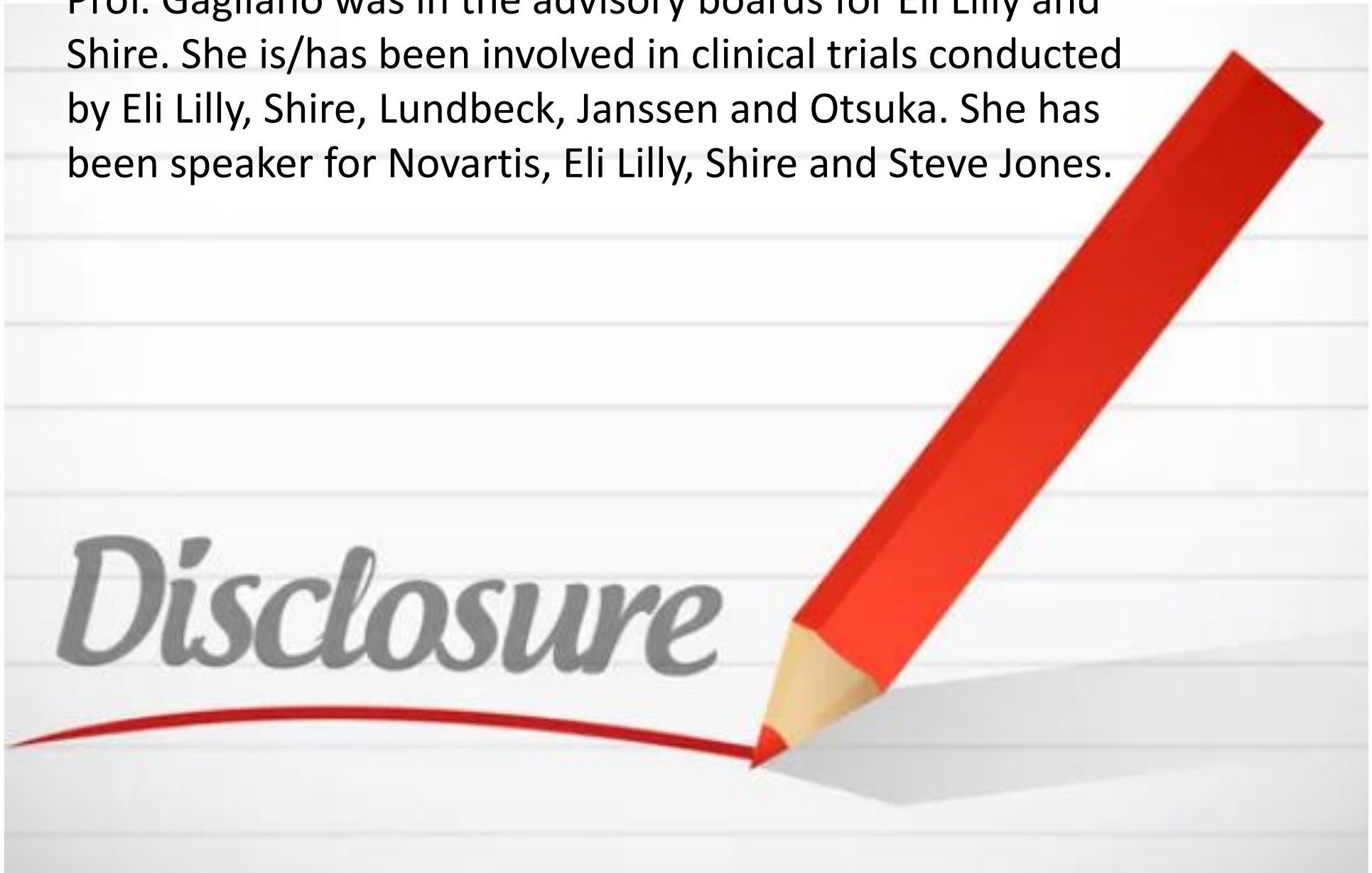
# Psicofarmacoterapia in età evolutiva

*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.



*When properly used,* medications have an important role in the treatment of **youth** with severe mental disorders…





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



*Primum non nocere…*

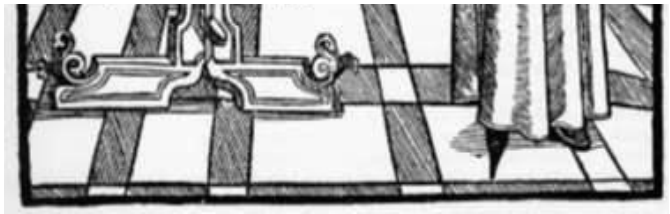


**Table 1. Evidence supporting atypical antipsychotic use for specific indications**

| 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

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

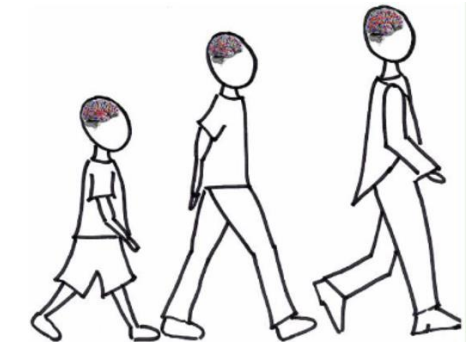
Daniele Piovani[1] · Antonio Clavenna[1] · Massimo Cartabia[1] · Maurizio Bonati[1]

Received: 16 December 2014 / Accepted: 18 May 2015 / Published online: 28 May 2015
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**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]<br>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



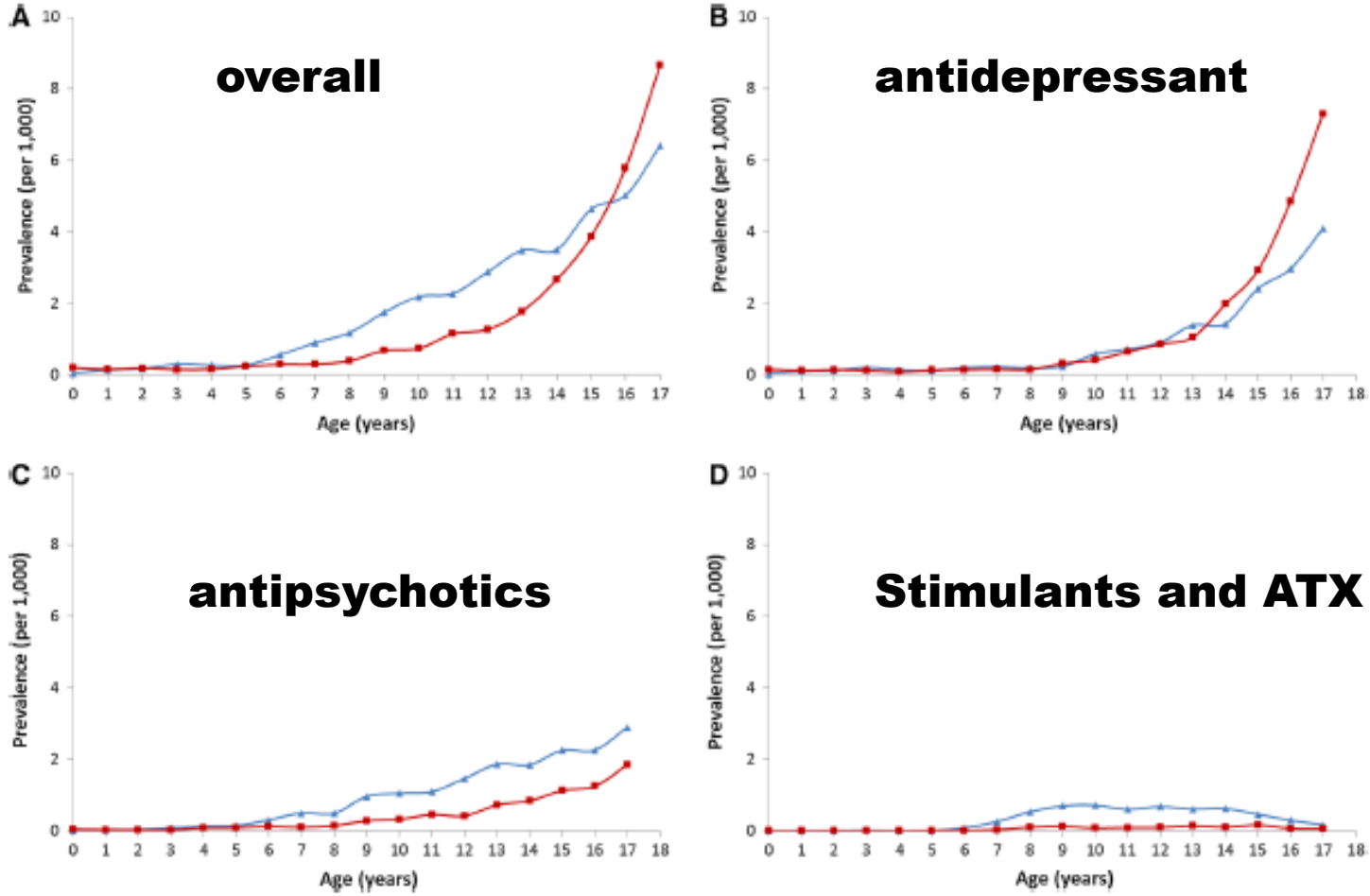



**Fig. 1** Prevalence (per 1,000) by age and gender (male: *blue lined triangle*; female: *red lined square*) of overall psychotropic drugs (**a**), antidepressants (**b**), antipsychotics (**c**), and ADHD medications (**d**)



