

***LA DEPRESSIONE IN
COMORBILITÀ CON
DISTURBO DA USO DI
SOSTANZE***

SERGIO DE FILIPPIS

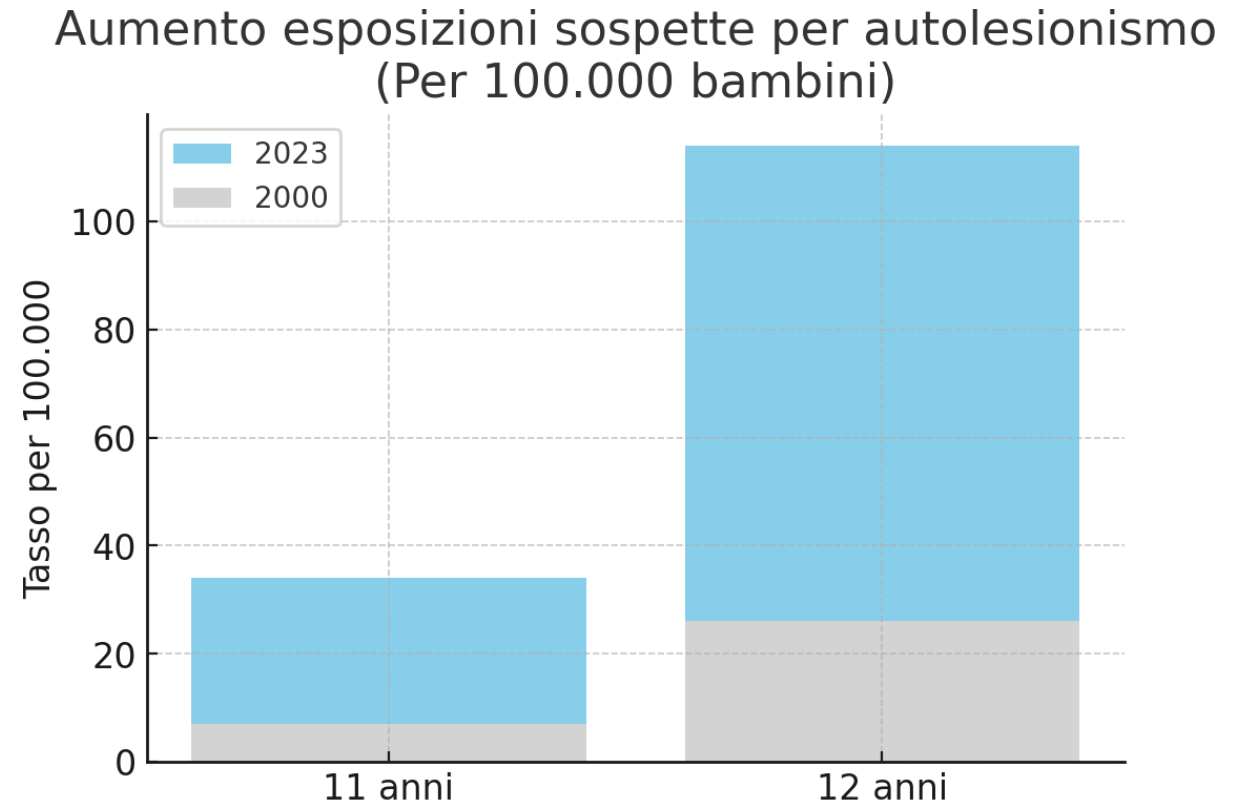


Esposizioni A Sostanze E Autolesionismo Nei Preadolescenti

- Studio basato su dati dei Poison Centers USA (2000–2023)
- Popolazione: bambini 6–12 anni
- Obiettivo: valutare le esposizioni a sostanze legate ad autolesionismo
- +54% chiamate per esposizioni a sostanze
- <6 anni: esposizioni perlopiù accidentali
- 6–12 anni: cresce ingestione intenzionale (esperimenti, autolesionismo)
- Esposizioni sospette per autolesionismo/suicidio:
 - – +400% negli 11enni (7 → 34 per 100.000)
 - – +350% nei 12enni (26 → 114 per 100.000)
 - Percentuali non intenzionali: 95% (6 anni) → 59% (12 anni)

Esposizioni A Sostanze E Autolesionismo Nei Preadolescenti

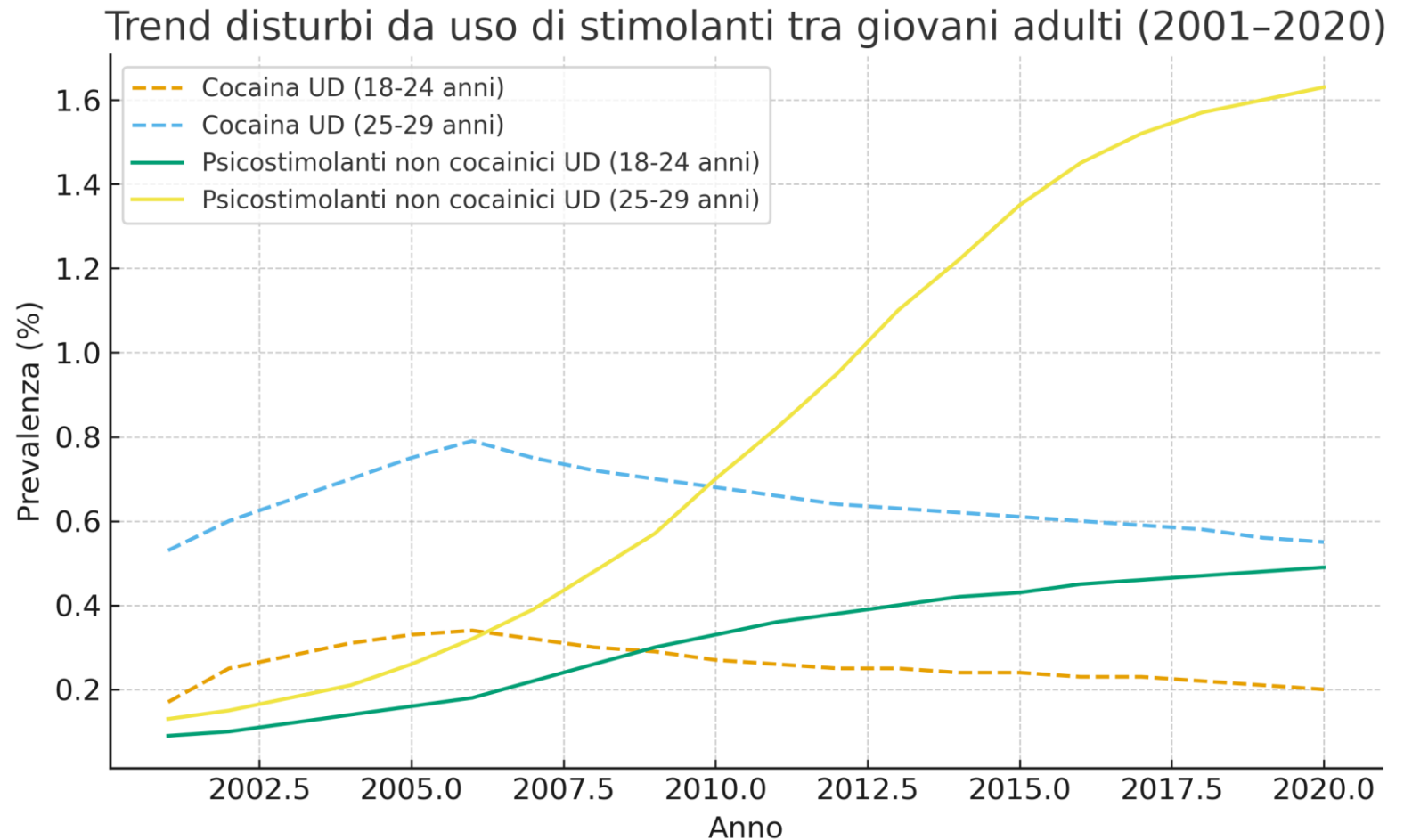
- Analgesici (i più frequenti)
- Antistaminici
- Farmaci per tosse e raffreddore
- Stimolanti e droghe da strada
- Luogo prevalente: domicilio



Disturbi da uso di stimolanti in adolescenti e giovani adulti (2001–2020)

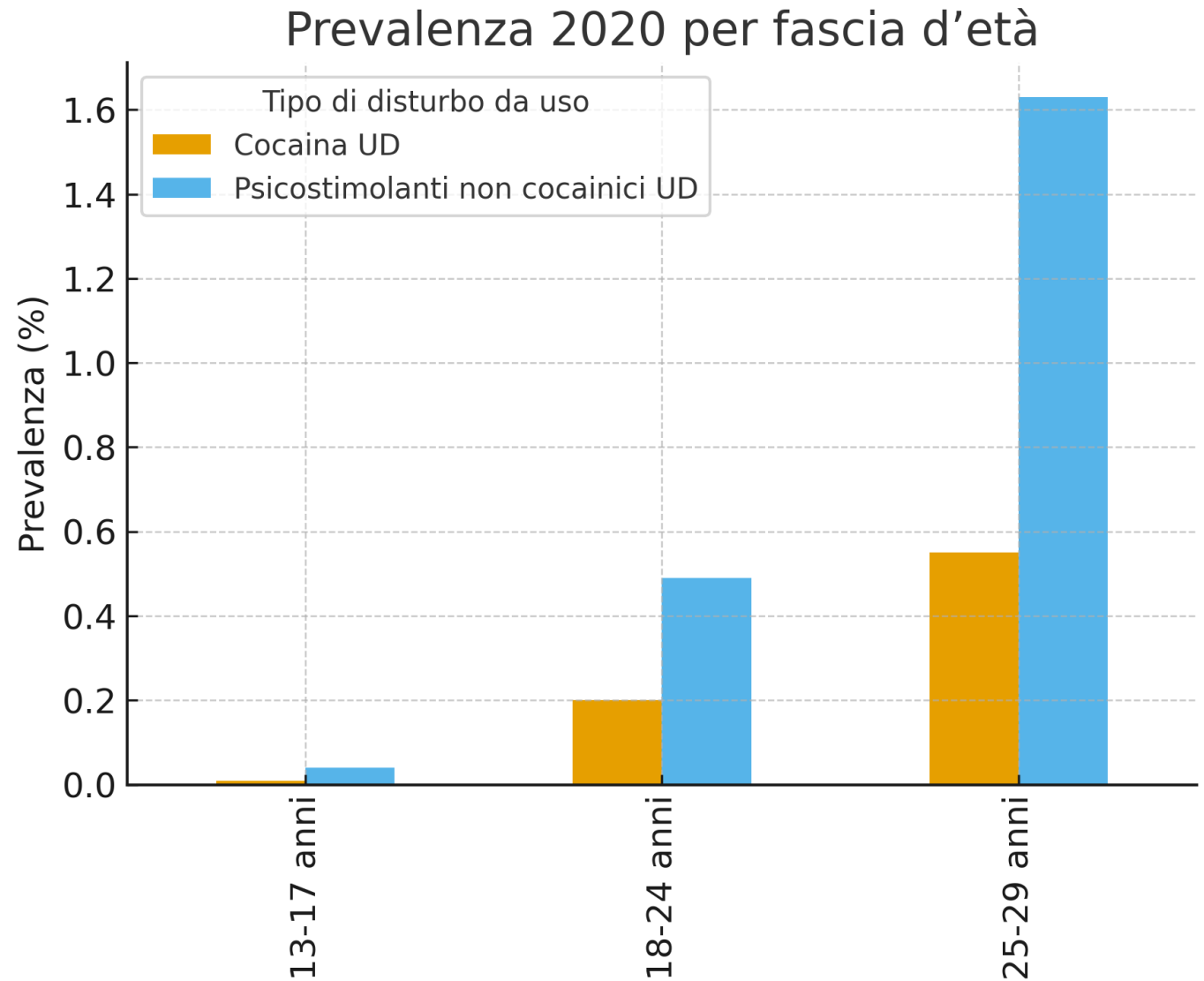
- **Bushnell et al., JAMA Psychiatry, 2025**

