Neuropsicofarmacologia in età evolutiva

Antonella Gagliano



Prof. Gagliano was in the advisory boards for Eli Lilly and Shire. She is/has been involved in clinical trials conducted by Eli Lilly, Shire, Lundbeck, Janssen and Otsuka. She has been speaker for Novartis, Eli Lilly, Shire and Steve Jones.

Se usati correttamente, i farmaci hanno un ruolo importante nel trattamento dei bambini e dei ragazzi con disturbi mentali...





First do no Harm: Promoting an Evidence-Based Approach to Atypical Antipsychotic use in Children and Adolescents



Primum non nocere…

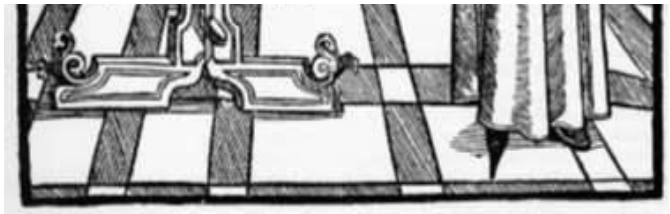


Table 1. Evidence supporting atypical antipsychotic use for specific indications

Antipsychotic	Indication	Target symptoms	Age range (years)	Evidence
Aripiprazole	Autism§	Irritability	6-17	Owen et al., 2009, Marcus et al., 2009.
	Bipolar I Disorder§	Manic or mixed episodes	8-17 (10-17)§	Findling et al., 2009, Tramontina et al., 2009.
	Schizophrenia§	Positive and negative symptoms	13-17	Findling et al., 2008.
Clozapine	Schizophrenia	Psychosis	8-18	Sporn et al., 2007.
Olanzapine	Bipolar I Disorder§	Manic or mixed episodes (acute and maintenance treatment)	13-17	Tohen et al., 2007
	PDD	Aggression	6-14	Hollander et al., 2006.
	Schizophrenia§	Positive and negative symptoms	13-17	Kryzhanovskaya et al., 2009.
Quetiapine	Schizophrenia§	Positive and negative symptoms	13-17	www.clinicaltrials.gov
	Bipolar I Disorder§	Manic episodes	12-18 (10-17)§	DelBello et al., 2006, Del Bello et al., 2002.
	Conduct disorder	Aggression	12-17	Connor et al., 2008.
Risperidone	Autism§	Irritability, Aggression, Communication, Hyperactivity, affect regulation	2-18 (5-16)§	Aman et al., 2008, Aman et al., 2005, McCracken et al., 2005, McCracken et al., 2002, McDougle et al., 2005, Miral et al., 2008, Nagaraj et al., 2006, Pandina et al., 2007, Shea et al., 2004.
	Bipolar I Disorder§	Manic or mixed episodes	10-17	www.clinicaltrials.gov, www.clinicaltrials.gov (Johnson et al., 2008), DelBello M et al., 2005, Wilson et al., 2009.
	Developmental Disabilities, Subaverage IQ	Aggression, SIB	6-18	Buitelaar et al., 2001, Zarcone et al., 2001.
	Disruptive Behaviour Disorders (including ADHD)	Conduct problems, Irritability, Hyperactivity, Aggression	4-14	Aman et al., 2009, Aman et al., 2002, Armenteros et al., 2007, Biederman et al., 2006, Correia Filho et al., 2005, Findling et al., 2004, Reyes et al., 2006, Snyder et al., 2002.
	Schizophrenia§	Positive and negative symptoms	13-17	Haas et al., 2009.
	Tourette Syndrome	Tics	7-17	Bruggeman et al., 2001, Gaffney et al., 2002, Gilbert et al., 2004, Scahill et al., 2003.
Ziprasidone	Bipolar I Disorder	Mania	10-17	DelBello et al., 2008.
	Tourette Syndrome	Tics	7-17	Salle et al., 2000.

Panagiotopoulos, Ronsley, Pharm, Davidson Derryck and Smith, J Can Acad Child Adolesc Psychiatry 19:2 May 2010

AIFA: online il Rapporto OsMed 2024 "L'uso dei farmaci in Italia"

Popolazione pediatrica

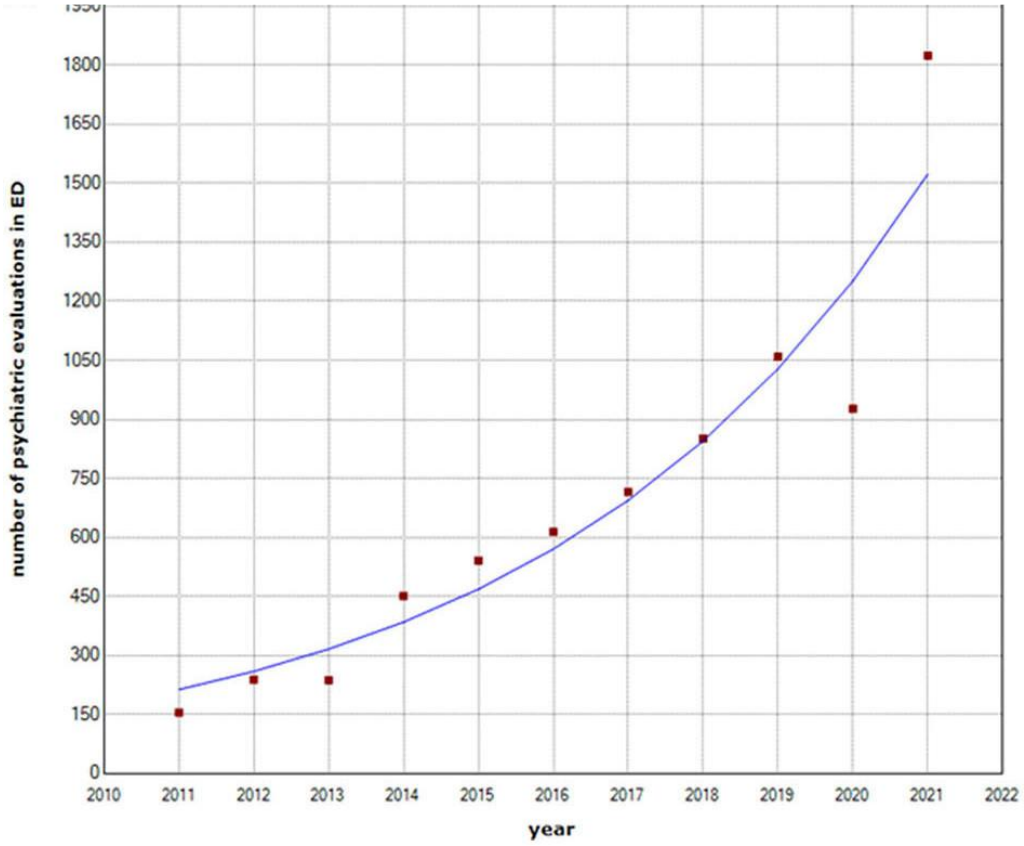
Il 50,9% della popolazione pediatrica (pari a 4,6 milioni di bambini e adolescenti) ha ricevuto almeno una prescrizione farmaceutica, con una prevalenza leggermente superiore nei maschi rispetto alle femmine (51,9% vs 49,9%). I farmaci più prescritti restano gli antimicrobici per uso sistemico, seguiti da quelli per l'apparato respiratorio e dai preparati ormonali sistemici. **I farmaci del sistema nervoso centrale si collocano al quarto posto tra i farmaci più prescritti, con un consumo pari all'8,0% del totale e un aumento del 4,1% rispetto al 2023**. Per tutte le categorie farmaceutiche si osserva un incremento dei consumi rispetto all'anno precedente. **Dal 2016 sono più che raddoppiate** sia la prevalenza che il consumo degli psicofarmaci, anche se si mantengono ancora **su livelli piuttosto contenuti:** la prevalenza passa infatti dallo 0,26% nel 2016 allo 0,57% nel 2024 e i consumi da 20,6 a 59,3 confezioni per 1000 bambini. **I farmaci più prescritti sono gli antipsicotici, gli antidepressivi e i farmaci per l'ADHD.** Il trend di crescita degli psicofarmaci è in linea con i dati di studi epidemiologici pubblicato a livello internazionale, che riportano una generale tendenza di aumento di questi farmaci a livello mondiale, soprattutto in seguito alla pandemia di COVID-19.


Bad news.

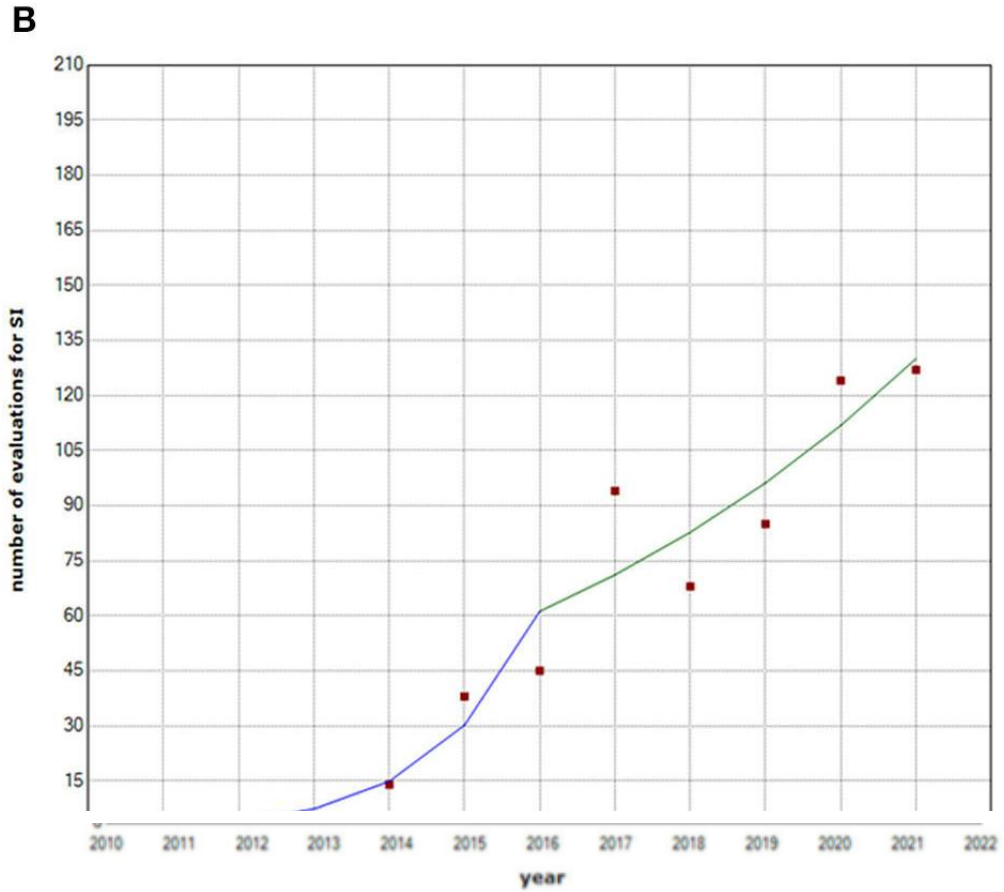

Good news.

Urgent psychiatric consultations for suicide attempt and suicidal ideation before and after the COVID-19 pandemic in an Italian pediatric emergency setting

Apicella et al., Front Psych 2023



B



Eur Child Adolesc Psychiatry (2016) 25:235–245
DOI 10.1007/s00787-015-0726-0

ORIGINAL CONTRIBUTION

Psychotropic medicine prescriptions in Italian youths: a multiregional study

Daniele Piovani[1] · Antonio Clavenna[1] · Massimo Cartabia[1] · Maurizio Bonati[1]

Received: 16 December 2014 / Accepted: 18 May 2015 / Published online: 28 May 2015
© Springer-Verlag Berlin Heidelberg 2015

Table 4 Prevalence rates (‰) of antidepressants (AD drugs), antipsychotics (AP drugs), and ADHD medications observed in ≤18 years old in western countries in the last 10 years

Country	AD drugs	AP drugs	ADHD drugs
USA (New England)	27–38 (2007–2010)[a]	7–26 (2007–2010)[a]	42–77 (2007–2010)[a]
UK	n.a.	0.77 (2005)	9.2 (2008)[b] 7.4 (2008)[c]
Germany	4.8 (2010)	3.2 (2012)	n.a.
The Netherlands	2.0 (2005)	6.8 (2005)	21 (2007)[d]
France	3 (2010)	3 (2010)	2 (2010)
Denmark	2.67 (2010)	2.05 (2010)	7.29 (2010)
Iceland	n.a.	n.a.	12.5 (2007)
Finland	5.93 (2005)	n.a.	1.2 (2007)
Sweden	n.a.	n.a.	2.5 (2007)
Norway	7.0 (2010)	n.a.	4.7 (2007)
Canada	15.4 (2007)	7.4 (2008)	21 (2007)
Italy	**1.02 (2011)**	**0.70 (2011)**	**0.19 (2011)**

Data concerning Italian children are reported in bold characters

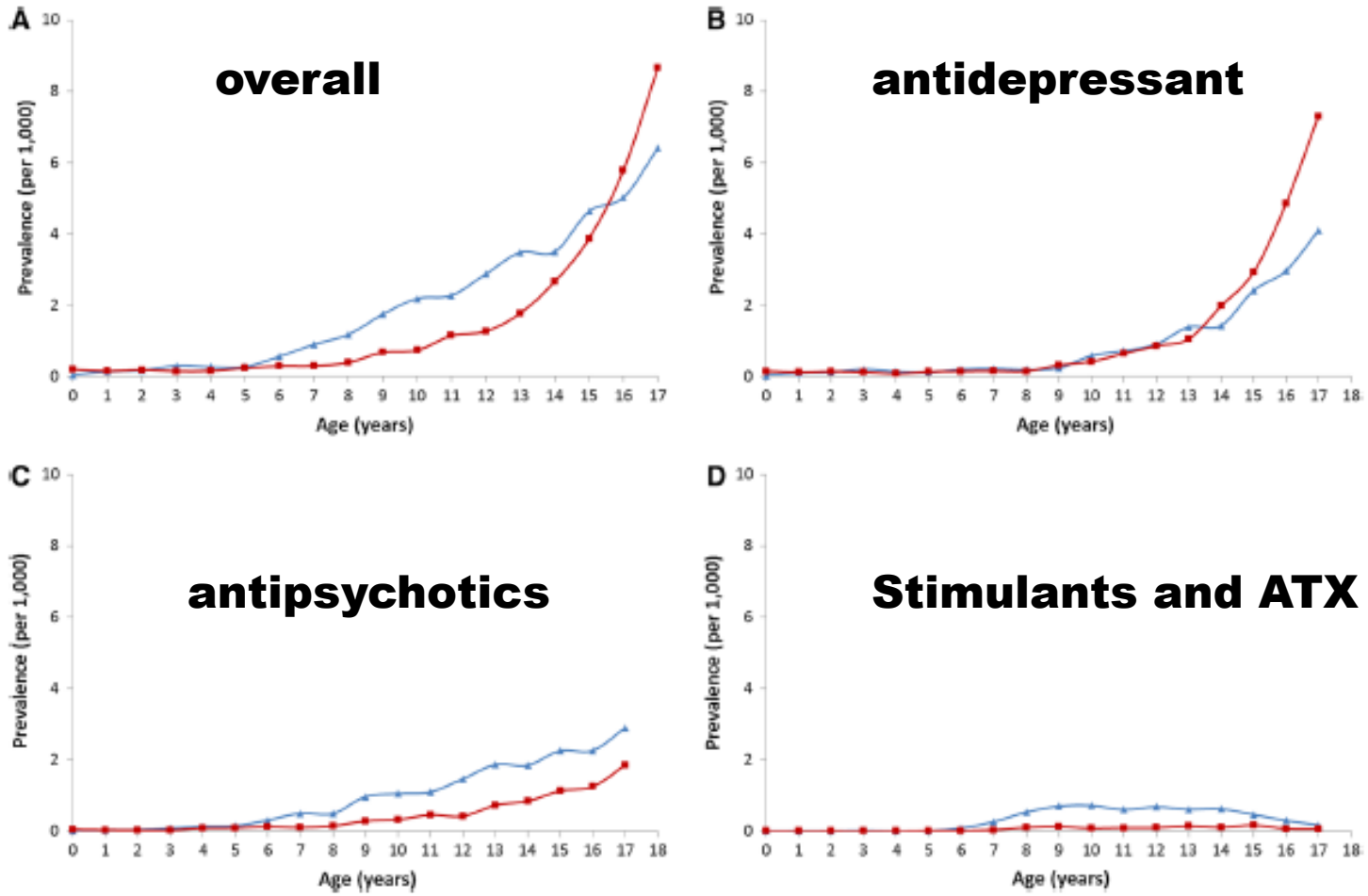


Fig. 1 Prevalence (per 1,000) by age and gender (male: *blue lined triangle*; female: *red lined square*) of overall psychotropic drugs (**a**), antidepressants (**b**), antipsychotics (**c**), and ADHD medications (**d**)



The therapeutic value of a number of psychotropics is now well documented in both the **short and intermediate-term**, while more research is needed to better understand the **long-term impact of pharmacotherapy**

INTRODUCTION | Chapter A.7

PRINCIPLES IN USING PSYCHOTROPIC MEDICATION IN CHILDREN AND ADOLESCENTS

2019 edition

Boris Lorberg, Chiara Davico, Dmytro Martsenkovskyi & Benedetto Vitiello

IACAPAP Textbook of Child and Adolescent Mental Health

Table A.7.6 Psychotropic drug groups: pharmacodynamic differences between children and adults

Drug group	Children	Adults
Tricyclic antidepressants	Not effective for pediatric depression	Effective for adult depression
Serotonergic antidepressants	Increase the risk of suicidal ideation	Do not increase the risk after age 25
Antipsychotics	Relatively greater metabolic side effects	Relatively lower metabolic side effects
Amphetamine-based stimulants	Less likely to induce euphoria	More likely to induce euphoria
Methylphenidate	Lower tolerability and efficacy in children with ADHD aged 3 to 5 years	Higher tolerability and efficacy in adults and children with ADHD above the age of 5 years

PRINCIPLES IN USING PSYCHOTROPIC MEDICATION IN CHILDREN AND ADOLESCENTS

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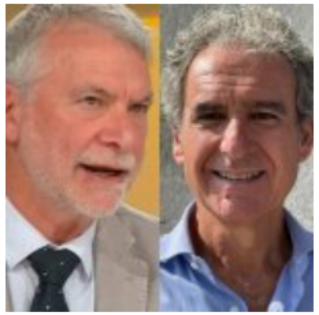
IACAPAP Textbook of Child and Adolescent Mental Health



Medication	Condition	Evidence for efficacy[1]	US FDA-approved indication and age, in years, for which it is approved
Quetiapine	Schizophrenia	Type II	13 and older
	Bipolar disorder	Type II	10 and older
Aripiprazole	Schizophrenia	Type II	13 and older
	Bipolar disorder	Type II	10 and older
	Aggression	Type I	"Irritability" in autism: 6 and older
Olanzapine	Schizophrenia	Type II	13 and older
	Bipolar disorder	Type II	10 and older
Lithium	Bipolar disorder	Type III	7 and older
	Aggression	Type II	
Valproate[2]	Bipolar disorder	Type II	
	Aggression	Type II	
Carbamazepine[2]	Bipolar disorder	Type V	
Oxcarbazepine[2]	Bipolar disorder	Type V	
Lamotrigine[2]	Bipolar depression	Type V	
Methylphenidate and dexmethylphenidate	ADHD	Type I	6 and older
Amphetamines	ADHD	Type I	3 and older
Atomoxetine	ADHD	Type I	6 and older
Clonidine	ADHD	Type I	6 and older
	Tourette's disorder	Type I	
Guanfacine	ADHD	Type I	6 and older
Fluoxetine	Major depression	Type I	8 and older
	OCD	Type II	7 and older
	GAD/SP	Type II	
Sertraline	OCD	Type I	6 and older
	Major depression	Type II	
	GAD/SP	Type I	
Citalopram	Major depression	Type II	
Escitalopram	Major depression	Type I	12 and older
Fluvoxamine	OCD	Type II	7 and older
	GAD/SP	Type I	
Venlafaxine	Major depression	Type V	
Bupropion	ADHD	Type II	
	Major depression	Type V	
Clomipramine	OCD	Type II	10 and older
Haloperidol	Tourette's disorder	Type I	3 and older
	Psychosis	Type II	3 and older
	Hyperactivity, severe behavioral problems, explosive hyperexcitability	Type II	3 and older
Pimozide	Tourette's disorder	Type I	12 and older
Risperidone	Schizophrenia	Type II	13 and older
	Bipolar disorder	Type I	10 and older
	Aggression	Type I	"Irritability" in autism: 5-16 years of age
	Tourette's disorder	Type I	

Psicofarmaci in età evolutiva, tra allarme e consapevolezza

di G. Masi, S. Vicari



12 NOV - *Gentile Direttore,*
scriviamo queste riflessioni come coordinatori dei primari reparti di emergenza psichiatrica per l'età evolutiva (0–18 anni), in un momento in cui i dati sull'uso di psicofarmaci nei minori stanno suscitando un ampio dibattito.

Il recente Rapporto OsMed sull'uso dei farmaci in Italia nel 2024 segnala che la prevalenza nell'uso di psicofarmaci sotto i 17 anni è più che raddoppiata rispetto al 2020, passando dallo 0,26% allo 0,57%.
Un dato che può facilmente generare allarme, ma che richiede invece una lettura attenta e articolata.
Prima di tutto, non è tanto l'aumento numerico in sé a essere significativo, quanto la domanda che dobbiamo porci: questo maggiore ricorso ai farmaci risponde davvero ai bisogni clinici dei bambini e degli adolescenti?

La prescrizione di psicofarmaci in età evolutiva deve sempre avvenire con grande prudenza e competenza, da parte di specialisti esperti, seguendo alcuni principi fondamentali:

1. Valutazione globale – La decisione di prescrivere un farmaco deve inserirsi in una comprensione approfondita della situazione del minore, tenendo conto non solo degli aspetti medici, ma anche di quelli psicologici, familiari e sociali.
2. Obiettivi chiari e verificabili – I sintomi da trattare devono essere ben definiti, osservabili e monitorabili nel tempo, così da poter valutare se il farmaco stia davvero aiutando.
3. Monitoraggio costante – Dopo l'inizio della terapia, è essenziale verificarne con regolarità efficacia e tollerabilità. Entro tre mesi deve essere effettuata una valutazione complessiva del rapporto rischi/benefici per decidere se proseguire, modificare o sospendere il trattamento.
4. Revisione periodica – Poiché i disturbi in età evolutiva possono cambiare con lo sviluppo o grazie ad altri interventi terapeutici, è necessario prevedere momenti in cui, anche in presenza di buoni risultati, si valuti una graduale riduzione o sospensione del farmaco, per verificare se il miglioramento possa mantenersi anche senza terapia.

12 Novembre 2025 @ 12:34

L'aumento riguarda l'intera fascia sotto i 18 anni, ma con un **picco tra i 12 e i 17 anni**, cioè soprattutto negli adolescenti.

Il vero problema è anche chi resta senza cure. In Italia, le stime indicano che **solo 1 ragazzo su 15-20** tra quelli che potrebbero trarre beneficio da una terapia farmacologica la riceve davvero. È la percentuale più bassa tra i Paesi europei a noi più simili. **In Francia le percentuali sono circa tre volte superiori, e in Spagna ancora più alte.**

i dati sull'aumento dell'uso di psicofarmaci in età evolutiva non devono essere letti come un segnale di allarme, ma come uno stimolo alla riflessione e alla responsabilità condivisa.


Bad news.


Good news.

Farmaci con indicazione in scheda tecnica per l'età evolutiva

Disturbo da deficit di attenzione ed iperattività (con intervento multimodale): **Metilfenidato IR ed ER, Atomoxetina (>6 aa)**

Trattamento sintomatico (6 settimane) dell'aggressività persistente dall'età di 5 anni con funzionamento intellettuale al di sotto della media o con ritardo mentale: **Risperidone**

Depressione media e grave (in assenza di risposta a 4-6 sedute di psicoterapia): **Fluoxetina (> 8 aa)**

Disturbo ossessivo-compulsivo: **Sertralina (>6 aa), Fluvoxamina (>8aa)**

Schizofrenia:

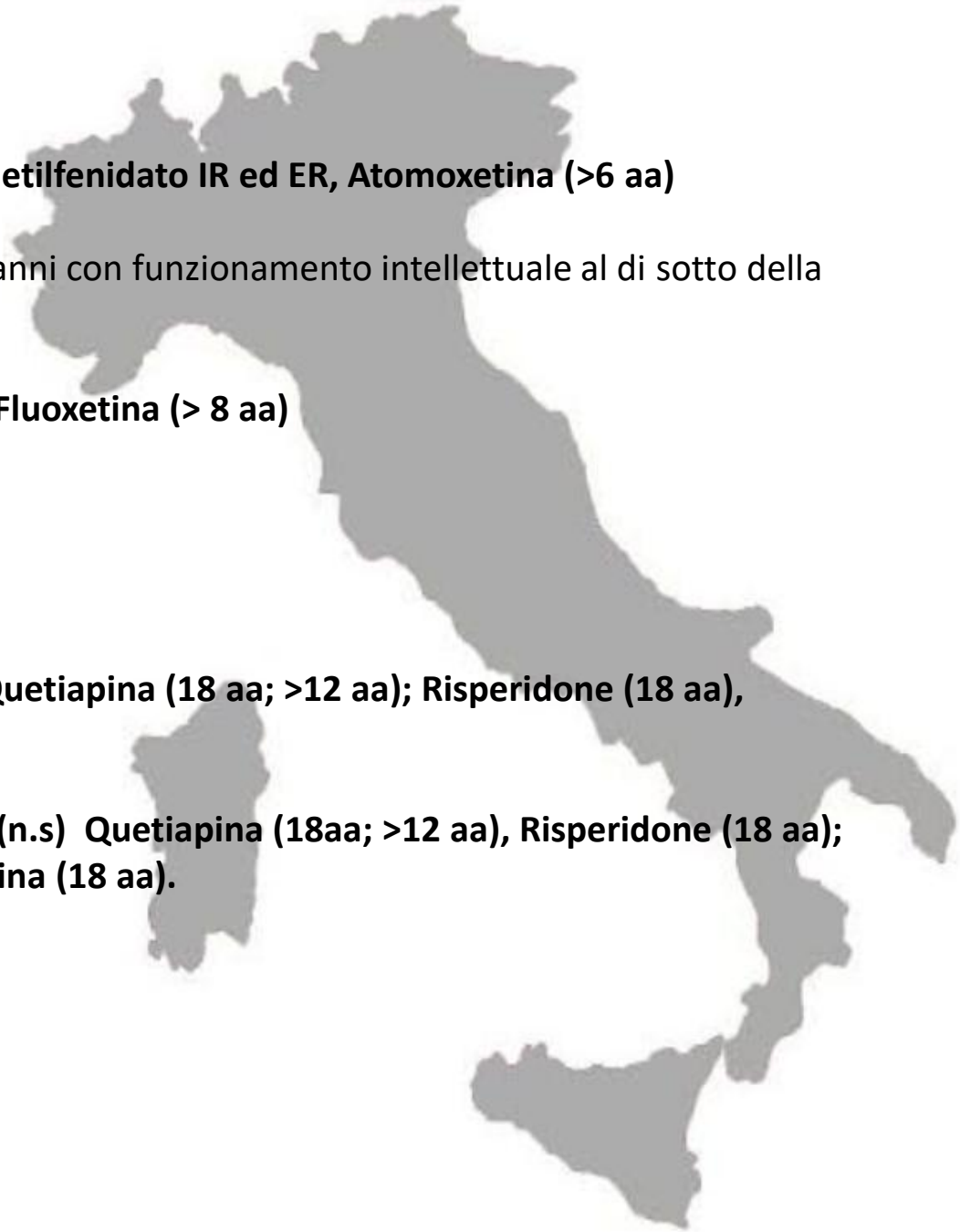
- Prima generazione**: Clorpromazina, Periciazina**
- Seconda generazione**: Clozapina (16 aa; >7 aa); Olanzapina (18 aa; > 7aa); Quetiapina (18 aa; >12 aa); Risperidone (18 aa), Aripiprazolo (>15 aa), Asenapina e Lurasidone (18 aa)**

Disturbo bipolare (mania): **Litio (> 12 aa), Ac.valproico (18 aa), Carbamazepina (n.s) Quetiapina (18aa; >12 aa), Risperidone (18 aa); Ziprasidone (> 10 aa); Olanzapina (18 aa; >7 aa); Aripiprazolo (>13 aa), Asenapina (18 aa).**

Disturbi d'ansia**: Diazepam, Lorazepam (no EN, Xanax)**

Tic e Disturbo di Tourette**: nessuno**

Disturbi del sonno**: nessuno**



farmacovigilanza.eu

https://www.farmacovigilanza.eu/node/15235

FOCUS / MARTEDÌ, MARZO 22, 2022 DRUGS & CHILDREN

Martedì, Marzo 22, 2022

Off-label drugs in paediatrics: from research to children and back again

As it often happens - even if it is not always apparent - a single “fil rouge” indissolubly links researchers, pediatricians and children. We are talking about the so-called off-label drugs that represent about 50% of potential prescriptions in the pediatric age. There is a wide range of drugs for which there is not yet an authorization for use in children and that, despite this, are commonly used, all over the world, with indications, dosages and formulations not specifically approved for the pediatric age (Table 1).[1-4] This phenomenon affects young children more than adolescents and the hospital setting more than the community care setting.



Table 1. Frequency of pediatric off-label prescriptions in different countries (modified from ref 3)

	Percentage of off-label prescriptions in pediatrics
France	42%
US	16-62% Neonatology: 55-80% Primary care: 11-37%
India	27,9-35,7%
Indonesia	50,8-65,9%
Brazil	56%
Canada	38,2%
Sweden	64%
Italy	**60%**
Spaina	41,4-53,9%
Jordan	28%
Palestine	35,3%
UK	65%
Malaysia	34,1%
Australia	54%
Iran	38,1%
Ethiopia	75,8%
China	47,9%



Obiettivi da raggiungere per un uso più appropriato dei farmaci in pediatria



1. **Incrementare le sperimentazioni cliniche in pediatria**
2. Incrementare la disponibilità di farmaci autorizzati per il loro impiego specifico in soggetti in età pediatrica
3. **Assicurare l'implementazione di meccanismi di farmacovigilanza**
4. Evitare lo svolgimento di studi clinici non necessari ottimizzando i flussi informativi relativi alle sperimentazioni in corso di svolgimento
5. **Stabilire una lista di priorità per la ricerca pediatrica**
6. **Sviluppare centri di eccellenza europei per la ricerca e la sperimentazione clinica in pediatria**
7. Assicurare il rispetto di elevati principi etici conformemente a quanto già previsto dalla direttiva 2001/20/EU sulla Buona Pratica Clinica♣

La direttiva definisce come assolutamente indispensabile la sperimentazione sui minori in quanto non sostituibile dalla sperimentazione su soggetti adulti, data peculiarità della farmacodinamica e della farmacocinetica nel bambino, nonché l'unicità di molte patologie pediatriche.

Quale diagnosi per Francesco?



- iperattività/impulsività
- disregolazione emozionale
- aggressività/isolamento
- depersonalizzazione e derealizzazione
- ideazione suicidaria
- insonnia
- tic



Jackson Pollock percorse tutta la vita sulla strada della autodistruzione, in un' escalation di eccessi consumati tra alcool e psicofarmaci, e finita in un terribile incidente d'auto a soli 44 anni.

Jackson Pollock, *Pali blu*, 1952. Olio, duco, colori ad alluminio su tela, 2,10 x 4,88 m. Canberra, National Gallery of Australia.

Quale classe di farmaci per Francesco……?

Appendix A: Color-Coded Psychotropic Medications - Match the Color with the Therapeutic Class Above		
Amphetamine Mixed Salts	Eszopiclone	Quetipine
Abilify	Fanapt	Quillivant XR
Adderall, Adderall XR	Fetzima	Ramelteon
Anafranil	Fluoxetine	Remeron
Aripiprazole	Fluvoxamine	Rexulti
Asenapine	Focalin, Focalin XR	Risperdal
Atomoxetine	Geodon	Risperidone
Benadryl	Guanfacine	Ritalin, Ritalin SR/LA
Brexpiprazole	Hydroxyzine	Rozerem
Brintellix	Iloperidone	Saphris
Bupropion	Invega	Seroquel, Seroquel XR
Carbamazepine	Lamictal	Sertraline
Catapres, Kapvay	Lexapro	Strattera
Celexa	Lithium	Tegretol, Tegretol XR, Epitol, Carbatrol, Equetro
Citalopram	Lixdexamfetamine	Tenex, Intuniv
Clomipramine	Lamotrigine	Trazodone
Clonidine	Latuda	Trileptal
Clozapine	Levmilnacipram	Trintellix
Clozaril, FazaClo, Versacloz	Lunesta	Venlafaxine
Concerta	Lurasidone	Vibryd
Cymbalta	Luvox	Vilazodone
Depakote, Depakote ER, Depakote Sprinkles	Melatonin	Vistaril, Atarax
Desvenlafaxine	Metadate ER, Metadate CD	Vortioxetine
Desyrel	Methylin, Methylin ER	Vyvanse
Dexedrine, Zenzedi	Methylphenidate	Wellbutrin, XL/SR
Dexmethylphenidate	Mirtazapine	Ziprasidone
Dextroamphetamine	Olanzapine	Zoloft
Diphenhydramine	Oxcarbazepine	Zyprexa
Divalproex Sodium	Paliperidone	
Duloxetine	Paroxetine	
Effexor, Effexor XR	Paxil	
Escitalopram	Pristiq	
Eskalith, Eskalith CR, Lithobid	Prozac	

Second Generation Antipsychotic Medications

Depression & Anxiety Medications

Mood Stabilizer Medications

ADHD Medications



Sleep Medications



Quale classe di farmaci per Francesco……?

iperattività/impulsività

disregolazione emozionale

aggressività/isolamento

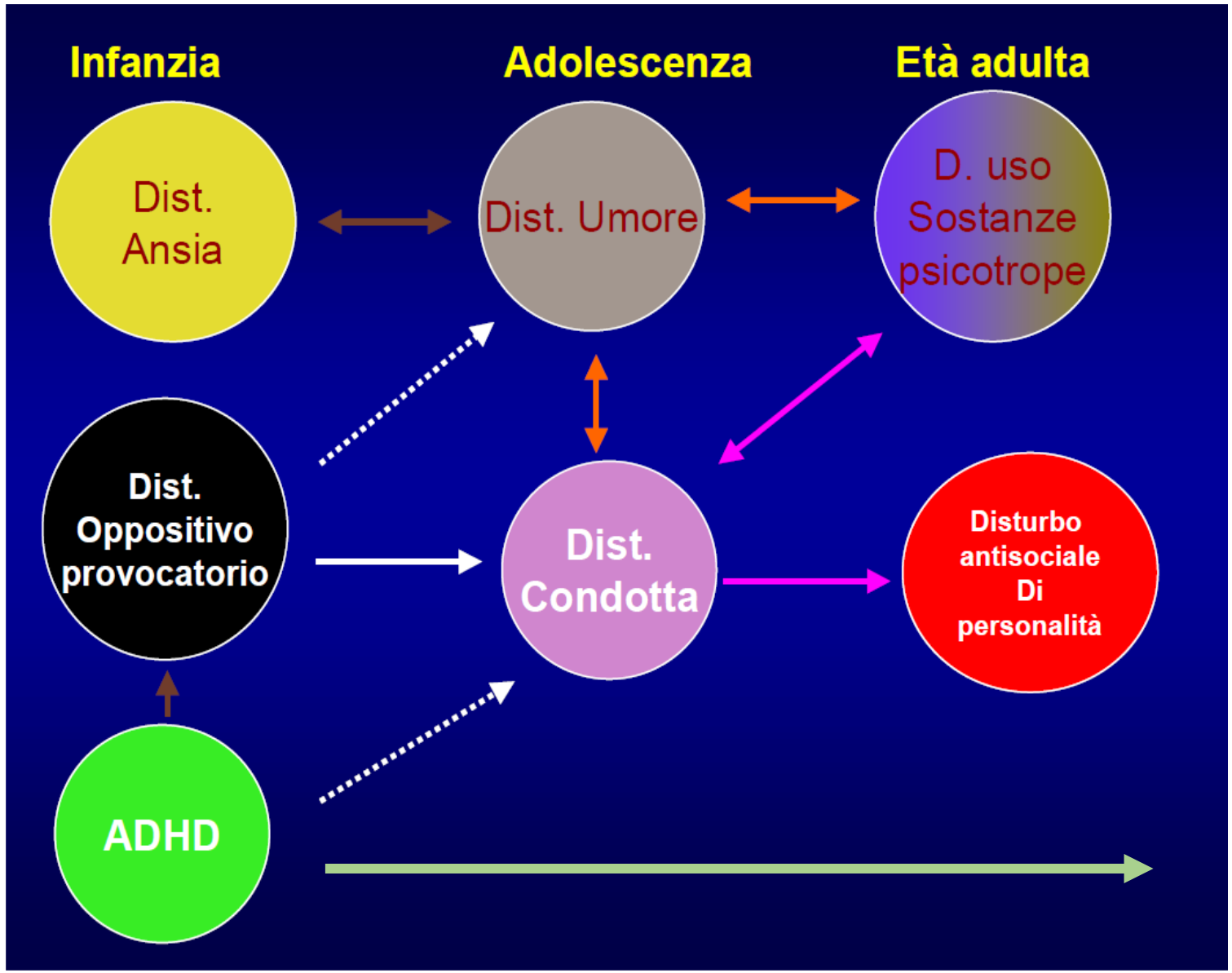
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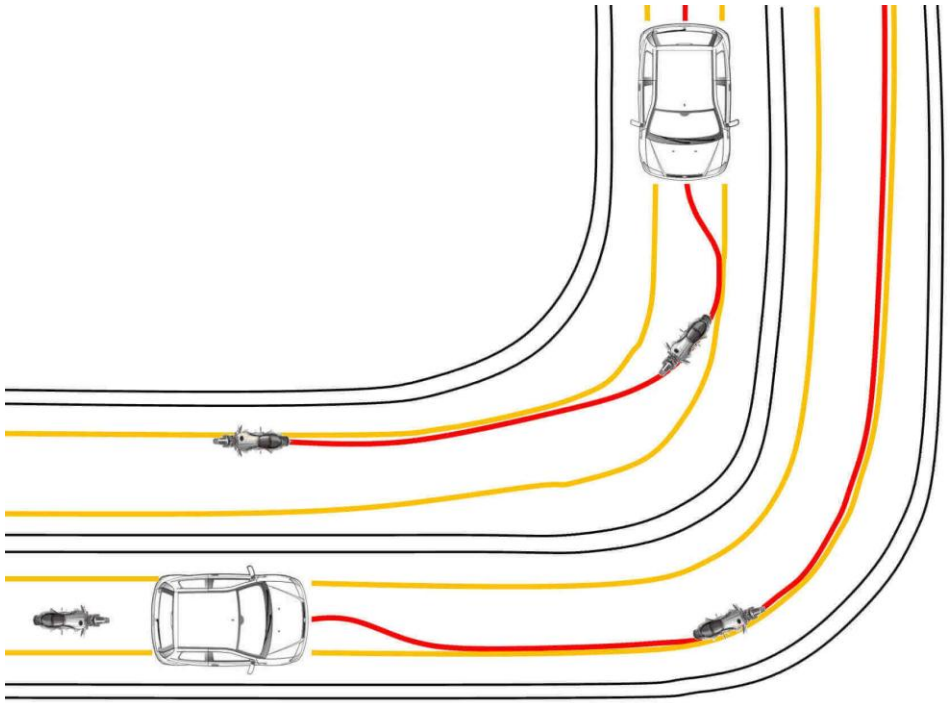
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REVIEW

J Am Acad Child Adolesc Psychiatry 2022;61(3):378–391. CME

Review: Adult Outcome as Seen Through Controlled Prospective Follow-up Studies of Children With Attention-Deficit/Hyperactivity Disorder Followed Into Adulthood

Mariya V. Cherkasova, PhD, Arunima Roy, PhD, Brooke S.G. Molina, PhD, Gabrielle Scott, BA, Gabrielle Weiss, MD, Russell A. Barkley, PhD, Joseph Biederman, MD, Mai Uchida, MD, Stephen P. Hinshaw, PhD, Elizabeth B. Owens, PhD, Lily Hechtman, MD, FRCP, ABPN

review of 7 North American controlled prospective follow-up studies from childhood (6-12 years of age) through adolescence into adulthood (20-40 years of age)



all studies observed high rates of **symptomatic persistence ranging from 60% to 86%**

participants with childhood-diagnosed ADHD had significant impairments in the areas of:

- ❑ educational functioning
- ❑ occupational functioning
- ❑ mental health
- ❑ physical health
- ❑ substance misuse
- ❑ antisocial behavior
- ❑ unsafe driving

The most consistent predictors of functional outcomes included

- ❑ **ADHD persistence**
- ❑ **comorbidity, especially with disruptive behavior disorders**



https://www.verywellhealth.com/untreated-adhd-in-adults-5213475

Credit: Illustration by Laura Porter for Verywell Health

French B, Nalbant G, Wright H, Sayal K, Daley D, Groom MJ, Cassidy S and Hall CL (**2024**) **The impacts associated with having ADHD: an umbrella review**. Front. Psychiatry 15:1343314.

TABLE 1 Summary of mental health reviews.

Mental health			
Mental health area	Number of reviews	Association	No association
Addiction	16 reviews*: 2 internet addiction 1 gambling 8 substance/ alcohol 4 gaming 1 mixed	2 reviews showed an association with internet addiction. 1 shows a positive association with gambling 8 reviews showed a positive association between ADHD and various forms of substance/alcohol addiction (including substance misuse, alcohol and cigarettes) 4 reviews showed a positive association between ADHD and gaming issues. 1 mixed showed a positive association with behavioural addiction (including gaming, sex and internet addiction)	1 of the 8 reviews on substance/ alcohol found no association between ADHD and alcohol misuse
Suicide and self-harm	8 reviews	8 reviews showed a positive association between ADHD and suicide or self-harming behaviours. 4 reviews specifically highlight the mediating link of co-morbidities in this relationship	
Mood and personality disorders	8 reviews 1 OCD 7 bipolar and mood disorders	8 reviews showed a positive association with mood disorders but with the caution that the relationship was less evident in longitudinal research. Two reviews showed a positive association in adults with anxiety. The review on OCD showed a link in children but not adults	
Other disorders	7 reviews 4 eating disorders 3 psychotic disorders	6 reviews explored other topics including eating disorders and psychotic disorders. Overall, the reviews indicated a positive relationship between ADHD and these disorders including schizophrenia and anxiety	
Self-esteem	1 review	The review showed a positive association among adults	

TABLE 2 Summary of physical health related reviews.

Physical health			
Health area	Number of reviews	Association	No association
Sleep	13 reviews	All reviews showed a significant relationship between sleep difficulties and ADHD.	However, 5 reviews reported caution in generalising findings due to lack of studies, methodological issues and continuity
Oral Health	6 reviews	Six reviews showed a link between poor oral health and habits and children with ADHD.	
Weight	9 reviews	All reviews have shown an association between obesity/ overweight and ADHD	The relationship between ADHD and obesity is well established, however, in children, the findings are mixed with 3 studies relaying contractive/ weaker results.
Accidents and injuries	8 reviews	Eight reviews showed an increased risk of accidents, injuries and mortality across the life span with significant differences between children and adults	
Other Diseases and impairments	15 reviews	One review showed an association with celiac disease in children Two reviews showed a link with asthma One with some vision impairments Two with restless leg syndrome One on chronic pain One on vision One on type 2 diabetes One on the allergic diseases One on neurodegenerative diseases One on cardiovascular diseases	One review showed no association with celiac disease

TABLE 3 Summary of social and lifestyle reviews.

Social and lifestyle			
Topic area	Number of reviews	Association	No association
Offending and criminality	9 reviews	All showed a positive association between ADHD and offending and criminal behaviour. One also showed a positive association between ADHD and being a victim of crime.	
Employment and education	5 reviews	All reviews showed poor educational and employment outcomes such as fewer attainment, prematurely leaving schools, more frequent changes	
Quality of life	5 reviews	All reviews showed poorer QoL in adults and children	
Relationship and social interactions	5 reviews	All reviews showed poorer social relationships including, peer functioning social skills, social dysfunction, peer interaction and intimate relationships.	
Risk-taking	6* reviews	All 6 reviews showed a positive relationship between ADHD and risk-taking – including pregnancy, driving offences and general risk-taking	2 of the 6 reviews noted no increased risk for vehicle crashes despite the overall risk of increased driving offences
Others	2 reviews	Association between gender dysphoria and ADHD, but limited data of poor quality One review showed an association with problematic internet use	

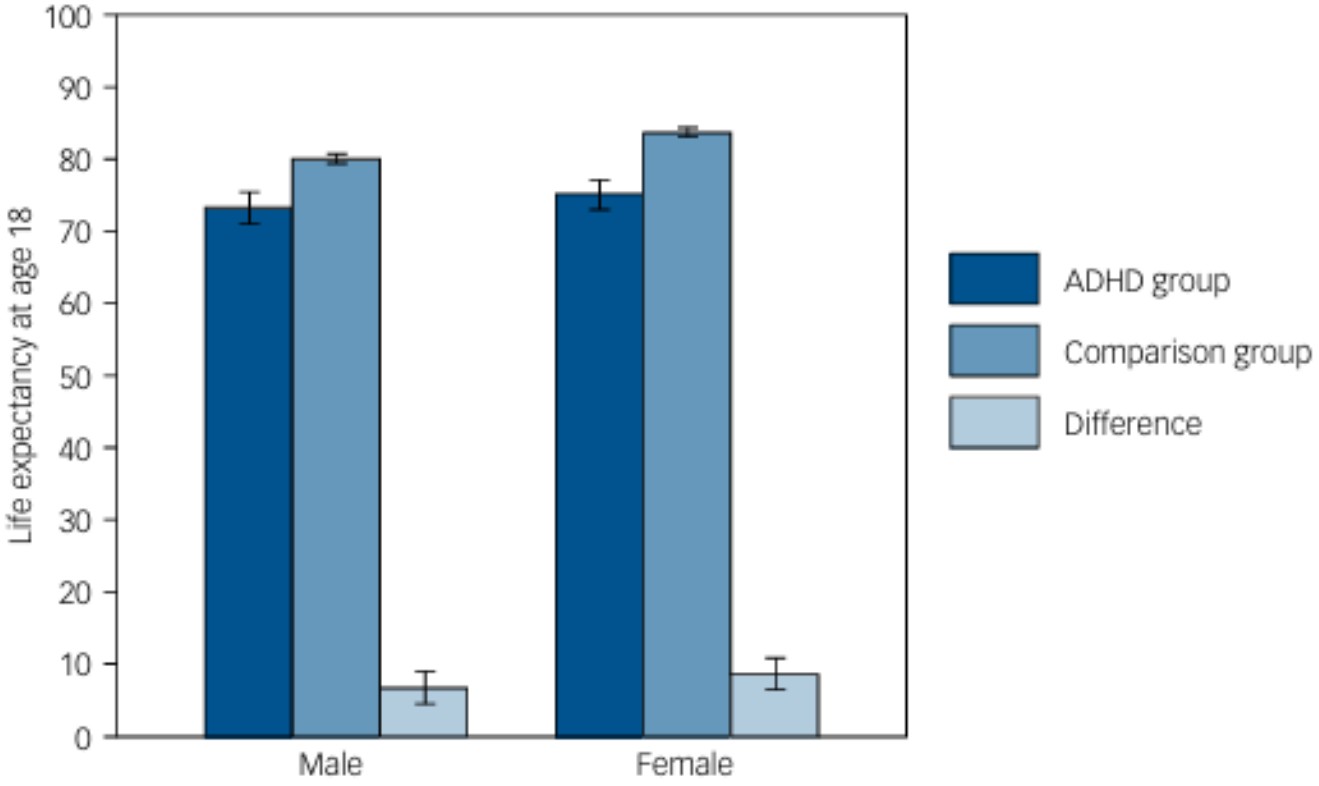
125 reviews

3 key domains of risks associated with ADHD

The findings reveal a **spectrum of health and lifestyle risks** associated with ADHD

This **holistic perspective** emphasizes the interconnectedness of ADHD with various aspects of an individual's life and societal dynamics…

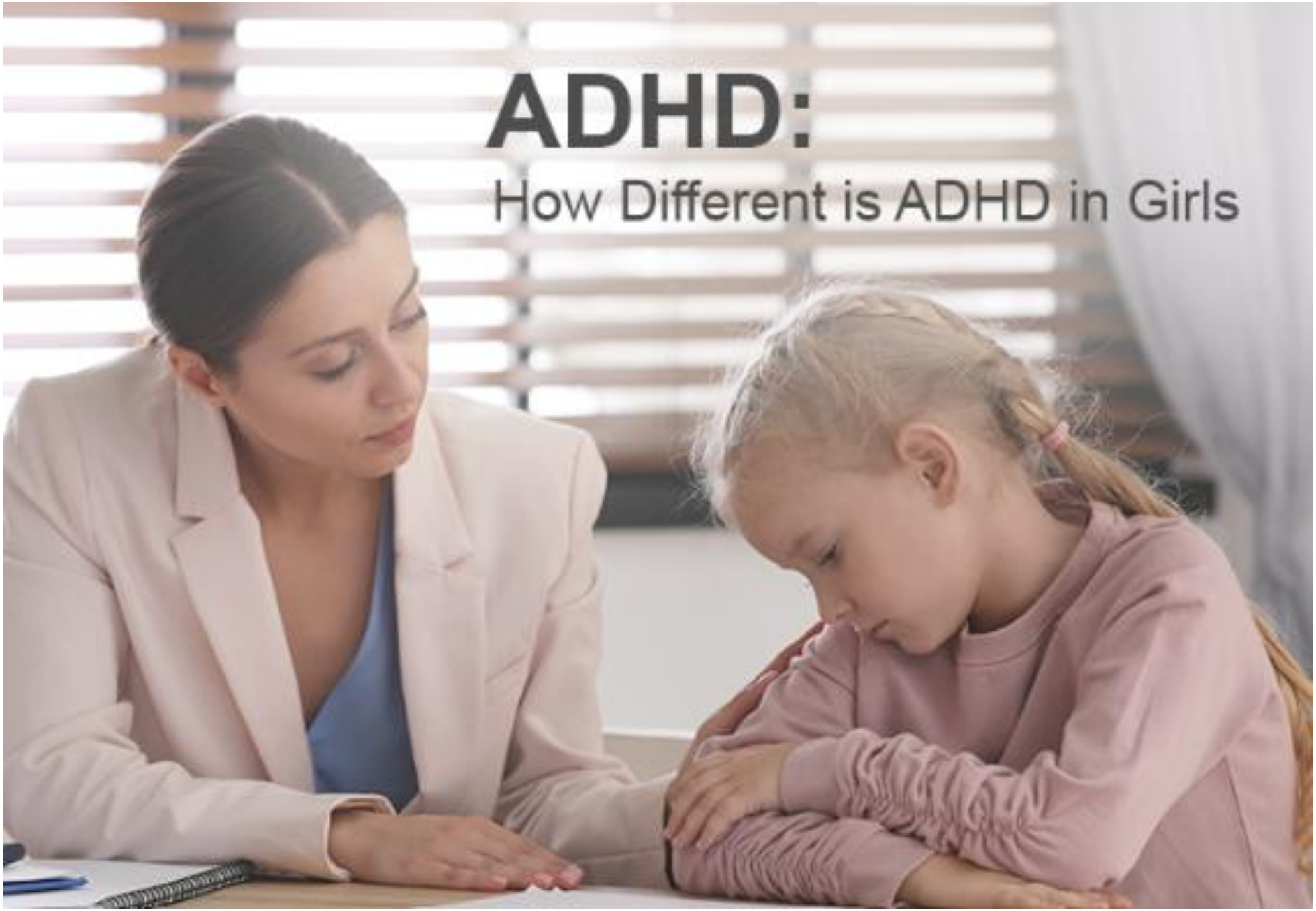
O'Nions E, El Baou C, John A, et al. **Life expectancy and years of life lost for adults with diagnosed ADHD in the UK**: matched cohort study. *The British Journal of Psychiatry*. **2025**;226(5):261-268.



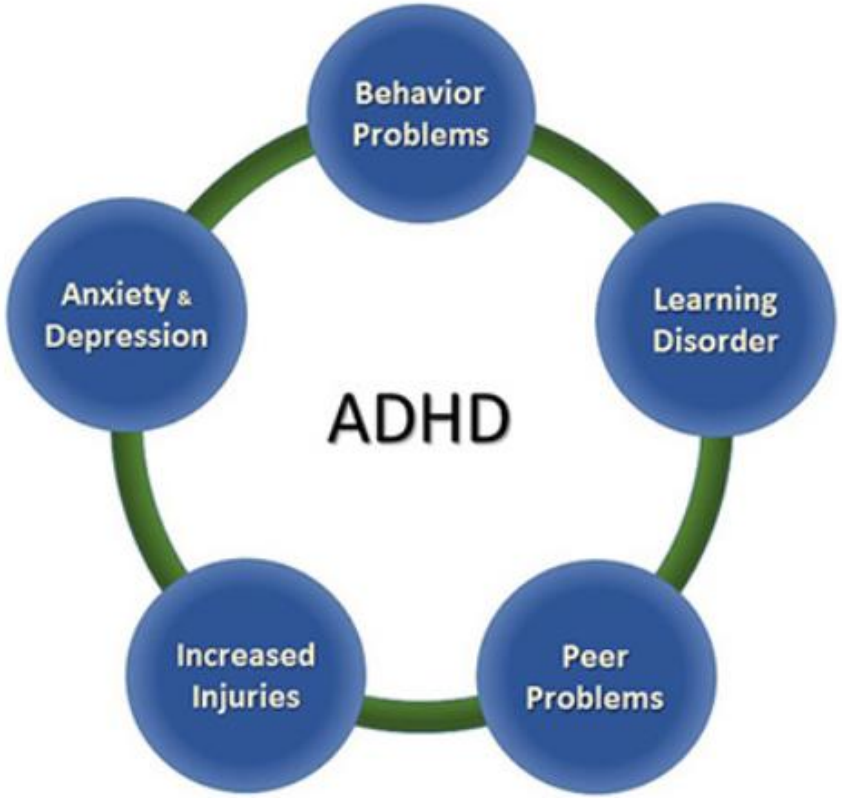


The **reduction in life expectancy** for adults with diagnosed ADHD relative to the general population was:

- **6.78 years for males**
- **8.64 years for females**


ADHD:
How Different is ADHD in Girls

Riconoscere il fenotipo femminile dell'ADHD…





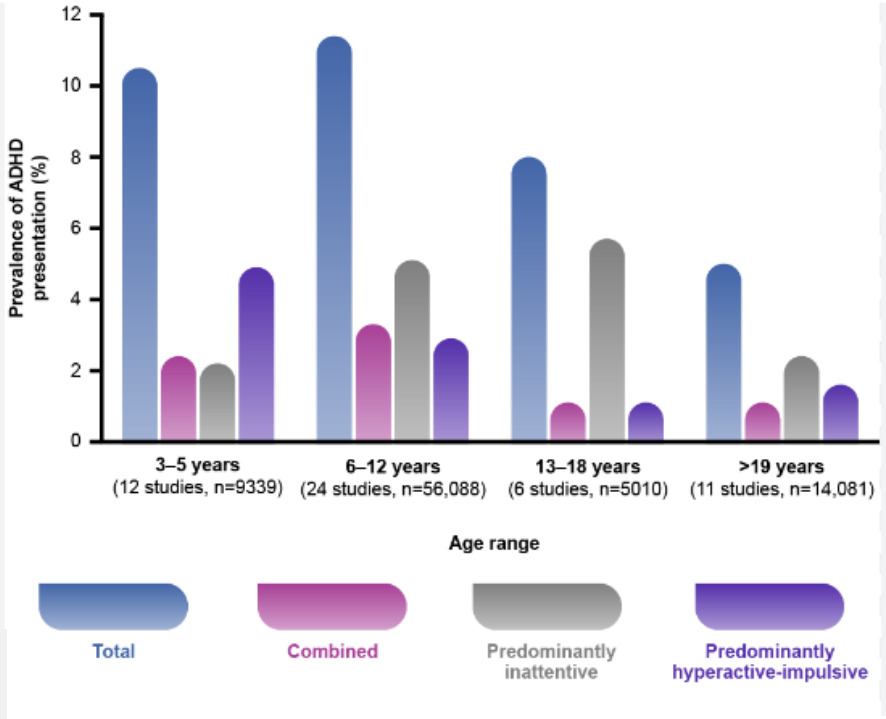
Vivian Bai, Steffi Arkilander and Ava George, ADHD In Women and Girls: Misconceptions July 13, 2020

Meta-analyses show…

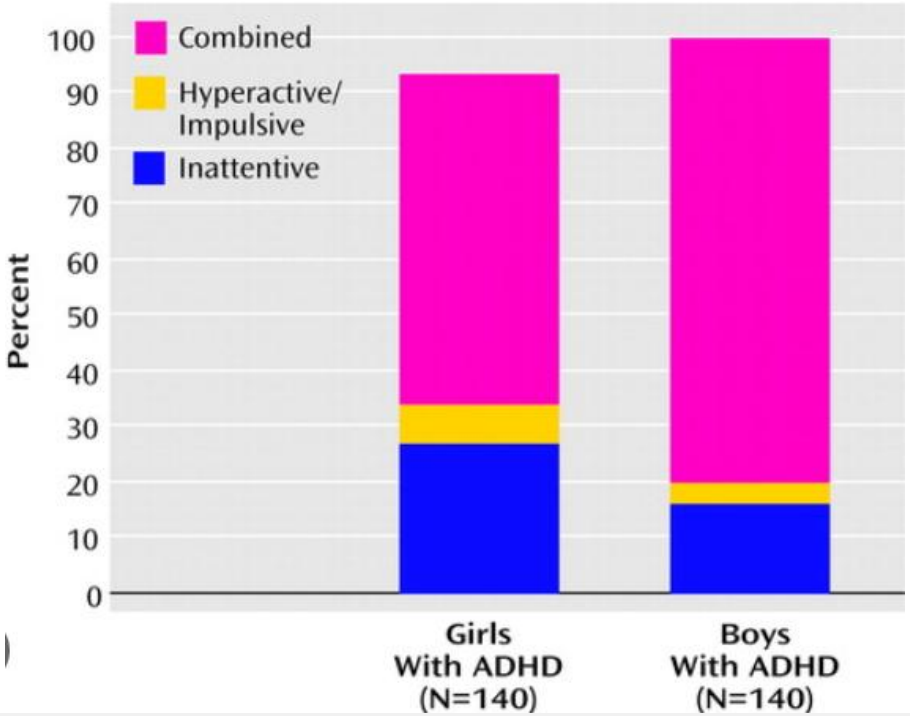
less **severe symptoms** in females versus males with ADHD in community populations, but similar levels in clinically ascertained samples with **inattention more common in females**

- Gershon J (2002) A meta-analytic review of gender differences in ADHD. J Atten Disord 5:143–154.
- Gaub M, Carlson CL (1997) Gender differences in ADHD: a meta-analysis and critical review. J Am Acad Child Adolesc Psychiatry 36:1036–1045
- Mitchison GM, Njardvik U (2015) Prevalence and gender differences of ODD, anxiety, and depression in a sample of children with ADHD. J Atten Disord
- Biederman J, Mick E, Faraone SV, Braaten E, Doyle A, Spencer T, Wilens TE, Frazier E, Johnson MA. Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiatry. 2002 Jan;159(1):36-42.

ADHD Institute



American Journal of Psychiatry - Psychiatry Online



predominantly inattentive symptoms and lower levels of disruptive behaviours

→ **less likely to receive a diagnosis of ADHD**

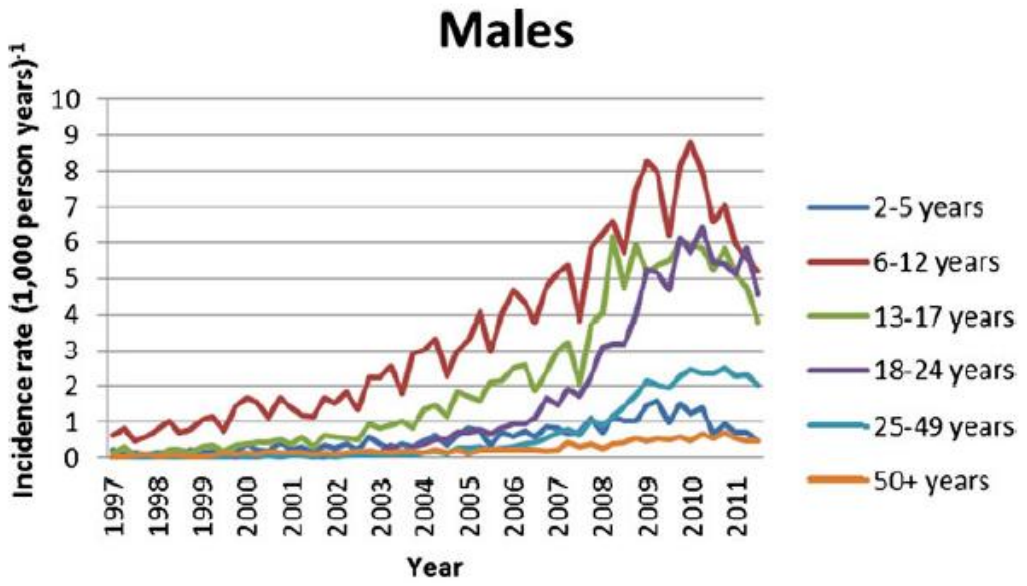
Males are more likely to receive ADHD medication than females

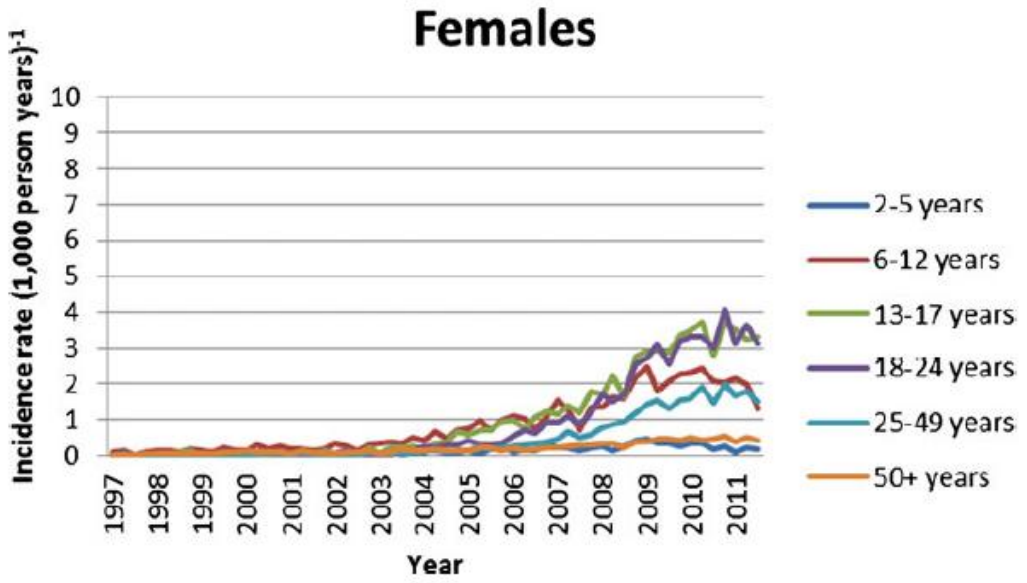
- Derks EM, Hudziak JJ, Boomsma DI (2007) Why more boys than girls with ADHD receive treatment: a study of Dutch twins. Twin Res Hum Genet 10:765–770.
- Angold A, Erkanli A, Egger HL, Costello EJ (2000) Stimulant treatment for children: a community perspective. J Am Acad Child Adolesc Psychiatry
- Pottegård A, Bjerregaard BK, Glintborg D, Kortegaard LS, Hallas J, Moreno SI. The use of medication against attention deficit/hyperactivity disorder in Denmark: a drug use study from a patient perspective. Eur J Clin Pharmacol. 2013 Mar;69(3):589-98
- Graetz BW, Sawyer MG, Baghurst P (2005) Gender differences among children with DSM-IV ADHD in Australia. J Am Acad Child Adolesc Psychiatry

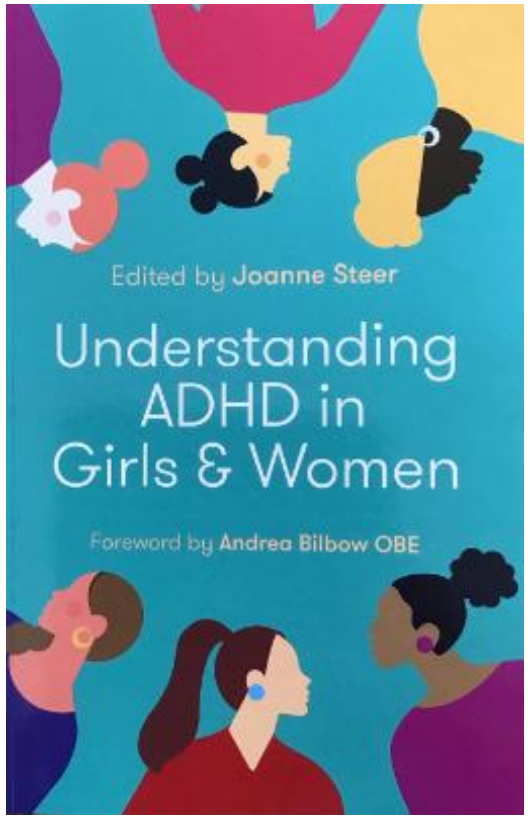
- **hyperactive symptoms** have greater influence on being prescribed pharmacological treatment
- females with ADHD are **less likely to have learning difficulties** or manifest problems at school compared to males

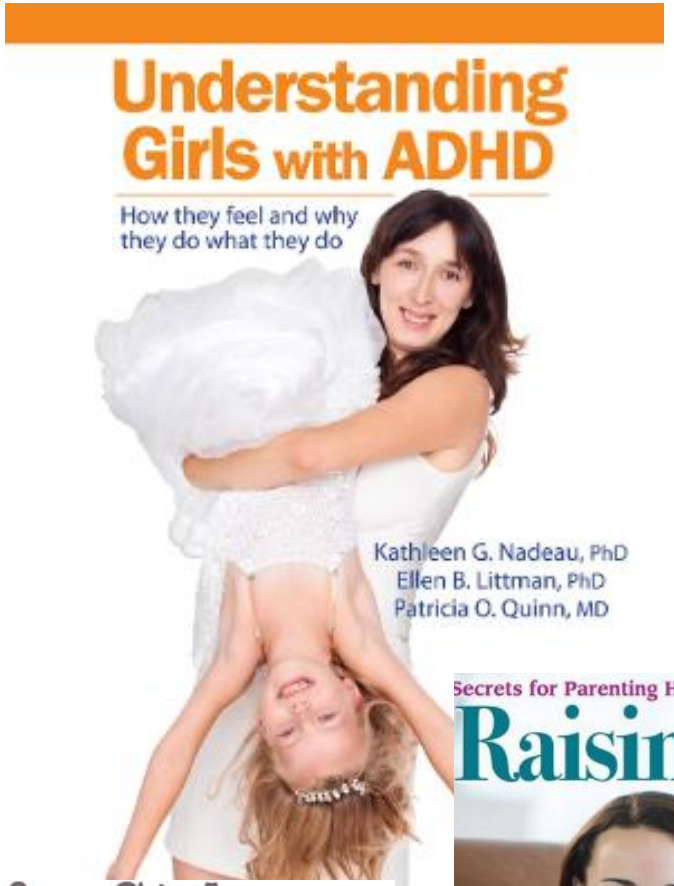
… females with ADHD are **often undertreated**

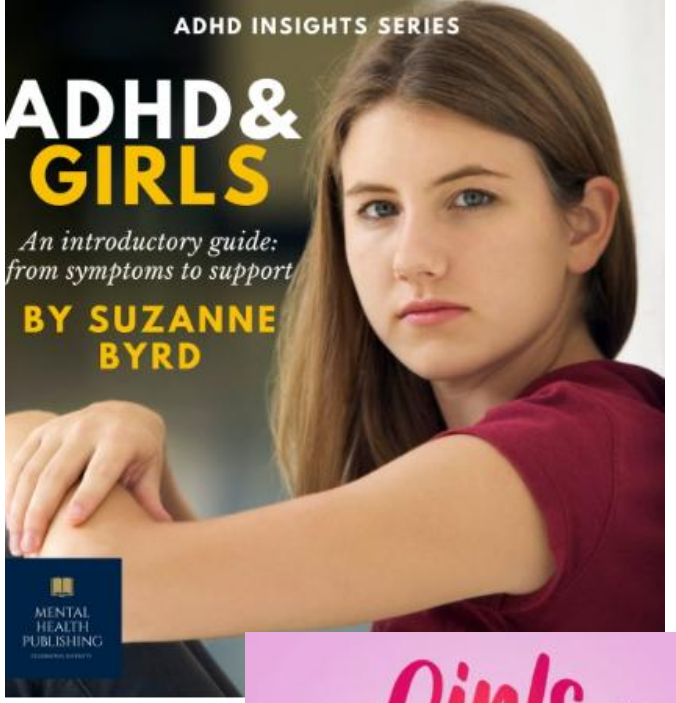


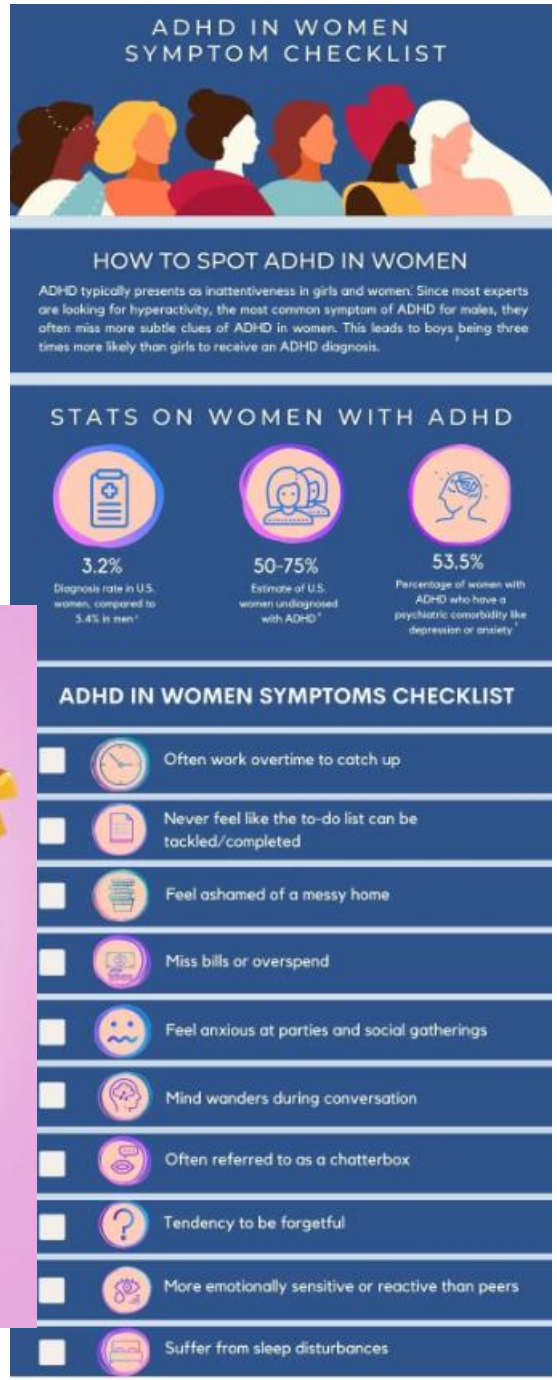




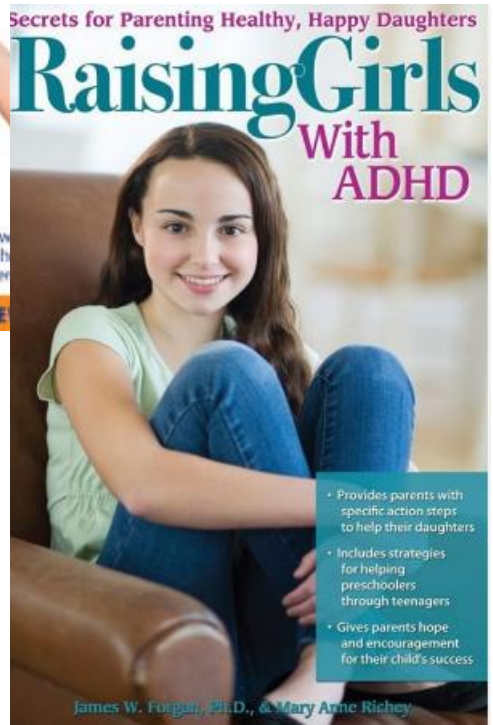

Edited by Joanne Steer
Understanding ADHD in Girls & Women
Foreword by Andrea Bilbow OBE

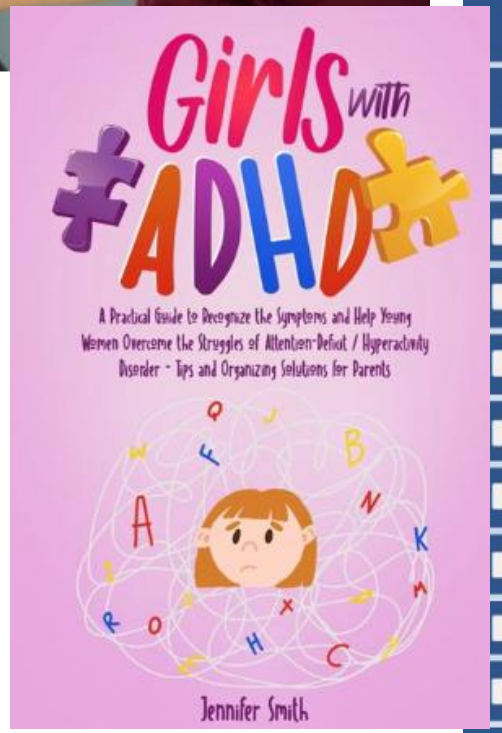

Understanding Girls with ADHD
How they feel and why they do what they do
Kathleen G. Nadeau, PhD
Ellen B. Littman, PhD
Patricia O. Quinn, MD

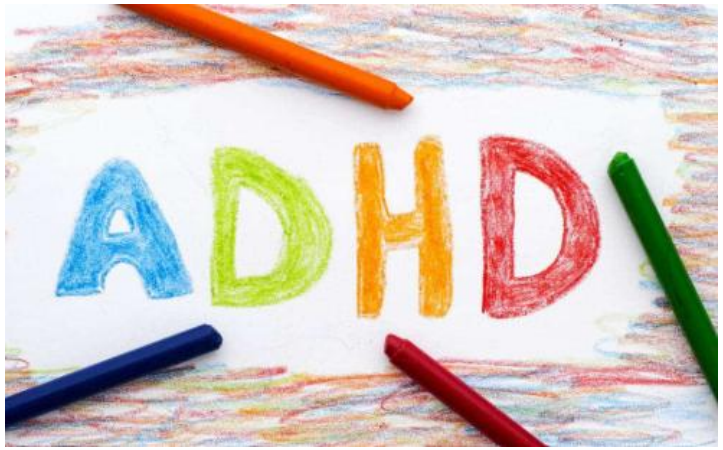

ADHD INSIGHTS SERIES
ADHD& GIRLS
An introductory guide: from symptoms to support
BY SUZANNE BYRD
MENTAL HEALTH PUBLISHING


ADHD IN WOMEN SYMPTOM CHECKLIST
HOW TO SPOT ADHD IN WOMEN
ADHD typically presents as inattentiveness in girls and women. Since most experts are looking for hyperactivity, the most common symptom of ADHD for males, they often miss more subtle clues of ADHD in women. This leads to boys being three times more likely than girls to receive an ADHD diagnosis.
STATS ON WOMEN WITH ADHD
3.2%
Diagnosis rate in U.S. women, compared to 5.4% in men
50-75%
Estimate of U.S. women undiagnosed with ADHD
53.5%
Percentage of women with ADHD who have a psychiatric comorbidity like depression or anxiety
ADHD IN WOMEN SYMPTOMS CHECKLIST
Often work overtime to catch up
Never feel like the to-do list can be tackled/completed
Feel ashamed of a messy home
Miss bills or overspend
Feel anxious at parties and social gatherings
Mind wanders during conversation
Often referred to as a chatterbox
Tendency to be forgetful
More emotionally sensitive or reactive than peers
Suffer from sleep disturbances


It's Different for Girls
A Quick Guide to Understanding and Supporting Your ADHD Daughter


Secrets for Parenting Healthy, Happy Daughters
RaisingGirls With ADHD
Provides parents with specific action steps to help their daughters
Includes strategies for helping preschoolers through teenagers
Gives parents hope and encouragement for their child's success
James W. Forgan, Ph.D., & Mary Anne Richey

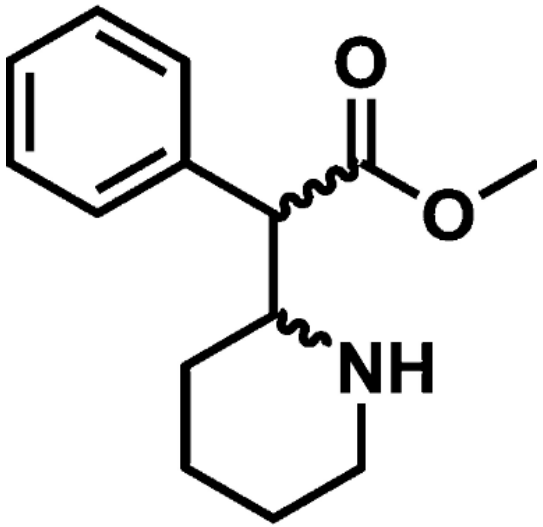

Girls with #ADHD
A Practical Guide to Recognize the Symptoms and Help Young Women Overcome the Struggles of Attention-Deficit / Hyperactivity Disorder - Tips and Organizing Solutions for Parents
Jennifer Smith





...to treat

...to treat well



Methylphenidate

The first-line treatment for ADHD

Efficacia (*Effect Size*)

Banaschewski et al. *ECAP 2006*

	Parent		Teacher		Clinician		
	SMD	No. of studies (rating scales used)	SMD	No. of studies (rating scales used)	SMD	No. of studies (rating scales used)	References
Adderall XR	0.9	1	1.1	1	1.2	1	Data on file Shire
Concerta XL	1.0	1	1.0	1			Wolraich et al.
Equasym XL	0.6	2	0.9	1	1.8	1	Greenhill et al. Swanson et al. Findling et al.
Medikinet retard	1.0	1	1.0	1	0.9	1	Döpfner et al.
Ritalin LA			1.0	1			Biederman et al.
ATX	0.7	6			0.7	11	Data on file Eli Lilly
Modafinil	0.6	3	0.7	3			Data on file Cephalon

Effect Size: MPH-IR = MPH-ER (approx 1) > ATX, Modafinil (approx 0.7)



Methylphenidate is the most widely available and most frequently prescribed medication for ADHD

It is effective at reducing the **symptoms** of ADHD with a **strong effect size (≈1)** when used appropriately

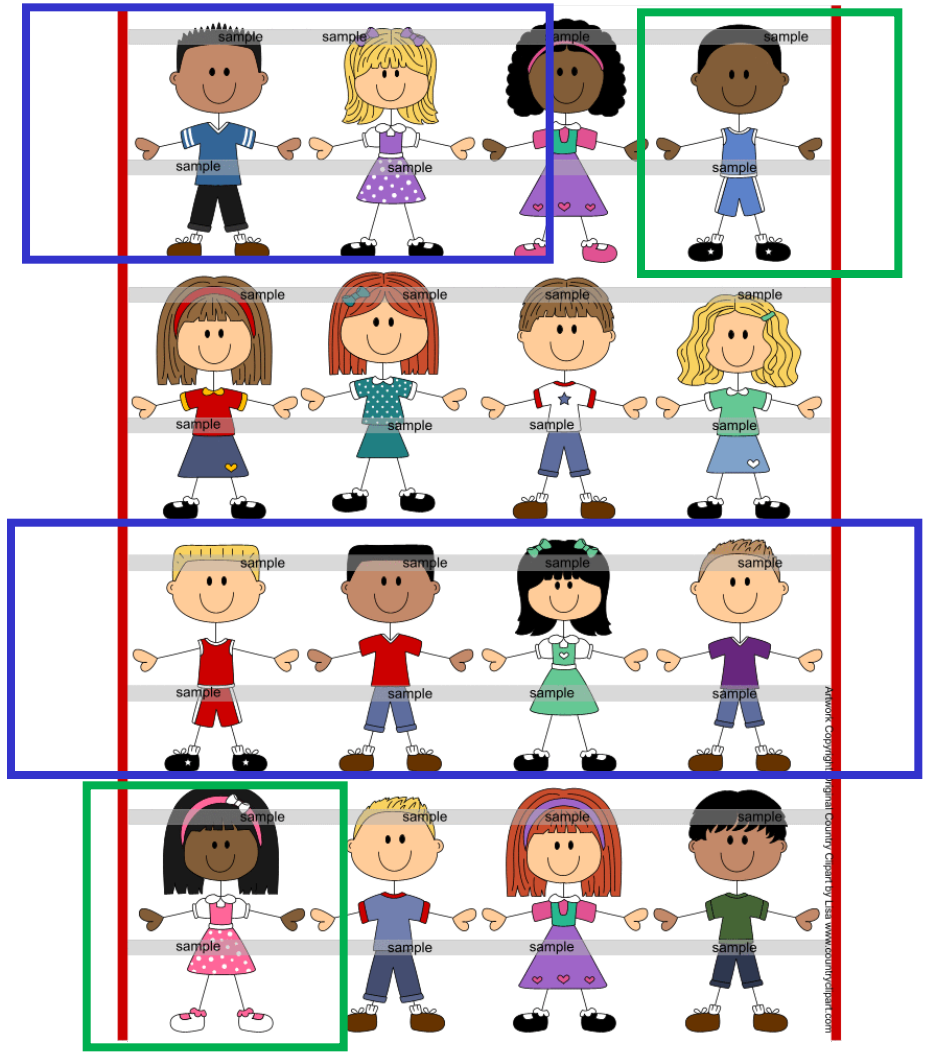
Banaschewski T, et al. Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry 2006 Dec;15(8):476-95.

