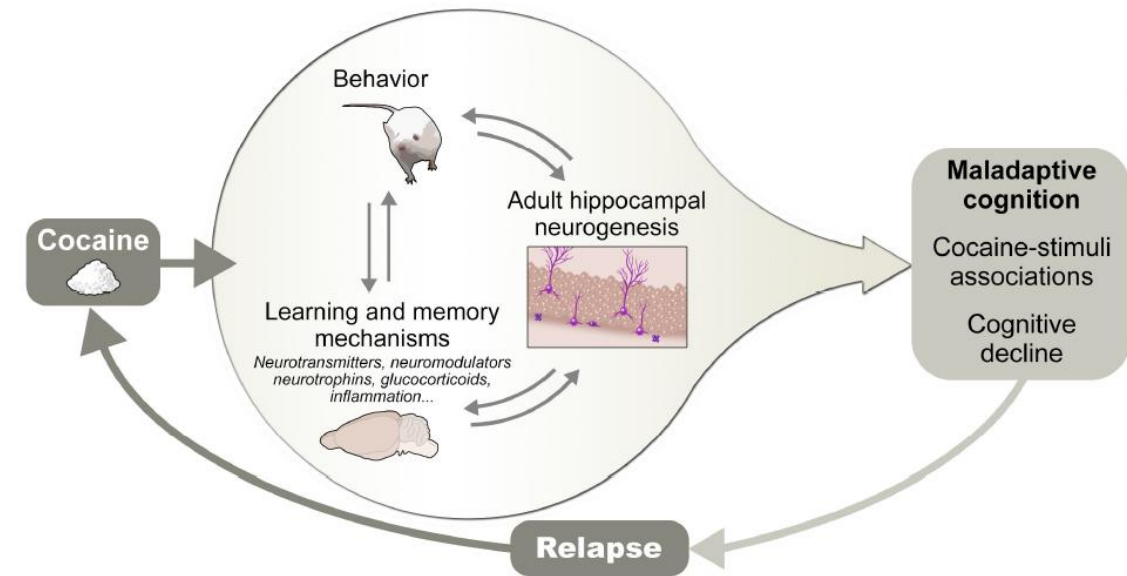
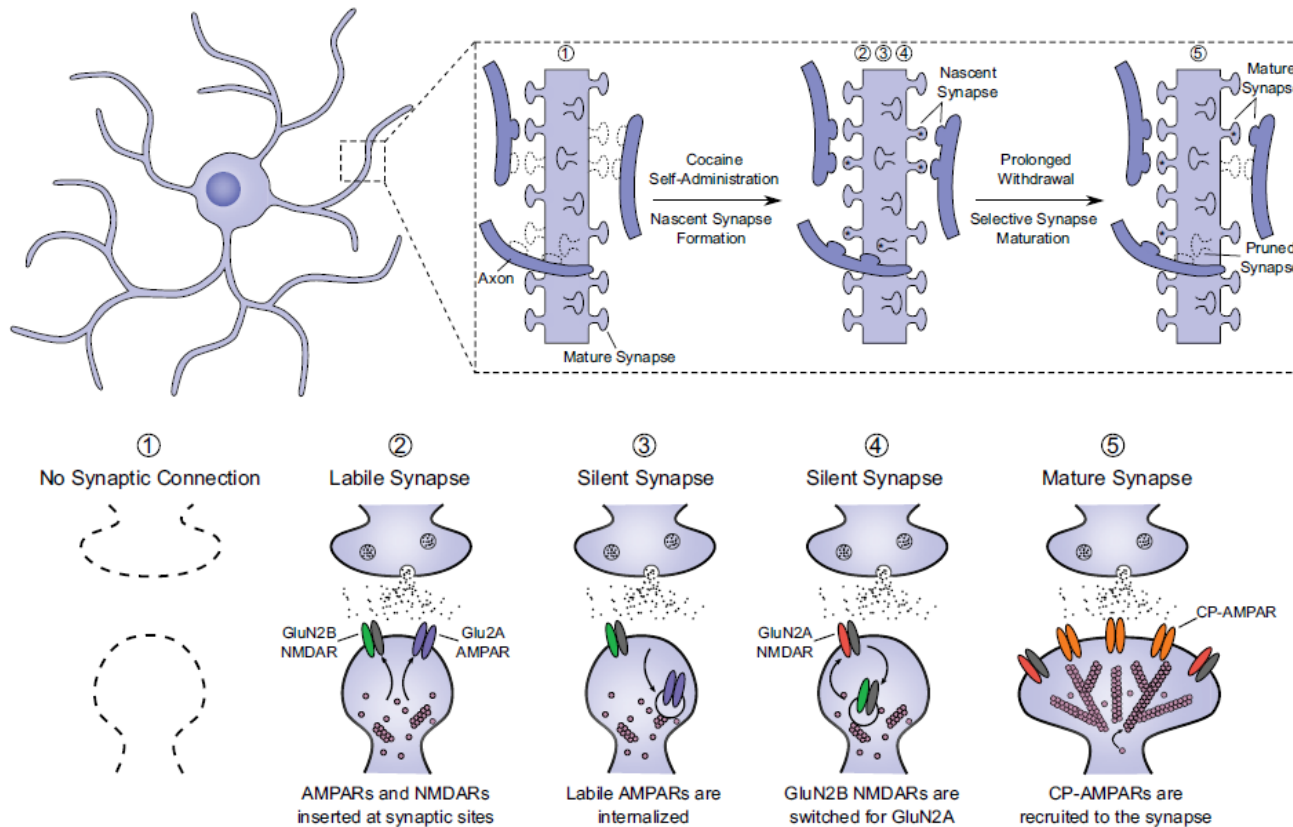