- **Incremento 12 volte maggiore del disturbo da uso di psicostimolanti non cocainici nei 25–29 anni (0,13% → 1,63%).**

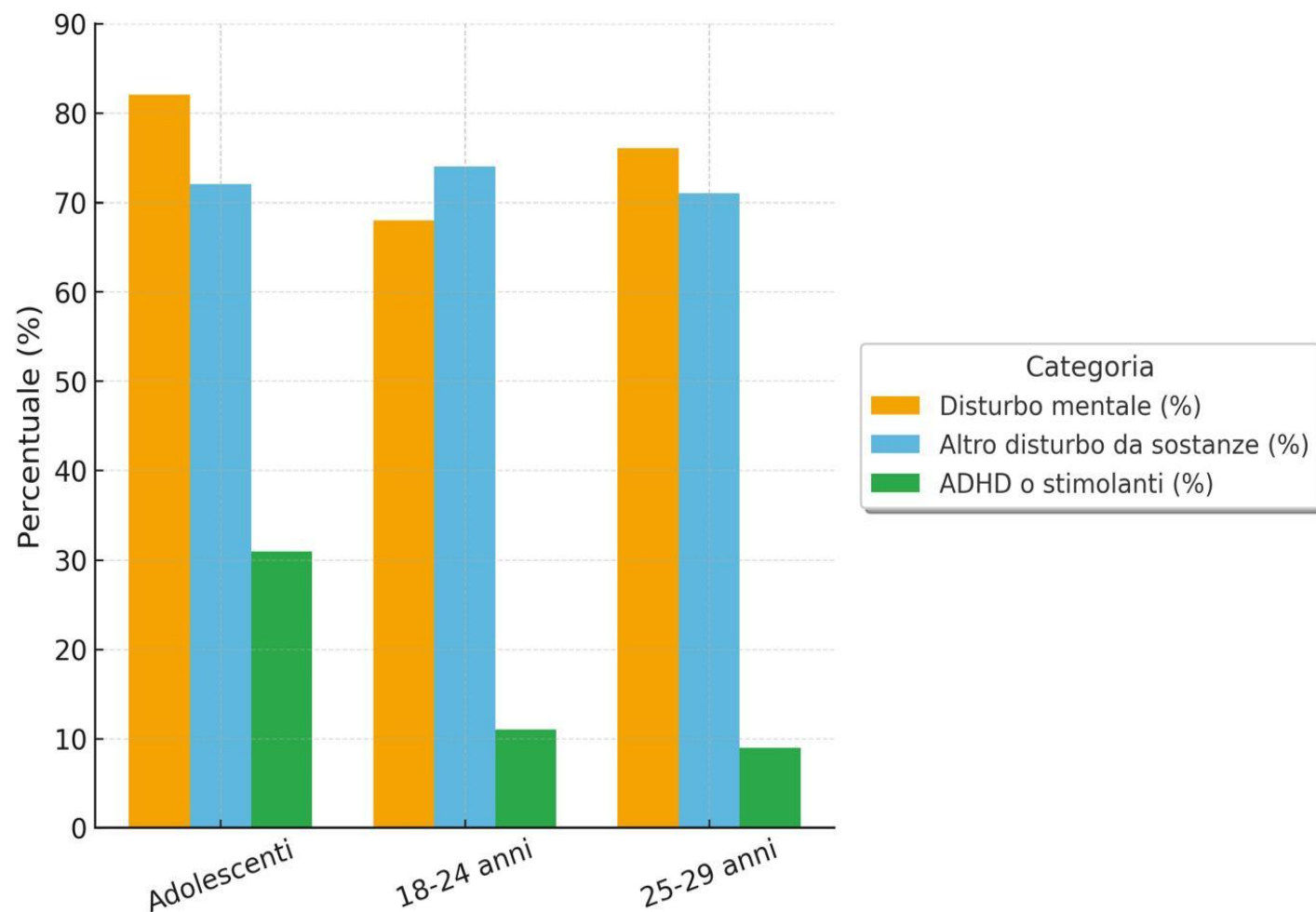


Disturbi da uso di stimolanti in adolescenti e giovani adulti (2001–2020)

- Bushnell et al., JAMA Psychiatry, 2025



Comorbidità nei soggetti con disturbo da uso di stimolanti (2025)



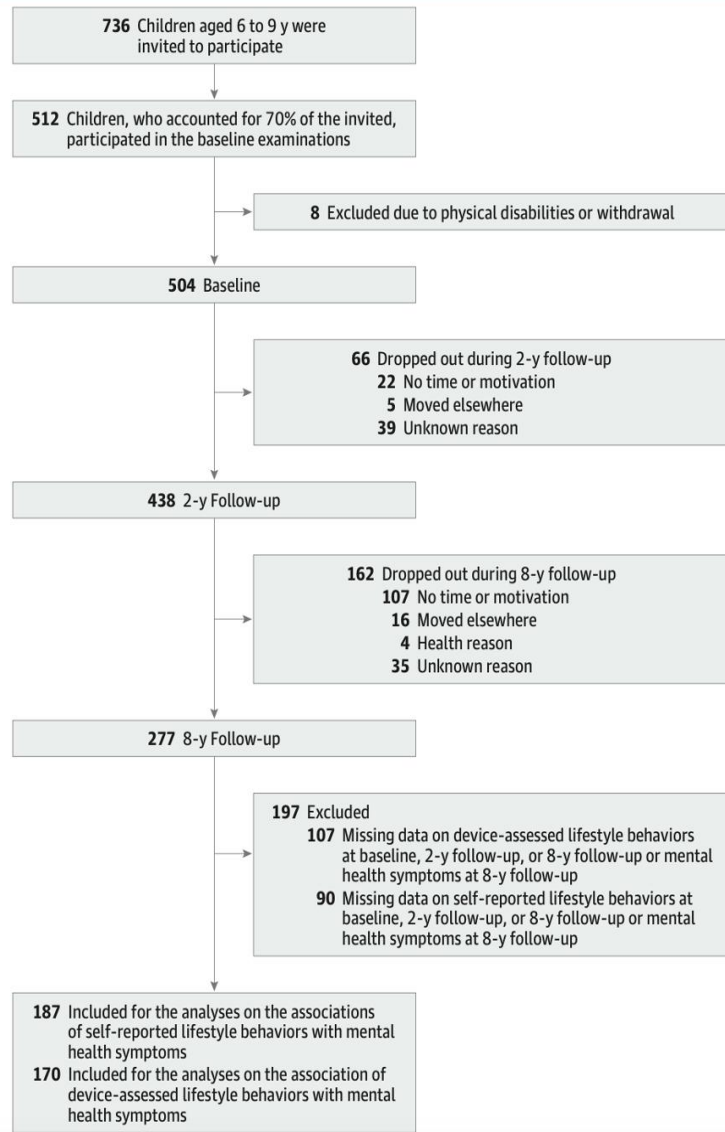
- 68–82% con disturbo mentale comorbido, 72–78% con altro SUD.
- 89,5% dei giovani adulti con SUD non ha diagnosi o prescrizione di ADHD.

Bushnell et al., JAMA Psychiatry, 2025

***Disagio,
Vulnerabilità,***



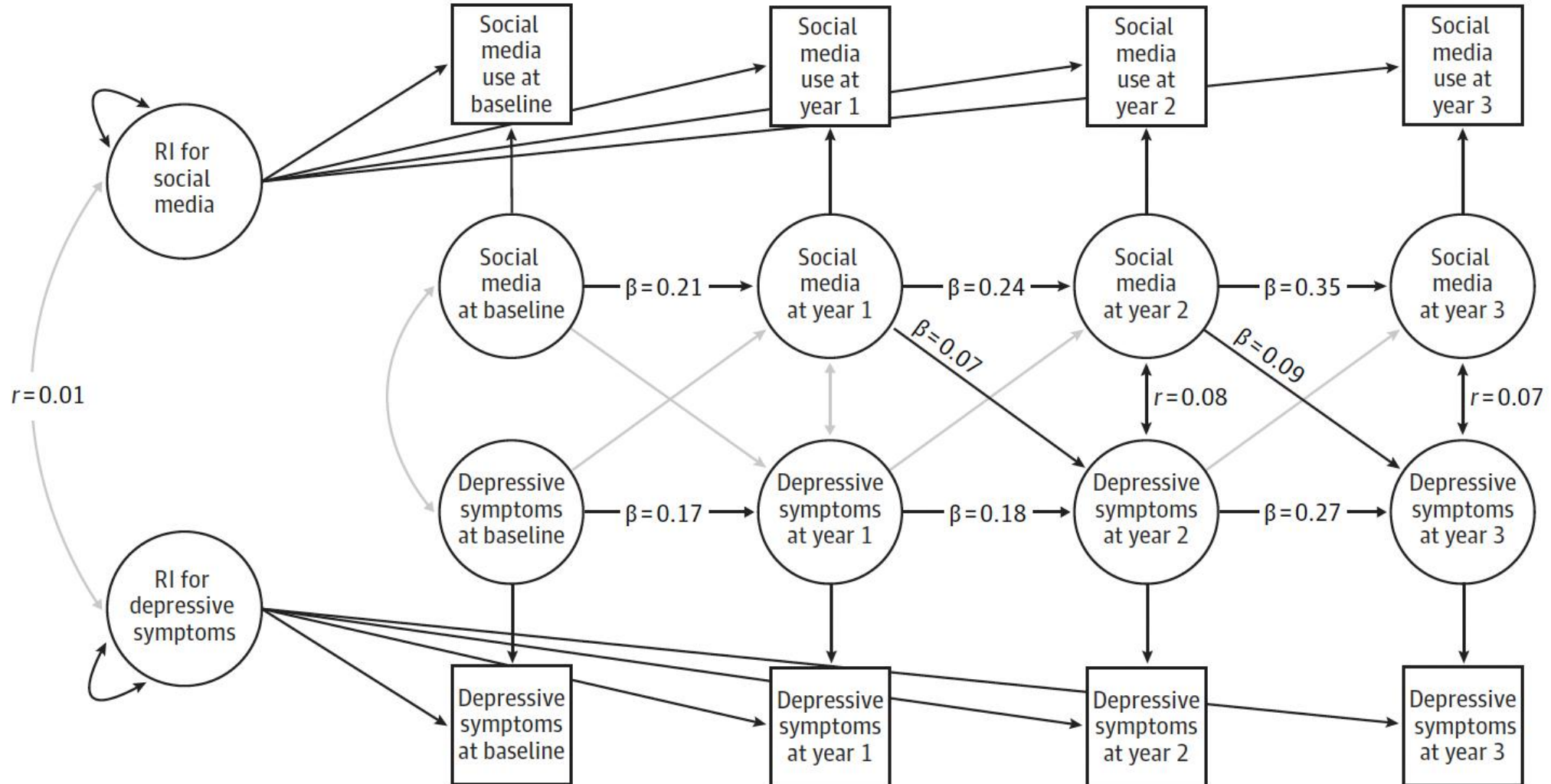
Childhood Lifestyle Behaviors and Mental Health Symptoms in Adolescence