Numbers needed to treat (NNT)

The number of patients needed to be treated in order for one to reach complete remission

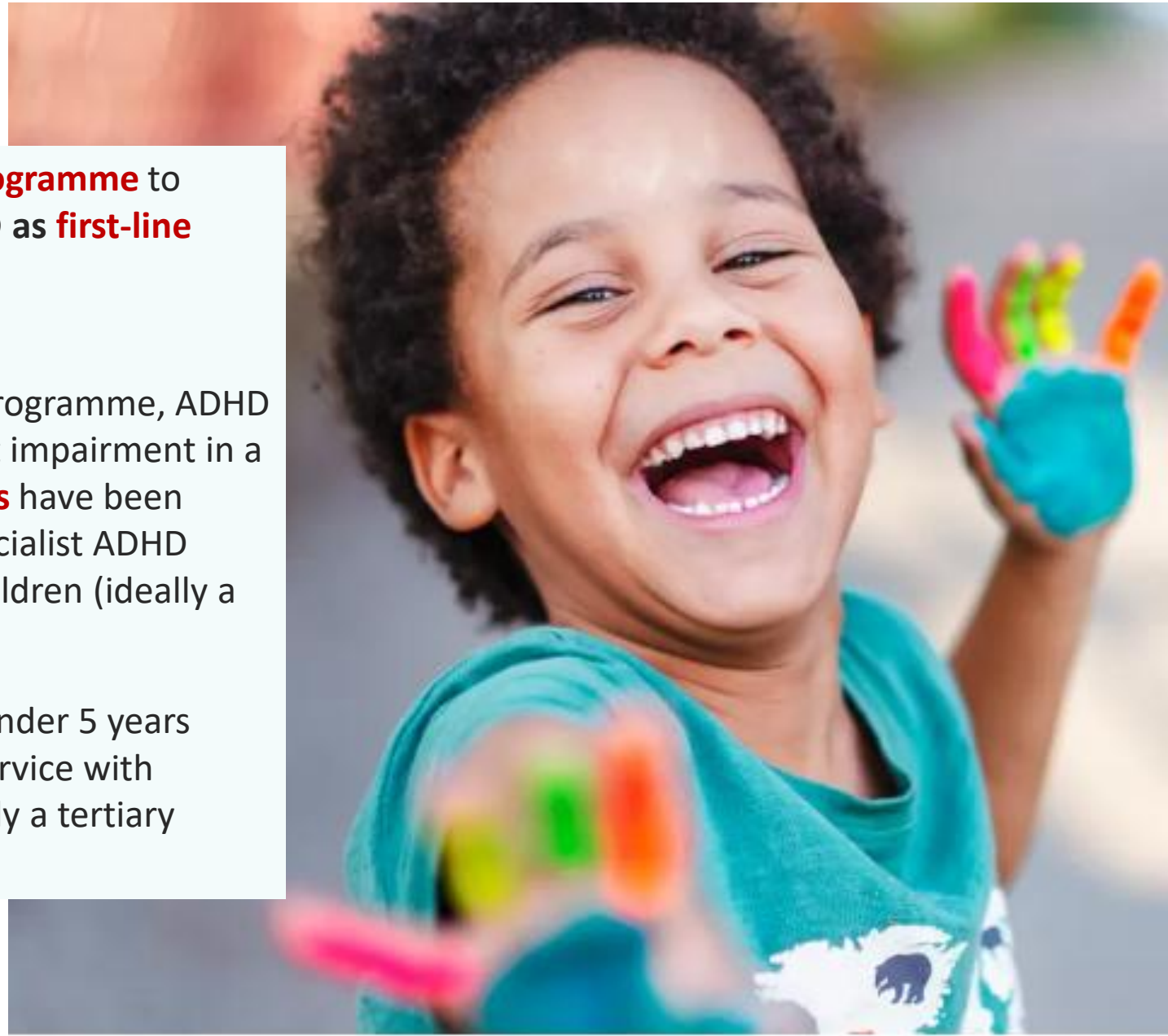
methylphenidate: 2.2

Atomoxetine 4



Attention deficit hyperactivity disorder: diagnosis and management (NG87) NICE guideline, Published: 14 March 2018, www.nice.org.uk/guidance/ng87

Children under 5 years



1.5.7 Offer an ADHD-focused group **parent-training programme** to parents or carers of children under 5 years with ADHD **as first-line treatment.**

1.5.8 If after an ADHD-focused group parent-training programme, ADHD symptoms across settings are still causing a significant impairment in a child under 5 years **after environmental modifications** have been implemented and reviewed, obtain advice from a specialist ADHD service with expertise in managing ADHD in young children (ideally a tertiary service).

1.5.9 **Do not offer medication** for ADHD for any child under 5 years **without a second specialist opinion** from an ADHD service with **expertise in managing ADHD in young children** (ideally a tertiary service).

Children aged 5 years and over and young people

1.5.10 **Give information about ADHD and offer additional support to parents and carers** of all children aged 5 years and over and young people with ADHD.

The support should be **ADHD focused**, can be **group based** and as few as **1 or 2 sessions**.

It should include:

- education and information on the causes and impact of ADHD
- advice on parenting strategies
- with consent, liaison with school, college or university
- both parents and carers if feasible.



Children aged 5 years and over and young people

1.5.11 If a child aged 5 years or over or young person has ADHD and symptoms of **oppositional defiant disorder or conduct disorder**, offer parents and carers a **parent-training programme**, as well as **group-based ADHD-focused support**.



1.5.12 **Consider individual parent-training programmes** for parents and carers of children and young people with ADHD and symptoms of oppositional defiant disorder or conduct disorder when:

- there are particular **difficulties** for families in attending group sessions (for example, because of disability, needs related to diversity such as language differences, learning disability [intellectual disability], parental ill-health, problems with transport, or where other factors suggest poor prospects for therapeutic engagement)
- a family's needs are **too complex** to be met by group-based parent-training programmes.

Children aged 5 years and over and young people

1.5.13 **Offer medication for children aged 5 years and over and young people only if:**

- their ADHD **symptoms are still causing a persistent significant impairment** in at least one domain after **environmental modifications have been implemented and reviewed**
- they and their parents and careers have discussed information about ADHD
- a baseline assessment has been carried out

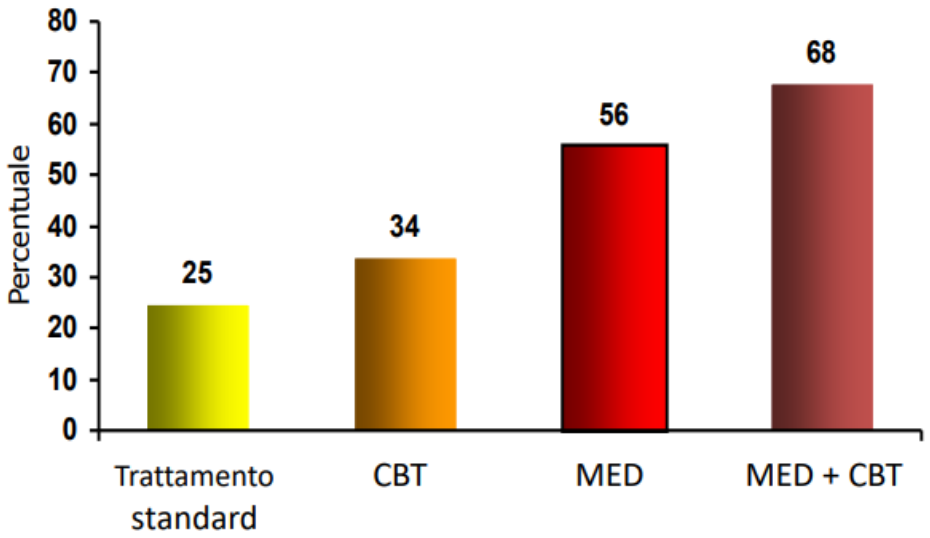
1.5.14 **Consider a course of cognitive behavioural therapy (CBT)** for young people with ADHD **who have benefited from medication but whose symptoms are still causing a significant impairment** in at least one domain, addressing the following areas:

- **social skills with peers**
- **problem-solving**
- **self-control**
- **active listening skills**
- **dealing with and expressing feelings**



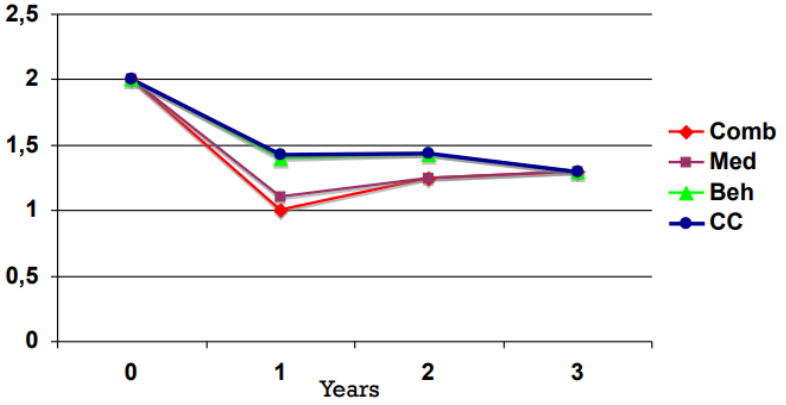
combination of behavioral therapy and stimulant medication

In the MTA study, although the combination of behavioral therapy and stimulant medication was not significantly more effective than treatment with medication alone for ADHD's core symptoms, after correcting for multiple tests in the primary analysis, a secondary analysis of a combined measure of parent and teacher ratings of ADHD symptoms did find a **significant advantage for the combination, with a small effect of d = 0.28.**

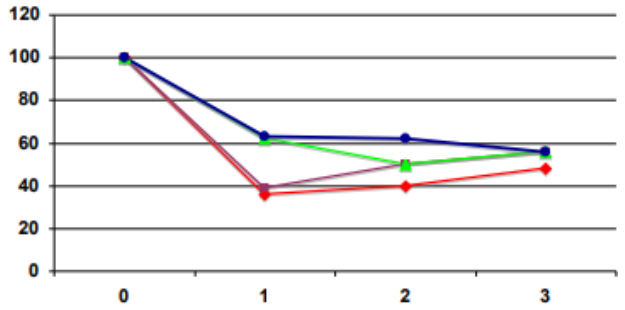


The combined treatment also offered:

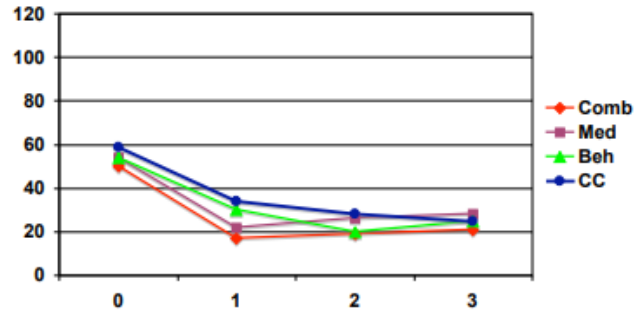
- greater improvements on academic and conduct measures
- Parents' and teachers' more satisfaction with the treatment plan.
- the use of lower stimulant dosages reducing adverse effects



ADHD



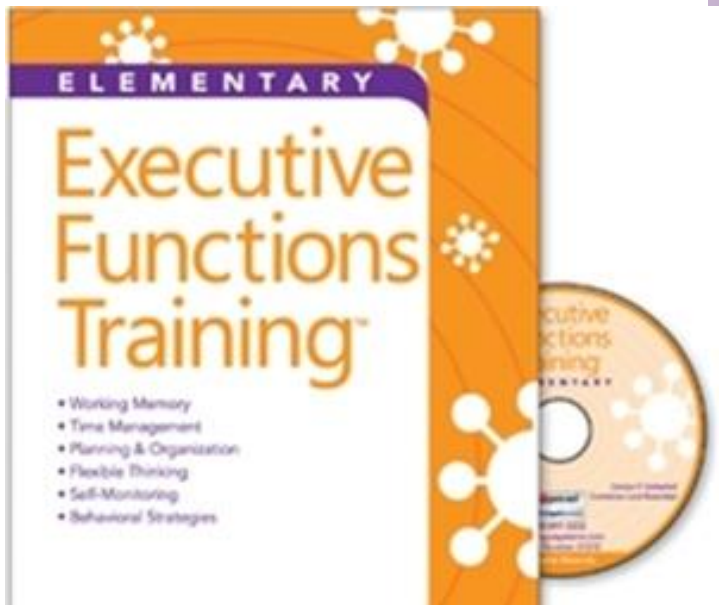
ODD



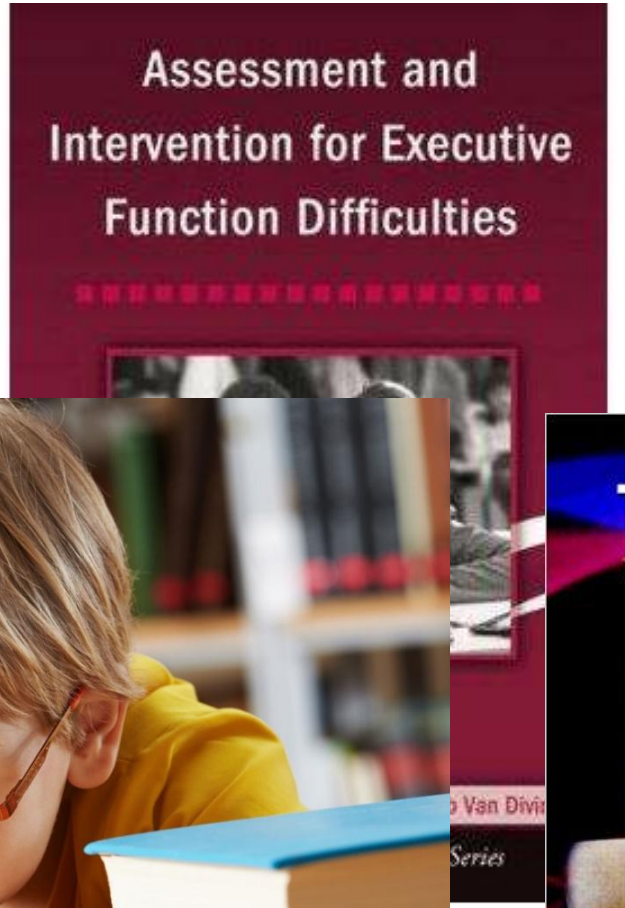
- The MTA Cooperative Group; Multimodal Treatment Study of Children with ADHD. A 14-month randomized clinical trial of treatment strategies for attentiondeficit/hyperactivity disorder. Arch Gen Psychiatry. 1999;56(12):1073–1086 140.
- Jensen PS, Hinshaw SP, Swanson JM, et al. Findings from the NIMH Multimodal Treatment Study of ADHD (MTA): implications and applications for primary care providers. J Dev Behav Pediatr. 2001;22(1):60–73 141.
- Pelham WE Jr, Gnagy EM. Psychosocial and combined treatments for ADHD. Ment Retard Dev Disabil Res Rev. 1999; 5(3):225–236

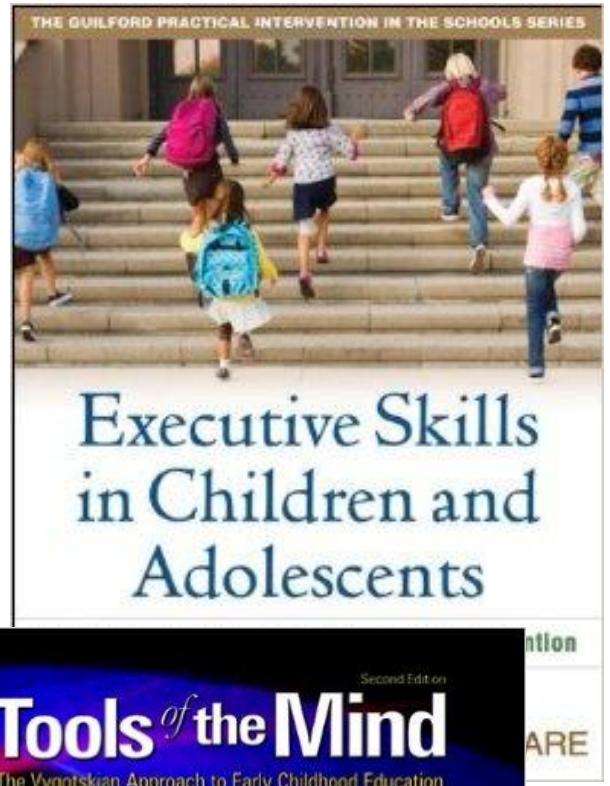
L’intervento sulle funzioni esecutive può migliorare sia le capacità di apprendimento che il funzionamento generale

(es. Diamond & Ling, 2016, Bree et al, 2016)

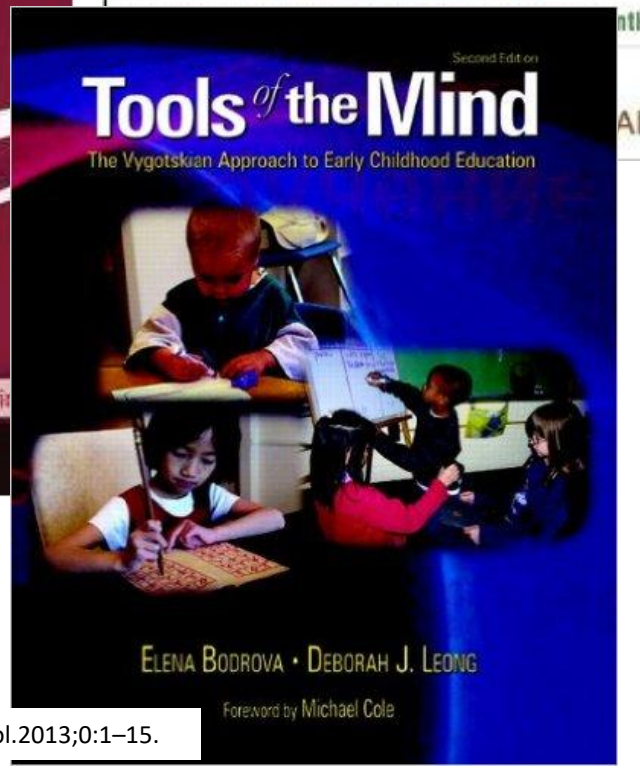














Feirsen et al, A. Cogmed working memory training for youth with ADHD: a closer examination of efficacy utilizing evidence-based criteria. J Clin Child Adolesc Psychol.2013;0:1–15.



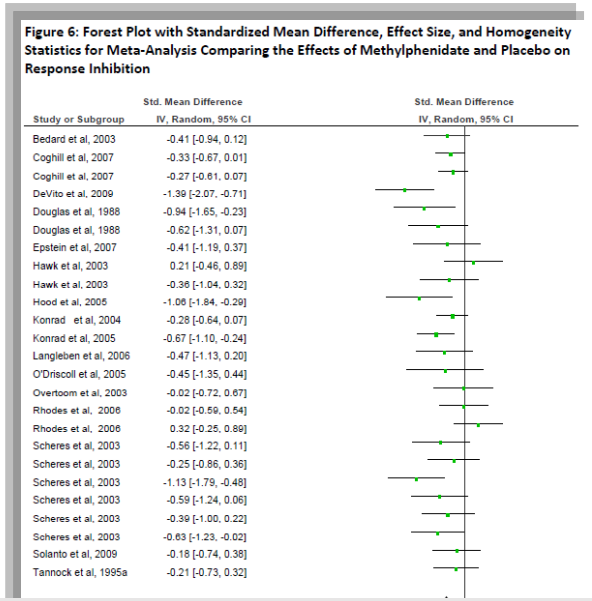
La terapia con Metilfenidato migliora le funzioni esecutive?

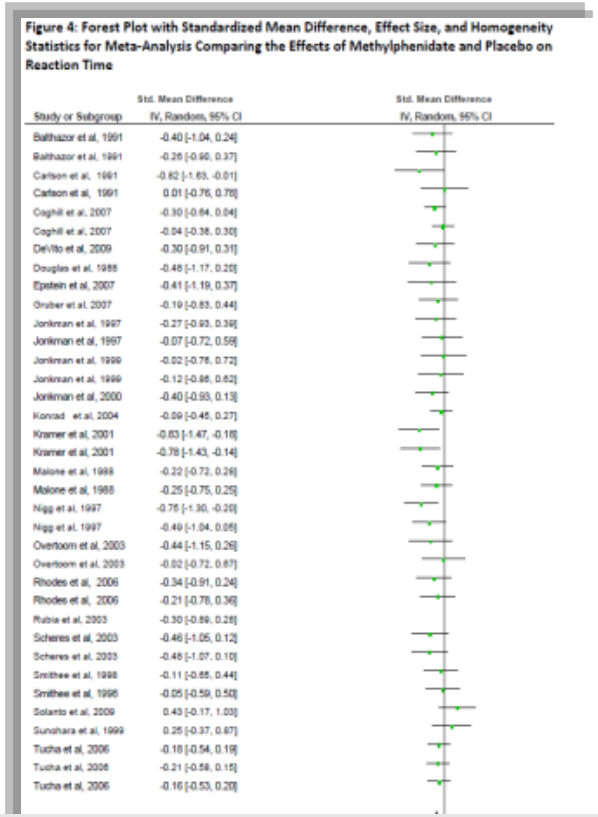
Coghill DR, Seth S, Pedroso S, Usala T, Currie J, Gagliano A
Effects of Methylphenidate on Cognitive Functions in children with ADHD: evidence from a systematic review and a meta-analysis, Biol Psychiatry, 2014

RCTs : methylphenidate vs placebo; children and adolescents (5-18 years) with ADHD

MPH was superior to placebo

1. **Executive memory**, SMD 0.26;95% CI -0.39 to -0.13;
2. **Non-executive memory**, SMD 0.60; 95% CI -0.79 to -0.41;
3. **Reaction Time** SMD 0.24; 95% CI -0.33 to -0.15;
4. **Reaction Time Variability**, SMD 0.62; 95% CI -0.90 to -0.34;
5. **Response Inhibition**, SMD 0.41; 95% CI - 0.55 to -0.27

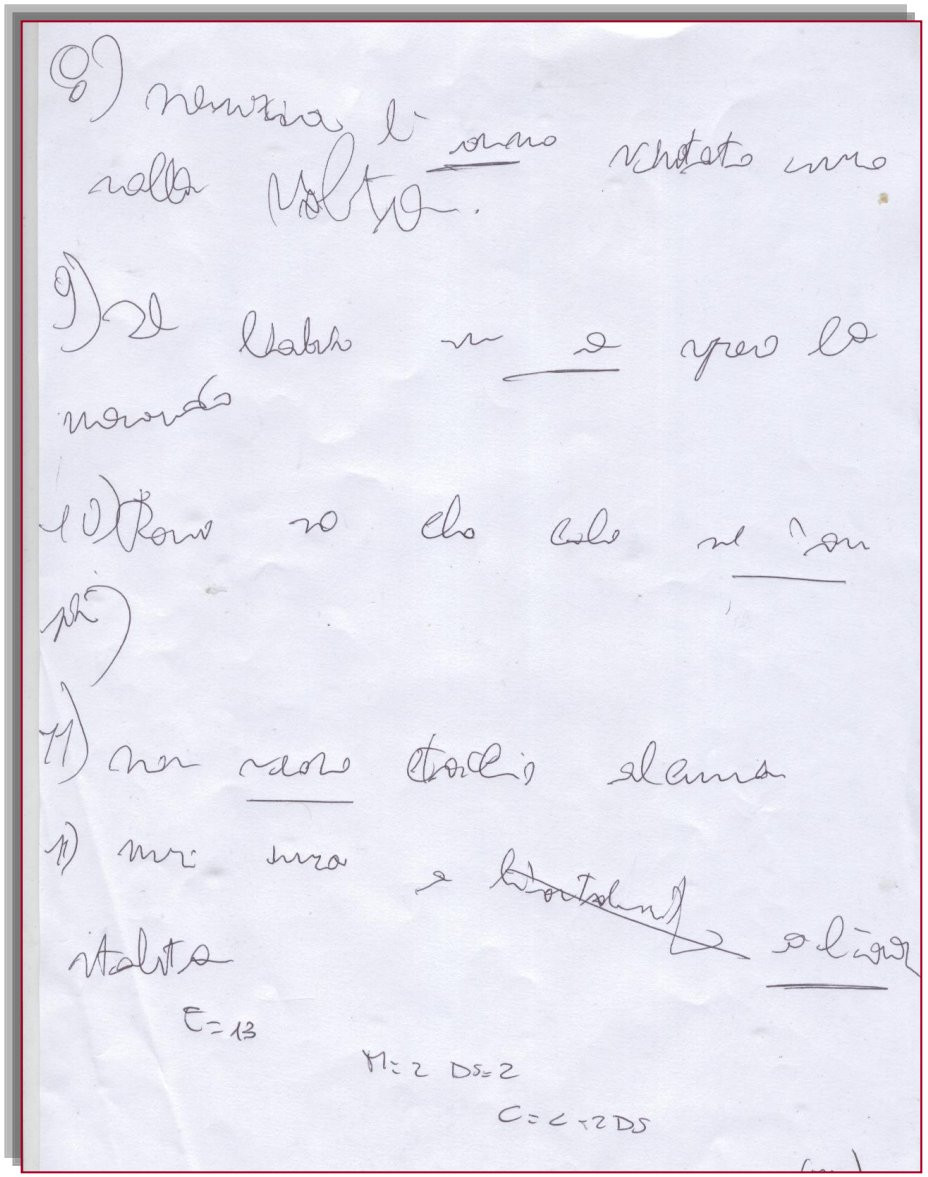




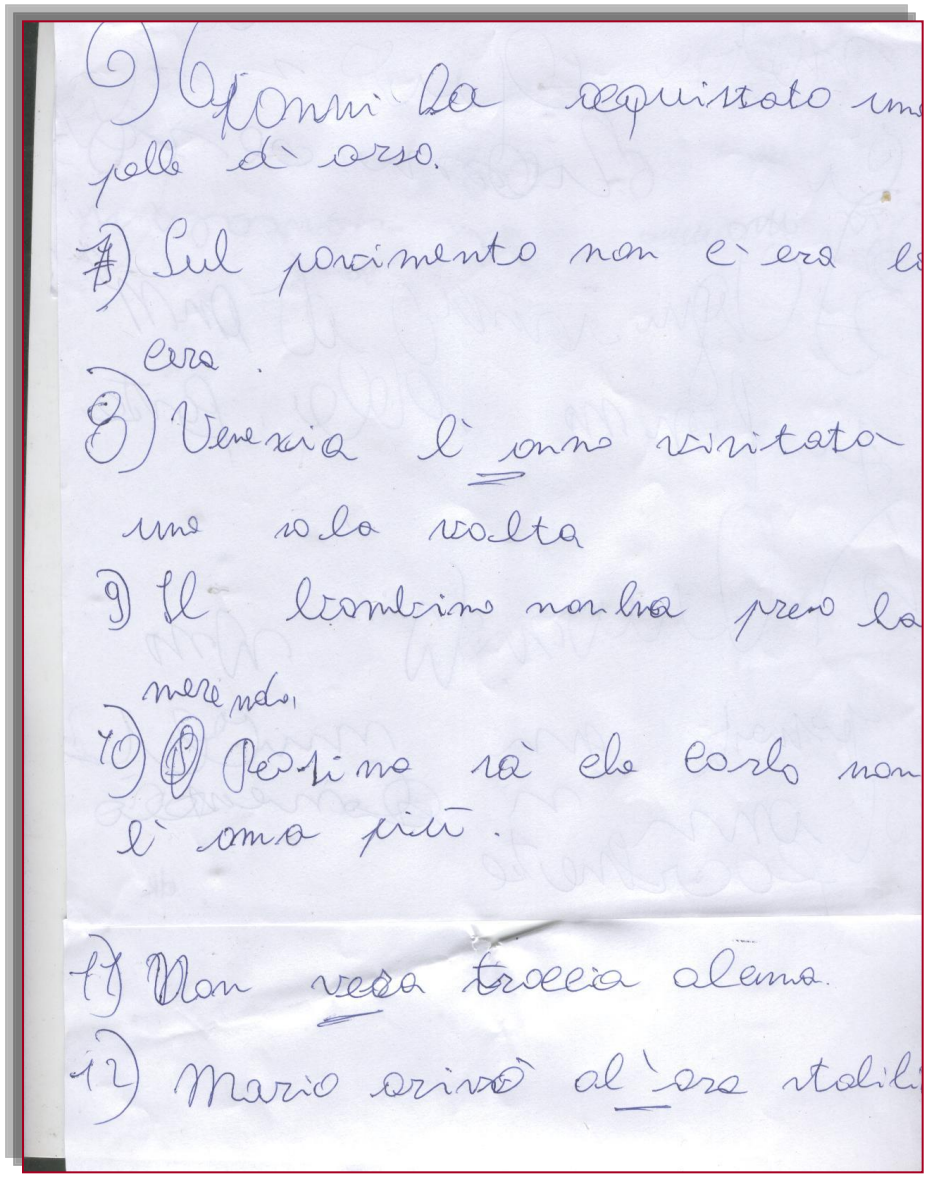
even if the effect sizes are smaller than those reported for behavioral symptoms, MPH has positive effects on:

- **executive and non-executive memory**
- **reaction time**
- **reaction time variability**
- **response inhibition**

A.G. a.11; **Dose test di MPH** (0.5 mg IR); osservazione personale Marzo 2012



Baseline

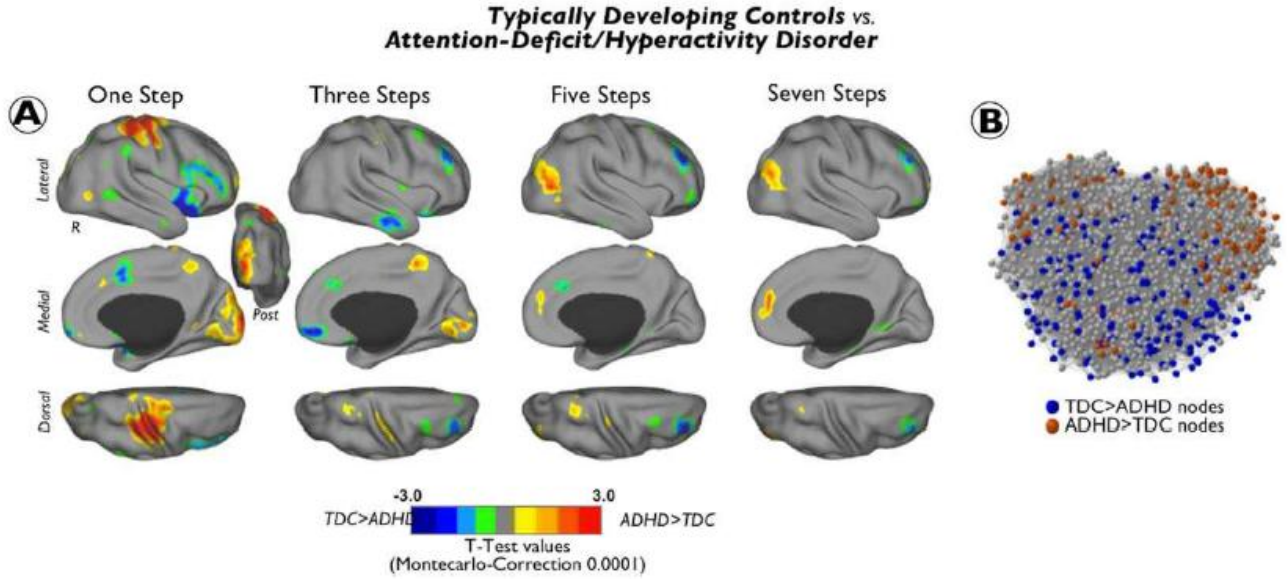


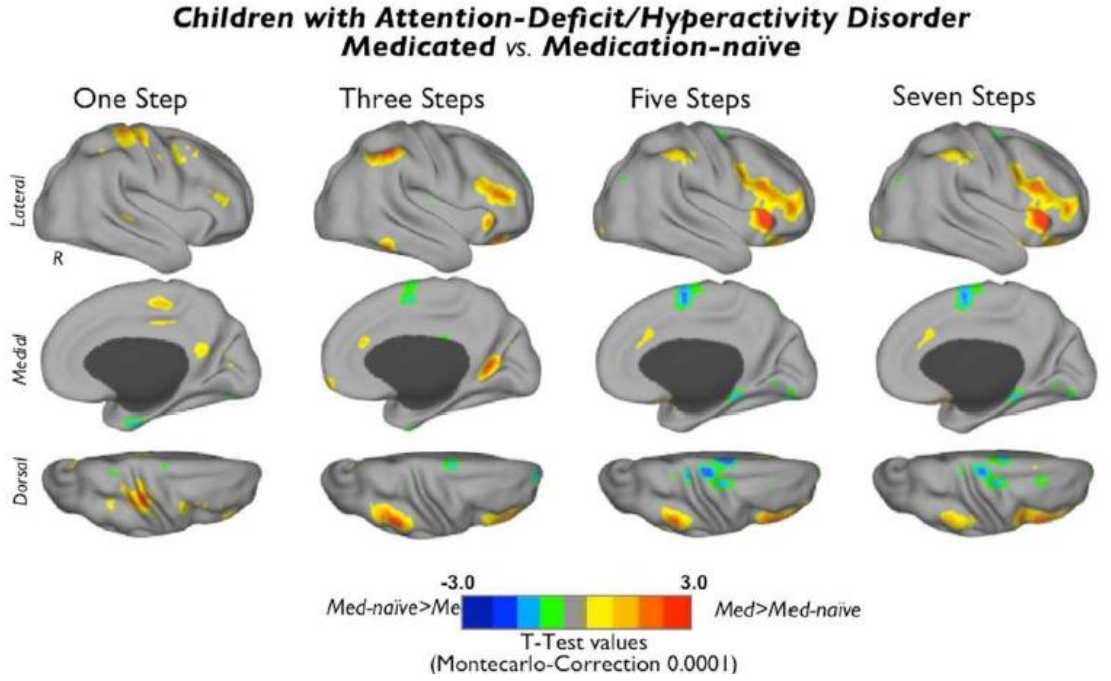
1.5 hours later

functional connectivity streams that link sensory, attentional, and higher-order cognitive circuits is atypical in ADHD

Carmona S, Hoekzema E, Castellanos FX, García-García D, et al. Sensation-to-cognition cortical streams in attention-deficit/hyperactivity disorder. Hum Brain Mapp. 2015 Jul;36(7):2544-57.

- graph-theory method to the **resting-state functional RM**
- **120 children with ADHD and 120 typically developing children (TDC)**

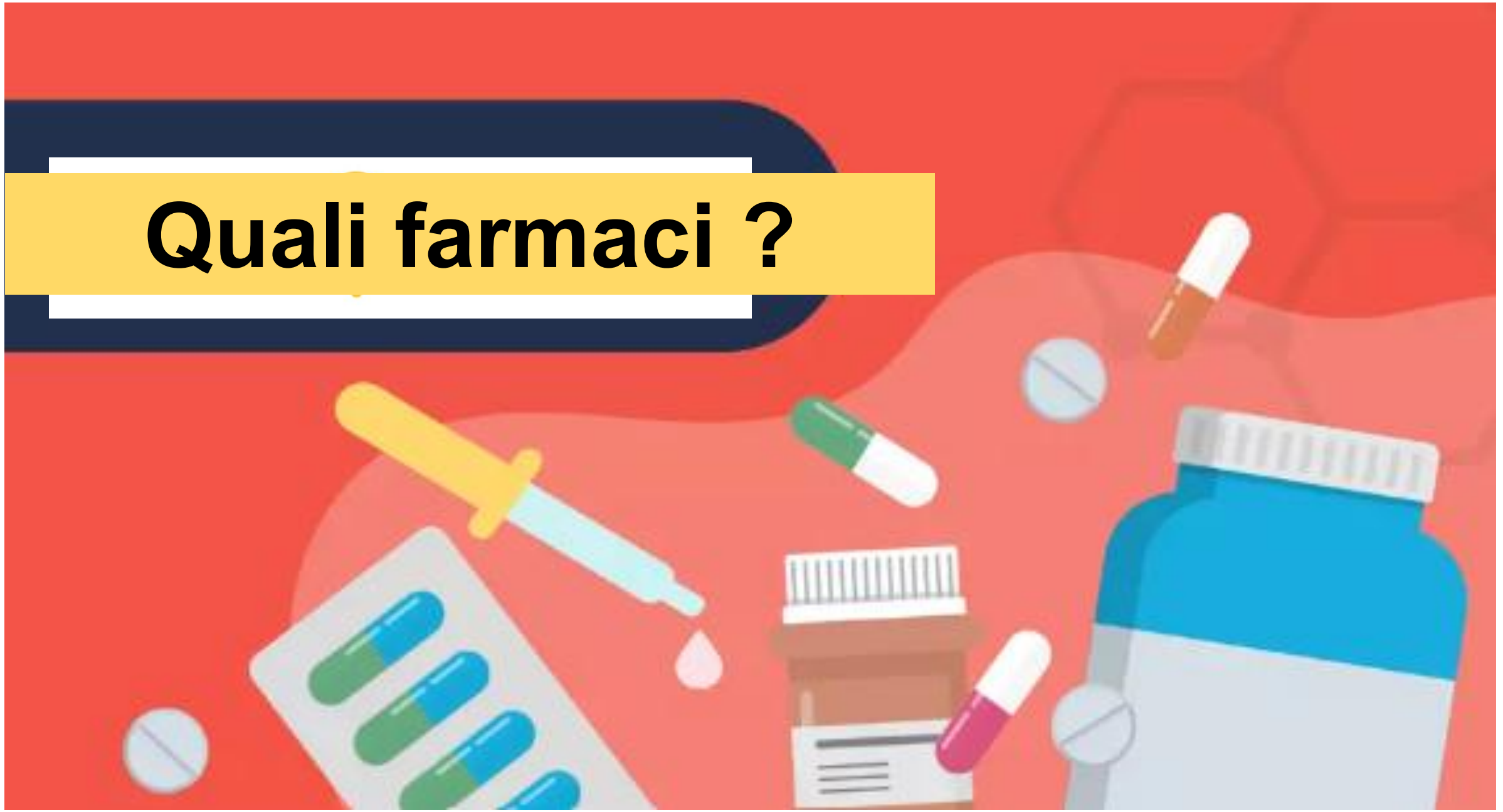




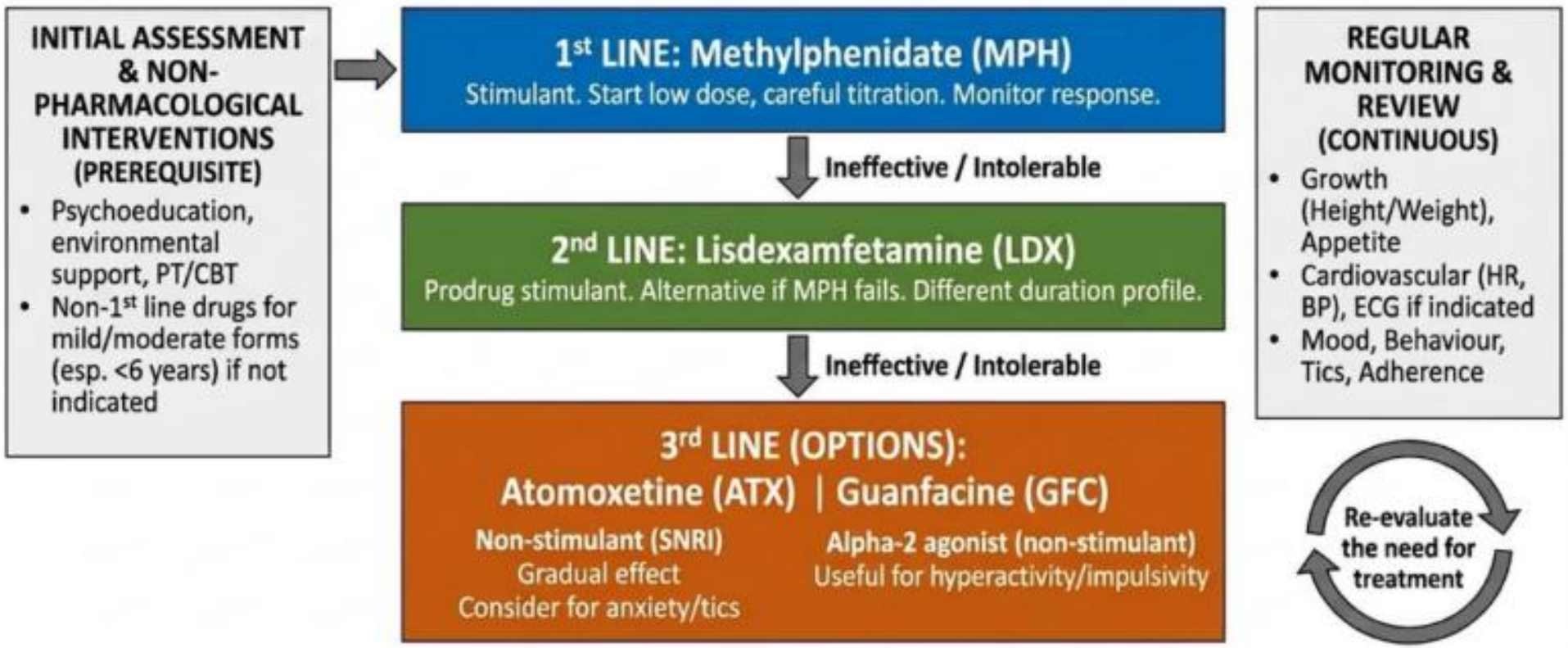
decreased connectivity to executive processing areas and increased degree of **connections to default mode regions**

psychostimulants improve the functional connectivity streams with higher degree of connectivity to regions subserving attentional and executive processes

Quali farmaci ?



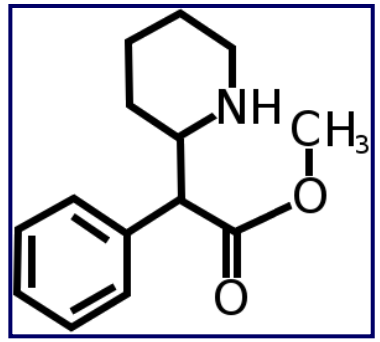
NICE 2018: Pharmacological Treatment Algorithm (Children & Young Adult): Stepwise Approach [1]



Note: This infographic is a summary for illustrative congress purposes. Always refer to the full NICE guideline text [NG87] (2018) for clinical details and official recommendations.

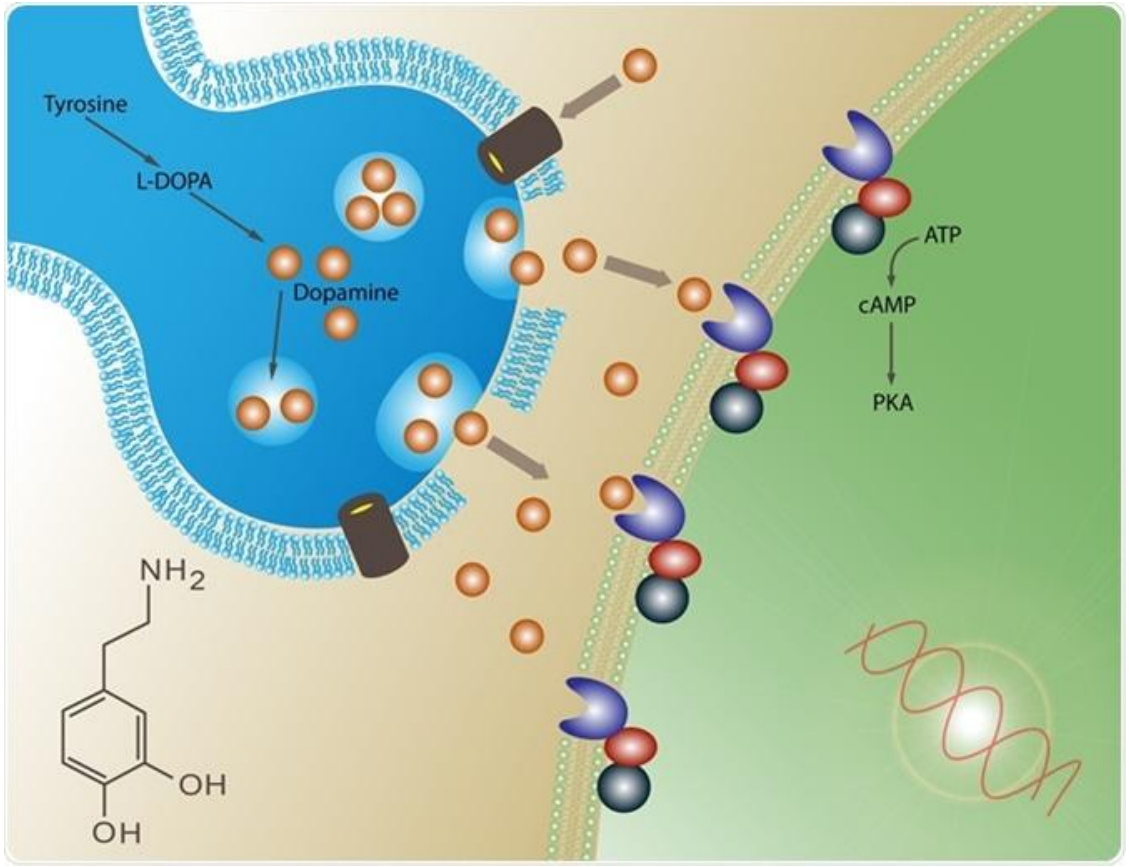
1, https://www.nice.org.uk/guidance/ng87

Methylphenidate hydrochloride



central nervous system stimulant

- **blocca il reuptake di dopamina e noradrenalina dal neurone presinaptico**
- **aumenta il rilascio di dopamina e noradrenalina**

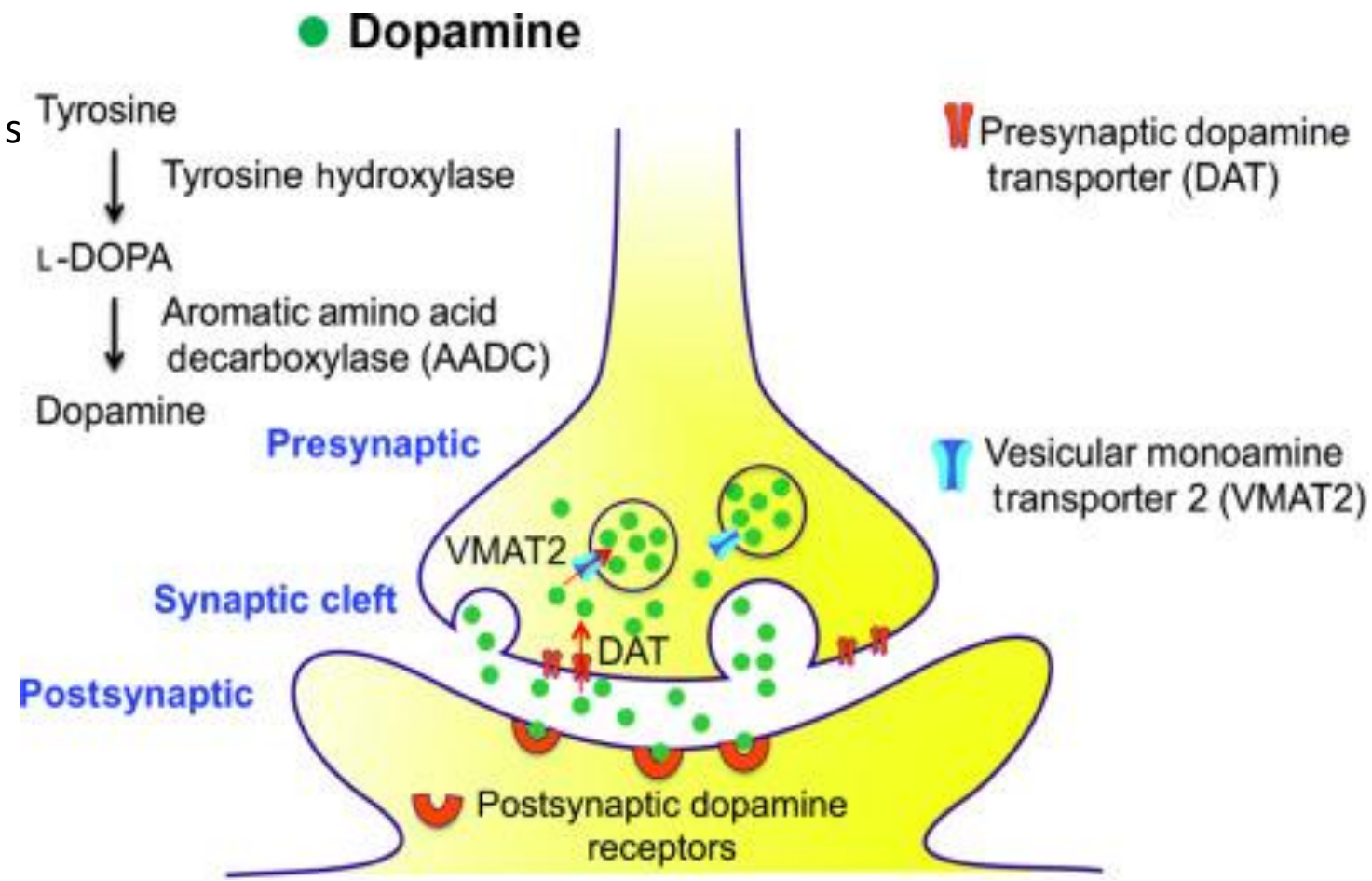


Metilfenidato: il blocco del trasportatore della dopamina induce **aumento della concentrazione della dopamina, in particolare nei gangli della base** che mostrano la più alta espressione del trasportatore

meccanismi alla base dell'ADHD

La proteina trasportatrice della dopamina (DAT) e il suo gene DAT1 (SLC6A3)

- **maggiore attività del trasportatore DAT1 nell'ADHD, rispetto agli individui sani** [Faraone et al., 2014]
- **diminuita trasmissione dopaminergica per alterazioni strutturali nei recettori della dopamina** [Volkow et al., 2007].



specifiche varianti geniche del gene DAT1

[Franke et al., 2010]

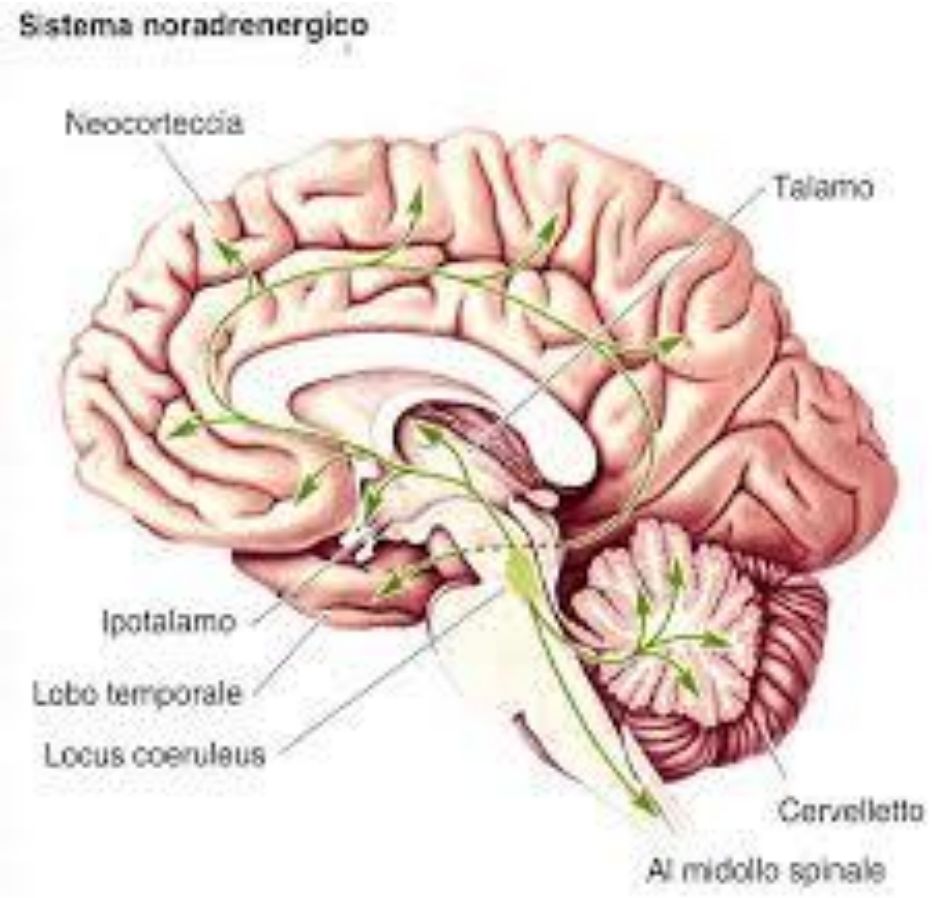
associazione di questo insieme di geni con la gravità dei sintomi nei bambini

[Bralten et al., 2013]

Noradrenalina

La trasmissione noradrenergica è collegata al sistema dopaminergico perché **la noradrenalina è un prodotto a valle del metabolismo della dopamina** che regola importanti funzioni cognitive, come la **memoria di lavoro e il controllo inibitorio**, attraverso le proiezioni che hanno origine nel **locus coeruleus e innervano aree della corteccia, del talamo e del cervelletto**

(Del Campo et al. 2011)



L'innervazione della corteccia prefrontale (PFC) da parte delle vie noradrenergiche è particolarmente importante nell'ADHD

I meccanismi di rilascio di noradrenalina e dopamina sono intimamente collegati nella PFC

(Arnsten e Pliszka, 2011; Xing et al. 2016)

AIFA - Concept Paper , 2014 -**GESTIONE FARMACOLOGICA DEL DISTURBO DA DEFICIT ATTENTIVO CON IPERATTIVITA' (ADHD)**



Le **formulazioni a rilascio immediato** (breve durata d'azione) vengono di solito somministrate 2 o 3 volte al giorno.

Il trattamento con le formulazioni a rilascio immediato dovrebbe iniziare alla **dose di 5 mg, 1 o 2 volte al giorno**, aumentando se necessario **fino ad un massimo di 60 mg/die**, suddivisa in 2-3 somministrazioni giornaliere

(NICE Technology appraisals, TA98 - Issued: March 2006)

Il trattamento deve essere **sospeso se non si rileva una risposta entro un mese** dall'inizio della terapia



MPH Long Acting Formulations

Sul supplemento ordinario n. 13 alla G.U. del 22 febbraio 2013 e con determinazione in G.U. 266 n.172 del 24 luglio 2013 sono state pubblicate le determinazioni di autorizzazione all'immissione in commercio (AIC) di

Medikinet®, (capsule rigide a rilascio modificato da 5, 10, 20, 30, 40 mg)

Equasym®,
capsule a rilascio modificato da 10, 20, 30 mg.

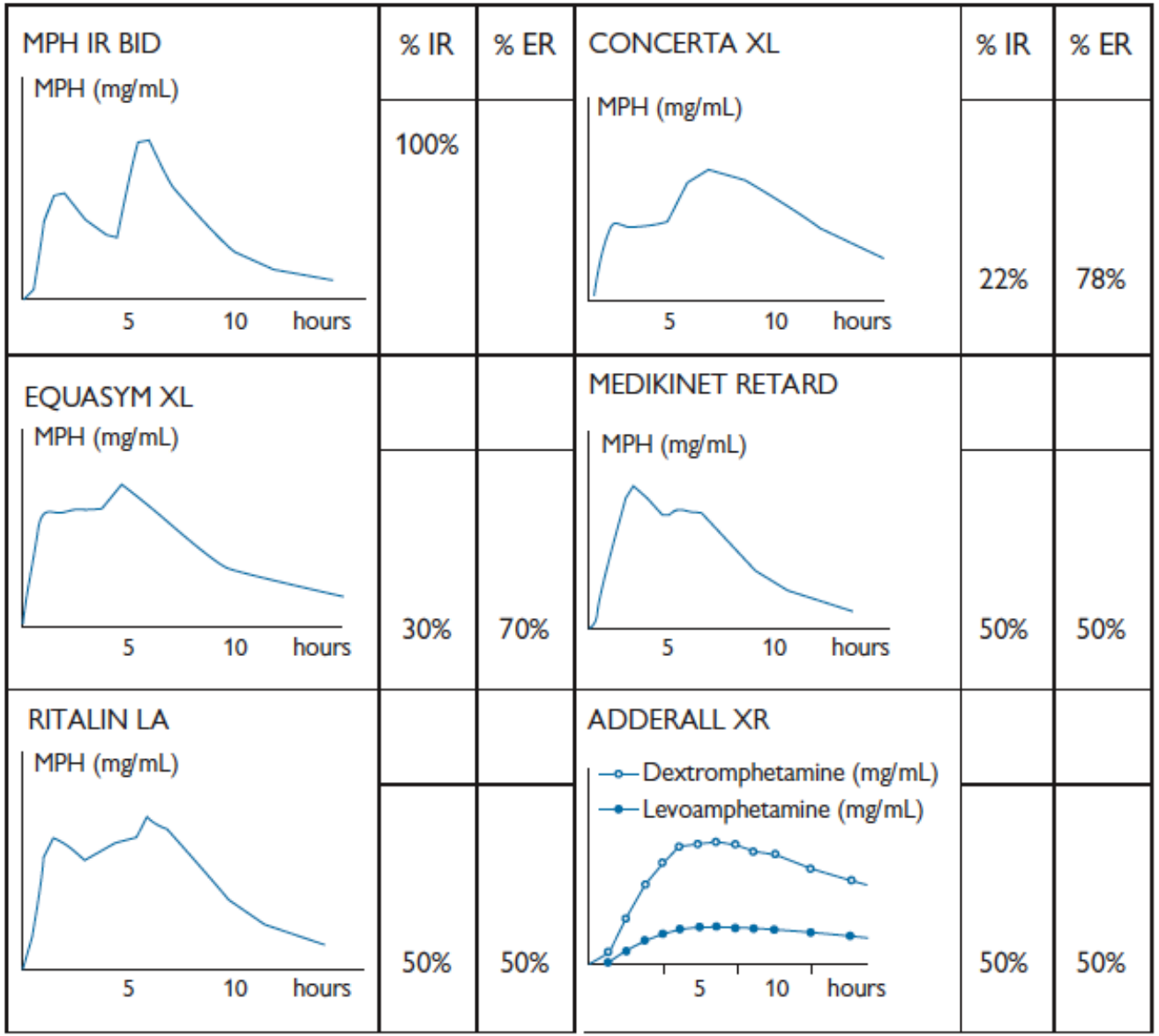
le **formulazioni a rilascio immediato** determinano delle **fluttuazioni dei picchi di concentrazione** associati ad ogni singola somministrazione:

un rapido aumento della concentrazione plasmatica di farmaco con un picco dopo 2 ore, seguito poi da un rapido declino **(t ½ ~ 2 ore)**

Il rapido aumento della concentrazione plasmatica è responsabile della **tolleranza acuta**, mentre il declino rapido successivo causa il ridotto beneficio terapeutico

AIFA - Concept Paper , 2014 -**GESTIONE FARMACOLOGICA DEL DISTURBO DA DEFICIT ATTENTIVO CON IPERATTIVITA' (ADHD)**

Figure 5.2 MPH and amphetamine plasma levels over time with different preparations and their IR/ER proportions



Le formulazioni **extended-release(ER)** sono dotate di un sistema di rilascio del farmaco: **una parte della dose viene rilasciata immediatamente**, garantendo una rapida azione, **la restante parte viene rilasciata come una dose costante/regolare** per un periodo di tempo prolungato, fino ad un massimo di 12 ore; richiedono **una sola somministrazione giornaliera**.

Pharmacokinetic profile

Equasym XL

8 h duration of effects

10,20,30 mg strengths

30% IR; 70% ER

Medikinet

8 h duration of effects

10,20,30,40 mg strengths

50% IR; 50% ER

Reference: 1. Presented in Banaschewski et al. Eur Child Adolesc Psychiatry (2006) 15: 476-495

La lista aggiornata dei farmaci per l'ADHD in Italia –

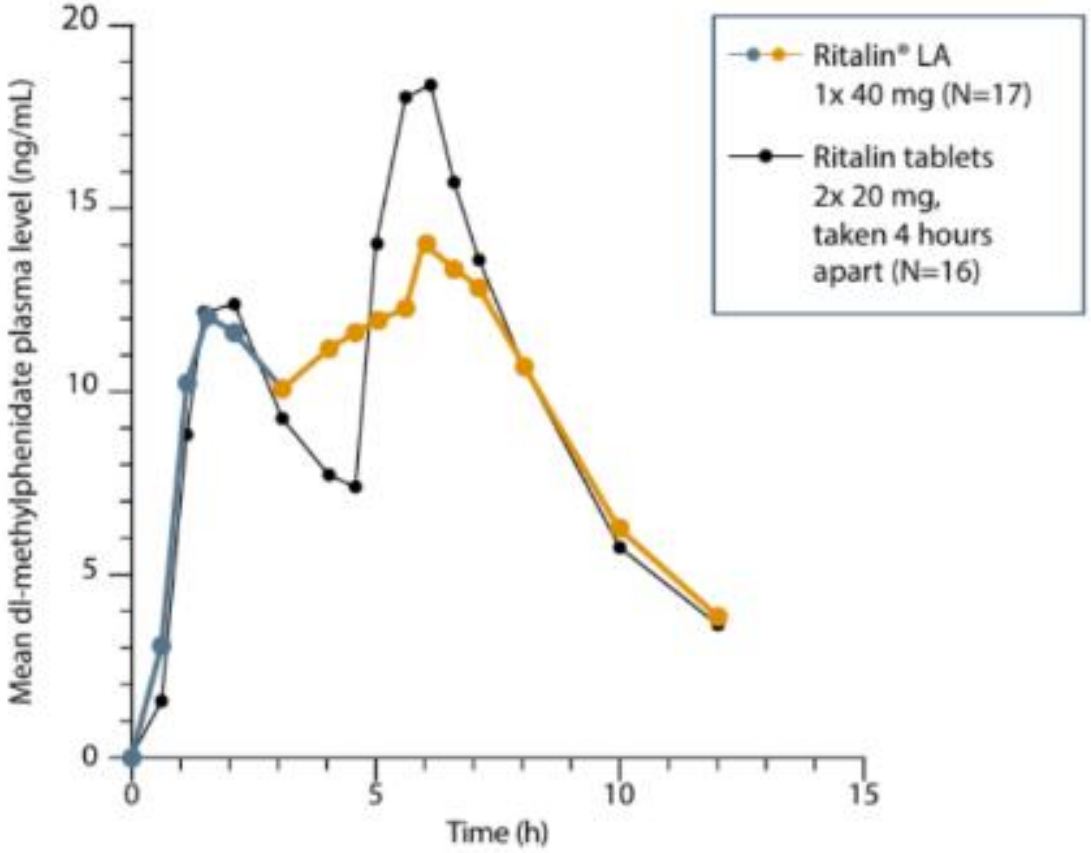
Farmaci per l'ADHD in Italia	
Farmaci Psicostimolanti	Ritalin (Metilfenidato)- Rilascio Immediato
	Ritalin Effetto Prolungato (metilfenidato) – rilascio modificato
	Equasym (Metilfenidato)
	Medikinet (Metilfenidato)
Farmaci non Psicostimolanti	Modafinil (Provigil)
	Bupropione (Wellbutrin o Zyban)
	Strattera (Atomoxetina)

Introducing Ritalin® Effetto Prolungato[1]

- Once daily dosing for both children (6 yrs and up) and adults (Up to 60 years) with ADHD
- Eight-hour duration of effect with 50:50 release profile
- Can be taken with, or without food
- Capsules may be swallowed whole, or the contents sprinkled onto a small amount of food.



1. Ritalin Effetto Prolungato SmPC



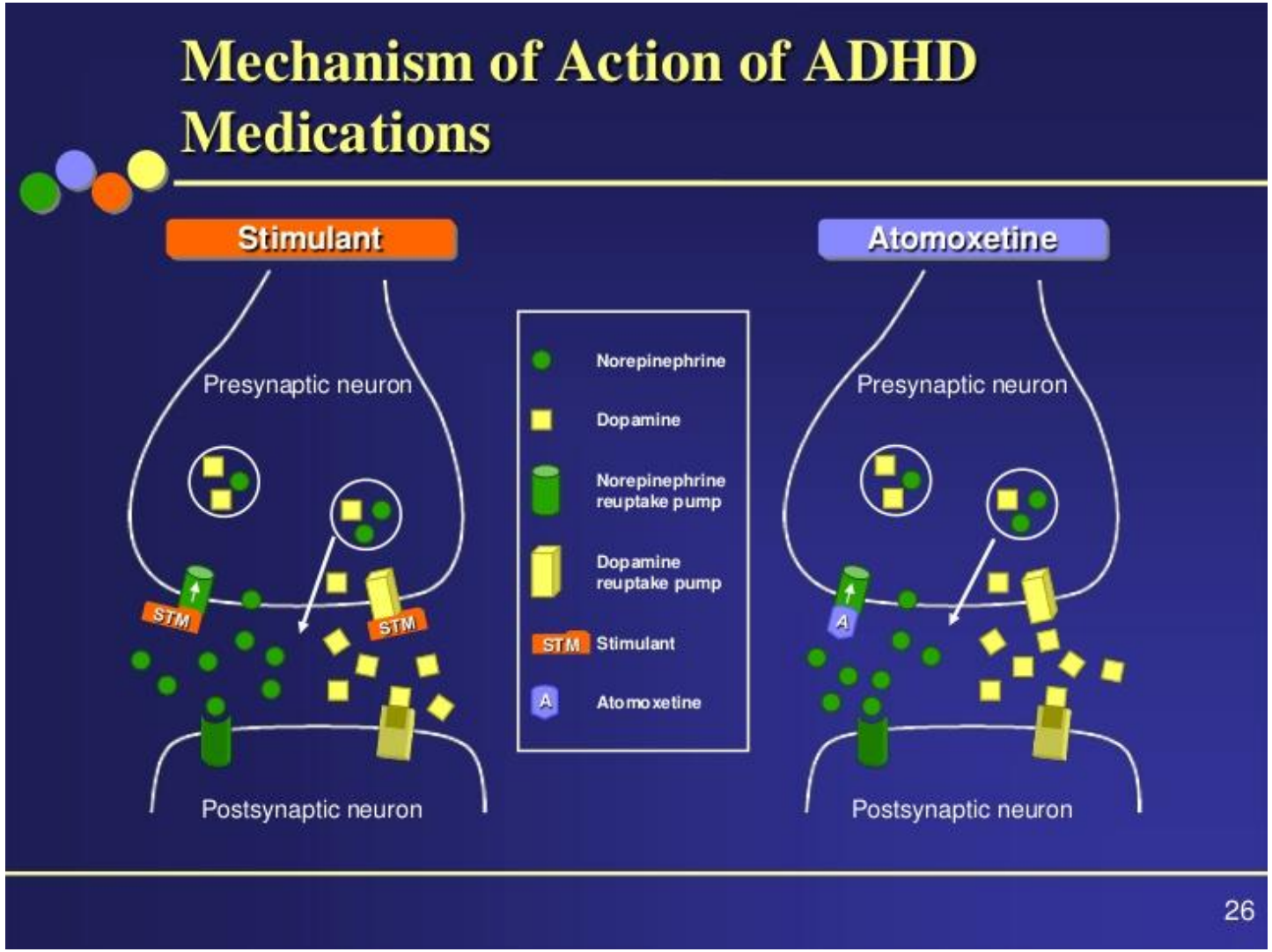
Mean plasma concentration time-profile of methylphenidate after a single dose of Ritalin LA 40 mg and Ritalin 20 mg given in two doses 4 hours apart

Adapted from Ritalin LA Prescribing Information Novartis 2021[19]

- Bioavailability study[1]
- Ritalin® LA 40mg (single dose) vs. Ritalin® Tablets 2x 20mg
- Open, randomised crossover study with adult healthy volunteers
- Ritalin® LA with biphasic plasma concentration curve with 2 distinct peaks
- **Fewer fluctuations in MPH levels with Ritalin® LA over 8 hours**
- Terminal half-life after single dose is comparable

1. https://www.novartis.com/us-en/sites/novartis_us/files/ritalin_la.pdf

Atomoxetina (inibitore selettivo del NET)



Inibitore altamente selettivo del reuptake della **Noradrenalina** *(Ki=4 nM)*

Comunque anche il MPH inibisce il trasportatore della noradrenalina (NET), oltre al DAT…

Zuddas A, Banaschewski T, Coghill D, Stein MA. (2018). ADHD treatment: psychostimulants. In: Banaschewski, T., Coghill, D., and Zuddas, A. (eds). Oxford Textbook of Attention Deficit Hyperactivity Disorder. Oxford University Press, Oxford. pp. 379-292

Zuddas A, Carucci S. (2020) Management and treatment of attention-deficit/ hyperactivity disorder. In: Geddes JR, Andreasen NC, Goodwin GM (eds). New Oxford Textbook of Psychiatry (3 edn), Oxford, pp. 344-355.

Il farmaco impiega diverse settimane per manifestare i suoi effetti terapeutici.



A seguito di presentazione di estensione delle indicazioni da parte dell'Azienda titolare di AIC anche nell'adulto (continuità terapeutica e nuove diagnosi), la CTS AIFA ha disposto che l'indicazione di Strattera® sia estesa al trattamento dell'ADHD nei bambini a partire dai 6 anni di età, degli adolescenti e negli adulti come parte di un programma multimodale.

AIFA ha concesso nella seduta di aprile 2014 la rimborsabilità dell'indicazione agli adulti.

Formulazioni e disponibilità in Italia

In Italia il medicinale a base di atomoxetina è autorizzato dal 2007 sotto forma di capsule rigide a rilascio immediato (Strattera® capsule rigide da 5-10-18-25-40-60-80-100 mg).

Strattera® può essere somministrato in una **singola dose giornaliera** al mattino, e inizialmente ad una dose giornaliera di circa **0,5 mg/kg/die**.

La dose iniziale deve essere **mantenuta per almeno 7 giorni** prima di aumentarla progressivamente in funzione della risposta clinica e della tollerabilità. La dose di mantenimento consigliata è di circa **1,2 mg/kg/die**

Prescrizione, distribuzione SSN e modalità di accesso
l'atomoxetina è soggetta a ricetta limitativa (RNRL). Il farmaco è in classe di rimborsabilità A/PT/PHT e regime di fornitura RNRL. 407

La prescrizione deve essere effettuata su diagnosi e piano terapeutico dei centri regionali di riferimento, che sono tenuti a trasmettere all'ISS i dati previsti dal "Protocollo diagnostico e terapeutico della sindrome da iperattività e deficit di attenzione per il Registro Nazionale ADHD".

modafinil

promuove la veglia, usato principalmente per trattare l'eccessiva sonnolenza legata a disturbi del sonno come la narcolessia.

Agisce sul sistema nervoso centrale aumentando i livelli di neurotrasmettitori come dopamina, istamina e orexina

- **Narcolessia:** Riduce gli attacchi di sonno improvvisi durante il giorno.
- **Altri disturbi del sonno:** Viene impiegato, per l'apnea ostruttiva del sonno e i disturbi da lavoro a turni.
- **Usi off-label:** A volte è usato per l'ADHD nell'adulto o per la depressione



Il bupropione appartiene alla classe degli **antidepressivi atipici**, utilizzato principalmente per il trattamento della depressione maggiore e, in alcuni contesti, per la cessazione del fumo.

Il bupropione agisce principalmente come **inibitore della ricaptazione di dopamina e noradrenalina**.



Differenza con gli stimolanti classici (metilfenidato, anfetamine)

Gli stimolanti aumentano rapidamente le catecolamine, il bupropione, invece, **esercita un'azione più graduale**, e, per questo motivo, **presenta un minor rischio di uso improprio**.

L’efficacia nell’ADHD è minore , ma il bupropione ha un potenziale di impiego nei soggetti adulti che non tollerano gli stimolanti.

Come monitorare la risposta



Linee Guida

Guida pratica SINPIA al trattamento farmacologico dell'ADHD in Età Evolutiva

SINPIA practical guide for the pharmacological treatment of ADHD in children and adolescents

Samuele Cortese[1-5], Sara Carucci[6], Antonella Gagliano[7], Luigi Mazzone[8], Stefania Millepiedi[9], Rosamaria Siracusano[10], Benedetto Vitiello[11], Gabriele Masi[12]

- **L'efficacia è valutata clinicamente** raccogliendo in modo sistematico informazioni sul comportamento del bambino da genitori/caregiver e, se possibile, dagli insegnanti.
- È opportuno utilizzare **scale standardizzate** (per esempio SNAP-IV o ADHD Rating Scale) per valutare la severità del quadro clinico prima di iniziare il trattamento.
- **Tali scale andrebbero ripetute entro un mese** dall'avvio della terapia, al fine di documentare eventuali cambiamenti.
- Il clinico dovrebbe **integrare le informazioni** ottenute da genitori/caregivers e, se possibile, insegnanti, e formulare una valutazione globale di severità e miglioramento.
- Una volta identificata la **dose efficace di mantenimento** per il paziente, la risposta va monitorata periodicamente a **intervalli di circa 3-6 mesi**



La terapia con Metilfenidato migliora le performance scolastiche dei ragazzini ADHD ?

Prasad et al, How effective are drug treatments for children with ADHD at **improving on-task behaviour and academic achievement** in the school classroom? A systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2013 Apr;22(4):203-16.