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

## 2019 edition

Boris Lorberg, Chiara Davico, Dmytro Martsenkovskyi & Benedetto Vitiello

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 | |

## 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:

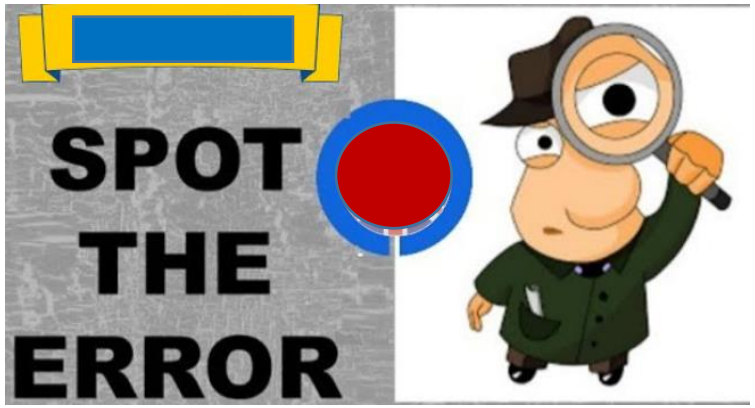
- Prima generazione**: Clorpromazina, Periciazina**
- Seconda generazione**: Clozapina (16 aa; >7 aa); Olanzapina (18 aa; > 7aa); Quetiapina (18 aa; >12 aa); Risperidone (18 aa), Aripiprazolo (>15 aa), Asenapina e Lurasidone (18 aa)**

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**



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Pp. 90–93
DOI: 10.1089/cap.2013.0133

*Brief Report*

# Child and Adolescent Psychiatrists' Attitudes and Practices Prescribing Second Generation Antipsychotics

Angie Mae Rodday, MS,[1,2] Susan K. Parsons, MD, MRP,[1,2,3] Christoph U. Correll, MD,[4] Adelaide S. Robb, MD,[5] Bonnie T. Zima, MD,[6] Tully S. Saunders, BS,[1] and Laurel K. Leslie, MD, MPH[1,2,3]

**off-label per indicazione**

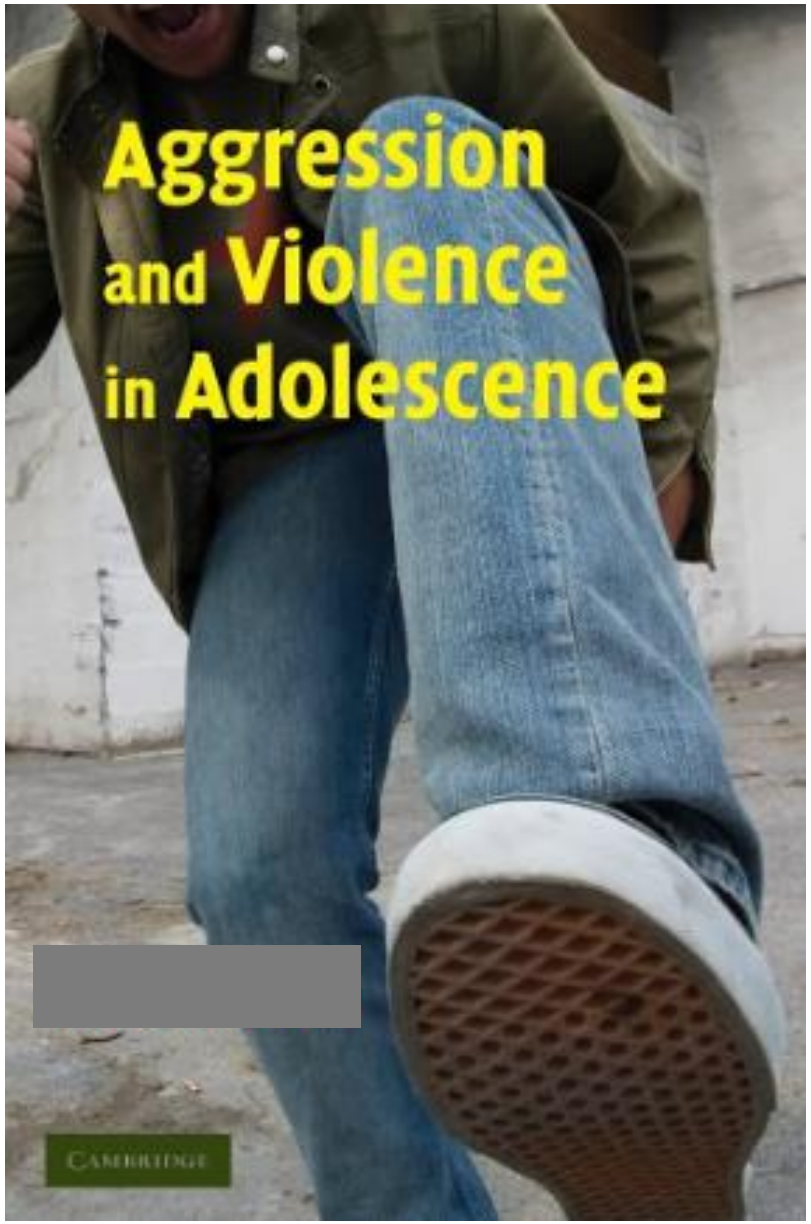
TABLE 1. REPORTED SGA USE AND APPROPRIATENESS OF SGA USE BY AGE GROUP

| | *Age 3–5* % *(num/denom)*[c] | *Age 6–12* % *(num/denom)*[c] | *Age 13–18* % *(num/denom)*[c] |
|---|---|---|---|
| Reported SGA use by disorders[a] | | | |
| FDA-approved indications | | | |
| Schizophrenia | 16.3% (33/202) | 47.2% (119/252) | 72.7% (218/300) |
| Bipolar disorder | 17.5% (44/252) | 36.3% (114/314) | 64.2% (210/327) |
| Autism spectrum disorders | 17.1% (52/305) | 30.8% (99/322) | 40.0% (130/325) |
| Off-label uses | | | |
| Mood disorders | 11.3% (33/291) | 16.7% (53/318) | 24.7% (82/332) |
| Disruptive behavior disorders (CD, ODD) | 7.3% (22/301) | 11.9% (38/320) | 18.5% (60/325) |
| ADHD/ADD | 4.0% (12/300) | 1.9% (6/319) | 2.5% (8/326) |
| Appropriateness of SGA use by symptoms[b] | | | |
| Target symptoms of disorders | | | |
| Has auditory hallucinations | 56.4% (186/330) | 87.0% (288/331) | 94.3% (315/334) |
| Has sudden mood changes | 15.1% (50/331) | 39.0% (130/333) | 55.9% (186/333) |
| Acts as if "driven by a motor" | 2.7% (9/332) | 8.5% (28/331) | 9.9% (33/333) |
| Aggressive symptoms | | | |
| Physically harms or hurts self on purpose | 35.4% (117/331) | 49.3% (164/333) | 59.0% (197/334) |
| Is explosive or easily angered | 16.9% (56/331) | 39.8% (132/332) | 53.5% (177/331) |
| Has prolonged temper tantrums | 15.8% (52/329) | 32.9% (110/334) | 50.0% (167/334) |
| Destroys property | 19.1% (63/330) | 31.3% (104/332) | 40.0% (134/335) |
| Gets into fights without thinking | 9.4% (31/329) | 25.5% (85/333) | 39.0% (130/333) |
| Threatens people verbally | 8.2% (27/328) | 22.6% (75/332) | 32.4% (108/333) |

# 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

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**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<br>• Tardive dyskinesia<br>• Neuroleptic malignant syndrome<br>• Hyperglycemia, diabetes mellitus<br>• Elevated prolactin, gynecomastia, amenorrhea<br>• Weight gain<br>• Dyslipidemia<br>• CBC abnormalities<br>• Lowered seizure threshold<br>• Dysphagia<br>• Hyperthermia/lowered heat tolerance<br>• 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<br>• EKG- baseline and periodically<br>• CBC- baseline and periodically<br>• Blood pressure each visit<br>• Pulse each visit<br>• Weight/height/BMI at each visit<br>• EPS evaluation baseline and weekly until dose stabilized<br>• Tardive dyskinesia evaluation every 3 months<br>• Clozapine-requires REMS<br>• Vision assessment for changes annually<br>• 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 attribuzione di significato a stimoli neutri o innocui**
- **ruolo fondamentale durante la formazione di sintomi psicotici**
- **disfunzione del sistema dopaminergico mesolimbico, implicato a sua volta nella regolazione del reward**
- **Scala di misurazione: Aberrant Salience Inventory**



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

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## Depression & Anxiety Medications