TABLE 4. Adjusted Odds Ratio of Clinical Characteristics by Mutually Exclusive Stimulant Type (NSDUH 2021–2022)

	AOR ^{II} (95% CI)								
	Past-year DSM-5 Impaired Control*	Past-year DSM-5 Social Impairment [†]	Past-year DSM-5 Risky Use [‡]	Past-year DSM-5 Pharmacologic Indicators [§]	Past-year DSM-5 Craving	Past-year Psychological Distress	Past-year Suicidal Ideation	Past-year Suicide Attempt	Past-year Major Depressive Episode
Stimulant type used									
Nonmedical prescription stimulants only	REF	REF	REF	REF	REF	REF	REF	REF	REF
Non-crack cocaine only	0.96 (0.67, 1.38)	1.12 (0.62, 2.01)	1.01 (0.57, 1.79)	0.68 (0.45, 1.03)	1.17 (0.76, 1.81)	0.63 [¶] (0.44, 0.92)	0.96 (0.66, 1.39)	0.52 (0.24, 1.13)	0.61 [¶] (0.40, 0.91)
Crack cocaine	4.13 [¶] (2.48, 6.88)	9.32 [¶] (4.43, 19.63)	3.93 [¶] (2.00, 7.75)	2.40 [¶] (1.33, 4.33)	4.39 [¶] (2.56, 7.51)	0.91 (0.50, 1.65)	1.70 (0.83, 3.47)	2.98 (0.85, 10.48)	0.76 (0.37, 1.55)
Methamphetamine only	4.65 [¶] (2.96, 7.29)	7.27 [¶] (3.90, 13.56)	4.05 [¶] (2.31, 7.11)	3.09 [¶] (1.97, 4.84)	4.79 [¶] (3.07, 7.49)	0.85 (0.55, 1.32)	1.40 (0.86, 2.26)	2.06 (0.75, 5.66)	0.84 (0.51, 1.38)
Polystimulants	6.18 [¶] (4.25, 9.00)	9.54 [¶] (5.57, 16.32)	6.72 [¶] (4.28, 10.55)	5.33 [¶] (3.64, 7.80)	6.49 [¶] (4.48, 9.40)	1.20 (0.84, 1.72)	1.20 (0.79, 1.83)	1.81 (0.77, 4.25)	1.16 (0.77, 1.75)

Truchan J, Schepis TS, Pasman E, McCabe VV, McCabe SE. DSM-5 Stimulant Use Disorder Severity, Stimulant Craving, and Other Clinical Characteristics Based on Stimulant Type (Cocaine, Methamphetamine, Nonmedical Prescription Stimulants, or Polystimulants). J Addict Med. 2025 Sep 3