43 studies (2,110 participants)

Drug treatment benefited children in **school work by up to 15%**

less consistently improved children's accuracy in specific types of academic assignments, such as arithmetic…



Similar improvements were seen in classroom behaviour, with up to **14% more** of children's **time spent "on task"**

Methylphenidate, dexamfetamine and mixed amfetamine formulations showed higher cognitive beneficial effects than Atomoxetine

OPEN ACCESS

Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials

Ole Jakob Storebø,[1,2,3] Helle B Krogh,[1,2] Erica Ramstad,[1,2] Carlos R Moreira-Maia,[4] Mathilde Holmskov,[1] Maria Skoog,[5] Trine Danvad Nilausen,[1] Frederik L Magnusson,[1] Morris Zwi,[6] Donna Gillies,[7] Susanne Rosendal,[8] Camilla Groth,[9] Kirsten Buch Rasmussen,[1] Dorothy Gauci,[10] Richard Kirubakaran,[11] Bente Forsbøl,[1] Erik Simonsen,[1,12] Christian Gluud[5,13]

Valutazione dell'efficacia del MPH effettuata dagli insegnanti

Study	Methylphenidate Mean	SD	No	Control Mean	SD	No
Arnold 2004	0.7	0.7	35	1.4	0.9	40
Biederman 2003	16.3	12.1	63	31.3	15.4	71
Brown 1985	15.1	4.6	10	15.7	2.9	10
Butter 1983	30.5	17.3	10	42.7	14.2	10
Childress 2009	16.4	13.4	57	30.0	13.1	63
Findling 2006	4.3	3.2	120	7.7	3.1	39
Findling 2008	18.3	17.4	94	31.6	20.1	88
Firestone 1981	8.9	4.9	18	11.8	4.8	13
Ialongo 1994	7.5	7.4	13	15.3	7.3	12
Jensen 1999 (MTA)	0.8	0.7	134	1.1	0.8	119
Kollins 2006 (PATS)	1.1	0.8	32	1.4	0.8	32
Lehmkuhl 2002	0.9	0.7	43	1.6	0.6	42
Moshe 2012	58.0	10.3	57	64.7	12.5	57
Palumbo 2008	-5.1	6.8	29	-3.2	6.4	30
Pliszka 2000	0.8	0.62	20	1.5	0.9	18
Schachar 1997	0.9	0.7	37	1.7	0.7	29
Taylor 1987	0.5	1.04	39	1.2	1.3	39
Van der Meere 1999	73.6	12.7	24	83.1	12.7	24
Wolraich 2001	5.7	3.8	81	9.9	4.1	46
Total (95% CI)			916			782

Test for heterogeneity: $\tau^2=0.03$, $\chi^2=28.78$, df=18, P=0.05, $I^2=37\%$

Test for overall effect: z=11.23, P<0.001

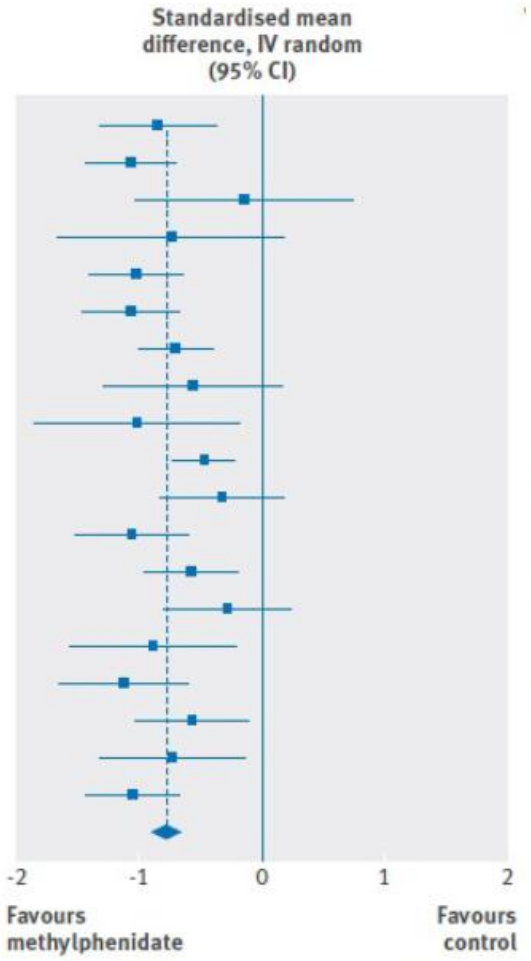


Fig 2 | Teacher rated symptoms of attention-deficit/hyperactivity disorder in parallel group trials.

Symptoms ES: 0.77

QoL ES: 0.87

No risk for
serious adverse events
RR: 0.98

Minor risk for
non-serious adverse events
RR: 1.29

BMJ 2015;351:h5203



Il trattamento deve essere diverso nelle ragazze ADHD ?

Young et al. BMC Psychiatry (2020) 20:404
https://doi.org/10.1186/s12888-020-02707-9

BMC Psychiatry

RESEARCH ARTICLE Open Access

Females with ADHD: An expert consensus statement taking a lifespan approach providing guidance for the identification and treatment of attention-deficit/hyperactivity disorder in girls and women

Susan Young[1,2*], Nicoletta Adamo[3,4], Bryndís Björk Ásgeirsdóttir[2], Polly Branney[5], Michelle Beckett[6], William Colley[7], Sally Cubbin[8], Quinton Deeley[9,10], Emad Farrag[11], Gisli Gudjonsson[2,12], Peter Hill[13], Jack Hollingdale[14], Ozge Kilic[15], Tony Lloyd[16], Peter Mason[17], Eleni Paliokosta[18], Sri Perecherla[19], Jane Sedgwick[3,20], Caroline Skirrow[21,22], Kevin Tierney[23], Kobus van Rensburg[24] and Emma Woodhouse[10,25]

Pharmacological treatment

- Medication recommendations do not differ by sex and differ only modestly by age.
- Treatment monitoring may require deviation from conventional outcomes from rating scales and behaviour management. Individualised targets (e.g. emotional lability, academic attainment) may be more appropriate.
- Prescribing needs to consider interactions between ADHD and other medications for comorbid conditions, where applicable.
- Where mood problems are apparent but not pervasive it is advisable to treat ADHD symptoms and monitor for improvement first, prior to considering or initiating treatment for mood disorders.
- Appetite suppression as a side effect of stimulant medication should be considered if eating disorders are a concern.
- Risks of substance use whilst on ADHD medications should be considered and discussed with patients.
- Treatment with ADHD medications is generally not advised during pregnancy or breastfeeding.
- Review is advised during and after key periods of hormonal change (menopause, pregnancy).
- Psychoeducation on pharmacological treatment options and treatment targets for parents and affected girls may help to improve adherence and engagement.
- Regular review is required throughout development and may be especially important at times of key transitions.

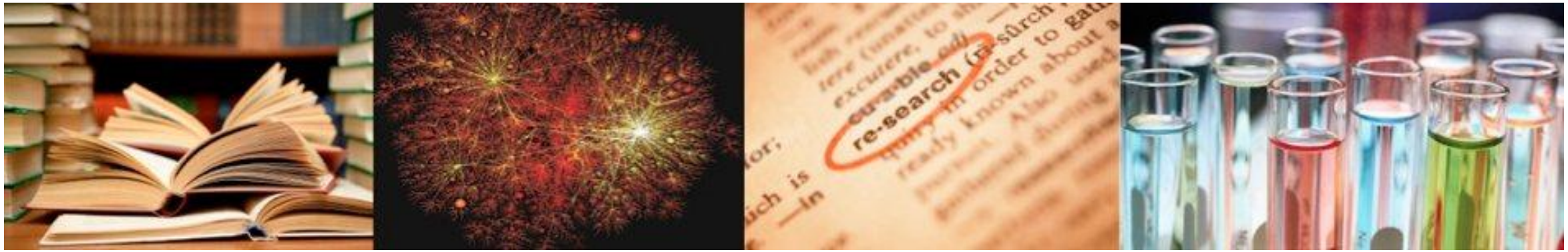
ADHD medications may differentially affect women depending on progression of their menstrual cycle due to a **link between dopamine systems (implicated in the aetiology of ADHD) and gonadal hormones**

Hormonal changes during the menstrual cycle (oestrogen and progesterone levels) may impact on the subjective **euphoric and stimulating effects**

In a case study, a woman with ADHD showed positive response to treatment adjustment around the menstrual cycle, which included **augmentation with an antidepressant (fluoxetine) during the immediate pre-menstrual period** to reduce problems with moodiness, irritability and inattention normally well controlled through stimulant medication alone



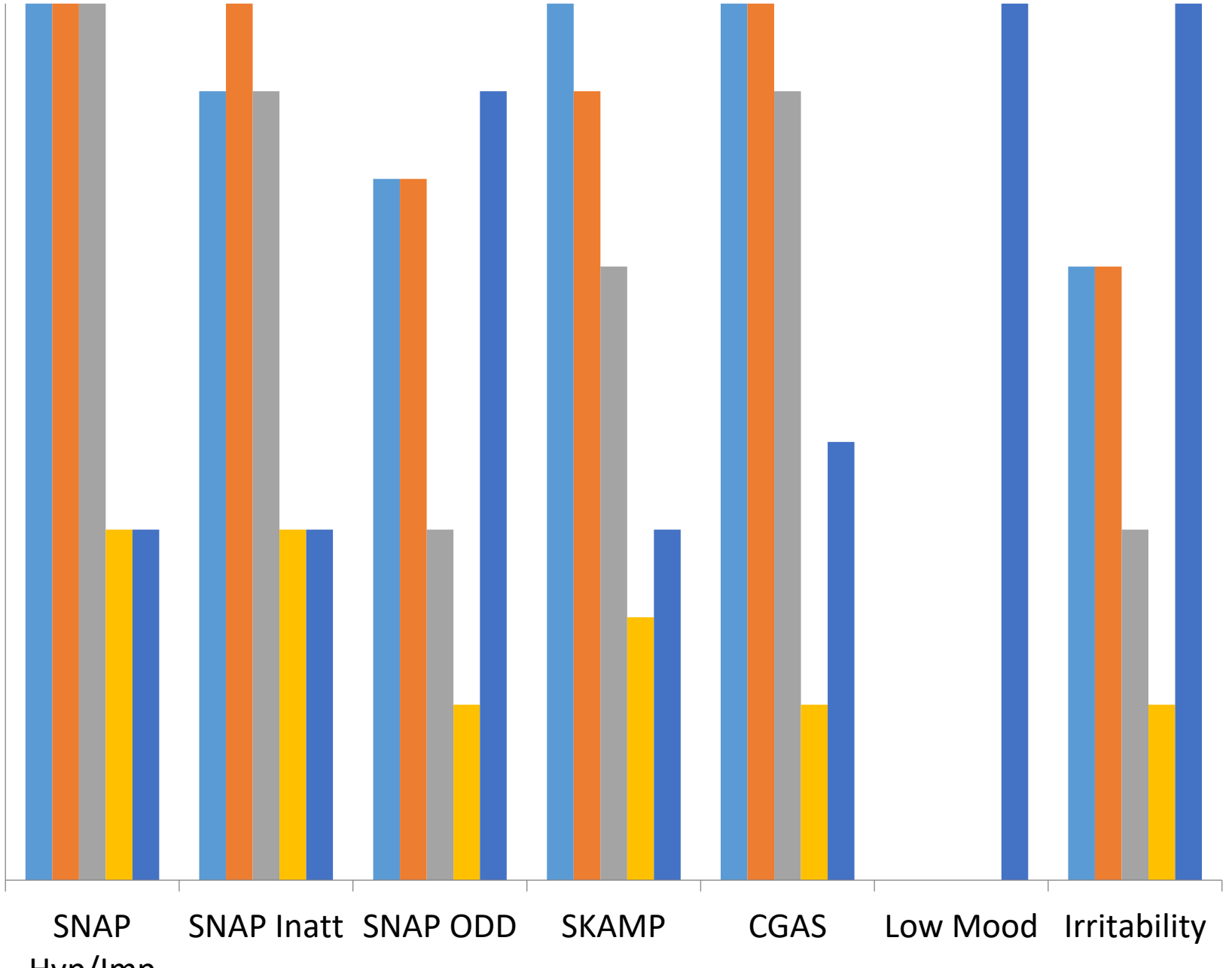
Quinn PO. Treating adolescent girls and women with ADHD: Gender specific issues. J Clin Psychol. 2005;61:579–87.



How and what drug dosage influence the response?

Coghill D, 2011

Forced Dose Titration



compared to low doses (0.25 mg/kg) **higher dose methylphenidate (0.5 mg/kg) is associated with larger effect sizes for RT and all neuropsychological measures *except* for inhibitory control**

(Konrad et al, Psychopharmacol 2005 Apr;15(2):180-90.

Methylphenidate

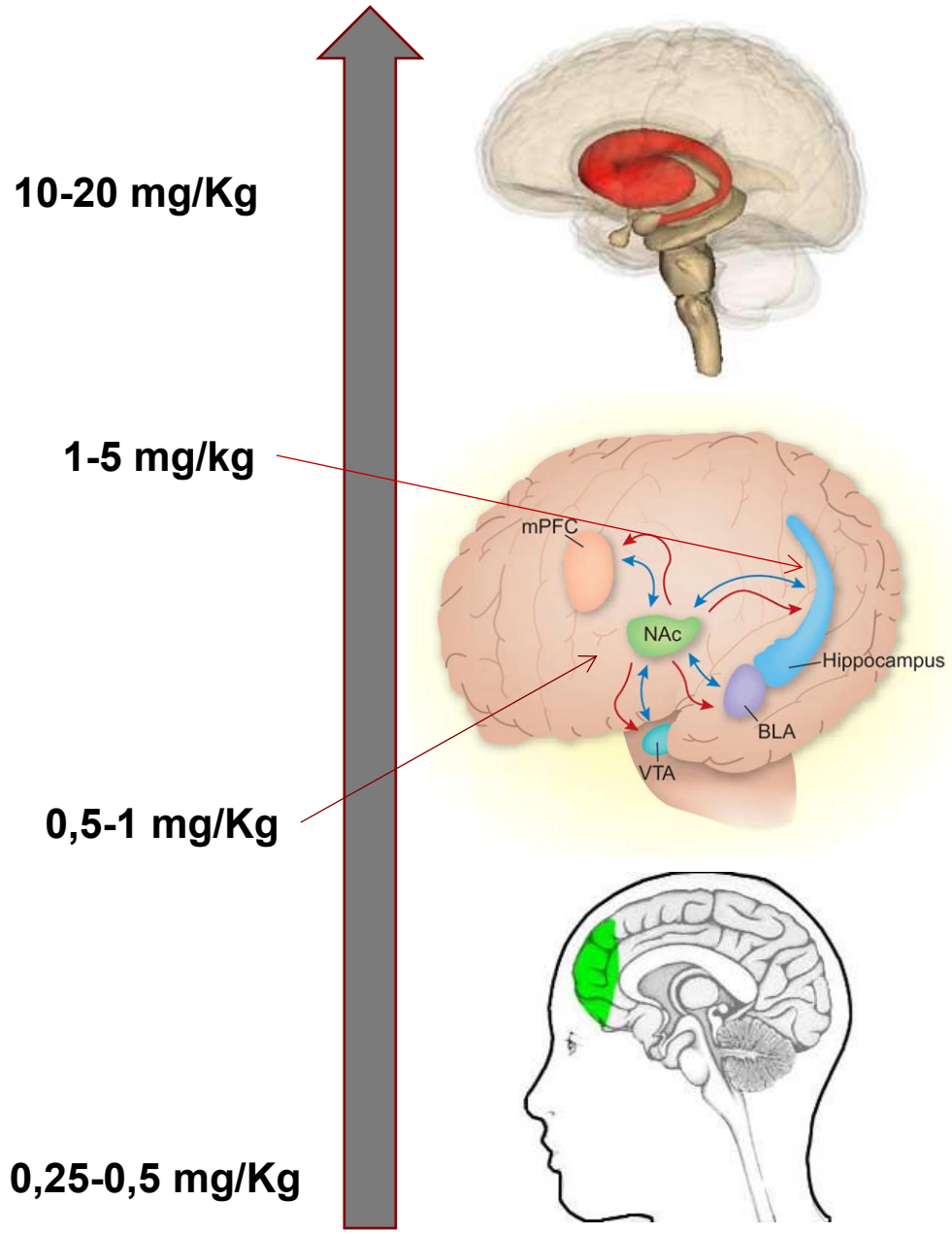
dose-dependent effect

Very high doses (**10 and 20 mg/kg** i.p.) of methylphenidate increase both NE in the prefrontal cortex and DA in the **striatum**

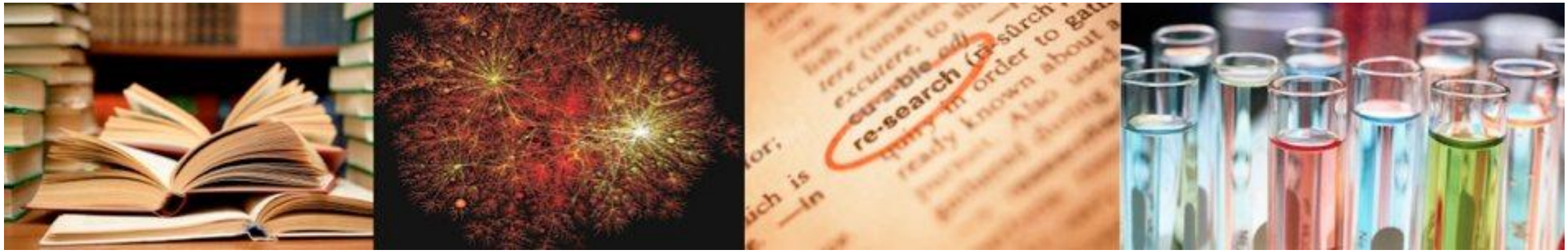
A range of doses of methylphenidate (**1.0, 2.5,and 5.0 mg/kg** p.o.) increased NE in the **hippocampus**

The higher doses (**0.5 and 1.0 mg/kg**) led to an increase in DA in the nucleus **accumbens** (the lowest dose- 0.25 mg/kg- had no effect in the nucleus accumbens)

Increase of extracellular levels of DA and NE in the **prefrontal cortex** (**0.25, 0.5**, mg/kg i.p.)



(Kuczenski and Segal, 2002, Heal et al., 2009)

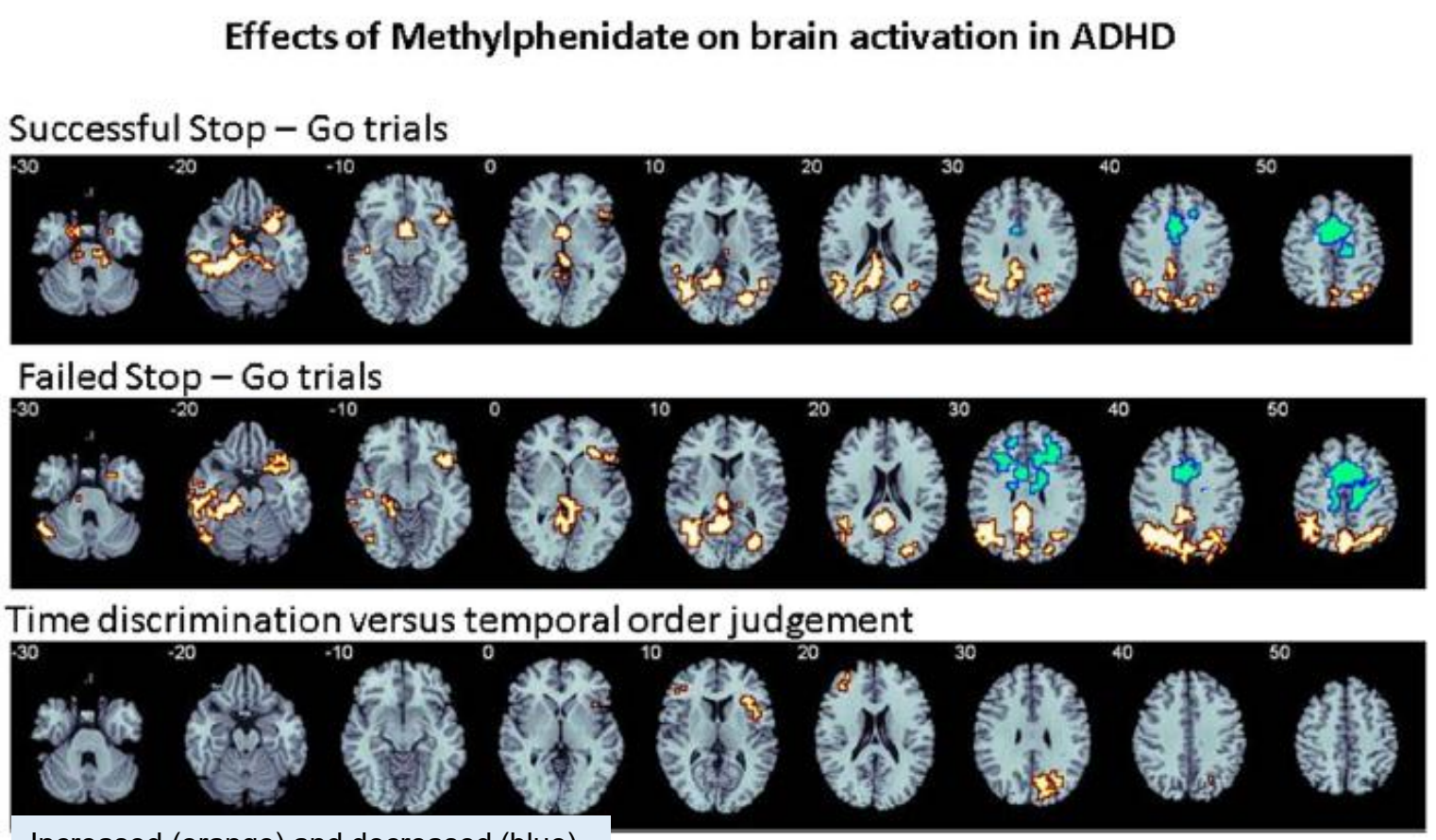


How and what drug treatments change brain activity?

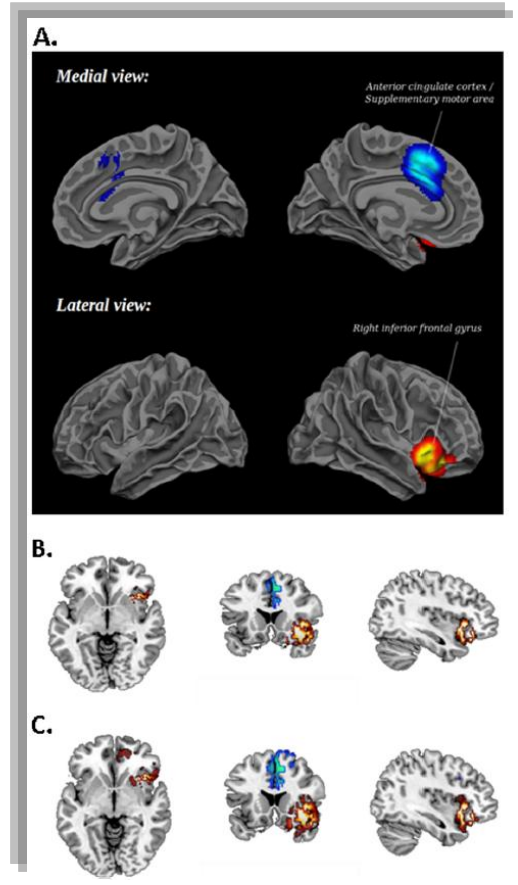
Rubia et al, BIOL PSYCHIATRY 2014;76:616–628

fMRI study

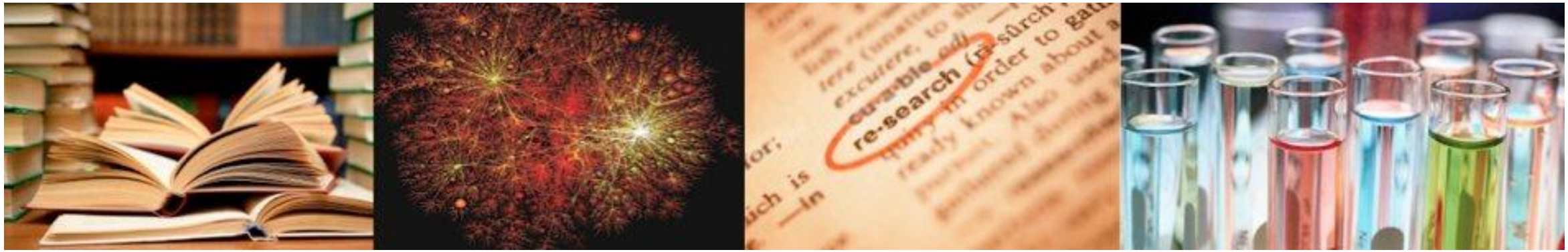
20 adolescents with ADHD under either placebo or MPH while performing stop and time discrimination tasks



Increased (orange) and decreased (blue) activation with MPH relative to placebo



MPH significantly enhanced activation in bilateral inferior frontal cortex (IFC) and insula during inhibition and time discrimination
(two of the most replicated neurocognitive dysfunctional regions in ADHD)

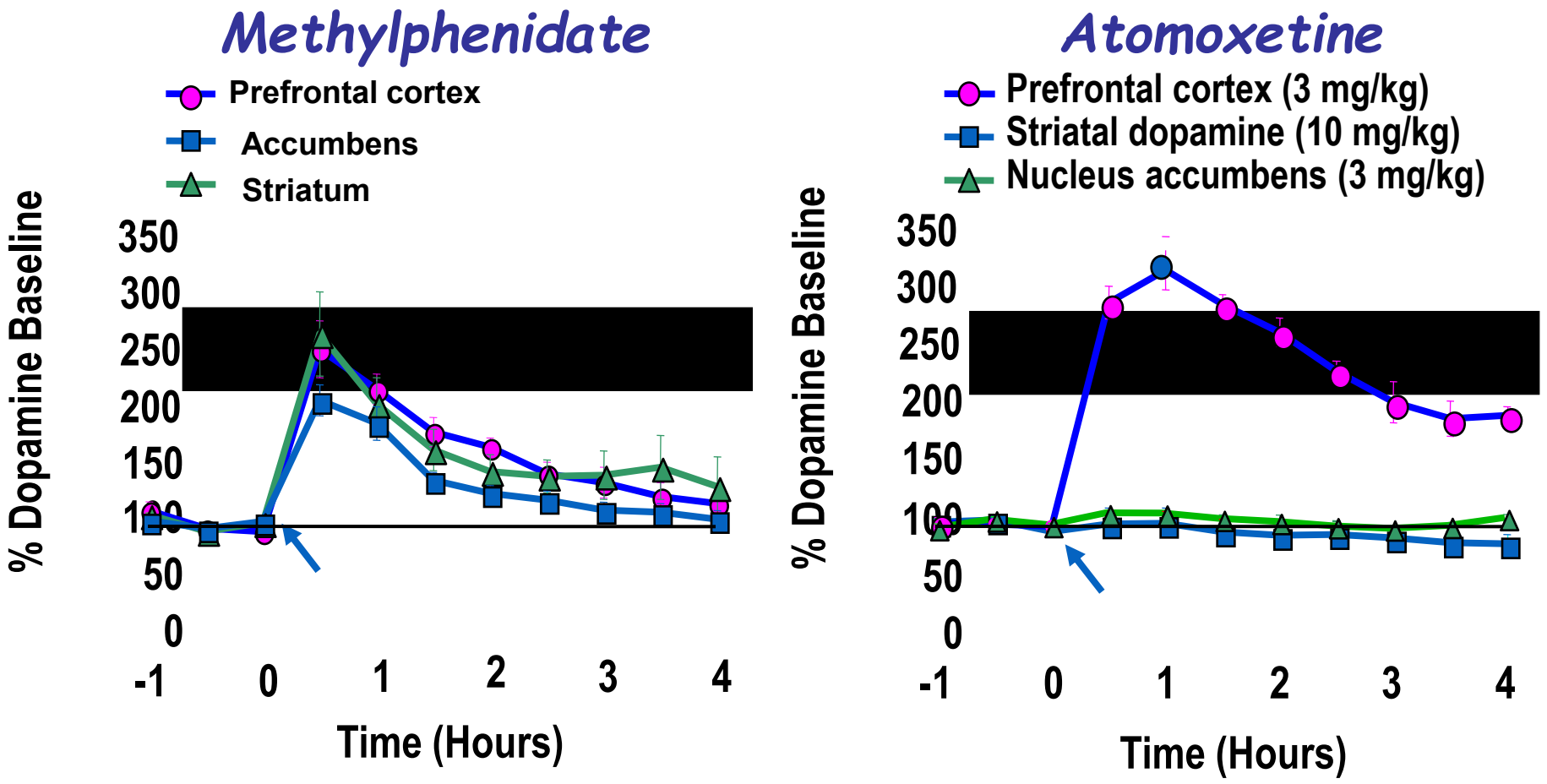


Confronto tra farmaci

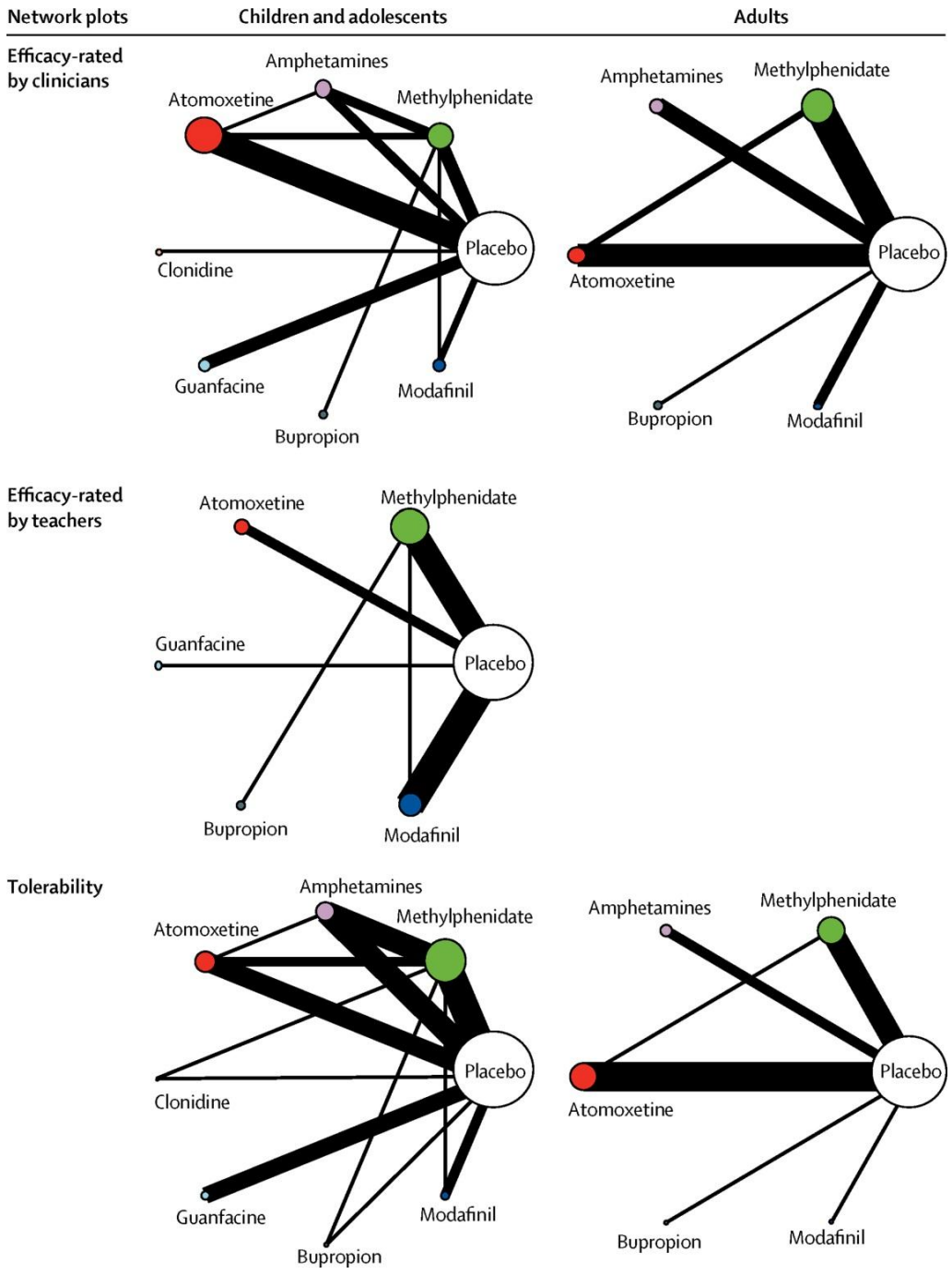
Atomoxetine vs Methylphenidate:

Effects on Extracellular Dopamine

in Rat Prefrontal Cortex, Nucleus Accumbens, and Striatum



Bymaster FP, et al. *Neuropsychopharmacology* 2002; 27(5): 699–711.



Cortes S, Adamo N, et al, Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis, **Lancet Psychiatry. 2018 Sep; 5(9): 727–738**.

Study based on **network meta-analyses** represents the most comprehensive synthesis to date on the comparative efficacy and tolerability of medications for ADHD across age groups

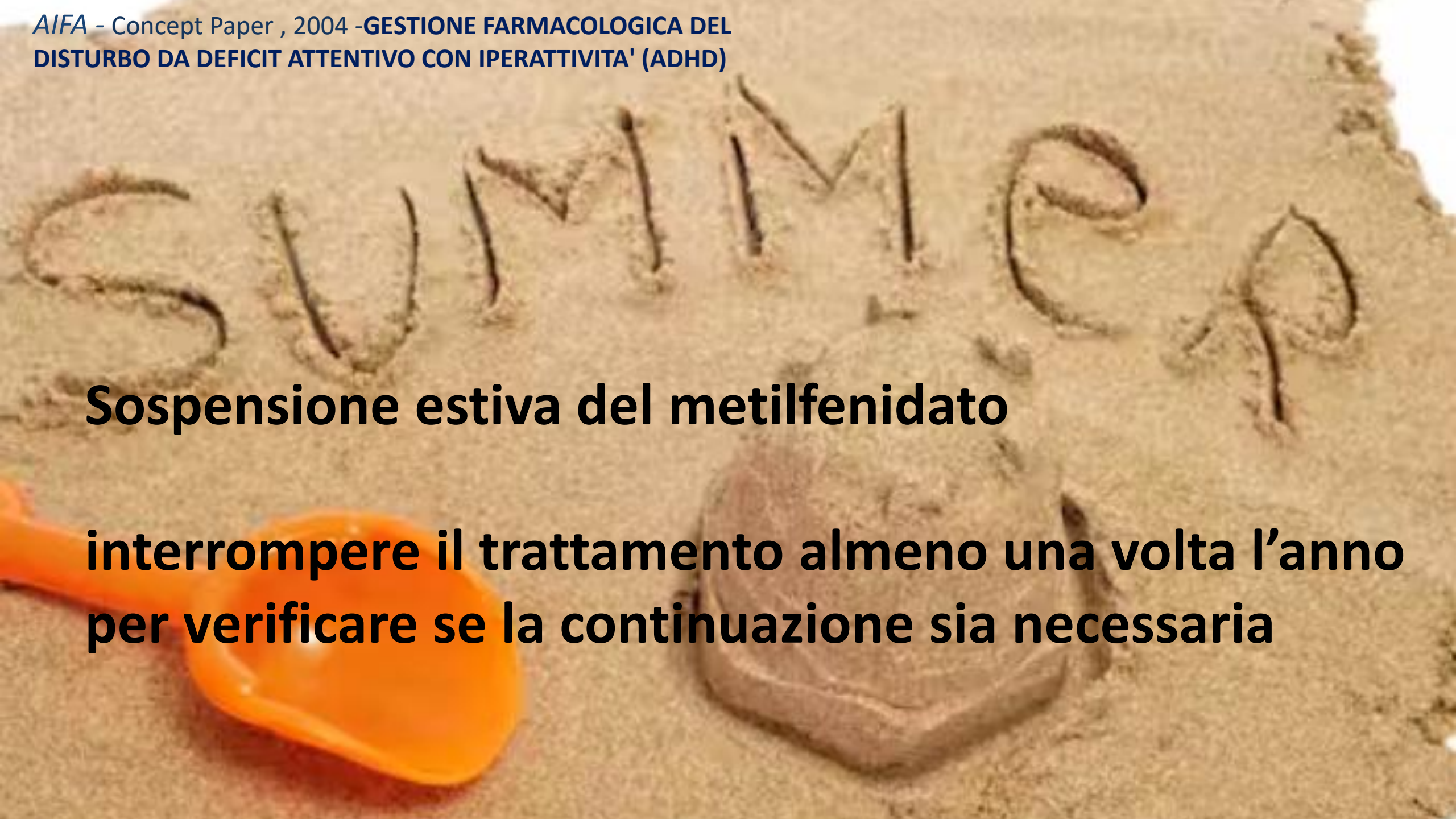
In children and adolescents, **all compounds were superior to placebo** on the CGI-I scale, except for clonidine (OR 2·78, 95% CI 0·91–8·53).

In adults, amphetamines (4·86, 3·30–7·17), bupropion (3·43, 1·45–8·14), and methylphenidate (3·08, 2·04–4·65) were superior to placebo on the CGI-I scale

Taking into account both efficacy and safety, evidence from this meta-analysis supports methylphenidate in children and adolescents, and amphetamines in adults, as preferred first-choice medications for the short-term treatment of ADHD


SAFETY

AIFA - Concept Paper , 2004 -**GESTIONE FARMACOLOGICA DEL DISTURBO DA DEFICIT ATTENTIVO CON IPERATTIVITA' (ADHD)**



Sospensione estiva del metilfenidato

interrompere il trattamento almeno una volta l'anno per verificare se la continuazione sia necessaria

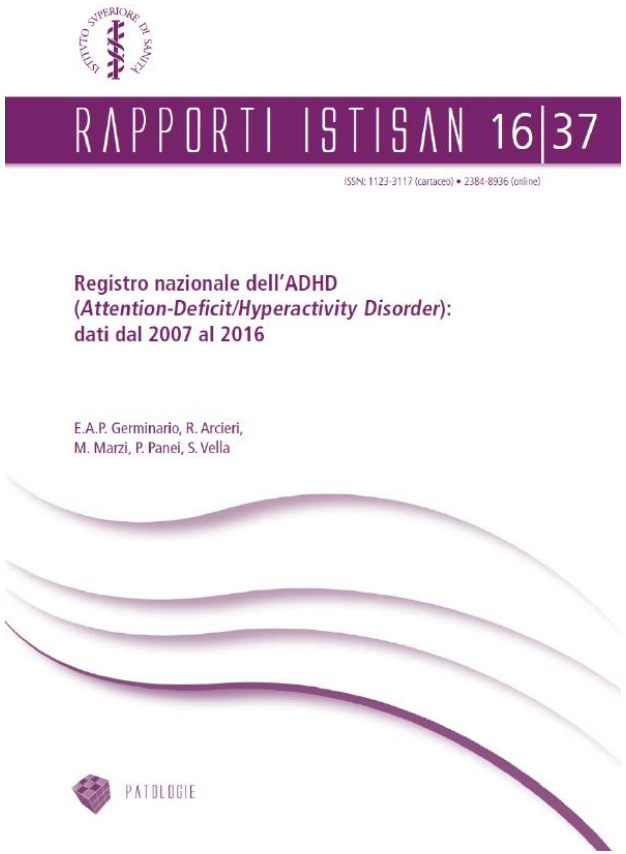


Tabella 13. Distribuzione dei SAE per tipo di trattamento nei soggetti ADHD in età evolutiva (Registro ADHD, 2007-2016)

Tipo evento	MPH (n. 2675)	ATX (n. 1021)
Disturbi cardiovascolari	0	3
Disturbi alimentari	2	10
Disturbi gastrointestinali	7	10
Allucinazioni	0	2
Cefalea	3	5
Epatomegalia	1	1
Iperbilirubinemia	1	3
Disturbi dell'umore	4	4
Disturbi neurologici	3	2
Prolungamento del QTc	0	1
Blocco di branca destro	1	0
Disturbi psichiatrici	12	6
Rash	0	3
Convulsioni	4	2
Ipertensione	3	1
Ipotensione	0	1
Disturbi della pelle	3	7
Disturbi del sonno	2	3
Ideazione suicidaria	0	7
Tachicardia	2	4
Altri disturbi	9	8
Totale	57	83

3696 bambini e adolescenti sono stati arruolati nel registro (settembre 2007-aprile 2016)

il MPH mostra un profilo di rischio migliore dell'ATX.

– **Neuropsichiatrici** : la **frequenza di ideazione suicidaria** è stata osservata solo nel gruppo dei soggetti trattati con ATX ed è pari a **0,69%** (7/1021). **Non sono stati osservati casi di suicidio**. La frequenza di ideazione suicidaria osservata è maggiore rispetto a quella attesa in base ai dati della FDA.

– **Cardiovascolari** sono state segnalate alterazioni dell'ECG, con un caso di **allungamento del tratto QTc** e un blocco di branca destro, e diversi casi di alterazioni pressorie e della frequenza cardiaca. **Tutti i casi segnalati erano asintomatici e sono stati rilevati strumentalmente**. Il trattamento farmacologico è stato modificato parzialmente nel dosaggio ed è stato interrotto solo nel caso di allungamento del tratto QTc segnalato come evento avverso.

- **Epatici:** si sono verificati **4 casi di iperbilirubinemia**, di cui 3 in soggetti che assumevano ATX.

AIFA - Concept Paper , 2014 -**GESTIONE FARMACOLOGICA DEL DISTURBO DA DEFICIT ATTENTIVO CON IPERATTIVITA' (ADHD)**

- Tutti i pazienti **prima del trattamento con MPH, e ogni 6 mesi in corso di terapia, devono essere controllati per verificare se presentano alterazioni della pressione arteriosa o del ritmo cardiaco** e anamnesi familiare o personale per sintomi di probabile origine cardiovascolare o malattie cardiache.

- Poiché la terapia prolungata con MPH può interferire con la crescita, **altezza e peso devono essere monitorati ad intervalli di almeno 6 mesi**. Questo effetto, che non sembra influenzare l'altezza e il peso finali in età adulta, può essere ridotto al minimo sospendendo il farmaco per periodi di tempo più o meno lunghi.

- L'uso del MPH può causare o peggiorare alcuni disturbi psichiatrici, come depressione, pensieri suicidari, ostilità, psicosi e mania. Tutti i pazienti devono essere attentamente sottoposti a delle verifiche per individuare la presenza di questi disturbi prima del trattamento e **monitorati attentamente per l'insorgenza di sintomi psichiatrici durante la terapia.**

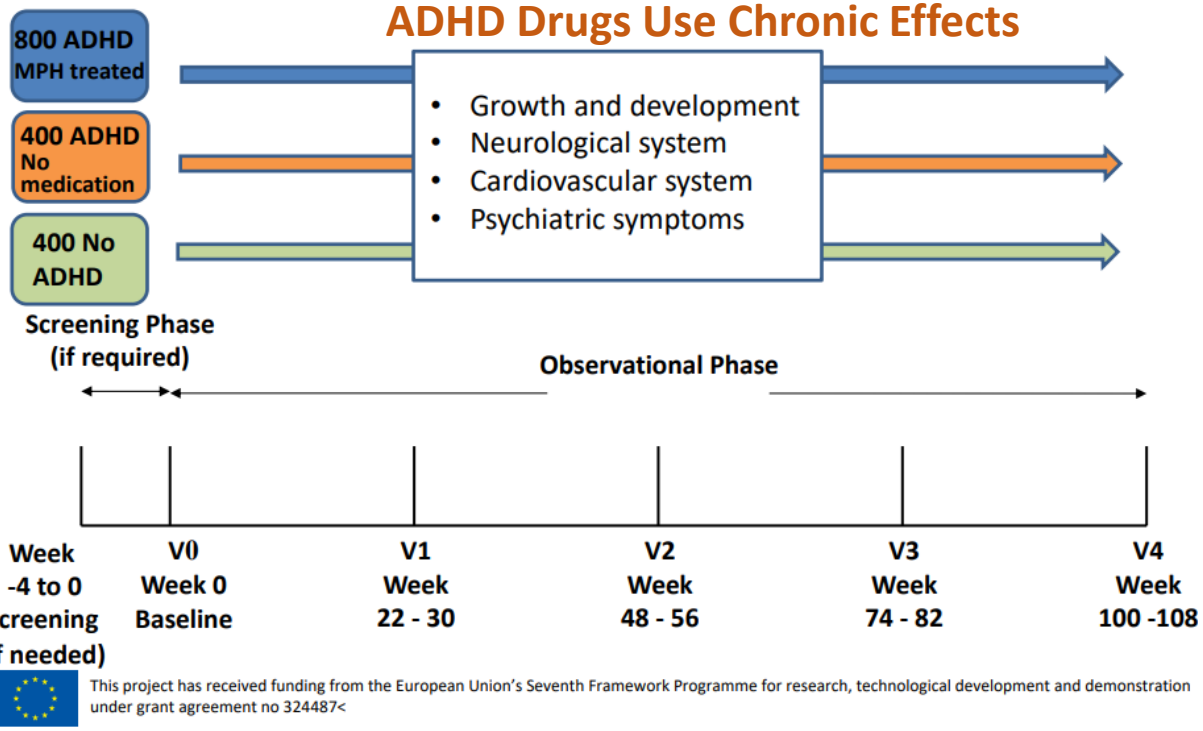
BMJ Open Prospective observational study protocol to investigate long-term adverse effects of methylphenidate in children and adolescents with ADHD: the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study

BMJ Open, 2016

S K Inglis,[1] S Consoli,[2] P Gorea,[3] A Hilge,[4] T Banaschewski,[4] J K Buitelaar,[5] R W Dittmann,[6] B Falissard,[7] C Hollis,[8] H Kovshoff,[9] E Liddle,[10] S McCarthy,[11] P Nagy,[12] A Neubert,[13] E Rosenthal,[14] E Sonuga-Barke,[15] I Wong,[16] A Zuddas,[17] D C Coghill,[18] and the ADDUCE Consortium

ADDUCE WP3 prospective study

ADHD Drugs Use Chronic Effects



This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 324487<

Summary of findings

No major safety or tolerability issues form ADDUCE results for:

Impact on growth
already well recognized, it should be identified and managed

Impact on height, weight and BMI
is more significant during the first months of pharmacological treatment

Increases in blood pressure
limited to the times during which MPH is in the system
no evidence of long term changes cardiac structure

Psychiatric adverse effects
no evidence that MPH over a 2 year period increases risk for
Depression, Suicidality, Psychotic symptoms, Substance misuse

No effects on:

- **Puberty** (female genital growth stage)
- **Substance Use** (Smoking, Alcohol, Marijuana, Total)
- **Sleep**

Effects on:
Puberty (male pubic hair stage, genital growth stage)

Nel febbraio 2006, la US Food and Drugs Administration (FDA) ha raccomandato un black box warning che descriva i rischi cardiovascolari dei farmaci stimolanti utilizzati per il trattamento dell'ADHD





Nel trattamento farmacologico teme in particolare qualche effetto collaterale? Se sì, quale?



Se SI, quale?	% di casi
Cuore, pressione	65,9
Alimentare	31,8
Agitazione comportamentale	9,1
Altezza	6,8
Tic	4,5
Cefalea	4,5
Insonnia	4,5
Convulsioni	2,3
Psichiatrici	2,3
Depressione	2,3
Mania	2,3
Abuso	2,3
Suicidio	2,3

Survey

100 NPI Italiani con competenze sull'ADHD
(Centri di Riferimento)

Fonte: Shire, 2013

Robert M. Hamiltona, Eric Rosenthala, Martin Hulpke-Wettea, John G. I. Graham, and Joseph Sergeanta
Cardiovascular considerations of attention deficit hyperactivity disorder medications: a report of the European Network on Hyperactivity Disorders work group, European Attention Deficit Hyperactivity Disorder Guidelines Group on attention deficit hyperactivity disorder drug safety meeting for the European Network of Hyperkinetic Disorders and the Association of European Paediatric Cardiology Cardiol Young. 2012 Feb;22(1):63-70. Epub 2011 Jul 19.

1. **sudden death does not appear to exceed that of the general population**
2. **There is no current evidence to suggest an incremental benefit to electrocardiography assessment of the general** ADHD **patient**
3. **Congenital heart disease patients have an increased prevalence of** ADHD, **and can benefit from** attention deficit hyperactivity disorder **therapies, including medication**
4. **The identification of risk factors for sudden death should not automatically exclude the use of** attention deficit hyperactivity disorder **medication.**

Lamberti M, Italiano D, Guerriero L, D'Amico G, Siracusano R, Ingrassia M, Germanò E, Calabrò MP, Spina E, Gagliano A., Neuropsychiatr Dis Treat. 2015 May 8;11:1169-74. doi: 10.2147/NDT.S79866. eCollection 2015

Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with attention-deficit hyperactivity disorder.

Lieve aumento della pressione arteriosa dopo 2 ore **non valori patologici**

Nessuna modifica significativa negli intervalli QTc e QTd pre e post assunzione del MPH-IR

	Pre-MPH	2 h Post-MPH	*P* value
Heart rate (bpm)	80,46 ± 15,53 (55-80)	87,72± 18,37 (55-165)	NS
Systolic BP (mmHg)	105,42 ±10,42 (85-131)	108,83±11,05 (90-135)	<0.05
Diastolic BP (mmHg)	59,3±7,1 (48-78)	63,2 ±7,9 (48-82)	<0.05
QTc max (ms)	420,5 ± 12 (379 - 440)	420,8 ± 12 (392 – 447)	NS
QTc min (ms)	394,7±13 (358 - 420)	391,7±10,4 (362 – 426)	NS
QTc mean (ms)	407,6 + 12,4 (377,5-430,6)	409,8 + 12,7 (376,7-436,2)	NS
QTd (ms)	25,7 ±9,3 (4-45)	25,1 ±8,4 (5-40)	NS

	Pre- MPH	2h Post-MPH	*P* value
Tp Te (ms)	75,9 ±6,2 (56-88)	77,4 ±6,2 (56-88)	NS
Tp Te/QTc	0,207 ±0,16 (0,140 - 0,235)	0,214 ±0,19 (0,156-0,253)	<0.01

Lieve modifica significativa dell'intervallo Tp-Te dopo l'assunzione del MPH-IR ma anche questo valore non rientra nel range patologico (v.n. 0.12–0.29)

Dati obiettivi che confermano che durante le prime ora dall'assunzione del metilfenidato non ci sono modifiche elettrocardiografiche clinicamente significative

Lamberti M, et al, Neuropsychiatr Dis Treat. 2015 May 8;11:1169-74. doi: 10.2147/NDT.S79866. eCollection 2015

Zhang et al, **Risk of Cardiovascular Diseases Associated With Medications Used in Attention-Deficit/Hyperactivity Disorder A Systematic Review and Meta-analysis**

JAMA Network Open. 2022;5(11):e2243597. doi:10.1001/jamanetworkopen.2022.43597

19 studies (with **3 931 532** participants including children, adolescents, and adults; 60.9%male)
Median follow-up time 1.5 years

Pooled adjusted relative risk (RR) did not show a significant association between ADHD medication use and any CVD

- among children and adolescents (RR, 1.18; 95%CI, 0.91-1.53)
- young or middle-aged adults (RR, 1.04; 95%CI, 0.43-2.48)
- older adults (RR, 1.59; 95%CI, 0.62-4.05).

No significant associations for:

- stimulants (RR, 1.24; 95%CI, 0.84-1.83)
- nonstimulants (RR, 1.22; 95% CI, 0.25-5.97)

For specific cardiovascular outcomes, no statistically significant association was found in relation to:

- cardiac arrest or arrhythmias (RR, 1.60; 95%CI, 0.94-2.72)
- cerebrovascular diseases (RR, 0.91; 95%CI, 0.72-1.15)
- myocardial infarction (RR, 1.06; 95%CI, 0.68-1.65).

There was no associations with any CVD in

- **female patients** (RR, 1.88; 95%CI, 0.43-8.24)
- **subjects with preexisting CVD** (RR, 1.31; 95%CI, 0.80-2.16).

This meta-analysis suggests no statistically significant association between ADHD medications and the risk of CVD across age groups, although a modest risk increase could not be ruled out, especially for the risk of cardiac arrest or tachyarrhythmias

Linee Guida

Guida pratica SINPIA al trattamento farmacologico dell'ADHD in Età Evolutiva

SINPIA practical guide for the pharmacological treatment of ADHD in children and adolescents

Samuele Cortese[1-5], Sara Carucci[6], Antonella Gagliano[7], Luigi Mazzone[8], Stefania Millepiedi[9], Rosamaria Siracusano[10], Benedetto Vitiello[11], Gabriele Masi[12]

Controindicazioni

1) **Le controindicazioni all'utilizzo del metilfenidato includono**:

• disturbi cardiovascolari gravi, quali grave ipertensione, insufficienza cardiaca, malattia occlusiva arteriosa, angina, cardiopatia congenita emodinamicamente significativa, cardiomiopatie, infarto del miocardio, aritmie potenzialmente letali e canalopatie
(disturbi causati dalla disfunzione dei canali ionici);

• disturbi cerebrovascolari preesistenti, aneurisma cerebrale, anomalie vascolari, inclusi vasculiti e ictus;

• anoressia nervosa non controllata;

• epilessia non controllata;

• ipertiroidismo o tireotossicosi;

• glaucoma;

• feocromocitoma;

• trattamento con inibitori irreversibili non selettivi della monoaminoossidasi (IMAO), almeno nei 14 giorni successivi alla loro sospensione, a causa del rischio di crisi ipertensive;

• ipersensibilità al metilfenidato o a uno qualsiasi degli eccipienti della formulazione usata;

• trattamento con metilfenidato in caso di comorbidità con il disturbo bipolare o in caso di sintomi psicotici, in tali casi il metilfenidato può essere intrapreso solo a seguito di un'adeguata stabilizzazione di queste condizioni.

2) **Le controindicazioni all'utilizzo dell'atomoxetina includono:**

• disturbi cardiovascolari gravi, quali grave ipertensione, insufficienza cardiaca, malattia occlusiva arteriosa, angina, cardiopatia congenita emodinamicamente significativa, cardiomiopatie, infarto del miocardio, aritmie potenzialmente letali e canalopatie
(disturbi causati dalla disfunzione dei canali ionici);

• disturbi cerebrovascolari preesistenti, aneurisma cerebrale, anomalie vascolari inclusi vasculiti e ictus;

• feocromocitoma o storia di feocromocitoma;

• il trattamento con inibitori irreversibili non selettivi della monoaminoossidasi (IMAO), almeno nei 14 giorni successivi alla loro sospensione;

• Ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti della formulazione usata.

Guida pratica SINPIA al trattamento farmacologico dell'ADHD in Età Evolutiva

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Tabella I. Gestione pratica dei principali effetti collaterali che possono presentarsi durante il trattamento farmacologico dell'ADHD (anche se non necessariamente correlati al trattamento farmacologico in termini di rapporto causa-effetto).

Effetto collaterale	Strategia di gestione suggerita
Diminuzione dell'appetito / Deficit di crescita in altezza e peso	- Misurare l'altezza ogni 6 mesi nei bambini e nei giovani. - Misurare il peso: • Ogni 3 mesi nei bambini ≤10 anni • A 3 e 6 mesi dall'inizio del trattamento nei bambini > 10 anni e nei giovani, poi ogni 6 mesi (o più frequentemente se necessario) • Ogni 6 mesi negli adulti - Se la perdita di peso è clinicamente significativa: • Assumere il farmaco con o dopo i pasti • Inserire pasti o spuntini extra al mattino presto o alla sera • Cercare consulenza nutrizionale • Consumare alimenti ad alto valore calorico e nutrizionale • Considerare una pausa programmata dal trattamento o cambiare il farmaco - Nei bambini con altezza inferiore al previsto: valutare pausa programmata durante le vacanze scolastiche - Rivolgersi a endocrinologo pediatrico o specialista della crescita se i valori cadono sotto soglie critiche (vedi Appendice)
Aumento della pressione arteriosa / frequenza cardiaca	- Misurare frequenza cardiaca e pressione arteriosa dopo ogni aggiustamento di dose e ogni 6 mesi - Se osservati due volte: tachicardia > 120 bpm, aritmia o pressione sistolica > 95° percentile (o aumento clinicamente significativo) → ridurre dose e riferire a specialista
Disturbi del sonno	-Se misure comportamentali (es. igiene del sonno) insufficienti e sospensione del farmaco non possibile, valutare cause dei disturbi - Trattare la sindrome delle gambe senza riposo se presente - Se effetto rebound da stimolante → considerare piccola dose di stimolante a breve durata la sera - Se trattamnento con stimolante in corso → valutare: ridurre dose, cambiare classe/formulazione, provare atomoxetina se disponibile - Se persistono problemi di sonno → considerare melatonina
Tics	- Monitorare per 3 mesi prima di modificare trattamento ADHD - Se correlati a stimolante → considerare: ridurre dose, passare a atomoxetina se disponibile, sospendere stimolante, aggiungere antipsicotico se indicato
Convulsioni	- Se nuove o peggioramento di convulsioni → rivedere farmaco e sospendere quelli contributivi - Se farmaco improbabile causa → considerare reintroduzione cauta sotto monitoraggio
Sintomi psicotici	- Se compaiono sintomi psicotici o maniacali a dosi terapeutiche → ridurre la dose o sospendere il farmaco senza introdurre sistematicamente un antipsicotico (la maggior parte dei sintomi psicotici si risolve una volta sospeso lo stimolante). - Dopo la risoluzione → valutare una reintroduzione cauta, se clinicamente appropriata.

Appendice:

Riferire a un endocrinologo pediatrico / specialista della crescita se i valori di altezza e peso risultano inferiori alle seguenti soglie critiche:

Altezza: 1,5 deviazioni standard (DS) al di sotto della media dell'altezza della madre e del padre.

Altezza: 2 DS al di sotto della media della popolazione più una velocità di crescita annuale 1 DS sotto la media, oppure una diminuzione di 0,5 DS in un anno.

Velocità di crescita annuale 2 DS sotto la media, oppure velocità di crescita biennale 1,5 DS sotto la media.

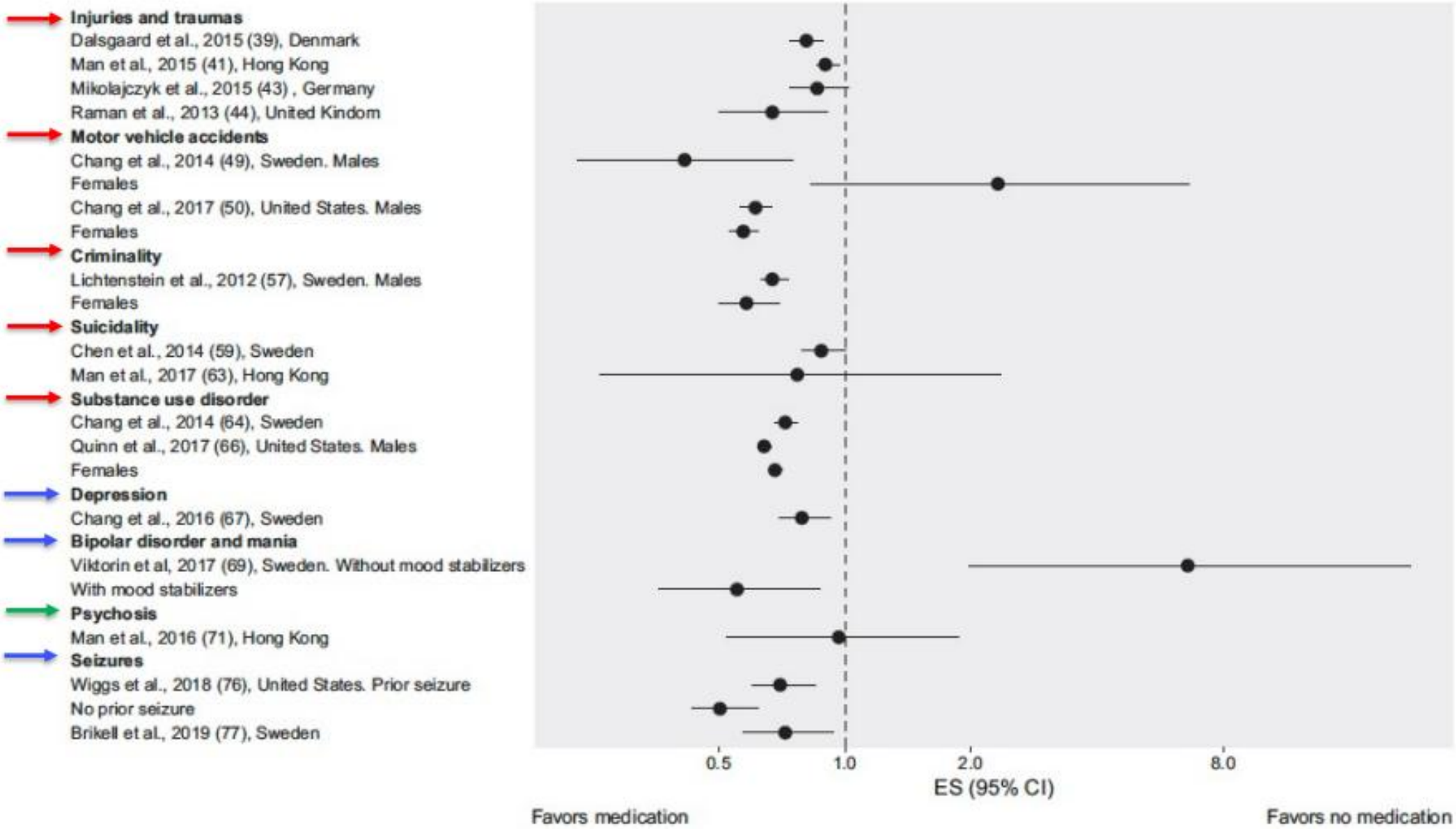


La terapia con MPH protegge dagli outcome sfavorevoli?

Risks and Benefits of Attention-Deficit/ Hyperactivity Disorder Medication on Behavioral and Neuropsychiatric Outcomes: A Qualitative Review of Pharmacoepidemiology Studies Using Linked Prescription Databases

Biol Psychiatry 2019

Zheng Chang, Laura Ghirardi, Patrick [
Henrik Larsson

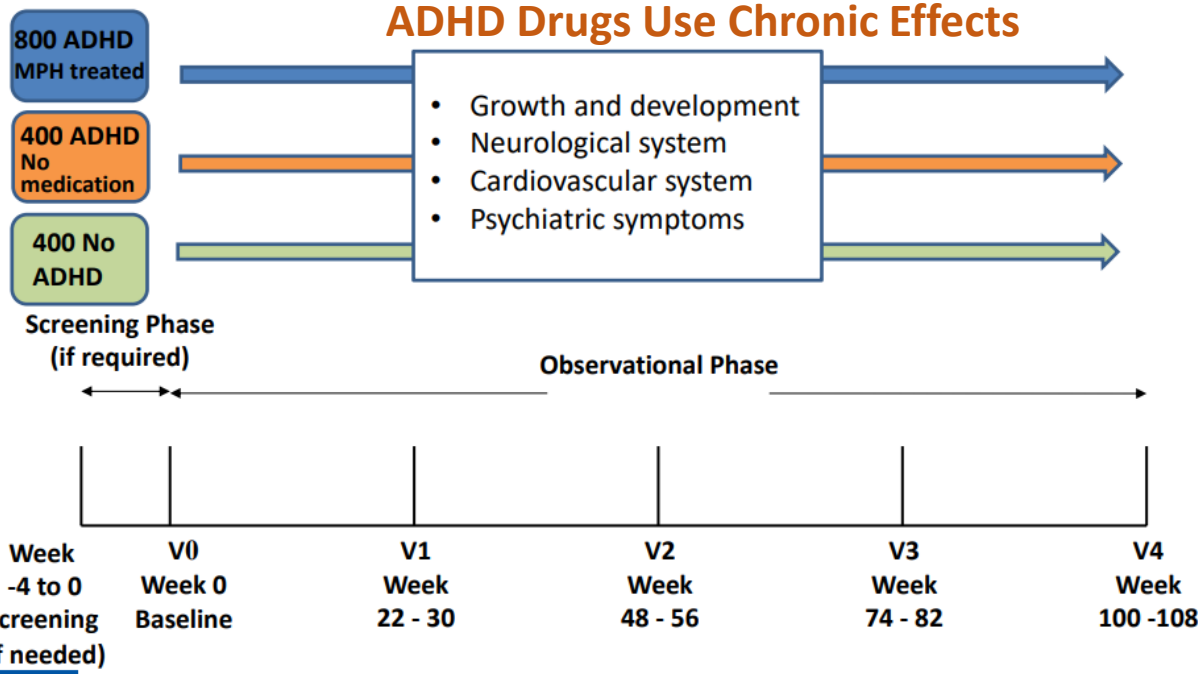


BMJ Open Prospective observational study protocol to investigate long-term adverse effects of methylphenidate in children and adolescents with ADHD: the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study

BMJ Open, 2016

ADDUCE WP3 prospective study

ADHD Drugs Use Chronic Effects



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- **Puberty** (female genital growth stage)
- **Substance Use** (Smoking, Alcohol, Marijuana, Total)
- **Sleep**

Effects on:
Puberty (male pubic hair stage, genital growth stage)

AuDHD

AUTISM

- Social Challenges
- Strict Routines
- Focus Difficulties
- Intense interests
- Limited Eye contact

AuDHD

- Executive Dysfunction
- Hyperactivity
- Stimming
- Emotional Dysregulation

ADHD

- Difficulty focusing
- Focus Difficulties
- Inattention Issues
- Inpulsivity



i sintomi ADHD nella popolazione dei soggetti con ASD non sempre vengono trattati in modo ***specifico e appropriato***

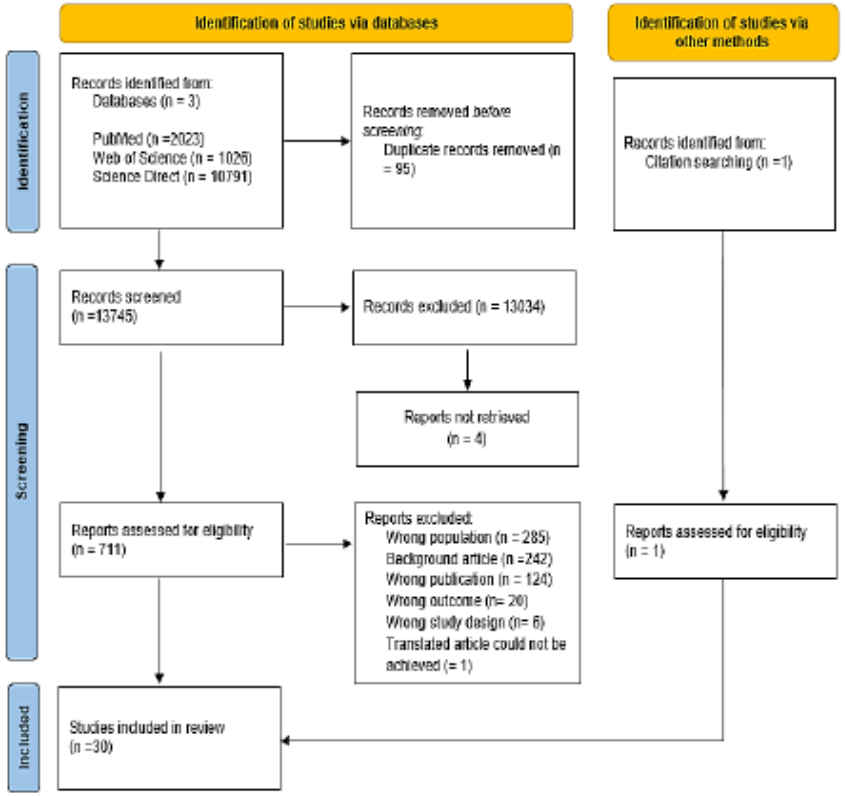


Studiare efficacia e sicurezza dei trattamenti per i sintomi ADHD nella popolazione pediatrica con ASD, con l'obiettivo di dare un contributo alla definizione di un algoritmo di intervento

The protocol of this review was registered in the PROSPERO database, with the following code: CRD42024526157, in accordance with the PRISMA guidelines

De Domenico, C.; Alito, A.; Leonardi, G.; Pironti, E.; Di Cara, M.; Piccolo, A.; Settimo, C.; Quartarone, A.; Gagliano, A.; Cucinotta, F. **Children and Adolescents with Co-Occurring Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder: A Systematic Review of Multimodal Interventions**. J. Clin. Med. 2025, 14, 4000. https://doi.org/10.3390/jcm14114000

Figure 1. PRISMA 2020 flow diagram



Età media 9,5±1,7anni

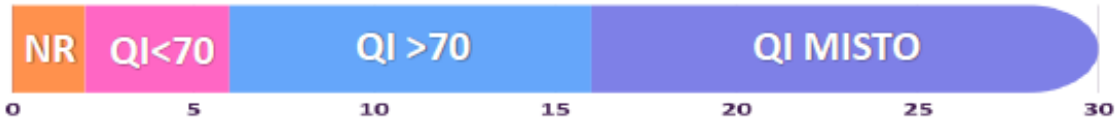


Fig.2- Studi Inclusi

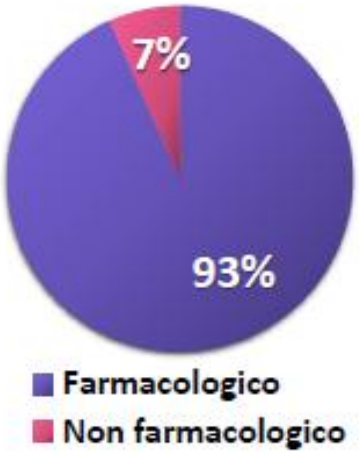
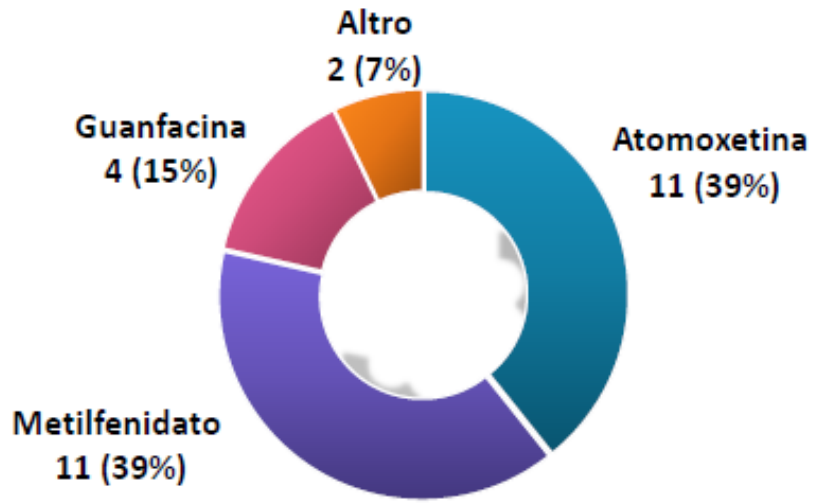


Fig.3 – Distribuzione geografica

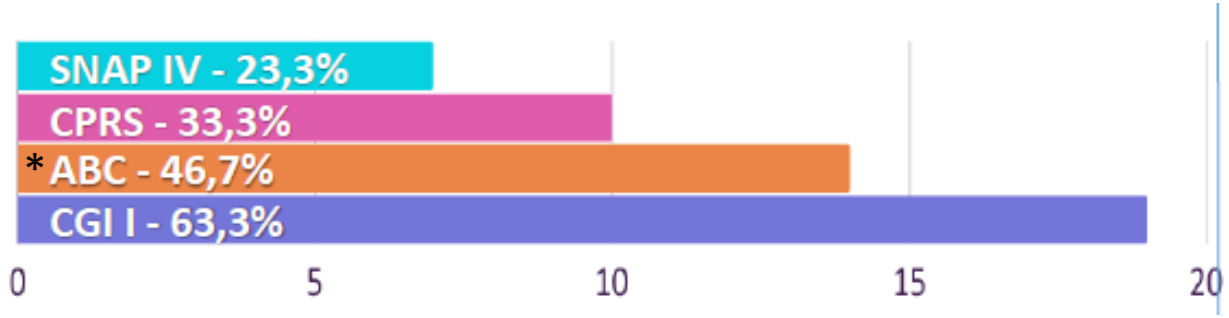


Registrazione su PROSPERO (CRD42024526157) ricerca sistematica secondo linee guida PRISMA

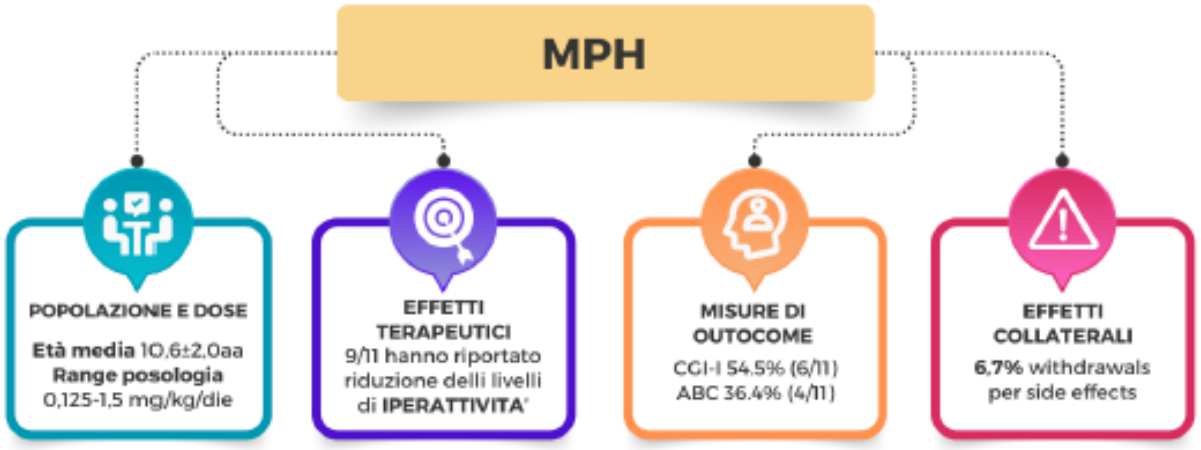
Fig.3 – Studi su interventi farmacologici



De Domenico, C.; Alito, A.; Leonardi, G.; Pironti, E.; Di Cara, M.; Piccolo, A.; Settimo, C.; Quartarone, A.; Gagliano, A.; Cucinotta, F. **Children and Adolescents with Co-Occurring Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder: A Systematic Review of Multimodal Interventions**. J. Clin. Med. 2025, 14, 4000. https://doi.org/10.3390/jcm14114000



* Aberrant Behavior Checklist



Metilfenidato (MPH) come prima scelta nel trattamento dei sintomi dell'ADHD anche in individui con ASD

- ❑ Efficacia lievemente più bassa rispetto a quella che il farmaco ha negli individui che hanno solo la componente ADHD
- ❑ Miglior funzionamento sulla dimensione iperattiva/impulsiva che su quella inattenta
- ❑ Più frequenti effetti avversi nella Popolazione ASD/ADHD, rispetto alla popolazione di soggetti con ADHD isolato

(Scahill and Pachler, 2017; Research Units on Pediatric Psychopharmacology Autism Network , 2005)

META-ANALYSIS | EMOTION DYSREGULATION

Check for updates

Systematic Review and Meta-analysis: Efficacy of Pharmacological Interventions for Irritability and Emotional Dysregulation in Autism Spectrum Disorder and Predictors of Response

Gonzalo Salazar de Pablo, MD, PhD, Carolina Pastor Jordá, MD, Julio Vaquerizo-Serrano, MD, Carmen Moreno, MD, PhD, Anna Cabras, MD, Celso Arango, MD, PhD, Patricia Hernández, MD, Jeremy Veenstra-VanderWeele, MD, PhD, Emily Simonoff, MD, FRCPsych, Paolo Fusar-Poli, MD, PhD, Paramala Santosh, MD, FRCPsych, PhD, Samuele Cortese, MD, PhD, Mara Parellada, MD, PhD

J Am Acad Child Adolesc Psychiatry 2023;62(2):151-168.

A total of **2,856 individuals** with ASD in 45 studies were included, among which 26.7% of RCTs had a high risk of bias.

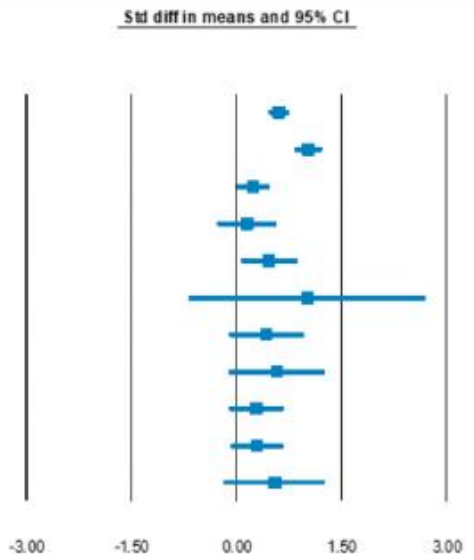
Two classes of drugs resulted significantly better than placebo in improving emotional dysregulation and irritability :

1. **antipsychotics** (smd ¼ 1.028, 95% CI ¼ 0.824-1.232)
2. **medications used to treat ADHD** (0.471, 0.061-0.881)

NO evidence of efficacy was found for other drug classes ($p > .05$)

FIGURE 2 Forest Plot Showing the Efficacy of Pharmacological Interventions for Emotional Dysregulation and Irritability in Individuals With Autism Spectrum Disorder

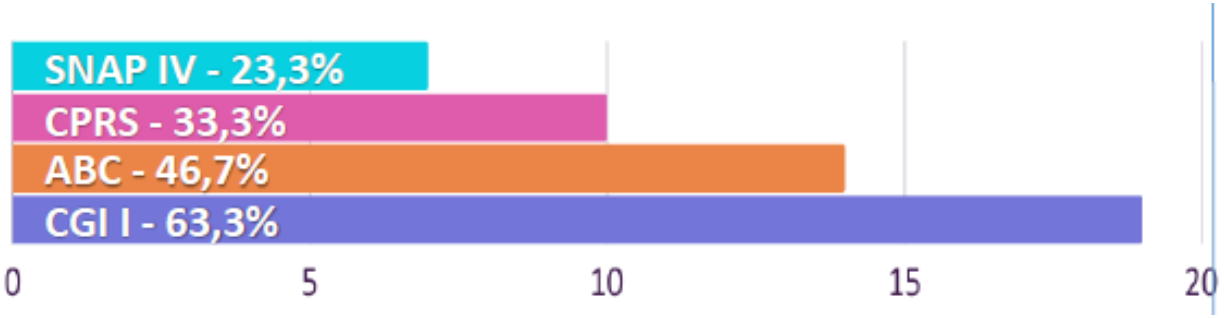
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	z	p
Any pharmacological group	0.611	0.078	0.006	0.458	0.764	7.830	0.000
Antipsychotics	1.028	0.104	0.011	0.824	1.232	9.885	0.000
Antidepressants	0.238	0.124	0.015	-0.004	0.480	1.925	0.054
Mood stabilizers	0.153	0.219	0.048	-0.277	0.583	0.698	0.485
ADHD medication	0.471	0.209	0.044	0.061	0.881	2.254	0.024
Opioid antagonists	1.014	0.867	0.752	-0.686	2.714	1.169	0.242
Glutamatergic blockers	0.431	0.275	0.075	-0.107	0.969	1.570	0.116
Diuretics	0.584	0.355	0.126	-0.111	1.279	1.646	0.100
Neuropeptides	0.287	0.202	0.041	-0.109	0.683	1.421	0.155
Fatty acids	0.297	0.194	0.038	-0.084	0.678	1.529	0.126
Others	0.550	0.372	0.138	-0.179	1.279	1.479	0.139



Within antipsychotics medications, evidence of efficacy was found for:

- **aripiprazole** (1.179, 0.838-1.520)
- **risperidone** (1.074, 0.818-1.331)

De Domenico, C.; Alito, A.; Leonardi, G.; Pironti, E.; Di Cara, M.; Piccolo, A.; Settimo, C.; Quartarone, A.; Gagliano, A.; Cucinotta, F. **Children and Adolescents with Co-Occurring Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder: A Systematic Review of Multimodal Interventions**. J. Clin. Med. 2025, 14, 4000. https://doi.org/10.3390/jcm14114000



first choice

- Methylphenidate
- Atomoxetine

Gli stimolanti devono essere sempre considerati la prima linea di intervento per i sintomi ADHD negli individui con ASD.
ATX può, in qualche caso, rappresentare un'alternativa

Second choice

- Guanfacine
- Clonidine

Gli α2-adrenergicican possono essere presi in considerazione come seconda linea di intervento dal momento che sono in grado di modulare molti comportamenti disfunzionali

third choice

- Risperidone
- Aripiprazole

Il loro uso dovrebbe essere limitato ai soggetti con condizioni associate che rispondono agli SGAs (es. tic, irritabilità, aggressività) o ai no-responders ai trattamenti di prima e seconda linea.