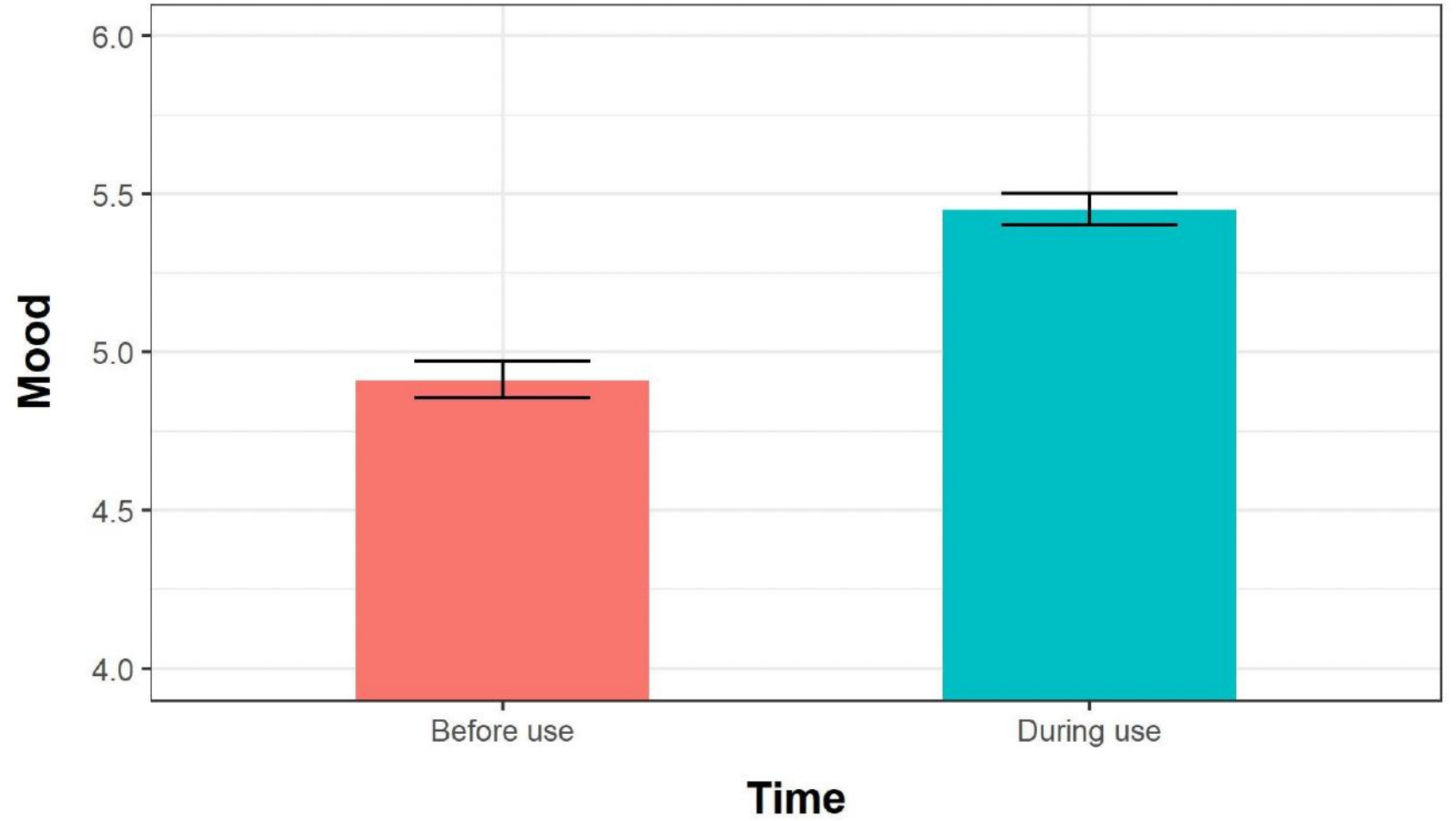
Self-reported lifestyle behaviors	Perceived stress score		Depressive symptoms score	
	β (95% CI) ^a	P value	β (95% CI) ^a	P value
Total physical activity, min/d	-0.15 (-0.30 to -0.01)	.04	-0.17 (-0.31 to -0.02)	.03
Unsupervised physical activity, min/d	-0.09 (-0.24 to 0.05)	.21	-0.14 (-0.29 to 0.01)	.06
Sports, min/d	-0.12 (-0.26 to 0.02)	.10	-0.11 (-0.26 to 0.03)	.13
Supervised exercise, min/d	-0.15 (-0.29 to -0.01)	.04	-0.14 (-0.29 to -0.00)	.05
Total screen time, min/d	0.27 (0.13 to 0.41)	<.001	0.30 (0.15 to 0.44)	<.001
TV watching, min/d	0.10 (-0.04 to 0.24)	.16	0.10 (-0.04 to 0.24)	.16
Computer use, min/d	0.16 (0.01 to 0.30)	.03	0.15 (0.00 to 0.30)	.05
Mobile device use, min/d	0.28 (0.16 to 0.41)	<.001	0.33 (0.19 to 0.46)	<.001
Baltic Sea Diet Score	-0.11 (-0.25 to 0.03)	.11	-0.08 (-0.23 to 0.06)	.25
Device-assessed lifestyle behaviors				
Sedentary time, min/d	-0.04 (-0.18 to 0.11)	.61	0.01 (-0.14 to 0.16)	.89
Light physical activity, min/d	0.02 (-0.14 to 0.18)	.76	0.03 (-0.13 to 0.20)	.68
Moderate to vigorous physical activity, min/d	0.09 (-0.11 to 0.29)	.40	-0.04 (-0.24 to 0.16)	.69
Vigorous physical activity, min/d	0.11 (-0.11 to 0.32)	.34	-0.04 (-0.26 to 0.18)	.74
Physical activity energy expenditure, min/d	0.11 (-0.07 to 0.28)	.23	-0.01 (-0.19 to 0.17)	.90
Sleep duration, min/d	-0.09 (-0.25 to 0.06)	.24	-0.08 (-0.24 to 0.07)	.29

Social Media Use and Depressive Symptoms During Early Adolescence

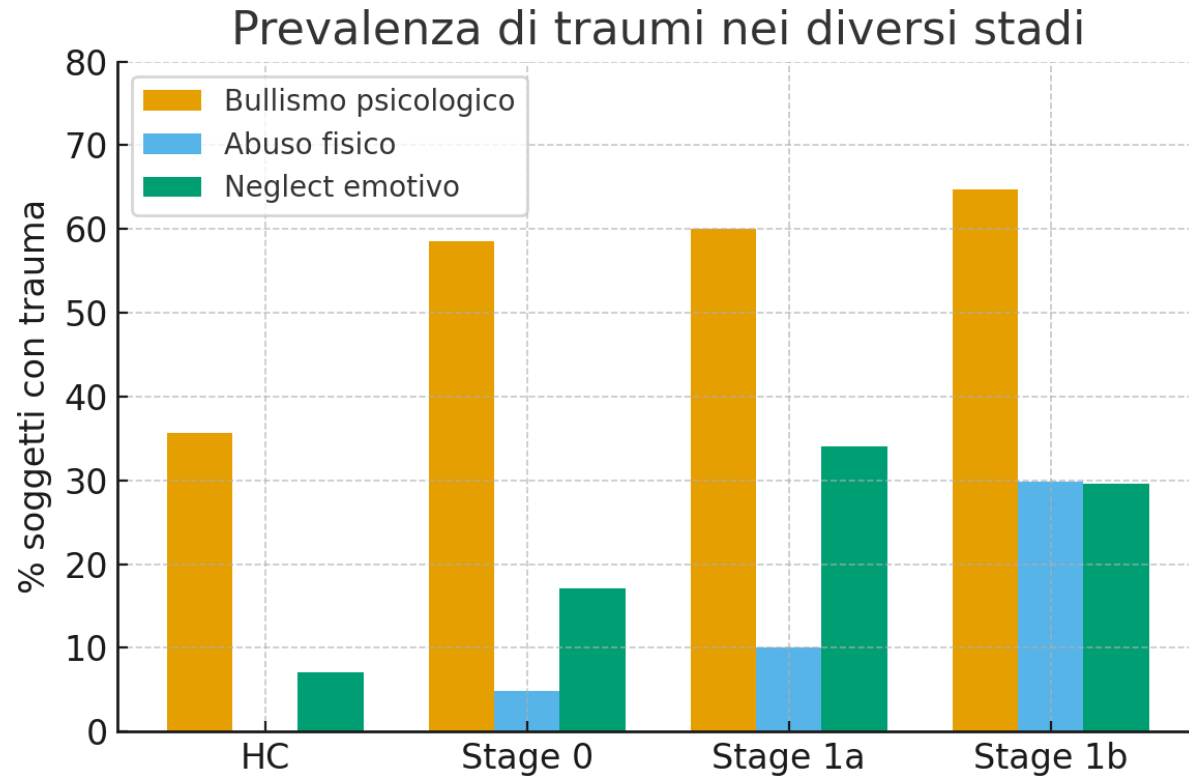
Nagata JM, Otmar CD, Shim J,Kiss O, He J, Baker FC.. JAMA Netw Open. 2025



***Real-world
Adolescent
Smartphone Use
Is Associated With
Improvements In
Mood: An
Ecological
Momentary
Assessment Study***



Trauma in Youth At-Risk for Serious Mental Illness



- Stimare prevalenza, impatto percepito e durata dei traumi <18 anni

Campione (n = 243, 12–25 anni):

- Stage 0 (rischio, asintomatici) = 41
- Stage 1a (sintomi lievi ansioso-depressivi) = 52
- Stage 1b (sindromi attenuate: CHR psicosi, umore moderato) = 108

Development and psychometric properties of the "Suicidality: Treatment Occurring in Paediatrics (STOP) Risk and Resilience Factors Scales" in adolescents

Rodríguez-Quiroga
A, Flamarique I,
Arango C, Santosh P;
STOP Consortium.
Eur Child Adolesc
Psychiatry. 2020

Exploratory factor analysis for the adolescent, parent, and clinician version of the STOP-SRiFS and STOP-SReFS

STOP-SRiFS	Anxiety and depression risk	Substance misuse risk	Interpersonal risk	Chronic risk	Risk due to life events
<i>Adolescent</i>					
Depressive thinking	0.960	– 0.076	– 0.011	0.001	– 0.057
Pessimism	0.928	0.007	0.028	– 0.091	– 0.003
Low self-esteem	0.905	0.009	0.017	– 0.126	0.080
Depressive mood	0.850	0.027	0.020	0.027	– 0.090
Anxiety	0.780	0.036	– 0.075	0.139	– 0.015
Worrying about school performance	0.472	0.036	0.127	0.026	0.091
Misuse of Cannabis	0.000	0.881	– 0.027	– 0.039	– 0.087
Smoking	0.073	0.810	– 0.096	0.066	0.019
Exaggerated use of alcohol	– 0.002	0.598	0.076	– 0.170	0.092
Misuse of other drugs	– 0.025	0.396	0.019	– 0.028	0.088
Relationship breakup	– 0.090	0.345	0.318	0.187	– 0.132
Searching Internet sites about suicide	0.140	– 0.035	0.815	– 0.154	– 0.056
History of suicidal attempt	– 0.032	0.024	0.713	0.131	– 0.026
Bullying	0.133	– 0.115	0.247	0.137	0.128