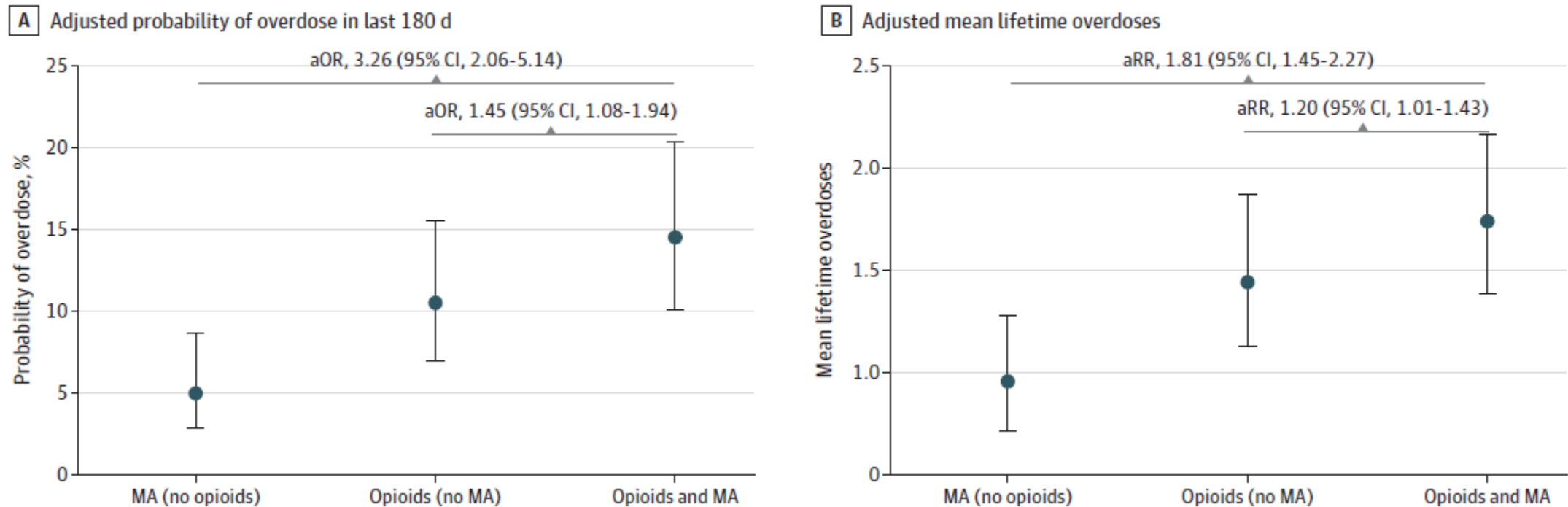


Synthetic Cathinones	The Reinforcing Potency	The Reinforcing Efficacy
Mephedrone	≥METH [81,82]	=METH [82]
Methylone	<mephedrone [82,83], >mephedrone [90] >MDMA [85] <cocaine [88]	<cocaine [88]
MDPV	>METH [86,89] ≥methylone [88] >cocaine [89]	≥METH [87,89] >cocaine [88,89]
α-PVP	=MDPV [91], =4-MePPP [77] >METH >4cl-α-PVP >4cl-α-PPP [78]	=MDPV [91], <Methylone [94] >METH [77] =MDMA [94] <cocaine [94]
Pentylone, pentedrone	>methylone [96]	>methylone [96]
Ethylone, dibutylone, N-ethylpentylone	<METH [97]	<METH [97]