Fig.2: A proposal for a possible pharmachological treatment algorithm targeting the ADHD symptoms in the ASD population



Quale classe di farmaci per Francesco……?

iperattività/impulsività

disregolazione emozionale

aggressività/isolamento

depersonalizzazione
e derealizzazione

ideazione suicidaria

insonnia

tic

META-ANALYSIS | EMOTION DYSREGULATION

Check for updates

Systematic Review and Meta-analysis: Efficacy of Pharmacological Interventions for Irritability and Emotional Dysregulation in Autism Spectrum Disorder and Predictors of Response

Gonzalo Salazar de Pablo, MD, PhD, Carolina Pastor Jordá, MD, Julio Vaquerizo-Serrano, MD, Carmen Moreno, MD, PhD, Anna Cabras, MD, Celso Arango, MD, PhD, Patricia Hernández, MD, Jeremy Veenstra-VanderWeele, MD, PhD, Emily Simonoff, MD, FRCPsych, Paolo Fusar-Poli, MD, PhD, Paramala Santosh, MD, FRCPsych, PhD, Samuele Cortese, MD, PhD, Mara Parellada, MD, PhD

J Am Acad Child Adolesc Psychiatry 2023;62(2):151-168.

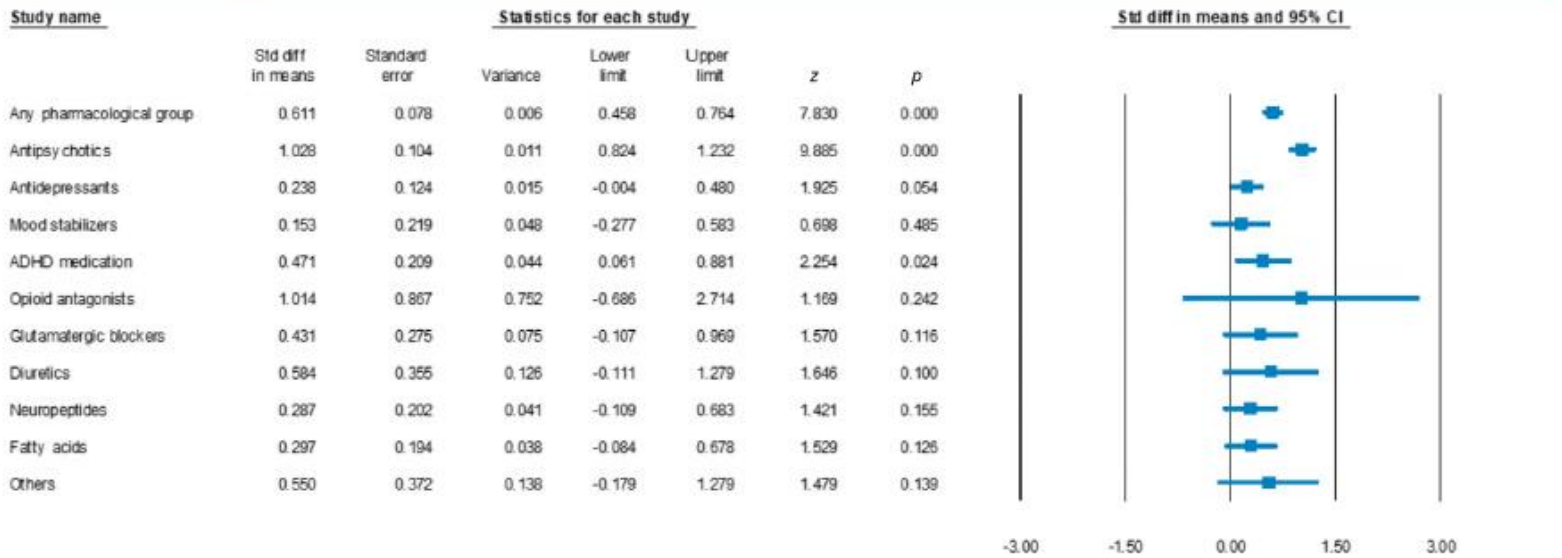
A total of **2,856 individuals** with ASD in 45 studies were included, among which 26.7% of RCTs had a high risk of bias.

Two classes of drugs resulted significantly better than placebo in improving emotional dysregulation and irritability :

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NO evidence of efficacy was found for other drug classes (p > .05)

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- **risperidone** (1.074, 0.818-1.331)

Increased rates of comorbid **epilepsy** (b ¼ 0.049, p ¼ .026) were associated with a **lower efficacy**



La terapia con Metilfenidato può migliorare il controllo emozionale ?

methylphenidate reduces ED by reducing impulsivity in children with ADHD

Kutlu A, Akyol Ardic U, Sabri Ercan E. Effect of methylphenidate on emotional dysregulation in children with attention-deficit/hyperactivity disorder and oppositional defiant disorder/conduct disorder. J Clin Psychopharmacol. (2017) 37:220–5.

Winters DE, Fukui S, Leibenluft E, Hulvershorn LA. Improvements in irritability with open-label methylphenidate treatment in youth with comorbid attention deficit/hyperactivity disorder and disruptive mood dysregulation disorder. J Child Adolesc Psychopharmacol. (2018) 28:298–305.

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Pp. 298–305
DOI: 10.1089/cap.2017.0124

Original Articles

Improvements in Irritability with Open-Label Methylphenidate Treatment in Youth with Comorbid Attention Deficit/Hyperactivity Disorder and Disruptive Mood Dysregulation Disorder

Drew E. Winters, MSW,[1] Sadaaki Fukui, PhD,[1] Ellen Leibenluft, MD,[2] and Leslie A. Hulvershorn, MD[3]

TABLE 2. *t*-TEST RESULTS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND EMOTIONAL MEASURES ($N=22$)

	Pretest		*Posttest*					
Variable	M	*SD*	M	*SD*	*95% CI for mean difference*	d	t	*df*
Primary								
Irritability scale	44.95	6.47	40.97	8.29	−7.14 to −0.82,	0.57++	−2.62*	20
Secondary								
ERC								
Lability	41.64	6.06	34.68	6.81	−30.39 to −23.79	0.85+++	−4.00**	21
Regulation[a]	23.09	4.15	24.45	2.53	−0.72 to −3.44	0.29+	1.36	21
DES–IV								
Anger	9.95	2.57	8.70	2.83	−2.83 to −0.07	0.55++	−2.20*	19
Surprise	10.00	2.23	8.30	2.52	−3.33 to −0.17	0.49++	−2.31*	19
Shame	10.23	2.84	8.95	2.67	−2.86 to −0.24	0.56++	−2.46*	19
Interest	10.36	3.14	9.55	2.82	−3.22 to 0.82	0.27+	−1.24	19
Joy	10.45	2.70	9.75	2.88	−2.18 to 1.28	0.12	−0.54	19
Sadness	9.05	2.61	12.0	7.80	−3.09 to 0.29	0.39+	−1.73	19
Disgust	8.32	2.77	15.0	7.75	−1.90 to 0.90	0.18	−0.75	19
Contempt	7.50	2.87	11.0	6.80	−2.01 to 0.91	0.18	−0.79	19
Hostility	7.27	2.75	14.0	6.70	−2.29 to 0.89	0.21+	−0.92	19
Fear	1.18	3.16	13.0	6.85	−2.63 to 1.23	0.17	−0.76	19
Shyness	8.36	3.11	12.0	7.50	−2.85 to 0.65	0.30+	−1.32	19
Guilt	9.0	2.51	12.0	8.50	−1.70 to 0.51	0.25+	−1.13	19
PANAS-C								
Negative affect	37.55	9.90	32.36	12.27	−8.18 to −0.14	0.50++	−2.17*	18
Positive affect[a]	44.18	9.26	42.11	8.61	−7.11 to 2.48	0.23+	−1.01	18
ADHD								
Hyperactivity	17.09	6.04	10.36	7.35	−10.09 to −3.36	0.89+++	−4.16**	21
Inattention	22.77	4.18	12.0	5.94	−14.12 to −7.43	1.43+++	−6.71**	21
Raw score	39.86	8.21	22.36	12.63	−23.67 to −11.33	1.26+++	−5.91**	21

22 DMDD and ADHD subjects (ages 9–15)

4-week trial of long-acting MPH treatment (Concerta)

primary outcome: self-report irritability
secondary outcomes: parent and child ratings of emotional frequency, emotional lability, and negative affect

Child-rated irritability as well as parent and child ratings of emotional lability, negative affect and anger significantly improved (medium to large effect sizes)

- 71% improved in child-rated irritability
- 19% symptoms worsened
- 10% no change

MPH treatment significantly improved mood and emotional symptoms associated with DMDD comorbid with ADHD.

MPH as a first-line treatment for DMDD

Medication with methylphenidate reduces ED by reducing impulsivity in children with ADHD

Kutlu A, Akyol Ardic U, Sabri Ercan E. Effect of methylphenidate on emotional dysregulation in children with attention-deficit/hyperactivity disorder and oppositional defiant disorder/conduct disorder. J Clin Psychopharmacol. (2017) 37:220–5.

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Pringsheim T, Hirsch L, Gardner D, Gorman DA. **The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD**, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 1: psychostimulants, alpha-2 agonists, and atomoxetine. Can J Psychiatry. 2015 Feb;60(2):42-51.

Figure 1a Psychostimulants, compared with placebo, for aggression, oppositional behaviour, and conduct problems as measured by teachers in youth with attention-deficit hyperactivity disorder, with and without oppositional defiant disorder, and conduct disorder

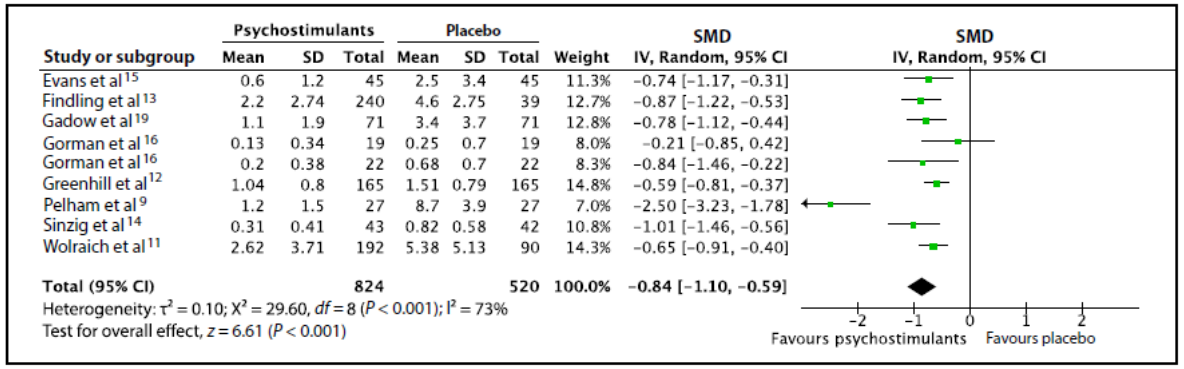
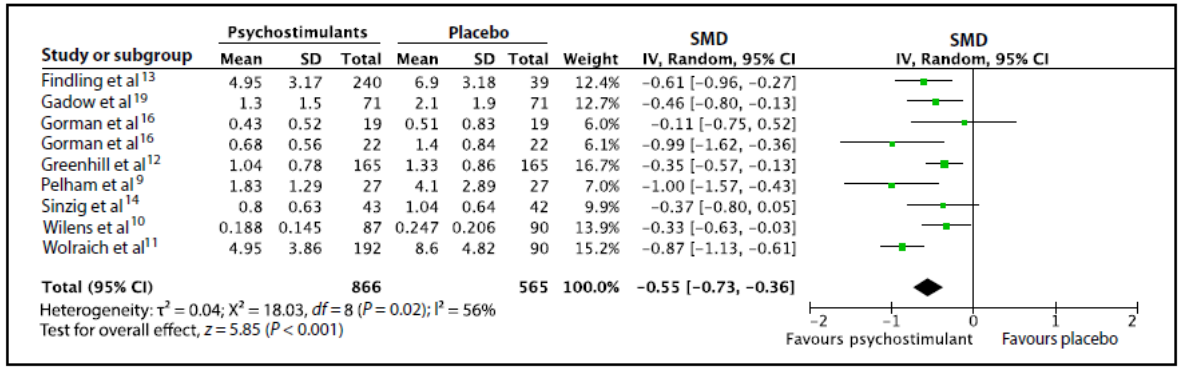


Figure 1b Psychostimulants, compared with placebo, for aggression, oppositional behaviour, and conduct problems as measured by parents in youth with attention-deficit hyperactivity disorder, with and without oppositional defiant disorder, and conduct disorder



Two systematic reviews and 20 randomized controlled trials were included.

There is **high-quality evidence** that **psychostimulants** have a **moderate-to-large effect** on **oppositional behaviour, conduct problems, and aggression** in youth with ADHD, with and without ODD or CD.

There is very-low-quality evidence that **clonidine** has a small effect on oppositional behaviour and conduct problems in youth with ADHD, with and without ODD or CD

There is **moderate-quality evidence** that **guanfacine** has a small-to-moderate effect on oppositional behaviour in youth with ADHD, with and without ODD.

There is high-quality evidence that **atomoxetine** has a small effect on oppositional behaviour in youth with ADHD, with and without ODD or CD.

psychostimulants, alpha-2 agonists, and atomoxetine can be beneficial for disruptive and aggressive behaviours in addition to core ADHD symptoms; however, **psychostimulants generally provide the most benefit**

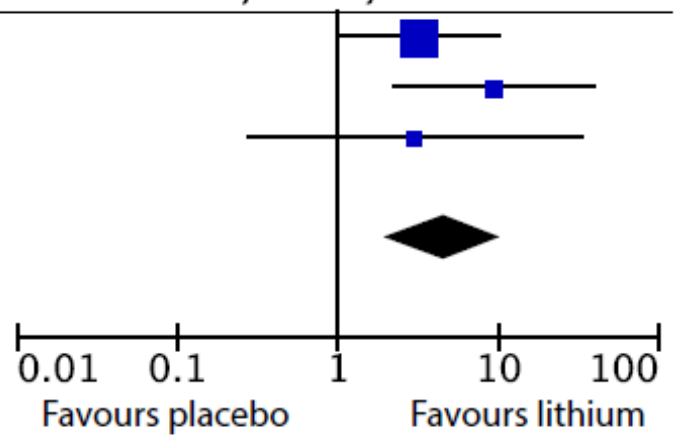
Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD and CD: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry. 2015 Feb;60(2):52-61.

Figure 3 Lithium, compared with placebo, for aggression in youth with conduct disorder

	Lithium		Placebo			OR	OR
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Campbell et al [26]	17	25	10	25	61.0%	3.19 [1.00, 10.17]	
Malone et al [25]	16	20	6	20	22.9%	9.33 [2.18, 39.96]	
Rifkin et al [24]	3	14	1	12	16.1%	3.00 [0.27, 33.49]	
Total (95% CI)		**59**		**57**	**100.0%**	**4.56 [1.97, 10.56]**	
Total events	36		17				

Heterogeneity: $X^2 = 1.41$, $df = 2$ ($P = 0.49$); $I^2 = 0\%$

Test for overall effect, $z = 3.55$ ($P < 0.001$)



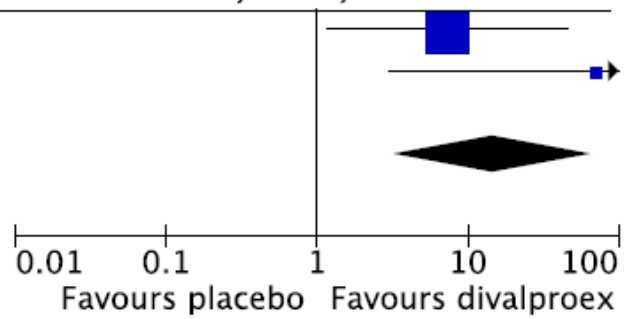
Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD and CD: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry. 2015 Feb;60(2):52-61.

Figure 4 Divalproex, compared with placebo, for aggressive behaviour in youth with oppositional defiant disorder or conduct disorder, with and without attention-deficit hyperactivity disorder

	Divalproex		Placebo			OR	OR
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M–H, Fixed, 95% CI**	**M–H, Fixed, 95% CI**
Blader et al [27]	8	14	2	13	88.7%	7.33 [1.16, 46.23]	
Donovan et al [28]	8	10	0	10	11.3%	71.40 [3.00, 1696.74]	
Total (95% CI)		**24**		**23**	**100.0%**	**14.60 [3.25, 65.61]**	
Total events	16		2				

Heterogeneity: $X^2 = 1.50$, $df = 1$ ($P = 0.22$); $I^2 = 33\%$

Test for overall effect, $z = 3.50$ ($P < 0.001$)



evidence supporting the use of divalproex in aggressive youth with ODD or CD is of low quality !!!

META-ANALYSIS | EMOTION DYSREGULATION

Check for updates

Systematic Review and Meta-analysis: Efficacy of Pharmacological Interventions for Irritability and Emotional Dysregulation in Autism Spectrum Disorder and Predictors of Response

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J Am Acad Child Adolesc Psychiatry 2023;62(2):151-168.

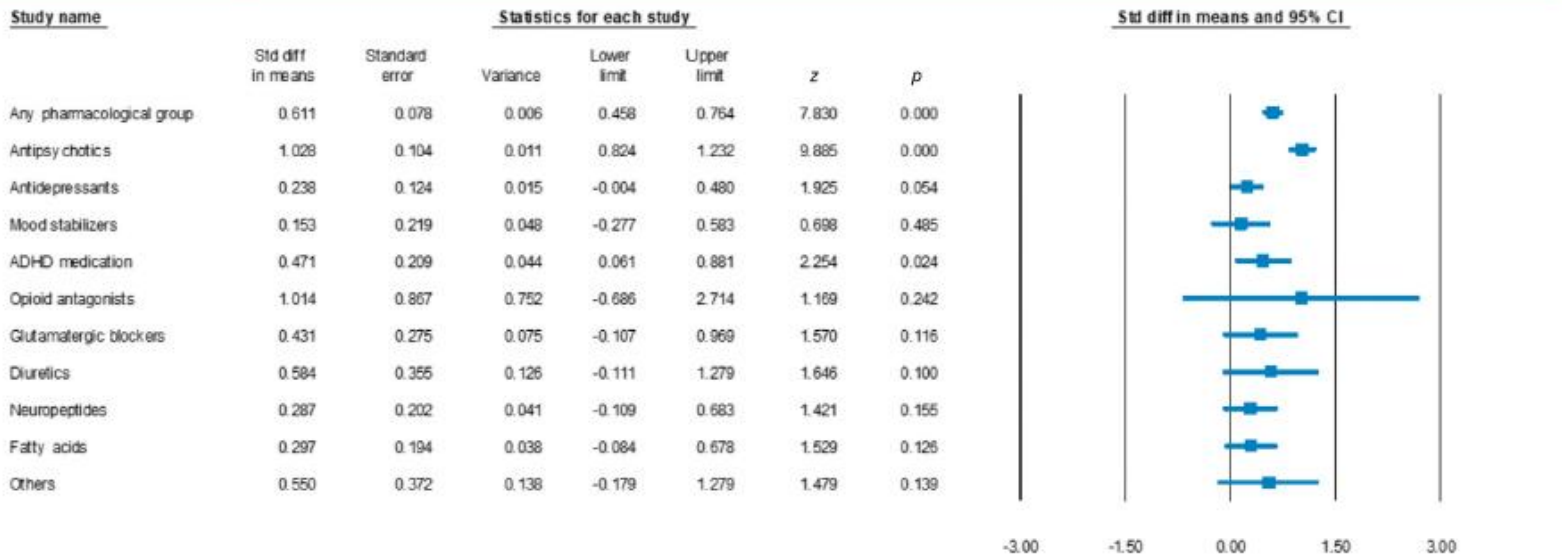
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Increased rates of comorbid **epilepsy** (b ¼ 0.049, p ¼ .026) were associated with a **lower efficacy**

Clozapine is also widely known for its **anti-aggressive effects** which have most commonly been demonstrated among schizophrenia patients…

- Frogley C, Taylor D, Dickens G, Picchioni M. A systematic review of the evidence of clozapine's anti-aggressive effects. Int J Neuropsychopharmacol. 2012; 15(9): 1351–1371.
- Chengappa KNR, Vasile J, Levine J, et al. Clozapine: its impact on aggressive behaviour among patients in a state psychiatric hospital. Schizophr Res. 2002; 53(1–2): 1–6.
- Citrome L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. Psychiatr Serv. 2001; 52(11):1510–1514.
- Rabinowitz J, Avnon M, Rosenberg V. Effect of clozapine on physical and verbal aggression. Schizophr Res. 1996; 22(3): 249–255.
- Ratey JJ, Leveroni C, Kilmer D, Gutheil C. The effects of clozapine on severely aggressive psychiatric inpatients in a state hospital. J Clin Psychiatry. 1993; 54(6): 219–223.

Table 1. Baseline patient characteristics and discharge diagnoses

	Males (n=10, 36%)	Females (n=18, 64%)	All patients (n=28)
Age at admission (years) Mean ± SD (min-max)	16 ± 1.5 (13.3–17.7)	15.5 ± 2.3 (10.7–18.9)	15.7 ± 2 (10.7–13.9)
Age at clozapine start (years) Mean ± SD (min-max)	16.1 ± 1.5 (13.6–17.9)	15.7 ± 2.3 (11.1–19.3)	15.8 ± 2 (11.1–19.3)
Weight (kg) at admission, Mean ± SD	84.3 ± 22.8	49.1 ± 11.4	61.7 ± 23.5
	n = 10	n = 18	n = 28
Race/Ethnicity			
White/Caucasian	3	5	8
Chinese	3	3	6
Filipino	-	3	3
Southeast Asian	3	-	3
Aboriginal	-	2	2
Black/African	-	2	2
South Asian	1	1	2
Latin American	-	1	1
Japanese	-	1	1
	n (%)	n (%)	n (%)
History of cannabis use	5 (50)	5 (27.7)	10 (35.7)
Tobacco smoking at clozapine initiation	1 (3.6)	1 (3.6)	2 (7.1)
Primary psychotic illness	10 (100)	15 (83.3)	25 (89.3)
Affective illness present	4 (40)	9 (50)	13 (46.4)
First mental health presentation	2 (20)	5 (27.8)	7 (25)
Antipsychotic drug trials prior to clozapine initiation, mean ± SD	2.8 ± 1.2	3.0 ± 1.5	2.9 ± 1.3
Discharge diagnoses (per treating psychiatrist / non-retrospective):			
Schizophreniform	1 (10)	2 (11.1)	3 (10.7)
Schizophrenia	5 (50)	6 (33.3)	11 (39.3)
Schizoaffective	4 (40)	7 (38.9)	11 (39.3)
Bipolar disorder	0 (0)	2 (11.1)	2 (7.1)
Non-psychotic non-bipolar illness	0 (0)	1 (5.6)	1 (3.6)

Komaryk A, Elbe D, Burgess L. **Retrospective Review of Clozapine Use in Children and Adolescents**. J Can Acad Child Adolesc Psychiatry. 2021 Feb;30(1):36-48. Epub 2021 Feb 1. PMID: 33552171; PMCID: PMC7837516.

Rachamallu V, Elberson BW, Vutam E, Aligeti M. Off-Label Use of Clozapine in Children and Adolescents-A Literature Review. Am J Ther. 2019 May/Jun;26(3):e406-e416. doi: 10.1097/MJT.0000000000000894. PMID: 31082865.

Berloffa S, Masi G, Falcone F, Simonelli V, Narzisi A, Valente E, Viglione V, Milone A, Sesso G. Clozapine Treatment for Aggressive Behaviors in Youths with Neurodevelopmental Disorders. J Child Adolesc Psychopharmacol. 2024 Apr;34(3):148-156. doi: 10.1089/cap.2023.0097. PMID: 38608010.

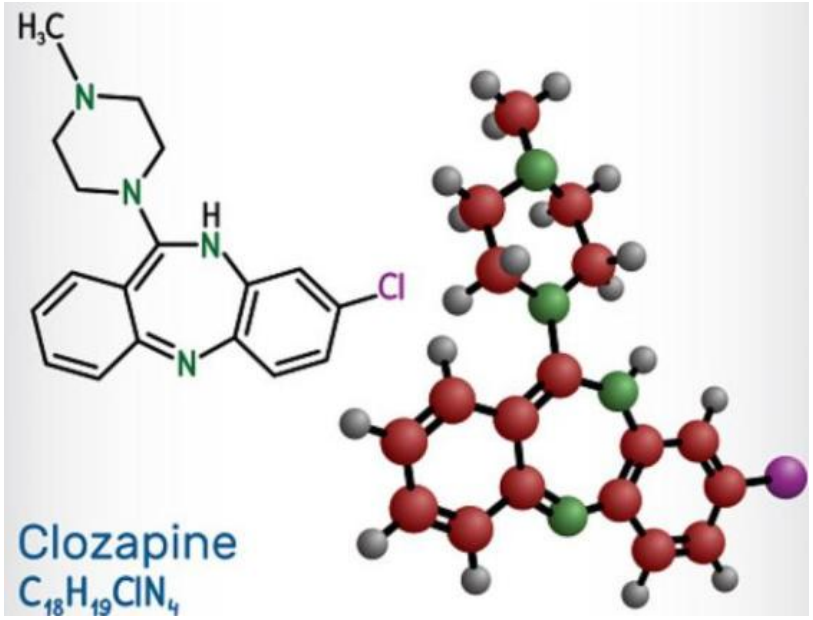


effectiveness and tolerability of Clozapine in the treatment of aggression in youth with Neurodevelopmental Disorders

26 children and adolescents (21 boys, age 13.47 ± 2.05 years, follow-up duration 9.77 ± 3.50 months) with

- **physical aggression**
- **two failed trials with other Second-Generation Antipsychotics (SGAs)**

16 (61.54%) were responders (CGI-I ≤2)
13 (50.00%) displayed remission of aberrant behaviors (ΔABC-Total >35)



Most frequent side effects

- increased appetite (50.00%)
- sialorrhea (38.46%)
- increased repetitive behaviors (26.92%)

- 2 subjects presented epileptic seizures
- Nobody presented leucopoenia

Clozapine may be helpful in ameliorating treatment-resistant aggression in youth with neurodevelopmental conditions

Quale classe di farmaci per Francesco……?

iperattività/impulsività

disregolazione emozionale

aggressività/isolamento

depersonalizzazione
e derealizzazione

ideazione suicidaria

insonnia

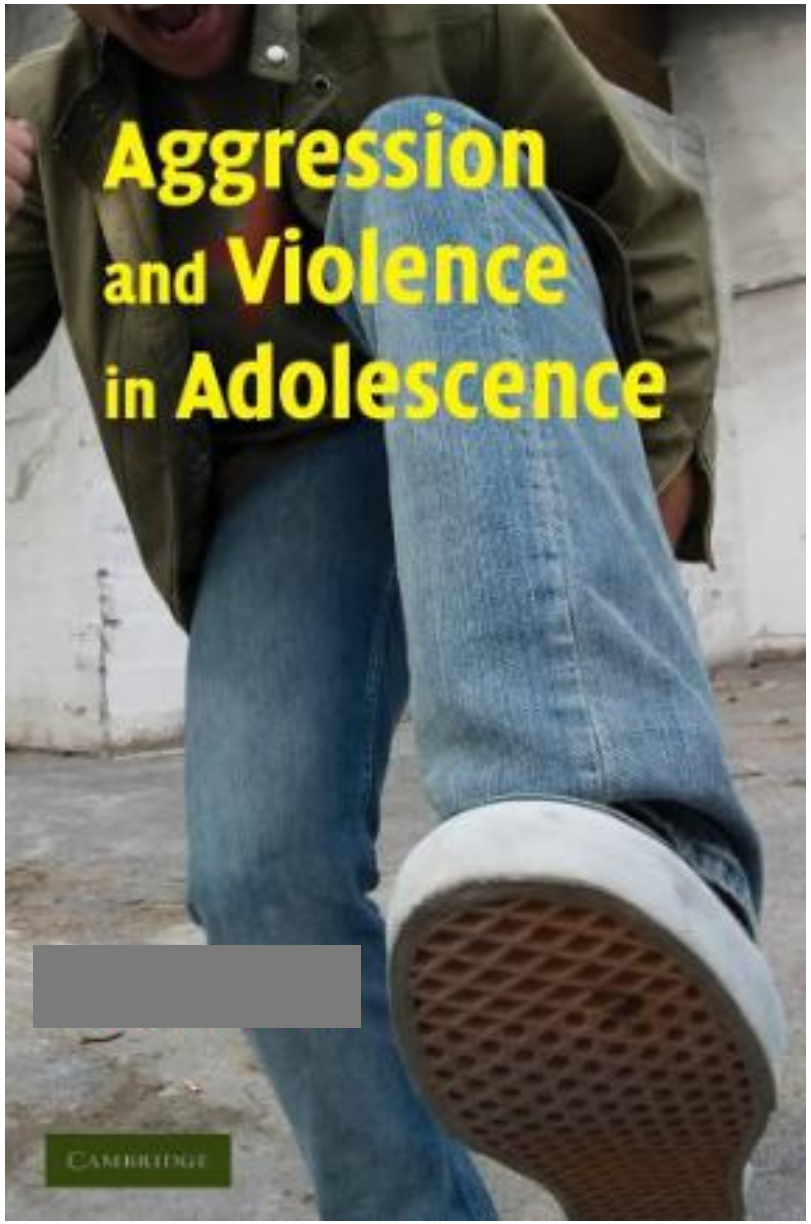
tic



AAPs have principally been used for non-psychotic conditions

DelBello M, Grcevich S. Phenomenology and epidemiology of childhood psychiatric disorders that may necessitate treatment with atypical antipsychotics. J Clin Psychiatry. 2004;65:12-19

- aggressive and dysfunctional behavior in the context of autism
- aggressive behavior in patients with disruptive behavioral disorders
- manic and mixed episodes in bipolar disorder
- resistant ADHD
- Tourette's syndrome and other tic disorders
- OCD
- eating disorders
- Depression
- sleep problems
- difficulties with impulse control



Aggression (no irritability or psychosis) is the most common target symptom for AAs use in youths

Pappadopulos et al, J Am Acad Child Adolesc Psychiatry. 2003;42:145-161.

Psychotropic Medications in Children and Adolescents: Guide for Use and Monitoring

This document was developed by Community Care of North Carolina with the assistance of the Medication Management Workgroup of the Fostering Health NC initiative, a project of the NC Pediatric Society (www.ncpeds.org/fosteringhealthnc). The information contained in this guide is not intended to substitute or act as medical advice. If you have any questions about a medication prescribed to a child or adolescent in your care, contact the prescriber or a licensed medical professional.

Author:
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Medical Affairs- Director of Pharmacy
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2300 Rexwoods Drive, Suite 100
Raleigh, NC 27607
☎ 919-516-8118 | ✉ jmckee@n3cn.org

Definition of Psychotropic Medication:
Medication used in the treatment of mental illnesses and capable of affecting the mind, emotions, and behavior.



Perché si usano gli SGA per aggressività e comportamenti dirompenti

Second Generation Antipsychotic Medications

Generic Name	Brand Names	FDA Approval Age/Indication	Other Common Uses in Children	Potential Side Effects	Monitoring
Aripiprazole	Abilify	Approved for children 10 and older for bipolar disorder, manic or mixed episodes. Approved for adolescents 13 to 17 -for schizophrenia and bipolar disorder. Approved for 6 to 17 year olds for irritability associated with autistic disorder	Approved for bipolar mania or mixed episodes (10-17 years); schizophrenia (13-17 years); irritability associated with autism spectrum disorder (6-17 years)	• Acute Extrapyramidal symptoms • Tardive dyskinesia • Neuroleptic malignant syndrome • Hyperglycemia, diabetes mellitus • Elevated prolactin, gynecomastia, amenorrhea • Weight gain • Dyslipidemia • CBC abnormalities • Lowered seizure threshold • Dysphagia • Hyperthermia/lowered heat tolerance • Cognitive impairment (confusion and/or inability to focus that differs from baseline)	• Fasting plasma glucose or hemoglobin A1c and lipids at baseline, 3 months, then every 6 months • EKG- baseline and periodically • CBC- baseline and periodically • Blood pressure each visit • Pulse each visit • Weight/height/BMI at each visit • EPS evaluation baseline and weekly until dose stabilized • Tardive dyskinesia evaluation every 3 months • Clozapine-requires REMS • Vision assessment for changes annually • Sexual function-at each visit for first 12 months then every 6 months
Quetipine	Seroquel, Seroquel XR	Approved for adolescents 13 and older for schizophrenia. Approved for young adults 18 and older for bipolar disorder. Approved for 10 to 17 years olds for manic and mixed episodes of bipolar disorder	Approved for bipolar mania (10-17 years); schizophrenia (13-17 years)		
Olanzapine	Zyprexa	ETC. 18 and older- schizophrenia; 13 to 17- second line treatment for manic or mixed episodes of bipolar disorder	Approved for bipolar mania or mixed episodes and schizophrenia (13-17 years)		
Risperidone	Risperdal	ETC. 13 and older- schizophrenia; 10 and older- bipolar mania and mixed episodes; 5 to 16- irritability associated with autism	Approved for schizophrenia (13-17 years); bipolar mania or mixed episodes (10-17 years); irritability associated with autism spectrum disorder (5-16 years)	Same as previous page	Same as previous page
Clozapine*	Clozaril, FazaClo, Versacloz	18 and older	None		
Asenapine	Saphris	18 and older	Approved for acute treatment of bipolar mania and mixed episodes (10-17 years)		
Iloperidone*	Fanapt	18 and older	None		
Paliperidone	Invega	12 and older	Approved for treatment of schizophrenia (12-17 years)		
Ziprasidone*	Geodon	18 and older	None		
Lurasidone*	Latuda	18 and older	None		
Brexpiprazole*	Rexulti	18 and older	None		

*not approved for children and adolescents

salienza

- Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 2003; 160: 13-23.
- Winton-Brown TT, Fusar-Poli P, Ungless MA, Howes OD. Dopaminergic basis of salience dysregulation in psychosis. Trends Neurosci 2014; 37: 85-94.

processo di integrazione grazie al quale oggetti e stimoli provenienti dall'ambiente esterno o dal nostro stato interno si impongono all'attenzione, acquistando rilevanza e influenzando così pensieri e comportamenti.

L'ambiente è sempre sensorialmente molto complesso occorre continuamente distinguere gli stimoli rilevanti (attrattivi o avversivi o neutri) per rispondere adeguatamente a essi

- **salienza aberrante non corretta come attribuzione di significato a stimoli neutri o innocui**

- **disfunzione del sistema dopaminergico mesolimbico, implicato a sua volta nella regolazione del reward**



Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD and CD: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry. 2015 Feb;60(2):52-61.

Table 1 Grading of Recommendations, Assessment, Development and Evaluation evidence profiles for antipsychotics

Outcome assessed; number of studies; number of patients; study duration	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Dose–response effect present?	Summary of findings	Overall quality
Risperidone for conduct problems and aggression in youth with subaverage IQ and ODD or CD, with and without ADHD								
Conduct problems and aggression 5 RCTs; 398 patients; 4 weeks to 6 months	Minor limitations in study quality	No serious inconsistency	No indirectness	No serious imprecision	Possible publication bias	No evidence of dose–response effect for this outcome	SMD, risperidone, compared with placebo: 0.72 (95% CI 0.47 to 0.97)	Moderate*
Risperidone for disruptive and aggressive behaviour in youth with ODD and CD, with and without ADHD								
Disruptive and aggressive behaviour 4 RCTs; 429 patients; 4 weeks to 6 months	No limitations in study quality	No serious inconsistency	No indirectness	No serious imprecision	Possible publication bias	No evidence of dose–response effect for this outcome	SMD, risperidone, compared with placebo: 0.60 (95% CI 0.31 to 0.89)	High
Quetiapine for conduct problems in youth with CD, with and without ADHD								
Conduct problems One RCT; 19 patients; 6 weeks	Major limitations in study quality	Unable to assess	No indirectness	Some imprecision	Possible publication bias	No evidence of dose–response effect for this outcome	Clinical Global Impression—Severity, quetiapine, compared with placebo, effect size 1.6 (95% CI 0.9 to 3.0)	Very low*
Haloperidol for aggression in youth with CD								
Aggression One RCT; 61 patients; 4 weeks	Major limitations in study quality	Unable to assess	No indirectness	Unable to assess	Possible publication bias	No evidence of dose–response effect for this outcome	Haloperidol was significantly different from placebo on measures of hostility and aggression (magnitude of effect not reported).	Very low*
Thioridazine for conduct problems in youth with subaverage IQ and ADHD or CD								
Conduct problems One RCT; 30 patients; 3 weeks	Major limitations in study quality	Unable to assess	No indirectness	Unable to assess	Possible publication bias	No evidence of dose–response effect for this outcome	Unable to calculate effect size for data; small difference between thioridazine and placebo on the Conduct Problems subscale of the Conners Teacher Questionnaire	Very low*

* Overall quality was downgraded based on limitations in study quality.



Evidence supporting the use of **haloperidol, thioridazine, quetiapine** in aggressive youth with CD is of **low or very-low quality**

carbamazepine is not different from placebo for the management of aggression in youth with CD.

Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD and CD: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry. 2015 Feb;60(2):52-61.

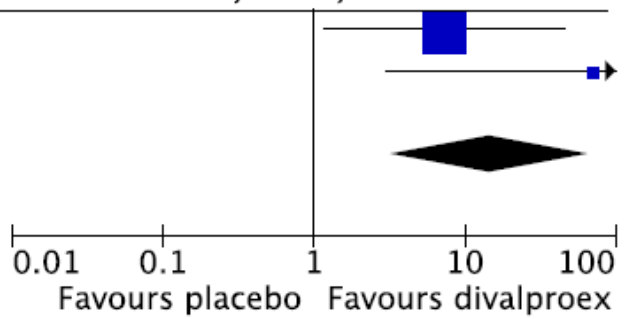


Figure 4 Divalproex, compared with placebo, for aggressive behaviour in youth with oppositional defiant disorder or conduct disorder, with and without attention-deficit hyperactivity disorder

	Divalproex		Placebo			OR	OR
Study or subgroup	Events	Total	Events	Total	Weight	M–H, Fixed, 95% CI	M–H, Fixed, 95% CI
Blader et al [27]	8	14	2	13	88.7%	7.33 [1.16, 46.23]	
Donovan et al [28]	8	10	0	10	11.3%	71.40 [3.00, 1696.74]	
Total (95% CI)		**24**		**23**	**100.0%**	**14.60 [3.25, 65.61]**	
Total events	16		2				

Heterogeneity: $X^2 = 1.50$, $df = 1$ ($P = 0.22$); $I^2 = 33\%$

Test for overall effect, $z = 3.50$ ($P < 0.001$)



evidence supporting the use of divalproex in aggressive youth with ODD or CD is of low quality !!!

Clozapine is also widely known for its **anti-aggressive effects** which have most commonly been demonstrated among schizophrenia patients…

- Frogley C, Taylor D, Dickens G, Picchioni M. A systematic review of the evidence of clozapine's anti-aggressive effects. Int J Neuropsychopharmacol. 2012; 15(9): 1351–1371.
- Chengappa KNR, Vasile J, Levine J, et al. Clozapine: its impact on aggressive behaviour among patients in a state psychiatric hospital. Schizophr Res. 2002; 53(1–2): 1–6.
- Citrome L, Volavka J, Czobor P, et al. Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia. Psychiatr Serv. 2001; 52(11):1510–1514.
- Rabinowitz J, Avnon M, Rosenberg V. Effect of clozapine on physical and verbal aggression. Schizophr Res. 1996; 22(3): 249–255.
- Ratey JJ, Leveroni C, Kilmer D, Gutheil C. The effects of clozapine on severely aggressive psychiatric inpatients in a state hospital. J Clin Psychiatry. 1993; 54(6): 219–223.

Table 1. Baseline patient characteristics and discharge diagnoses

	Males (n=10, 36%)	Females (n=18, 64%)	All patients (n=28)
Age at admission (years)	16 ± 1.5	15.5 ± 2.3	15.7 ± 2
Mean ± SD (min-max)	(13.3–17.7)	(10.7–18.9)	(10.7–13.9)
Age at clozapine start (years)	16.1 ± 1.5	15.7 ± 2.3	15.8 ± 2
Mean ± SD (min-max)	(13.6–17.9)	(11.1–19.3)	(11.1–19.3)
Weight (kg) at admission, Mean ± SD	84.3 ± 22.8	49.1 ± 11.4	61.7 ± 23.5
	n = 10	n = 18	n = 28
Race/Ethnicity			
White/Caucasian	3	5	8
Chinese	3	3	6
Filipino	-	3	3
Southeast Asian	3	-	3
Aboriginal	-	2	2
Black/African	-	2	2
South Asian	1	1	2
Latin American	-	1	1
Japanese	-	1	1
	n (%)	n (%)	n (%)
History of cannabis use	5 (50)	5 (27.7)	10 (35.7)
Tobacco smoking at clozapine initiation	1 (3.6)	1 (3.6)	2 (7.1)
Primary psychotic illness	10 (100)	15 (83.3)	25 (89.3)
Affective illness present	4 (40)	9 (50)	13 (46.4)
First mental health presentation	2 (20)	5 (27.8)	7 (25)
Antipsychotic drug trials prior to clozapine initiation, mean ± SD	2.8 ± 1.2	3.0 ± 1.5	2.9 ± 1.3
Discharge diagnoses (per treating psychiatrist / non-retrospective):			
Schizophreniform	1 (10)	2 (11.1)	3 (10.7)
Schizophrenia	5 (50)	6 (33.3)	11 (39.3)
Schizoaffective	4 (40)	7 (38.9)	11 (39.3)
Bipolar disorder	0 (0)	2 (11.1)	2 (7.1)
Non-psychotic non-bipolar illness	0 (0)	1 (5.6)	1 (3.6)



Komaryk A, Elbe D, Burgess L. **Retrospective Review of Clozapine Use in Children and Adolescents**. J Can Acad Child Adolesc Psychiatry. 2021 Feb;30(1):36-48..

Rachamallu V, Elberson BW, Vutam E, Aligeti M. **Off-Label Use of Clozapine in Children and Adolescents-A Literature Review**. Am J Ther. 2019 May/Jun;26(3):e406-e416.

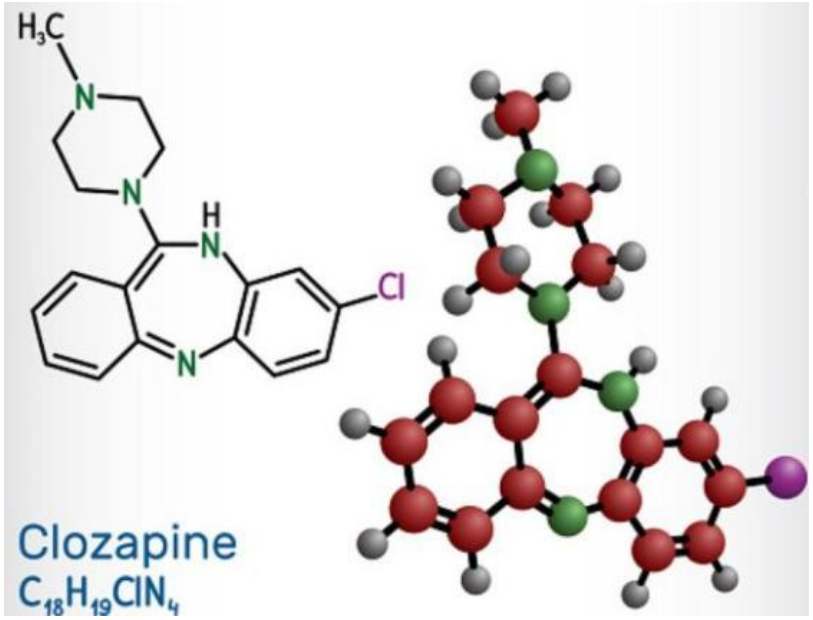
Berloffa S, Masi G, Falcone F, Simonelli V, Narzisi A, Valente E, Viglione V, Milone A, Sesso G. Clozapine Treatment for Aggressive Behaviors in Youths with Neurodevelopmental Disorders. J Child Adolesc Psychopharmacol. 2024 Apr;34(3):148-156. doi: 10.1089/cap.2023.0097. PMID: 38608010.

effectiveness and tolerability of Clozapine in the treatment of aggression in youth with Neurodevelopmental Disorders

26 children and adolescents (21 boys, age 13.47 ± 2.05 years, follow-up duration 9.77 ± 3.50 months) with

- **physical aggression**
- **two failed trials with other Second-Generation Antipsychotics (SGAs)**

16 (61.54%) were responders (CGI-I ≤2)
13 (50.00%) displayed remission of aberrant behaviors (ΔABC-Total >35)



Most frequent side effects

- increased appetite (50.00%)
- sialorrhea (38.46%)
- increased repetitive behaviors (26.92%)

- 2 subjects presented epileptic seizures
- Nobody presented leucopoenia

Clozapine may be helpful in ameliorating treatment-resistant aggression in youth with neurodevelopmental conditions


WARNING!

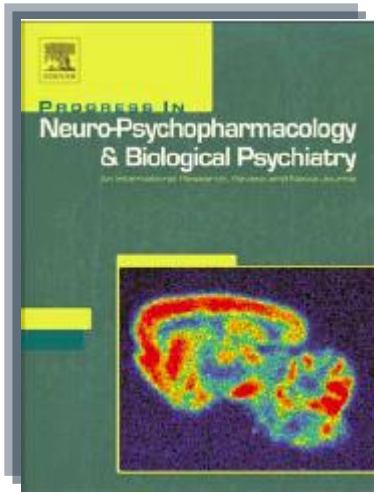
Cardiovascular side effects



ECG PARAMETERS IN CHILDREN AND ADOLESCENTS TREATED WITH ARIPIPRAZOLE AND RISPERIDONE

Eva Germanò, MD, PhD[1]*, Domenico Italiano, MD, PhD [2]*, Marco Lamberti, MD [1], Laura Guerriero, MD [1], Carmen Privitera, MD [3], Gessica D'Amico, MD [3], Rosamaria Siracusano, MD, PhD [1], Massimo Ingrassia, PsyD [4], Edoardo Spina, MD, PhD [2], Maria Pia Calabrò MD [3†], Antonella Gagliano MD, PhD [1†]

2014 Jun 3;51:23-7



AAPs may cause QT prolongation on the ECG which predisposes patients to an increased risk of developing threatening ventricular arrhythmias

open-label, prospective study
60 drug naïve patients (55M/5F, mean age 10,2 + 2,6 years) starting aripiprazole (29) or risperidone (31) in monotherapy

Basal and post-treatment (2 months) ECG parameters:

- **mean QT (QTc)**
- **QT dispersion (QTd)**

The treatment with risperidone and aripiprazole in children is not associated with clinically relevant modifications of QT interval



Metabolic side effects

- **aumento di peso** (Tandon & Halbreich, 2003)
- **iperlipidemia** (Meyer & Koro, 2004)
- **insulinoresistenza** (Nasrallah & Newcomer, 2004; Wu et al., 2006)
- **sindrome metabolica** (Meyer, Koro, & L'Italien, 2005; Shirzadi & Ghaemi, 2006)
- **diabete di tipo 2** (Cohen, 2004; Henderson, 2002; Melkersson, 2004; Newcomer, 2005)

Martin et al, 2004; Fleischhaker et al., 2007; Correll et al, 2009; Panagiotopoulos, Ronsley, & Davidson, 2009

Il peso si mantiene alto anche a 12 settimane di distanza dalla sospensione del farmaco !!!

Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Database Syst Rev. 2017 Aug 9;8(8):CD008559.

Analysis 1.2. Comparison 1 Medication vs. placebo, Outcome 2 Final scores (OAS-M and OAS).

Review: Atypical antipsychotics for disruptive behaviour disorders in children and youths

Comparison: 1 Medication vs. placebo

Outcome: 2 Final scores (OAS-M and OAS)

Study or subgroup	Antipsychotic N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Buitelaar 2001	19	6.7 (6.3)	19	8.1 (6.9)		66.7 %	-0.21 [-0.85, 0.43]
Connor 2008	9	43.3 (55.6)	10	49.4 (27.8)		33.3 %	-0.13 [-1.04, 0.77]
Total (95% CI)	**28**		**29**			**100.0 %**	**-0.18 [-0.70, 0.34]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable

-4 -2 0 2 4

Favours experimental Favours control

Analysis 1.3. Comparison 1 Medication vs. placebo, Outcome 3 Weight gain.

Review: Atypical antipsychotics for disruptive behaviour disorders in children and youths

Comparison: 1 Medication vs. placebo

Outcome: 3 Weight gain

Study or subgroup	Antipsychotic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mean change scores							
Aman 2002	55	2.2 (1.8)	63	0.9 (1.5)		50.4 %	1.30 [0.70, 1.90]
Findling 2000	10	4.2 (0.7)	10	0.74 (0.9)		49.6 %	3.46 [2.75, 4.17]
Total (95% CI)	**65**		**73**			**100.0 %**	**2.37 [0.26, 4.49]**

Heterogeneity: $Tau^2 = 2.22$; $Chi^2 = 20.77$, df = 1 (P<0.00001); $I^2 = 95\%$

Test for overall effect: Z = 2.20 (P = 0.028)

Test for subgroup differences: Not applicable

-10 -5 0 5 10

Favours antipsychotic Favours placebo

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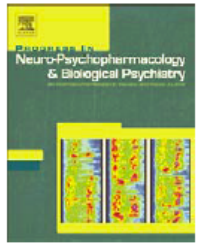


Progress in Neuro-Psychopharmacology & Biological Psychiatry 33 (2009) 1496–1501

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



Short- and long-term effects on prolactin of risperidone and olanzapine treatments in children and adolescents

Gaetana Migliardi [a], Edoardo Spina [a,b], Concetta D'Arrigo [a,b], Antonella Gagliano [c], Eva Germanò [c], Rosamaria Siracusano [c], Francisco J. Diaz [d], Jose de Leon [e,f,*]

- 41 patients : 6 F and 22 M on risperidone, 6 F and 7 M on olanzapine
- **prolactin levels on risperidone were 4.9 ng/mL higher than on olanzapine** (10.3 times higher after controlling for dosing potency)
- prolactin elevation was associated with transitory symptoms only in a girl on risperidone

Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD and CD: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry. 2015 Feb;60(2):52-61.

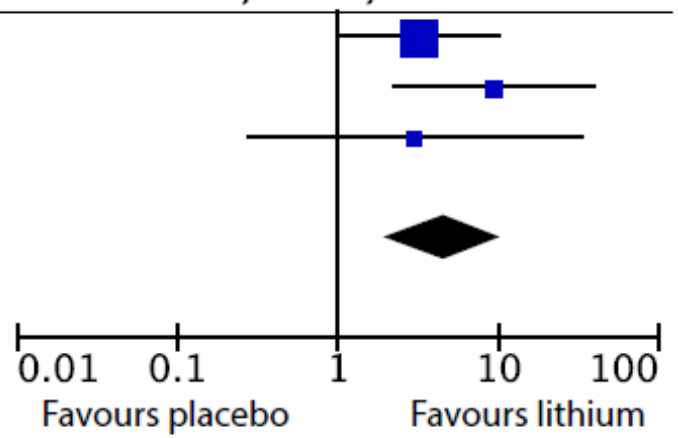


Figure 3 Lithium, compared with placebo, for aggression in youth with conduct disorder

	Lithium		Placebo			OR	OR
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M–H, Fixed, 95% CI**	**M–H, Fixed, 95% CI**
Campbell et al [26]	17	25	10	25	61.0%	3.19 [1.00, 10.17]	
Malone et al [25]	16	20	6	20	22.9%	9.33 [2.18, 39.96]	
Rifkin et al [24]	3	14	1	12	16.1%	3.00 [0.27, 33.49]	
Total (95% CI)		**59**		**57**	**100.0%**	**4.56 [1.97, 10.56]**	
Total events	36		17				

Heterogeneity: $X^2 = 1.41$, $df = 2$ ($P = 0.49$); $I^2 = 0\%$

Test for overall effect, $z = 3.55$ ($P < 0.001$)



Pringsheim T, Hirsch L, Gardner D, Gorman DA. **The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD**, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 1: psychostimulants, alpha-2 agonists, and atomoxetine. Can J Psychiatry. 2015 Feb;60(2):42-51.

Figure 1a Psychostimulants, compared with placebo, for aggression, oppositional behaviour, and conduct problems as measured by teachers in youth with attention-deficit hyperactivity disorder, with and without oppositional defiant disorder, and conduct disorder

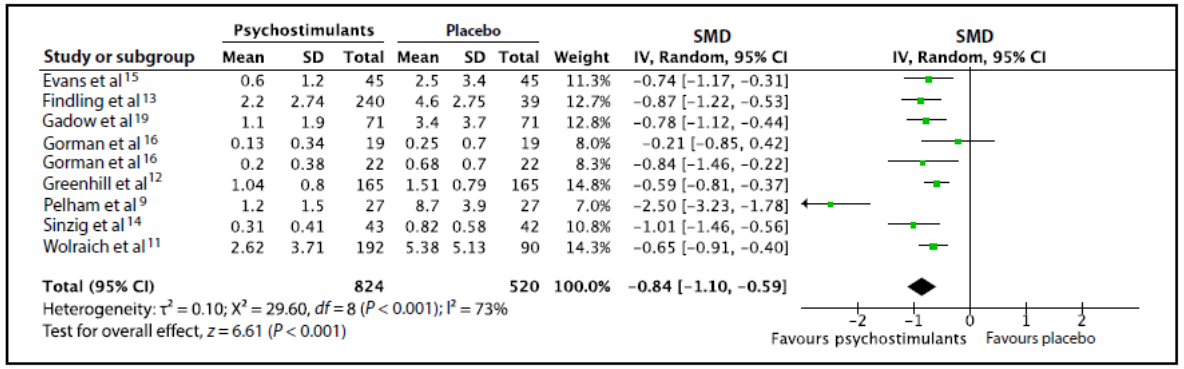
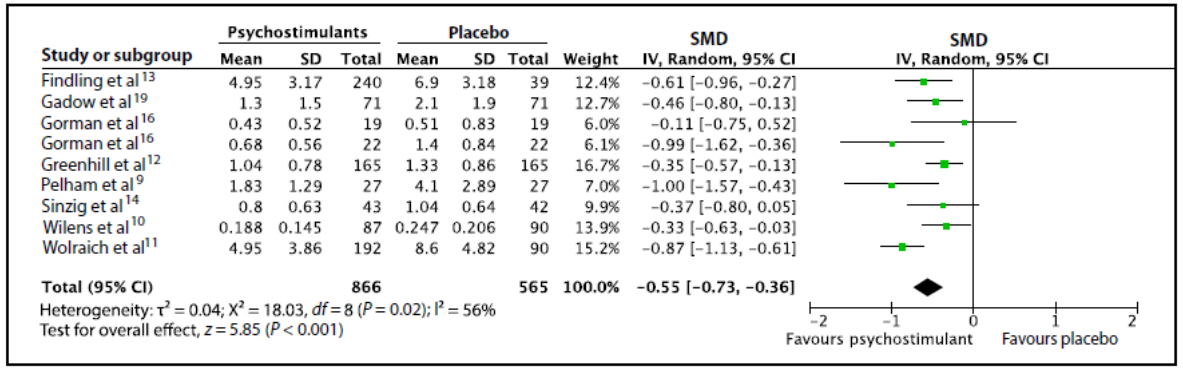


Figure 1b Psychostimulants, compared with placebo, for aggression, oppositional behaviour, and conduct problems as measured by parents in youth with attention-deficit hyperactivity disorder, with and without oppositional defiant disorder, and conduct disorder



Two systematic reviews and 20 randomized controlled trials were included.

There is **high-quality evidence** that **psychostimulants** have a **moderate-to-large effect** on **oppositional behaviour, conduct problems, and aggression** in youth with ADHD, with and without ODD or CD.

There is very-low-quality evidence that **clonidine** has a small effect on oppositional behaviour and conduct problems in youth with ADHD, with and without ODD or CD

There is **moderate-quality evidence** that **guanfacine** has a small-to-moderate effect on oppositional behaviour in youth with ADHD, with and without ODD.

There is high-quality evidence that **atomoxetine** has a small effect on oppositional behaviour in youth with ADHD, with and without ODD or CD.

psychostimulants, alpha-2 agonists, and atomoxetine can be beneficial for disruptive and aggressive behaviours in addition to core ADHD symptoms; however, **psychostimulants generally provide the most benefit**

Quale classe di farmaci per Francesco……?

iperattività/impulsività

disregolazione emozionale

aggressività/isolamento

depersonalizzazione e derealizzazione

ideazione suicidaria

insonnia

tic





I sintomi psicotici (allucinazioni, delirio, disorganizzazione del pensiero e del comportamento) rappresentano una via finale comune di molti disturbi, inclusa la schizofrenia, e rappresentano indicatori non specifici di malattia mentale severa

(Rutter & Taylor, Child and Adolescent Psychiatry IV ed., 2002)

“**psychotic symptom**” denotes a manifestation of cognitive or perceptual dysfunction, mainly delusions or hallucinations….

….whereas “**psychotic disorder**” refers to a condition in which psychotic symptoms meet specific diagnostic criteria for a disease

Jeffrey A. Lieberman, M.D., and Michael B. First, M.D. **Psychotic Disorders N Engl J Med 2018;379:270-280, DOI: 10.1056/NEJMra1801490**

I sintomi psicotici non sono rari in età evolutiva

cohort of **12-year-old twins**

5.9% reported definite psychotic symptoms, with auditory and visual hallucinations as the most common symptoms
(van Os et al, 2009; Polanczyk et al. 2010)



Psychotic experiences
(subclinical psychotic experiences)

46% of community sample with psychotic experiences **had no common mental disorder**

Morgan C, Reininghaus U, Reichenberg A et al. Br J Psychiatry 2014;204:346-53

Early-life PEs are associated with increased risk of psychosis in adulthood

- Zammit S. Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. Am J Psychiatry. 2013;170(7):742–750
- Yung AR, Lin A. Psychotic experiences and their significance. World Psychiatry. 2016 Jun;15(2):130-1. doi: 10.1002/wps.20328. PMID: 27265701; PMCID: PMC4911755.

sindrome psicotica attenuata (APS -Attenuated Psychosis Syndrome)

introdotta nel DSM-5 come condizione che necessita di ulteriori studi/approfondimenti

- sintomi psicotici sottosoglia
- disagio significativo e disabilita

Gli individui con questi sintomi sono considerati a rischio di sviluppare successivamente un disturbo psicotico



sintomi psicotici attenuati in adolescenti asintomatici

- Fusar-poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transintion outcomes in individuals at high clinical risk. Arch Gen Psychiatry 2012;69:220-9
- Linscott RJ, Van Os J. An update and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med 2013;43:1133-49.

McHugh MJ, McGorry PD, et al,. **The Ultra-High-Risk for psychosis groups**: Evidence to maintain the status quo. Schizophr Res. 2018 May;195:543-548.



21 million people worldwide
(World Health Organization, 2017)

La schizofrenia è un **disturbo mentale spesso cronico con un forte effetto negativo sugli esiti funzionali**

The **etiology** of schizophrenia involves:

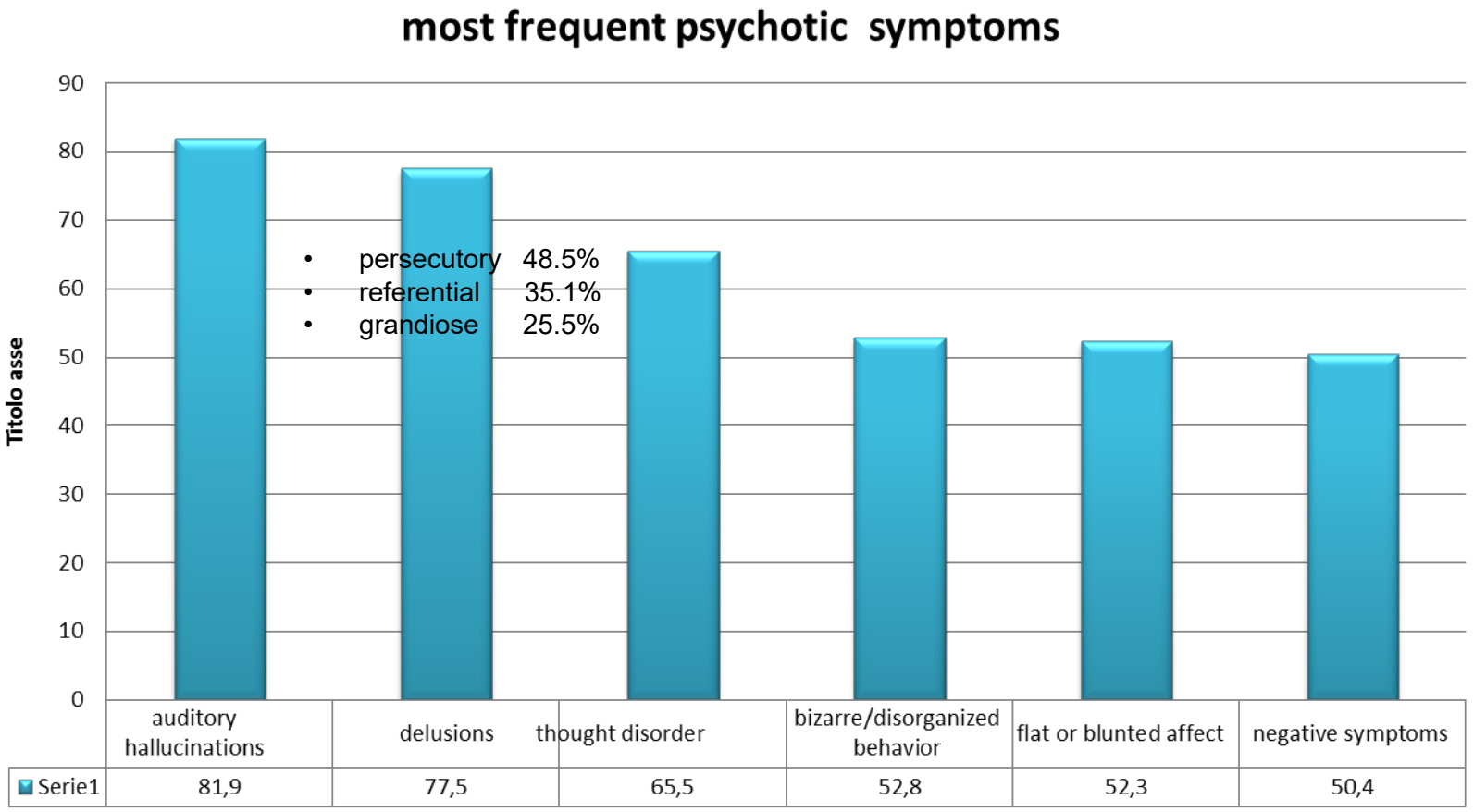
- genetic susceptibility
- environmental exposures
- neurobiological factors

(Howes and Shatalina, 2022; Jauhar et al., 2022; Rapoport et al., 2005; Rund, 2018)

- **substantial disability burden**
(GBD 2019 Diseases and Injuries Collaborators, 2020)
- **mortality**
(Hjorthøj et al., 2017).

Childhood-onset schizophrenia (COS)

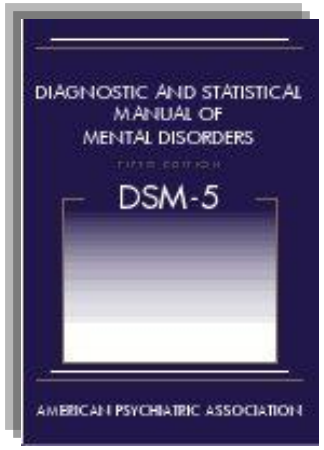
- VEOS: **1:10.000** bambini
- EOS: dopo i 13 anni si incrementa progressivamente fino a raggiungere a 18 anni la prevalenza di **17:10.000**



Stentebjerg-Olesen, Correll et al, Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: **A Systematic Review ,** JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY Volume 26, Number 5, **2016**



Schizophrenia spectrum and other psychotic disorders



Perché «SPETTRO SCHIZOFRENICO» ?

- struttura dimensionale della psicosi
- grande eterogeneità dei profili sintomatologici
- diversità nella risposta ai trattamenti
- variabilità degli esiti funzionali e sociali

The peak age at schizophrenia onset is 20.5 years with a median age at onset of 25 years

(interquartile range 21–35)

(Solmi et al., 2022)

- ❑ **Childhood-onset schizophrenia (COS)** occurs before age 13
- ❑ **Early onset schizophrenia (EOS)** between age 13 and 17
  (Clemmensen et al., 2012).



- 2 % of schizophrenias are diagnosed before age 14
- 8.2 % before age 18

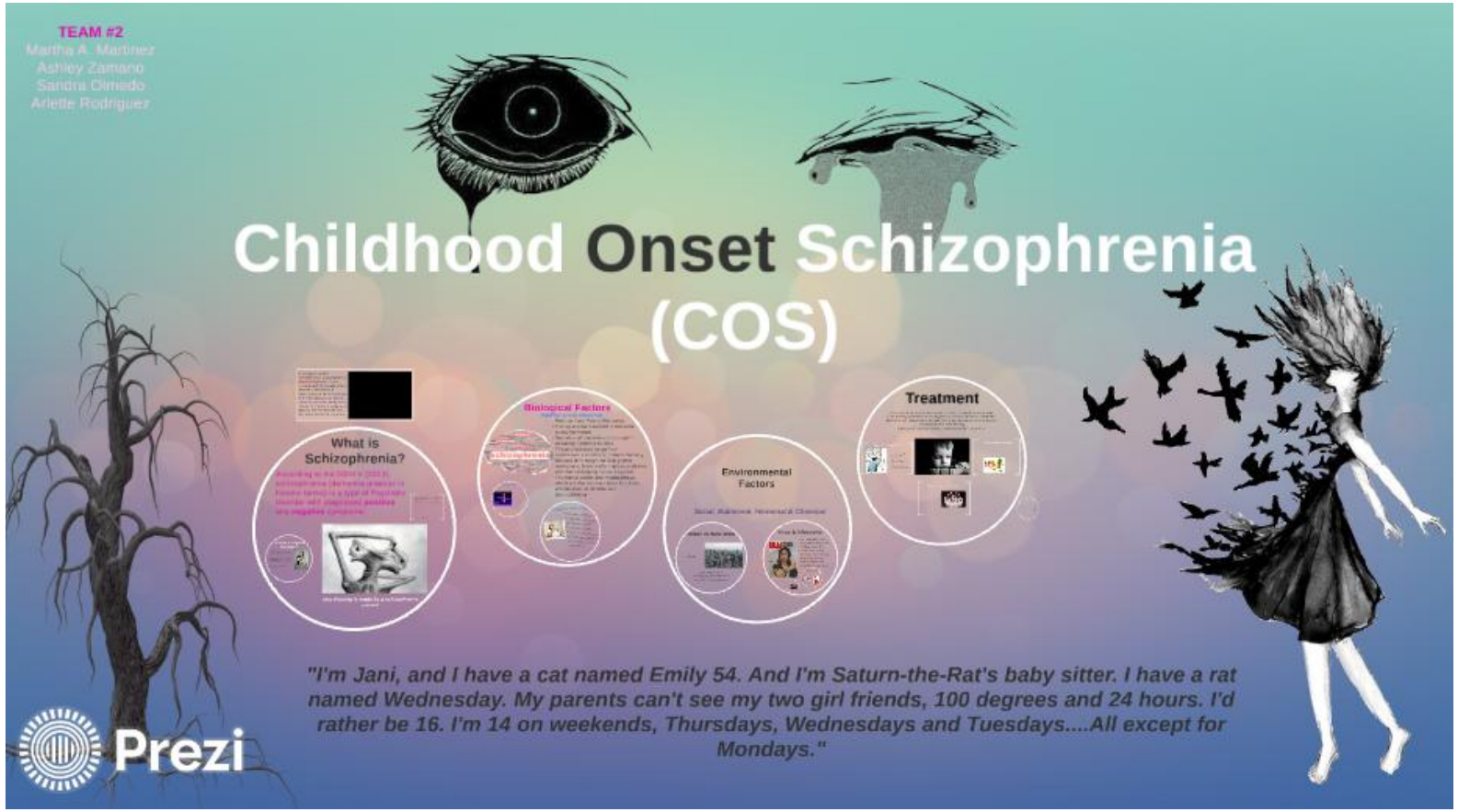
The percentage increases to 12 % when considering schizophrenia-spectrum diagnoses, and as many as 18 % of individuals have their first symptoms before age 18

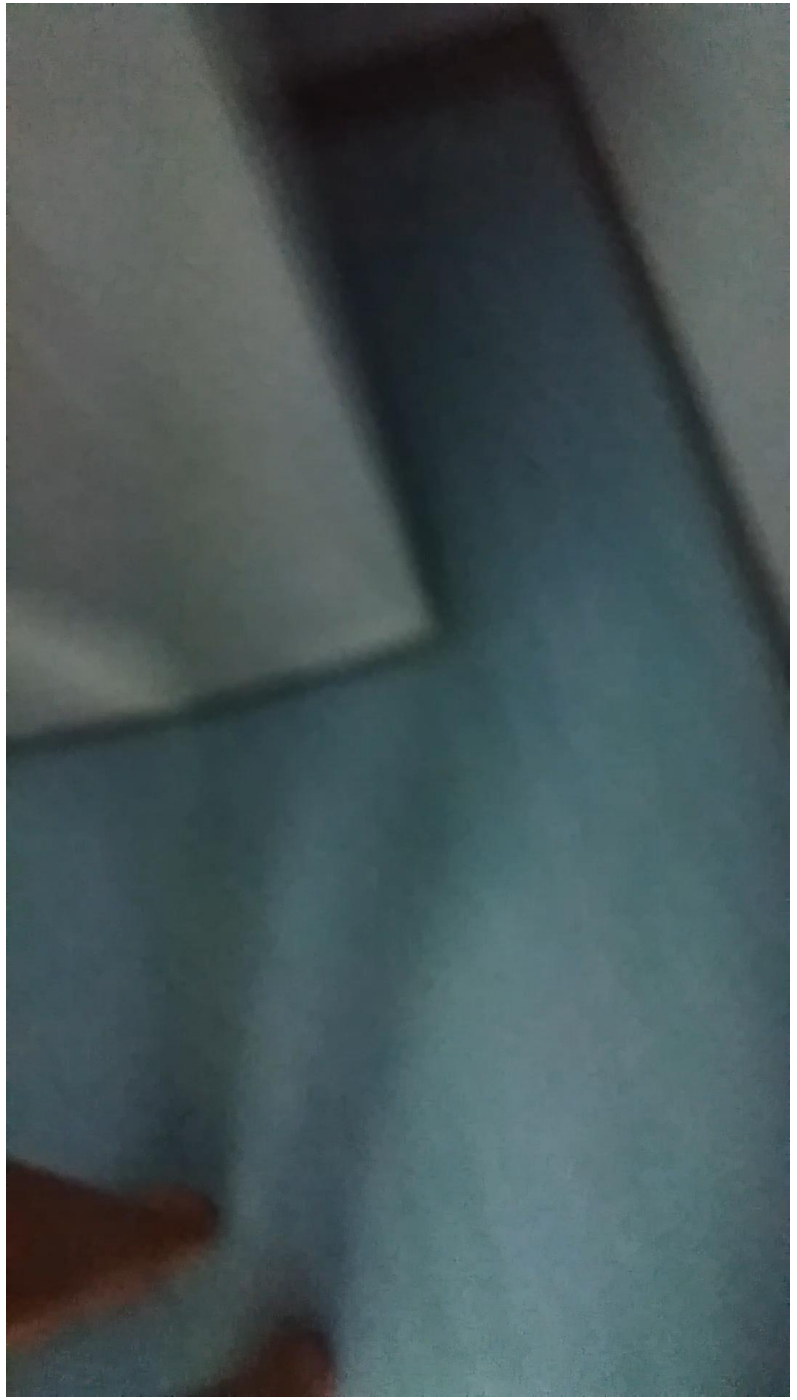
(Solmi et al., 2022).

The estimated incidence of

- EOS is 0.25 % or less of the general population
- COS is 0.05 %

(Driver et al., 2013; Jerrell and McIntyre, 2016)





Disturbo del neurosviluppo caratterizzato da specifiche anomalie del pensiero (contenuto e forma), delle senso-percezioni, delle emozioni che si associa a deficit delle capacita' cognitive, dell'affettivita' e del funzionamento sociale



Onset of Schizophrenia in Children and Adolescents

Children	Adolescents
Insidious and gradual	Gradual or acute
Preceded by a significant decline in functioning	-
Odd and eccentric behaviors	Hallucinations, disordered thoughts, and affective flattening
Negative symptoms	Negative symptoms

https://psychopharmacologyinstitute.com/section/onset-and-unique-features-of-schizophrenia-in-children-and-adolescents-2654-5206/

Cognitive deficits in EOS affect:

- processing speed
- learning and memory
- attention
- social cognition
- executive functions

(Bombin et al., 2013; Frangou, 2010; Gochman et al., 2005; Rajji et al., 2009; Reichenberg et al., 2010; Zabala et al., 2010).

Compared to patients with EOS, those **with COS tend to have**

- more speech, language disorders
- more educational disabilities
- more severe intelligence deficits

(Jerrell and McIntyre, 2016).

…se confrontati alla forma ad insorgenza in età adulta, COS vs EOS hanno:



more **premorbid** deficits
Luoma et al., 2008

higher burden of **NDDs associated with cytogenetic alterations**
Addington and Rapoport, 2009;; Fernandez et al., 2019

more **severe** symptoms
Coulon et al., 2020

more **negative** symptoms: cognitive functioning is often impaired at the onset. **Full IQ is reduced** (around 80) with particular deficits in verbal comprehension, language, and short-term memory; attention and executive function may also be impaired
Rammou et al., 2019

hallucinations, often auditory, are the most commonly reported symptom of psychosis
Di Luzio M, Pontillo M, et al (2023) Clinical features and comorbidity in very early-onset schizophrenia: a systematic review. Front. Psychiatry 14:1270799.

experience significant **sleep disturbances** that highly relate to symptom severity
Markovic A, et al. Sleep neurophysiology in childhood onset schizophrenia. J Sleep Res. 2021 Apr;30(2):e13039.

poorer **outcomes**
Díaz-Caneja et al., 2015; Immonen et al., 2017; Reichert et al., 2008; Stentebjerg-Olesen et al., 2016

higher risk of treatment **resistance**
Lasevoli et al., 2022; Siskind et al., 2022; Smart et al., 2021; Zhu et al., 2017

EOS and NDDs

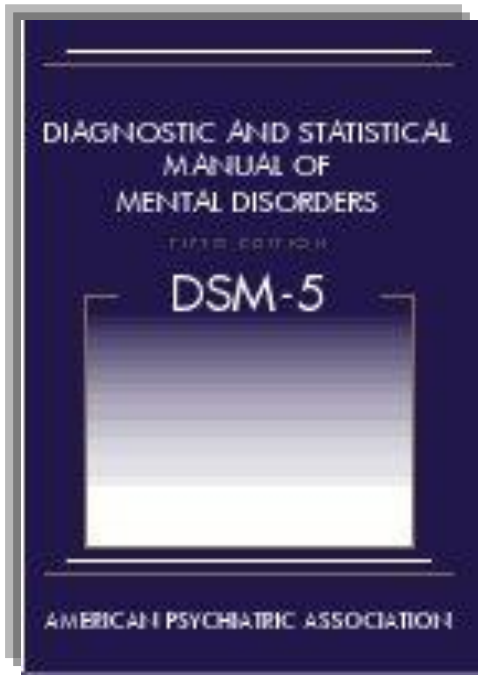


La schizofrenia può essere considerata un disturbo del neurosviluppo ?

Schizophrenia may be considered a neurodevelopmental disorder *in its own right**…

*di diritto

Chandrasekhar T, Copeland JN, Spanos M, Sikich L. Autism, Psychosis, or Both? Unraveling Complex Patient Presentations. Child Adolesc Psychiatr Clin N Am. 2020 Jan;29(1):103-113. doi: 10.1016/j.chc.2019.08.003. Epub 2019 Sep 18. PMID: 31708040.





DSM-5 (APA, 2013)

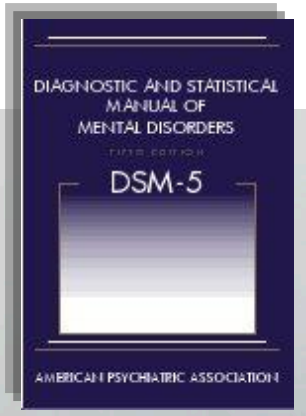
Macroarea definita

“**Neurodevelopmental Disorders**”

1. Disabilità intellettiva
2. Disturbi della Comunicazione (Linguaggio)
3. Disturbo Specifico dell’Apprendimento
4. Attention-Deficit/Hyperactivity Disorder (ADHD)
5. Disturbo dello Spettro Autistico
6. Disturbo della Coordinazione Motoria e Disturbo da Tic

…Il settimo?

Si ammette la possibilità che si inscriva su un disturbo del neurosviluppo



la diagnosi aggiuntiva di Schizofrenia puo essere posta in caso di "**storia di disturbo dello spettro autistico** *o di un altro disturbo della comunicazione a esordio nell'infanzia*" solo se allucinazioni o deliri "**preminenti**" sono presenti da almeno un mese

Child Adolesc Psychiatr Clin N Am. 2020 Jan;29(1):103-113

Autism, Psychosis, or Both? Unraveling Complex Patient Presentations

Tara Chandrasekhar, MD[a,*], John Nathan Copeland, MD[a], Marina Spanos, PhD[b], Linmarie Sikich, MD[a]

*Individuals with both **ASDs and SSDs** may experience :*

- **more severe symptoms**
- **catatonia** (frequently overlooked)
- **lack of response** from multiple antipsychotic medications

Autism spectrum disorders (ASDs) and schizophrenia spectrum disorders (SSDs) co-occur at **elevated rates**, likely in part due to **shared genetic risk factors**

La catatonia è un disturbo comportamentale caratterizzato dalla perdita dell'iniziativa motoria e dall'insensibilità agli stimoli esterni.



I segni più comuni di catatonia comprendono:

• inerzia motoria sono alternate ad episodi di iperattività e agitazione scoordinata
•mantenimento di posture statiche
•inespressività e mutismo
•rifiuto di mangiare,
•sguardo fisso,
•aumentato tono muscolare a riposo
•rigidità del pensiero con ripetizione di parole o frasi (ecolalia), o verbigerazione (ripetizione di frasi prive di significato, sconnesse),
•ecoprassia (ripetizione per imitazione dei movimenti altrui,).

psychomotor syndrome characterized by several signs and symptoms, occurs with multiple neuropsychiatric and medical causes, including ASDs and SSDs.







- Billstedt E, Gillberg IC, Gillberg C. Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. J AutismDevDisord 2005;35(3):351–60.
- Wing L, Shah A. Catatonia in autistic spectrum disorders. Br J Psychiatry 2000; 176(4):357–62.