### SSRIs (Selective Serotonin Reuptake Inhibitors)

| Generic Name | Brand Names | FDA Approval Age/Indication | Other Common Uses in Children | Potential Side Effects | Monitoring |
|---|---|---|---|---|---|
| Citalopram* | Celexa | 18 and older | Obsessive Compulsive Disorder (OCD) | • Suicidal thoughts or behavior<br>• Weight gain<br>• Headache<br>• Stomach discomfort<br>• Sleep disturbance<br>• Flu-like symptoms if stopped too quickly<br>• Abnormal generalized bleeding risk | • Suicidal thoughts or behavior<br>• Height<br>• Weight<br>• Sodium levels in the blood |
| Escitalopram | Lexapro | 12-17 for depression | | | |
| Fluoxetine | Prozac | 8 and older for depression | | | |
| Paroxetine* | Paxil | 18 and older | | | |
| Fluvoxamine | Luvox | 8 and older for OCD | | | |
| Sertraline | Zoloft | 6 and older for OCD | | | |
| Vilazodone* | Vibryd | 18 and older | | | |
| *not approved for children and adolescents | | | | | |

### SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors)

| Generic Name | Brand Names | FDA Approval Age/Indication | Other Common Uses in Children | Potential Side Effects | Monitoring |
|---|---|---|---|---|---|
| Venlafaxine* | Effexor, Effexor XR | 18 and older | Obsessive Compulsive Disorder (OCD) | • Suicidal thoughts or behavior<br>• Weight gain<br>• Headache<br>• Seizures<br>• Hyponatremia/low blood sodium levels<br>• Hepatic toxicity/liver damage<br>• Skin reactions<br>• Stomach discomfort<br>• Sleep disturbance<br>• Flu-like symptoms if stopped too quickly<br>• Elevated blood pressure/pulse<br>• Abnormal bleeding risk | • Suicidal thoughts or behavior<br>• Height<br>• Weight<br>• Blood pressure during initial dose adjustment and periodically thereafter<br>• Hepatic function testing baseline and periodically<br>• CBC and EKG baseline and periodically |
| Duloxetine | Cymbalta | 18 and older | | | |
| Desvenlafaxine* | Pristiq | 18 and older | | | |
| Clomipramine | Anafranil | 10 and older for OCD | | | |
| Levmilnacipram* | Fetzima | 18 and older | | | |
| *not approved for children and adolescents | | | | | |

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Secondo Rystad energy la capacità di estrazione del litio non riuscirà più a soddisfare la domanda crescente tra il 2025 e il 2026, causando un ritardo nella produzione di veicoli elettrici a partire dal 2027…

## Mood Stabilizer Medications

| Generic Name | Brand Names | FDA Approval Age/Indication | Other Common Uses in Children | Potential Side Effects | Monitoring |
|---|---|---|---|---|---|
| Lithium | Eskalith, Eskalith CR, Lithobid | Approved for adolescents age 12 and older for bipolar disorder | Approved for manic episodes and bipolar maintenance for children >=12 years | • Narrow therapeutic index drug<br>• Chronic renal impairment<br>• Polyurea/polydipsia<br>• Tremor of hands, upper extremities<br>• Diarrhea<br>• Nausea/vomiting (take with food)<br>• Lethargy, weakness, confusion<br>• Hypothyroidism<br>• Teratogenicity | • Baseline then every 6-12 months CBC with differential, comprehensive chemistry panel‡, EKG, thyroid function testing<br>• Pregnancy test at baseline<br>• Drug levels after 1-2 weeks of treatment or each dosage change, monthly for 3 months, then every 3-6 months |
| Lamotrigine | Lamictal | Not FDA approved for bipolar disorder or mood lability in children and adolescents* | FDA approved for seizures ages 2 and older | • Potential Stevens-Johnson Syndrome (severe rash)-risk increases with rapid titration<br>• Multi-organ hypersensitivity reaction<br>• Suicidal ideation<br>• Dizziness/Ataxia<br>• Headache<br>• Nausea/vomiting<br>• Diplopia<br>• Aseptic meningitis<br>• Drug interaction with divalproex increases lamotrigine; with carbamazepine, phenytoin decreases lamotrigine levels<br>• Concomitant use with oral contraceptives decreases lamotrigine levels<br>• Withdrawal seizures | • Dermatologic evaluation at baseline and patient education regarding reporting of new skin rash<br>• Suicidal thoughts or behavior |

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

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## ADHD Medications

### Stimulants

| Generic Name | Brand Names | FDA Approval Age/Indication | Other Common Uses in Children | Potential Side Effects | Monitoring |
|---|---|---|---|---|---|
| Amphetamine Mixed Salts | Adderall, Adderall XR | 3 and older; 6 and older (XR) | None | • Increased blood pressure<br>• Increased heart rate<br>• Tics (abnormal movement most often in the face)<br>• Weight loss<br>• Loss of appetite<br>• Sleep disturbance<br>• Irritability/anxiety | • Height<br>• Weight<br>• Heart rate<br>• Blood pressure |
| Dextroamphetamine | Dexedrine, Zenzedi | 3 and older | | | |
| Lixdexamfetamine | Vyvanse | 6 and older | | | |
| Methylphenidate | Ritalin, Ritalin SR, Ritalin LA, Methylin, Methylin ER, Metadate ER, Metadate CD, Quillivant XR, Concerta | 6 and older | | | |
| Dexmethylphenidate | Focalin, Focalin XR | 6 and older | | | |

### Other ADHD Medications

| Generic Name | Brand Names | FDA Approval Age/Indication | Other Common Uses in Children | Potential Side Effects | Monitoring |
|---|---|---|---|---|---|
| Atomoxetine | Strattera | 6 and older | None | • Increased blood pressure<br>• Increased heart rate<br>• Sleep disturbance<br>• Stomach discomfort<br>• Dizziness | • Height<br>• Weight<br>• Heart rate<br>• Blood pressure |
| Clonidine | Catapres, Kapvay | IR form not FDA approved for children; ER form ages 6-17 | None | • Low blood pressure<br>• Decreased heart rate<br>• Feeling faint or dizzy<br>• Feeling tired | • Heart rate<br>• Blood pressure |
| Guanfacine | Tenex, Intuniv | 6 and older | None | | |

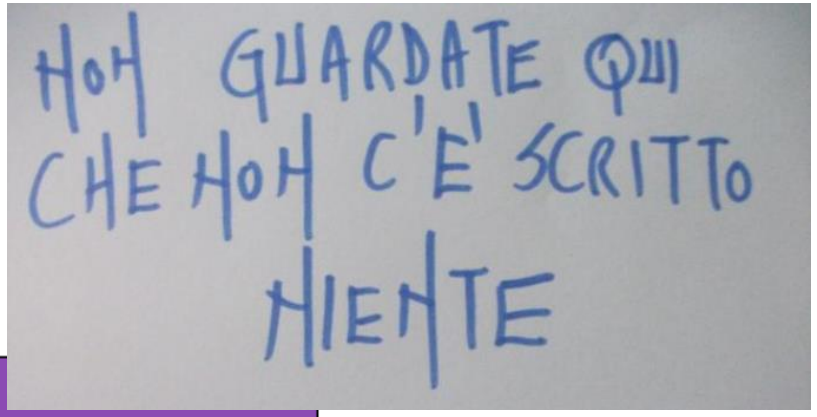


Psychotropic Medications in Children and Adolescents: Guide for Use and Monitoring

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**Definition of Psychotropic Medication:**
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# Sleep Medications

| Generic Name | Brand Names | FDA Approval Age/Indication | Other Common Uses in Children | Potential Side Effects | Monitoring |
|---|---|---|---|---|---|
| Melatonin | Dosing: 0.05-0.15mg/kg/day up to total dose of 5mg/day in children and adolescents | Not FDA regulated | Regulated by FDA as a dietary supplement and not as a medication | • Sedation<br>• May adversely affect reproductive organ development<br>• Give directly before sleep onset desired due to short half-life | • Caution - Do not operate machinery or power equipment until medication effects with use of this medication<br>• Daytime sedation/hangover |
| Ramelteon* | Rozerem | 18 and older | None | • Abnormal thinking and behavioral changes<br>• CNS depression<br>• Decreased testosterone<br>• Hyperprolactinemia | • Caution - Do not operate machinery or power equipment until medication effects with use of this medication<br>• Daytime sedation/hangover |
| Hydroxyzine | Vistaril, Atarax | All ages for anxiety- and all ages for Pruritis/ for the treatment of Itchy skin- | Approved for anxiety and tension; approved as pre-procedural sedation and following general anesthesia | • Drowsiness<br>• Dizziness<br>• Dry mouth<br>• Nausea<br>• Nervousness<br>• Blurred vision<br>• Decreased mental alertness<br>• Paradoxical excitation associated with small risk of QT prolongation and Torsades | • Caution - Do not operate machinery or power equipment until medication effects with use of this medication<br>• Daytime sedation/hangover |