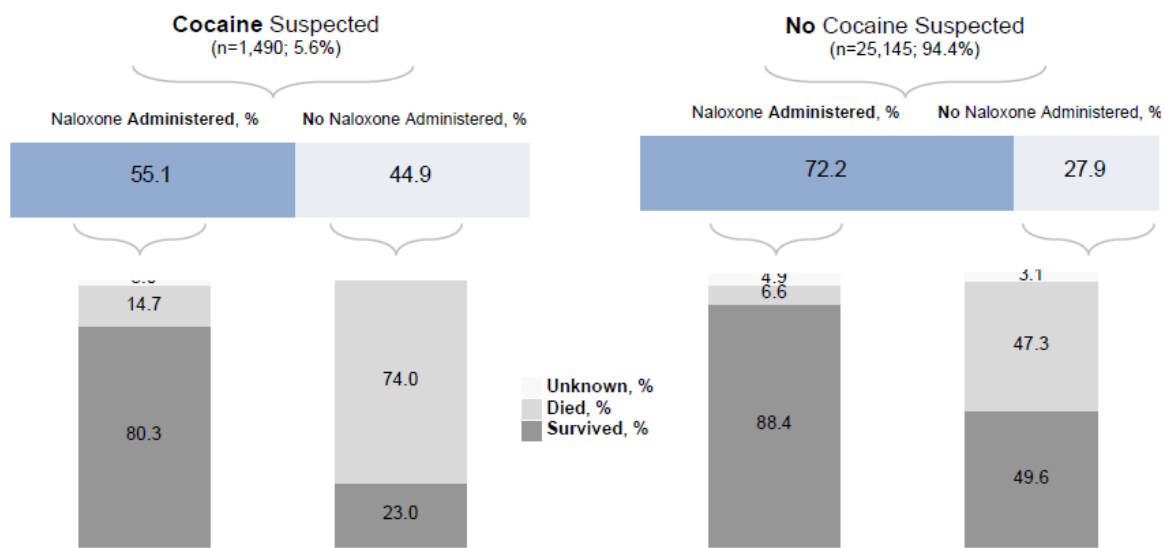


OVERDOSE

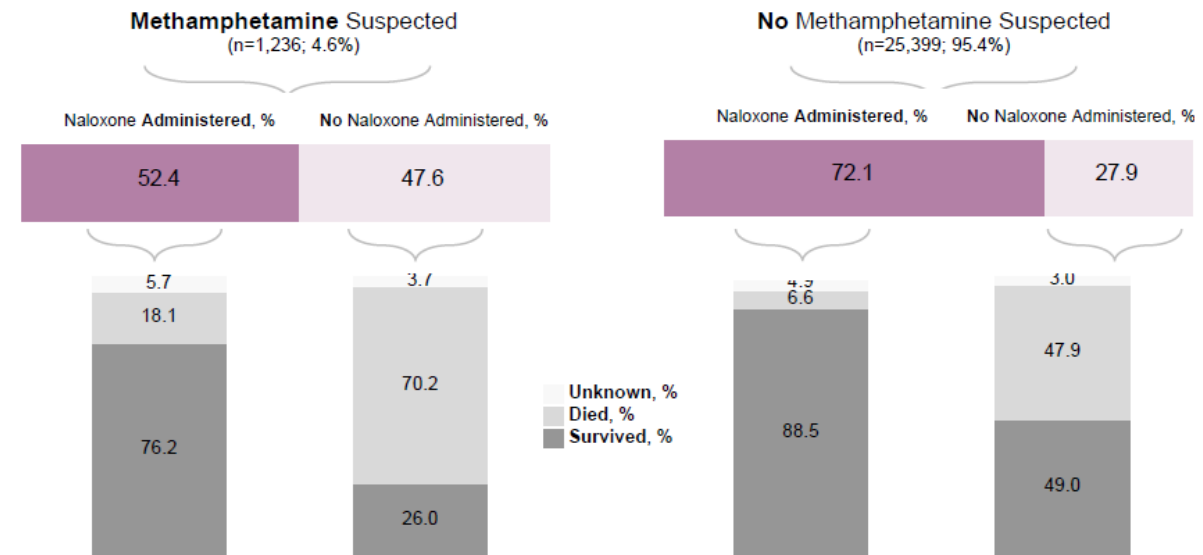
Figure. Adjusted Probability of Methamphetamine (MA) Overdose in Last 180 Days and Adjusted Mean Lifetime Overdoses



Suspected Opioid-Involved Overdoses
(n=26,635)



Suspected Opioid-Involved Overdoses
(n=26,635)





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C'ERA UNA VOLTA

General treatment directives

Maintain total abstinence from cocaine, alcohol, opioids, marijuana, and addictive pills.

Avoid people, places and things associated with cocaine use.

Overcome denial and admit to the consequences of the addiction.

Attend treatment sessions on a regular basis.

Maintain openness and honesty in treatment.

Discuss emotionally important issues.

Learn drug-free coping skills.

Utilize craving reduction techniques.