Red Flags for Psychosis in Autism



A clinician should consider a diagnosis of a psychotic disorder in an individual with ASD who exhibits:

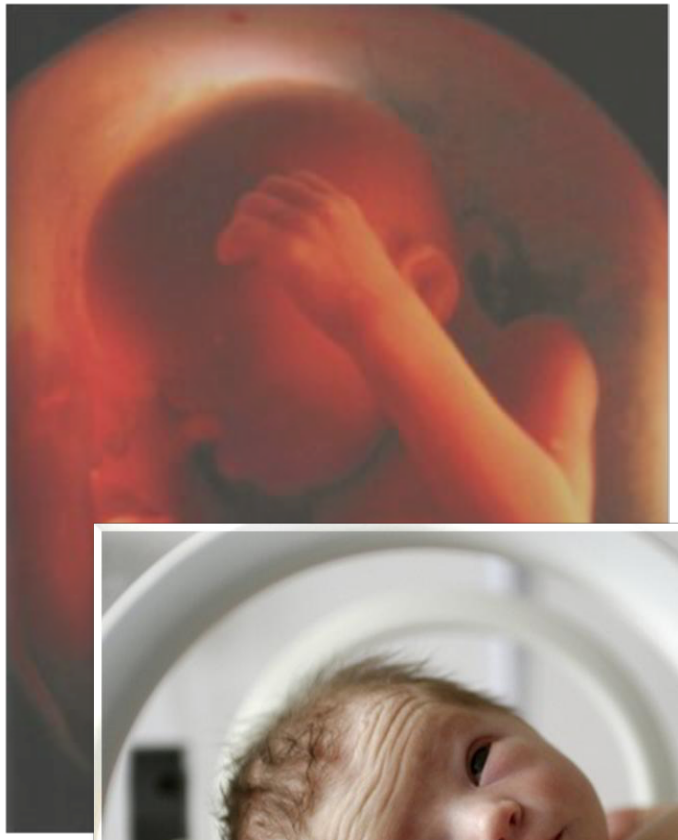


- Anomalie percettive
- Credenze insolite
- Comportamenti diversi dal basale
- Cambiamenti nel funzionamento cognitivo o adattativo
- Cambiamento nelle interazioni sociali
- Aumento del ritiro
- Presenza di comportamenti strani o insoliti che non corrispondono agli interessi o ai rituali tipici dell'individuo.

- Una valutazione longitudinale dei sintomi e dello stato mentale è utile
- Genitori e caregiver spesso riescono a identificare meglio i cambiamenti comportamentali rispetto al basale
- Se un genitore o un caregiver non riesce a decifrare il significato sottostante dei pensieri e delle parole di un bambino, il sospetto di psicosi dovrebbe essere posto

Chandrasekhar T, Copeland JN, Spanos M, Sikich L. Autism, Psychosis, or Both? Unraveling Complex Patient Presentations. Child Adolesc Psychiatr Clin N Am. 2020 Jan;29(1):103-113. doi: 10.1016/j.chc.2019.08.003. Epub 2019 Sep 18. PMID: 31708040.

I periodi critici





severe disorders with onset during adolescence or early adulthood, such as schizophrenia, are associated with prenatal and perinatal risks

(Arango, C.,Fraguas,D.,Parellada,M.,2014.Differential neurodevelopmental trajectories in patients with early-onset bipolar and schizophrenia disorders. Schizophr. Bull.40,S138–S146.)



Fase pre-perinatale

in individui vulnerabili fattori genetici e ambientali interagiscono determinando anomalie funzionali e strutturali che divengono evidenti solo durante l'adolescenza o la prima età adulta

many adult psychiatric disorders become manifest by age 14 and the large majority by age 24

(Kessler et al.,2005)



Major hormonal and neurobiological changes under the influence of sex hormones

A typical ‘double-hit’

Autism in early life with the addition of Schizophrenia later in adolescence or adulthood



1 case in **100,000**
in their **20**s

Skills affected

- Behavior and cognition
- Speech, language
- Coordination
- Social skills
- Illogical thinking
- Inattention and hyperactivity



Medication

Atypical (second generation) antipsychotics are the general frontline treatments.

Significant weight gain was seen with all medications

Treatment*

- Social skills training
- Special education program
- Supportive environment
- Supportive psychotherapy
- Substance abuse treatment
- Weight monitoring and diet



*long term monitoring is critical for a successful treatment

Alcuni punti fermi….



- I sintomi gravi o potenzialmente letali devono essere affrontati come priorità assoluta in acuto, tempestivamente (McClellan et al., 2013)

- I farmaci antipsicotici, insieme agli interventi psicoterapeutici, sono trattamenti di prima linea per gli adolescenti con EOS (Abidi et al., 2017; National Institute of Health and Care Excellence, 2013).

- L'efficacia(Correll et al., 2021) e la sicurezza(Solmi et al., 2020) di farmaci antipsicotici per adolescenti con disturbi psicotici, inclusi COS/EOS, è stata sufficientemente studiata.

- L'efficacia è in gran parte simile a quella osservate nei pazienti adulti(Correll et al., 2021; Leucht et al., 2022); tuttavia, gli adolescenti sono generalmente più sensibili agli effetti collaterali (Correll and Carlson, 2006; Liu et al., 2019).

- Nella scelta di un farmaco è importante considerare i potenziali effetti collaterali(Correll, 2008) e l'accettabilità(Correll et al., 2021), così come l'approvazione normativa

- Diversi farmaci antipsicotici sono stati approvati per l'uso negli adolescenti con schizofrenia(Lopez-Morinigo et al., 2022; Smogur et al., 2022) (Table 1); tuttavia, anche l'uso off-label è comune(Sharma et al., 2016).

Neurolettici Tradizionali

- **Azione farmacologica singola: antagonismo del recettore D2 della dopamina**

blocco della via mesolimbica con controllo dei sintomi positivi

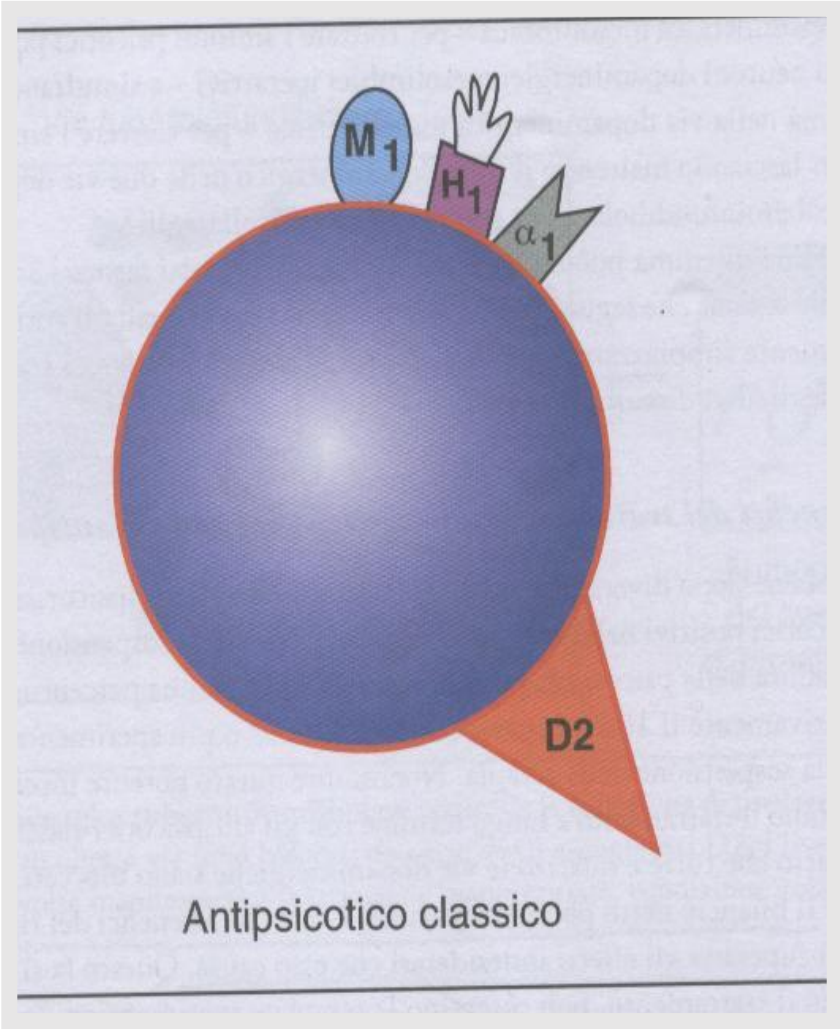


Immagine tratta da: Stahal, Psicofarmacologia essenziale

Conseguenze del blocco dei recettori D_2

① ***Nigrostriale***

↳ Effetti extrapiramidali

② ***Mesolimbica***

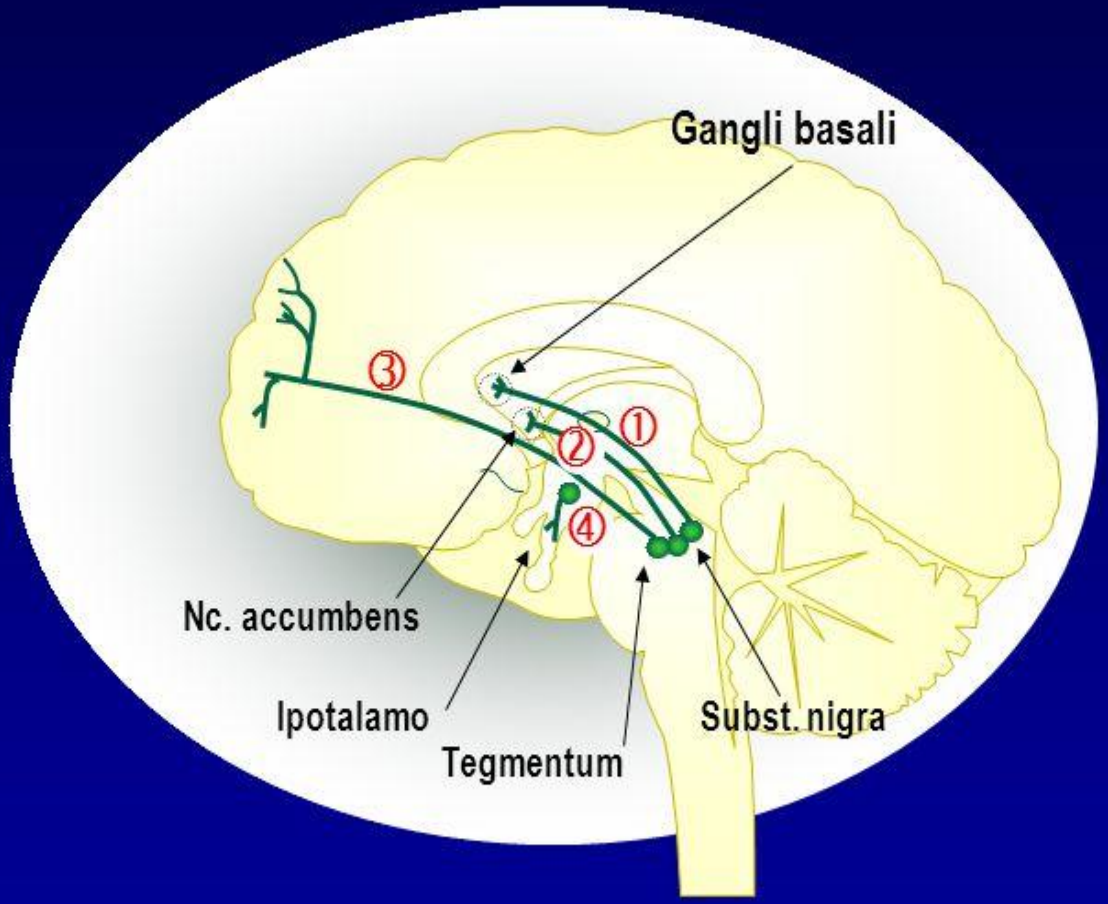
↳ Effetto antipsicotico

③ ***Mesocorticale***

↳ Peggioramento sintomi negativi
e deficit funzioni cognitive

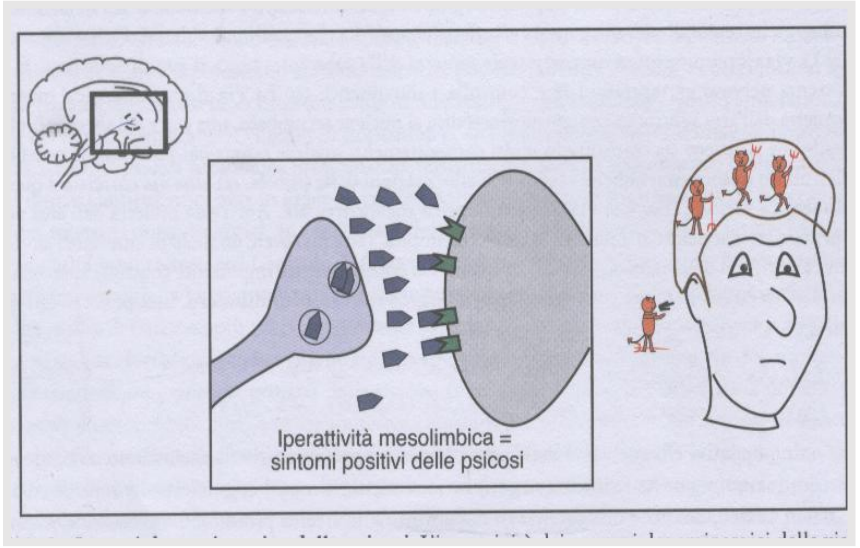
④ ***Tuberoinfundibolare***

↳ Iperprolattinemia

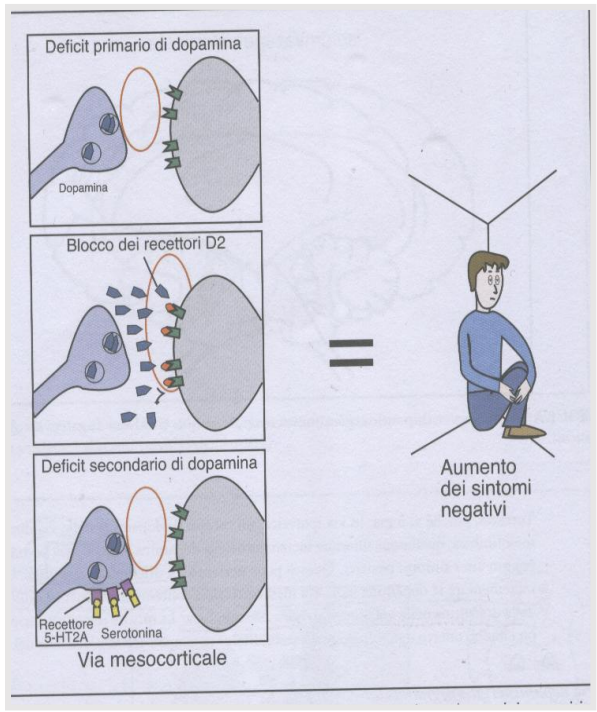


Antipsicotici Tradizionali : “Neurolettici”

- **elevata efficacia sui sintomi positivi** (delirio, allucinazioni, eloquio disorganizzato, comportamento disorganizzato, catatonia, agitazione, distorsioni linguistiche e comunicative)

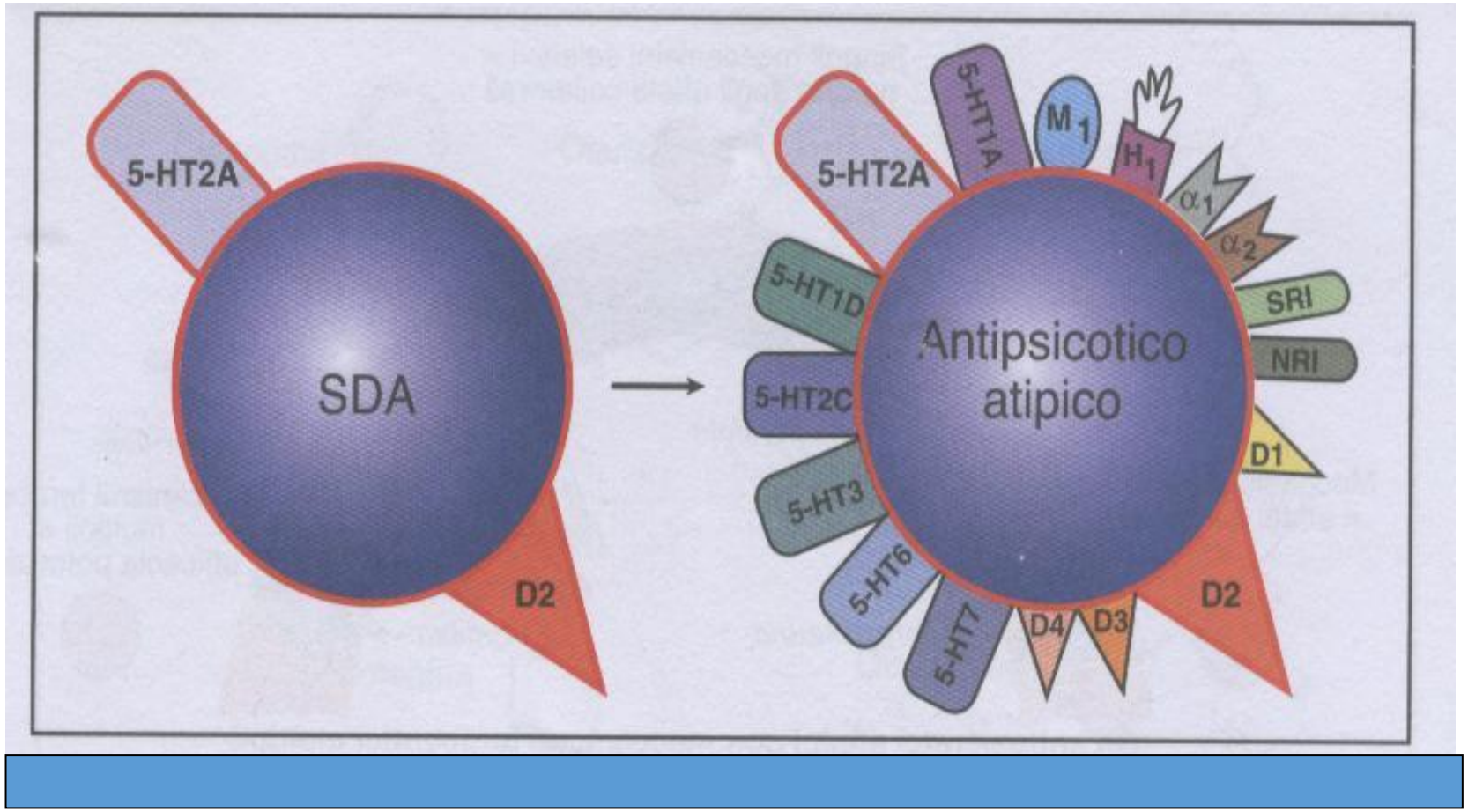


- **scarsa azione sui sintomi negativi** (appiattimento affettivo, ritiro sociale, disturbi dell’attenzione, pensiero stereotipato, alogia, anedonia, apatia, mancanza di spontaneità) che possono anche risultare aggravati dal trattamento farmacologico



antipsicotici “atipici”

Immagine tratta da: Stahal, Psicofarmacologia essenziale



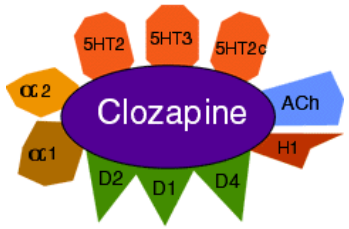
antagonisti serotonino-dopaminergici (la serotonina inibisce il rilascio di dopamina, quindi la dopamina viene incrementata dal blocco dei recettori 5 –HT2A,)

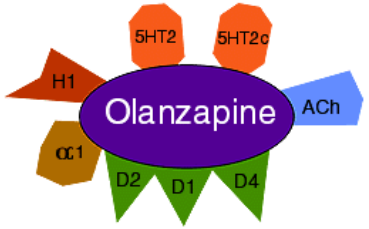
Interagiscono con molti altri sottotipi di recettori, tanto dopaminergici che serotoninergici ognuno con un diverso profilo

- antipsicotici dotati di una affinità ad ampio spettro per i siti dopaminergici e serotonergici
- determinano con frequenza sensibilmente minore i sintomi extrapiramidali
- sono efficaci nel trattamento sia dei sintomi positivi che negativi

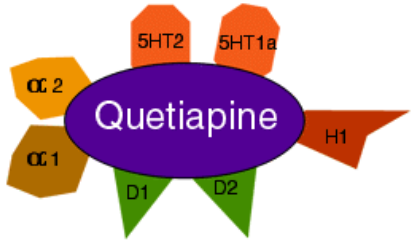
Cochrane Database Syst Rev. 2013 Oct 15;10:. **Atypical antipsychotics for psychosis in adolescents.** Kumar A[1], Datta SS, Wright SD, Furtado VA, Russell PS.

Second generation of antipsychotic medications may be more acceptable to young people because fewer symptomatic adverse effects









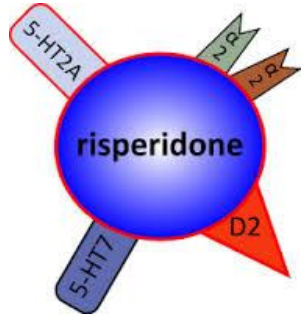


Table 3. Relative receptor-binding affinities of atypical antipsychotics.[13-15]

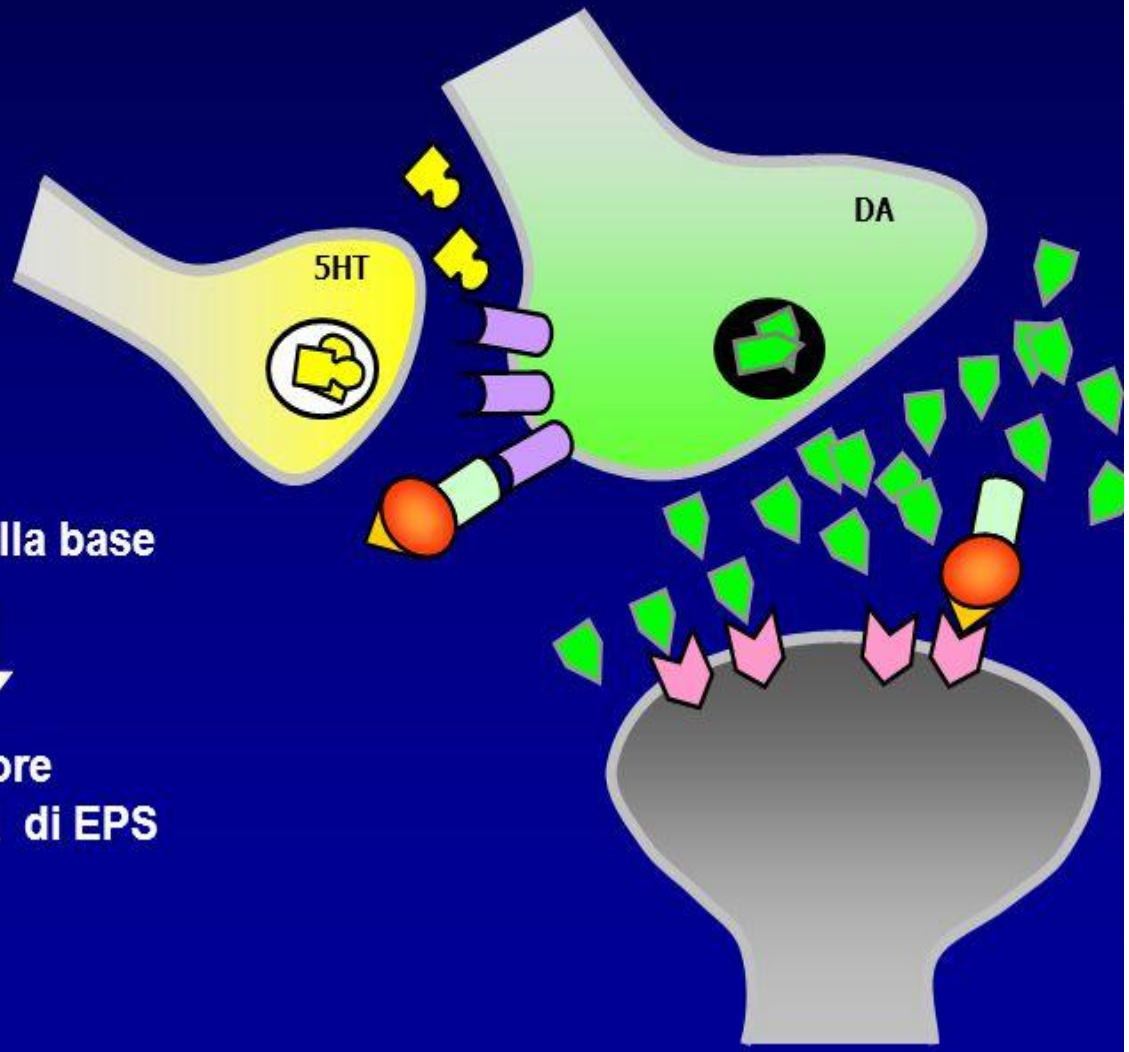
Receptor	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine	Aripiprazole
D_2	++++	++++	++	+	+	++++‡
5-HT_{2A}	+++++	+++++	++++	+	++++	++++
5-HT_{2C}	+++++	++++	++++	–	++	++
5-HT_{1A}	++++‡	+	–	+	+	++++‡
5-HT_{1D}*	++++	+	+	–	–	–
α_1-adrenergic	++	++++	++	++	++++	++
M_1-muscarinic	–	–	++++	++	++++	–
H_1-histaminergic	++	++	++++	++++	++++	++
5-HT/NE reuptake†	++	–	–	– 5-HT + NE	– 5-HT + NE	++ 5-HT

+++++=very high; ++++=high; ++=moderate; +=low; –=negligible; 5-HT=serotonin; NE=norepinephrine.
*Bovine binding affinity. †Rat synaptosomes; all other affinities human. ‡Partial agonist.
Casey DE, Zorn SH, The Pharmacology of Weight Gain With Antipsychotics, *The Journal of Clinical Psychiatry*, vol 62, pp 4-10, 2001.
Copyright 2001, Physicians Postgraduate Press. Adapted by permission.

Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications

Ruolo dei recettori $5HT_{2A}$ nel meccanismo d'azione degli antipsicotici

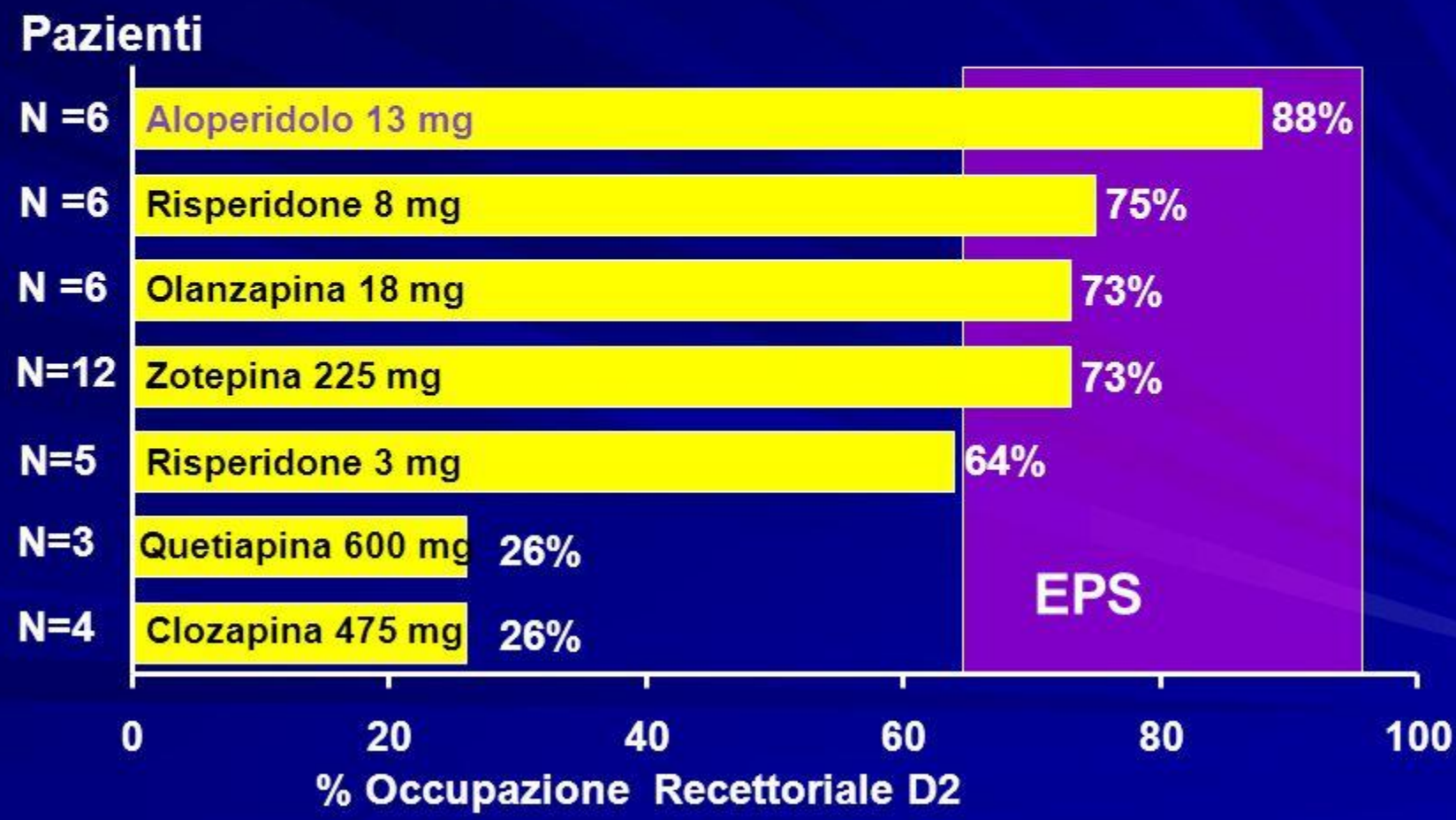
Gli antipsicotici atipici aumentano il rilascio di dopamina bloccando i recettori $5\text{-}HT_{2A}$



Corteccia prefrontale → **Miglioramento dei sintomi negativi, cognitivi e depressivi**

Gangli della base → **Minore incidenza di EPS**

ANTIPSICOTICI:
Occupazione dei recettori striatali D2



Kasper et al. 1999

Persico and European Child and Adolescent Clinical Psychopharmacology Network, Unmet needs in paediatric psychopharmacology:Present scenario and future perspectives, European Neuropsychopharmacology(2015) 25, 1513–1531

Table 2 Psychotropic medications approved in Europe for use in children and adolescents.

Medication	Indication	Age for prescription
Aripiprazole	Schizophrenia	≥ 15 years
	Bipolar disorder, manic or mixed episodes	≥ 13 years
Amphetamines (incl. Lisdexamphetamine)	Attention-Deficit Hyperactivity Disorder[a]	≥ 6 years
Atomoxetine	Attention-Deficit Hyperactivity Disorder	≥ 6 years
Fluoxetine	Major depressive episode	≥ 8 years
Fluvoxamine	Obsessive-compulsive disorder	≥ 8 years
Methylphenidate	Attention-Deficit Hyperactivity Disorder	≥ 6 years
Risperidone	Aggression[b]	≥ 5 years
Sertraline	Obsessive-compulsive disorder	≥ 6 years
Ziprasidone	Bipolar disorder, manic or mixed episode[c]	≥ 10 years

[a]Approved only in some European countries for children and adolescents with ADHD.
[b]Approved only in some European countries for children and adolescents with conduct disorder, in the presence of sub-average intellectual functioning or intellectual disability and when all non-pharmacological strategies have been found insufficient.
[c]Approved only in some European countries based on one randomized controlled trial (Findling et al., 2013), found by the US Food and Drug Administration to have quality assurance issues, requiring the sponsor to repeat the trial.

NNT * for schizophrenia

- Risperidone 3
- Olanzapine 10
- Quetiapine 10
- Aripiprazole 10

(Correll et al.,2011; Zuddas et al.,2011)

*NNT: the number of patients that need to be treated for one to benefit compared with a control in a clinical trial

Correll et al, European Neuropsychopharmacology 82 (2024) 57–71

Table 1
Antipsychotic drugs approved for treating early-onset schizophrenia in adolescents.

Antipsychotic drug	European medicine agency (EMA)				US food and drug administration (FDA)			
	Age range (years)	Dose (mg/d)			Age range (years)	Dose (mg/d)		
		Starting	Maximum	Recommended		Starting	Maximum	Recommended
First generation								
Haloperidol	Non approved				≥12	0.05 mg/kg	0.075 mg/kg	
Molindone	Non approved				≥12	50–75	225	100
Second generation								
Aripiprazole	≥15	2	30	2–10	≥13	2	30	10–20
Paliperidone	≥15	3	<51 kg →6 ≥51 kg →12	<51 kg →3–6 ≥51 kg →3–12	≥12	3	<51 kg →6 ≥51 kg →12	<51 kg →3–6 ≥51 kg →3–12
Brexpiprazole	Non approved				≥13	0.5	4	2–4
Clozapine	≥16	12.5	900	100–300	Non approved			
Risperidone	Non approved (in some european countries, ≥15)				≥13	0.5	6	2–4
Quetiapine	Non approved				≥13	25–50	800	400–600
Lurasidone	≥13	20	80	20–80	≥13	40	80	40–80
Olanzapine	Non approved				≥13	2.5–5	20	10–20
Amisulpride	Non approved (in some European countries ≥15)				Non approved			

Information adapted from Lopez-Morinigo. Pharmacopsychiatry. 2022;55:233–245. (Lopez-Morinigo et al., 2022) .

Gli antipsicotici di seconda generazione sono generalmente preferiti per la migliore tollerabilità, soprattutto per quanto riguarda gli effetti collaterali extrapiramidali(Hayes and Kyriakopoulos, 2018).

Tuttavia, la tollerabilità varia tra i singoli agenti e pazienti(Pagsberg et al., 2017; Krause et al.,2018; .Arango et al., 2020; Sarkar et al., 2013 Kumar et al., 2013; Solmi et al., 2020)

L'olanzapina è più associata a effetti cardiometabolici potenzialmente gravi(Galling et al., 2016; Pagsberg et al., 2017), mentre risperidone e paliperidone sono associati maggiormente all'aumento della prolattina(Pagsberg et al., 2017; Koch et al., 2023).

Il dosaggio è particolarmente importante nei pazienti giovani

- **Dosi più elevate aumentavano il rischio di effetti collaterali**
- **La dose minima efficace di mantenimento aumenta esponenzialmente il rischio di ricaduta** (Højlund et al., 2022, 2021; Leucht et al., 2021)
- **necessità di identificare e mantenere la dose minima efficace personalizzata per ogni paziente**

- Le concentrazioni stimate correlate alla dose in bambini e adolescenti possono differire in parte da quelle degli adulti a causa di possibili differenze dipendenti dall'età nel metabolismo dei farmaci(Fekete et al., 2020).

- Alcuni bambini e adolescenti possono rispondere a dosi più basse rispetto agli adulti con schizofrenia cronica, e in passato sono state raccomandate riduzioni della dose fino al 60% per i bambini e il 30% per gli adolescenti(Gardner et al., 2010).

- Tuttavia, dosi efficaci e tollerate possono essere considerevolmente più alte e devono essere personalizzate, con alcuni pazienti che rispondono e tollerano solo dosi elevate come negli adulti con malattie croniche.

- In tali pazienti, la sottodosazione e la conseguente pseudo-resistenza rappresentano un rischio potenziale.

- Pertanto, il trattamento dovrebbe generalmente iniziare a una dose bassa, seguita da una lenta titolazione con dosi che aumentano fino a raggiungere una risposta sintomatica sufficiente o a emergere effetti collaterali limitanti, seguendo il principio

“start low, go slow, but go”

un position paper sul trattamento farmacologico dell'EOS ha presentato evidenze sull'efficacia e la tollerabilità degli antipsicotici approvati per l'EOS, e ha suggerito che

- **aripiprazolo e lurasidone presentano i migliori profili di sicurezza metabolica**
- olanzapina è associata al maggior aumento di peso
- aloperidolo ha i maggiori effetti collaterali extrapiramidali

(Lopez-Morinigo et al., 2022).

Una revisione sistematica e una meta-analisi della risposta a diversi farmaci antipsicotici in sottogruppi di pazienti con schizofrenia **non hanno rivelato differenze significative tra adulti, bambini e adolescenti**, suggerendo che potrebbe essere possibile utilizzare dati di "pazienti generici con schizofrenia" quando i dati su sottogruppi specifici sono scarsi, come per i pazienti più giovani (Leucht et al., 2022)

Pertanto aripiprazolo, brexpiprazolo, cariprazina e lurasidone possono essere utili anche nel trattamento di pazienti giovani.

Efficacy and safety of brexpiprazole in adolescents with schizophrenia: a multicountry, randomised, double-blind, placebo-controlled, phase 3 trial with an active reference

Caroline Ward, Milica Pejović Milovančević, Eva Kohegyi, Nanco Hefting, Catherine Aurang, Dalei Chen, Klaus Groes Larsen, Mary Hobart, Christoph U Correll

Lancet Psychiatry 2025; 12: 345–54
https://doi.org/10.1016/S2215-0366(25)00043-4

In adolescents with schizophrenia, brexpiprazole 2–4 mg/day was associated with greater reduction in symptom severity than placebo over 6 weeks.

	Brexpiprazole group (n=110)			Aripiprazole group (n=101)			Placebo group (n=103)
	LS mean change (SE)	LS mean difference *vs* placebo (95% CI)	p value *vs* placebo	LS mean change (SE)	LS mean difference *vs* placebo (95% CI)	p value *vs* placebo	LS mean change (SE)
PANSS total score (primary)*	−22·8 (1·5)	−5·33 (−9·55 to −1·10)	0·014	−24·0 (1·6)	−6·53 (−10·8 to −2·21)	0·0032	−17·4 (1·6)
PANSS Positive subscale score*	−6·6 (0·4)	−1·44 (−2·65 to −0·22)	0·021	−7·3 (0·5)	−2·15 (−3·40 −0·91)	0·0008	−5·1 (0·5)
PANSS Negative subscale score*	−4·7 (0·4)	−0·88 (−2·04 to 0·28)	0·14	−4·8 (0·4)	−0·95 (−2·14 to 0·24)	0·12	−3·8 (0·4)
PANSS General Psychopathology subscale score*	−11·5 (0·8)	−2·89 (−5·08 to −0·70)	0·0098	−12·0 (0·8)	−3·31 (−5·55 to −1·07)	0·0039	−8·7 (0·8)
Response rate†‡	48 (43·6%)	RR 1·55 (1·09 to 2·20)	0·011	44 (43·6%)	RR 1·51 (1·06 to 2·16)	0·022	29 (28·2%)
Remission rate†§	32 (29·1%)	RR 1·18 (0·77 to 1·81)	0·44	36 (35·6%)	RR 1·48 (1·01 to 2·16)	0·047	24 (23·3%)
CGAS score*	10·6 (1·0)	2·48 (−0·35 to 5·31)	0·085	12·1 (1·1)	3·99 (1·09 to 6·88)	0·0072	8·1 (1·1)
CGI-S score*	−0·9 (0·1)	−0·11 (−0·36 to 0·13)	0·36	−1·0 (0·1)	−0·20 (−0·45 to 0·05)	0·11	−0·8 (0·1)
Mean CGI-I score¶	2·9 (SD 1·0)	−0·29 (−0·56 to −0·03)	0·029	2·8 (SD 1·0)	−0·34 (−0·62 to −0·06)	0·018	3·2 (SD 1·1)
P-Q-LES-Q total score‖	4·0 (0·7); n=104	0·44 (−1·62 to 2·50)	0·67	4·5 (0·8); n=93	1·04 (−1·08 to 3·16)	0·34	3·5 (0·8); n=92

Treatment-emergent adverse events were reported in 44 (40%) of 110 patients in the brexpiprazole group, 42 (40%) of 104 in the placebo group, and 53 (52%) of 102 in the aripiprazole group.

The most common (incidence ≥5%) treatment-emergent adverse events were headache (n=7) and nausea (n=7) with brexpiprazole and somnolence (n=11), fatigue (n=8), and akathisia (n=7) with aripiprazole.

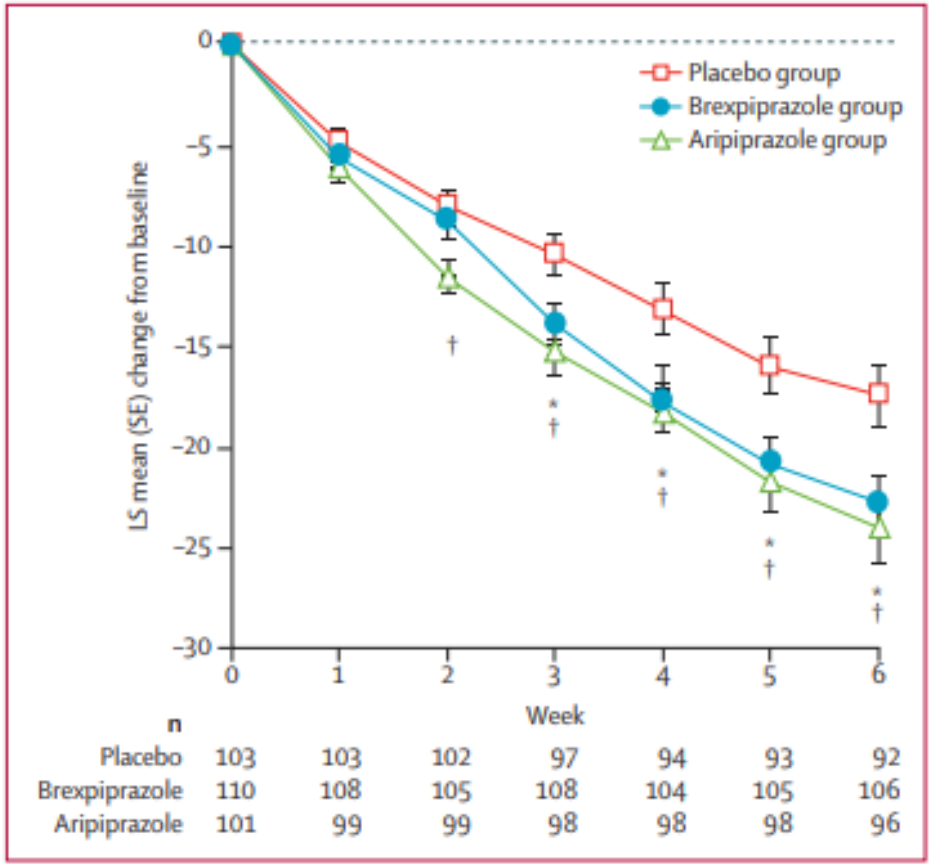
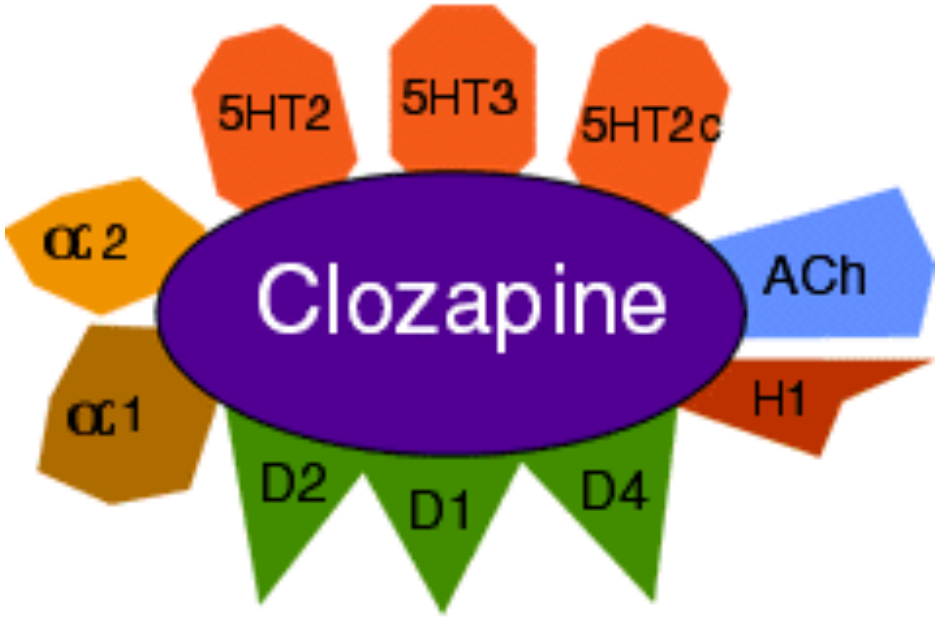


Figure 2: **Change in PANSS total score**

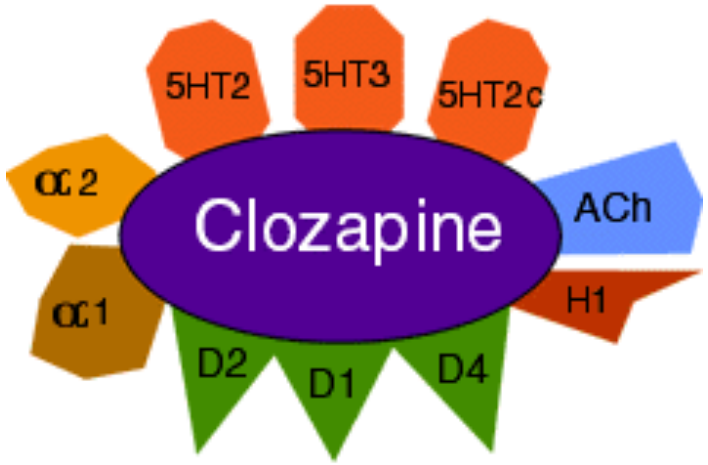
Clozapina

E’ il gold standard

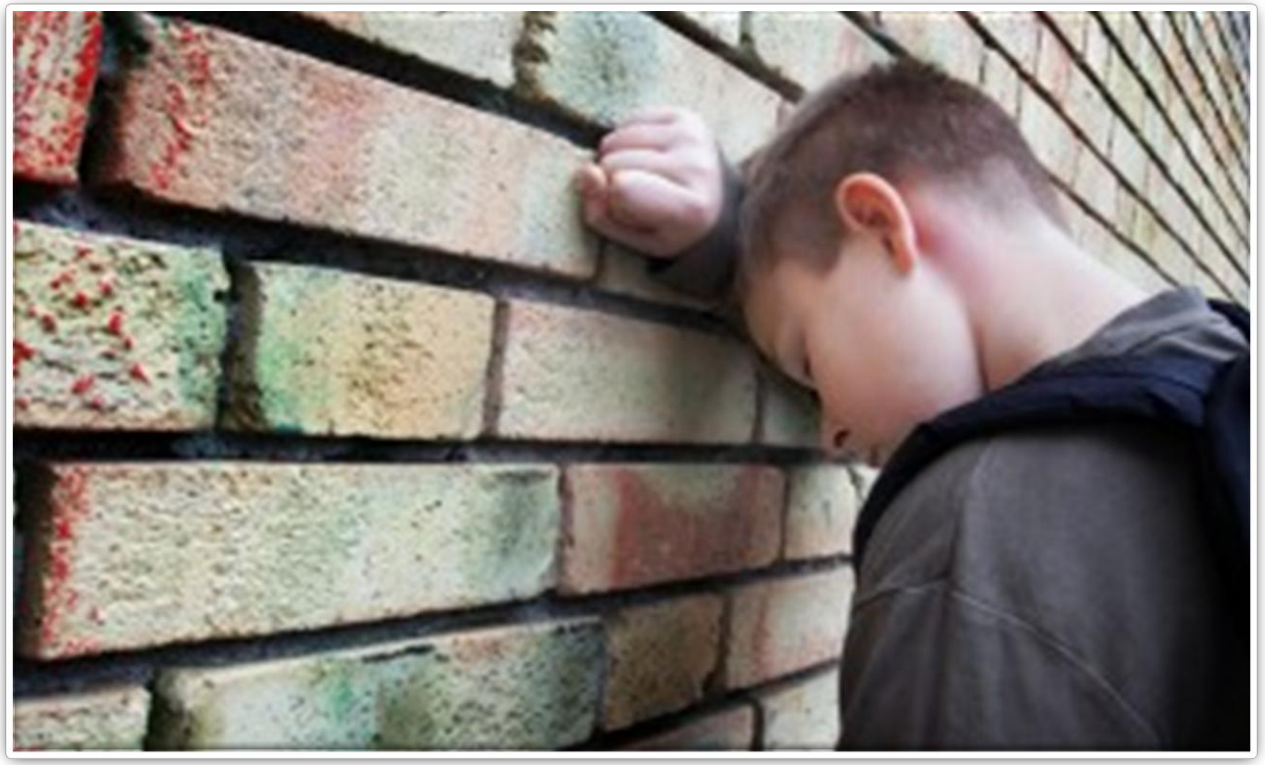


Kranzler HN, Cohen SD. **Psychopharmacologic treatment of psychosis in children and adolescents**: **efficacy and management,** Child Adolesc Psychiatr Clin N Am. 2013 Oct;22(4):727-44.

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AAPs are effective in controlling psychosis in children and adolescents



- **Clozapine has the best efficacy** of all antipsychotic medications in adults as well as children and adolescents who are treatment resistant

- Clozapine should be part of the menu of options for treatment-resistant psychosis including **schizophrenia, schizoaffective disorder**, **and bipolar disorder with psychosis and mania**

Clozapina è **più efficace degli altri antipsicotici**

short term double-blind studies of 6 and 8 weeks

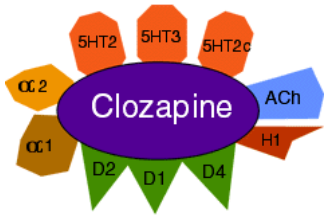


TABLE 1. CLOZAPINE VERSUS ACTIVE TREATMENT STUDIES FOR ADULT-AND EARLY-ONSET SCHIZOPHRENIA, EARLY-ONSET SCHIZOPHRENIA STUDIES

Study	*Design*	*Length (wks)*	*Age at enrollment (yrs)*	*Comparison drug dosage (mg/d)*	*Clozapine dosage (mg/d)*	n	*Cohen's* d	p
Kumra et al. (1996)	Parallel randomized DB	6	Mean: 14.0±2.3 Range: 6–18	Typical: Haldoperidol 16±8	Clozapine 176±149	21	SANS: 1.156 SAPS: 0.675 BPRS: 0.258 CGAS: 1.370	0.002 0.01 0.04 0.01
Shaw et al. (2006)	Parallel randomized DB	8	Mean: 12.3 Range: 7–16	Atypical: Olanzapine 18.1±4.3	Clozapine 327±113	25	SANS: 0.7 SAPS: 0.4 BPRS: 1 CGI-S: 0.6	0.08 0.14 0.12 0.39
Kumra et al. (2008)	Parallel randomized DB	12	Mean: 15.6±2.1[a] Range: 10–18	Atypical: Olanzapine 26.2±6.5	Clozapine 403.1±201.8	39	SANS: 0.92 BPRS: 0.29 CGI-S: 0.4 CGI-Improvement: 0.59	0.02 0.78 0.8 0.38

clozapina è più efficace degli altri antipsicotici sui sintomi negativi

SANS d = 0.22, d = 0.566, p < 0.01

BPRS d = 0.243, p = 0.06; d = 0.017, p = 0.84; d = 0.021

clozapina è più efficace nella polazione pediatrica che in quella adulta

(McGough JJ, Faraone SV: Estimating the size of treatment effects: moving beyond p values. Psychiatry (Edgmont) 6:21–9, 2009.)

Larger effect sizes in EOS studies, than in AOS studies

- Kumra 1996: **1.15**
- Shaw 2006: **0.7**
- Kumra 2008: **0.92**

Questo effetto è più vero rispetto agli antipsicotici di prima generazione

(Pickar et al. 1992; Azorin et al. 2001; Bitter et al. 2004; Meltzer et al. 2008)

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Original Articles

Strong Treatment Response and High Maintenance Rates of Clozapine in Childhood-Onset Schizophrenia

Lauren I. Kasoff, BS, Kwangmi Ahn, PhD, Peter Gochman, MA,
Diane D. Broadnax, LICSW, and Judith L. Rapoport, MD

Child Psychiatry Branch, Division of Intramural Research Program, NIMH, Bethesda, Maryland



cohort of 131 patients with COS

91.6% **(120)** available for follow-up information

long-term medication maintenance over a **24 year observation** period

72.5% **(87/120)** **adhered to long-term** clozapine maintenance therapy

this rate **exceeds** the rates reported for AOS patients

dosages ranging from 50 to 900 mg **(median dosage of 500 mg)**

First antipsychotic

6–8 weeks

Second antipsychotic

no responders

6–8 weeks

Clozapine

consider a multidisciplinary review (including measuring therapeutic drug levels) and a review of adherence

8-10 weeks

augmentation with a drug that does not compound the common side effects of clozapine



NICE Guidelines for children and young people with psychosis and Schizophrenia
http://pathways.nice.org.uk/pathways/psychosis-and-schizophrenia Pathway last updated: 24 May 2016

Antipsicotici Atipici per via iniettiva

preparati a lunga azione (**Long Acting injection**) che possono permettere di assicurare l'assunzione del farmaco per un mese inter sottoponendosi alla somministrazione intramuscolare una 1v/mese o 2v/mese

Il **Risperdal** Long acting (Risperdal) : INDICATO per il trattamento della schizofrenia :1 iniezione ogni 2 settimane, si potrà sospendere la somministrazione orale del farmaco dopo 4 somministrazioni intramuscolo, mai prima.

Il **Paliperidone** Long Acting (Xeplion) : INDICATO per il trattamento della schizofrenia sia in acuzie chee mantenimento dei pz adulti: 1 iniezione al mese, prime due somministrazioni 8 giorni +/- 4, sospensione trattamento orale dopo la seconda somministrazione.

Olanzapina long acting: (Zypadhera) INDICATO per il trattamento della SCZ: 1 iniezione ogni 2/4 settimane, prime 4 somministrazioni ogni 2 settimane, riduzione trattamento orale dopo prima somministrazione.

Aripiprazolo long acting: (Maintena) INDICATO per il trattamento della SCZ: 1 iniezione 4 settimane, mantenere dosaggio per os per 14 gg dopo prima somministrazione.

possono essere somministrati presso ambulatori pubblici o servizi autorizzati e/o accreditati, per l'olanzapina è necessario che dopo la somministrazione il paziente stia in osservazione per 3 ore.

Lytle S, McVoy M, Sajatovic M. Long-Acting Injectable Antipsychotics in Children and Adolescents. J Child Adolesc Psychopharmacol. 2017 Feb;27(1):2-9. doi: 10.1089/cap.2016.0055.

LAI use in youth with serious mental illness may improve clinical outcomes and adherence

Side effects of LAIs among youth appear are similar to oral preparations.

There is a paucity of data despite issues with nonadherence in youth and the fact that they have **much to lose and much to gain.**

Shorter and Wachtel have suggested that the **triad of autism, psychosis, and catatonia** (a so-called **Iron Triangle**) may encompass **3 different manifestations of the same underlying brain disorder** rather than separate conditions, underscoring the complex genetic relationship, pathophysiology, and treatment.

Wachtel LE, Schuldt S, Ghaziuddin N, et al. The potential role of electroconvulsive therapy in the 'Iron Triangle' of pediatric catatonia, autism, and psychosis. ActaPsychiatrScand 2013;128(5):408–9.

Fink and colleagues proposed a medication treatment algorithm that suggests initial use of high-dose **lorazepam (6–24 mg/d) followed by electroconvulsive therapy (ECT) if there is lack of response.**

Fink M, Taylor MA, Ghaziuddin N. Catatonia in autistic spectrum disorders: a medical treatment algorithm. Int Rev Neurobiol 2006;72:233–44

Some case reports suggest the utility of a more rapid initiation of ECT over benzodiazepines

Shorter E, Wachtel LE. Childhood catatonia, autism and psychosis past and present: is there an 'iron triangle'? ActaPsychiatrScand 2013;128(1):21–33.

Lee ES, Kronsberg H, Findling RL. Psychopharmacologic Treatment of Schizophrenia in Adolescents and Children. Child Adolesc Psychiatr **Clin N Am. 2020** Jan;29(1):183-210. doi: 10.1016/j.chc.2019.08.009.

Key points

- Several antipsychotic medications have demonstrated efficacy in the treatment of children and adolescents with schizophrenia.…
- As with adults, clozapine demonstrated superior efficacy in treating adolescent schizophrenia in treatment-resistant patients.…
- In large head-to-head studies, several of which included first-generation agents, symptom improvement was often comparable among different medications.…
- Side-effect profiles vary considerably across medications and can often be more severe in youths…

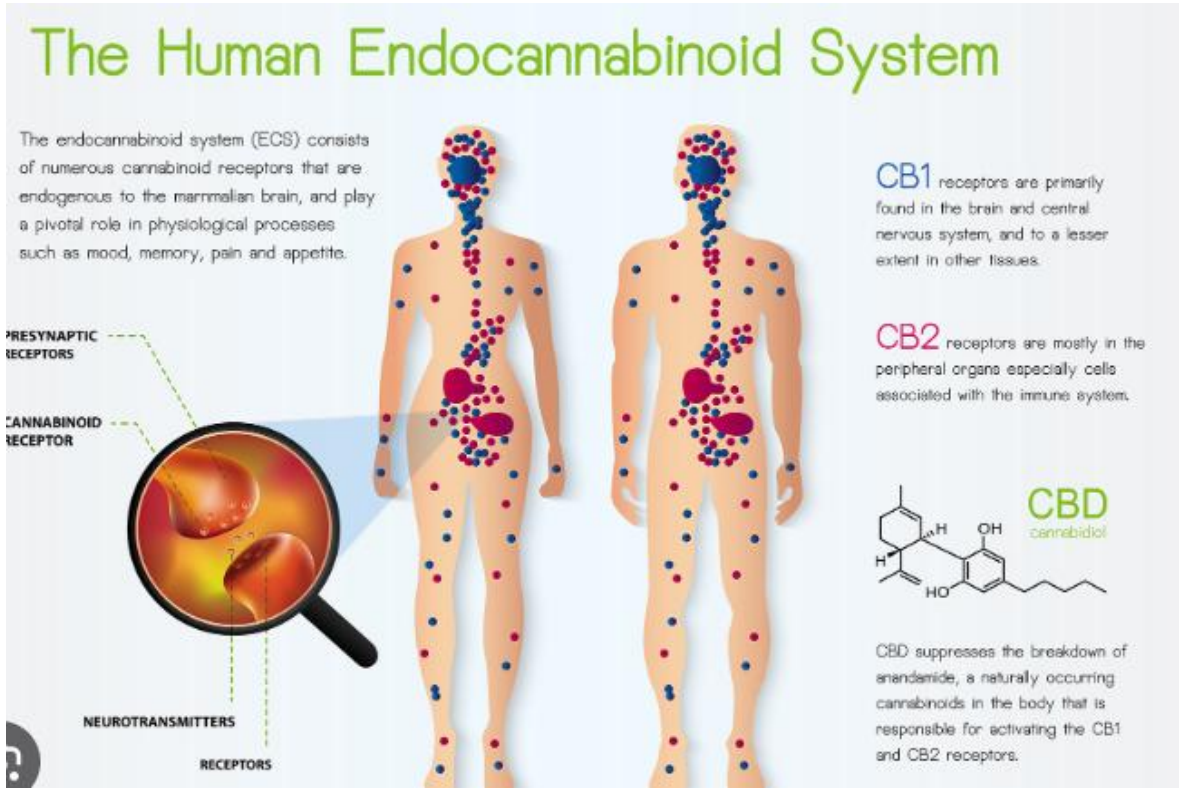


the endocannabinoid system

the endocannabinoid system has been suggested to modulate neural circuits during the early stage of neurodevelopment, with implications for both autism and psychosis.

human and animal studies examining the endocannabinoid system and its biobehavioral correlates in the association between autism and psychosis indicate overlapping biobehavioral aberrancies between autism and schizophrenia, subject to correction by modulation of the endocannabinoid system.

There is a strong evidence of a developmental continuum between autism and psychosis as a function of the endocannabinoid system dysregulation



exogenous **alteration of the endocannabinoid system promotes progression to inheritable psychosis phenotypes** in the context of bio-behavioral autism vulnerability

common cannabinoid-based pharmacological strategies have been identified, exerting epigenetic effects across genes controlling neural mechanisms shared between autism and schizophrenia.

Randomized controlled trials examining the **effectiveness of CBD in psychosis** have produced mixed results...



One trial showed that 800 mg/day of CBD for 4 weeks was as effective as **amisulpride** in treating both positive and negative symptoms of schizophrenia and had fewer associated side effects

Leweke FM, Piomelli D, Pahlisch F, et al: Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry 2012; 2:e94

Another trial, comparing 1000 mg/day of CBD for 6 weeks to placebo as **adjunctive pharmacotherapy for schizophrenia**, demonstrated a significant improvement in positive symptoms, without any difference in adverse effect compared with placebo

McGuire P, Robson P, Cubala WJ, et al: Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry 2018; 175: 225–231

However, in another trial comparing 600 mg/day of CBD for 6 weeks to placebo as **adjunctive pharmacotherapy** for schizophrenia, CBD **did not produce any significant change in positive symptoms or cognition**.

Boggs DL, Surti T, et al: The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia: a randomized placebo controlled trial. Psychopharmacology (Berl) 2018; 235:1923–1932

Two cannabinoids related to THC, **dronabinol and nabilone**, were approved by the FDA

A third cannabinoid, **CBD,** was approved by the FDA in 2018 **for two forms of pediatric epilepsy, and for seizures associated with tuberous sclerosis complex**

Beyond the FDA-approved…

…. the best evidence for the medical use of cannabinoids is in **chronic pain (including neuropathic pain)** and **muscle spasticity associated with multiple sclerosis**

TABLE 2. FDA-approved cannabinoids

Cannabinoid and Indication	Year Approved
Dronabinol	
Chemotherapy-induced nausea and vomiting	1985
Appetite stimulation in wasting conditions (e.g., HIV infection)	1992
Nabilone	
Chemotherapy-induced nausea and vomiting	1985
Cannabidiol	
Seizures associated with Dravet syndrome and Lennox-Gastaut syndrome	2018
Seizures associated with tuberous sclerosis complex	2020

Kevin et al, Risks and Benefits of Cannabis and Cannabinoids in Psychiatry, Am J Psychiatry 2022; 179:98–109; doi: 10.1176/appi.ajp.2021.21030320

Cannabinoids for the Treatment of Psychiatric Disorders
(anxiety, depression, PTSD, psychosis, ADHD, and Tourette's syndrome)

The available evidence* describes **limited efficacy of cannabinoids in treating anxiety disorders in patients with co-occurring medical conditions**

* They are limited by lack of high-quality randomized controlled trials, small sample sizes, and lack of standardization across trials.

No clear evidence exists supporting cannabinoid pharmacotherapy for the other psychiatric indications

Black N, Stockings E, Campbell G, et al: Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry 2019; 6:995–1010

Most CBD is obtained without a prescription, in products that are unregulated with regard to purity, potency, and accuracy of labeling

Bonn-Miller MO, Loflin MJE, Thomas BF, et al: Labeling accuracy of cannabidiol extracts sold online. JAMA 2017; 318:1708–1709

The literature on CBD is nascent

While CBD appears to have a more favorable risk profile than THC, high daily doses of CBD (1500 mg/day) caused an important **transaminase elevations**

CBD has a number of **interactions** with medications commonly prescribed to psychiatric patients.

It interacts with

- antiepileptic drugs
- antidepressants
- opioid analgesics
- acetaminophen
- alcohol

CBD increases the level or effect of lorazepam

Balachandran P, Elsohly M, Hill KP: Cannabidiol interactions with medications, illicit substances, and alcohol: a comprehensive review. J Gen Intern Med 2021; 36:2074–2084

Watkins PB, Church RJ, Li J, Knappertz V: Cannabidiol and abnormal liver chemistries in healthy adults: results of a phase I clinical trial. Clinical Pharm Ther 2021; 109:1224–1231

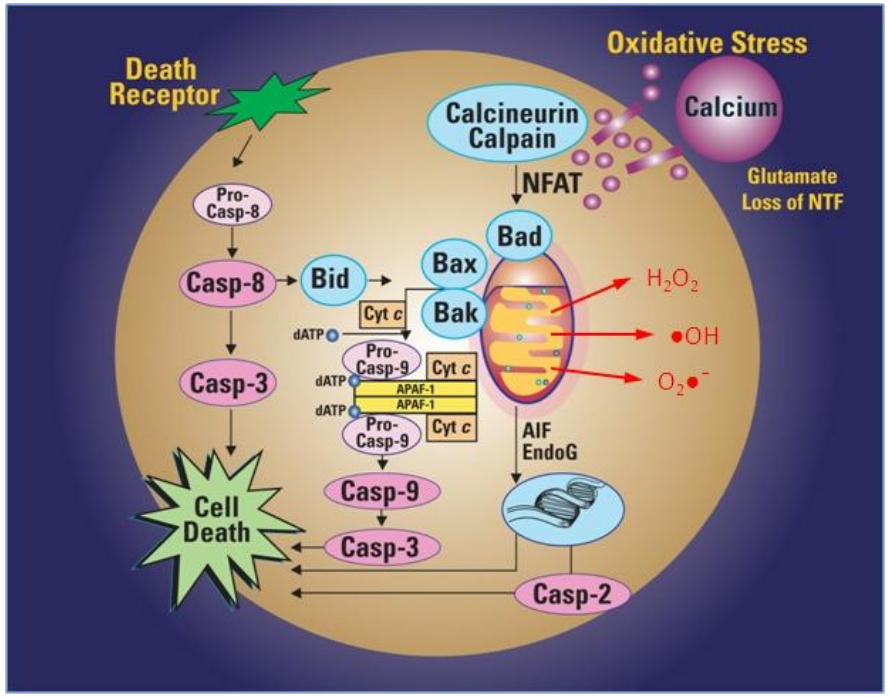


Identify potential novel pharmaceutical agents based on the insight into the implicated biological pathways

Vorstman,J.A.,Spooren,W.,Persico, A.M.,Collier,D.A.,Aigner,S.,Jagasia, Glennon,J.C., Buitelaar,J.K., 2014.Using genetic findings in autism for the development of new pharmaceutical compounds. Psychopharmacology (Berl.)231(6),1063–1078.

medications able to attenuate neuroinflammation and oxidative stress in the CNS

- Glutathione
- N-acetylcysteine
- Sulforaphane
- Polyunsatured fatty acids
- Glycine agonists



promising preliminary results in several psychiatric/neurodevelopmental disorders

- Pandya,C.D.,Howell,K.R.,Pillai,A.,2013.Antioxidants as potential therapeutics for neuropsychiatric disorders.Prog. Neuropsychopharmacol. Biol.Psychiatry 46,214–223.
- Parellada,Amminger et al, 2015. Predictors of treatment response in young people at ultrahigh risk for psychosis who received longchain omega-3 fatty acids. Transl.Psychiatry 5,e495.
- Chue, P.,Lalonde,J.K.,2014.Addressing the unmet needs of patients with persistent negative symptoms of schizophrenia: emerging pharmacological treatment options.Neuropsychiatr. Dis. Treat.10,777–789.
- Singh, K.,et al .,2014.Sulforaphane treatment of autism spectrum disorder (ASD).Proc.Natl.Acad.Sci.U.S.A.111 (43),15550–15555.

Excitation and inhibition imbalance – a new therapeutic target for autism and psychosis?

The homeostatic unbalance between excitation and inhibition alters the neural stability and may explain shared symptoms observed in autism and psychosis.

Evidences suggest that altered levels of gamma-amino butyric acid (GABA) may underlie both disorders, providing a potential cross-diagnostic therapeutic target

- GABAA and GABAB receptor agonists (Clonazepam, Baclofen) have yielded promising behavioural effects in mouse models, reversing social deficits.
- Bumetanide, a diuretic that reinforces GABAergic inhibition, improves emotional face processing in adolescents with autism
- Evidence for other GABAergic drugs such as Tiagabine, Riluzole and Vigabatrin is still limited and controversial.

Heinze K, Barron HC, Howes EK, Ramaswami M, Broome MR. Impaired inhibitory processing: a new therapeutic target for autism and psychosis? Br J Psychiatry. 2021 Jun;218(6):295-298.

Quale classe di farmaci per Francesco……?

iperattività/impulsività

disregolazione emozionale

aggressività/isolamento

depersonalizzazione
e derealizzazione

ideazione suicidaria

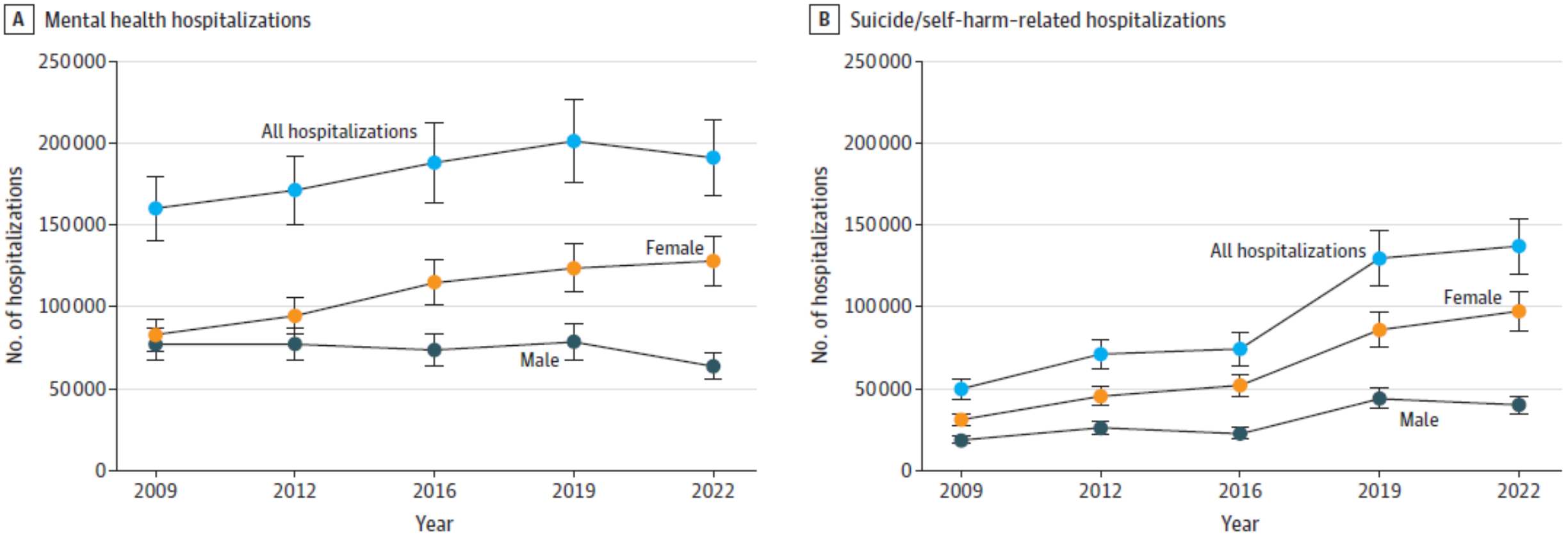
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JAMA August 19, 2025 Volume 334, Number 7

Figure 1. Pediatric Hospitalizations at Acute Care Hospitals for Mental Health and Suicide/Self-Harm–Related Diagnoses, 2009 to 2022, Weighted National Estimates

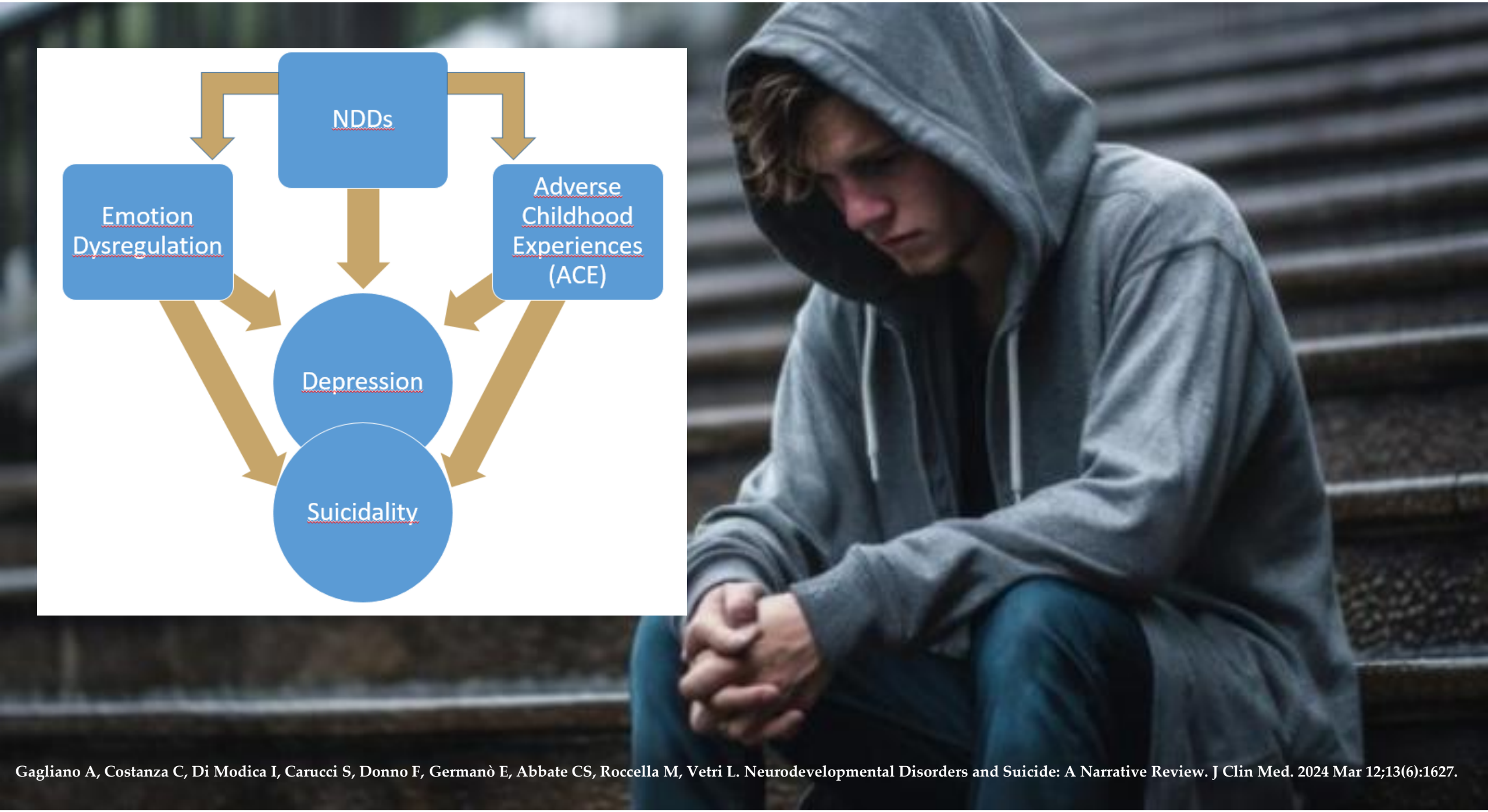


suicide attempts and non-suicidal self-harm are reported by a high proportion of the adolescent population mean lifetime prevalence 17–18%

Muehlenkamp JJ, Claes L, Havertape L, Plener PL, International prevalence of adolescent non-suicidal self-injury and deliberate self-harm,Child Adolesc Psychiatry Ment Health 2012, 6:6–10

L'autolesionismo aumenta la probabilità di morire per suicidio di 50 volte

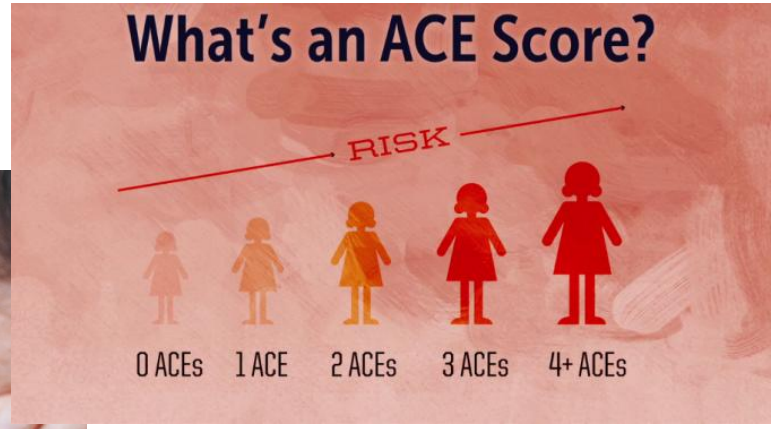


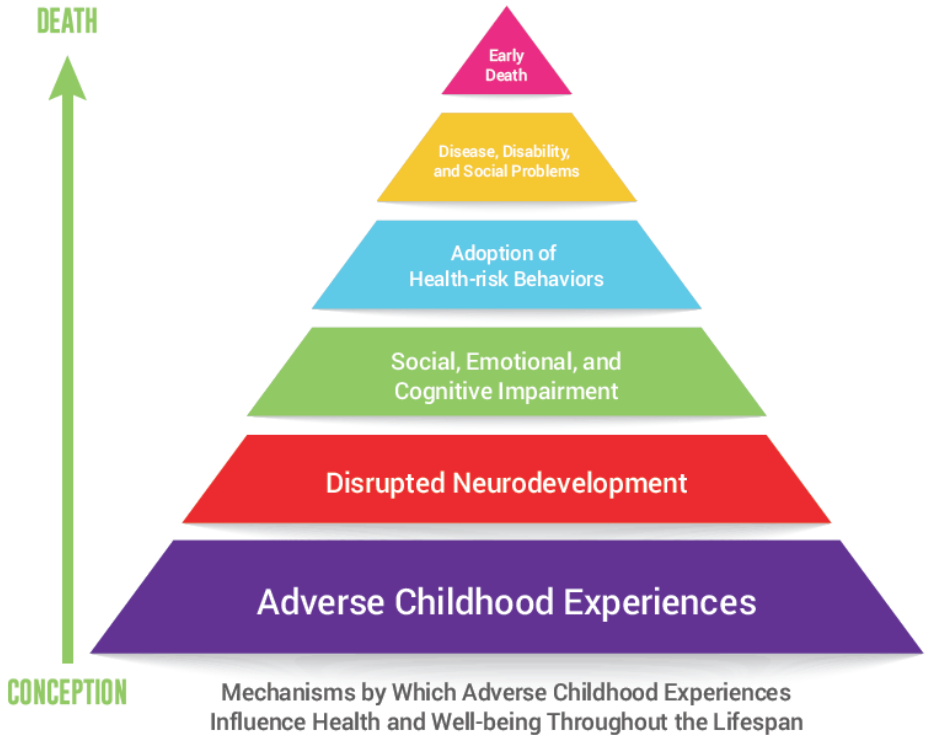


Gagliano A, Costanza C, Di Modica I, Carucci S, Donno F, Germanò E, Abbate CS, Roccella M, Vetri L. Neurodevelopmental Disorders and Suicide: A Narrative Review. J Clin Med. 2024 Mar 12;13(6):1627.