*not approved as a sedative/hypnotic in children and adolescents

## *Quale classe di farmaci per Francesco……?*

Iperattività/impulsività/inattenzione

disregolazione emozionale

Ideazione suicidaria

Depersonalizzazione
e derealizzazione

Insonnia



# *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

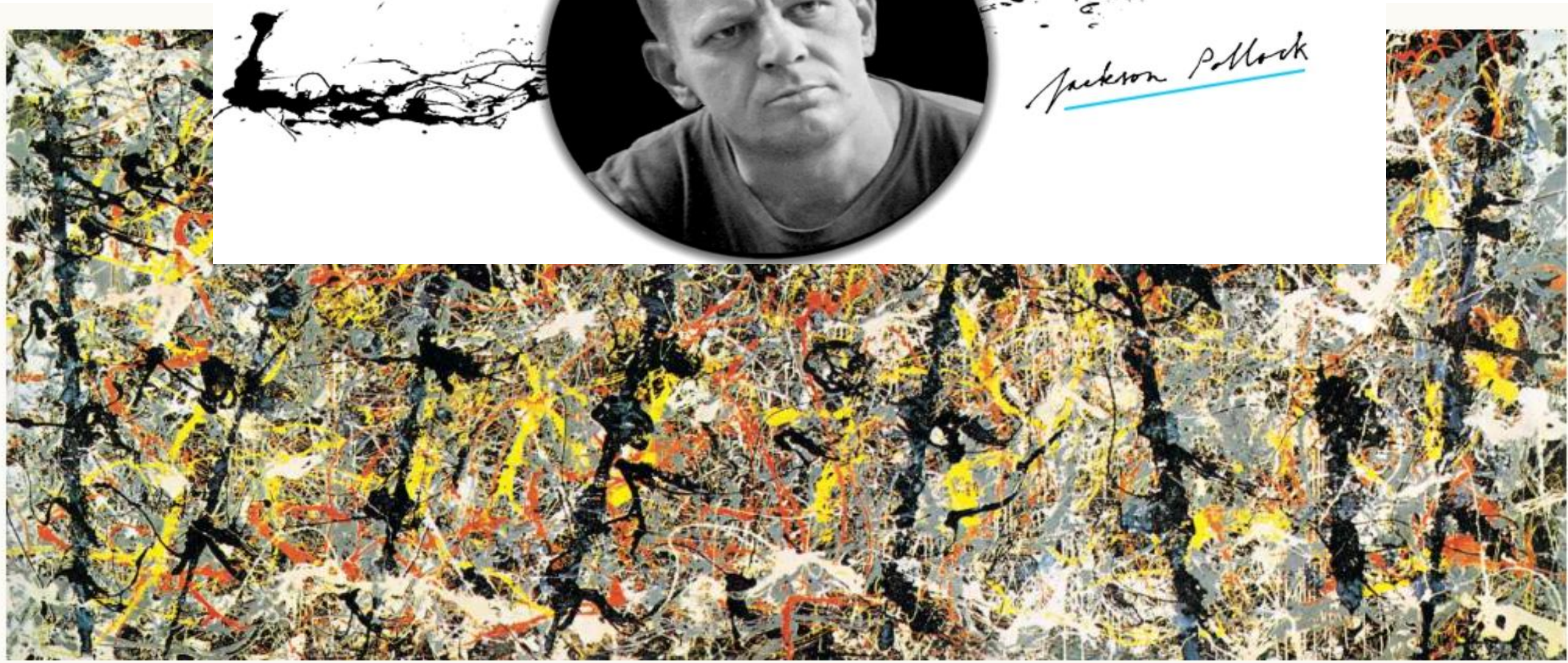
Depression & Anxiety Medications

Mood Stabilizer Medications

ADHD Medications

Sleep Medications






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

# Are neurodevelopmental disorders discrete conditions?

Emilia Misheva considers the evidence

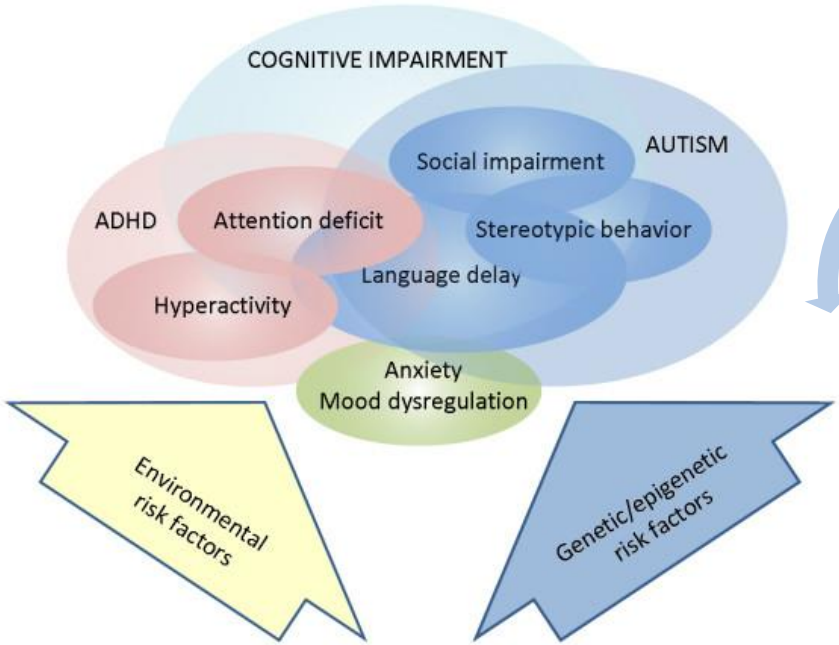
There is abundant evidence to indicate that neurodevelopmental disorders tend to co-occur, rather than existing as individual conditions. Could this 'comorbidity' reflect an overall atypical course of neural development, which manifests in various ways?

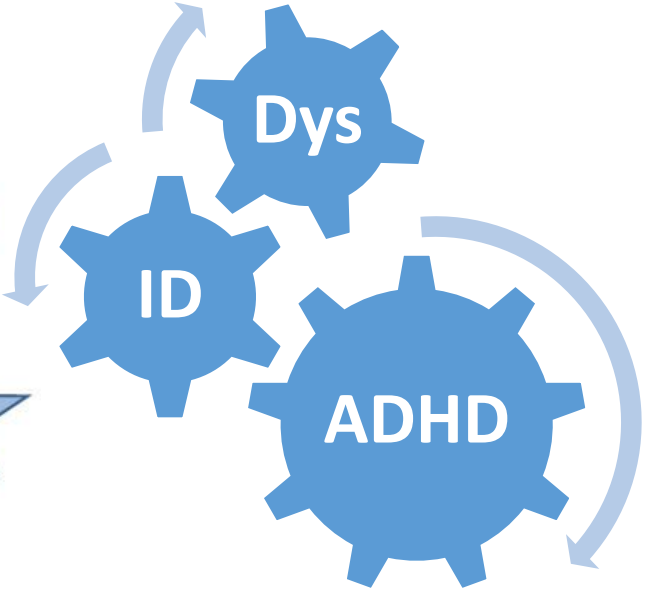
As psychologists, many of us are familiar with the idea that diagnostic labels could stifle the thinking of both those they're attached to and the practitioners supposedly helping them. Do these labels describe discrete, objectively defined conditions, with different established causal origins and presentations? The evidence paints a more complex picture.

Instead, some researchers in the field have argued that comorbidity shows neurodevelopmental disorders are not completely distinct conditions. Improved awareness in this area is important: the evidence can help practitioners develop more sophisticated formulations and interventions that incorporate a [illegible] of neurodevelopment as