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LE EVIDENZE

	Abstinence	Use	Lapse	Relapse	Retention	Harms
All Antidepressants: Bupropion, Desipramine, Fluoxetine, Mirtazapine, Nefazodone, Paroxetine, Sertraline, Venlafaxine	★★	★★	★	★	★★★	★★
Aminoketone: Bupropion	★	★	NA	NA	★★	∅
SSRIs: Fluoxetine, Paroxetine, and Sertraline	NA	NA	∅	∅	★★	★
SSRI in patients abstinent at Baseline: Sertraline	NA	NA	★	★	★	∅
All Antipsychotics: Aripiprazole, Haloperidol, Lamotrigine, Olanzapine, Quetiapine, Risperidone, Reserpine	★	★	∅	∅	★★	∅
Psychostimulants: Dexamphetamine, Lisdexamfetamine, Mazindol, Methamphetamine, Methylphenidate, Mixed Amphetamine Salts, Modafinil, Selegiline	★	★	NA	NA	★★	★★
Cognitive Enhancing Drugs: Memantine, Atomoxetine	∅	∅	NA	∅	∅	∅
Anxiolytic: Buspirone	∅	NA	∅	∅	∅	∅
Anticonvulsants/Muscle Relaxants: Baclofen, Carbamazepine, Gabapentin, Lamotrigine, Phenytoin, Tiagabine, Topiramate, Vigabatrin	NA	★★	NA	NA	★★	∅
Anticonvulsant: Topiramate	★	∅	NA	NA	★★	∅
Drugs for other substance use disorders: Acamprosate, Buprenorphine, Buprenorphine + Naloxone, Disulfiram, Naltrexone, Methadone, Varenicline	★	∅	∅	∅	∅	∅
Disulfiram	★	★	NA	NA	★★	★
Dopamine agonists: Amantadine, bromocriptine, L dopa/Carbidopa, pergolide, cabergoline, pramipexole, and pramipexole	★	NA	NA	NA	★★	NA

Shading represents the direction of effect:

(No color)

Unclear

Grey

No difference

Green

Evidence of benefit

Red

Favors placebo

Symbols represent the strength of the evidence:

NA

No evidence or not applicable

∅

Insufficient

★

Low

★★

Moderate

★★★

High



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LE LINEE GUIDA

NO PHARMACOTHERAPIES approved for the treatment of Stimulant Use Disorder (StUD).

Pharmacotherapies may be prescribed **OFF-LABEL**.

The existing evidence is relatively **LOW QUALITY**.

Importance of **CAREFUL AND ONGOING RISK–
BENEFIT ASSESSMENTS** and close monitoring when
prescribing medications for StUD. Clinicians should
**MONITOR MEDICATION ADHERENCE AND
NONMEDICAL USE** through strategies such as frequent
clinical contact, drug testing, pill counts, and prescription
drug monitoring program (PDMP) checks.

The ASAM/AAAP
CLINICAL PRACTICE GUIDELINE ON THE

Management of Stimulant Use Disorder



ASAM American Society of
Addiction Medicine



AAP American Academy of
Addiction Psychiatry



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LE LINEE GUIDA

NON-PSYCHOSTIMULANT MEDICATIONS

(+ mirtazapine 30-60 mg/die for ATS use disorder)

- BUPROPION 150-300 mg/die
(+ naltrexone for ATS use disorder)
- TOPIRAMATE 150-200 mg/die

PSYCHOSTIMULANT MEDICATIONS

(+ methylphenidate 20-72 mg/die for ATS use disorder)

- MODAFINIL 200-400 mg/die
- TOPIRAMATE AND
EXTENDED-RELEASE MIXED
AMPHETAMINE SALTS (MAS-
ER) 100+60 mg/die
- AMPHETAMINE
FORMULATIONS 60 mg/die



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LE LINEE GUIDA

CO-OCCURRING DISORDERS: PSYCHOSIS OR MANIA

Clinicians should **TREAT StUD AND ANY CO-OCCURRING PSYCHIATRIC DISORDERS CONCURRENTLY**.

Clinicians should generally avoid use of psychostimulant medications to treat StUD in patients with histories of psychosis, whether substance-induced or preexisting. Similarly, clinicians should generally avoid use of psychostimulant medications to treat StUD in patients with histories of stimulant-induced mood disorders.