"**Adverse Childhood Experiences**," or "ACEs," comes from the 1998 Adverse Childhood Experiences Study (ACE Study), one of the largest investigations ever conducted to **assess connections between chronic stress caused by early adversity and long-term health.**







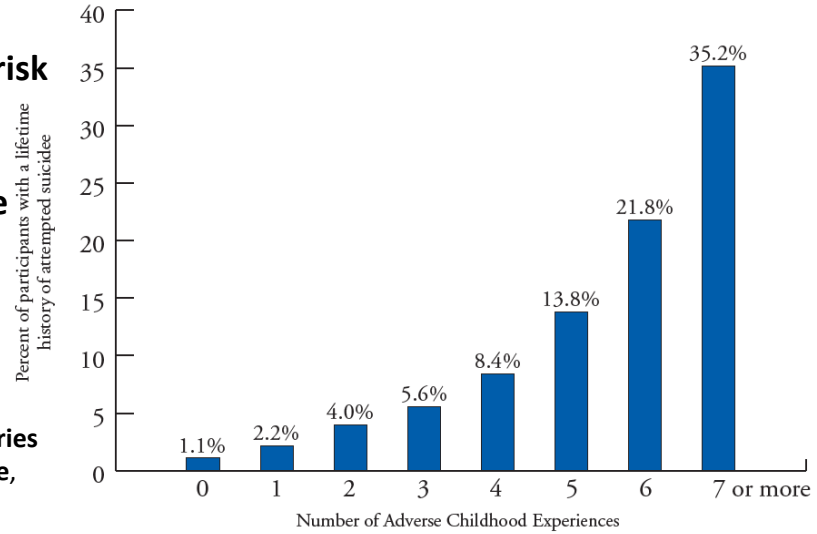
Mechanisms by Which Adverse Childhood Experiences Influence Health and Well-being Throughout the Lifespan

Whitfield CL. Adverse childhood experiences and traumaExternal. Am J Prev Med. 1998;14:361–363.

- **3.8% of study participants reported having attempted suicide at least once**
- **Experiencing one ACE increased the risk of attempted suicide two to five times**
- **As the ACE score increased so did the likelihood of attempting suicide**

N J. Sachs-Ericsson, NC. Rushing, I H. S & J Sheffler, **In my end is my beginning: developmental trajectories of adverse childhood experiences to late-life suicide,** Pages 139-165 |: 11 Aug 2015,

The Link between ACE and Suicide Attempts



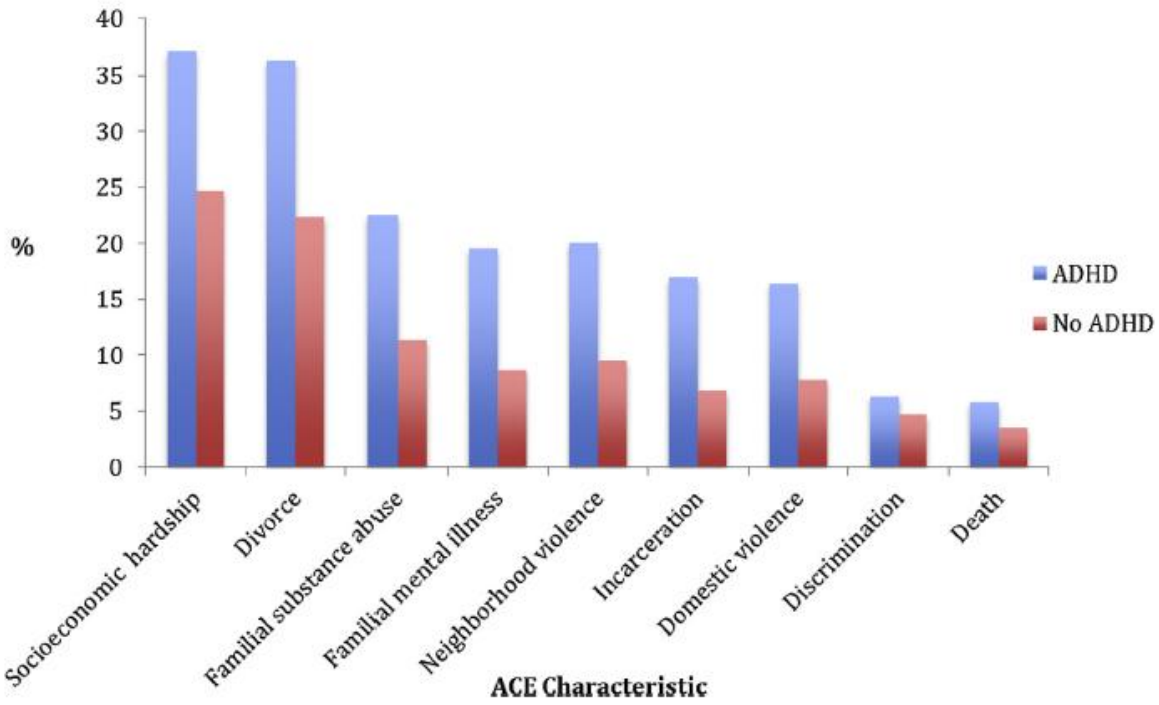
Brown et al, **Associations Between Adverse Childhood Experiences and ADHD Diagnosis and Severity**. Acad Pediatr. 2017 May - Jun;17(4):349-355.

Sample (N = 76,227 from 2011 to 2012 National Survey of Children's Health)

burden of ACEs among children with ADHD

Children were more likely to have ADHD if they had experienced

- socioeconomic hardship (aOR 1.39; 95% CI, 1.21-1.59)
- divorce (aOR, 1.34; 95% CI, 1.16-1.55)
- familial mental illness (aOR, 1.55; 95% CI, 1.26-1.90)
- neighborhood violence (aOR, 1.47; 95% CI, 1.23-1.75)
- incarceration (aOR, 1.39; 95% CI, 1.12-1.72).



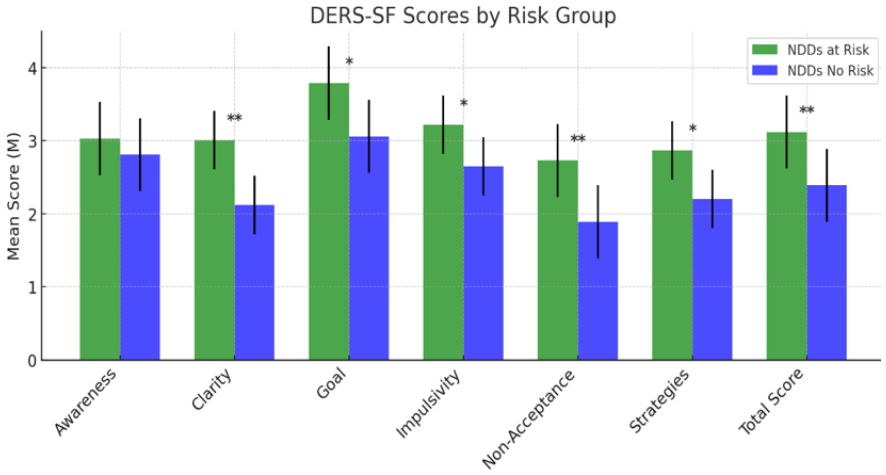


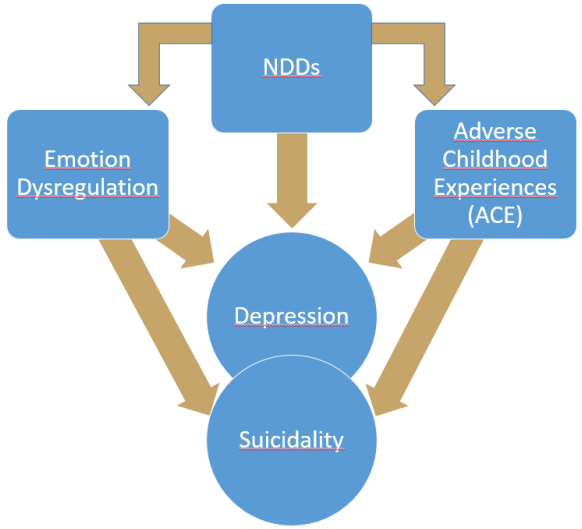
ADHD had a higher prevalence of each ACE compared with children without ADHD

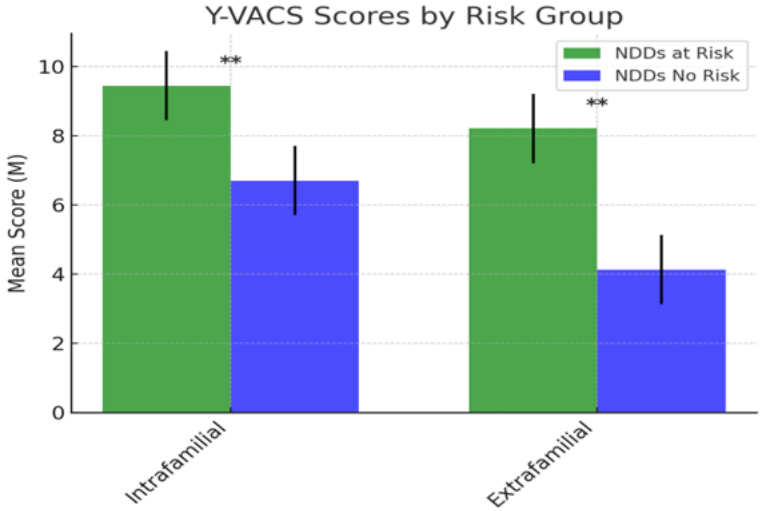
Suicidal Risk and Psychopathological Profiles in Adolescents with Neurodevelopmental Disorders: An Italian Multicentric study

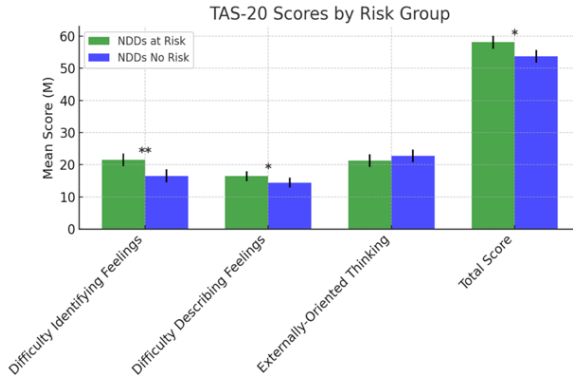
Cardillo, Gagliano et al, Frontiers in Psychiatry, 2025

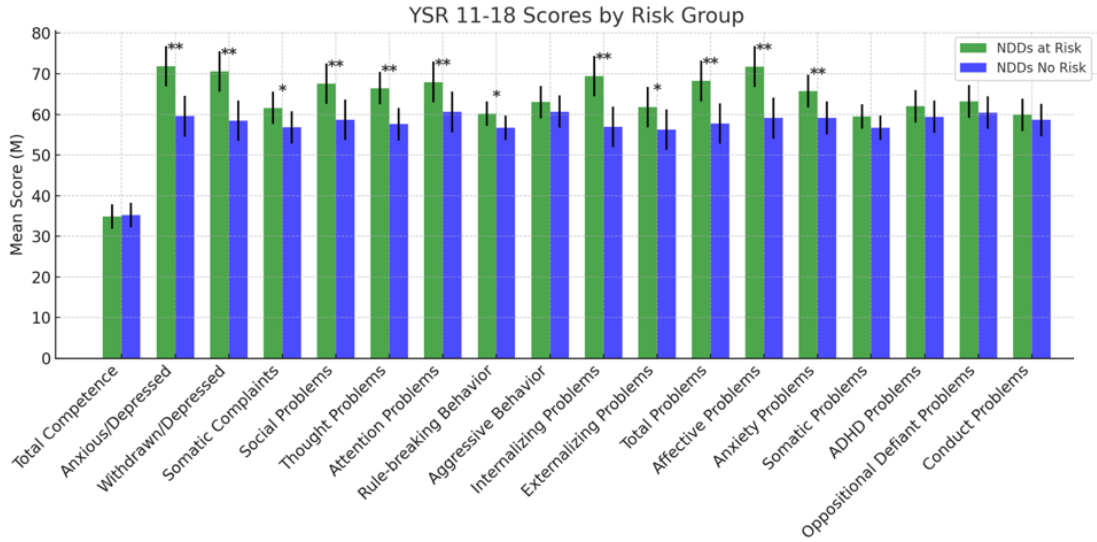
127 soggetti con NDDS,

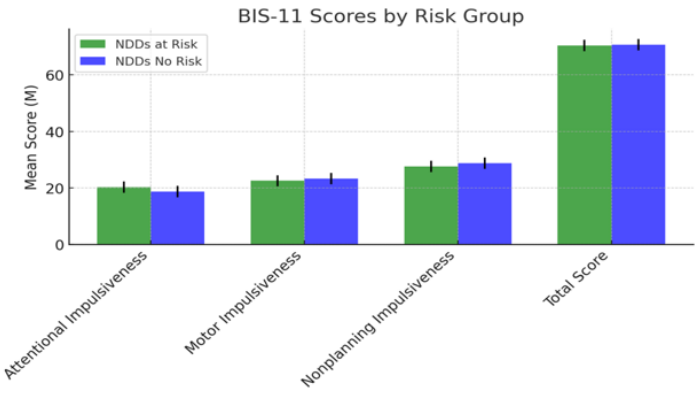














REVIEW

Lithium Suicide Prevention: A Brief Review and Reminder

by SIMRAT KAUR SARAI, MD; HEMA MADHURI MEKALA, MD; and STEVEN LIPPMANN, MD

Drs. Sarai and Mekala are research scholars and Dr. Lippmann is Emeritus Professor for the Department of Psychiatry and Behavioral Sciences at University of Louisville School of Medicine in Louisville, Kentucky.

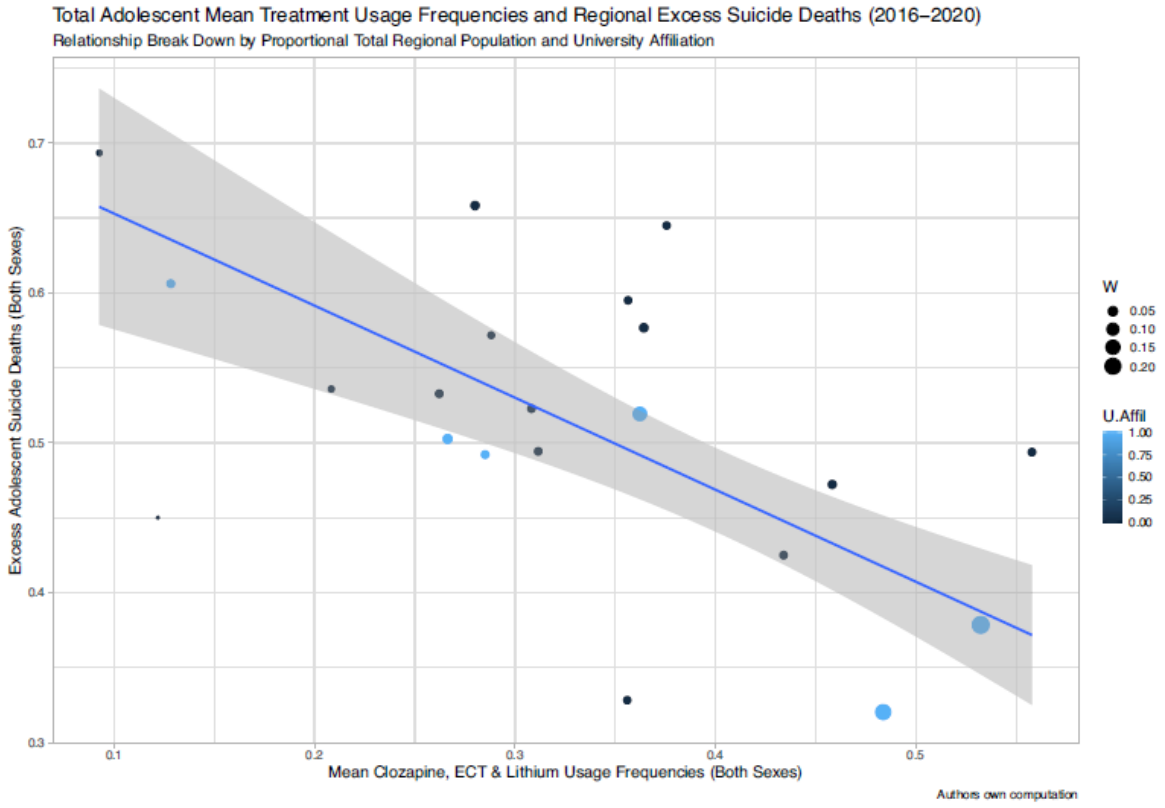
Innov Clin Neurosci. 2018;15(11–12):30–32

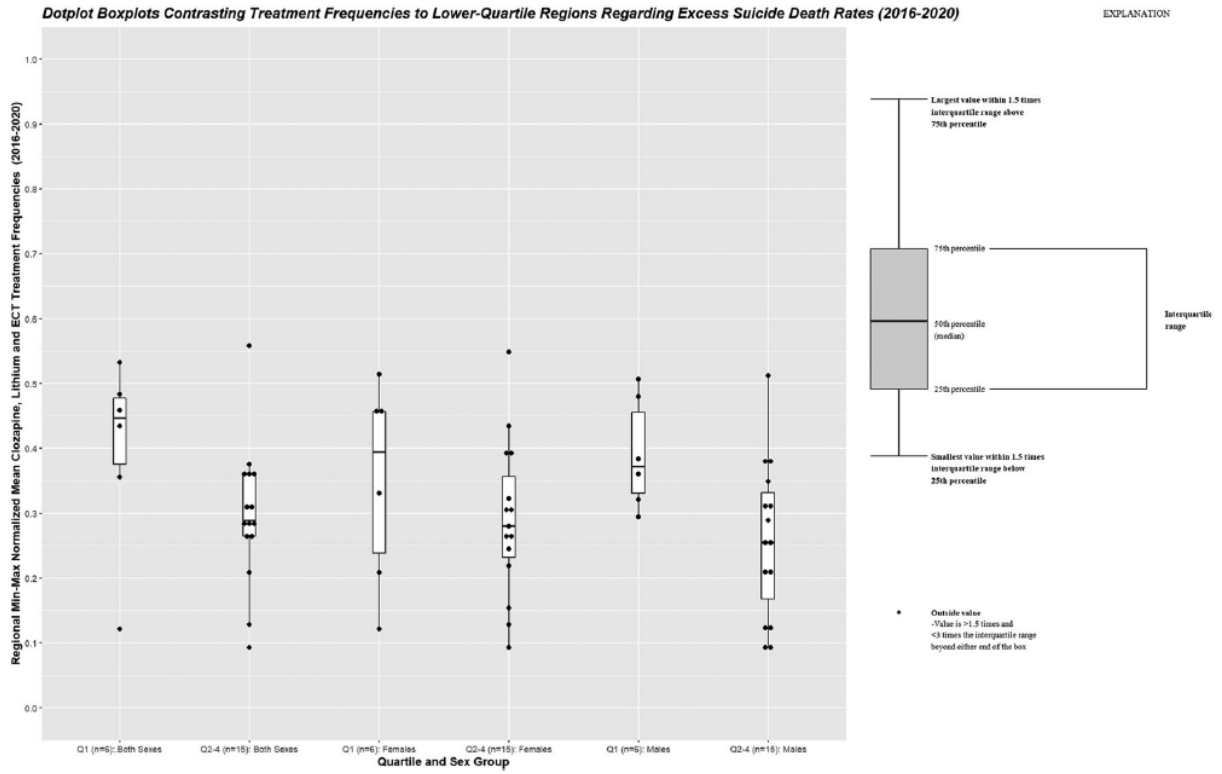
Use of lithium is thought to reduce risk for suicidality, even if mood stabilization is not achieved and serum concentration is lower than the conventionally accepted therapeutic blood level ranges.

This report serves as a reminder to clinicians to include lithium in their armamentarium for the treatment of an active disorder, especially when symptoms of suicidality are present.

Desai Boström AE, Andersson P, Rask-Andersen M, Jarbin H, Lundberg J, Jokinen J. Regional clozapine, ECT and lithium usage inversely associated with excess suicide rates in male adolescents. Nat Commun. **2023 Mar**

Across the 21 Swedish regions, using nationwide registers between 2016–2020, we found negative correlation between adolescent excess suicide mortality (AESM) and regional frequencies of **clozapine, Electroconvulsive therapy (ECT), and lithium (CEL) usage among adolescents** (β = −0.613, p = 0.0003, 95% CI: −0.338, −0.889) and **males** (β = −0.404, p=0.009, 95% CI: −0.130, −0.678). No correlation was found among females (p = 0.197).





Suicide prevention may benefit from **early recognition and lithium treatment** for severe mental illness in male adolescents.

The Treatment for Adolescents With Depression Study (TADS)

Long-term Effectiveness and Safety Outcomes

The TADS Team

Arch Gen Psychiatry. 2007;64(10):1132-1144

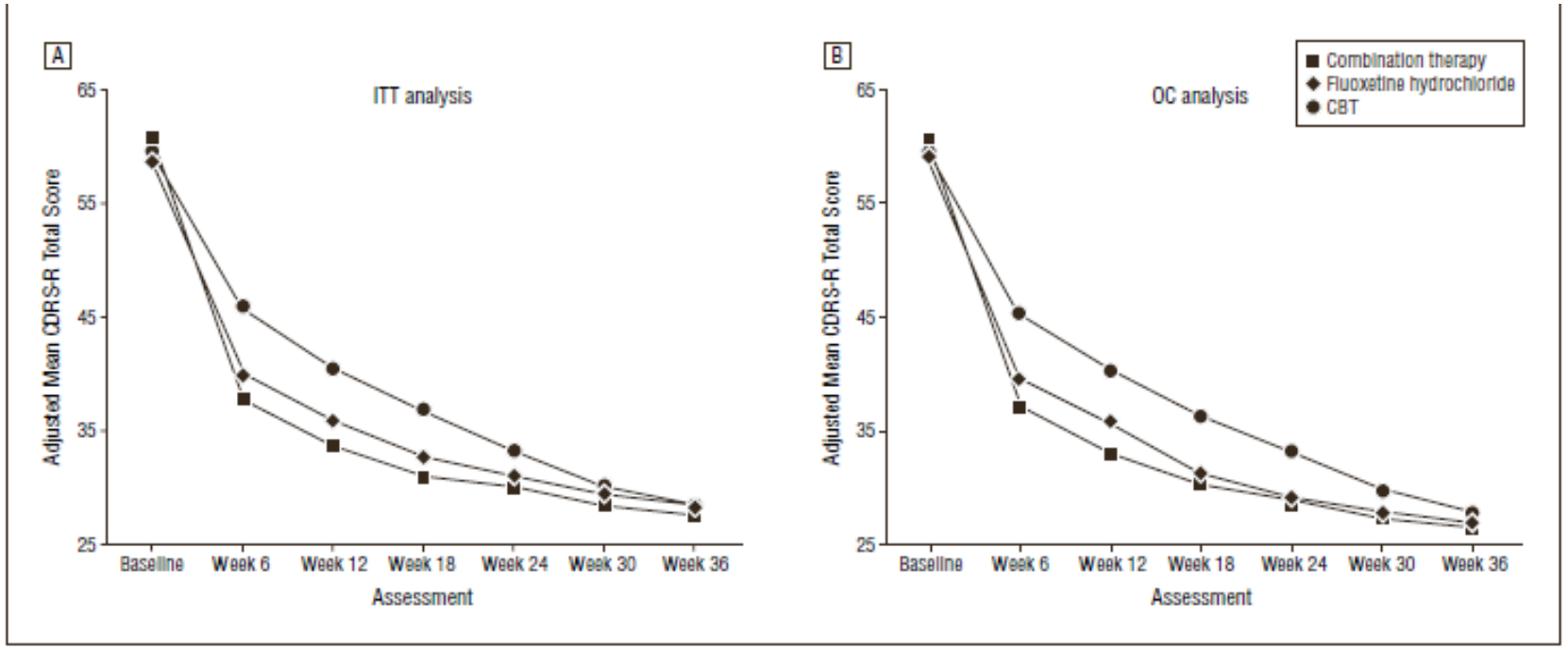
327 patients aged 12 to 17 years

Significant time x treatment interaction (P.001)

Table 3. Magnitude of the Effect of Combination Therapy and Fluoxetine Relative to CBT

		ITT Population			OC Population		
		Effect Size, Hedges *g*			Effect Size, Hedges *g*		
Week	Contrast	CDRS-R	RADS	CGI-I, NNT	CDRS-R	RADS	CGI-I, NNT
12	Combination-CBT	0.71	0.59	4	0.81	0.63	4
	FLX-CBT	0.48	0.39	7.0	0.49	0.38	7
18	Combination-CBT	0.55	0.52	5	0.71	0.61	4
	FLX-CBT	0.38	0.33	25	0.57	0.30	14
36	Combination-CBT	0.07	0.31	20	0.17	0.34	13
	FLX-CBT	−0.01	0.12	>100	0.12	−0.01	33

effectiveness outcomes across 36 weeks of randomized treatment



Rates of response

at week 12

combination therapy	73%
Fluoxetine	62%
CBT	48%

at week 18

combination therapy	85%
Fluoxetine	69%
CBT	65%

at week 36

combination therapy	86%
Fluoxetine	81%
CBT	81%

I choice

SSRIs (monotherapy)

fluoxetine

II choice

SSRIs (monotherapy)

sertraline, citalopram, escitalopram

III choice (in adolescents non responders to SSRI)

SNRI (monotherapy)

Venlafaxine

(at lower doses it inhibits the re-uptake of 5HT, at higher doses >150 mg/d also of NE, at the highest doses also of DA)

SSRI + Augmentation

Lower evidences for antiepileptic drugs

- **lamotrigine**
- **valproic acid**

Scarce evidence for:

- thyroid hormone T3
- S-adenosil-L-metionine
- psychostimulants
- omega-3 fatty acids
- methylfolat
- pindolo
- dopamine agonists pramipexole/ropirinole

Black Box Warning per il rischio suicidario



FDA Public Health Advisory. Worsening depression and suicidality in patients being treated with antidepressant medications. www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm (citato il 9 marzo 2006).

metanalisi di 24 studi placebo controllati (4582 pazienti)

Gli SSRI aumentano in modo significativo, rispetto al placebo, il rischio significativo di sviluppare suicidalità (ideazione suicidaria e tentativi di suicidio)

Hammad TA, Laughren T, Racoosin J.: Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006, 63:332-9.

I trials clinici in età pediatrica sugli SSRI non hanno mai riportato un caso di suicidio

Mancuso E, Faro A, Joshi G, Geller DA: Treatment of pediatric obsessivecompulsive disorder: a review. J Child Adolesc Psychopharmacol 2010, 20: 299-308.

I benefici superano i rischi

titolazione lenta

attento monitoraggio dell'assetto psico-emotivo soprattutto nelle prime fasi del trattamento

Effetto protettivo della CBT sulla suicidalità se aggiunta al farmaco

.



- Riduzione del rischio di passaggio dalla ideazione al tentativo
- Migliore gestione della esposizione ad eventi stressanti
- Riduzione dell’impatto di conflitti familiari
- Maggiori strumenti per gestire agitazione, irritabilità
- Maggiore possibilità di monitoraggio

Quale classe di farmaci per Francesco……?

iperattività/impulsività

disregolazione emozionale

aggressività/isolamento

depersonalizzazione
e derealizzazione

ideazione suicidaria

insonnia

tic

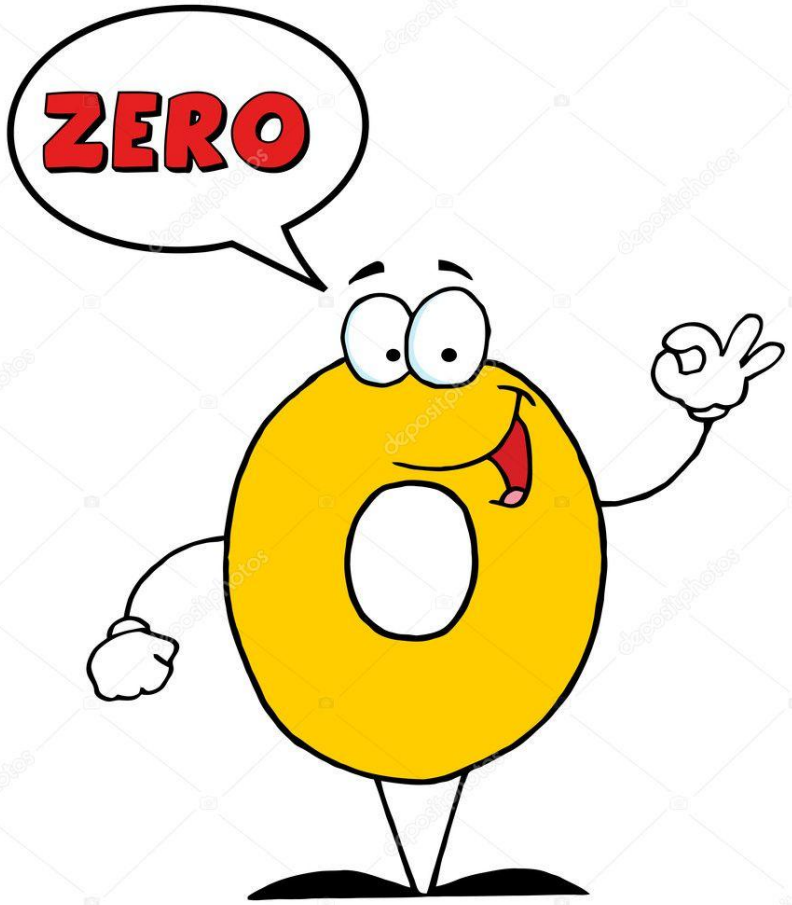


Treatment





How many drugs are approved* for sleep disorders in childhood ?



*FDA and Agenzia italiana del farmaco per l’età pediatrica

Bruni O, Angriman M, Calisti F, Comandini A, Esposito G, Cortese S, Ferri R. Practitioner Review: Treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. J Child Psychol Psychiatry. 2018 May;59(5):489-508. doi: 10.1111/jcpp.12812.

Review on drugs and nonpharmacological interventions used for sleep disturbances in children with NDDs

Good sleep practices and behavioral interventions

- first recommended treatments
- from moderate-to-low level evidence and challenging to implement

First line treatment

Antihistamine agents (es. hydroxyzine or diphenhydramine)

- the most widely prescribed sedatives in the pediatric practice
- **evidence supporting their use is limited**

Melatonin

- **is the safest choice for children**

Safest treatment

Benzodiazepines

- **not recommended** in children and should only be used for transient insomnia

Zolpidem, zaleplon, and eszopiclone, alpha-agonists (es. Clonidine)

- limited evidence supports their use

Tricyclic antidepressants

- not recommended in children because of their safety profile

Trazodone and mirtazapine

- hold promise but require further studies

EXPERT REVIEW OF NEUROTHERAPEUTICS
2024, VOL. 24, NO. 6, 585–596
https://doi.org/10.1080/14737175.2024.2353692

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REVIEW

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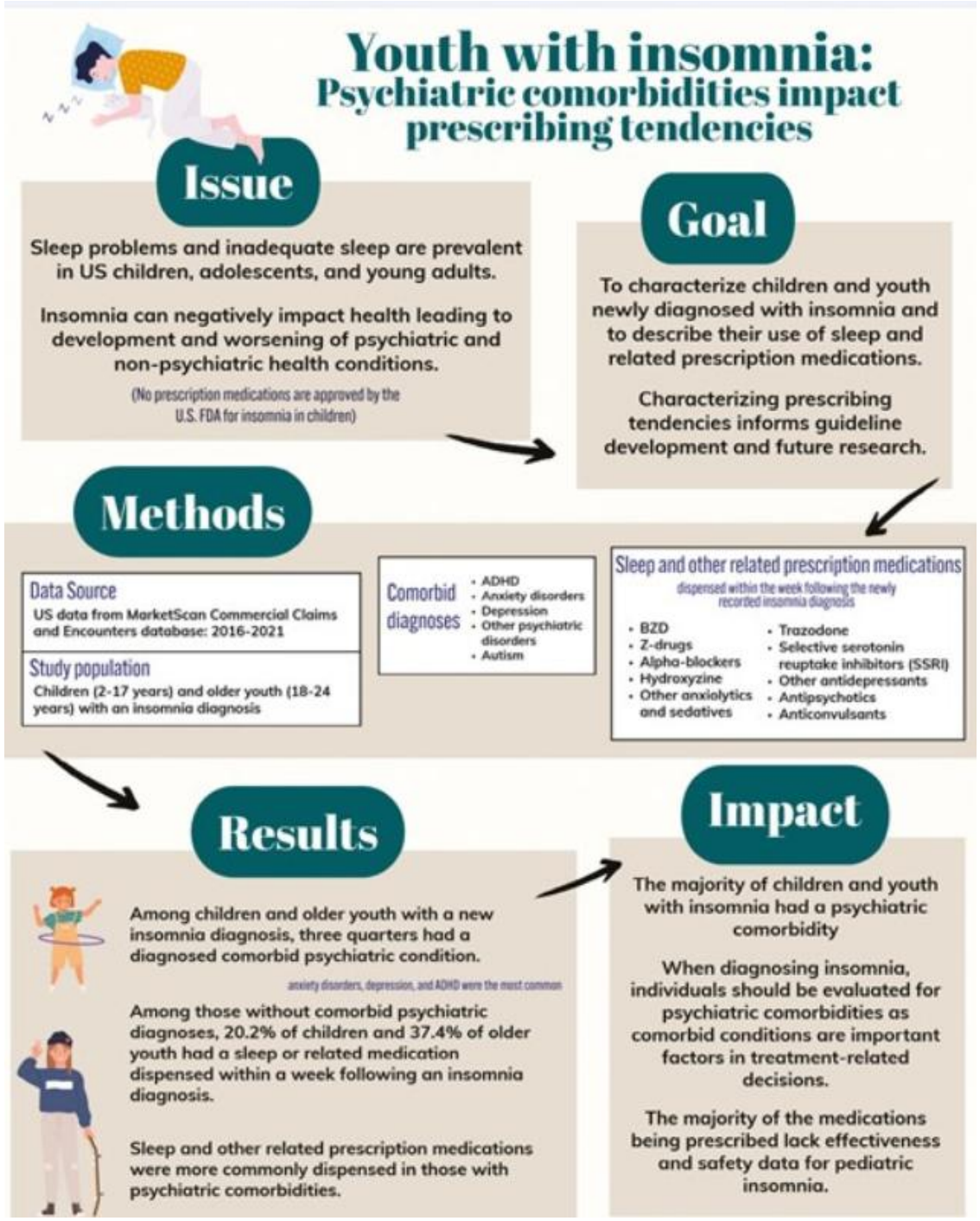
The management of sleep disturbances in children with attention-deficit/ hyperactivity disorder (ADHD): an update of the literature

Samuele Cortese[a,b,c,d,e], Guilherme Fusetto Veronesi[f], Alessandra Gabellone[g], Anna Margari[h], Lucia Marzulli[g], Emilia Matera[e], Maria Giuseppina Petruzelli[g], Francesco Maria Piarulli[g], Fabio Tarantino[e], Alessio Bellato[a,i,j,k,l], Valeria Parlatini[a,b,c], Ebba Du Rietz[m], Henrik Larsson[a,j,n], Samantha Hornsey[b], Cathy Hill[b] and Lucia Margari[e]

RCTs published up to 4 January 2024 on any intervention for sleep disorders associated with ADHD

- **16 RCTs** (8 on pharmacological and 8 on non-pharmacological interventions) **support behavioral intervention and melatonin**

- 9 ongoing RCTs registered on clinicaltrials.gov.



Greta Bushnell, Anna Ivanenko, Daniel B Horton, Jessica R Lunsford-Avery, Jonathan Posner, Tobias Gerhard, Elizabeth Suarez, Mark Olfson, Psychiatric comorbidities and prescribing tendencies of sleep medications and related medications in young people with insomnia: a United States commercial claims-based analysis, Sleep, Volume 47, Issue 5, May 2024, zsae057

This nationwide sample of young people with new insomnia diagnosis (68 698 children and 108 118 older youth 18–24 years) highlight the **high prevalence of psychiatric comorbidities (3/4)** and **variety of sleep and related medications** they receive.

In children with a psychiatric diagnosis, **trazodone** was the most common medication **followed by hydroxyzine, z-drugs, and SSRIs**

- comorbid anxiety or depression → SSRIs
- comorbid ADHD → alpha-agonists
- comorbid anxiety disorder → BZDs
- autism → second generation antipsychotics

From 2017 to 2021, there was an **increase in hydroxyzine** prescriptions following a and **decline in z-drug and benzodiazepine** prescriptions.

Mirtazapina

farmaco antidepressivo di seconda generazione appartenente alla classe farmacologica dei NaSSA (**Noradrenergic and Specific Serotoninergic Antidepressant**) utilizzato nel trattamento della depressione maggiore, dei disturbi d'ansia specie se misti ad insonnia per via delle sue proprietà sedative

Utilizzato negli adulti con depressione

- Dolder CR, Nelson MH, Iler CA. The effects of mirtazapine on sleep in patients with major depressive disorder. Ann Clin Psychiatry. 2012 Aug;24(3):215-24. PMID: 2286024
- Winokur A, Sateia MJ, Hayes JB, Bayles-Dazet W, MacDonald MM, Gary KA. Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. Biol Psychiatry. 2000



Hanzlik E, Klinger SA, Carson R, Duis J. Mirtazapine for sleep disturbances in Angelman syndrome: a retrospective chart review of 8 pediatric cases. J Clin Sleep Med. 2020 Apr 15;16(4):591-595.

Letter

Use of mirtazapine in children and adolescents

A 16-year-old female presented with a resistant depression and sleep difficulties. She had been previously prescribed two selective serotonin reuptake inhibitors (SSRIs) in the last 18 months – fluoxetine and sertraline. She requested mirtazapine due to the resistant nature of her depression and hoped the medication would address her sleep difficulties.

Mirtazapine use is not licensed in patients younger than 18 years old.[1] We conducted a literature search using Medline, Embase and PsycInfo. We wanted to know if mirtazapine could be used safely in young people for major depressive disorder (MDD). There were only very few studies in this population dealing with our question. Most of the evidence comes from adult population. Here we present a brief report on our findings.

A multicentre, open-label study with a duration of 85 days was performed to evaluate the antidepressant efficacy and safety of mirtazapine in 12–18-year-old adolescents diagnosed with major depression.[2] Mirtazapine showed a marked efficacy on all rating scales and was well tolerated. Mirtazapine had a beneficial effect on sleep: a rapid onset of sleep and pattern of action was seen. The most common treatment-emergent adverse events were tiredness, increased appetite, and dizziness.

A multiple-treatment meta-analysis showed that sertraline and mirtazapine exhibited optimally balanced efficacy, acceptability, and safety for first-line acute treatment of child and adolescent major depressive disorder.[3] In another study, authors investigated the efficacy and tolerability of mirtazapine in combination with methylphenidate in young subjects with a diagnosis of attention deficit hyperactivity disorder (ADHD) and comorbid anxiety or depressive disorders.[4] They concluded that young subjects with ADHD and comorbid anxiety or depressive disorders may benefit from mirtazapine addition, particularly in the presence of methylphenidate or SSRI-related sleep and/or appetite problems.

There is uncertainty about the safety and efficacy of antidepressant medications in the younger population. It has been suggested that the treatment of depression requires a multimodal approach,[5] starting with a comprehensive assessment and psychological treatments such as cognitive behavioural therapy, family therapy and interpersonal therapy. Currently, fluoxetine has the most robust evidence demonstrating that benefits outweigh the risks for children and adolescents aged 8–18 years.[6,7] The risk-benefit balance for fluoxetine in child and youth depression is favourable and current data do not support the use of mirtazapine (an SNRI) as primary treatment in youth depression,[8] as studies in children and adolescents are limited. However, mirtazapine may be used where the benefits of treatment outweigh any potential risks[1] (for example, side effects) but we need to take a cautious approach – start low and go slow – with robust clinical follow up.

Dr Imran Mushtaq, Locum Consultant Child & Adolescent Psychiatrist, Centenary House CAMHS, Sheffield
Dr Piyush Satyawadi, Locum Consultant Psychiatrist, Folly Hall Mills, Huddersfield

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1. www.sussexpartnership.nhs.uk/sites/default/files/documents/information_on_the_use_of_mirtazapine_in_young_people_large_print_.pdf (last accessed January 2018).
2. Haapasalo-Pesu KM, Vuola T, Lahelma L, *et al.* Mirtazapine in the treatment of adolescents with major depression: an open-label, multicenter pilot study. *J Child Adolesc Psychopharmacol* 2004;14(2):175–84.
3. Ma D, Zhang Z, Zhang X, *et al.* Comparative efficacy, acceptability, and safety of medicinal, cognitive-behavioral therapy, and placebo treatments for acute major depressive disorder in children and adolescents: A multiple-treatments meta-analysis. *Curr Med Res Opin* 2014;30(6):971–95.
4. Coskun M, Ahmetoglu E, Ozturk, M. Mirtazapine treatment for comorbid anxiety/depressive disorders in young subjects with attention-deficit hyperactivity disorder: case series. *Bulletin of Clinical Psychopharmacology* 2010;20(3):246–51.
5. James A. Resistant depression in childhood and adolescence. *Clin Child Psychol Psychiatry* 1999;4(4):483–91.
6. March JS, Silva S, Petrycki S, *et al.* The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry* 2007;64(10):1132–43.
7. March JS, Entusah AR, Rynn M, *et al.* A randomized controlled trial of venlafaxine ER versus placebo in pediatric social anxiety disorder. *Biol Psychiatry* 2007;62(10):1149–54.
8. Garland EJ, Kutcher S, Virani A, *et al.* Update on the Use of SSRIs and SNRIs with Children and Adolescents in Clinical Practice. *J Can Acad Child Adolesc Psychiatry* 2016;25(1):4–10.

Trazodone (Trittico)

https://www.mskcc.org/cancer-care/patient education/medications/pediatric/trazodone

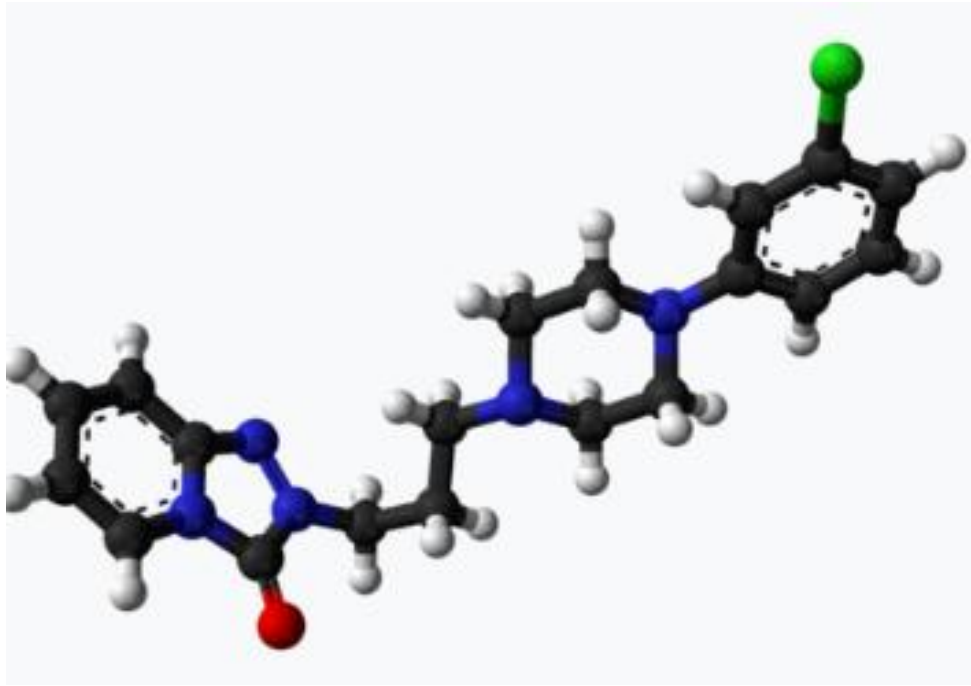
proprietà antidepressive, ansiolitiche e ipnotiche

classe degli antagonisti e inibitori della ricaptazione della serotonina (SARI).

(piperazine e triazolopiridine, antidepressivo di seconda generazione)

Warning

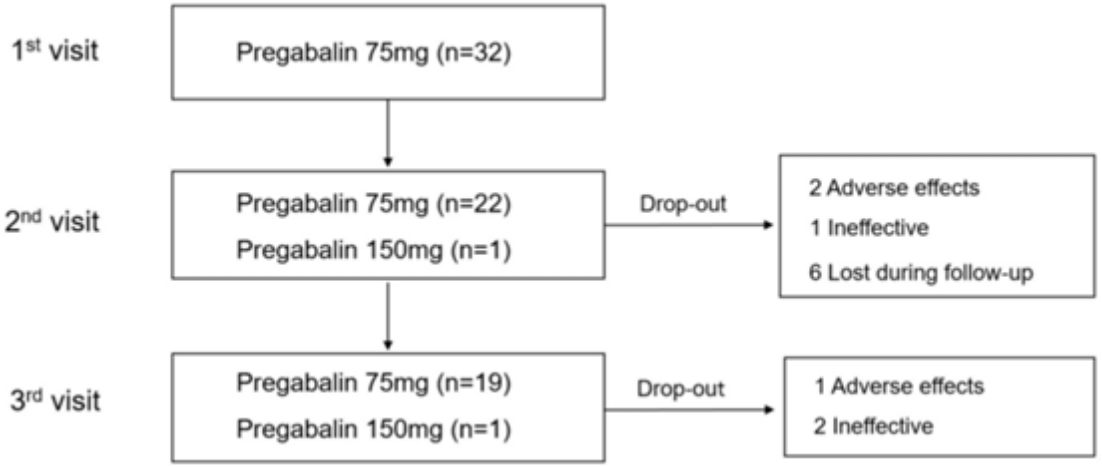
- Drugs like this one have raised the chance of suicidal thoughts or actions in children and young adults. The risk may be greater in people who have had these thoughts or actions in the past. All people who take this drug need to be watched closely. Call the doctor right away if signs like depression, nervousness, restlessness, grouchiness, panic attacks, or changes in mood or actions are new or worse. Call the doctor right away if any thoughts or actions of suicide occur.
- This drug is not approved for use in children. However, the doctor may decide the benefits of taking this drug outweigh the risks. If your child has been given this drug, ask the doctor for information about the benefits and risks. Talk with the doctor if you have questions about giving this drug to your child.



Bae H, Cho YW, Kim KT, Allen RP, Earley CJ. **The Safety and Efficacy of Pregabalin Add-on Therapy in Restless Legs Syndrome Patients**. Front Neurol. **2021** Nov 29;12:786408

Pregabalin is increasingly being used as a **first-line treatment for symptomatic control of restless legs syndrome (RLS)**

(strutturalmente simile all'acido γ-aminobutirrico esercita i suoi effetti legandosi alla subunità α2δ dei canali del calcio voltaggio dipendenti)



the **mean IRLS score showed significant improvement** compared to the baseline ($p < 0.001$).

The **insomnia** severity index score also **improved** ($p = 0.036$)

No serious adverse effects were observed.

STUDIO SU ADULTI

efficacy and safety of pregabalin as add-on therapy in RLS patients already taking dopamine agonists (DA) but still in need of further management.

TABLE 1 | Mean (± SD) for the pre- and post-treatment RLS severity and sleep scale score.

	At baseline	Post-treatment	*p*
IRLS	26.48 ± 8.10	20.91 ± 8.66	<0.001
RLS QoI	68.63 ± 20.58	69.50 ± 22.38	0.068
RLS VAS	57.14 ± 34.81	42.38 ± 29.82	0.139
ISI	13.60 ± 7.65	12.65 ± 7.97	0.036
PSQI	11.24 ± 4.35	11.00 ± 4.59	0.093
BAI	11.10 ± 9.48	10.62 ± 9.63	0.431
BDI	13.05 ± 9.94	13.57 ± 9.53	0.330

RLS, Restless legs syndrome; IRLS, International Restless Legs Scale; RLS QoI, RLS specific quality of life questionnaire; VAS, visual analog scale of severity; ISI, Insomnia Severity Index; PSQI, Pittsburg sleep quality index; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.

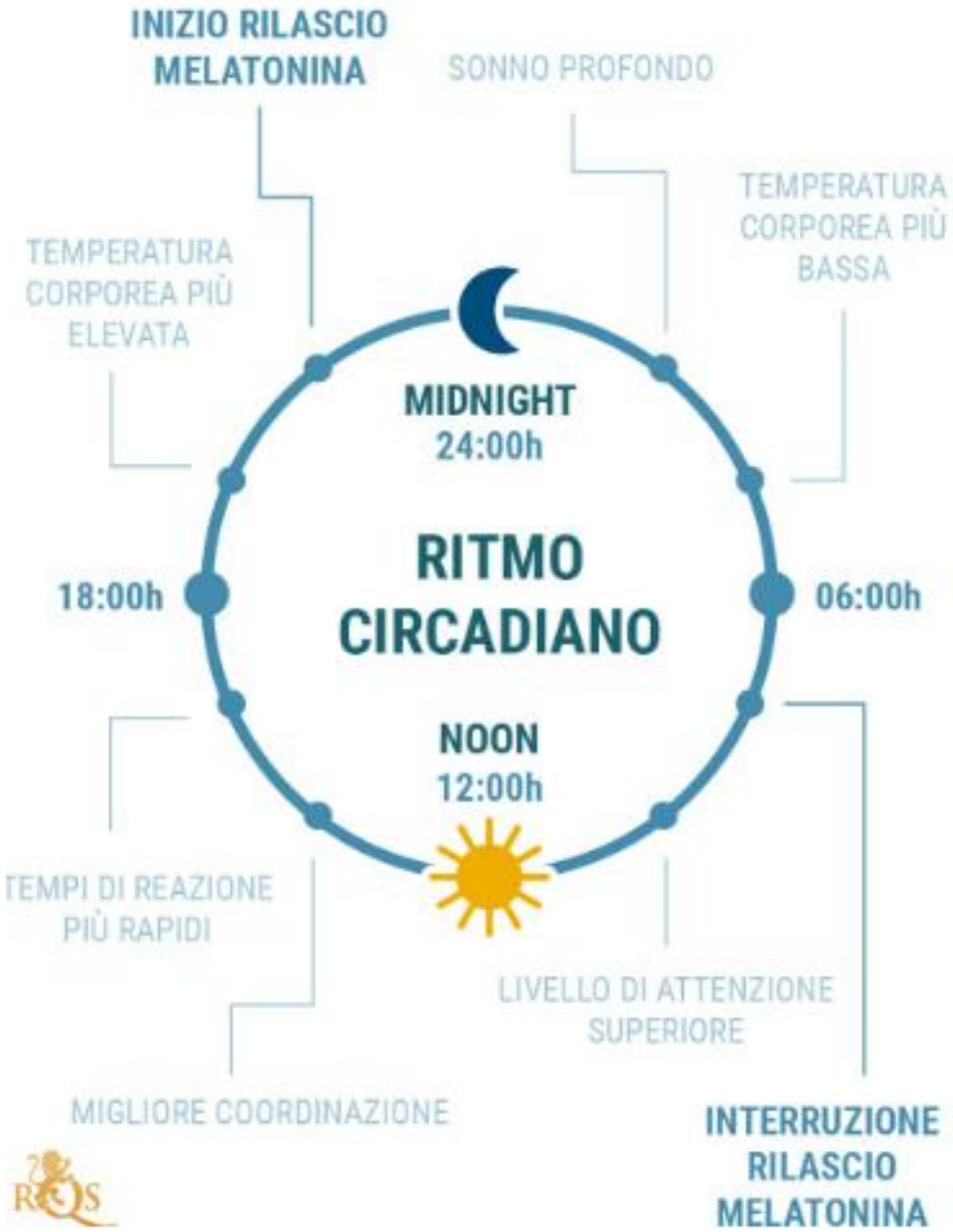
fitoterapici e nutraceutici…

Melatonin is **the second most popular natural product** used by children in the United States (second only to fish oil)

Andersen, L.P.H.; Gögenur, I.; Rosenberg, J.; Reiter, R.J. Pharmacokinetics of Melatonin: The Missing Link in Clinical Efficacy? Clin. Pharmacokinet. 2016, 55, 1027–1030.

Melatonin:

- works best as a **chronobiotic, not a hypnotic, agent**
- shortened sleep latency by a mean of 4 min
- increased sleep efficiency by 2.2%
- lengthened sleep duration by 12.8 min

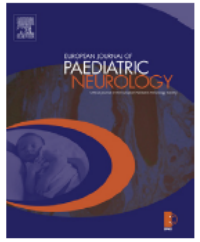


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EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 19 (2015) 122–133

ELSEVIER

Official Journal of the European Paediatric Neurology Society



Review article

Current role of melatonin in pediatric neurology: Clinical recommendations

Oliviero Bruni [a], Daniel Alonso-Alconada [b,c], Frank Besag [d], Valerie Biran [e,f], Wiebe Braam [g,h], Samuele Cortese [i,j,k], Romina Moavero [l,m], Pasquale Parisi [n], Marcel Smits [h,o], Kristiaan Van der Heijden [p], Paolo Curatolo [l,*]



A European consensus conference was held in Rome on October 4th 2014 with the aims of assessing the current role of melatonin in childhood sleep disturbances

Melatonin is prescribed by pediatricians mainly for **sleep onset insomnia** (89%), **delayed sleep phase syndrome**(66%) and **night-time awakenings** (30%).

It is prescribed both for **typically developing children** and for **children with developmental disorders**, including autism, developmental delay, ADHD, and behavioral disorders

Heussler H, Chan P, Price AM, et al. Pharmacological and non-pharmacological management of sleep disturbance in children: an Australian paediatric research network survey. Sleep Med 2013;14:189e94.

Recommendations for prescribing melatonin in children with sleep-wake rhythm disorders or sleep onset insomnia.

Minimum age for administration	No studies reported the minimum age for administering melatonin. Since it has been used in high dosage in infants to prevent neuronal injuries without side effects we can expect that melatonin administration after 6 months of age could be quite safe
Time of administration in children	If used as chronobiotic, 2–3 h before DLMO (dim light melatonin onset *) When DLMO cannot be measured: administer melatonin 3–4 h before actual sleep onset time If used as sleep inductor 30 min before bedtime
Dosage	If used as chronobiotic, start with a low dose of 0.2–0.5 mg fast release melatonin 3–4 h before bedtime; increase by 0.2–0.5 mg every week as needed (maximum 3 mg; adolescents: 5 mg) until effect If no response after 1 week: increase dose by 1 mg every week until effect appears When 1 mg is effective: try lower dose Maximum dose: <40 Kg: 3 mg; >40 Kg: 5 mg If used as a sleep inductor start with 1–3 mg 30 min before sleep of before the examination (EEG, Evoked potentials or MRI)
Treatment duration	Treatment duration should be tailored to the specific patient in relation to the peculiar neurodevelopmental disabilities but in general should be not less than 1 month Treatment can be withdrawn just before puberty (age around 12 yrs) or shortly after puberty (18–24 yrs) Stopping successful treatment too early (i.e. 4 weeks after its start) may results in reappearance of insomnia Stop melatonin treatment once a year during one week (preferably in summer) after a normal sleep cycle is established



*DLMO test usually takes place from 8pm until 3am. During the test patients are asked to stay in dim lighting and every hour samples of saliva, in the form of chewed on cotton balls, are collected. Afterwards, the melatonin concentration of the samples is measured

Bruni O, Alonso-Alconada D, Besag F, Biran V, Braam W, Cortese S, Moavero R, Parisi P, Smits M, Van der Heijden K, Curatolo P. Current role of melatonin in pediatric neurology: clinical recommendations. Eur J Paediatr Neurol. 2015 Mar;19(2):122-33.

Oral melatonin is **rapidly absorbed** with **peak levels 20 to 30 min after oral ingestion** (Tmax) but a **very short elimination half-life** (t1/2) of only **40 to 60 min**.

DeMuro RL, Nafziger AN, Blask DE, Menhinick AM, Bertino JS., Jr The absolute bioavailability of oral melatonin. J Clin Pharmacol. 2000;40(7):781–784.

Melatonin is **poorly absorbed** for all formulations

- The **bioavailability ranging from 2.5% to 33%** (in vitro protein binding of 60%)
- It undergoes hepatic metabolism, particularly for oral formulations with high hepatic first pass effect

The combination of both **poor absorption** and substantial **hepatic first pass metabolism** explains much of the **low bioavailability**

Andersen, L.P.H.; Gögenur, I.; Rosenberg, J.; Reiter, R.J. Pharmacokinetics of Melatonin: The Missing Link in Clinical Efficacy? Clin. Pharmacokinet. 2016, 55, 1027–1030.

- Melatonin content varied from −83% to +478% of labeled melatonin
- 70% had melatonin concentration ≤ 10% of what was claimed
- The content of melatonin between lots of the same product varied by as much as 465%.



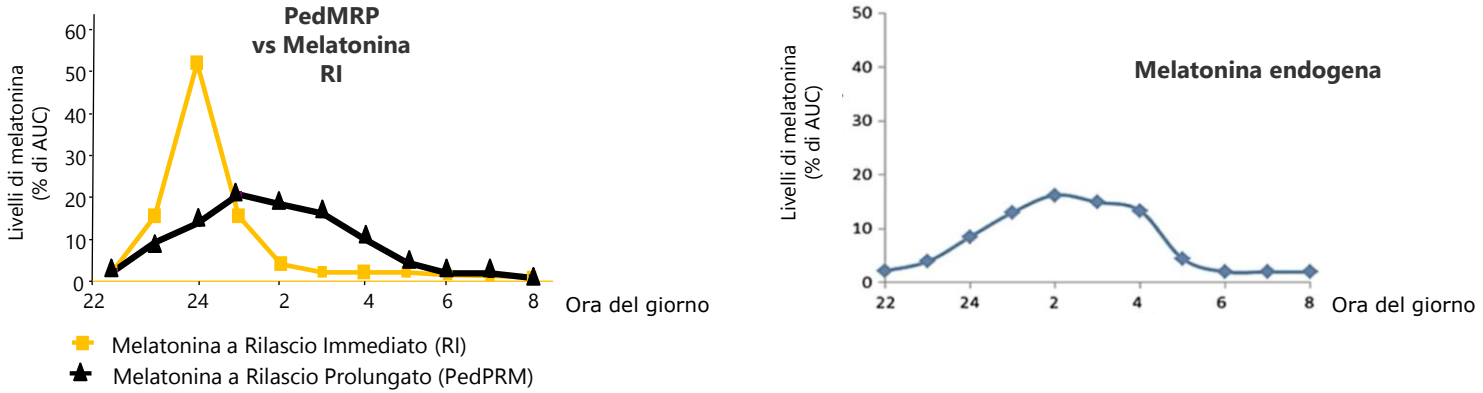
- Grigg-Damberger MM, Ianakieva D. Poor Quality Control of Over-the-Counter Melatonin: What They Say Is Often Not What You Get. J Clin Sleep Med. 2017 Feb 15;13(2):163-165
- Erland LA, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. J Clin Sleep Med. 2017;13(2):275–281.

MELATONIN **long acting** IN PEDIATRIC INSOMNIA

effective in improving both **sleep onset and sleep maintenance** whereas immediate release melatonin formulations is effective in sleep induction but less with sleep maintenance

impact on behavior can be explained by the **improvement in duration of uninterrupted sleep**.

- **PedPRM** mima il profilo fisiologico di secrezione della melatonina endogena, garantendo concentrazioni efficaci dell'ormone del sonno per tutta la durata della notte (6-8 ore)**.** [1]
- La **Melatonina a Rilascio Immediato (RI)** ha un rapido picco plasmatico (20-30 min post assunzione) e una altrettanto rapida metabolizzazione (emivita elim. 40-50 min).[1]



Elaborazione grafica da fig. 2 ref. 2

PedPRM – profilo farmacocinetico

1. Zisapel N. Melatonin and sleep. The Open Neuroendocrinology Journal, 2010, 3: 85-95

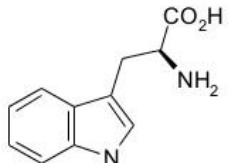
2. Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. British Journal of Pharmacology 2018

Schroder CM, Malow BA, Maras A, Melmed RD, Findling RL, Breddy J, Nir T, Shahmoon S, Zisapel N, Gringras P. Pediatric Prolonged-Release Melatonin for Sleep in Children with Autism Spectrum Disorder: Impact on Child Behavior and Caregiver's Quality of Life. J Autism Dev Disord. 2019 Aug;49(8):3218-3230

E se si associa la melatonina al triptofano



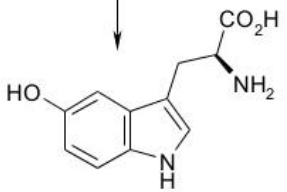
99% towards chinurenine pathway



L-tryptophan

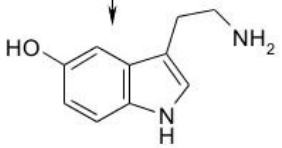
Triptofano idrossilasi [O]

1%



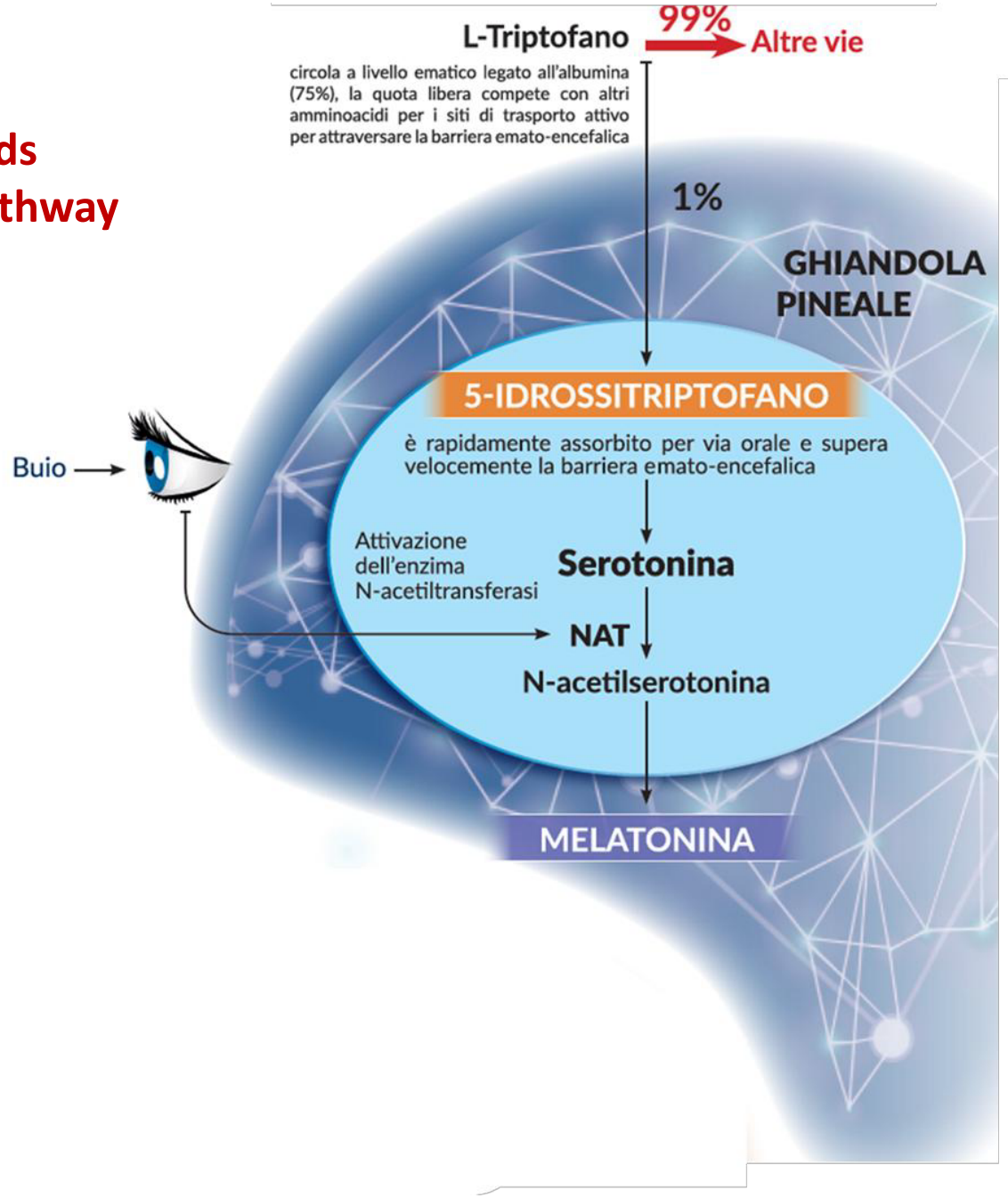
5-OH-tryptophan

5-idrossitriptofano decarbossilasi $-CO_2$



5-idrossitriptammina
Serotonina

serotonin



Carotenuto M, Angriman M, Bruni O. Efficacia del 5-idrossitriptofano (Griffonia simplicifolia) sull'insonnia cronica in età pediatrica: studio pilota multicentrico in aperto. il Medico Pediatra 2020;29(1):28-31.



- nei semi maturi di griffonia è contenuto 5-HTP
- efficacia di 5HTP su insonnia cronica e risvegli notturni

è stato utilizzato uno sciroppo a base di **Griffonia simplicifolia** titolata al 25% in 5-HTP di cui 1 ml di prodotto corrisponde a 40 mg di Griffonia pari a **10 mg di 5-HTP**.

Triptofano (TRP)

È uno dei 9 aminoacidi essenziali per l'uomo che non possono essere sintetizzati in maniera endogena ma necessariamente introdotti con l'alimentazione. Presente in alcuni alimenti (frutta secca, riso, spinaci crudi, formaggi), può favorire il sonno senza particolari effetti collaterali.
Precursore della serotonina, ha effetti diretti sulla regolazione omeostatica del sonno aumentando la disponibilità di serotonina cerebrale e di melatonina [2], tende a diminuire la latenza di sonno e ad aumentare la durata del sonno a onde lente [3], oltre a ridurre l'agitazione notturna [4].

5-idrossitriptofano (5HTP)

Derivato dal TRP, si trova in natura come estratto di Griffonia simplicifolia, diffusa principalmente nelle aree tropicali umide dell'Africa. È preferibile in ambito clinico al TRP per una serie di ragioni: attraversa direttamente la barriera emato-encefalica, si impegna esclusivamente nella sintesi della serotonina e non impegna la catena metabolica della chinurenina, ha una maggiore biodisponibilità ed è ottenuto da fonti vegetali mentre il TRP è prodotto dalla fermentazione batterica; pertanto, vi è una minore possibilità di contaminazione con rischio inferiore di sindrome eosinofilia-mialgia.

Prima del trattamento, la frequenza media di risvegli intrasonno era di 3,83 risvegli con un massimo di 10 risvegli per notte.

In 17/46 casi (**37%) si è riscontrata una riduzione dei risvegli pari al 100% o 75%;**

una **riduzione del 50% dei risvegli è stata rilevata in 17/46 casi (37%)**

non si è verificata nessuna variazione in 12/42 casi (26%)

Nessun bambino ha riportato effetti avversi



Es. la L-teanina, presente nel tè verde(Camellia sinensis) è un fitochimico che ha il potenziale per diventare un nutraceutico utile nel mitigare gli effetti dello stress

studio randomizzato, in doppio cieco, placebo controllato

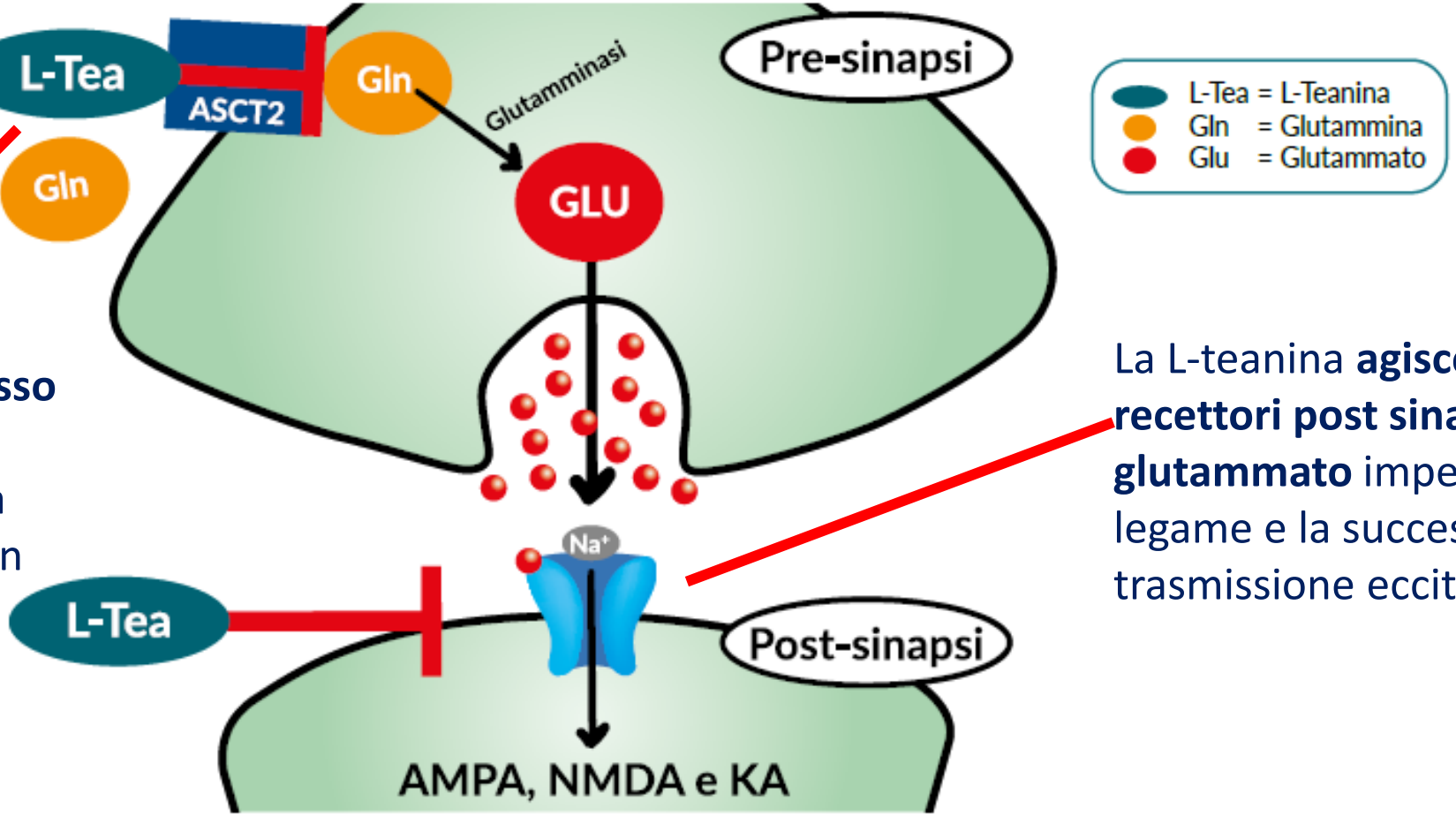
effetti di L-teanina somministrata per 4 settimane sui sintomi legati allo stress e sulle funzioni cognitive

Hidese S, Ogawa S, Ota M, et al. Effects of L-Theanine Administration on Stress-Related Symptoms and Cognitive Functions in Healthy Adults: A Randomized Controlled Trial. Nutrients. 2019

L-TEANINA: farmacocinetica e farmacodinamica

Meccanismo d'azione: riduzione attività eccitatoria del glutammato

La L-teanina **inibisce l' ingresso della glutammina (Gln)** nei neuroni. Questo sopprime la conversione di glutammina in glutammato (Glu)



La L-teanina **agisce sui recettori post sinaptici del glutammato** impedendo il legame e la successiva trasmissione eccitatoria.

T. Kakuda et al Neuroprotective effects of theanine and its preventive effects on cognitive dysfunction, Pharmacol. Res. 64 (2011) 162–16

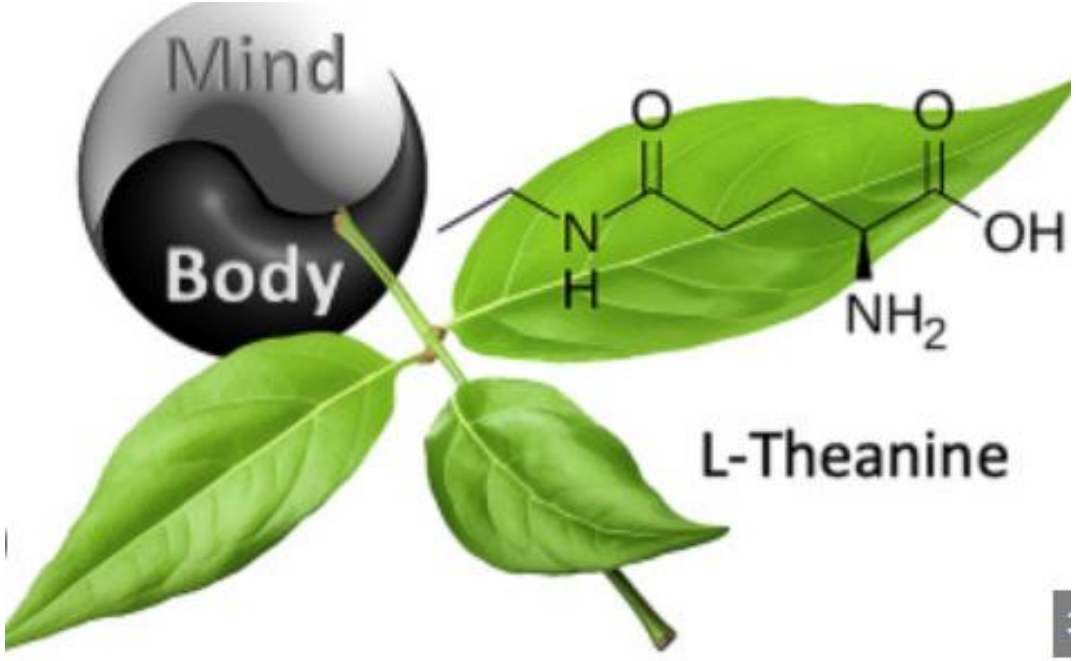
Sakamoto et al. Pharmacological research 147 (2019)

Bulman, A.; D'Cunha, N.; Marx,W.; Turner, M.; McKune, A.;Naumovski, N. The Effects of **L-Theanine Supplementation on Quality of Sleep: A Systematic Review**. Proceedings **2023**, 91, 32.

La maggior parte degli studi è stata condotta su adulti (n = 373), mentre due studi sono stati completati in bambini (n = 107).

Miglioramenti in diversi parametri del sonno (tutti i $p < 0,05$), tra cui:

-
- Latenza di insorgenza del sonno (7)
- Totale tempo di sonno (2)
- Durata del sonno (2)
- Efficienza del sonno (2)
- Qualità generale del sonno (5)
- Disfunzioni diurne (2)
- Risvegli precoci (1)
- sonnolenza mattutina (3)
- l'uso di farmaci per il sonno (1)
- Disturbi del sonno (4)



L-THE (50-655 mg) è efficace nel migliorare la qualità del sonno sia come integratore individuale che in combinazione con altri bioattivi.

L-THE a dosi superiori a 655 mg può non essere benefico e può essere dannoso per la qualità generale del sonno

The bioactive decaptide present in lactium™ was shown to have an affinity for $GABA_A$ receptors
It has a sequence homology with DBI (diazepam binding inhibitor, an endogenous ligand of $GABA_A$ receptors)

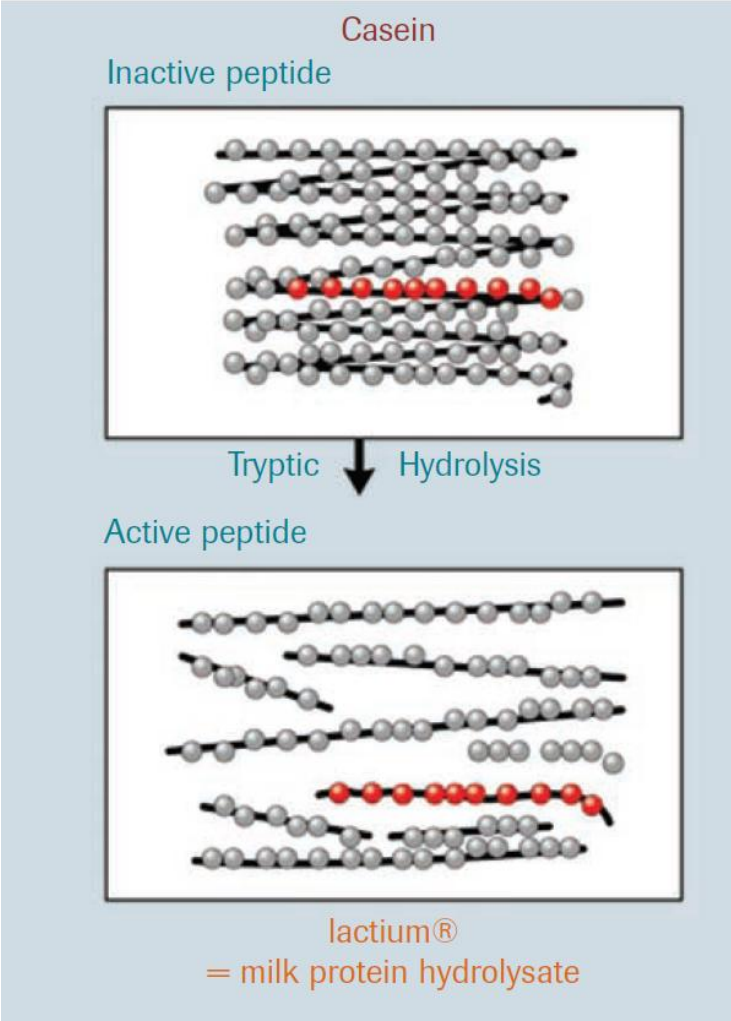
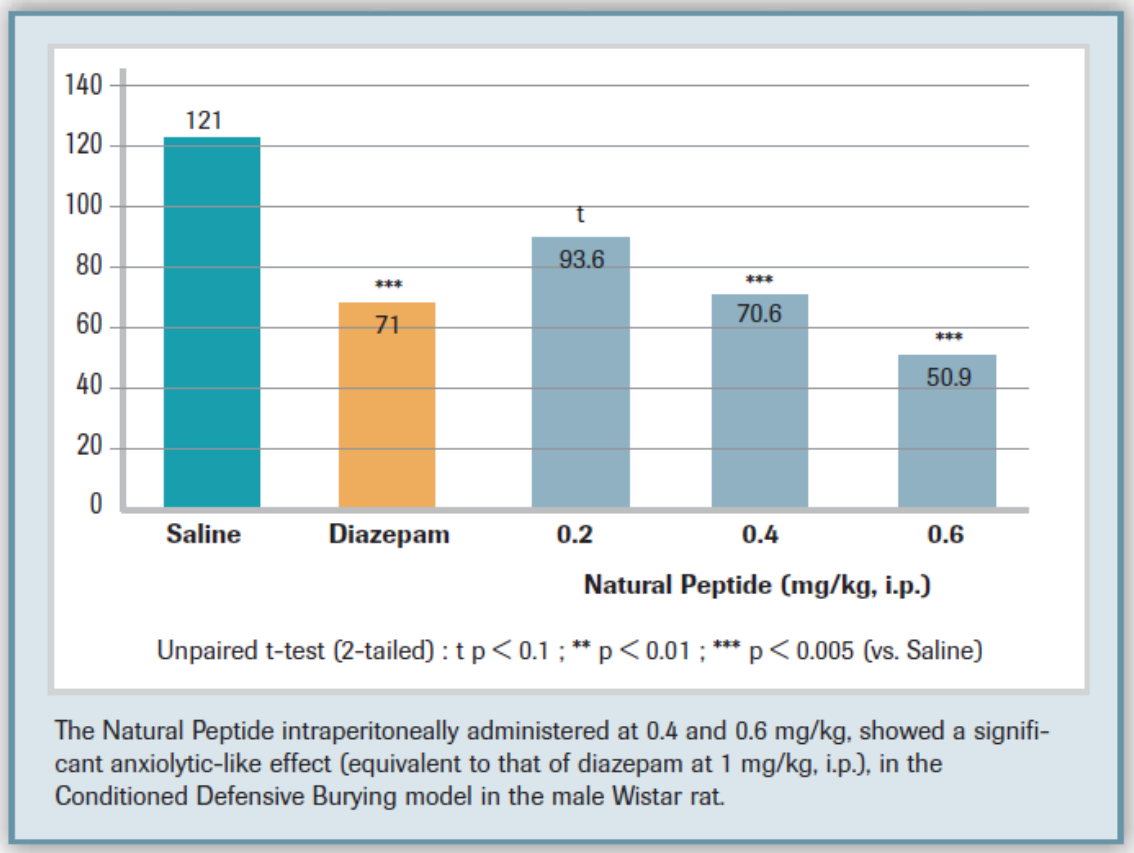


Figure 1 — **Anxiety Global**



The Natural Peptide intraperitoneally administered at 0.4 and 0.6 mg/kg, showed a significant anxiolytic-like effect (equivalent to that of diazepam at 1 mg/kg, i.p.), in the Conditioned Defensive Burying model in the male Wistar rat.