Disregolazione affettiva



Concetto di sé
estremamente negativo



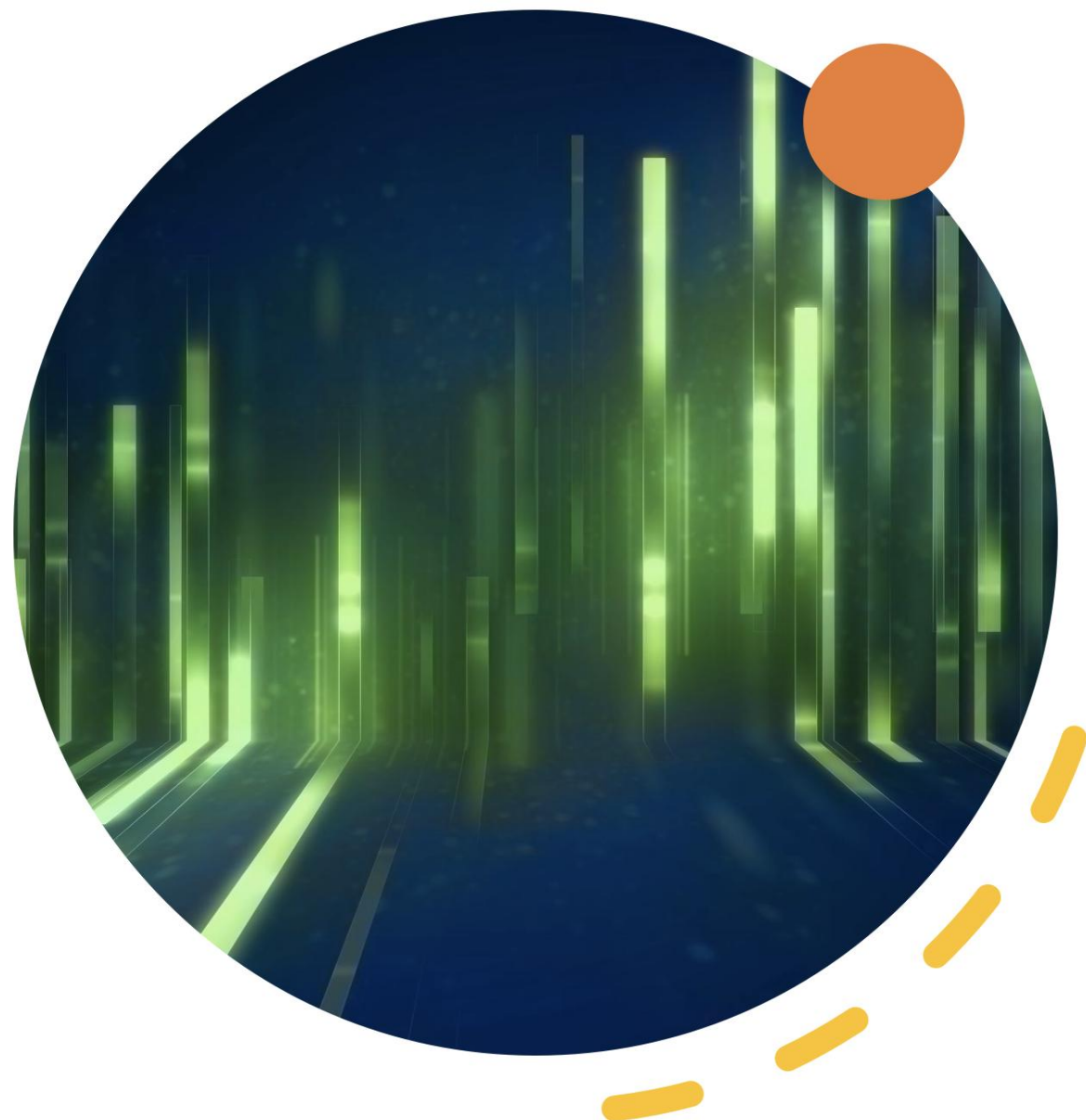
Difficoltà nel formare e
mantenere relazioni



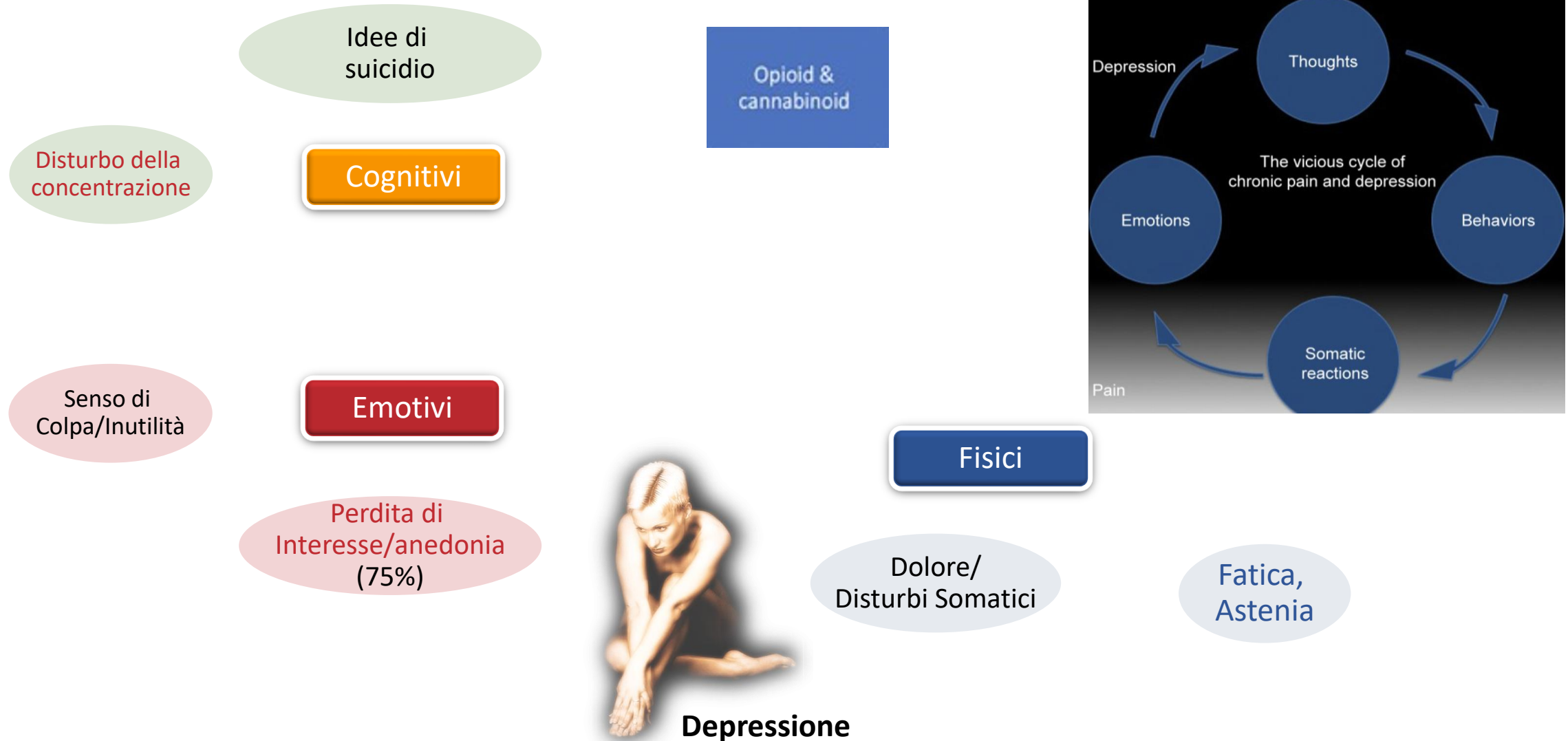
Depressione



Comportamenti
anticonservativi



Role of proinflammatory cytokines in dopaminergic system disturbances, implications for anhedonic features of MDD



Altered Task-Evoked
Corticolimbic
Responsivity in
Generalized Anxiety
Disorder

Increased reactivity in GAD to
negative stimuli but decreased
reactivity associated with
cognitive control of emotion

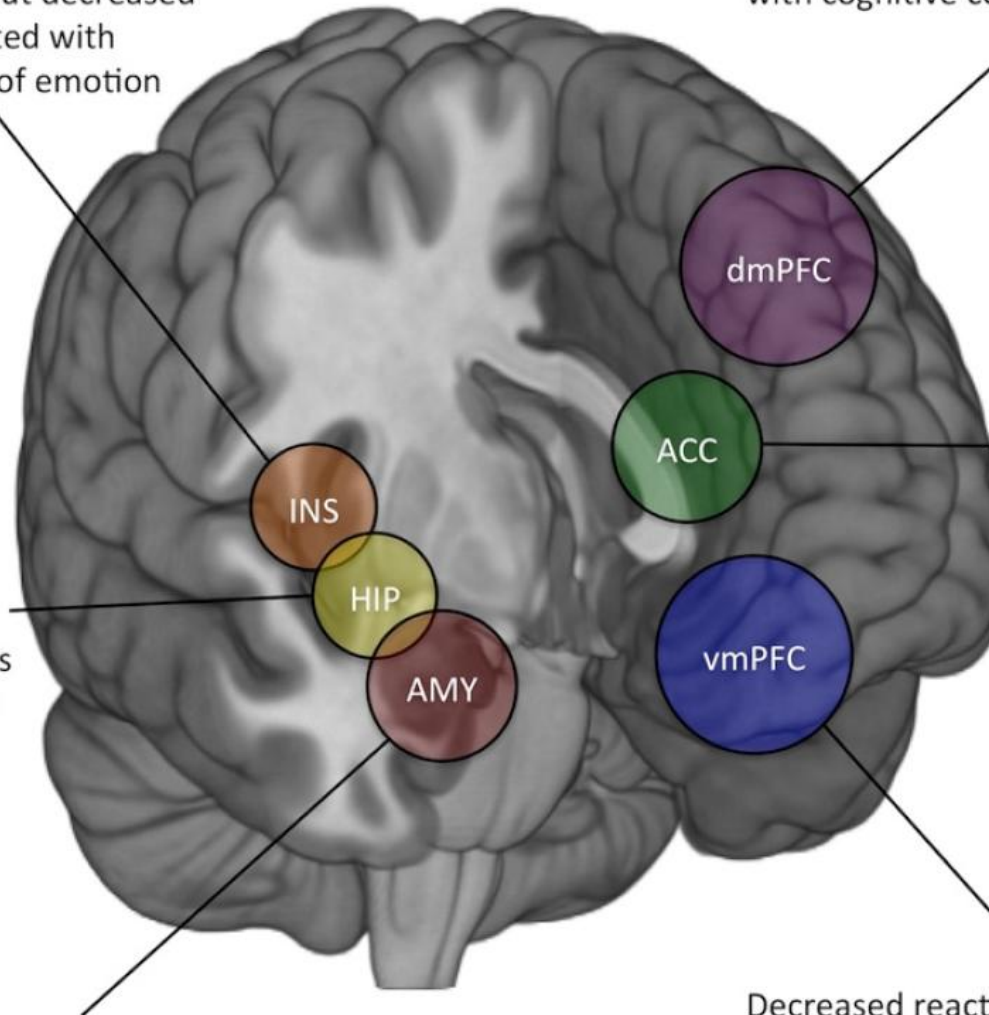
Decreased reactivity in GAD associated
with cognitive control of emotion

Decreased
reactivity in GAD
to threat signals
but mixed findings
for memory tasks

Increased reactivity
in GAD to worry
induction but
decreased reactivity
to most other tasks

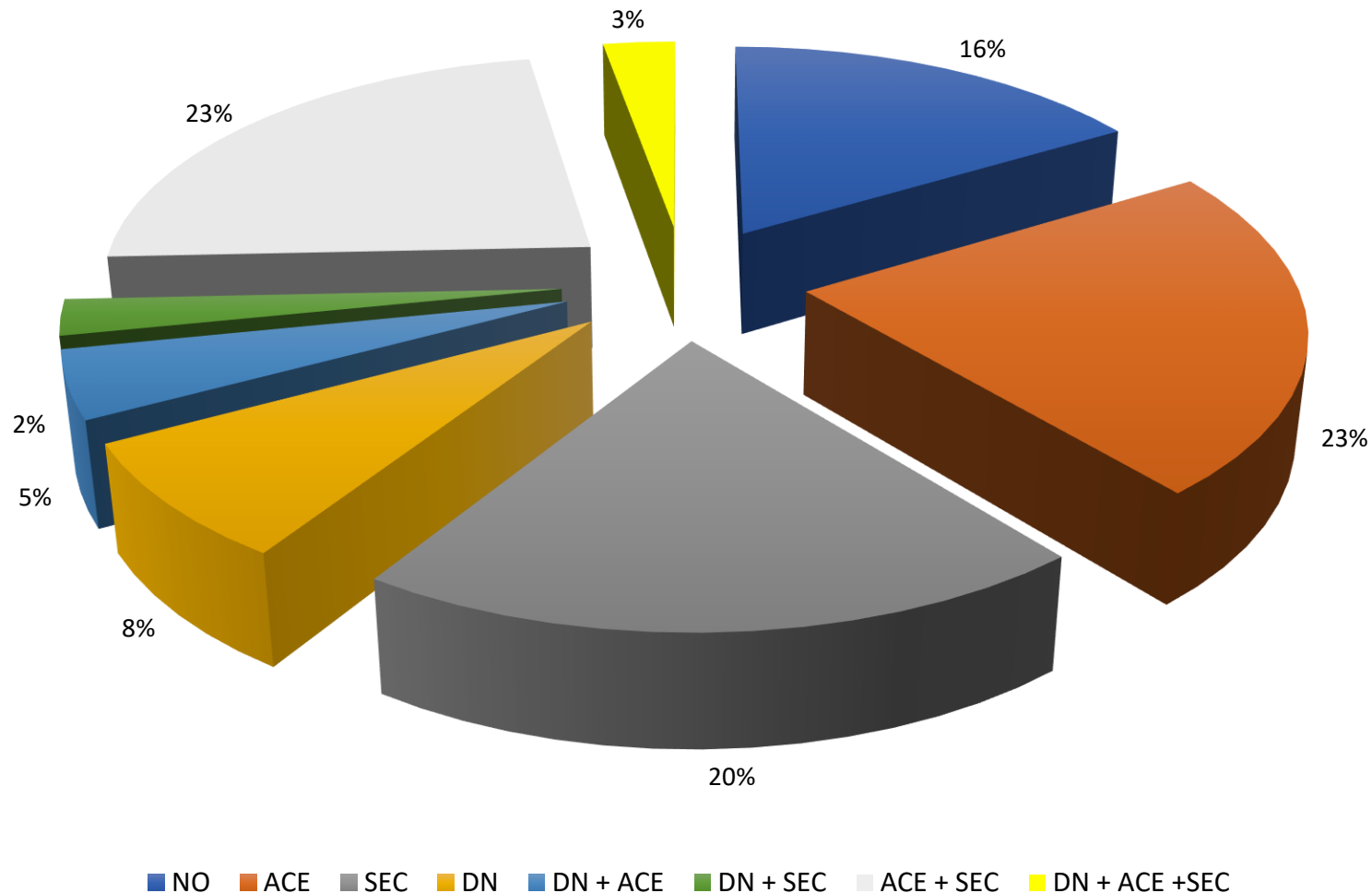
Increased reactivity in GAD with mixed findings