If stimulant-induced psychosis or mania is suspected, clinicians should consider a **GRADUAL TAPER OFF ANTIPSYCHOTIC MEDICATION AFTER A PERIOD OF REMISSION OF PSYCHOTIC SYMPTOMS** (Moderate certainty, Strong Recommendation).



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LE LINEE GUIDA

CO-OCCURRING DISORDERS: ADHD

Clinicians should address ADHD symptoms as part of the treatment of StUD.

Clinicians should consider prescribing **PSYCHOSTIMULANT MEDICATIONS** to manage ADHD when the benefits of the medication outweigh the risks.

For adolescent and young adult patients, clinicians should additionally consider arranging for a parent, health professional or other trusted adult to **DIRECTLY OBSERVE ADMINISTRATION OF THE MEDICATION** (Clinical consensus, Strong Recommendation).

Use of **EXTENDED-RELEASE OR PRODRUG FORMULATIONS** can mitigate risks related to misuse and the addictive potential of prescription stimulants by producing less rapid onset of effect, maintaining more steady serum levels of medication, and/or preventing or reducing effects when alternative routes of administration are used.



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DEI DIPARTIMENTI E DEI SERVIZI DELLE DIPENDENZE

LE LINEE GUIDA

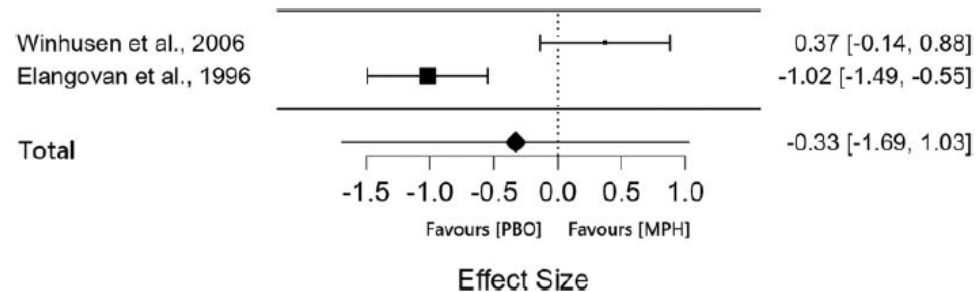
POPULATION-SPECIFIC CONSIDERATIONS: ADOLESCENTS AND YOUNG ADULTS

Adolescents with ADHD are at increased risk for SUD. **PHARMACOLOGICAL TREATMENT** of ADHD in this population, including with psychostimulant medications, **REDUCES THE RISK FOR DEVELOPMENT OF SUD**.

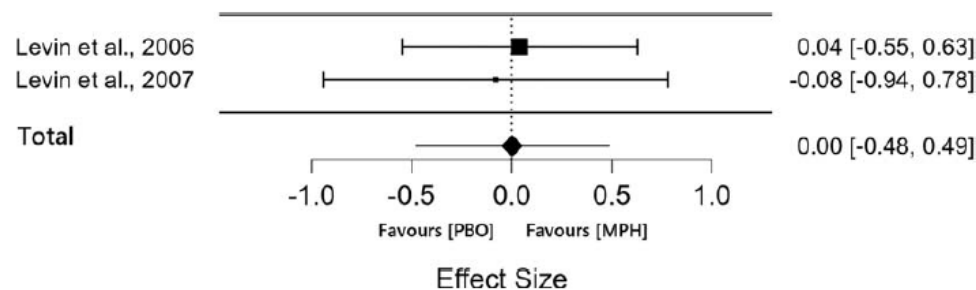
Data are limited on the **POTENTIAL BENEFITS AND HARMS OF DRUG TESTING** for adolescents and young adults with StUD. Testing could be utilized when the outcome would impact clinical decision-making or be important for medication monitoring or psychiatric follow-up. Clinicians should consider the technical limitations of the selected matrix and drug panel.

While adolescent and young adult patients with StUD can present with a range of co-occurring mental health conditions (eg, depression, anxiety), clinicians should pay particular attention to signs or symptoms of **ADHD AND EATING DISORDERS**, as these are particularly common comorbidities in these populations.

Forest plot for the meta-analysis of **craving for cocaine**.