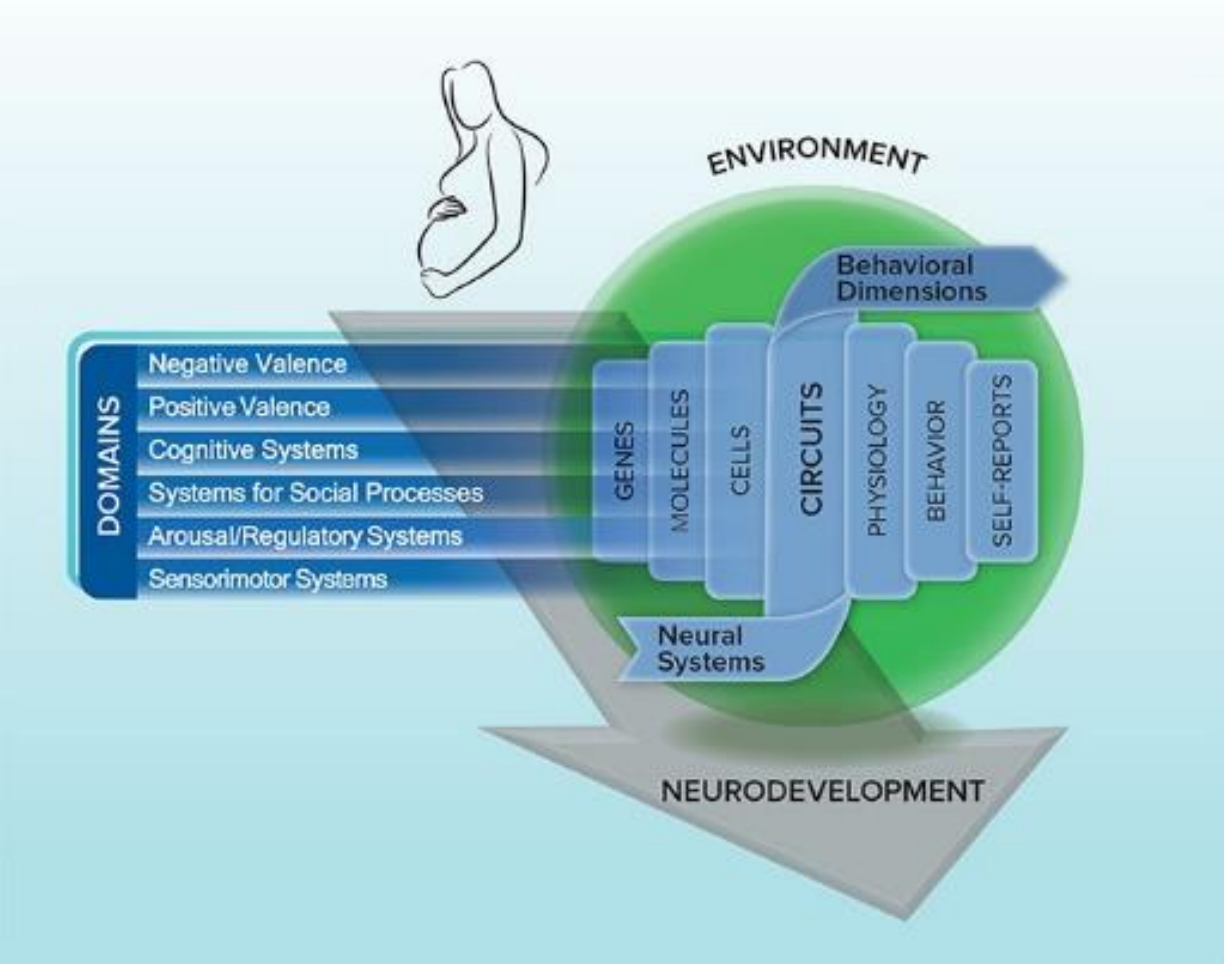




…it cannot be ruled out that in the future neurodevelopmental disorders **will be considered basically as a single large group** that encompasses numerous subgroups characterized by a predominant impairment, respectively, of intellectual functions (intellectual disability), intersubjectivity (autism spectrum disorder), or language (communication disorders)…

Annio Posar and Paola Visconti, Neurodevelopmental Disorders between Past and Future, Pediatr Neurosci. 2017 Jul-Sep; 12(3): 301–302.

Freeman D, Sheaves B, Waite F, Harvey AG, Harrison PJ. **Sleep disturbance and psychiatric disorders**. Lancet Psychiatry. 2020 Jul;7(7):628-637

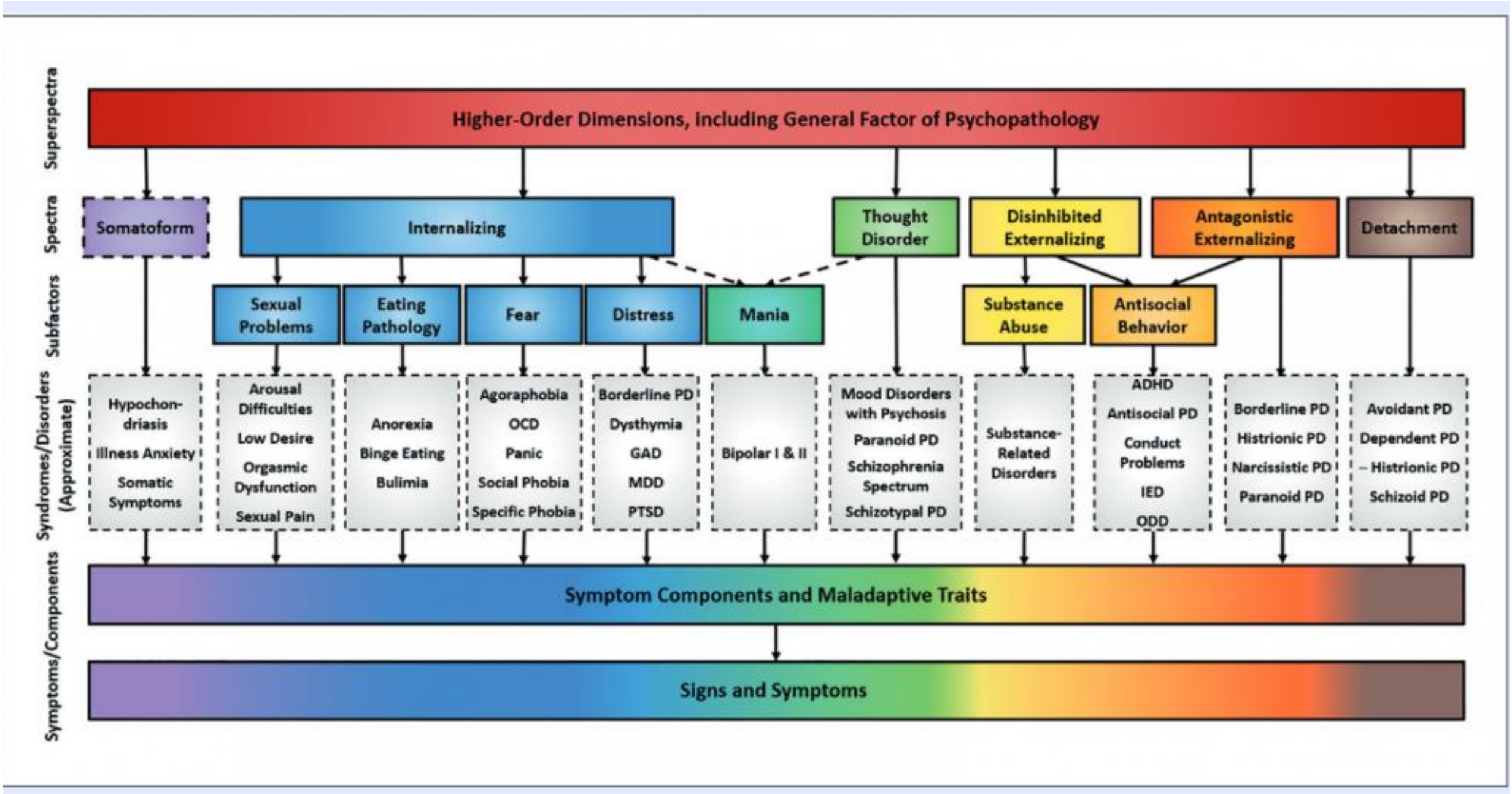
The importance of disruption to sleep and circadian rhythms across multiple mental health problems is also seen in the *Research Domain Criteria framework*, with the **arousal and regulatory system** **being one of the six key domains of human functioning likely to affect mental health**




**The RDoC framework is a research strategy that is implemented as a matrix of elements**

The matrix is a dynamic structure that currently focuses on six major domains of human functioning (e.g., Negative Valence Systems, Cognitive Systems).

Kozak MJ, Cuthbert BN. The NIMH Research Domain Criteria initiative: background, issues, and pragmatics. Psychophysiology 2016; 53: 286–97.




*Kotov,, et al. (7 May 2021). "The Hierarchical Taxonomy of Psychopathology (HiTOP): A Quantitative Nosology Based on Consensus of Evidence". Annual Review of Clinical Psychology. **17** (1): 83–108. doi:10.1146/annurev-clinpsy-081219-093304. PMID 33577350. S2CID 231909649.*

Michelini G, et al, **Where do neurodevelopmental conditions fit in transdiagnostic psychiatric frameworks? Incorporating a new neurodevelopmental spectrum**. World Psychiatry. 2024 Oct;23(3):333-357.

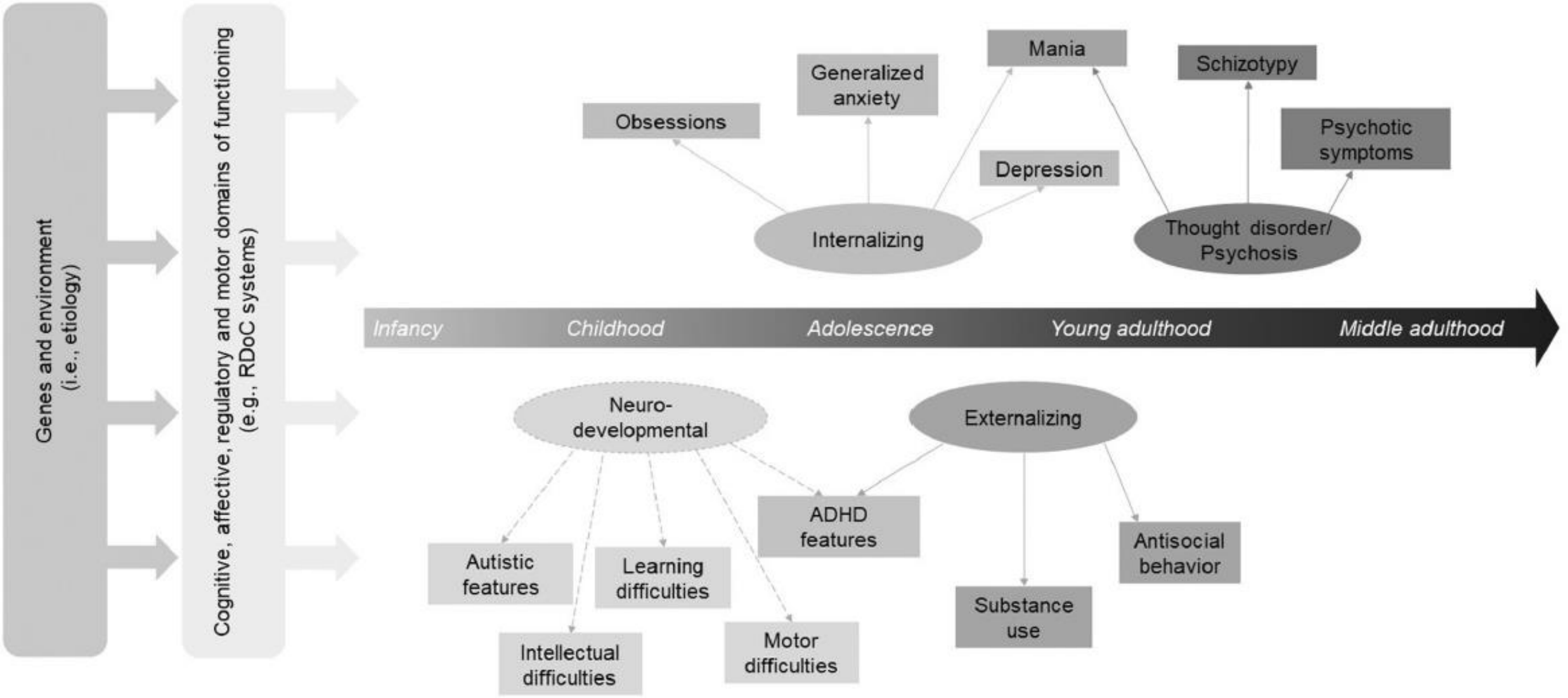



**Figure 1** Graphic representation of the proposed neurodevelopmental spectrum alongside dimensions currently in transdiagnostic frameworks. ADHD – attention- deficit/hyperactivity disorder, RDoC – Research Domain Criteria.