Decreased reactivity in GAD associated
with overgeneralization of learned fear

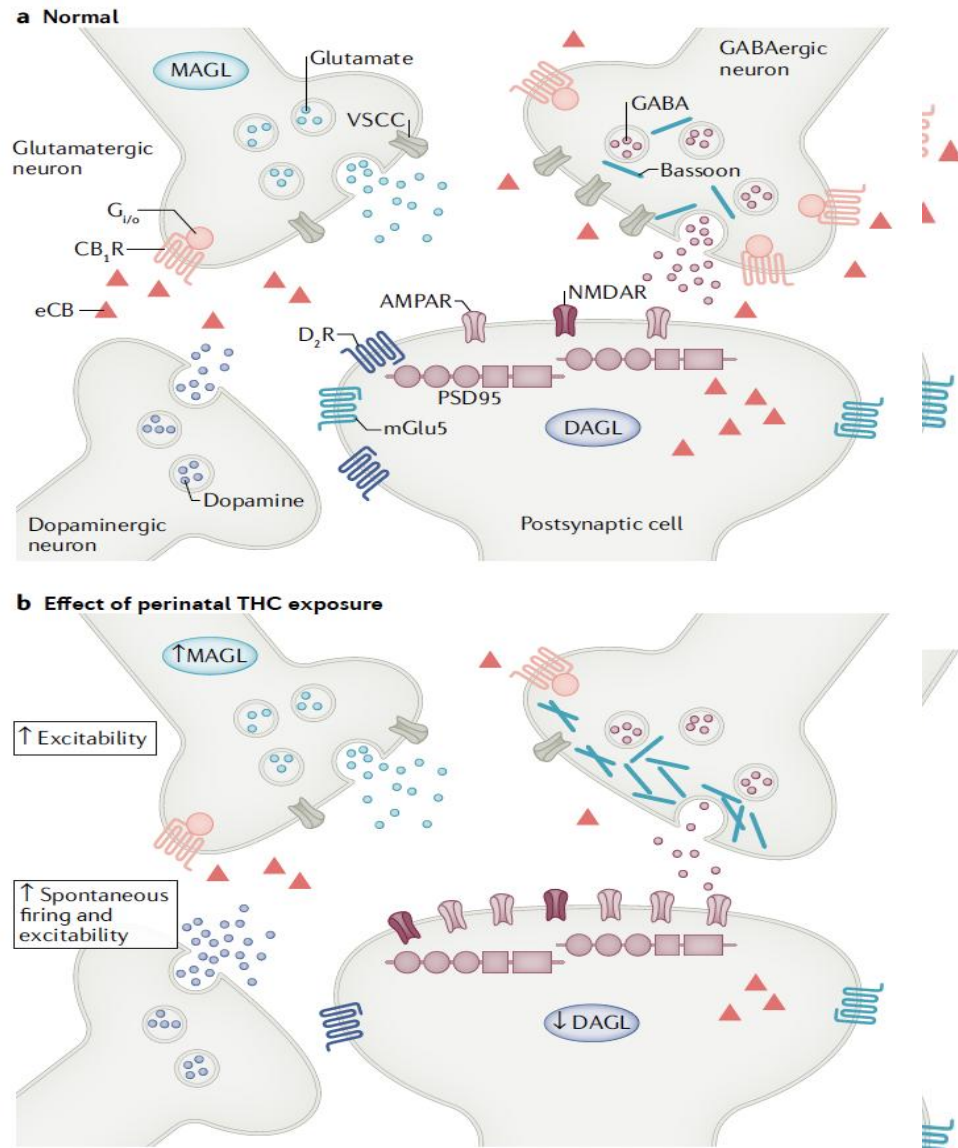


A comprehensive evaluation of adverse childhood experiences, social-emotional impairments, and neurodevelopmental disorders in cannabis-use disorder: Implications for clinical practice