Global anxiety and latency are statistically lower in the treated groups compared to the placebo

Lim SE, Kim HS, Lee S, Kang EY, Lim J-H, Kim B-Y, Shin S-M and Baek Y (2024) Dietary supplementation with Lactium and L-theanine alleviates sleep disturbance in adults: a double-blind, randomized, placebo-controlled clinical study. *Front. Nutr.* 11:1419978.

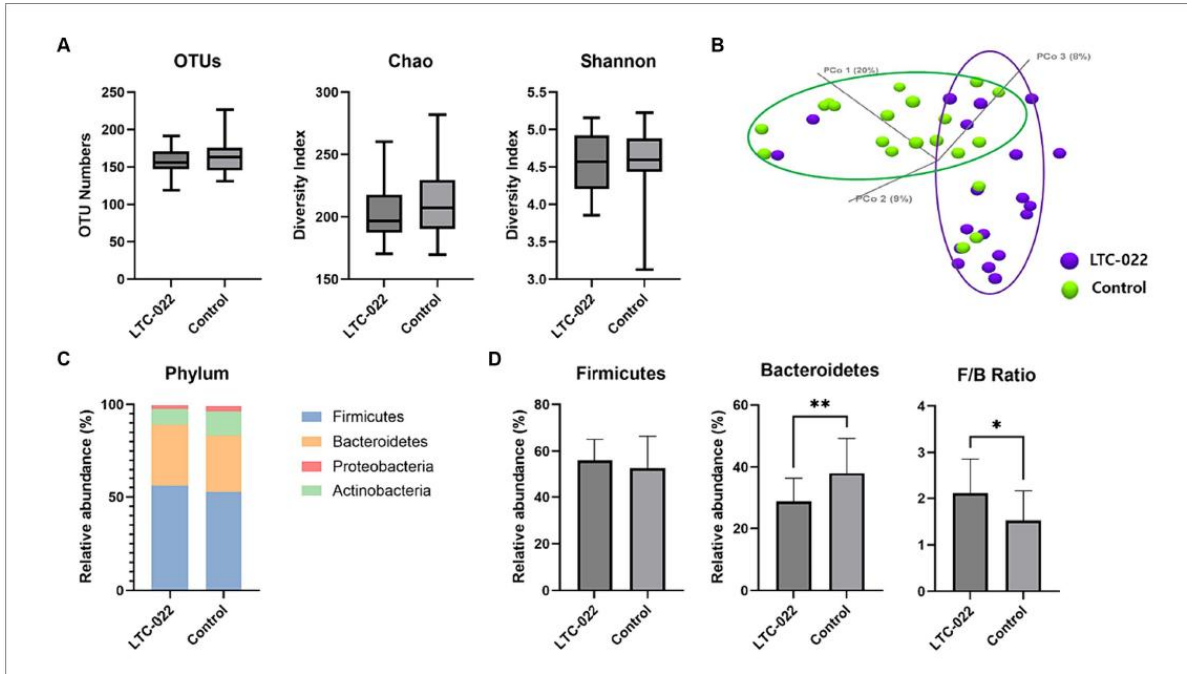
Variables	Weekday				Weekend			
	LTC-022	Control	*p*-value	p-interaction†	LTC-022	Control	*p*-value	p-interaction†
TIB (min)								
Baseline	456.70 (57.70)	455.35 (72.05)	0.949[a]	0.864	453.88 (57.50)	453.33 (73.77)	0.980[a]	0.656
Week 4	458.28 (47.64)	450.09 (76.19)	0.744[b]		476.27 (74.51)	474.72 (116.3)	0.839[b]	
Week 8	465.09 (55.82)	457.17 (112.63)	0.767[b]		482.88 (65.18)	462.29 (81.43)	0.345[b]	
TST (min)								
Baseline	392.40 (58.04)	400.39 (49.73)	0.648[a]	0.367	401.13 (52.49)	412.38 (56.38)	0.523[a]	0.300
Week 4	412.45 (45.41)*	397.70 (53.69)	0.143[b]		428.94 (82.58)	421.71 (86.08)	0.444[b]	
Week 8	419.75 (53.98)*	407.86 (80.42)	0.404[b]		443.25 (65.26)*	414.50 (59.31)	0.123[b]	
SOL (min)								
Baseline	64.30 (40.53)	54.96 (59.80)	0.570[a]	0.355	52.75 (41.97)	40.96 (52.29)	0.441[a]	0.359
Week 4	45.83 (31.84)*	52.39 (66.08)	0.135[b]		47.33 (41.30)	53.01 (69.36)	0.280[b]	
Week 8	45.34 (41.67)	49.30 (58.81)	0.499[b]		39.63 (34.78)	47.79 (58.65)	0.273[b]	
SE (%)								
Baseline	86.04 (8.58)	88.93 (10.27)	0.346[a]	0.222	88.75 (8.46)	91.72 (8.49)	0.281[a]	0.349
Week 4	90.14 (6.17)*	89.34 (10.32)	0.124[b]		89.91 (8.23)	90.21 (10.17)	0.528[b]	
Week 8	90.50 (8.06)*	90.56 (8.97)	0.527[b]		91.81 (6.51)	90.65 (10.09)	0.253[b]	
WASO (counts)								
Baseline	2.42 (1.49)	1.66 (0.74)	0.053[a]	0.007	1.95 (0.97)	1.89 (0.80)	0.824[a]	0.601
Week 4	1.62 (1.68)*	1.55 (0.71)	0.119[b]		1.50 (1.67)	1.79 (0.94)	0.499[b]	
Week 8	1.31 (1.83)*	1.63 (0.96)	**0.010**[b]		1.60 (2.55)	1.53 (0.99)	0.926[b]	
Bedtime (hh:mm)								
Baseline	24:33 (59.66)	24:22 (67.06)	0.605[a]	0.083	24:43 (53.01)	24:28 (85.43)	0.524[a]	0.193
Week 4	24:06 (48.32)*	24:25 (66.72)	**0.021**[b]		24:20 (66.33)	24:25 (84.43)	0.503[b]	
Week 8	24:01 (56.44)*	24:25 (68.58)	0.090[b]		24:01 (62.02)*	24:29 (66.34)	0.055[b]	

No significant differences were observed in sleep quality and insomnia scale characteristics between the LTC-022 and control groups but in the LTC-022 group significant differences were observed in the increase in TST, decrease in SOL, increase in SE, decrease in WASO counts, and earlier bedtime.

continuous LTC-022 intake has a beneficial effect on maintaining sleep duration and an appropriate bedtime.

Additionally, changes in the gut microbiota may be linked to changes in sleep patterns resulting from the consumption of Lactium and L-theanine

Microbiome analysis revealed that the abundance of the genera Blautia and Ruminococcus increased in fecal samples from the LTC-022 group



Arab A, Rafie N, Amani R, Shirani F. The Role of Magnesium in Sleep Health: a Systematic Review of Available Literature. Biol Trace Elem Res. 2023 Jan;201(1):121-128..

systematic review (7,582 subjects from 9 published cross-sectional, cohort and RCT) to assess the association between Mg and sleep patterns



magnesium improves status and sleep quality (daytime falling asleep, sleepiness, snoring, and sleep duration) according to the **observational studies**

While…

the **randomized clinical trials** showed an **uncertain association** between magnesium supplementation and sleep disorders

McWilliams, S.; Hill, O.; Ipsiroglu, O.S.; Clemens, S.;Weber, A.M.; Chen, M.; Connor, J.; Felt, B.T.; Manconi, M.; Mattman, A.; et al. **Iron Deficiency and Sleep/Wake Behaviors: A Scoping Review of Clinical Practice Guidelines**—How to Overcome the Current Conundrum? Nutrients **2024**, 16, 2559.

Effects of Central Iron Deficiency

	Upregulated	Downregulated
	Cytosolic transferrin Striatal transferrin receptors Striatal dopamine levels Striatal D1 receptor levels Tyrosine hydroxylase levels	Ventral midbrain iron Nucleus accumbens iron Striatal D2 receptor levels Striatal A1 receptor levels REM sleep Sleep onset
	Transferrin levels D1 receptor levels Spinal cord excitability Motor activity	Iron levels

L'ID può essere associato a pattern di movimento alterati

La carenza di ferro (ID) svolge un ruolo chiave nella patogenesi di condizioni che si manifestano con iperattività come il disturbo da deficit di attenzione e iperattività (ADHD) e la sindrome delle gambe senza riposo (RLS).

- La ferritina è il biomarcatore più citato
- Le raccomandazioni relative ai biomarcatori misurabili del ferro e ai cutoff variano tra le linee guida;
- la maggior parte delle linee guida sull'ID non include i disturbi associati all'ID, l'ADHD e la RLS.



Quale classe di farmaci per Francesco……?

iperattività/impulsività

disregolazione emozionale

aggressività/isolamento

depersonalizzazione
e derealizzazione

ideazione suicidaria

insonnia

tic

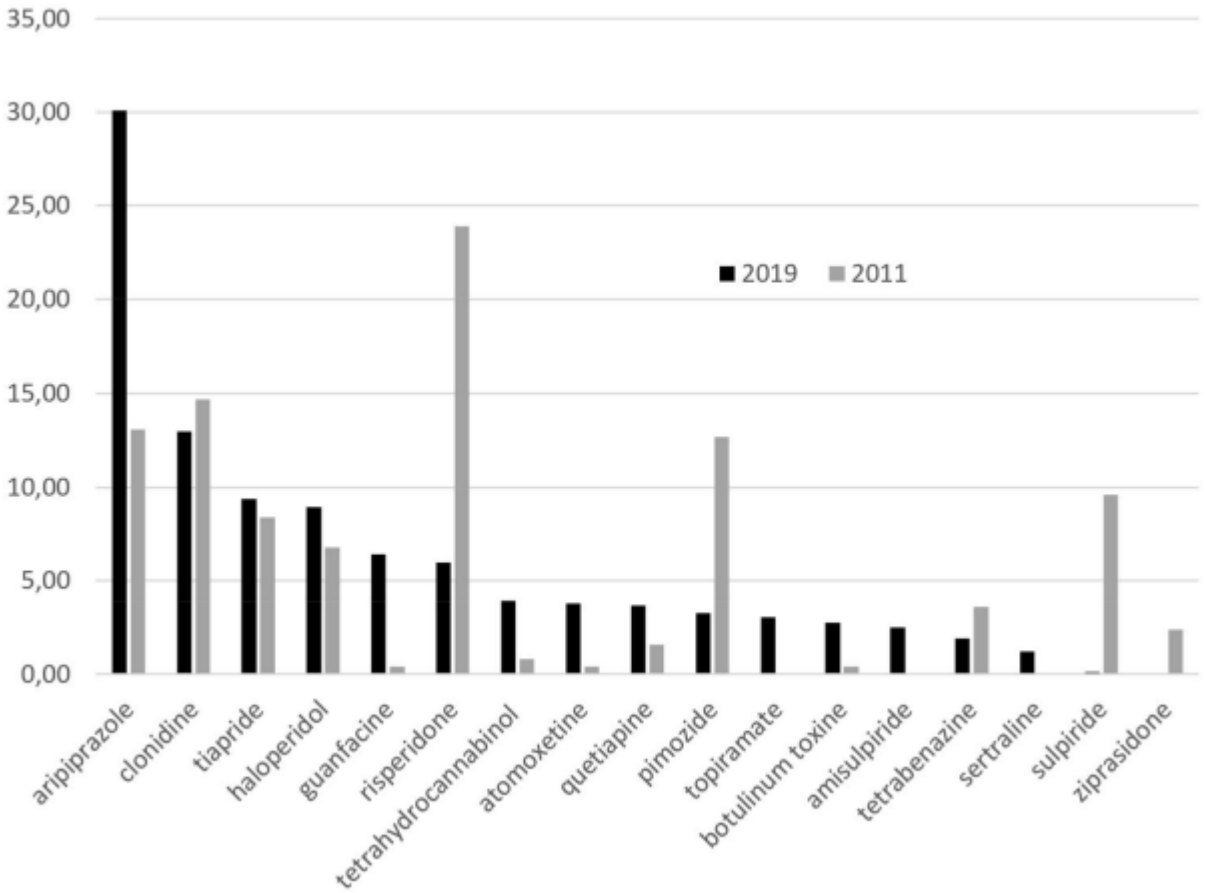
European Child & Adolescent Psychiatry (2022) 31:425–441
https://doi.org/10.1007/s00787-021-01899-z

REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part III: pharmacological treatment

Veit Roessner[1] · Heike Eichele[2,3] · Jeremy S. Stern[4] · Liselotte Skov[5] · Renata Rizzo[6] · Nanette Mol Debes[5] · Péter Nagy[7] · Andrea E. Cavanna[8] · Cristiano Termine[9] · Christos Ganos[10] · Alexander Münchau[11] · Natalia Szejko[12,13,14] · Danielle Cath[15] · Kirsten R. Müller-Vahl[16] · Cara Verdellen[17,18] · Andreas Hartmann[19,20] · Aribert Rothenberger[21] · Pieter J. Hoekstra[22] · Kerstin J. Plessen[23,24]

Received: 28 March 2021 / Accepted: 24 October 2021 / Published online: 10 November 2021
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The largest amount of evidence supports the use of dopamine blocking agents, **preferably aripiprazole because of a more favorable profle of adverse events** than frst- and second-generation antipsychotics.

Other agents that can be considered include **tiapride, risperidone, and especially in case of co-existing attention defcit hyperactivity disorder (ADHD), clonidine and guanfacine.**

This view is supported by the results of our survey on medication preference among members of ESSTS, in which aripiprazole was indicated as the drug of first choice both in children and adults

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In treatment resistant cases, treatment with agents with either a limited evidence base or risk of extrapyramidal adverse effects might be considered, including **pimozide, haloperidol, topiramate, cannabis-based agents, and botulinum toxin injections**

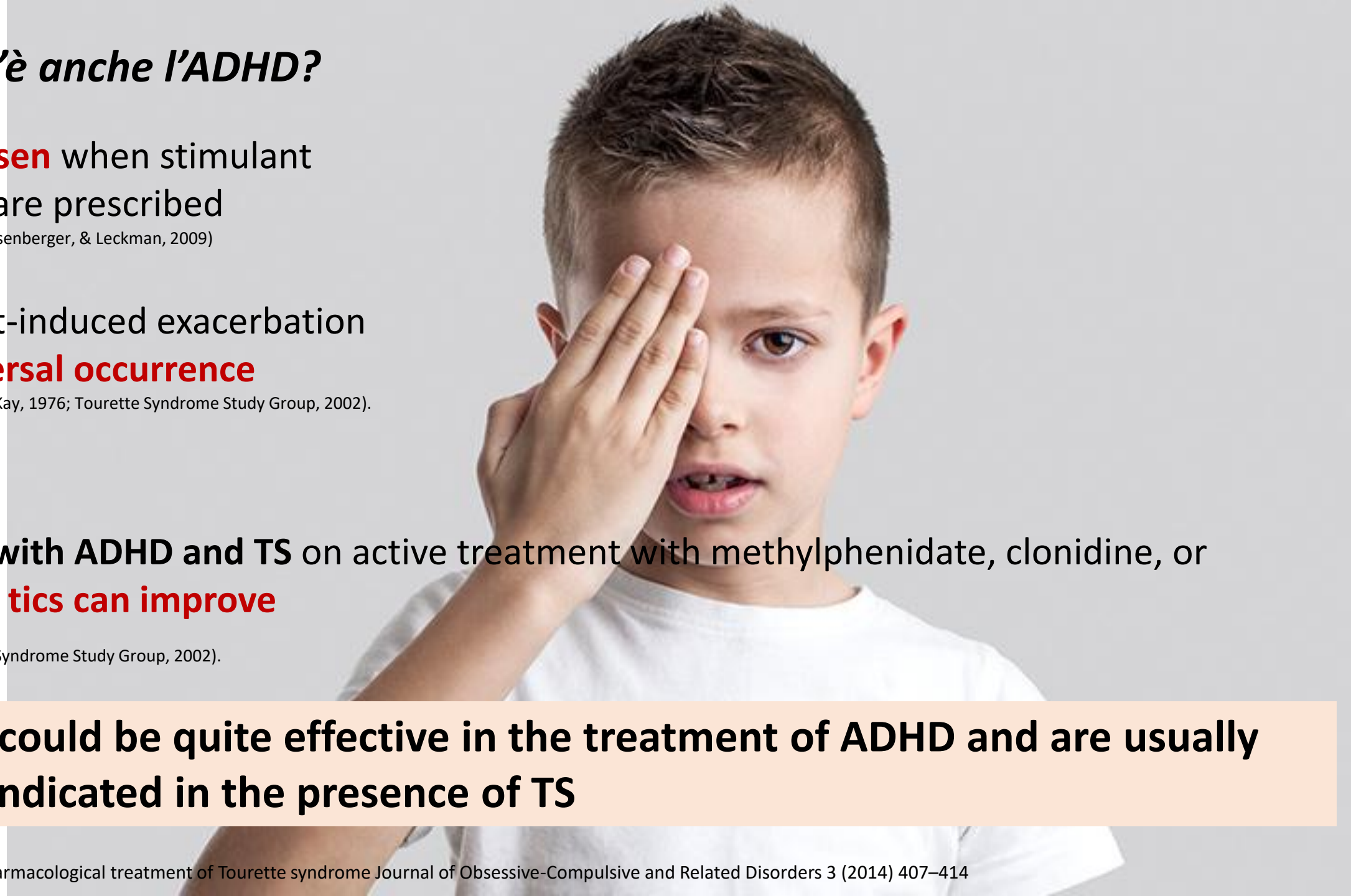
Table 2 Most common medications for Tourette syndrome and other chronic tic disorders

Medication	Indication	Start dosage (mg)	Therapeutic range per day (mg)	Effect size*	Confidence in the quality of the evidence**	Very common adverse events (> 10%)***	Physical and laboratory Examinations at the start and at follow-ups
α-2 adrenergic agonists							
Clonidine	ADHD/TS	0.025	0.025–0.3 (titrated according to BP and HR)	0.29 (0.12–0.47) [90]	Moderate	Dizziness, orthostatic hypotension, dry mouth	Blood pressure, ECG
First generation antipsychotics							
Haloperidol	TS	0.25–0.5	0.25–3.0	3.20 (0.14–6.52) [6]	Moderate	Agitation, insomnia, EPS, hyperkinesia, headache	ECG, weight
Pimozide	TS	0.5–1.0	1.0–4.0	0.42 (−0.07–0.90) [6]	Low	Dizziness, somnolence, hyperhidrosis, nocturia	ECG, weight
Newer antipsychotics							
Aripiprazole	TS	2.50	2.5–30	4.74 (1.06–8.67) [6]	Moderate	Somnolence, sedation	Weight, blood lipids, and glucose
Risperidone	TS/DBD	0.25	0.25–3.0	3.47 (0.37–6.87) [6]	Moderate	Insomnia, sedation/somnolence, parkinsonism, headache	Weight, prolactin, blood lipids, and glucose
Benzamides							
Tiapride	TS	50–100 (2 mg/kg)	100–600 (2–10 mg/kg)	0.47 (−3.89–5.06) [6]	Moderate	Hyperprolactinemia*, sleepiness, insomnia, agitation, impassivity, vertigo, headache	ECG, weight, prolactin
Others							
Botulinum toxin	TS	Vocal tics: 1–2.5 U Motor tics: 50–75 U	1–2.5 75–250	1.27 (0.51–2.03) [4]	Moderate	Weakness of the injected muscles	

E quando c'è anche l'ADHD?

tics may worsen when stimulant medications are prescribed
(Bloch, Panza, Landeros-Weisenberger, & Leckman, 2009)

this stimulant-induced exacerbation
is not a universal occurrence
(Denckla, Bemporad, & MacKay, 1976; Tourette Syndrome Study Group, 2002).



For children with ADHD and TS on active treatment with methylphenidate, clonidine, or atomoxetine, **tics can improve**

(Allen et al., 2006; Tourette Syndrome Study Group, 2002).

stimulants could be quite effective in the treatment of ADHD and are usually not contraindicated in the presence of TS

D.L. Gilbert, J. Jankovic Pharmacological treatment of Tourette syndrome Journal of Obsessive-Compulsive and Related Disorders 3 (2014) 407–414

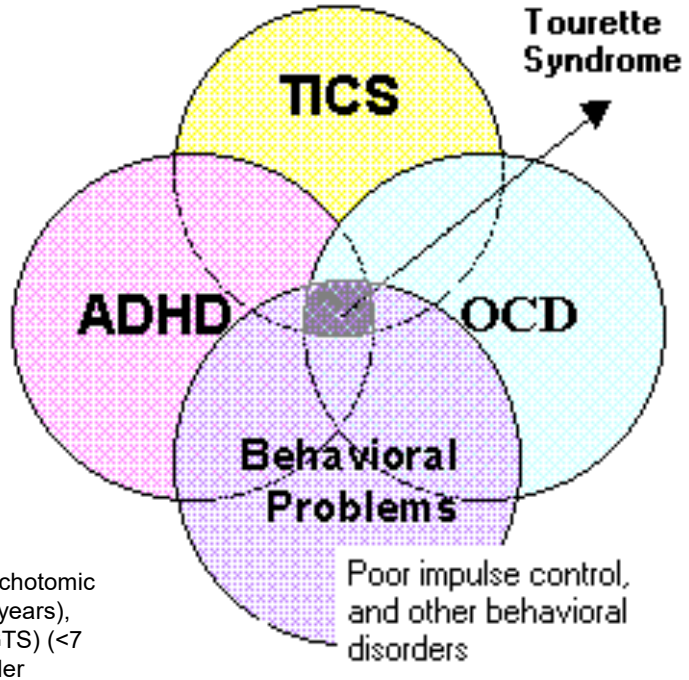
Masi G, Gagliano A, et al, J Child Adolesc Psychopharmacol. 2012 Apr

Aripiprazole in children with Tourette's disorder and co-morbid attention-deficit/hyperactivity disorder: a 12-week, open-label, preliminary study

Aripiprazole as a possible therapeutic option, addressing both tics/OCD and ADHD

aripiprazole resulted in

1. **very effective treatment for TD**
2. **moderately effective on co-occurring ADHD symptomatology**
3. **response of ADHD symptoms more likely in the OCD comorbid group**



Predictors	ADHD responders (improvement > 30% at the ADHD-RS) [1]			GTS responders (reduction > 50% at YGTSS) [2]				
	ODDS Ratio	95% C.I.		ODDS Ratio	95% C.I.		P[1]	P[2]
Age <11 vs >11	4.333	0.799	23.487	5.81	0.601	56.294	n.s.	n.s.
Age of onset of GTS (<7 vs >7 ys)	1.400	0.310	6.332	0.450	0.086	2.35	n.s.	n.s.
OCD Comorbidity *	8.333	1.344	51.671	2.14	0.428	10.738	<0.01	n.s.
Psychotherapy	0.333	0.065	1.707	0.728	0.146	3.654	n.s.	n.s

Logistic regression

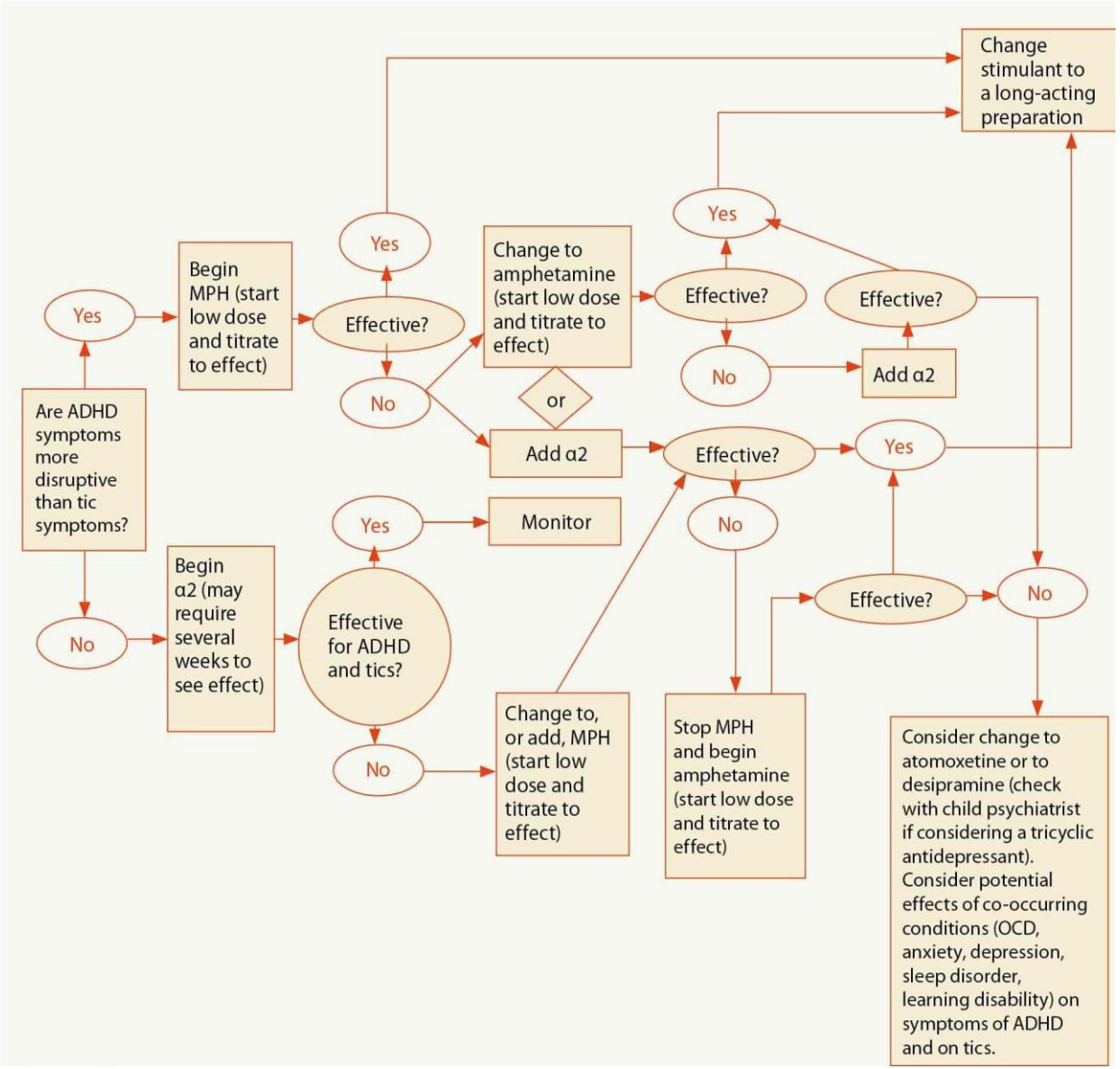
the odds ratio and 95% confidence interval of 4 dichotomic variables were assessed: Age (<11 years vs >11 years), age at onset of Gilles de la Tourette Syndrome (GTS) (<7 years vs >7 years), Obsessive Compulsive Disorder (OCD) Comorbidity, Psychotherapy (combined treatment).

The response of ADHD symptoms to treatment is more likely to occur in the OCD comorbid group

TABLE 3 Medications used in treating ADHD and co-occurring tics

	Medication		Starting dose	Maximum dose	Considerations
Stimulants	Methylphenidate		2.5-5 mg/d	60 mg/d	For children aged 6 y and older. Short- and long-acting preparations available. Common adverse effects include reduced appetite suppression, insomnia, headache, abdominal discomfort, and irritability.
	Dexmethylphenidate		2.5 mg/d	30 mg/d	Similar to methylphenidate.
	Amphetamine salts		2.5-5 mg/d	40 mg/d	For children aged 3 y and older. Short- and long-acting preparations available. Common adverse effects include reduced appetite suppression, insomnia, headache, abdominal discomfort, and irritability.
	Dextroamphetamine		2.5-5 mg/d	40 mg/d	Similar to amphetamine salts.
Nonstimulants	Clonidine	Weight <45 kg	0.025 mg/d	0.3 mg/d	For children aged 6 y and older. Sedation is a frequent adverse effect. May lower blood pressure and heart rate.
		Weight >45 kg	0.05 mg/d	0.3 mg/d	
	Guanfacine	Weight <45 kg	0.25 mg/d	3.5 mg/d	Similar to clonidine.
		Weight >45 kg	0.5 mg/d	4 mg/d	
			0.5 mg/kg/d	1.5 mg/kg/d or 100 mg/d (whichever is lower)	For children aged 6 y and older. Common adverse effects include sedation, gastrointestinal upset, and irritability.
		Aged 6-12 y	1 mg/kg/d	5 mg/kg/d	Consult psychiatry before administering. Caution using dosage >3 mg/kg/d.
		Adolescent	10 mg/d	150 mg/d	

From Bloch MH, et al[5]; Roessner V, et al[30]; Scahill L, et al.[31]



a beneficial outcome may be achieved with nonstimulants for ADHD, such as **atomoxetine**

- Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: treatment of ADHD in children with comorbid tic disorders. J Am Acad Child Adolesc Psychiatry. 2009;48(9):884-893.
- Roessner V, Becker A, Banaschewski T, Freeman RD, Rothenberger A; Tourette Syndrome International Database Consortium. Developmental psychopathology of children and adolescents with Tourette syndrome-impact of ADHD. Eur Child Adolesc Psychiatry. 2007;16(suppl 1):24-35. Erratum in: Eur Child Adolesc Psychiatry. 2007;16(8):536.
- Scahill L, Erenberg G, Berlin CM Jr, et al; Tourette Syndrome Association Medical Advisory Board; Practice Committee. Contemporary assessment and pharmacotherapy of Tourette syndrome. NeuroRx. 2006;3(2):192-206.â
- Pringsheim T, Steeves T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev. 2011;(4):CD007990.

E quando c’è un disturbo del neurosviluppo e anche un’epilessia?…

ADHD is the most common co-occurring disorder in children with epilepsy



30-40% of children with epilepsy have ADHD

2.5- 5.5 times higher than general population

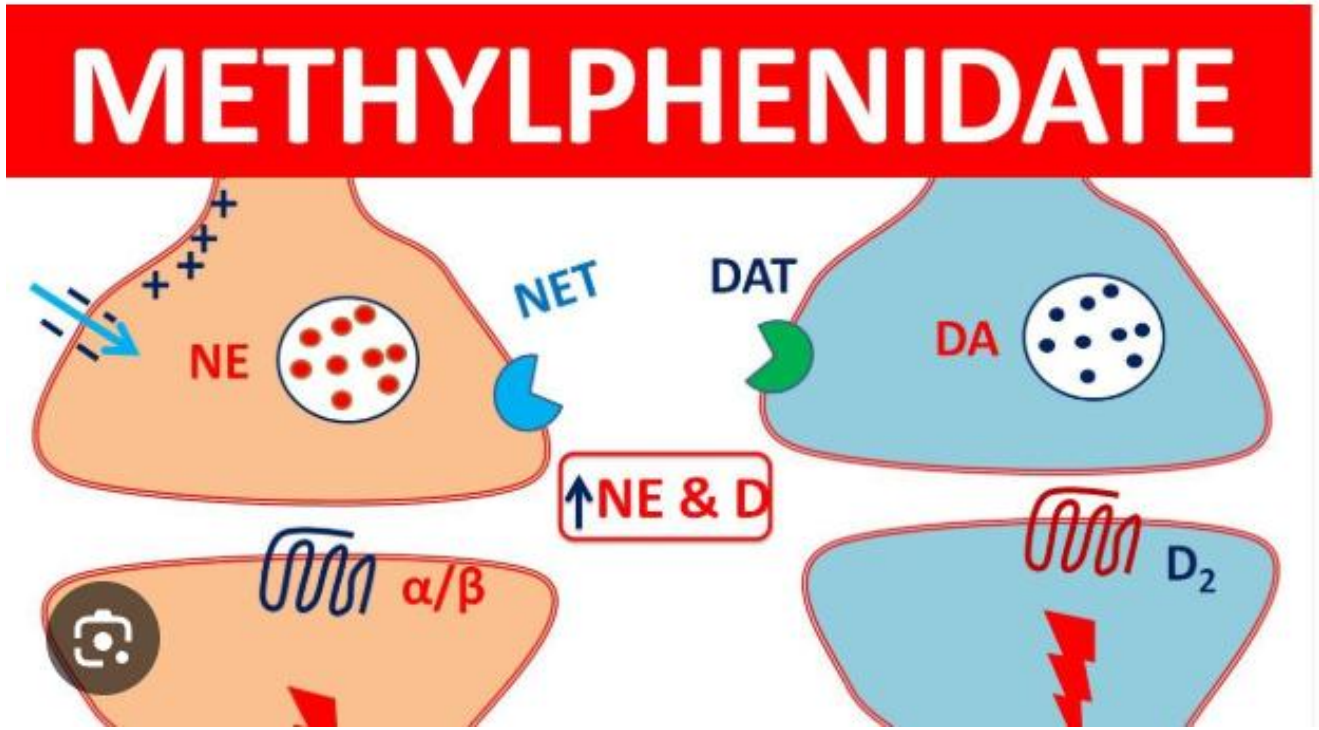
Highest risk of ADHD among epileptic children if have…

- other developmental delays
- intellectual disability
- poor seizure control

Dunn DW, Kronenberger WG. Childhood epilepsy, attention problems, and ADHD: review and practical considerations. Semin Pediatr Neurol. 2005 Dec;12(4):222-8.

Fan, H.-C.; Chiang, K.-L.; Chang, K.-H.; Chen, C.-M.; Tsai, J.-D. Epilepsy and Attention Deficit Hyperactivity Disorder: Connection, Chance, and Challenges. Int. J. Mol. Sci. 2023, 24, 5270.

Fan, H.-C.; Chiang, K.-L.; Chang, K.-H.; Chen, C.-M.; Tsai, J.-D. Epilepsy and ADHD: Connection, Chance, and Challenges. Int. J. Mol. Sci. 2023, 24, 5270.



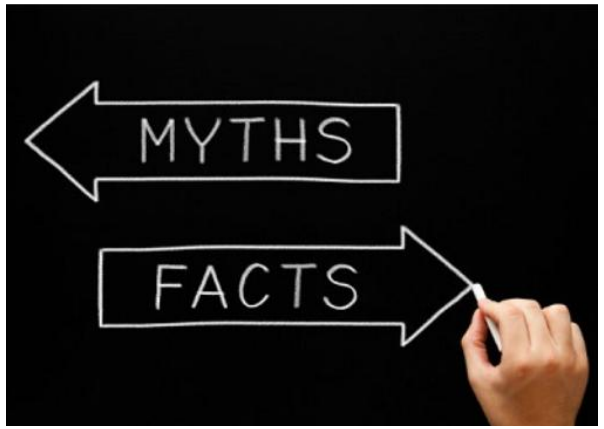
MPH achieved a response rate of 60–70% in CWE and comorbid ADHD

MPH **improves attention and memory, executive function, cognition, and the overall health-related quality of life**

The effect of MPH on cognition and memory is **dose-dependent**

The efficacy of stimulants is **also evident in patients with refractory epilepsy with a response rate of 63–73%**, even three months after treatment, regardless of the degree of learning disability

Górska N, Słupski J, Cubała WJ. Antipsychotic drugs in epilepsy. Neurol Neurochir Pol. 2019;53(6):408–12.



The False Myth of Increased Risk of Seizures with Stimulants

A retrospective study on **18,166 stimulant users** and 54,197 non-users in CWE, indicated **no difference in the risk of seizure**-related hospitalization between users and non-users

Liu, X.; Carney, P.R.; Bussing, R.; Segal, R.; Cottler, L.B.; Winterstein, A.G. Stimulants Do Not Increase the Risk of Seizure-Related Hospitalizations in Children with Epilepsy. J. Child Adolesc. Psychopharmacol. 2018, 28, 111–116.

a **review of seven prospective studies** concluded that **MPH does not increase the seizure frequency or incidence of new-onset seizures**

Ravi, M.; Ickowicz, A. Epilepsy, Attention-Deficit/Hyperactivity Disorder and Methylphenidate: Critical Examination of Guiding Evidence. J. Can. Acad. Child Adolesc. Psychiatry 2016, 25, 50–58

the evidence supports the safety of stimulants in CWE, but it is still limited by the small sample size and uncontrolled design

However…

…regulatory agencies indeed issued a caution for the use of stimulants in CWE and comorbid ADHD

www.fda.gov (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013 /010187s077lbl.pdf accessed on 2 March 2023 "Prescriber's Digital Reference", www.pdr.net (https://www.pdr.net/drug-summary/Ritalin-LA-methylphenidate-hydrochloride-1003 , accessed on 2 March 2023

The risk of seizure was also reported to be dose-dependent

Gonzalez-Heydrich, J.; Hsin, O.; Gumlak, S.; Kimball, K.; Rober, A.; Azeem, M.W.; Hickory, M.; Mrakotsky, C.; Torres, A.; Mezzacappa, E.; et al. Comparing stimulant effects in youth with ADHD symptoms and epilepsy. Epilepsy Behav. 2014, 36, 102–107.



Holmes GL. **Drug Treatment of Epilepsy Neuropsychiatric Comorbidities in Children**. Paediatr Drugs. 2021 Jan;23(1):55-73. doi: 10.1007/s40272-020-00428-w.

Despite the high efficacy of stimulants in ADHD, even in CWE, and in refractory epilepsy, many treating clinicians are reluctant to prescribe stimulants in CWE with comorbid ADHD due to the concern of the increased risk of seizure.



Drugs used to treat attention-deficit hyperactive disorder.

Drug	Mechanism of Action	Drugs	Adverse Effects	Effect on Seizure Susceptibility
Methylphenidate	DA and NA reuptake inhibitor	Methylphenidate Dexmethylphenidate	Appetite suppression Emotional lability Insomnia Psychotic symptoms	None
D,L-Amphetamine	DA and NA reuptake inhibitor Monoamine oxidase activity inhibition VMAT-2 inhibition	Amphetamine sulfate Dextroamphetamine Lisdexamfetamine	Appetite suppression Emotional lability Insomnia Psychotic symptoms	None
Atomoxetine	NA-reuptake inhibition Increases DA indirectly	Atomoxetine	Appetite suppression Nausea Drowsiness	None
Guanfacine	Selective α2-adrenergic agonists	Guanfacine	Drowsiness Dizziness Dry mouth Constipation Tiredness	None
Clonidine	Selective α2-adrenergic agonists	Clonidine	Constipation. Dizziness Drowsiness Dry mouth Weakness Irritability	None

DA dopaime; *NA* noradrenaline (norepinephrine)

Quale classe di farmaci per Francesco……?

Dice di sentirsi meglio se si fa le canne…

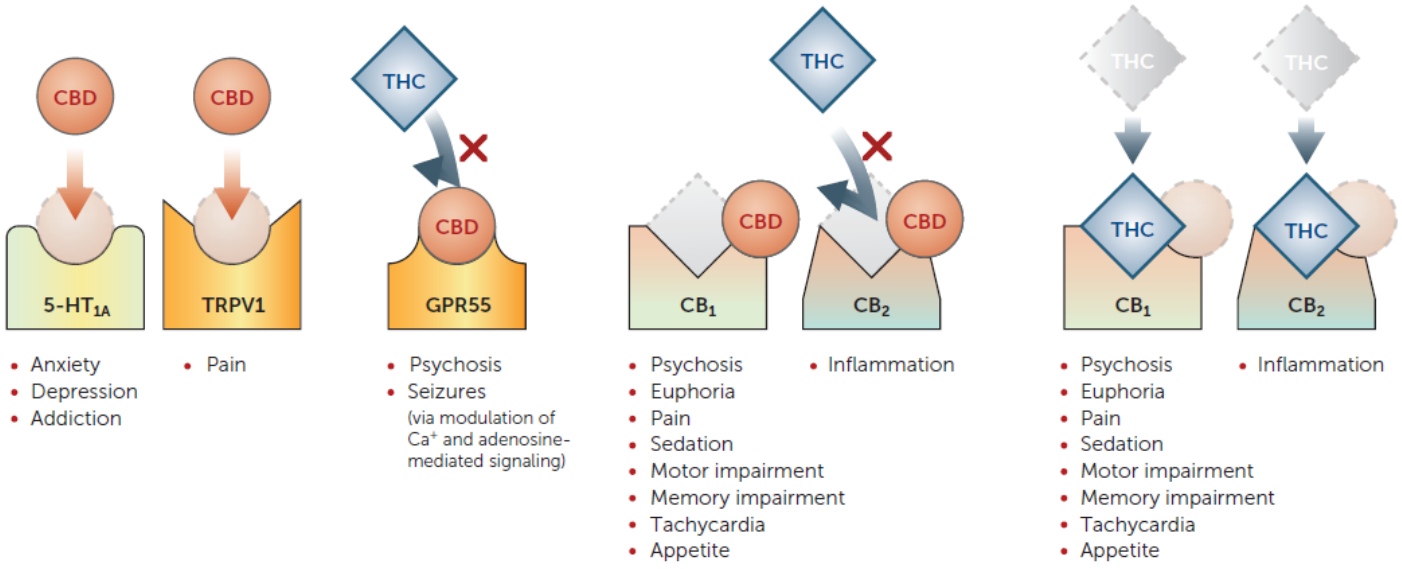


Am J Psychiatry 2022; 179:98–109; doi: 10.1176/appi.ajp.2021.21030320

Risks and Benefits of Cannabis and Cannabinoids in Psychiatry

Kevin P. Hill, M.D., M.H.S., Mark S. Gold, M.D., Charles B. Nemeroff, M.D., Ph.D., William McDonald, M.D., Adrienne Grzenda, M.D., Ph.D., Alik S. Widge, M.D., Ph.D., Carolyn Rodriguez, M.D., Ph.D., Nina V. Kraguljac, M.D., John H. Krystal, M.D., Linda L. Carpenter, M.D.

FIGURE 1. Cannabinoid interactions with receptors and neurotransmitter systems in human brain and proposed target symptoms and conditions[a]



Delta-9-tetrahydrocannabinol (THC), the plant's psychoactive constituent, is a **partial agonist at both CB1 and CB2**

It can cause

- euphoria
- psychosis
- cognitive dysfunction

It has analgesic and anti-inflammatory effects

The THC content in available cannabis preparations varies widely

Cannabidiol (CBD) is a **CB1 antagonist, a negative allosteric modulator at CB2**, and an agonist at the transient receptor potential cation channel subfamily V member 1 (TRPV1) and serotonin 1A (5-HT1A) receptors, with anxiolytic, antipsychotic, anticonvulsant, antioxidant, analgesic, and immunomodulatory functions, some of which may buffer the harmful effects of THC, such as psychosis.

CBD also functions as a G protein-coupled receptor (GPR55) antagonist and suppresses GPR55's activities. The GPR55-dependent mechanism is thought to play a major role in CBD's antipsychotic and antiepileptic activities



PASSPARTOUT ?

Two cannabinoids related to THC, **dronabinol and nabilone**, were approved by the FDA

A third cannabinoid, **CBD,** was approved by the FDA in 2018 **for two forms of pediatric epilepsy, and for seizures associated with tuberous sclerosis complex**

Beyond the FDA-approved…

…. the best evidence for the medical use of cannabinoids is in **chronic pain (including neuropathic pain)** and **muscle spasticity associated with multiple sclerosis**

TABLE 2. FDA-approved cannabinoids

Cannabinoid and Indication	Year Approved
Dronabinol	
Chemotherapy-induced nausea and vomiting	1985
Appetite stimulation in wasting conditions (e.g., HIV infection)	1992
Nabilone	
Chemotherapy-induced nausea and vomiting	1985
Cannabidiol	
Seizures associated with Dravet syndrome and Lennox-Gastaut syndrome	2018
Seizures associated with tuberous sclerosis complex	2020

Kevin et al, Risks and Benefits of Cannabis and Cannabinoids in Psychiatry, Am J Psychiatry 2022; 179:98–109; doi: 10.1176/appi.ajp.2021.21030320

Cannabinoids for the Treatment of Psychiatric Disorders
(anxiety, depression, PTSD, psychosis, ADHD, and Tourette's syndrome)

The available evidence* describes **limited efficacy of cannabinoids in treating anxiety disorders in patients with co-occurring medical conditions**

* They are limited by lack of high-quality randomized controlled trials, small sample sizes, and lack of standardization across trials.

No clear evidence exists supporting cannabinoid pharmacotherapy for the other psychiatric indications

Black N, Stockings E, Campbell G, et al: Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry 2019; 6:995–1010

Most CBD is obtained without a prescription, in products that are unregulated with regard to purity, potency, and accuracy of labeling

Bonn-Miller MO, Loflin MJE, Thomas BF, et al: Labeling accuracy of cannabidiol extracts sold online. JAMA 2017; 318:1708–1709

Randomized controlled trials examining the **effectiveness of CBD in psychosis** have produced mixed results...



One trial showed that 800 mg/day of CBD for 4 weeks was as effective as **amisulpride** in treating both positive and negative symptoms of schizophrenia and had fewer associated side effects

Leweke FM, Piomelli D, Pahlisch F, et al: Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Transl Psychiatry 2012; 2:e94

Another trial, comparing 1000 mg/day of CBD for 6 weeks to placebo as **adjunctive pharmacotherapy for schizophrenia**, demonstrated a significant improvement in positive symptoms, without any difference in adverse effect compared with placebo

McGuire P, Robson P, Cubala WJ, et al: Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry 2018; 175: 225–231

However, in another trial comparing 600 mg/day of CBD for 6 weeks to placebo as **adjunctive pharmacotherapy** for schizophrenia, CBD **did not produce any significant change in positive symptoms or cognition**.

Boggs DL, Surti T, et al: The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia: a randomized placebo controlled trial. Psychopharmacology (Berl) 2018; 235:1923–1932

The literature on CBD is nascent

While CBD appears to have a more favorable risk profile than THC, high daily doses of CBD (1500 mg/day) caused an important **transaminase elevations**

CBD has a number of **interactions** with medications commonly prescribed to psychiatric patients.

It interacts with

- antiepileptic drugs
- antidepressants
- opioid analgesics
- acetaminophen
- alcohol

CBD increases the level or effect of lorazepam

Balachandran P, Elsohly M, Hill KP: Cannabidiol interactions with medications, illicit substances, and alcohol: a comprehensive review. J Gen Intern Med 2021; 36:2074–2084

Watkins PB, Church RJ, Li J, Knappertz V: Cannabidiol and abnormal liver chemistries in healthy adults: results of a phase I clinical trial. Clinical Pharm Ther 2021; 109:1224–1231

Quale classe di farmaci per Alessia……?



Sono tanto triste…

…e ho paura di tutto,
anche della paura!

La depressione ha caratteristiche diverse nei bambini e negli adolescenti rispetto agli adulti



Rice F, Riglin L, Lomax T, Souter E, Potter R, Smith DJ, Thapar AK, Thapar A. Adolescent and adult differences in major depression symptom profiles. J Affect Disord. 2019 Jan 15;243:175-181.

Depression is the leading global cause of disability and **often begins in adolescence**.

The genetic architecture and treatment response profiles for adults and adolescents differ even though identical criteria are used to diagnose depression across different age groups.

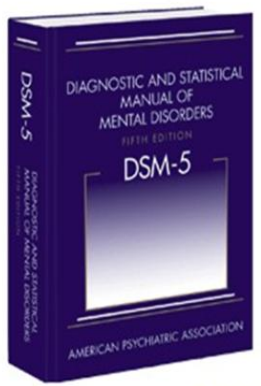
Anhedonia/loss of interest and concentration problems were more common in adults with MDD



Vegetative symptoms (appetite and weight change, loss of energy and insomnia) were more common in adolescent MDD

a **vegetative symptom profile** was seen in adolescent depression only (latent class analysis)

disruptive mood dysregulation disorder" (DMDD)



DSM-5
2013

Disturbi Depressivi

Disturbo da disregolazione dell'umore dirompente
Disturbo Depressivo Maggiore
Disturbo Depressivo persistente (distimia)

DISTURBO DEPRESSIVO PERSISTENTE

(in precedenza Disturbo Distimico)

- meno intenso del Disturbo Depressivo Maggiore, ma cronico e pervasivo
- esordio più precoce, lunga durata (fino 3-4 anni)
- **impatto più elevato in età evolutiva** (personalità in formazione)
- porta di ingresso verso altri disturbi dell'umore

Episodi acuti (Depressione Doppia)

maggiore gravità e compromissione funzionale

In children and adolescents, mood can be irritable and duration must be at least 1 year





Core feature

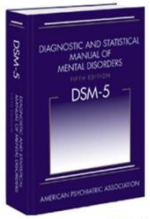
chronic, severe, persistent irritability

2 prominent clinical manifestations

Temper outbursts
(in response to frustration)

Severe irritability
(chronic, persistently, irritable or angry mood that is present between the severe temper outbursts)

Disturbo da disregolazione dell'umore dirompente



DSM-5 2013

A. **Gravi e ricorrenti scoppi di collera** manifestati verbalmente e/o in modo comportamentale che sono grossolanamente sproporzionati nell'intensità o nella durata alla situazione o alla provocazione

B. Gli scoppi di collera non sono coerenti con lo stadio di sviluppo

C. Gli scoppi di collera si verificano, in media, tre o più volte la settimana

D. **L'umore tra uno scoppio di collera e l'altro è persistentemente irritabile o arrabbiato** per la maggior parte della giornata, quasi tutti i giorni, ed è osservabile da parte di altri

E. I criteri A-D sono stati presenti per 12 mesi o più. Durante tale periodo, l'individuo non ha avuto un periodo della durata di 3 mesi o più consecutivi senza tutti i sintomi dei criteri A-D

F. I criteri A e D sono presenti **in almeno due contesti** (casa, scuola, coetanei) e sono gravi in almeno uno di questi

G**. La diagnosi non dovrebbe essere posta per la prima volta prima dei 6 anni o dopo i 18 anni di età**

H. Dall'anamnesi o dall'osservazione, **l'età di esordio dei criteri A-E è prima dei 10 anni**

I. Non vi è mai stato un periodo distinto della durata di più di un giorno durante il quale sono stati soddisfatti i criteri sintomatologici completi, a eccezione della durata, per un episodio maniacale o ipomaniacale

J. Esclusione DDM e altri disturbi mentali

K. Esclusione sostanze e condizione medica generale

il tratto distintivo più forte appare l'irritabilità



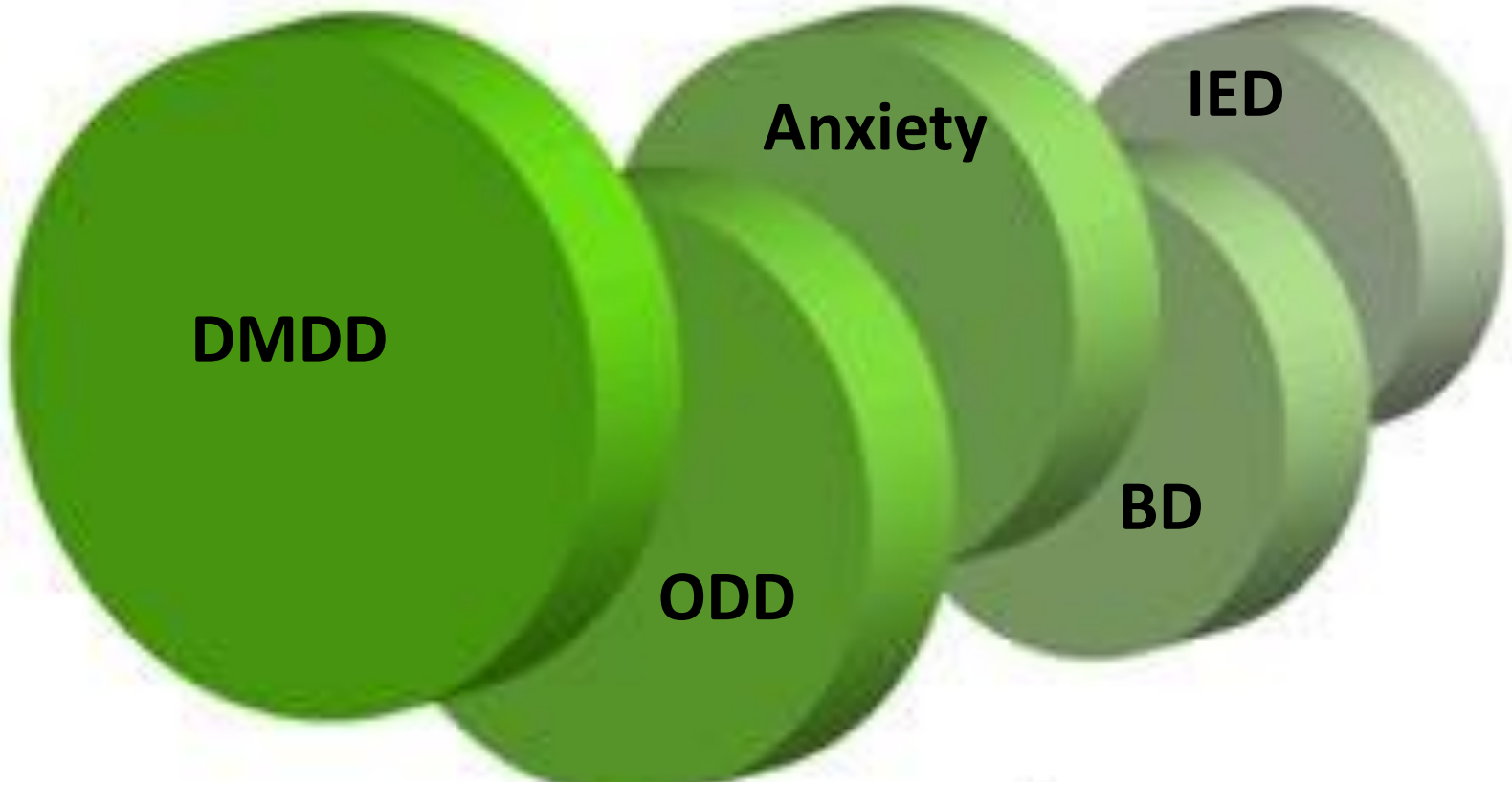
Ma…

Una significativa percentuale di bambini con esplosioni di collera e umore irritabile non incontra i criteri per DMDD

Copeland WE, Angold A, Costello EJ, Egger H. Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. Am J Psychiatry. 2013;170(2):173–179.

DMDD may overlap with other psychiatric disorders, most commonly disruptive behavior disorders, anxiety and mood disorders

ODD= Oppositional Defiant Disorder
BD= Bipolar Disorder
IED=intermittent explosive disorder

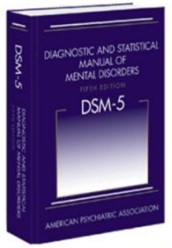


Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. Am J Psychiatry. 2011; 168(2):129–142.
Axelson D, Findling RL, Fristad MA, et al. Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. J Clin Psychiatry. 2012;73(10):1342–1350.
Roy AK, Klein RG, Angelosante A, et al. Clinical features of young children referred for impairing temper outbursts. J Child Adolesc Psychopharmacol. 2013;23(9):588–596.



I bambini DMDD sviluppano in età adolescenziale e adulta disturbi depressivi unipolari o disturbi d’ansia piuttosto che disturbi dirompenti o bipolarismo

DIAGNOSI DIFFERENZIALE



DSM-5
2013

Disturbo Bipolare (BD)

Il DMDD è un disturbo continuo e non episodico come il BD
(un criterio per fare diagnosi di DB è il cambiamento evidente rispetto allo stato basale)

Nella Mania si descrivono umore espanso e grandiosità, assenti nel DMDD

Table 1

Differences between DMDD and bipolar disorder

Factor	DMDD	Bipolar disorder
Irritability	Severe, chronic	Episodic
Age of onset	Before age 18	Can be diagnosed at any age, but typical onset in young adults
Psychotic symptoms	Rare	Can be present
Comorbidity	Depression, ADHD	
Prognosis	Chronic irritability, depression	Chronic
Specific symptoms	Temper outbursts	Grandiosity, increased risk-taking behaviors (eg, sex or overspending), decreased need for sleep

ADHD: attention-deficit/hyperactivity disorder; DMDD: disruptive mood dysregulation disorder

Source: References 11-13

MAJOR DEPRESSION COURSE

High rate (33%) of later emergence of mania in children and adolescents with pre-puberal MDD



A major depressive episode can be the first manifestation of bipolarity in youth

FREQUENZA DEL DISTURBO BIPOLARE 10 ANNI DOPO LA DEPRESSIONE PREPUBERALE

Geller et al. *Am J Psychiatry*. 2001;158:125-7.

	Depressione prepuberale (n = 72)	Controlli normali (n = 28)	*P* Value
Bipolare I o II	48.6%	7.1%	.0001
Bipolare I	33.3%	0	.001
Bipolare II	15.3%	7.1%	.34

La presenza di mania in un genitore o in un nonno è un fattore predittivo di evoluzione bipolare *(P*=0.02)

Indicatori di bipolarità nascosta ("hidden bipolarity") nella depressione adolescenziale

- Familiarità per disturbo bipolare (alcolismo, suicidio)
- Esordio precoce (prepuberale) di depressione
- Episodica irritabilità ed aggressività, elevata energia
- Alterazioni combinate di disturbi di umore - energia
- **Depressione psicotica, atipica, ricorrente**
- Destabilizzazione da antidepressivi

farmacoterapia



AACAP Guidelines, Walter et al, 2020

AACAP OFFICIAL ACTION

Check for updates

Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders

Heather J. Walter, MD, MPH, Oscar G. Bukstein, MD, MPH, A. Reese Abright, MD,
Helene Keable, MD, Ujjwal Ramtekkar, MD, MPE, MBA,
Jane Ripperger-Suhler, MD, Carol Rockhill, MD, PhD, MPH

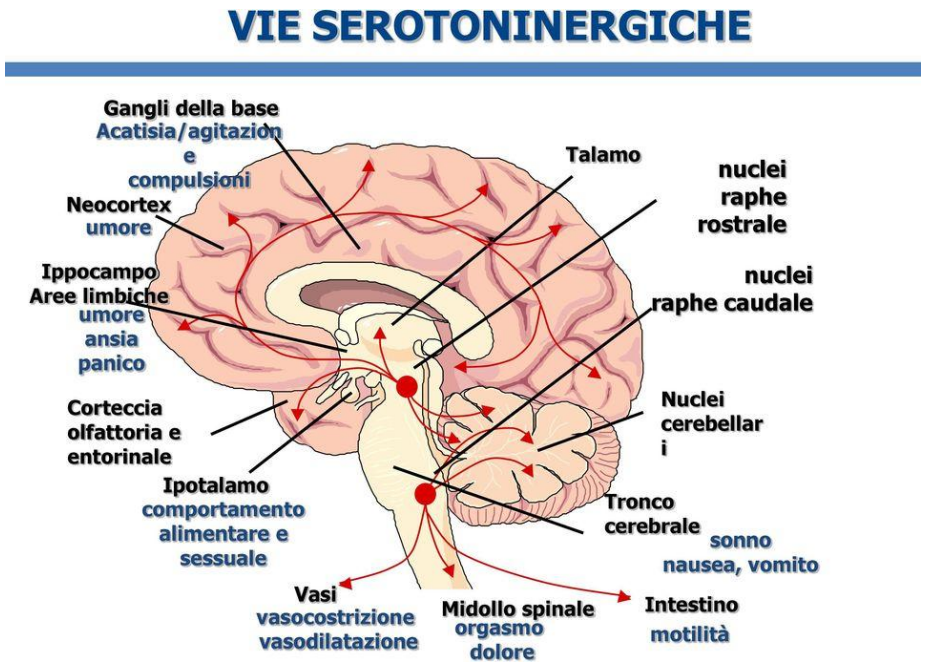
Anxiety disorders are among the most common psychiatric disorders in children and adolescents. As reviewed in this guideline, both cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) medication have considerable empirical support as safe and effective short-term treatments for anxiety in children and adolescents. Serotonin norepinephrine reuptake inhibitor (SNRI) medication has some empirical support as an additional treatment option. In the context of a protracted severe shortage of child and adolescent–trained behavioral health specialists, research demonstrating convenient, efficient, cost-effective, and user-friendly delivery mechanisms for safe and effective treatments for child and adolescent anxiety disorders is an urgent priority. The comparative effectiveness of anxiety treatments, delineation of mediators and moderators of effective anxiety treatments, long-term effects of SSRI and SNRI use in children and adolescents, and additional evaluation of the degree of suicide risk associated with SSRIs and SNRIs remain other key research needs.

Key Words: clinical practice guideline, anxiety, child psychiatry, assessment, treatment

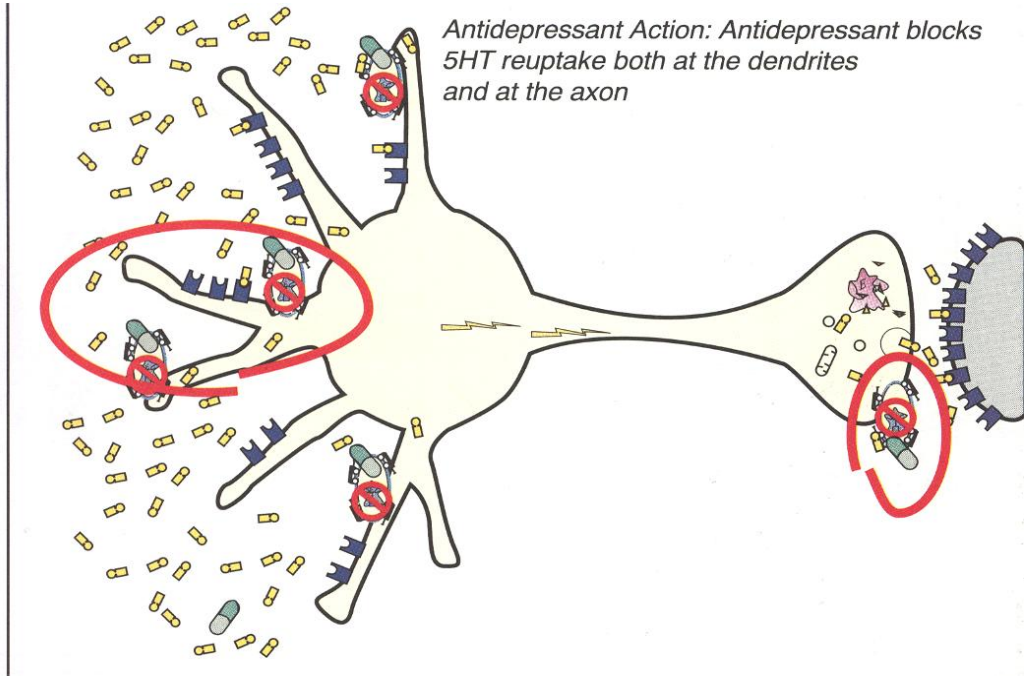
J Am Acad Child Adolesc Psychiatry 2020;59(10):1107–1124. CME

Compared to pill placebo, SSRIs as a class improved primary anxiety symptoms (parent and clinician report), response to treatment, and remission of disorder, as well as global function

Serotonergic function plays a key role in the ability of the brain to modulate fear, worry, and stress as well as to facilitate cognitive processing of those emotions.



SSRI:
potenziamento delle vie serotonergiche a partenza dal rafe



Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety. 2000;12(Suppl 1):2-19.

SSRI

Effetti clinici: potenziamento di **tutte** le vie serotoninergiche

- Rafe-lobi frontali: **effetto antidepressivo**
- Rafe-lobo limbico ed ippocampo: **effetto anti ansia-panico**
- Rafe-nuclei della base: **effetto anti- ossessivo-compulsivo**
- Rafe-ipotalamo: **effetto antibulimico e condotte binge-eating**

fluoxetina, paroxetina, sertralina, fluvoxamina, citalopram, escitalopram.

- Assenza di effetti anticolinergici
- **Assenza di cardiotossicità**
- Minimo incremento ponderale
- **Pochi sintomi da sospensione**
- **Assenza di letalità in overdose**
- Ampio spettro di indicazioni

SSRI: Effetti collaterali

- Vie limbiche (5HT2A e C): ansia, agitazione
- Nuclei della base (5HT2A):acatisia, parkinsonismo
- Centri del sonno (5HT2A): ritmo sonno-veglia
- Vie spinali discendenti (5HT2A): **problemi sessuali** (anorgasmia, difficoltà di eiaculazione, ecc.)
- Ipotalamo-tronco (5HT3): **nausea, vomito**
- Tratto gastrointestinale (5HT3 e 4) : dolori, crampi, diarrea
- Centri mesocorticali (5HT2A): apatia, calo di libido

In genere non gravi e transitori **(eccetto sessuali)**

Tutti gli SSRIs have a boxed warning per l'ideazione e i comportamenti suicidari fino ai 24 anni

The pooled absolute rates for suicidal ideation across all antidepressant classes are **1%** for youths treated with an antidepressant and **0.2%** for youths treated with a placebo

The pooled risk difference is 0.7% (95% confidence interval 0.4% to 2%; p ¼ .21),

The **number needed to harm (NNH) is 143**

The **number needed to treat is 3**

Nonostante il basso e apparente rischio, una stretta sorveglianza per la suicidalità è raccomandata dall'FDA…

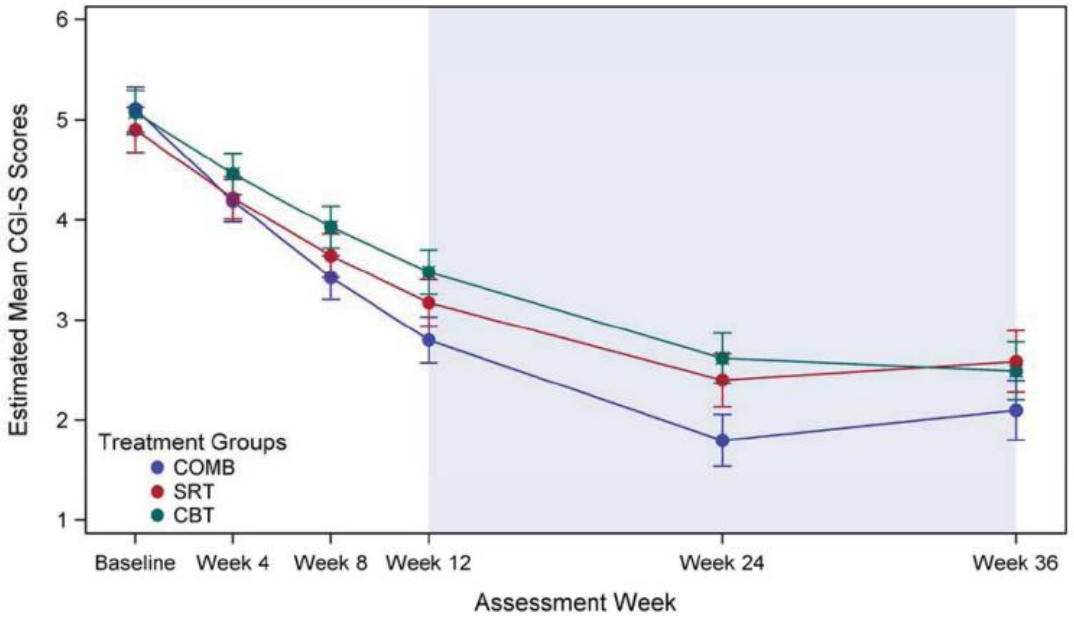
...specie nei primi mesi di trattamento e dopo ogni aggiustamento posologico

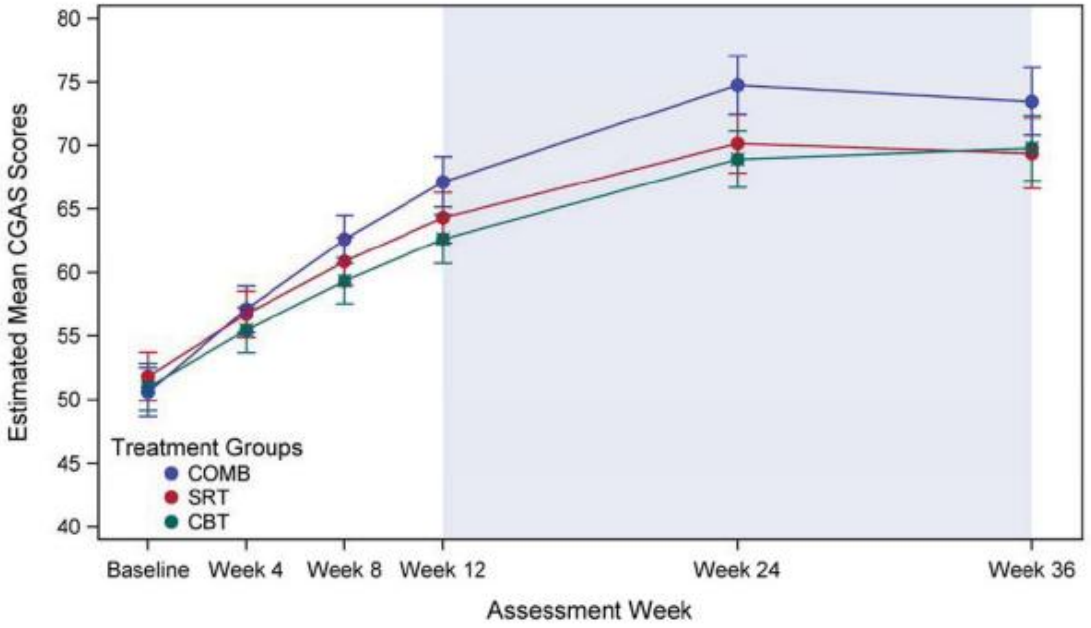
Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment. A meta-analysis of randomized controlled trials. JAMA. 2007;297:1683-1696.

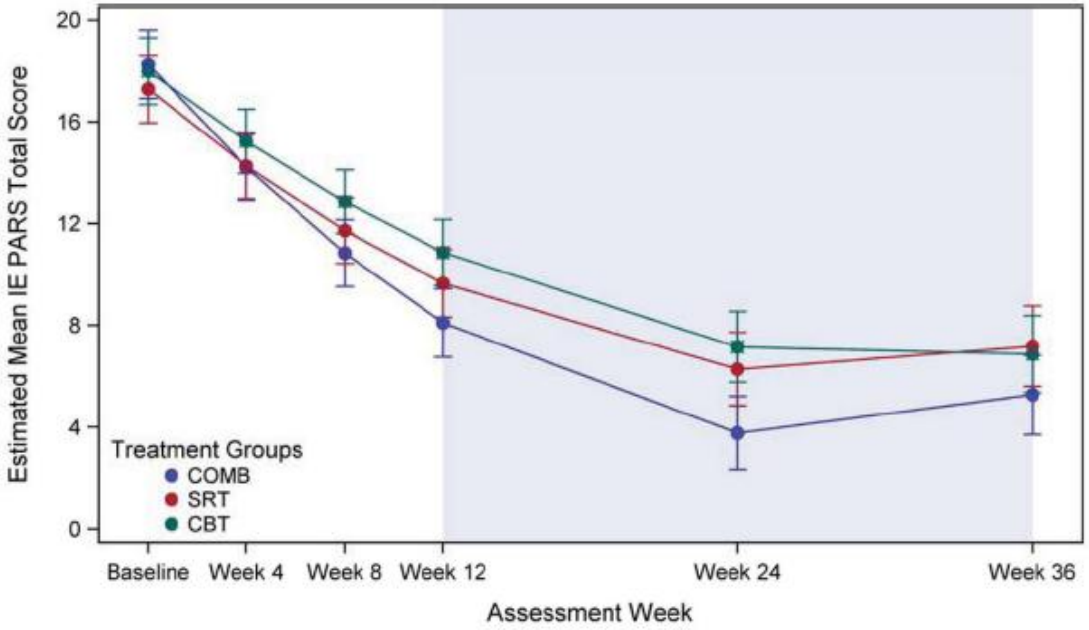
Studi di efficacia su CBT ed SSRI

Piacentini J, Bennett S, Compton SN, Kendall PC, Birmaher B, Albano AM, March J, Sherrill J, Sakolsky D, Ginsburg G, Rynn M, Bergman RL, Gosch E, Waslick B, Iyengar S, McCracken J, Walkup J. 24- and 36-week outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS). J Am Acad Child Adolesc Psychiatry. 2014 Mar;53(3):297-310. doi: 10.1016/j.jaac.2013.11.010.

Child/Adolescent Anxiety Multimodal Study (CAMS)
active treatment group differences on response and remission rates and changes in anxiety severity at weeks 24 and 36







COMB mantiene il vantaggio su CBT e SRT su alcune misure anche a 36 mesi mentre le due monoterapie rimangono indistinguibili

La tendenza a convergere di COMB e monoterapie può essere dovuta al largo uso di trattamenti educativi durante il follow up anche per chi era in monoterapia

AACAP OFFICIAL ACTION

Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders

Heather J. Walter, MD, MPH, Oscar G. Bukstein, MD, MPH, A. Reese Abright, MD,
Helene Keable, MD, Ujjwal Ramtekkar, MD, MPE, MBA,
Jane Ripperger-Suhler, MD, Carol Rockhill, MD, PhD, MPH

AACAP recommends that :

(1B) **selective serotonergic reuptake inhibitors (SSRIs) be offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, or panic disorder.**

Fluoxetina, Sertralina, Fluvoxamina, Paroxetina hanno i dati più solidi). Esiste un warning per ideazione e comportamenti suicidari (NNH 143, NNT 3)

(1C) **cognitive-behavioral therapy (CBT) be offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, specific phobia, or panic disorder**

(2C) **serotonin norepinephrine reuptake inhibitors** (SNRIs) could be offered to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, or panic disorder.

Venlafaxina (lieve maggior rischio di comportamento e ideazione suicidari); duloxetine (rischio epatico)

(2C) **combination treatment (CBT and an SSRI) could be offered preferentially over CBT alone or an SSRI alone** to patients 6 to 18 years old with social anxiety, generalized anxiety, separation anxiety, or panic disorder

Depressione

Psychotherapy and medication

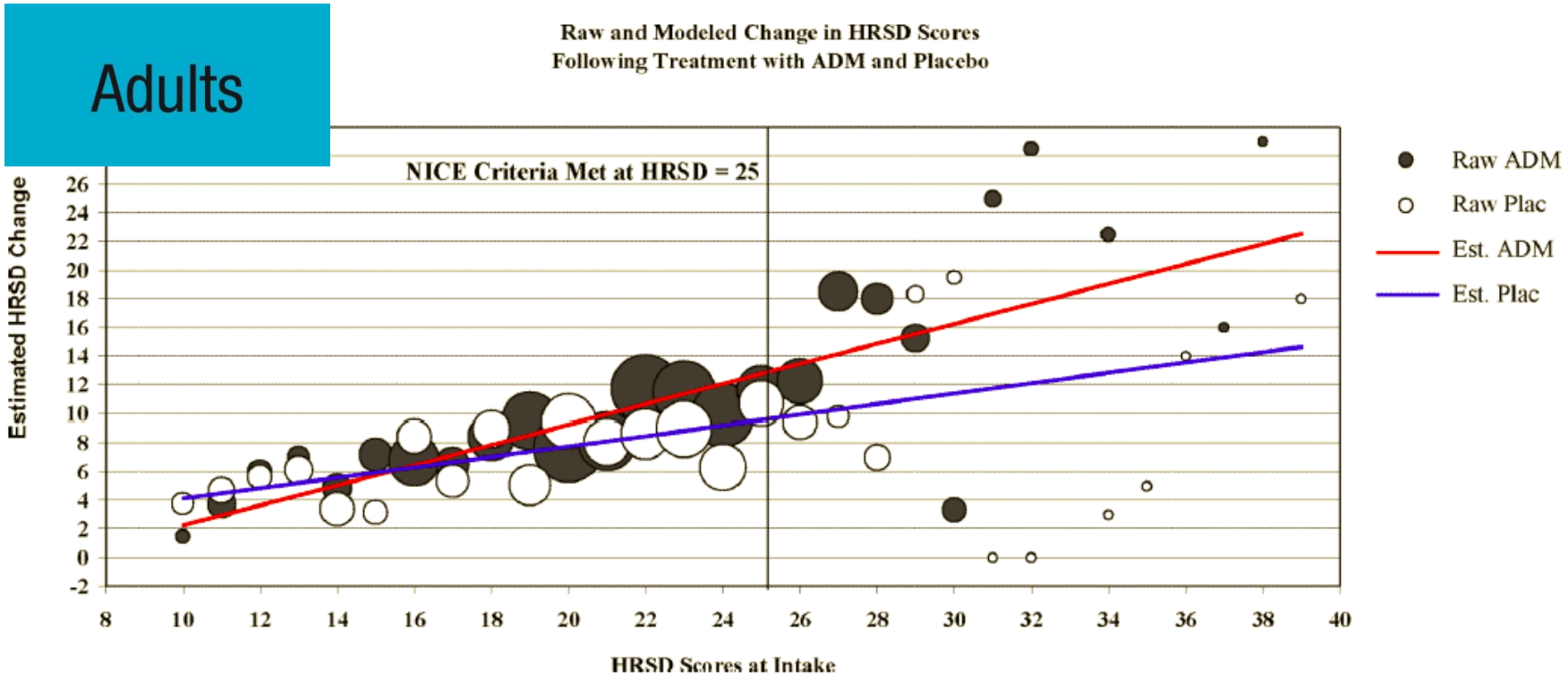


Jay C. Fournier et al, Antidepressant Drug effects and Depression Severity: A PatientLevel Meta-Analysis JAMA. 2010 January 6; 303(1): 47–53.