***Quale classe di farmaci per Francesco……?***

Iperattività/impulsività/inattenzione



Linee guida **SINPIA**
***ADHD: diagnosi & terapia farmacologiche***
Approvazione CD: 24 giugno 2002

# Linee-guida per la diagnosi e la terapia farmacologica del Disturbo da Deficit Attentivo con Iperattività (ADHD) in età evolutiva.

**12a Raccomandazione**
*(Linee Guida Cliniche; forza delle evidenze: buona; forza della raccomandazione: forte):*
Prima di iniziare il trattamento, occorre definire le modalità di titolazione del farmaco (es. 5 mg/die di metilfenidato con successivi incrementi posologici di 5mg/dose/giorno) ed i metodi/ strumenti per valutare la risposta al farmaco (es. questionari per genitori ed insegnanti) e gli eventuali effetti collaterali.

**13a Raccomandazione**
*(Standard Minimo; forza dellíevidenze: buona; forza della raccomandazione: forte):*
Prima di iniziare la terapia con psicostimolanti è indispensabile concordare con i genitori ed il paziente la periodicità dei controlli clinici. Tali controlli dovrebbero avere cadenza settimanale durante la fase di titolazione, mensile durante la fase di mantenimento. Ad ogni controllo clinico saranno valutati effetti terpautici , segni vitali ed eventuali effetti indesiderati.

**14a Raccomandazione**
*(LineeGuida Cliniche; forza dell'evidenze: buona; forza della raccomandazione: forte):*
Gli effetti collaterali degli psicostimolanti sono rari, di breve durata; quelli più comuni sono: ritardo nell'addormentamento, diminuzione dell'appetito, perdita di peso, tics, dolori addominali, cefalea, ed irrequietezza. Tali effetti sono rapidamente responsivi a modificazioni di dose od alla sospensione del trattamento.

**15a Raccomandazione**
*(Linee Guida Cliniche; forza dell'evidenza: scarsa; forza della raccomandazione: forte):*
Quando la modalità di trattamento prescelta risulti inefficace, il clinico deve riconsiderare: la diagnosi iniziale, l'aderenza al trattamento da parte del paziente e della sua famiglia, la presenza di altre patologie associate, la possibilità di trattamenti alternativi.

Nel **2003, a Cagliari**, si sono riuniti numerosi specialisti della salute mentale dell'età evolutiva e rappresentanti delle associazioni mediche specialistiche, per discutere del percorso diagnostico e del trattamento delle sindromi da ADHD in Italia.

In seguito alla Conferenza, è stato avviato un processo per l'apertura di un Registro nazionale per l'ADHD, primo esempio al mondo nel suo genere, che inizierà ad operare nel **settembre 2004** con l'avvio del prossimo anno scolastico.

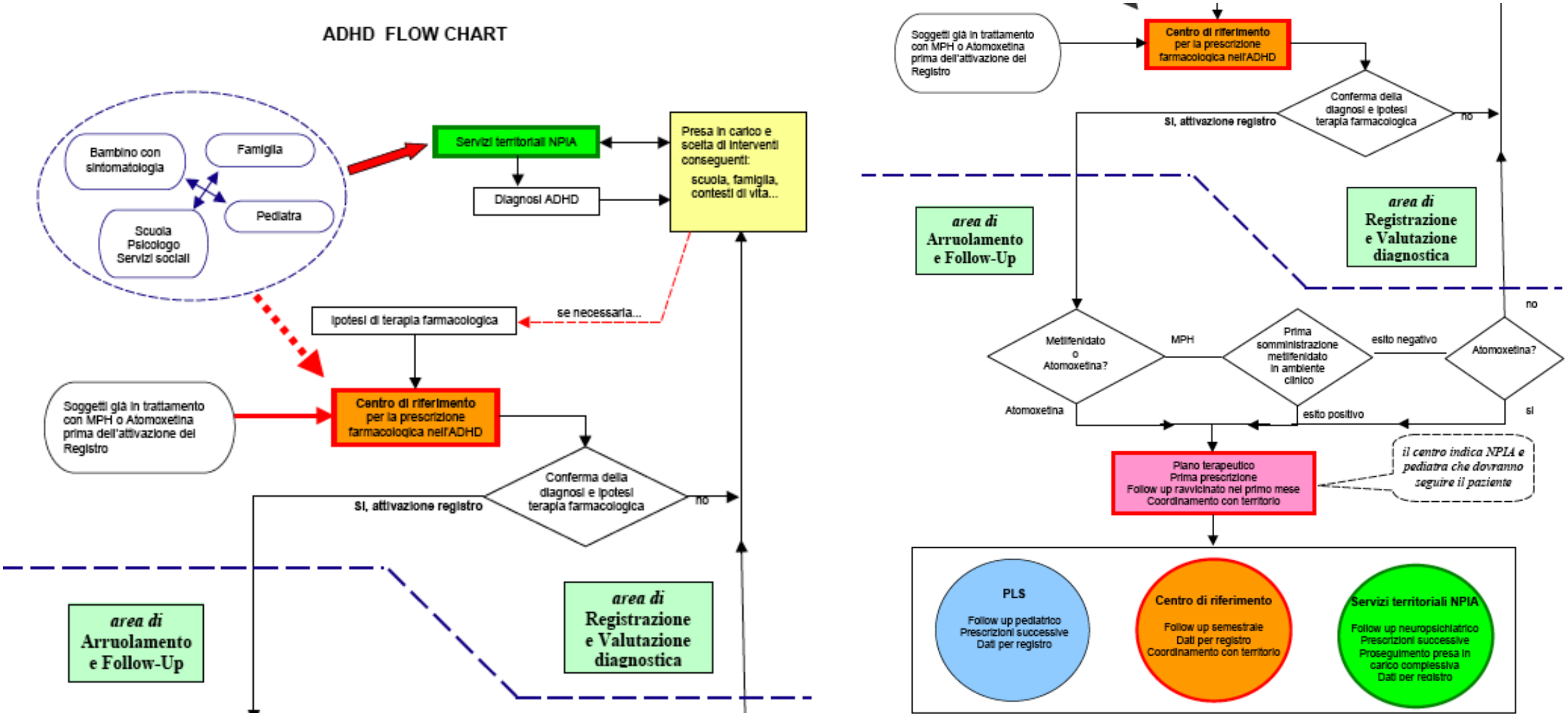



**L'attività di farmacovigilanza è stata avviata nell'aprile 2007**

nel giugno dello stesso anno è stato attivato il Registro nazionale per l'ADHD (età 6-18 anni) **dall'Istituto Superiore di Sanità** su **mandato dell'Agenzia Italiana del Farmaco** (AIFA).