***Trovini,..... De Filippis,
European Psychiatry 2023***

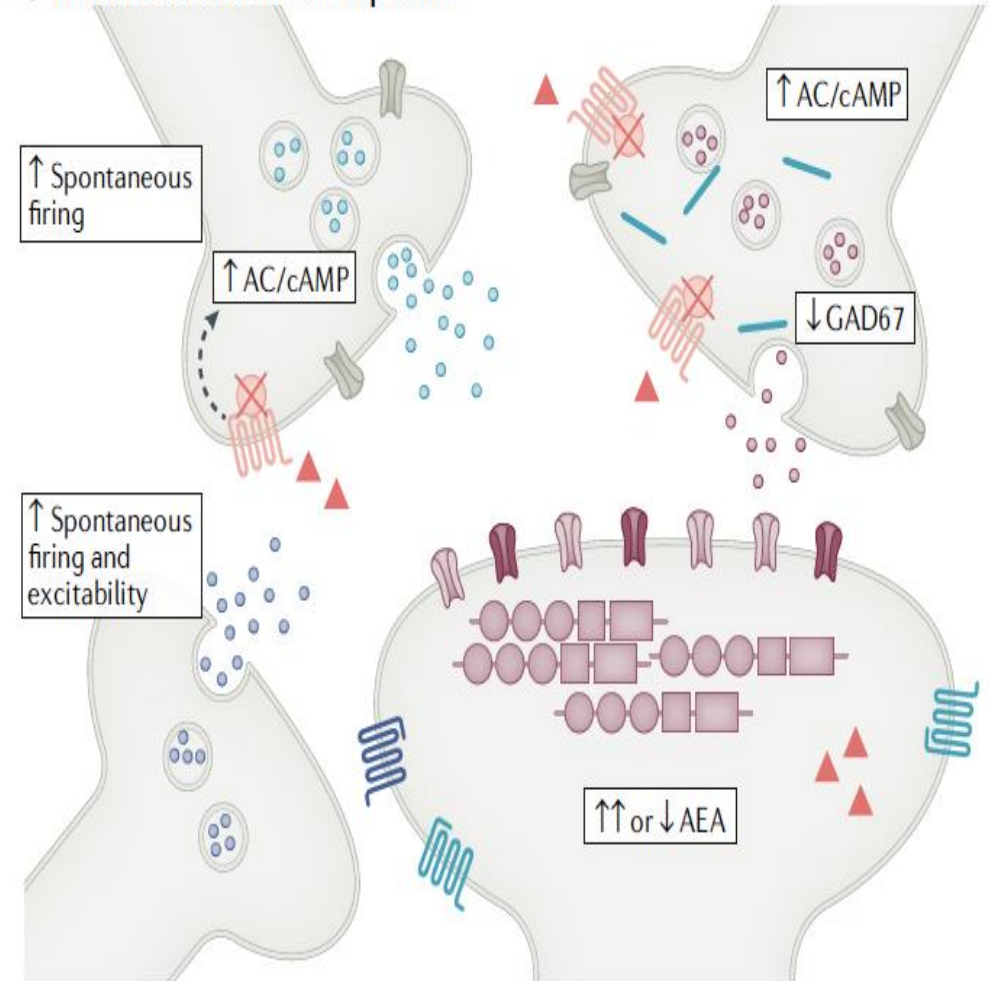


Cannabis And Synaptic Reprogramming Of The Developing Brain



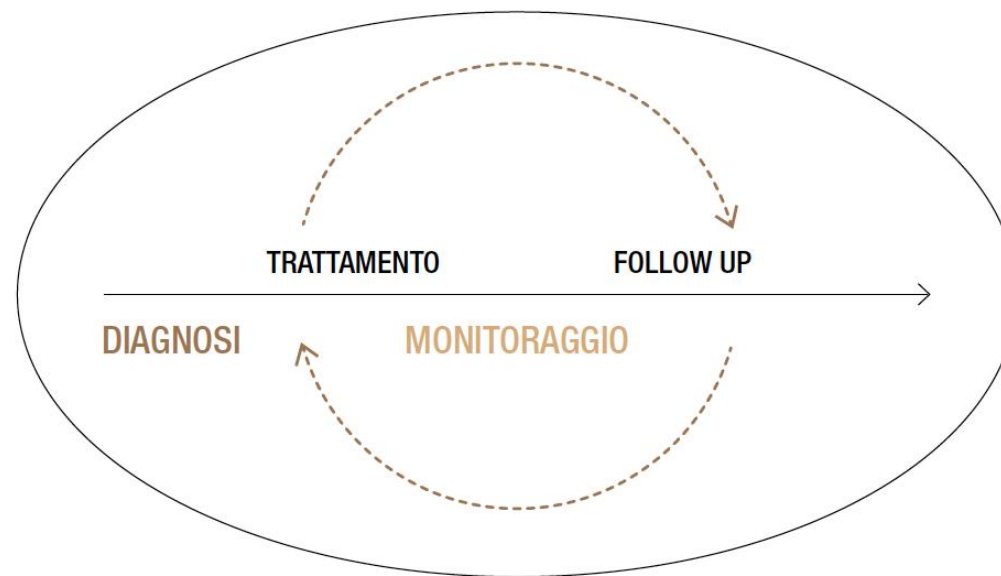
Effect of adolescent THC exposure

c Effect of adolescent THC exposure



Moos RH, Moos BS, Andrassy JM.
Psychiatr Serv. 1999 Dec

La Presa In Carica E La Cura Dei Pazienti Con DUA

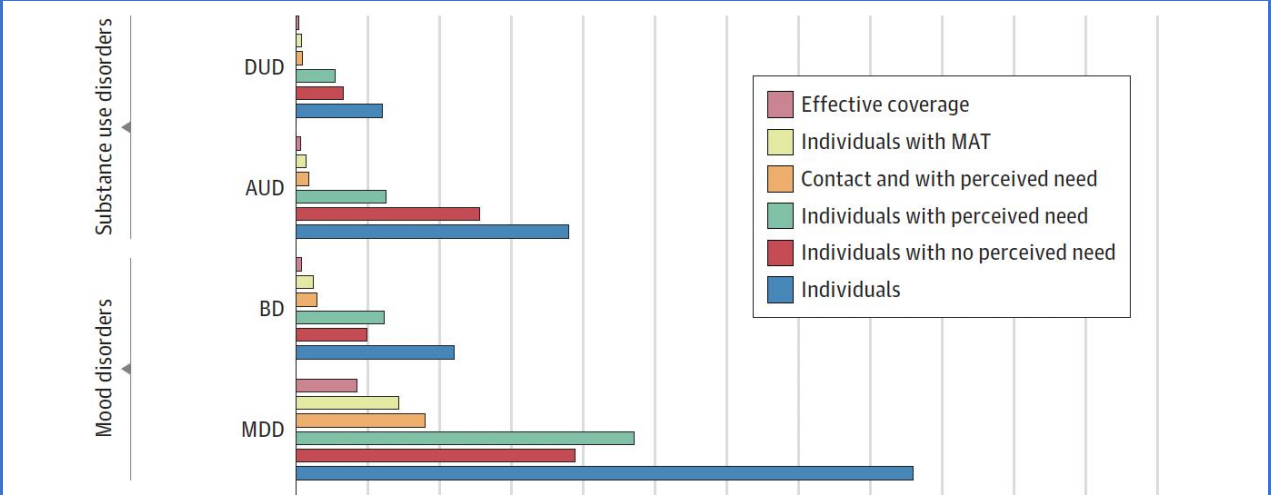
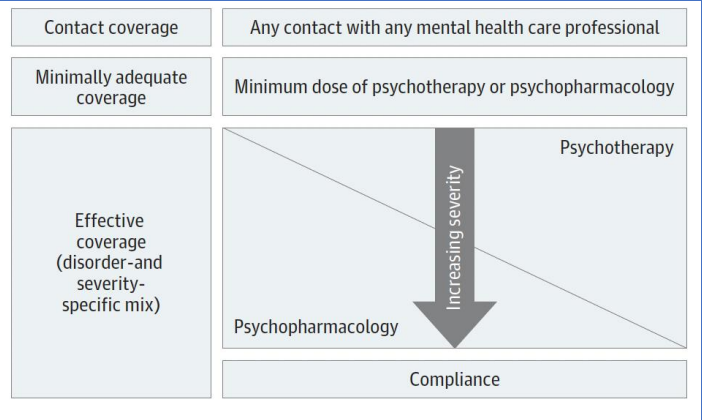


MDE severity*	Summary recommendations for initial treatment selection
Mild with low safety risk.	• Psychotherapy and pharmacotherapy demonstrate similar benefits . – Psychotherapy (if readily accessible) is preferred because of fewer risks . • Exercise, certain CAM treatments, or guided DHIs may be considered as monotherapy, especially if preferred by patients .
Moderate, with low-moderate safety risk.	• Initial choice is between pharmacotherapy and psychotherapy . – Pharmacotherapy is slightly more efficacious in reducing depressed mood, guilt, suicidal thoughts, anxiety, and somatic symptoms during acute treatment . – Structured psychotherapy, specifically CBT, is slightly more efficacious in the medium-term (6–12 months) . • Combination of pharmacotherapy and psychotherapy may be considered . • Exercise, certain CAM treatments and/or DHIs may be considered as adjuncts to psychotherapy and/or pharmacotherapy, especially if preferred by patients .
Severe, with moderate to high safety risk.	• For severe MDE without psychotic symptoms, use a combination of pharmacotherapy and psychotherapy . • For severe MDE with psychotic symptoms, use a combination of antidepressant and antipsychotic medication . • For very severe and/or life-threatening situations, consider electroconvulsive therapy .



Visione negativa di sé	Visione negativa del mondo	Visione negativa del futuro (pessimismo)
• Inadeguato • Difettoso indesiderabile • Inutile • Carente di risorse • Sentimenti di autobiasimo e autocritica • Incapace di raggiungere le mete prefissate, di godere di buona salute, di avere una buona posizione sociale, di essere in grado di suscitare interesse nelle persone che lo circondano	• Sconfitte • Privazioni • Denigrazioni • Umiliazioni • Senso di insopportabilità e irrisolvibilità dei problemi quotidiani • Scherno e disprezzo in ciò che le altre persone dicono sul suo conto	• Pieno di frustrazioni e di difficoltà • Inevitabile prolungamento della sofferenza • Revisione di una sicura sconfitta e un senso di inutilità (de-motivazione)

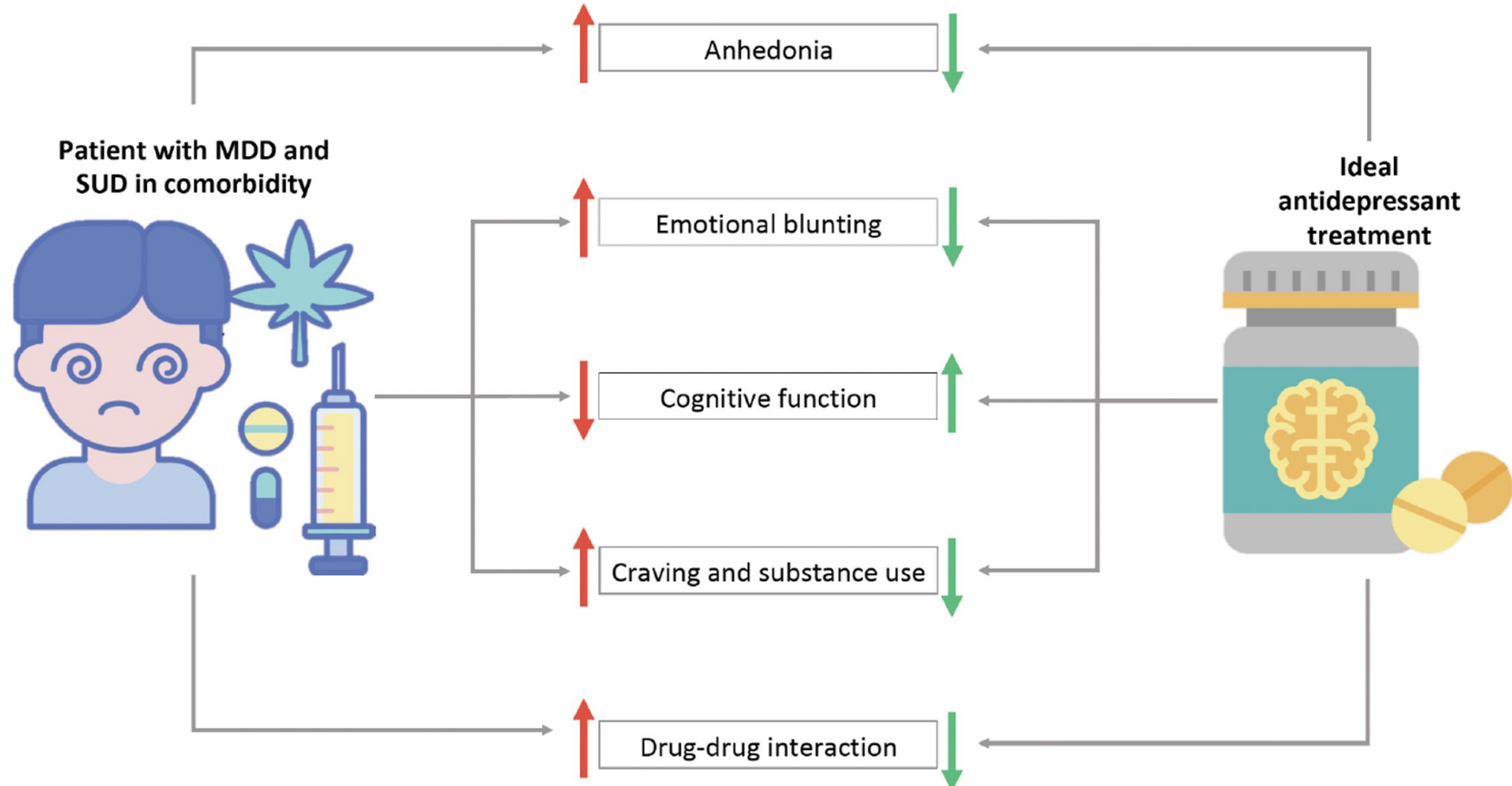
World Mental Health Survey Collaborators. Effective Treatment for Mental and Substance Use Disorders in 21 Countries



Campanelli D'allarme» Per La Salute Mentale Dei Ragazzi

- **Cambiamenti emotivi e comportamentali repentini che implicano:**
 - Incapacità di far fronte alle attività quotidiane con l'efficienza solita
 - Cambiamenti nel ritmo del sonno e/o delle abitudini alimentari
 - Stati d'animo negativi di lunga durata, spesso accompagnati da pensieri di morte
 - Appiattimento affettivo, fenomeni dispercettivi o atteggiamenti autoreferenziali
- **Estremo ritiro sociale**
- **Aumento dell'aggressività rivolta ai familiari**

Major Depression in Comorbidity with Substance use Disorders: Patients' Features and Clinical-Neurobiological Rationale of Antidepressant Treatments



- È stato avviato uno studio retrospettivo per valutare i tassi e gli indicatori di ricaduta in 544 giovani con primo episodio di psicosi¹

|| **61%**

dei pazienti **ha interrotto il trattamento antipsicotico** dopo una mediana di 6 mesi di trattamento¹



|| **46%**

di coloro che hanno interrotto il trattamento **ha avuto una ricaduta entro un anno**^{1,a}

- Una revisione sistematica della letteratura ha esaminato gli indicatori di remissione continua o ricaduta in seguito alla sospensione dei farmaci antipsicotici dopo un primo episodio di psicosi^{2,b}



La percentuale di soggetti con ricaduta dopo l'interruzione dei farmaci antipsicotici variava dal **19% al 97%** in dieci studi²



Risultati predittivi di un'interruzione efficace o di una ricaduta non sono ancora stati replicati in letteratura²



Table 3 Descriptive statistics of outcomes at 2 months (short term) and at 12 months (long term)