The magnitude of benefit of antidepressant medication compared with placebo increases with severity of depression symptoms, and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms.

For patients with very severe depression, the benefit of medications over placebo is substantial.

Adults



Circles represent raw mean change in depressive symptoms from intake to the end of treatment at each initial HRSD score for both the antidepressant medication (ADM) and placebo (Plac) conditions. The **regression lines** represent the estimates of change in depression symptoms from intake to the end of treatment for ADM and Plac conditions as a function of baseline symptom severity.

T A D S

Treatment for Adolescents with Depression Study

The Treatment for Adolescents With Depression Study (TADS)

Long-term Effectiveness and Safety Outcomes

The TADS Team

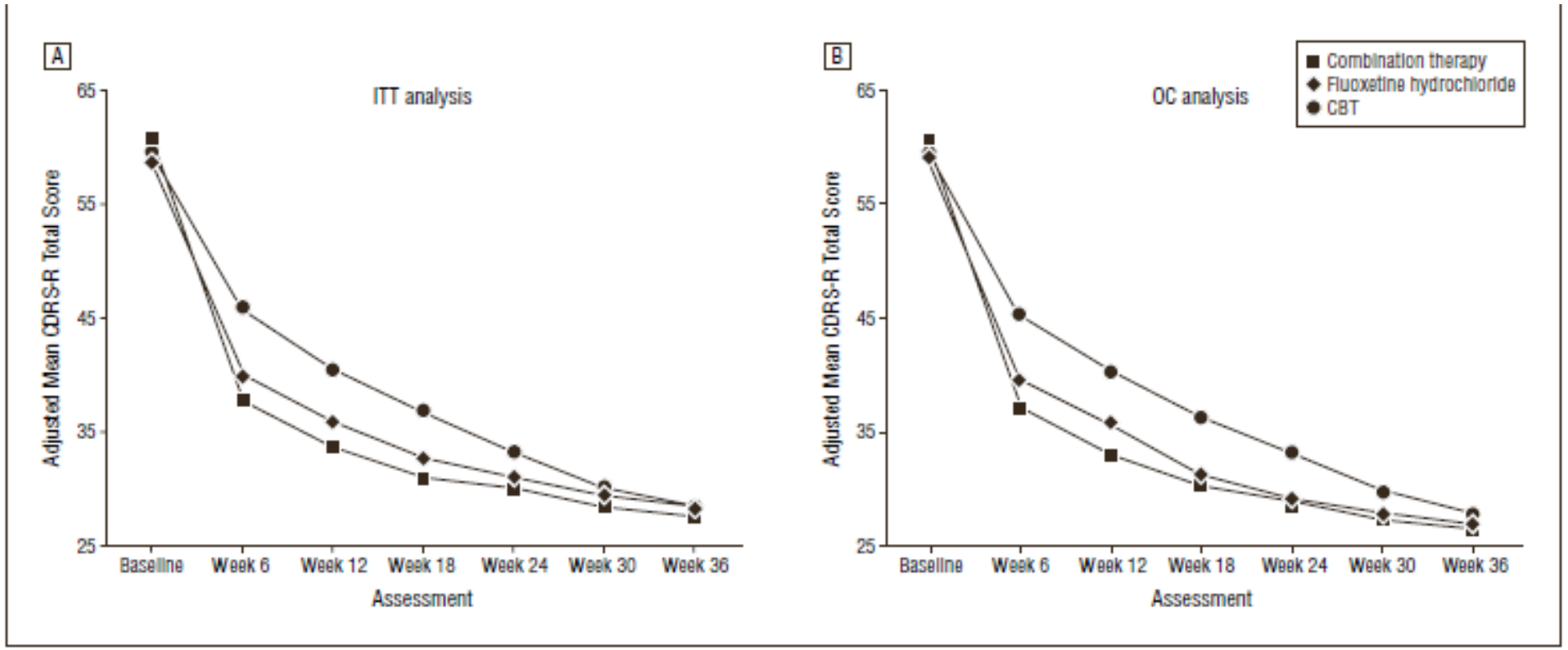
Arch Gen Psychiatry. 2007;64(10):1132-1144

327 patients aged 12 to 17 years

Children's Depression Rating Scale–Revised

Significant time x treatment interaction (P.001)

effectiveness outcomes across 36 weeks of randomized treatment



Rates of response

Arch Gen Psychiatry. 2007;64(10):1132-1144

at week 12

combination therapy	73%
Fluoxetine	62%
CBT	48%

at week 18

combination therapy	85%
Fluoxetine	69%
CBT	65%

at week 36

combination therapy	86%
Fluoxetine	81%
CBT	81%



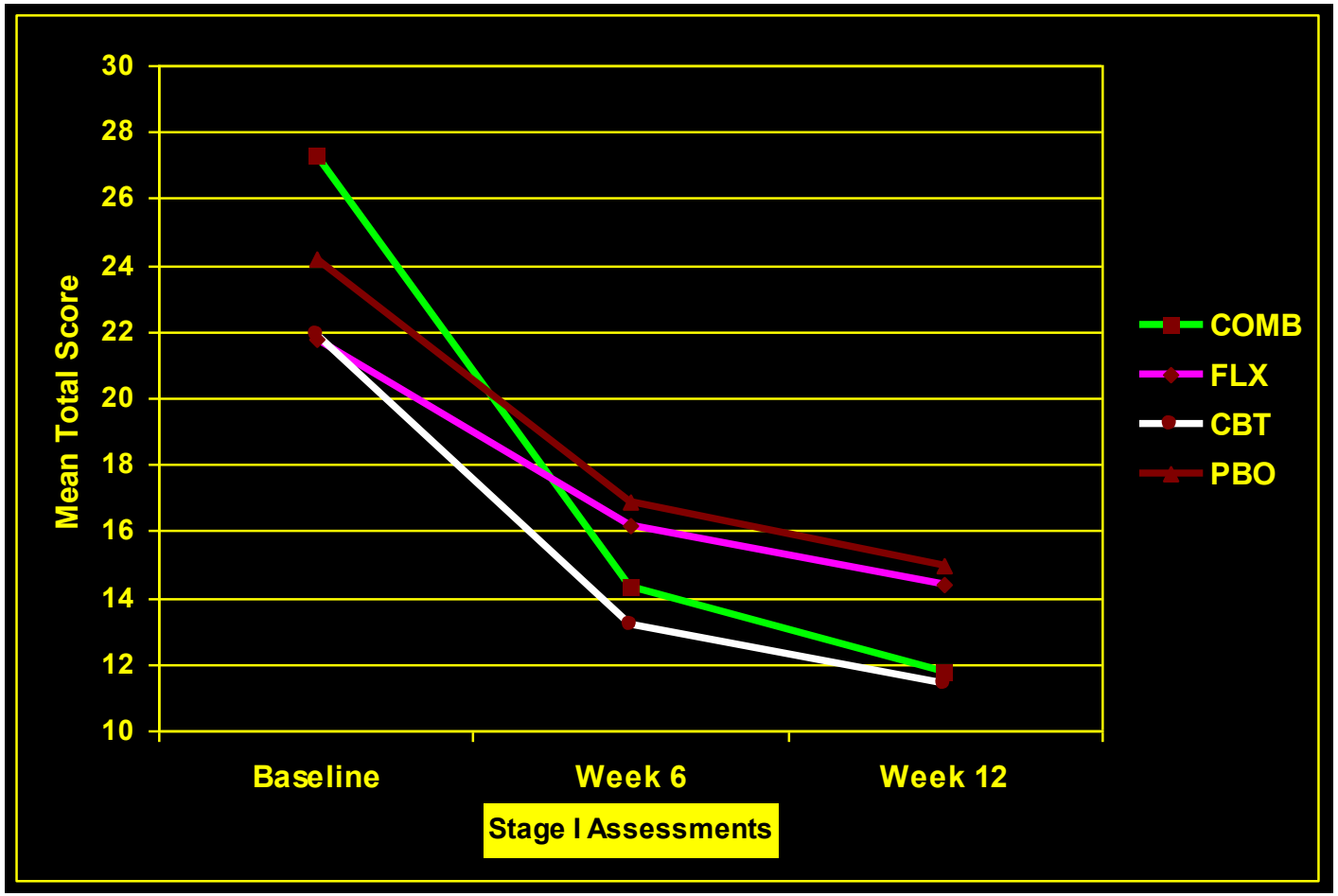
Table 3. Magnitude of the Effect of Combination Therapy and Fluoxetine Relative to CBT

		ITT Population			OC Population		
		Effect Size, Hedges *g*			Effect Size, Hedges *g*		
Week	Contrast	CDRS-R	RADS	CGI-I, NNT	CDRS-R	RADS	CGI-I, NNT
12	Combination-CBT	0.71	0.59	4	0.81	0.63	4
	FLX-CBT	0.48	0.39	7.0	0.49	0.38	7
18	Combination-CBT	0.55	0.52	5	0.71	0.61	4
	FLX-CBT	0.38	0.33	25	0.57	0.30	14
36	Combination-CBT	0.07	0.31	20	0.17	0.34	13
	FLX-CBT	−0.01	0.12	>100	0.12	−0.01	33

Suicidal ideation decreased less with fluoxetine therapy than with combination therapy or CBT alone

Table 4. Patients With Suicidal Events[a]

Treatment	No. of Patients	No. (%) of Patients: ITT Population	No. (%) of Patients: OC Population
Stage 1			
Combination	107	5 (4.7)	5 (4.7)
FLX	109	12 (11.0)	10 (9.2)
CBT	111	5 (4.5)	5 (4.5)
Total	**327**	**22** (6.7)	**20** (6.1)
Stages 1-3			
Combination	107	9 (8.4)	8 (7.5)
FLX	109	16 (14.7)	12 (11.0)
CBT	111	7 (6.3)	6 (5.4)
Total	**327**	**32** (9.8)	26 (8.0)



Suicidal events

14.7% fluoxetine
8.4% combination therapy
6.3% CBT

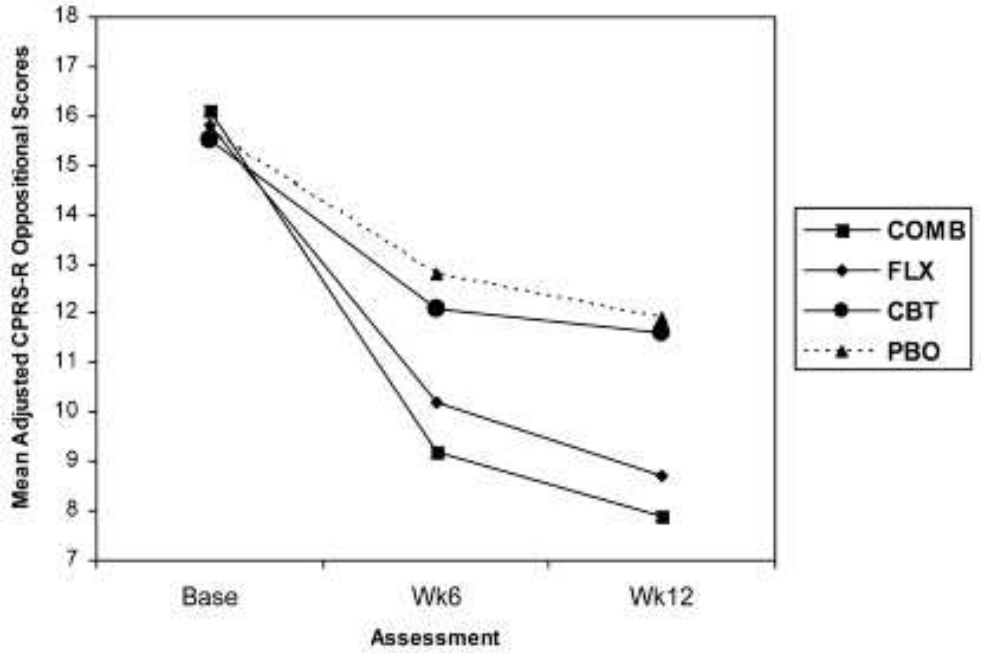
Arch Gen Psychiatry. 2007;64(10):1132-1144

TADS

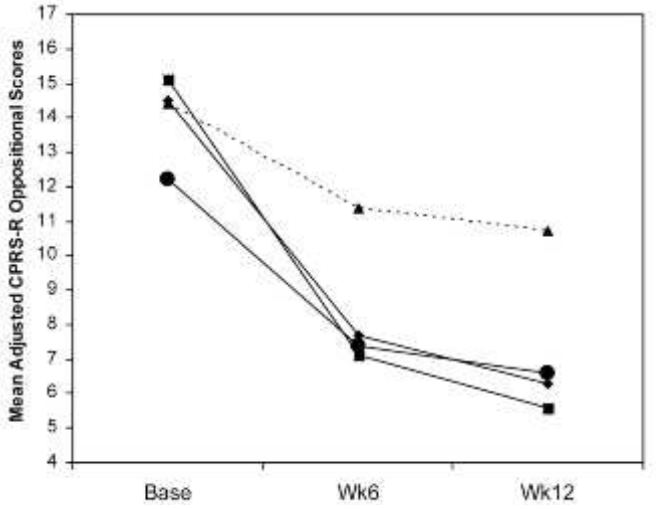
Treatment for Adolescents with Depression Study

change in oppositionality across the acute treatment period

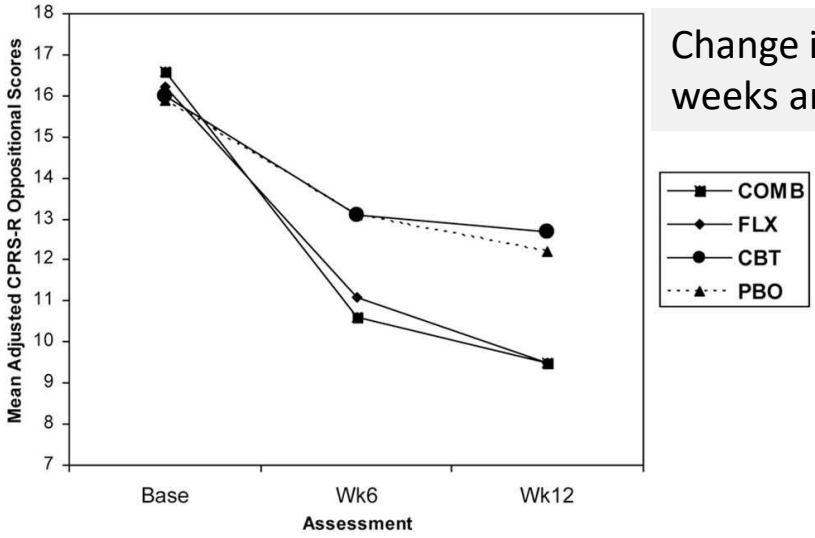
Jacobs et al, Treating Depression and Oppositional Behavior in Adolescents, Clin Child Adolesc Psychol. 2010 ; 39(4): 559–567.



The correlation coefficient for change (baseline to Week 12) in depression with baseline oppositionality was r =−.03; p > .05. At Week 6, r = .19; p < .01, and at Week 12, r = .29, p < .01



Change in oppositionality over 12 weeks among **remitters**



Change in oppositionality over 12 weeks among **no-remitters**

Adolescents receiving **fluoxetine**, either alone or in combination with CBT, had **greater reductions in oppositionality** than adolescents not receiving antidepressant medication

TADS

Treatment for Adolescents with Depression Study

Jacobs et al, Treating Depression and Oppositional Behavior in Adolescents, Clin Child Adolesc Psychol. 2010 ; 39(4): 559–567.



…treatments designed to alleviate depression can ***reduce oppositionality*** *among youth with a primary diagnosis of depression…*

Safety

Most important side effects of SSRIs

. Behavioral activation, aggression, hostility

. Gastrointestinal symptoms: first days, nausea, dyspepsia, reflux, dose related, go away with time

. Sexual symptoms: less studied in adolescents, less frequent than in adults (?). Management with $5HT2_a$ blockers mirtazapine, trazodone

. Frontal lobe syndrome: apathy, disinterest, not caring about consequences, lack of emotional involvement and responsiveness, dose-related (disinhibition if provoked).

. Headache, increased sweating, disruptive sleep

. Manic switch

. Suicidality

Psychopharmacological treatment

I choice

SSRIs (monotherapy)

fluoxetine

II choice

SSRIs (monotherapy)

sertraline, citalopram, escitalopram

III choice (in adolescents non responders to SSRI)

SNRI (monotherapy)

Venlafaxine

(at lower doses it inhibits the re-uptake of 5HT, at higher doses >150 mg/d also of NE, at the highest doses also of DA)

Selective Serotonin Reuptake Inhibitors

(SSRI)

Fluoxetina (cp 20 mg, soluzione 5 ml= 20 mg)
Sertralina (cp 50-100, soluzione 20 mg/ml)
Fluvoxamina (cp 50-100 mg)
Paroxetina (cp 20, gocce: 1 gtt = 1 mg)
Citalopram (20 mg, gocce 1 goccia = 2 mg),
Escitalopram (5-10-15-20 mg)

- **Assenza di effetti anticolinergici**
- **assenza di cardiotossicità**
- **non incremento ponderale (eccetto paroxetina)**
- **assenza di letalità in overdose**
- **ampio spettro di indicazioni (comorbidità)**



Alternative Antidepressant Monotherapy

Monotherapy with AD with different mechanism of action: Tryciclics, Mirtazapine, Trazodone, Bupropion, Duloxetine, MAOi, Agomelatine, Vortioxetine

Combination of Antidepressants

Combination: SSRI (Fluoxetine) plus: Mirtazapine/Trazodone/Venlafaxine/Tryciclics/ Bupropion.

SSRI + Augmentation

Adolescents with partial response to SSRI

Lithium

hidden bipolarity, bipolar depression, suicidality, partial responders.

New generation antipsychotics

- aripiprazole, (5/5 trials)
- quetiapine (3/3 trials)
- olanzapine (+FLX: Symbyax) (3/6 trials)

SSRI + Augmentation

Lower evidences for antiepileptic drugs

lamotrigine

valproic acid

Scarce evidence for:

- thyroid hormone T3
- S-adenosil-L-metionine
- psychostimulants
- omega-3 fatty acids
- methylfolat
- pindolo
- dopamine agonists pramipexole/ropirinole

In realtà…

Table 2 Psychotropic medications approved in Europe for use in children and adolescents.

Medication	Indication	Age for prescription
Aripiprazole	Schizophrenia	≥ 15 years
	Bipolar disorder, manic or mixed episodes	≥ 13 years
Amphetamines (incl. Lisdexamphetamine)	Attention-Deficit Hyperactivity Disorder[a]	≥ 6 years
Atomoxetine	Attention-Deficit Hyperactivity Disorder	≥ 6 years
Fluoxetine	Major depressive episode	≥ 8 years
Fluvoxamine	Obsessive-compulsive disorder	≥ 8 years
Methylphenidate	Attention-Deficit Hyperactivity Disorder	≥ 6 years
Risperidone	Aggression[b]	≥ 5 years
Sertraline	Obsessive-compulsive disorder	≥ 6 years
Ziprasidone	Bipolar disorder, manic or mixed episode[c]	≥ 10 years

[a]Approved only in some European countries for children and adolescents with ADHD.
[b]Approved only in some European countries for children and adolescents with conduct disorder, in the presence of sub-average intellectual functioning or intellectual disability and when all non-pharmacological strategies have been found insufficient.
[c]Approved only in some European countries based on one randomized controlled trial (Findling et al., 2013), found by the US Food and Drug Administration to have quality assurance issues, requiring the sponsor to repeat the trial.

for all the rest…



Duration of treatment

After the response, treatment must be continued at least for additional **8-12 months** to achieve full remission and preventing relapse.

Early discontinuation entails a substantial risk of relapse

After about 5 months of fluoxetine, relapse occurred in about 60% of youth switched to placebo, as compared with 34% who continued fluoxetine

(Emslie et al, 2004)

SSRI and Suicide

FDA Public Health Advisory. Worsening depression and suicidality in patients being treated with antidepressant medications.

The treatment of depression in children and adolescents was significantly altered when in **October 2003** the FDA released a public health advisory alerting the healthcare profession to increased suicidality (ideation and attempts) in clinical trials of antidepressants in the pediatric population. I**n 2004, a black box warning** was issued for all antidepressants for patients under 18 years of age



Suicidal ideations and behaviors is about 4% for youth receiving antidepressants compared with 2% on placebo

metanalisi di 24 studi placebo controllati (4582 pazienti)

Gli SSRI aumentano in modo significativo, rispetto al placebo, il rischio significativo di sviluppare suicidalità (ideazione suicidaria e tentativi di suicidio)

Hammad TA, Laughren T, Racoosin J.: Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006, 63:332-9.

Una metanalisi recente conferma l'incremento del rischio di suicidio in bambini/adolescenti che assumono SSRI

Li, K.; Zhou, G.; Xiao, Y.; Gu, J.; Chen, Q.; Xie, S.; Wu, J. Risk of Suicidal Behaviors and Antidepressant Exposure Among Children and Adolescents: A Meta-Analysis of Observational Studies. Front Psychiatry 2022, 13

Tuttavia…
…i trials clinici in età pediatrica sugli SSRI non hanno mai riportato un caso di suicidio

Mancuso E, Faro A, Joshi G, Geller DA: Treatment of pediatric obsessivecompulsive disorder: a review. J Child Adolesc Psychopharmacol 2010, 20: 299-308.



The 2004 warning prompted a precipitous **drop of 25% in rates of both diagnosis and treatment of depression** by pediatric and non-pediatric primary care physicians (PCPs)

Birmaher, B., Brent, D., & the AACAP Work Group on Quality Issues: Bernet, W., Bukstein, O., Walter, H., Benson, R. S., Chrisman, A., Farchione, T., Greenhill, L., Hamilton, J., Keable, H., Kinlan, J., Schoettle, U., & Stock, S. (2007). Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. Journal of the American Academy of Child Adolescent Psychiatry, 46(11), 1503–1526.

trepidation in using antidepressants actually created a barrier to treatment and resulted in a **25% increase in the completed suicide rate** in children and adults

Correll, C. U., Kratochvil, C. J., & March, J. S. (2011). Developments in pediatric psychopharmacology: Focus on stimulants, antidepressants, and antipsychotics. Journal of Clinical Psychiatry, 72(5), 655–670.

SSRI: troppi o troppo pochi ?

I benefici dell’uso di fluoxetina superano i rischi

- all’aumento degli SSRI corrisponde una riduzione di suicidi completati, sia negli adulti che negli adolescenti (Gibbons, 2005; Isacsson et al., 2005)
- all’aumento di un punto percentuale nell’uso di SSRI ha corrisposto ad una riduzione di 0.23 suicidi per 100.000 adolescenti all’anno (Olfson, 2003)

A multinational European study indicated that **antidepressants decrease risk of suicide at the population level**

Gusmão, et al, Antidepressant Utilization and Suicide in Europe: An Ecological Multi-National Study". PLoS ONE. 8 (6): e66455. Bibcode:2013

European Medicines Agency (EMEA)

06.06.2006

"..estensione della indicazione della fluoxetina in bambini di 8 anni o più, con depressione moderata o grave, che non hanno risposto a terapia psicologica.

Titolazione lenta:

dose iniziale 10 mg

eventualmente **20 mg dopo 2 settimane**

Monitoraggio attento per almeno **9 settimane**

the AACAP Parents Medical Guide Workgroup recommends to parents and caregivers that :

through careful monitoring, the development of a **safety plan**, and the combination of medication with **psychotherapy**, **the risks for increased suicidal thoughts can be managed**



for moderate to severe depression, **there is benefit** in the use of medication because of a **higher rate of relief**, and more complete relief, **from depressive symptoms** than not using any medication

Brent, D., Emslie, G., Fassler, D., Kratochvil, C., March, J., Robb, A., Shaffer, D., & Singh, M. (2010). The use of medication in the treatment of childhood and adolescent depression: Information for patients and families. Parents Med Guide. http://www.parentsmedguide.org/parentsmedguide.htm#9

ELEMENTI DI RISCHIO SUICIDARIO

Il rischio è massimo nelle prime settimane!

- Preesistente ideazione autolesiva con apatia, migliorata nelle prime fasi di trattamento (suicidio in corrispondenza con il miglioramento!)
- Aumento di ansia, irritabilità, insonnia
- Acatisia
- Sintomi (ipo)maniacali o stato misto, legato alla somministrazione di antidepressivi in soggetti con precedenti o familiarità bipolare

Peculiar responses emerging **early in the course of antidepressant treatment**

- Provide a **close clinical follow-up** in order to assess the risk of suicide

- When this risk is present, **modify the treatment** appropriately

- ❑ changing antidepressant medication
- ❑ adding sedating or antipsychotic
- ❑ starting a **mood-stabilizing treatments**
- ❑ providing additional individual support

Possible existence, particularly in younger patients, of many **unrecognized pseudo-unipolar mixed states**, which can be a clinical substrate for suicidality,

This **can explain the increased suicide rate** associated with the use of antidepressants in adolescent patients

- **Decrease the dose or suspend antidepressant therapy, if agitation, insomnia or anger emerge**.

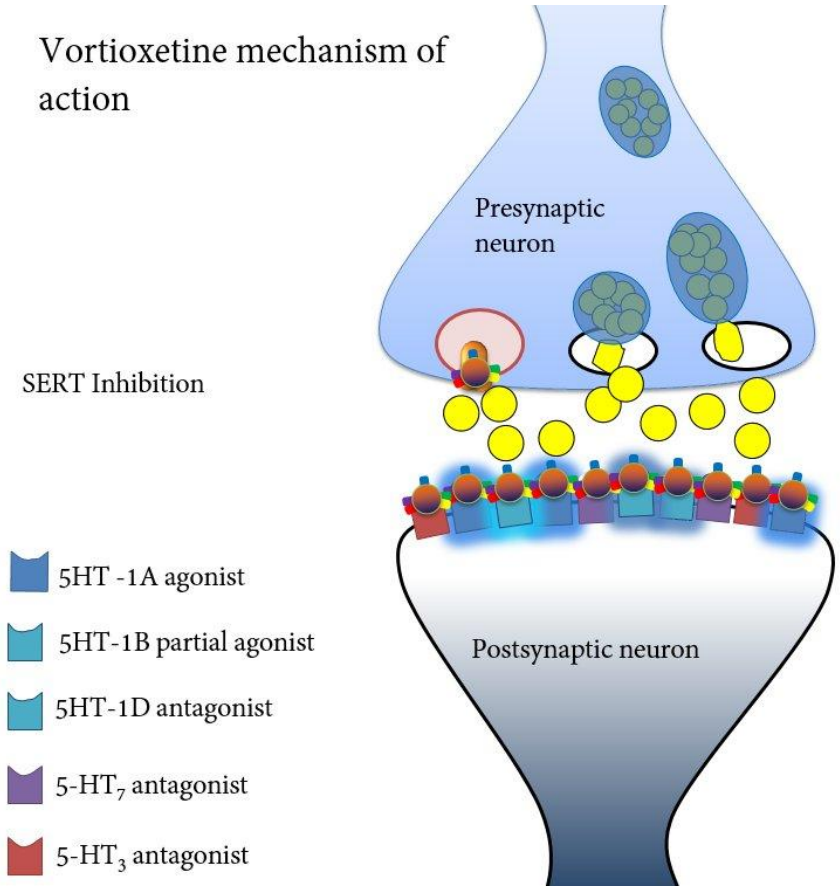
- **Add lithium for cooperative patients, especially following an inadequate antidepressant response**

Pompili et al, Antidepressants and Suicide Risk: A Comprehensive Overview Pharmaceuticals 2010, 3, 2861-2883; doi:10.3390/ph3092861



ONGOING CLINICAL TRIALS

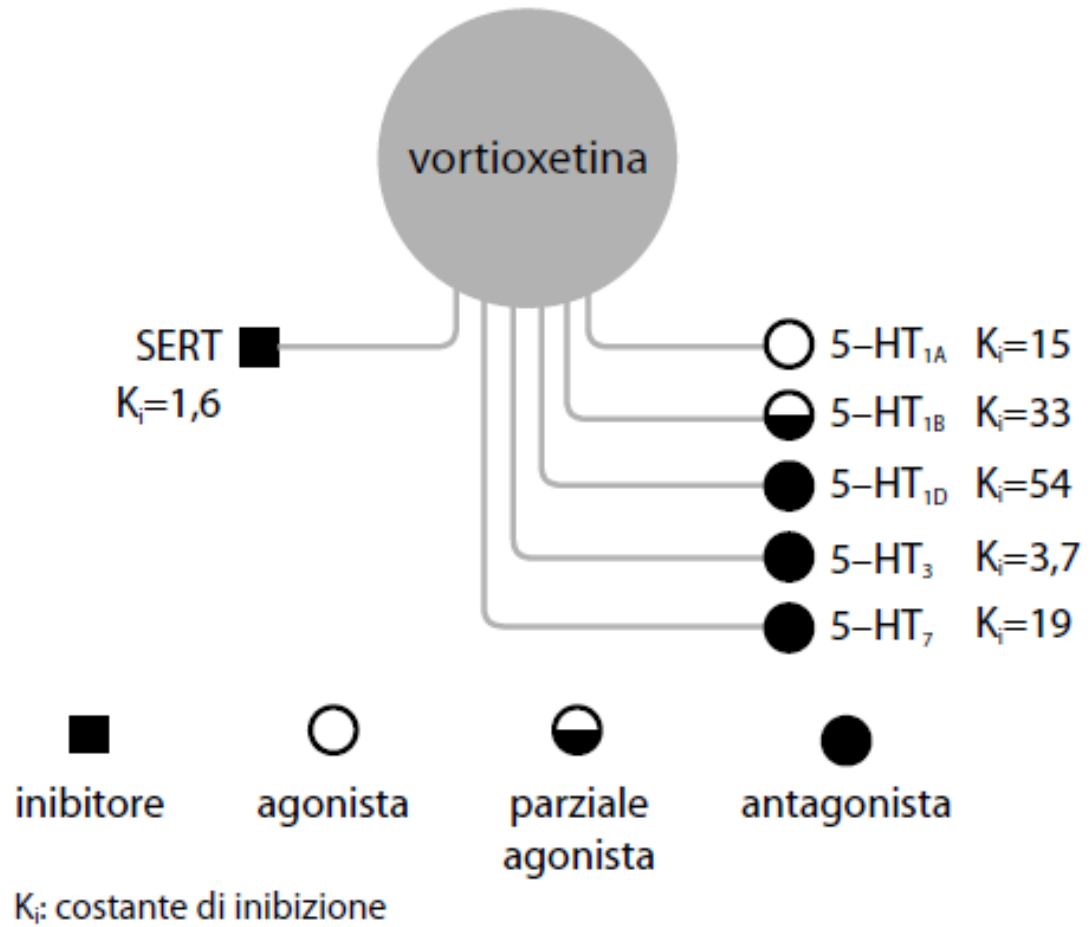
Vortioxetina (cp 5-10-15-20) approvata nel 2013 da EMA per trattamento di episodi depressivi maggiori nell'adulto, a dosi comprese tra 5 e 20 mg/die.



Effetti **antidepressivo e ansiolitico-simile**, miglioramento di attività cognitive (apprendimento e memoria)

Attività multimodale:

1) Inibizione della ricaptazione di 5HT2;
2) Blocco 5-HT3 (effetto su alterazioni cognitive correlate alla depressione)
3) agonista parziale 5-HT1B e antagonista dei recettori 5-HT7 e 5-HT1D.
4) Attività indiretta di modulazione di neurotrasmissione NA, DA, H, Ach, GABA e glutammato



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Mary Ann Liebert, Inc.
Pp. 1–9
DOI: 10.1089/cap.2016.0155

Original Research

Pharmacokinetics and Safety of Vortioxetine in Pediatric Patients

Robert L. Findling, MD, MBA,[1] Adelaide S. Robb, MD,[2] Melissa DelBello, MD, MS,[3] Michael Huss, MD,[4] Nora McNamara, MD,[5] Elias Sarkis, MD,[6] Russell Scheffer, MD,[7] Lis H. Poulsen, MD, PhD,[8] Grace Chen, PhD,[9] Ole Michael Lemming, MSc,[8] Johan Areberg, PhD,[8] and Philippe Auby, MD[8]

prospective, open-label, multinational, multisite, multiple-dose trial

48 patients (children and adolescents; 1:1 ratio) with **depression or anxiety disorder**

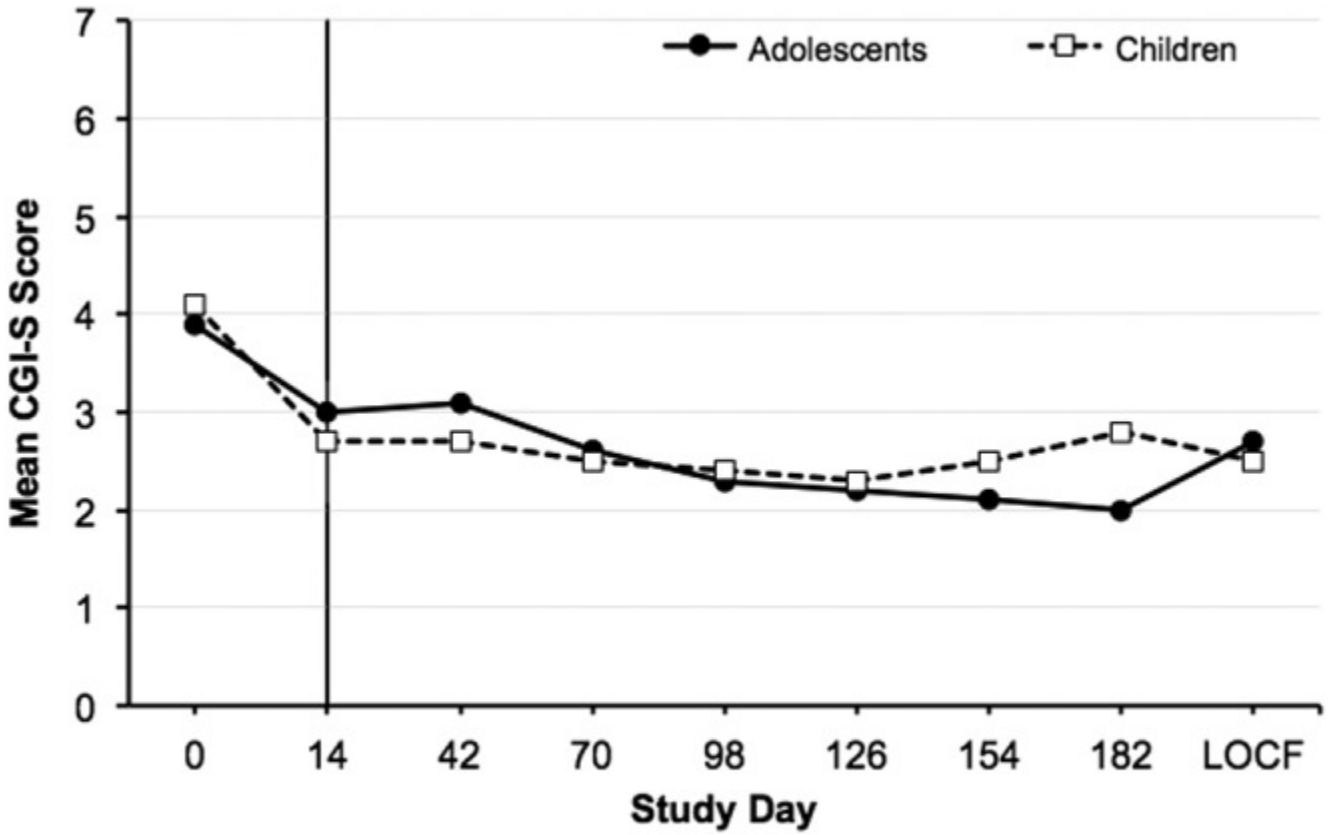
Most adverse events were mild in severity and consistent with those seen in adults.

The dosages of vortioxetine evaluated (5–20 mg q.d.; approved for treatment in adults) and the uptitration schedule used are appropriate for pediatric efficacy and safety trials.

J Child Adolesc Psychopharmacol. 2018 Feb 1; 28(1): 47–54. PMCID: PMC5771527
Published online 2018 Feb 1. doi: 10.1089/cap.2017.0047

A 6-Month Open-Label Extension Study of Vortioxetine in Pediatric Patients with Depressive or Anxiety Disorders

Robert L. Findling, MD, MBA,[✉1] Adelaide S. Robb, MD,[2] Melissa P. DelBello, MD, MS,[3] Michael Huss, MD,[4] Nora K. McNamara, MD,[5] Elias H. Sarkis, MD,[6] Russell E. Scheffer, MD,[7] Lis H. Poulsen, MD, PhD,[8] Grace Chen, PhD,[9] Ole M. Lemming, MSc,[10] and Philippe Auby, MD[8]

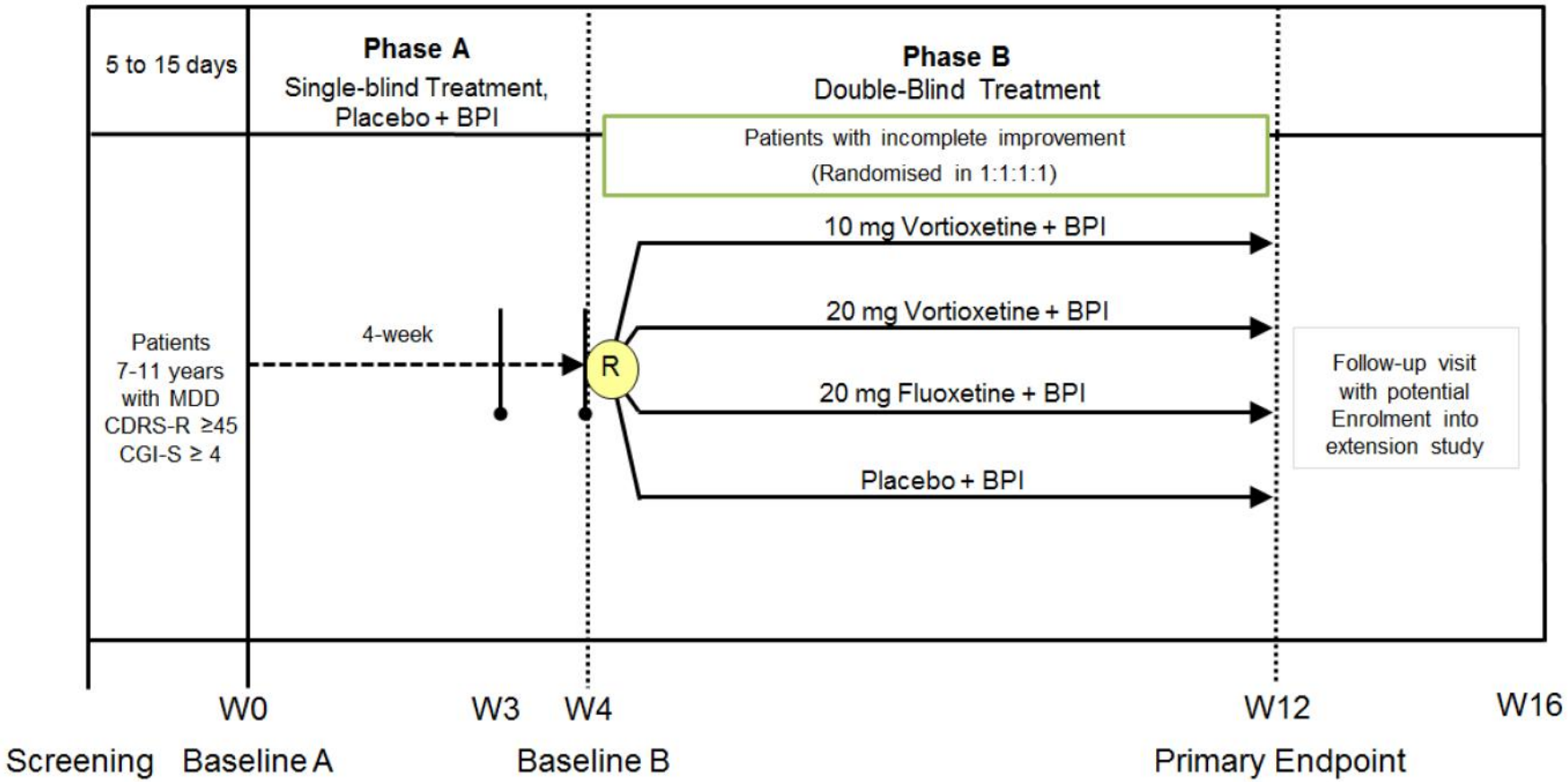


Mean CGI-S score during the lead-in period (days 1–14) and extension period (days 14–182) in children and adolescents (OC). LOCF reported for day 182. CGI-S, Clinical Global Impressions–Severity of Illness; LOCF, last observation carried forward; OC, observed cases.

Synopsis – Study 12712A

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Vortioxetine	**EudraCT No./IND No.** 2008-005356-25/ 112581
Title of Study Long-term, open-label, flexible-dose, extension study of vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 18 years of age		
Study Sites and Number of Patients Planned Sites involved in studies 12709A and 12710A. Approximately 120 sites are planned in approximately 20 countries worldwide (specialists, mainly outpatient clinics)		
Objectives • Primary objective: – to evaluate the long-term safety and tolerability of vortioxetine in child and adolescent patients with a DSM-5™/diagnosis of MDD • Secondary objectives: – to evaluate the long-term effectiveness of flexible doses of vortioxetine in a range of 5 mg/day to 20 mg/day on: • depressive symptoms • clinical global impression • cognitive function • functionality		

Studio Kites

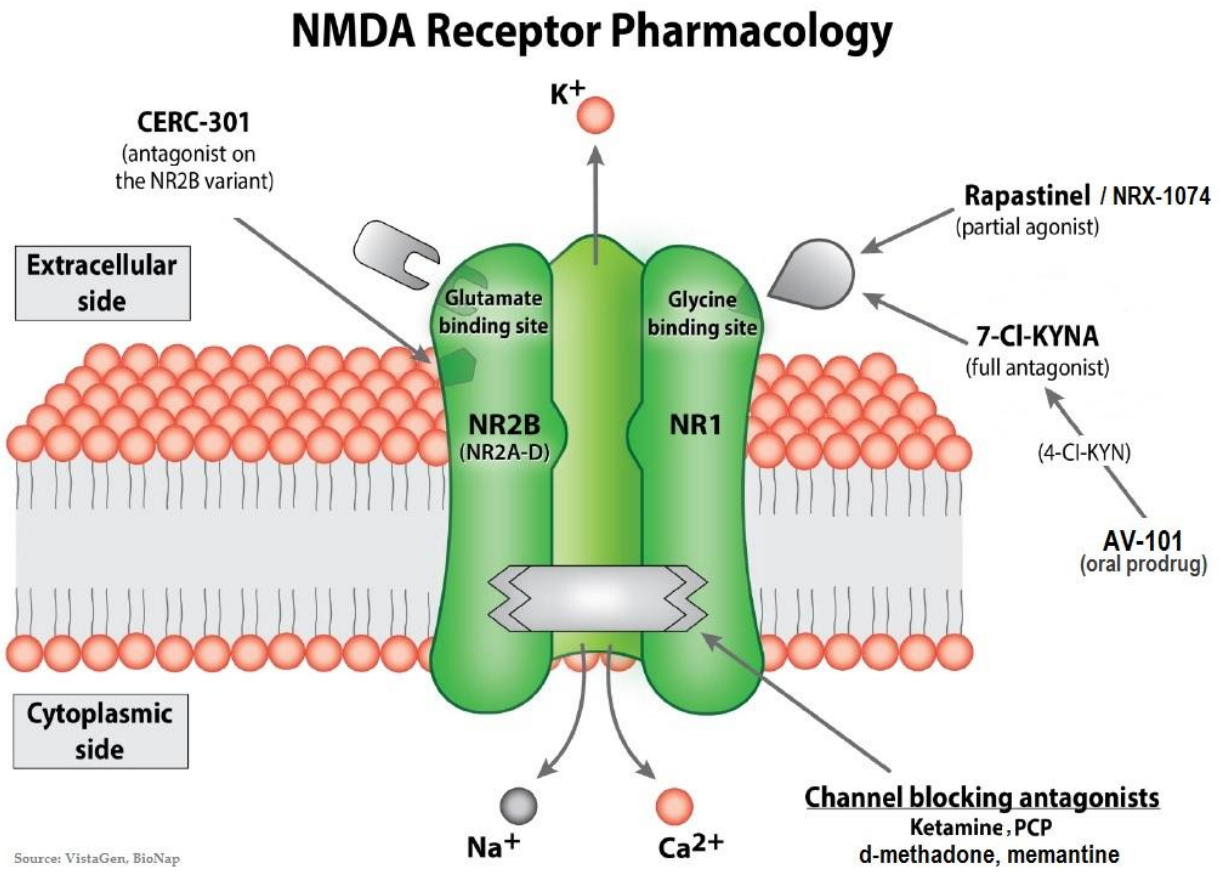


= Patients improving significantly at Week 3 (Phase A) will be excluded before Week 4 (Phase A); patients improving at week 4 (Phase A) will not be randomized to the double-blind Phase B of the study. These patients may receive up to 4 outpatient visits to the study site for consultations over a two-month period.

R = Randomization BPI = Brief Psychosocial Intervention



Esketamine is the S-enantiomer of ketamine, which has been used for the induction and maintenance of anesthesia since the 1970s.



Because of its **ability to block the N-methyl-D-aspartate (NMDA) glutamate receptor**, ketamine has shown efficacy in the treatment of symptoms of major depressive disorder (MDD)

The mechanism of action of esketamine is distinct from conventional antidepressant treatments, which target modulatory monoaminergic neurotransmitters (serotonin, norepinephrine, and/or dopamine)

Esketamine…

- Affects fast excitatory glutamate transmission
- increases brain-derived neurotrophic factor (BDNF) release
- stimulates synaptogenesis

A higher NMDA receptor binding affinity of **esketamine** compared to ketamine allows a lower volume of medication **to be administered via the non-invasive and rapidly-absorbed intranasal route**.



Several pilot studies and 2 independent randomized, double-blind trials using IV ketamine in subjects with MDD or bipolar depression suggested that **ketamine may reduce suicidal ideation within hours of administration**.

DiazGranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry. 2010;71(12):1605-1611

Ballard ED, Luckenbaugh DA, Richards EM, et al. Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. J Psychiatr Res. 2015;68:68-73

Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol. 2011;14 (8):1127-1131

Rasmussen KG, Lineberry TW, Galardy CW, et al. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol. 2013; 27(5):444-450.

Zarate C, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry. 2012;71: 939-946.

Murrough JW, Soleimani L, deWilde KE, et al. Ketamine for rapid reduction of suicide ideation: a randomized controlled trial. Psychol Med. 2015;45(16);3571-3580.

Although MDD with imminent risk for suicide is a potentially lethal condition that requires immediate intervention, **there is no approved treatment**

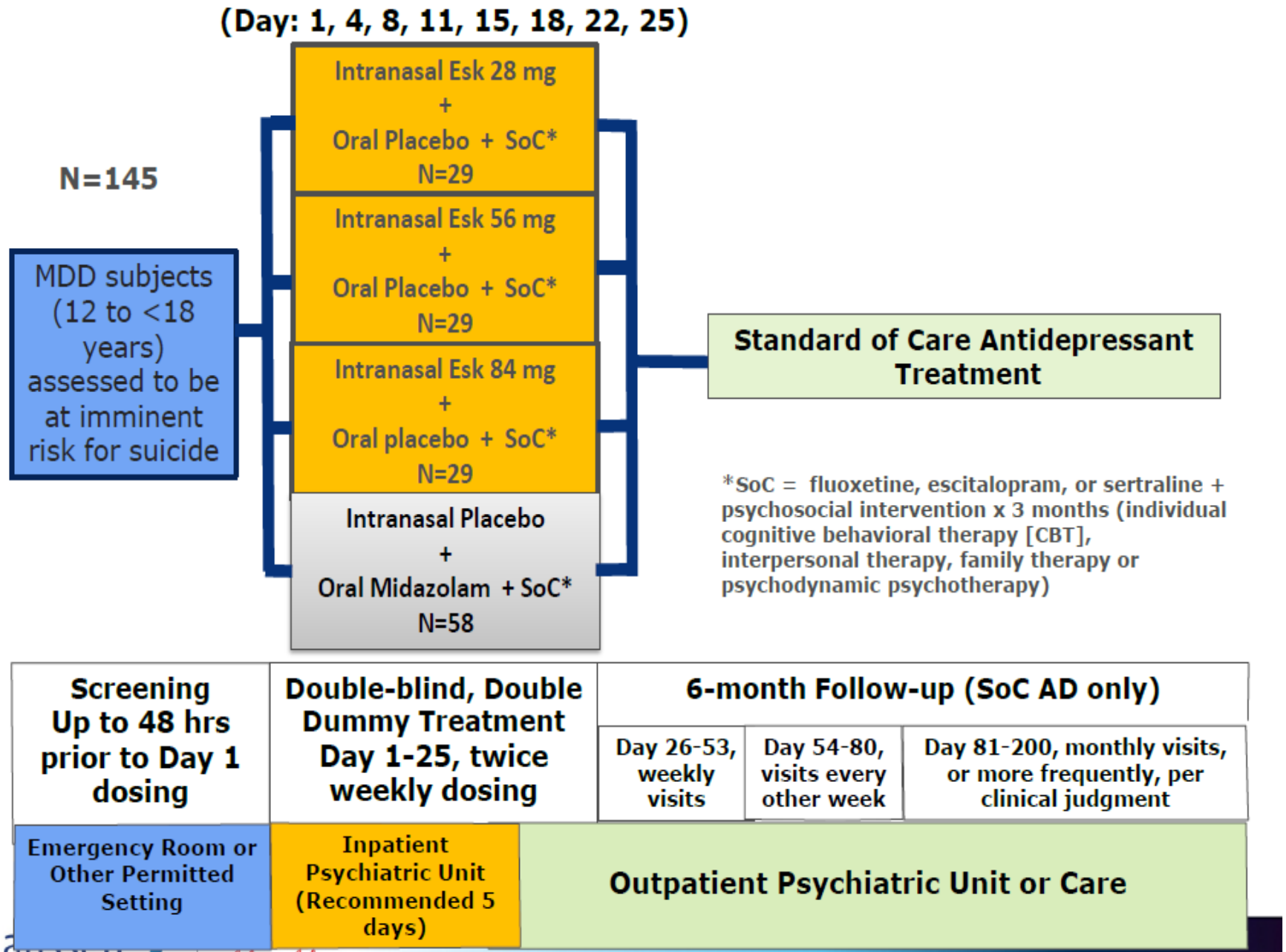
Sponsor: Janssen Research & Development
Protocol: ESKETINSUI2002

5 September 2017

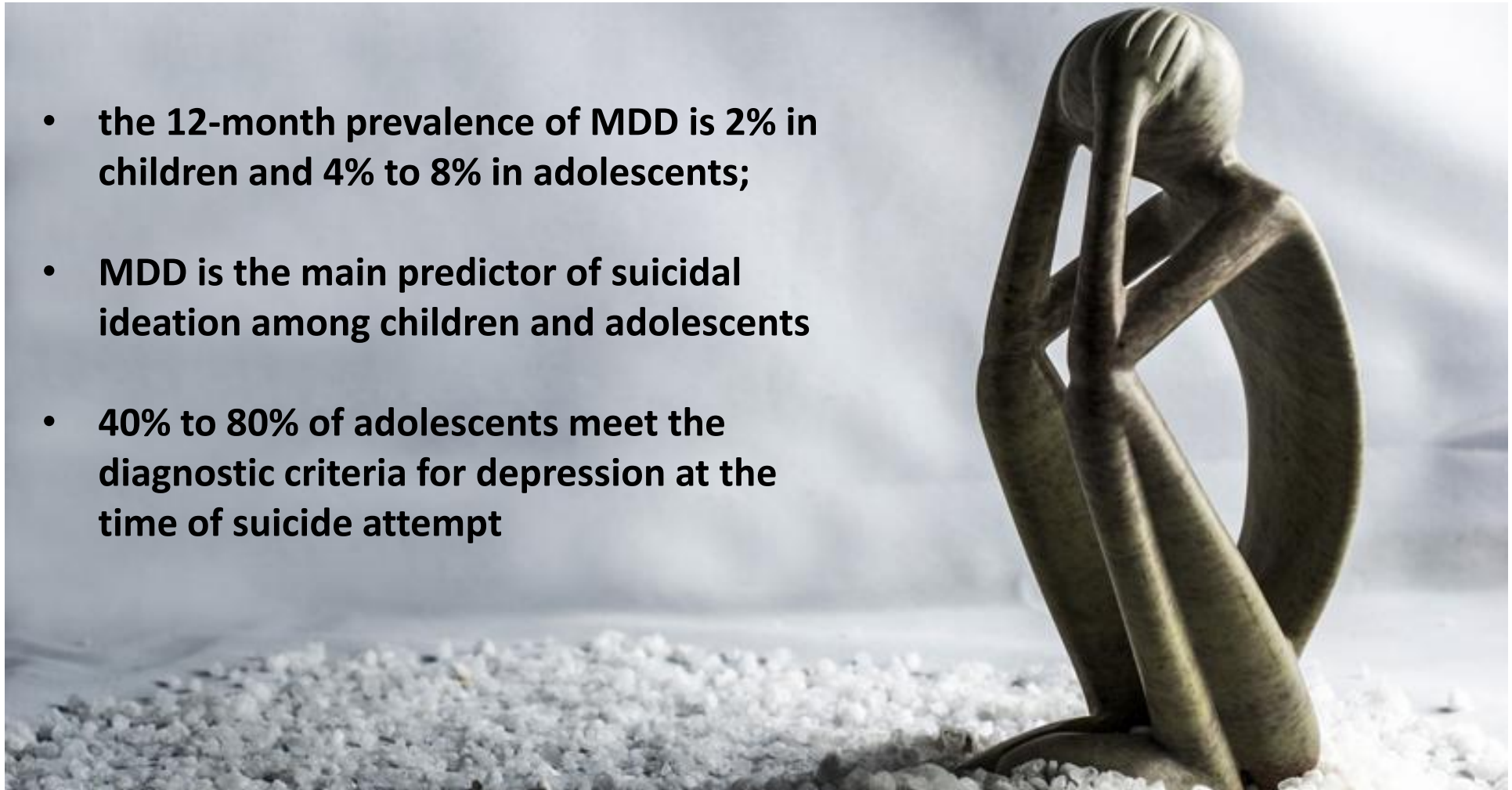
Study Title: A Double-blind, Randomized, Psychoactive Placebo-controlled, Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (28 mg, 56 mg and 84 mg) of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Pediatric Subjects Assessed to be at Imminent Risk for Suicide

this study is evaluating the efficacy, safety and dose response of esketamine in subjects 12 to <18 years of age with MDD who are assessed to be at imminent risk for suicide

Study Design ESKETINSUI2002



Major depressive disorder is the most prevalent mental health condition and the psychiatric diagnosis most commonly associated with suicide



- the 12-month prevalence of MDD is 2% in children and 4% to 8% in adolescents;
- MDD is the main predictor of suicidal ideation among children and adolescents
- 40% to 80% of adolescents meet the diagnostic criteria for depression at the time of suicide attempt

Therefore, MDD is a serious, potentially lethal condition that requires immediate intervention



Quale classe di farmaci per Francesco……?



E se sospettiamo una genesi neuroflogistica?

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REVIEW ARTICLE OPEN

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Immunological causes of obsessive-compulsive disorder: is it time for the concept of an "autoimmune OCD" subtype?

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A subgroup of patients may have a secondary form of OCD with an organic cause, which often appears to be autoimmune mediated

The DSM-5 distinguishes primary and "secondary organic OCD forms"

In the novel ICD-11 criteria, reflecting DSM-5 nosology, this aspect is taken into account by introducing the category "secondary OCD or related syndrome"

However, neither DSM-5 nor ICD-11 criteria provide specific instructions regarding the detection and delimitation of secondary forms

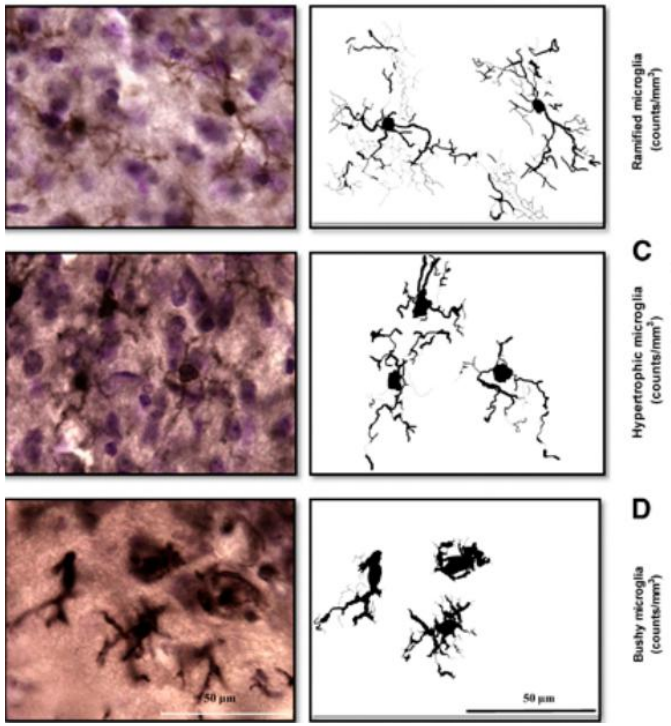
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Position Paper

low-grade neuroinflammation (ie cellular-infiltrative or humoral inflammation below the threshold) and **immune dysfunction** are linked to pathophysiology of **psychosis** in a subset of individuals who have been diagnosed with acute psychosis or schizophrenia-spectrum disorders

Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin

Thomas A Pollak, Belinda R Lennox, Sabine Müller, Michael E Benros, Harald Prüss, Ludger Tebartz van Elst, Hans Klein, Johann Steiner, Thomas Frodl, Bernhard Bogerts, Li Tian, Laurent Groc, Alkomiet Hasan, Bernhard T Baune, Dominique Endres, Ebrahim Haroon, Robert Yolken, Francesco Benedetti, Angelos Halaris, Jeffrey H Meyer, Hans Stassen, Marion Leboyer, Dietmar Fuchs, Markus Otto, David A Brown, Angela Vincent, Souhel Najjar*, Karl Bechter**



	Schizophrenia and psychotic disorders	Autoimmune encephalitis
Immunogenetic associations	A strong and diffuse association has been found at the MHC locus;[16] causal HLA variants have proved elusive; the association could arise in part because of structurally diverse alleles of the complement component 4 genes.[17] Genetic associations are also strongly enriched in genes that are expressed in tissues with important immune functions, particularly B-lymphocyte lineages (CD19 and CD20).[16]	LGI1 antibody associated encephalitis is most strongly associated with HLA-DRB1*07:01;[111,112] is it also associated with HLA-DR7 and HLA-DRB4.[113] CASPR2 antibodies are less strongly associated with HLA-DRB1*11:01.[111] NMDAR antibody encephalitis is weakly associated with HLA-I allele B*07:02.[112]
Autoimmunity in patients with psychosis or first degree relatives	The presence of autoimmune disease increases the risk of psychosis and vice versa.[20–22,114,115] A family history of autoimmunity increases the risk of psychoses by 10% and a family history of psychosis increases the risk of autoimmune diseases by 6%.[19]	Autoimmunity in the patient and their family is variable.
Serum biomarkers	Raised CRP, IL-6, IL-1β, and TGF-α are increased in patients with acute psychosis compared with healthy controls;[23] raised IL-12, IFN-γ, TNF-α, and sIL-2R could be trait markers.[23] An increased prevalence of multiple neuronal or non-neuronal antibodies versus controls has been reported in a systematic review[116] (although this review conflated multiple assay methods and positivity thresholds, often with small sample sizes in the studies included). The prevalence of NMDAR antibodies could be dependent on the assay used.[32,38]	Antibodies to neuronal surface antigens, particularly NMDAR have been identified in patients with autoimmune encephalitis.[28] There are no consistent cytokine or chemokine abnormalities in peripheral blood;[117] increased Th17 pathway markers could help differentiate autoimmune encephalitis with antibodies to neuronal surface antigens from other autoimmune CNS conditions and healthy controls.[118]
CSF biomarkers	The ratio of CSF to serum albumin, CSF to serum IgG, CSF protein, IL-6, and IL-8 is increased in patients with psychosis compared with healthy controls.[1] Pleocytosis is 3–10%[50,51,119], the proportion of oligoclonal bands restricted to the CSF is 7–15%,[50,51] and neopterin is increased (34%).[119]	Pleocytosis is frequent, specific antibodies are usually present, and intrathecal antibody synthesis occurs in most cases.[28,52,120] NMDAR encephalitis is characterised by few but frequent NR1-specific intrathecal B cells.[49] Levels of CSF TNF-α, IL-6, IL-10, IFN-γ, IL-17A, and CXCL13 are increased in NMDAR encephalitis.[117,121,122] Increased neopterin is common in NMDAR encephalitis.[121]
Infectious antecedents	The risk of psychosis is increased by specific viral and protozoal infections during pregnancy,[123] childhood,[124] or adulthood.[125,126] The effect of multiple infections on psychosis risk is cumulative (ie, the quantitative risk of a subsequent psychosis diagnosis increases with successive infections). A diagnosis of psychosis shows a temporal relationship with preceding infectious episodes, indicating that risk of psychosis is increased nearer the time of infection.[127]	There is a strong association between NMDAR encephalitis and preceding or concurrent HSV encephalitis in a proportion of patients.[7,128] Also associated with non-encephalitic HSV-1 infection.[129] Other viral organisms (mainly herpesviruses) also implicated in multiple subtypes of autoimmune encephalitis.[130] HSV encephalitis is also associated with the production of NMDAR antibodies without resulting secondary encephalitis.[131]
Immunopathology	There is marked variability in studies but there is evidence of increased microglial activation[4] and density,[5] and *SERPINA3*[4] and *IFITM* expression.[4] Evidence from meta-analyses shows increased expression of pro-inflammatory genes at the protein and transcript level.[5] In two studies,[26,27] lymphocyte infiltration occurs in approximately 20% of brains of individuals who had schizophrenia, particularly in the hippocampus.	High concentrations of CD8 and CD3 T-cell infiltrates in patients with paraneoplastic or GAD antibody related conditions.[132] There is neuronal loss and complement activation in patients with LGI1 antibody encephalitis.[133] There is minimal neuronal loss or complement deposits and variable cellular infiltrates in patients with NMDAR antibody encephalitis.[133–135]

CRP=C-reactive protein. CSF=cerebrospinal fluid. CXCL13=C-X-C motif chemokine ligand 13. GAD=glutamic acid decarboxylase. HSV=herpes simplex virus. IFN-γ=interferon gamma. IL=interleukin. LGI1=leucine-rich glioma inactivated 1. NMDAR=N-Methyl-D-aspartic acid receptor. NR1=nuclear receptor 1. sIL-2R=soluble IL-2 receptor. Th17=T-helper cell 17. TGF-α=transforming growth factor α. TNF-α=tumour necrosis factor α.

Table 1: **Evidence linking inflammation, immune dysregulation, and autoimmunity to psychotic disorders and autoimmune encephalitis**

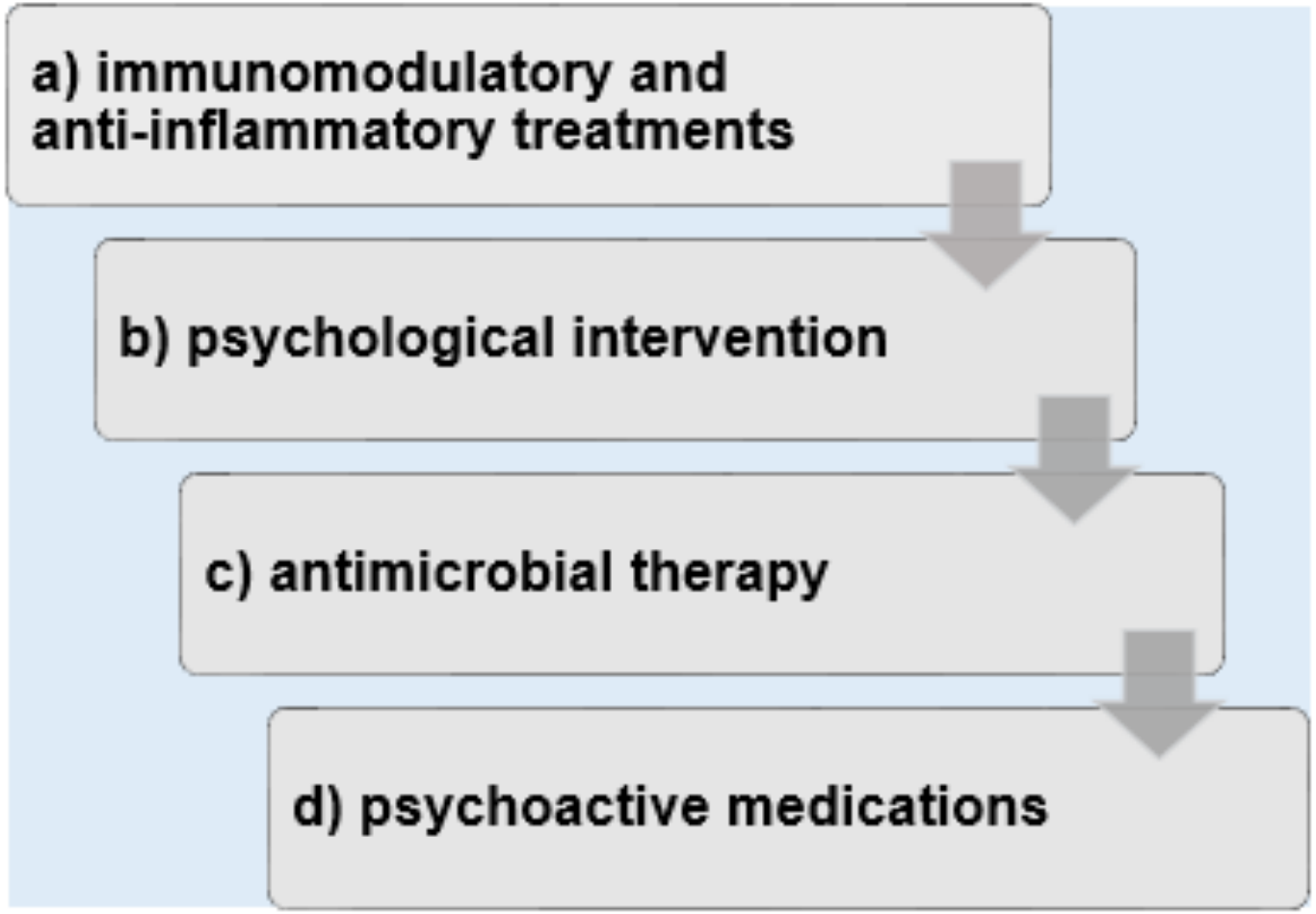
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Pediatric acute-onset neuropsychiatric syndrome (PANS) is featured by a heterogeneous constellation of acute obsessive-compulsive disorder (OCD), eating restriction, cognitive, behavioural and/or affective symptoms, often followed by a chronic course with cognitive deterioration. An immune-mediated etiology is advocated in which the CNS is hit by different pathogen-driven (auto)immune responses.

Figure 2: Treatment work-up:



a) and b) the immunomodulatory/anti-inflammatory treatments and the psychological treatments **should be guaranteed to all patients**;

c) the antimicrobial treatments should be administered if an infective condition is active or if a prophylaxis of recurrent infections is needed.;

d) psychoactive medications may be adopted when a patient does not respond satisfactory to the immunotherapy or **during the acute phases with the purpose to reduce the symptoms**.

A Gagliano, A Carta, MG. Tanca, S Sotgiu, **Pediatric Acute-onset Neuropsychiatric Syndrome: Current perspectives.** Under revision on Neuropsychiatric Disease and Treatment


So how do you write a conclusion?

Figure A.7.2 General approach to pharmacotherapy in child psychiatry

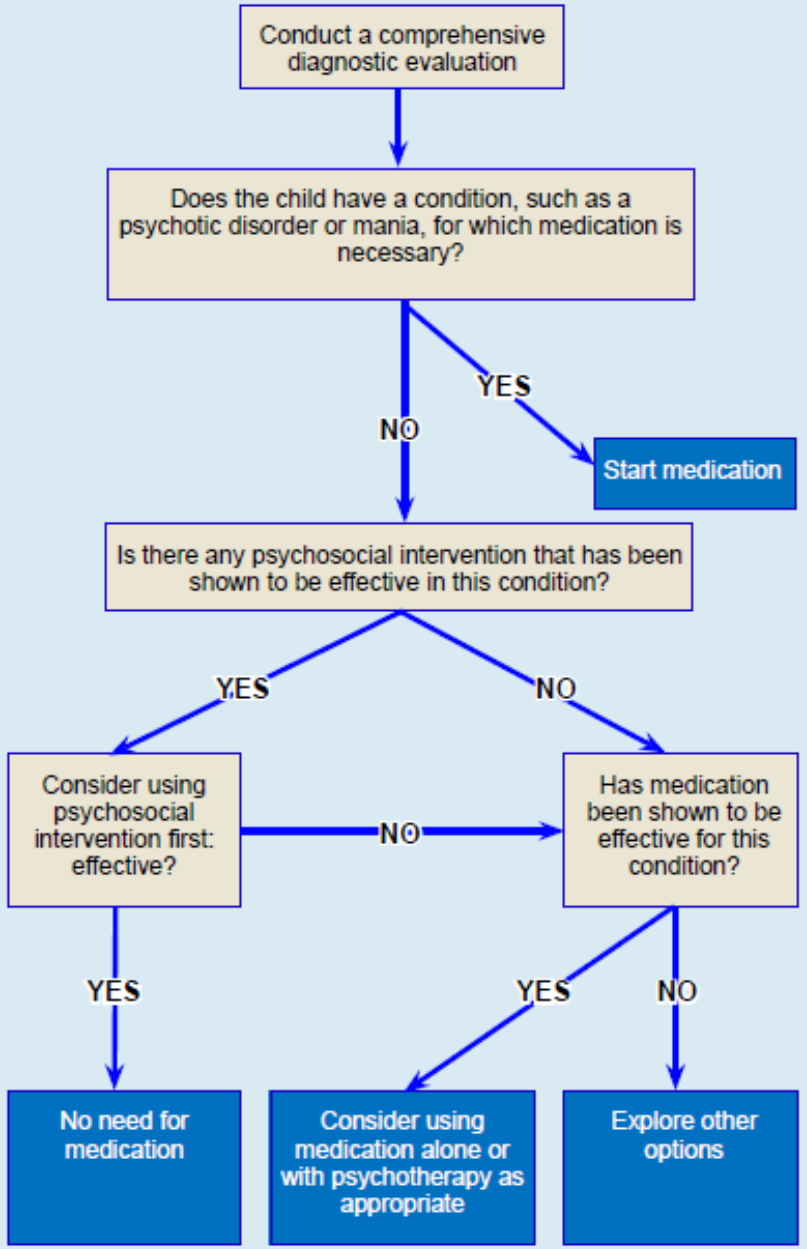


Table A.7.7 Key steps in implementing pharmacotherapy in child and adolescent psychiatry

1. Complete a comprehensive diagnostic evaluation documenting the presence of a condition for which medication is indicated
2. Inform parents and child (to the extent allowed by developmental level and cognitive functioning) of the potential benefits and risks of medication as compared with alternative options
3. If the medication does not have a regulatory-approved indication for use in children with the condition, inform parents and child that the medication is being used "off-label"
4. Identify and measure the target symptoms and functions that medication is expected to improve
5. Based on the medication, obtain baseline clinical or laboratory parameters (e.g., weight, height, blood pressure, pulse rate, cholesterol level, renal function)
6. Start medication at a dose in the lower end of the usually effective dose range aiming at identifying the lowest possible dose that produces the desired outcome
7. Monitor effects, side effects and, if appropriate, plasma levels (e.g., lithium levels) in the first few weeks of treatment, and adjust the dose as appropriate
8. If there is improvement, optimize the dose aiming at maximum resolution of symptoms and improvement in functioning
9. Determine the maintenance dose and, based on the condition and medication, establish a tentative duration of treatment
10. As appropriate, periodically consider the need for continuous treatment vs. discontinuation
11. When discontinuing treatment, examine the need for gradual taper, which is recommended for most medications after chronic treatment (e.g., antidepressants, lithium, antipsychotics), vs. abrupt discontinuation, which can be appropriate for some medications (e.g., methylphenidate)

PRINCIPLES IN USING PSYCHOTROPIC MEDICATION IN CHILDREN AND ADOLESCENTS

2019 edition

Boris Lorberg, Chiara Davico, Dmytro Martsenkovskyi & Benedetto Vitiello

IACAPAP Textbook of Child and Adolescent Mental Health



La terapia psicofarmacologica: i 10 comandamenti

1. Non avrai principio più importante di: "*primum non nocere*" (il rapporto costo/beneficio deve sempre essere un numero inferiore a 1)
2. La monoterapia deve essere la regola, la politerapia l'eccezione
3. I farmaci stimolanti sono la prima scelta, le benzodiazepine l'ultima
4. Il Carbolithium è efficace e non penalizza il neurosviluppo
5. Gli antiepilettici sono soprattutto antiepilettici (non regolano il comportamento e fanno poco sull'umore)
6. A prescindere dalla "generazione" (I° o II°), gli antipsicotici sono sempre D2 bloccanti (freno a mano tirato sul neurosviluppo)
7. L'obesità e la sindrome metabolica sono una malattia più grave di quella che pretendiamo di curare
8. Non temere di usare un SSRI (temi piuttosto di non usarlo) ma segui il principio *slow and low*
9. Se sospetti che i sintomi siano espressione di una condizione neuroflogistica, non vergognarti di usare gli antiinfiammatori (non è stregoneria, è medicina)
10. Ricorda sempre che la farmacoterapia, bene che vada, è solo ¼ dell'intervento terapeutico: psicoterapia, famiglia, scuola, lavoro, sport e tempo libero, sono gli altri ¾



il difficile equilibrio tra modificare e rispettare



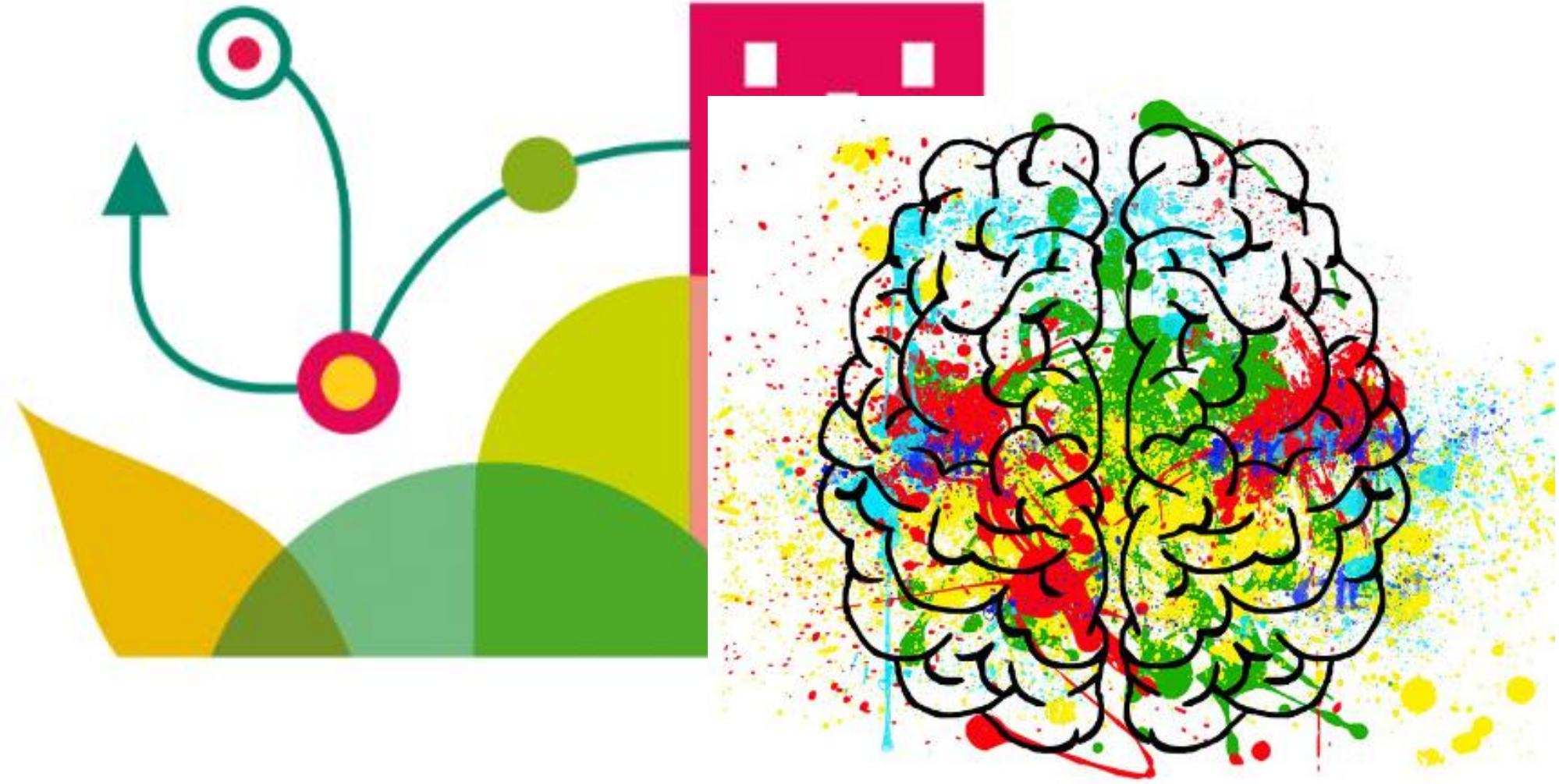
“It is easier to build a strong child than to repair broken men”

Frederick Douglass

Make a long story short…



Conoscere le traiettorie evolutive è importante per prevenire outcomes sfavorevoli



“Tutto ciò che ha valore nella società umana dipende dalle opportunità di progredire che vengono accordate ad ogni individuo.”

ALBERT EINSTEIN