## Obiettivi del Registro

- Accuratezza della diagnosi
- Appropriatezza terapeutica
- Sicurezza d'uso del farmaco
- Integrazione dei vari strumenti terapeutici


ADHD FLOW CHART
Bambino con sintomatologia
Famiglia
Pediatra
Scuola
Psicologo
Servizi sociali
Servizi territoriali NPIA
Diagnosi ADHD
Presa in carico e scelta di interventi conseguenti:
scuola, famiglia, contesti di vita...
Ipotesi di terapia farmacologica
se necessaria...
Soggetti già in trattamento con MPH o Atomoxetina prima dell'attivazione del Registro
Centro di riferimento per la prescrizione farmacologica nell'ADHD
Conferma della diagnosi e ipotesi terapia farmacologica
SI, attivazione registro
no
area di Arruolamento e Follow-Up
area di Registrazione e Valutazione diagnostica
Soggetti già in trattamento con MPH o Atomoxetina prima dell'attivazione del Registro
Centro di riferimento per la prescrizione farmacologica nell'ADHD
Conferma della diagnosi e ipotesi terapia farmacologica
SI, attivazione registro
no
area di Arruolamento e Follow-Up
area di Registrazione e Valutazione diagnostica
Metilfenidato o Atomoxetina?
MPH
Prima somministrazione metilfenidato in ambiente clinico
esito negativo
Atomoxetina?
no
Atomoxetina
esito positivo
si
Piano terapeutico
Prima prescrizione
Follow up ravvicinato nel primo mese
Coordinamento con territorio
il centro indica NPIA e pediatra che dovranno seguire il paziente
PLS
Follow up pediatrico
Prescrizioni successive
Dati per registro
Centro di riferimento
Follow up semestrale
Dati per registro
Coordinamento con territorio
Servizi territoriali NPIA
Follow up neuropsichiatrico
Prescrizioni successive
Proseguimento presa in carico complessiva
Dati per registro




**Negli USA** prevale l'indicazione al trattamento farmacologico da subito.

Invece **in Europa**:

- in seguito alla diagnosi, viene **dato inizio alla terapia psico-comportamentale,** in accordo con le Linee Guida europee, internazionali e nazionali

- **la terapia farmacologica viene considerata solo se quella comportamentale non risulta sufficiente** per un adeguato controllo della sintomatologia

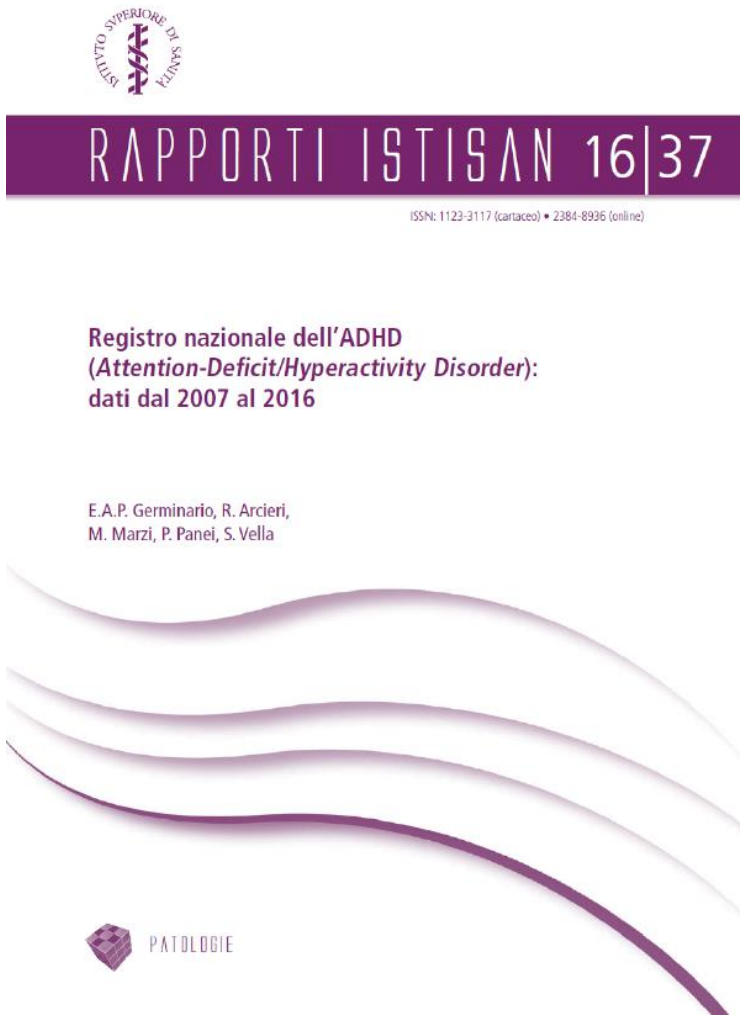
alcune linee guida Europee riconoscono che per nelle forme più gravi del disturbo sia quasi sempre necessario il trattamento farmacologico

qualora alcune settimane di intervento psicoeducativo dovessero risultare inefficaci, il trattamento farmacologico dovrebbe essere sempre consigliato in combinazione con interventi psico-comportamentali (Taylor et at, Eur, Child Adolesc, 104 Psychiatry 13: S1 7-30, 2004)

**la prima linea di trattamento è costituita dai farmaci psicostimolanti**

**nel caso tale categoria di farmaci non dimostri l'effetto desiderato, può essere utilizzato un farmaco non stimolante.**

al momento della stesura del presente documento, il farmaco psicostimolante approvato in Italia è il **metilfenidato**; mentre l'**atomoxetin**a è l'unico farmaco tra i non stimolanti




# Registro ADHD nell'età evolutiva

Tutti i bambini con sospetto ADHD vengono inviati ad un centro di riferimento che è il solo autorizzato a prescrivere i farmaci.

Il centro di riferimento è responsabile della diagnosi e della verifica dell'appropriatezza del piano terapeutico.

Il pediatra è responsabile del paziente per quanto riguarda la visita mensile, la prescrizione dei farmaci in base al piano terapeutico e la rilevazione e segnalazione degli eventi avversi.

La terapia comportamentale è assicurata dalle UONPIA territoriali

**Il 72% dei pazienti ha assunto il MPH come farmaco di prima scelta.**

È importante sottolineare il passaggio progressivo dall'uso prevalente dell'ATX, come farmaco di prima scelta al MPH, con un'inversione nel rapporto tra i due principi attivi

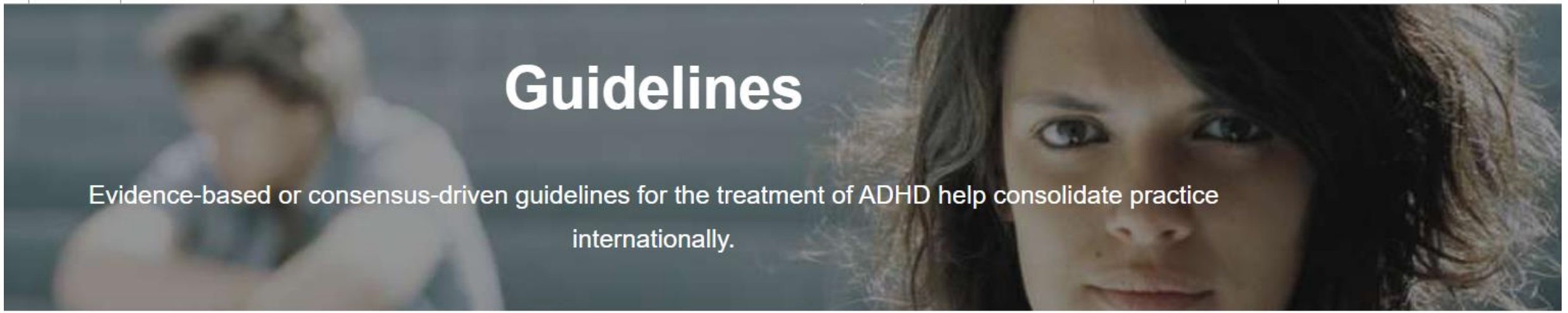
Quindi, l'attitudine prescrittiva dei neuropsichiatri italiani si è allineata a quella di altri paesi europei

https://adhd-institute.com/disease-management/guidelines/

ADHD INSTITUTE
an educational platform developed and funded by Takeda

Takeda

BURDEN OF ADHD | ASSESSMENT & DIAGNOSIS | DISEASE MANAGEMENT | MEETINGS & EVENTS | PUBLICATIONS 2022




Home | Disease management » Guidelines

There are multiple guidelines available to guide clinicians working in the field of ADHD in children, adolescents and adults, and different guidelines may also have different recommendations about specific treatment approaches.[1-4] These guidelines have been continually updated as new evidence becomes available and new therapeutics are developed, including the[1-4]:

- Canadian ADHD Resource Alliance (CADDRA) guidelines 2020
- German guidelines 2018
- National Institute of Health and Care Excellence (NICE) guidelines 2018
- Spanish guidelines 2017.

**Please note that this is a selection of guidelines and not an exhaustive list.**

## What is ‘optimal management of ADHD?

Individual’s level of symptoms and functional impairment are reduced, quality of life is improved and symptom benefits outweigh any unwanted adverse effects.