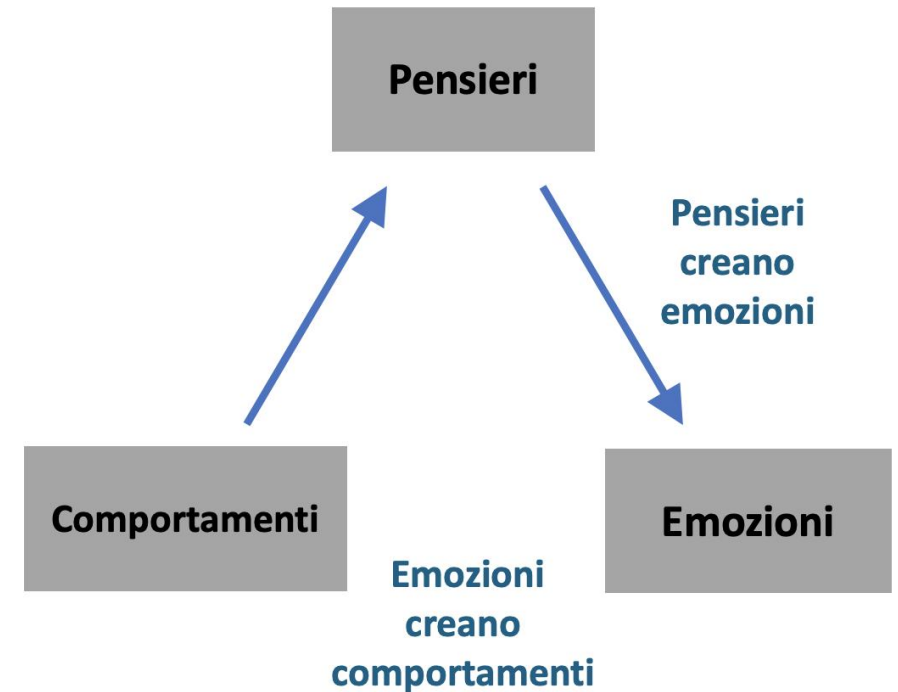
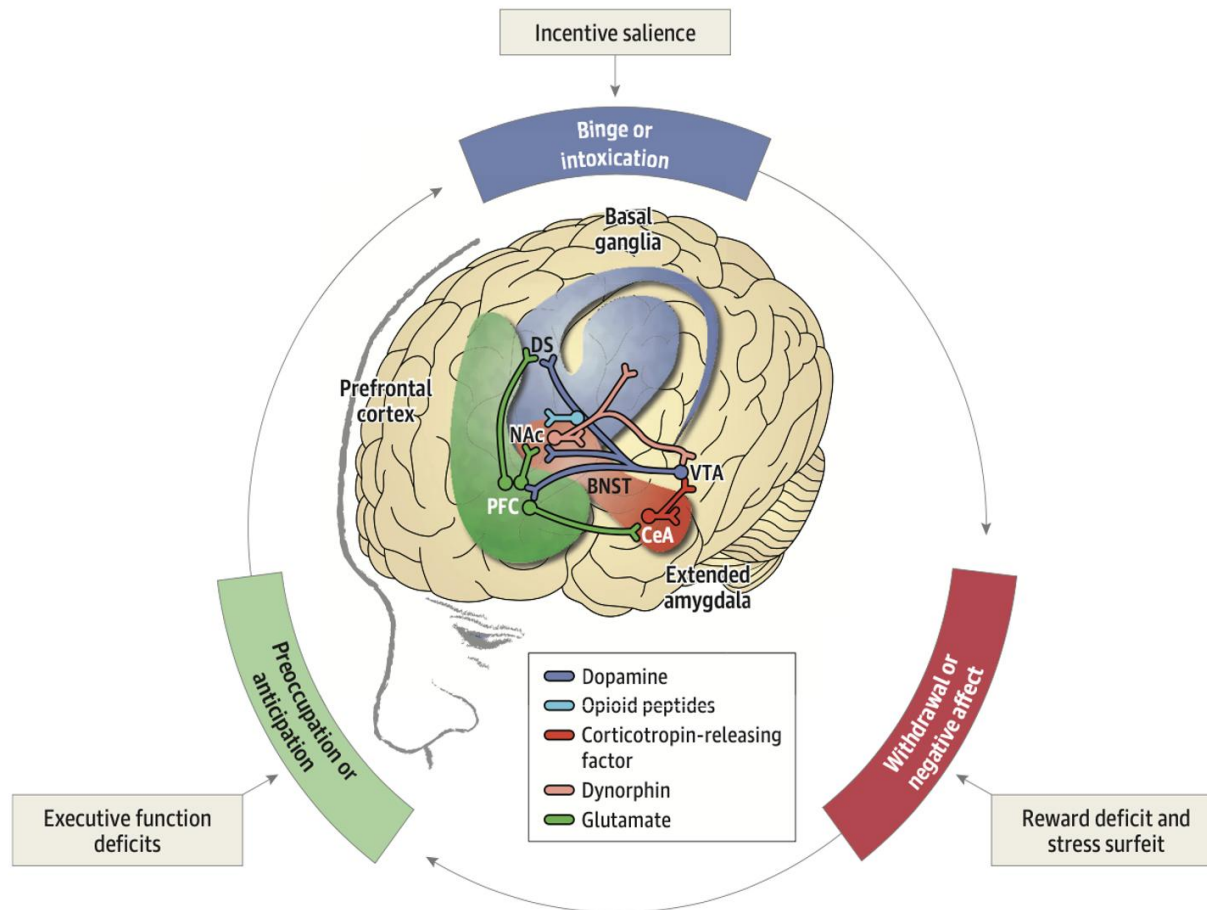
Outcome	Short-term outcome – 2 months N = 673 177		Long-term outcome – 12 months N = 673 177
Acceptability			
Treatment accepted	413 442 (61.4%)		82 524 (12.3%)
Treatment not accepted	259 735 (38.6%)		590 653 (87.7%)
Tolerability			
Treatment tolerated	635 417 (94.4%)		589 321 (87.5%)
Treatment non-tolerated	37 760 (5.6%)		83 856 (12.5%)
Safety			
At least one adverse event	306 655 (45.6%)		479 039 (71.2%)
Death	4082 (0.6%)		17 380 (2.6%)
	Baseline N = 144 347	Short-term outcome – 2 months N = 72 457	Long-term outcome – 12 months N = 11 764
Efficacy – Patient Health Questionnaire (PHQ)-9 mean [s.d.]	17.1 [5.0]	12.3 [6.5]	12.9 [6.8]

*Real-world Effects Of
Antidepressants For Depressive
Disorder In Primary Care:
Population-based Cohort Study*

- De Crescenzo F, De Giorgi R, Garriga C, Liu Q, Fazel S, Efthimiou O, Hippisley-Cox J, Cipriani A. Br J Psychiatry. 2024

Addiction

N D. Volkow; E B. Jones; E B. Einstein; E M. Wargo ; *YAMA Psychiatry* 2019



Day	TRAZODONE FIALE IN 250 CC FISIOLÓGICA	TRAZODONE 150 CONTRAMID	TRAZODONE 300 MG CONTRAMID	Morning	Afternoon	Evening
1-6	×			×		×
7-12	×	●		×		●
13			●			●

- Infusione endovenosa lenta (30-50 gocce al minuto) due volte al giorno
- Il legame con le proteine plasmatiche è dell'89%–95%

Protein	K _i (nM) for trazodone*	K _i (nM) for mCPP
SERT	367.3	265.1
NET	>10000	3150
DAT	>7000	ND
5-HT _{1A}	118	43.9
5-HT _{1B}	>10000	251.9
5-HT _{1D}	106	285.5
5-HT _{1E}	>10000	ND
5-HT _{2A}	35.8	54.5
5-HT _{2B}	78.4	30.3
5-HT _{2C}	223.9	13.04
5-HT ₃	>10000	427
5-HT _{5A}	>10000	1354
5-HT ₆	>10000	1748
5-HT ₇	1782	162.5

Protein	K _i (nM) for trazodone*	K _i (nM) for mCPP
α_{1A}	153	1386
α_{1B}	ND	914.6
α_{2A}	728	145.1
α_{2B}	ND	105.8
α_{2C}	155	123.5
β_1	>10000	2359
β_2	>10000	3474
D ₁	3730	7000 (HB)
D ₂	4142	>10000 (HB)
D ₃	ND	>10000 (RC)
D ₄	703	ND
D ₅	>10000	>10000
BDZ acceptor	>10000 (RK,P)	>10000 (HB,C)
Ca ²⁺ channel	>10000	>10000
CB receptors	>10000	ND

Protein	K _i (nM) for trazodone*	K _i (nM) for mCPP
I ₁	ND	758.9 (RPC12)
σ_1	>10000	ND
σ_2	536 (RPC12)	8350 (RPC12)
H ₁	220	326.3
H ₂	3290	ND
H ₃	>10000 (GPC)	ND
H ₄	>10000	ND
mAChR _s	>10000	>10000 (HB)
nAChRs	>10000	ND
μ -opioid	>10000	ND
δ -opioid	>10000	ND
κ -opioid	>10000 (RC)	ND
E ₃	>10000	ND
E ₄	>10000	ND

Algoritmo Trazodone Nella Diagnosi Duale

**Paziente con diagnosi duale:
depressione + uso di sostanze**

Depressione + alcol
→ Sedazione notturna,
antidepressivo

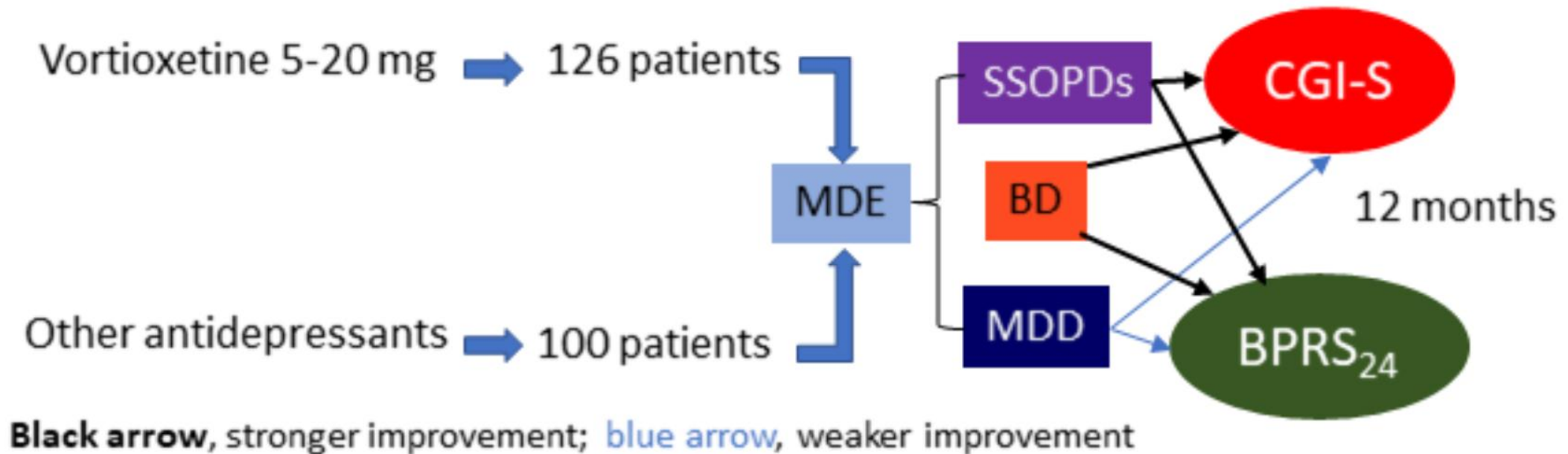
Depressione + cannabis
→ **Stabilizzante sonno e
umore**

**Insonnia da sospensione
BZD**
→ **Basso rischio abuso**

Astinenza da cocaina
→ **Aiuto su sonno e disforia**

Vortioxetine Vs. Other Antidepressants In Patients With Major Depressive Episode With Or Without Substance Use Disorder

G D. Kotzalidis, G Lombardozi, M Matrone, E Amici, F Perrini, I Cuomo, S De Filippis; Current Neuropharmacology 2021