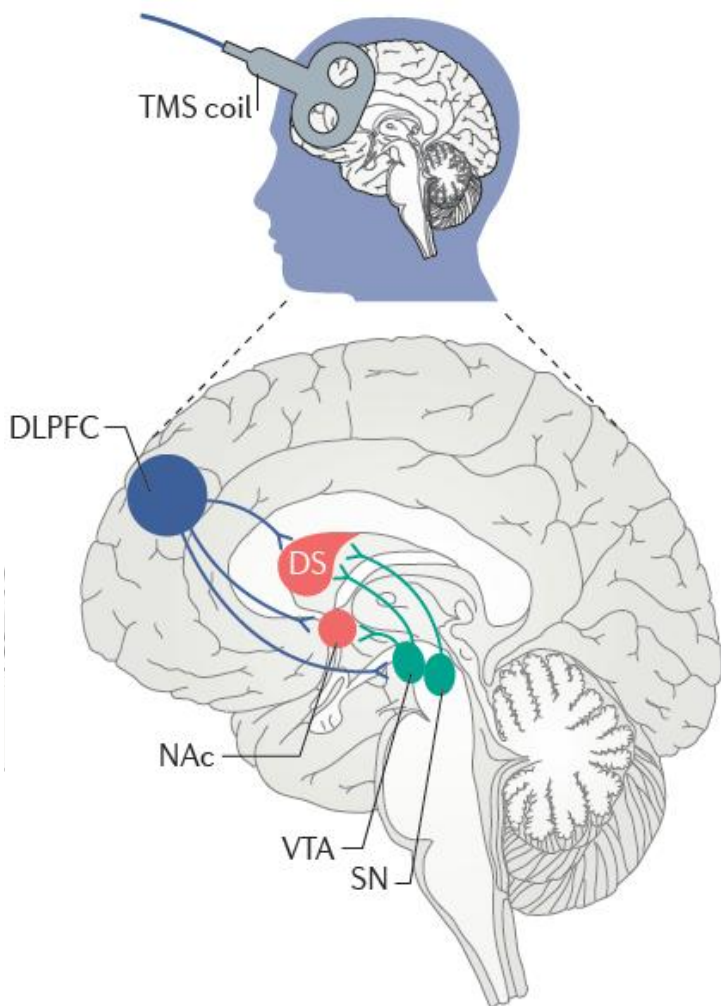
Forest plot for the of the % of pts who could remain **abstinent for at least 2 weeks**.



CONCLUSION

The current evidence on the use of MPH for the treatment of CUD remains **INCONCLUSIVE**, due to limited number and high heterogeneity of the studies. Nevertheless, considering the extensive use of MPH, its tolerability in clinical practice, and the lack of approved treatments for CUD, future research should further investigate its efficacy in patients with Stimulant Use Disorder.

There might be a rationale for MPH in **patients with CUD and ADHD**, which should be carefully assessed with rigorous clinical studies in this specific population.



Included Studies/Protocols Stratified According to the Type of Brain Stimulation and Substance They Focused on.

Condition	TMS	tDCS	tACS	DBS	VNS	Multiple	Total	%
Alcohol	23	19	1	6	1	–	50	30.7
Opioid	14	5	–	10	1	1 ^a	31	19.0
Nicotine	20	8	–	–	–	–	28	17.2
Cocaine	12	5	–	1	–	–	18	11.0
Cannabis	13	4	–	–	–	–	17	10.4
Any stimulant ^b	12	1	–	1	–	–	14	8.6
Multiple	2 ^{c,d}	2 ^{e,f}	–	–	–	1 ^g	5	3.1
Total	96	44	1	18	2	2	163	100.0
%	58.9	27.0	0.6	11.0	1.2	1.2	100.0	–

TMS, transcranial magnetic stimulation; tDCS, transcranial direct-current stimulation; tACS, transcranial alternating current stimulation; DBS, deep brain stimulation; VNS, vagus nerve stimulation.

^aTMS, tDCS.^bIncludes 10 studies focused only on amphetamine/methamphetamine.^cAlcohol, opioid, cocaine.^dAlcohol, cocaine.

^eAny substance (not limited to specific few).

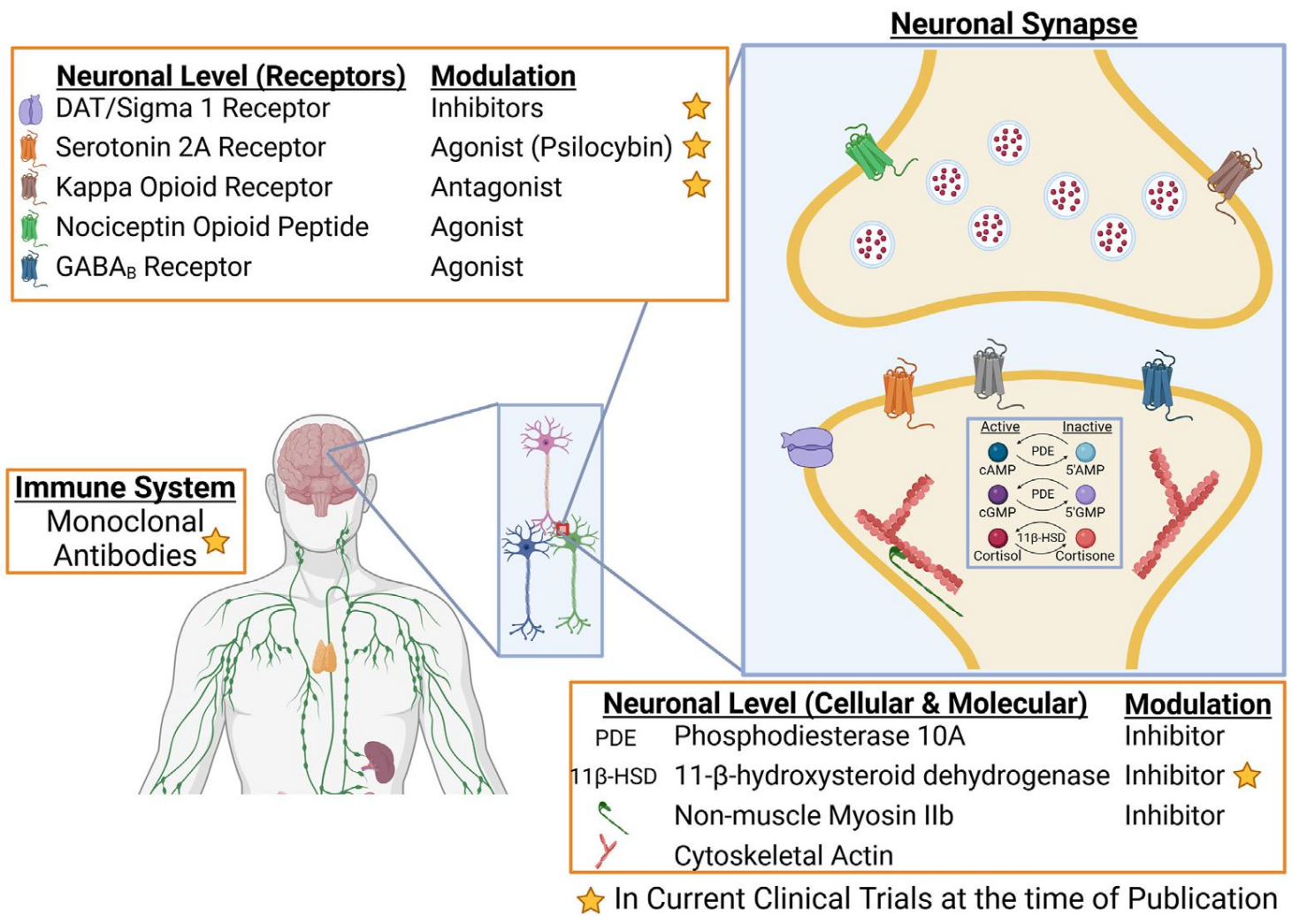
^fAlcohol, stimulants.

^gNicotine, opioid: DBS, tDCS.



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CONCLUSIONI

- Valutazione del/dei tipo/i di stimolante/i assunto/i
- Valutazione dei quadri di poliabuso
- Valutazione di eventuali comorbidità psichiatriche e organiche
- **Setting di trattamento**
- Conoscenza e applicazione delle linee guida disponibili
- **Interventi psicoterapeutici e socio-educativi**
- Nuovi approcci (realtà virtuale, rTMS)
- Applicazione di interventi di Riduzione del Danno



Grazie!!!

UNA DOMANDA SENZA RISPOSTE? TOSSICOLOGIA CLINICA DEGLI PSICO STIMOLANTI

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