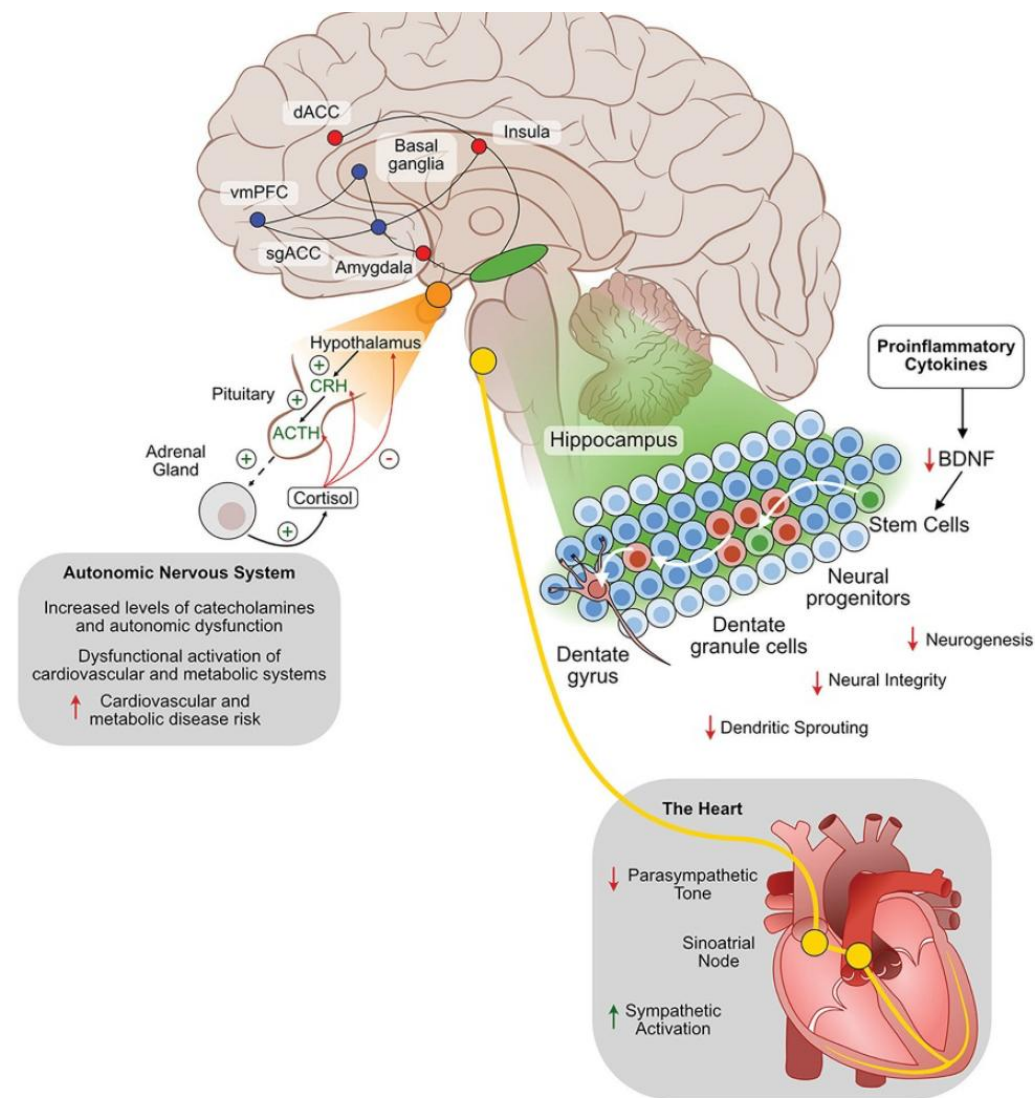


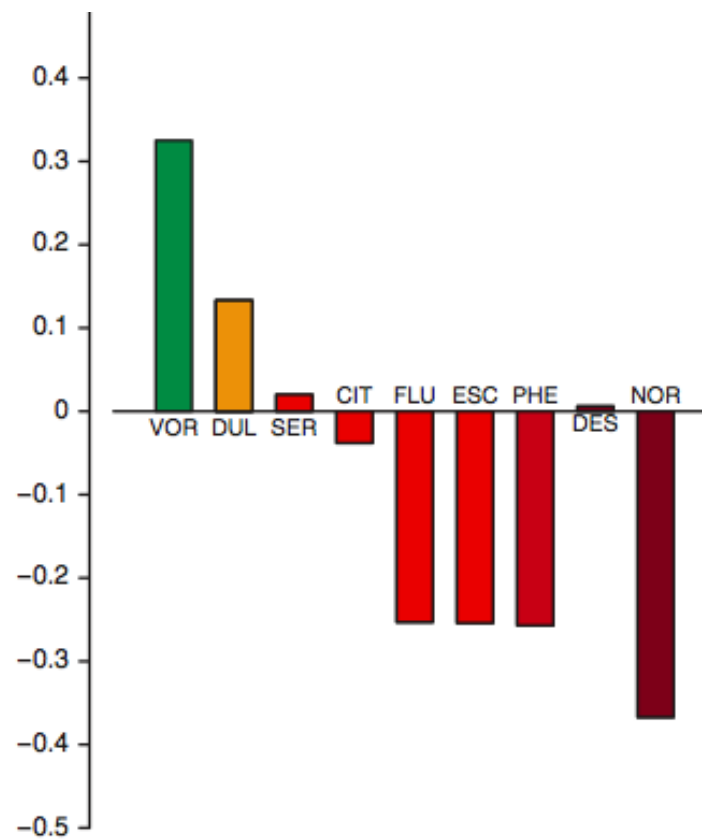
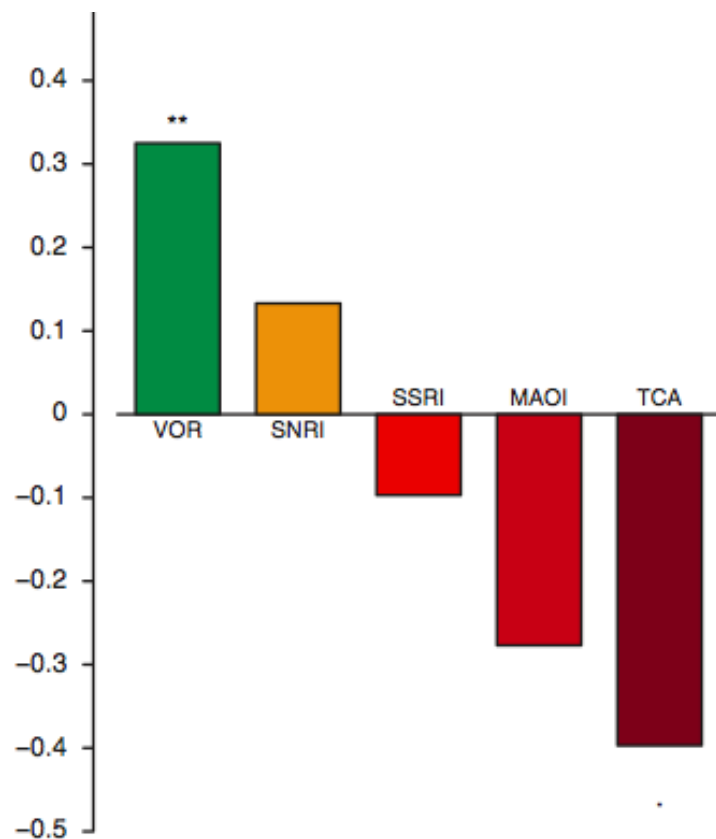
Vortioxetine Vs. Other Antidepressants In Patients With Major Depressive Episode With Or Without Substance Use Disorder

G D. Kotzalidis, G Lombardozi, M Matrone, E Amici, F Perrini, I Cuomo, S De Filippis; Current Neuropharmacology 2021

Treatment group (N)	Criterion	Responders, N (%)	Remitters, N (%)
Vortioxetine (N=126)	CGI-S	99 (78.57%)	77 (61.11%)
	MADRS	87 (69.05%)	67 (53.17%)
	Both	70 (55.56%)	59 (46.82%)
NonSUD (N=84)	CGI-S	64 (76.19%)	48 (57.14%)
	MADRS	56 (66.67%)	42 (50%)
	Both	53 (63.10%)	37 (44.04%)
SUD (N=42)	CGI-S	35 (83.33%)	29 (69.04%)
	MADRS	31 (73.81%)	25 (59.52%)
	Both	30 (71.43%)	22 (52.38%)
Other antidepressants (ADs) (N=100)	CGI-S	75 (75%)	51 (51%)
	MADRS	36 (36%)	15 (15%)
	Both	36 (36%)	12 (12%)
NonSUD (N=62)	CGI-S	44 (70.97%)	31 (50%)
	MADRS	23 (37.10%)	12 (19.35%)
	Both	33 (53.23%)	(16.12%)
SUD (N=38)	CGI-S	31 (81.58%)	20 (52.63%)
	MADRS	13 (34.21%)	3 (7.89%)
	Both	13 (34.21%)	2 (5.26%)

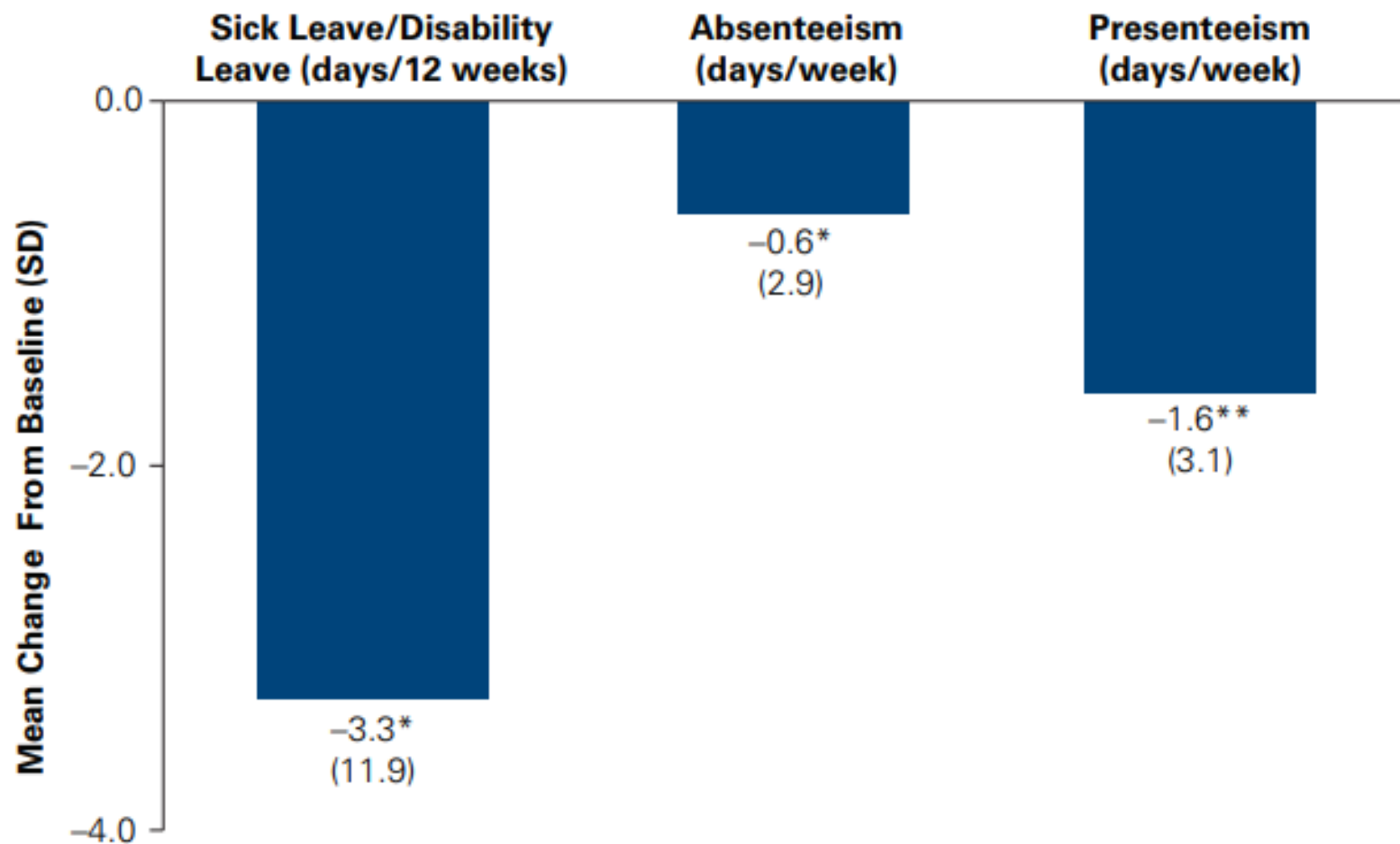
- Vortioxetina ha aumentato l'espressione del BDNF dell'ippocampo nei soggetti sottoposti a CUMS
- Vortioxetina ha sensibilmente ridotto l'anedonia inducendo effetti neuroprotettivi nei soggetti depressi sottoposti a CUMS





*A Network
Analysis Of Ads
On Cognition
With The DSST
In MDD*

**Baune et al., Intern. J.
Neuropsychopharm., 2018**



* $P=0.03$.

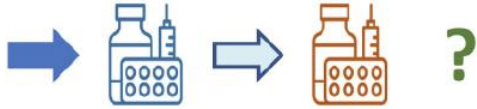
** $P<0.001$.

Work
productivity
improved over
entire study
duration with
vortioxetine

De Filippis et al. 2022;
Neuropsychiatric Disease
and Treatment 2022:18;
1665–1677

Management Of Schizophrenia And Comorbid Substance Use Disorders: Expert Review And Guidance

SEQUENTIAL MODEL



- Patient is offered treatment for either SCHZ or SUD.
- Separate services sequentially and independently treat SCHZ and SUD.
- Treatment delays, decreased motivations and poorer outcomes.

PARALLEL MODEL



- Patient receives concurrent treatment for both SCHZ and the SUD.
- Treatment provided by different services.
- Probable coordination problems and patient drop out.

INTEGRATED MODEL



- The patient benefits from a broader and collaborative approach.
- Single treatment plan.
- Multidisciplinary management and follow-up, enhancing continuity of support.