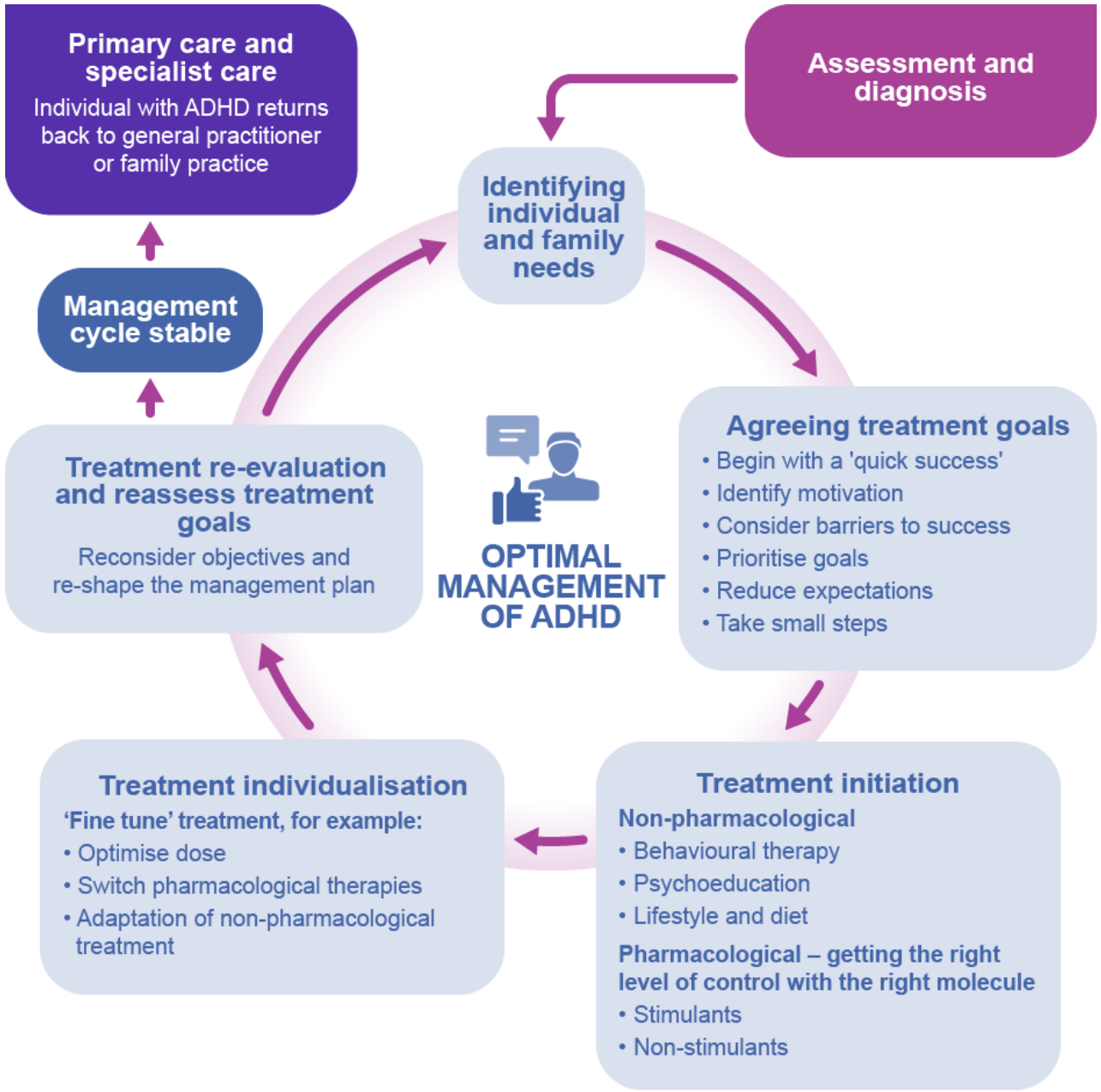
This description is supported by some of the European and international guidelines for ADHD and in the literature.

## How may ‘optimal management of ADHD’ be achieved?

A treatment plan for ADHD is recommended to follow clinical guidelines.

*It is also important for clinicians to adopt an optimised approach to management of ADHD to:*

- identify the unique needs of the individual with ADHD and their family;
- agree treatment goals;
- develop a personalized treatment plan;
- re-evaluate treatment response;
- ensure goals are updated in line with the individual’s needs




https://adhd-institute.com/disease-management/guidelines/

https://adhd-institute.com/disease-management/guidelines/




**Personalised treatment may be key to meeting individualised goals**.

The 'optimal management of ADHD' process should consider **input from the individual with ADHD, family or careers, and school to help establish goals and appropriate therapy** (non-pharmacological and/or pharmacological).
In adults with ADHD, input from spouses, siblings and friends may be considered.

**A tailored multimodal treatment plan centered** should aim to address multiple aspects of the disorder including social, emotional, behavioural and academic or work-related issues

Guidelines recommend that psychoeducation be initially available to the individual with ADHD, and to their family or careers and the people who interact often with them.

**For children aged <6 years:**
•Non-pharmacological interventions are recommended.

**For children or adolescents aged ≥6 years and adults with ADHD:**
•Non-pharmacological interventions are recommended,
with pharmacological treatment available for those who request it or have persisting symptoms.

**For children or adolescents aged ≥6 years with severe ADHD and adults with ADHD:**
•Pharmacological treatment is recommended as the first line of therapy, supported by non-pharmacological interventions

Attention-Deficit / Hyperactivity Disorder (ADHD) CDC Centers for Disease Control and Prevention

# Attention-Deficit / Hyperactivity Disorder (ADHD)

Attention-Deficit / Hyperactivity Disorder (ADHD) Home

## ADHD Treatment Recommendations

The American Academy of Pediatrics (AAP) published a clinical practice guideline that provides recommendations for the diagnosis and treatment of children with attention-deficit/hyperactivity disorder (ADHD). This guideline is based on the best available evidence, and is intended for use by primary care providers, such as pediatricians, family physicians, and other healthcare providers.



## Diagnosis and Evaluation of ADHD

The AAP guidelines for diagnosis and evaluation of ADHD recommend that primary care providers complete these steps:

- Evaluate children and adolescents ages 4 to 18 years for ADHD if they are having academic or behavioral problems and show inattention, hyperactivity, or impulsivity.
- Get reports on the child's symptoms from parents or guardians, school staff, and mental health workers involved with their care, and get information from the child or adolescent as well.
- Use rating scales and other sources to document the symptoms and ensure that DSM-5 criteria have been met.
- Rule out any other possible conditions that can cause similar symptoms.
- Screen for other conditions that might coexist with ADHD, including emotional or behavioral disorders (such as anxiety, depression, and behavior problems), developmental disorders (such as learning and language disorders or autism spectrum disorder), and physical conditions (such as tics, sleep disorders, or apnea).
- Refer children to a specialist if they detect co-occurring conditions that they are not experienced in treating or diagnosing.

Read more about this recommendation.

**Did you know?**

The behavior therapy with best evidence with young children with ADHD is **Parent Training in Behavior Management**.

## Treatment

The AAP guidelines for treatment of ADHD recommend:

Children and adolescents with ADHD should be treated the same as would any other child or adolescent with special healthcare needs, following the principles of the chronic care model and the medical home.





### Children ages 4-6 years

- The first line of treatment should include
  - Parent training in behavior management; and/or
  - Behavioral classroom interventions (if available).
- Methylphenidate may be used if behavioral interventions do not provide significant improvement and the child continues to have serious problems.

### Children and adolescents 6-18 years

Recommended treatment for children and adolescents includes

- FDA-approved medications along with
- Parent training in behavior management and/or
- Behavioral classroom interventions.

Treatments often work best when used together.

For all children attending school, the school is a necessary part of any treatment plan. These plans can include

- Educational interventions; and
- Individual school supports, such as school environment and behavioral supports.

School treatment plans often include an Individualized Education Program (IEP) or a 504 plan that describes accommodations.

### Any child or adolescent who is taking medication

The AAP guidelines for treatment of ADHD recommend that

- The primary care provider adjusts the patient's medication dose as needed to achieve the most benefit with the least amount of tolerable side effects.
- For adolescents, medications should be used with patient approval.

Read more about this recommendation.

Read more about the role of healthcare providers in assisting children with special needs.

## Reference

American Academy of Pediatrics, Subcommittee on Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*, September 30th, 2019.

Page last reviewed: August 9, 2022



The updated guideline, ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents, was **developed by the American Academy of Pediatrics and endorsed by the American Academy of Family Physicians.**

This guideline is based on the best available evidence, and is intended for use by primary care providers, such as pediatricians, family physicians, and other healthcare providers.

NICE National Institute for Health and Care Excellence

NICE guideline

# Attention deficit hyperactivity disorder: diagnosis and management

NICE guideline
Published: 14 March 2018
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## Service organisation

1.1.2 Mental health services for children, young people and adults, and child health services, **should form multidisciplinary specialist ADHD teams** and/or clinics for children and young people, and separate teams and/or clinics for adults. These teams and clinics should have **expertise** in the diagnosis and management of ADHD, and should:

- provide diagnostic, treatment and consultation services for people with ADHD who have complex needs, or where general psychiatric services are in doubt about the diagnosis and/or management of ADHD
- put in place systems of communication and protocols for information sharing among paediatric, child and adolescent, forensic, and adult mental health services for people with ADHD, including arrangements for transition between child and adult services
- produce local protocols for shared care arrangements with primary care providers, and ensure that clear lines of communication between primary and secondary care are maintained
- ensure age-appropriate psychological services are available for children, young people and adults with ADHD, and for parents or carers.

NICE National Institute for Health and Care Excellence

NICE guideline

# Attention deficit hyperactivity disorder: diagnosis and management

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## Service organisation

A young person with ADHD receiving treatment and care from CAMHS or paediatric services should be **reassessed at school-leaving age to establish the need for continuing treatment into adulthood**. If treatment is necessary, arrangements should be made for **a smooth transition to adult services** with details of the anticipated treatment and services that the young person will require.

1.1.5 During the transition to adult services, a **formal meeting** involving CAMHS and/or paediatrics and adult psychiatric services should be considered, and full information provided to the young person about adult services. For young people aged 16 years and older, the **care programme approach (CPA)** should be used as an aid to transfer between services. The young person, and when appropriate the parent or carer, should be involved in the planning. **[2008]**

1.1.6 After transition to adult services, adult healthcare professionals should carry out a comprehensive assessment of the person with ADHD that includes personal, educational, occupational and social functioning, **and assessment of any coexisting conditions, especially drug misuse, personality disorders, emotional problems and learning difficulties**. **[2008]**

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

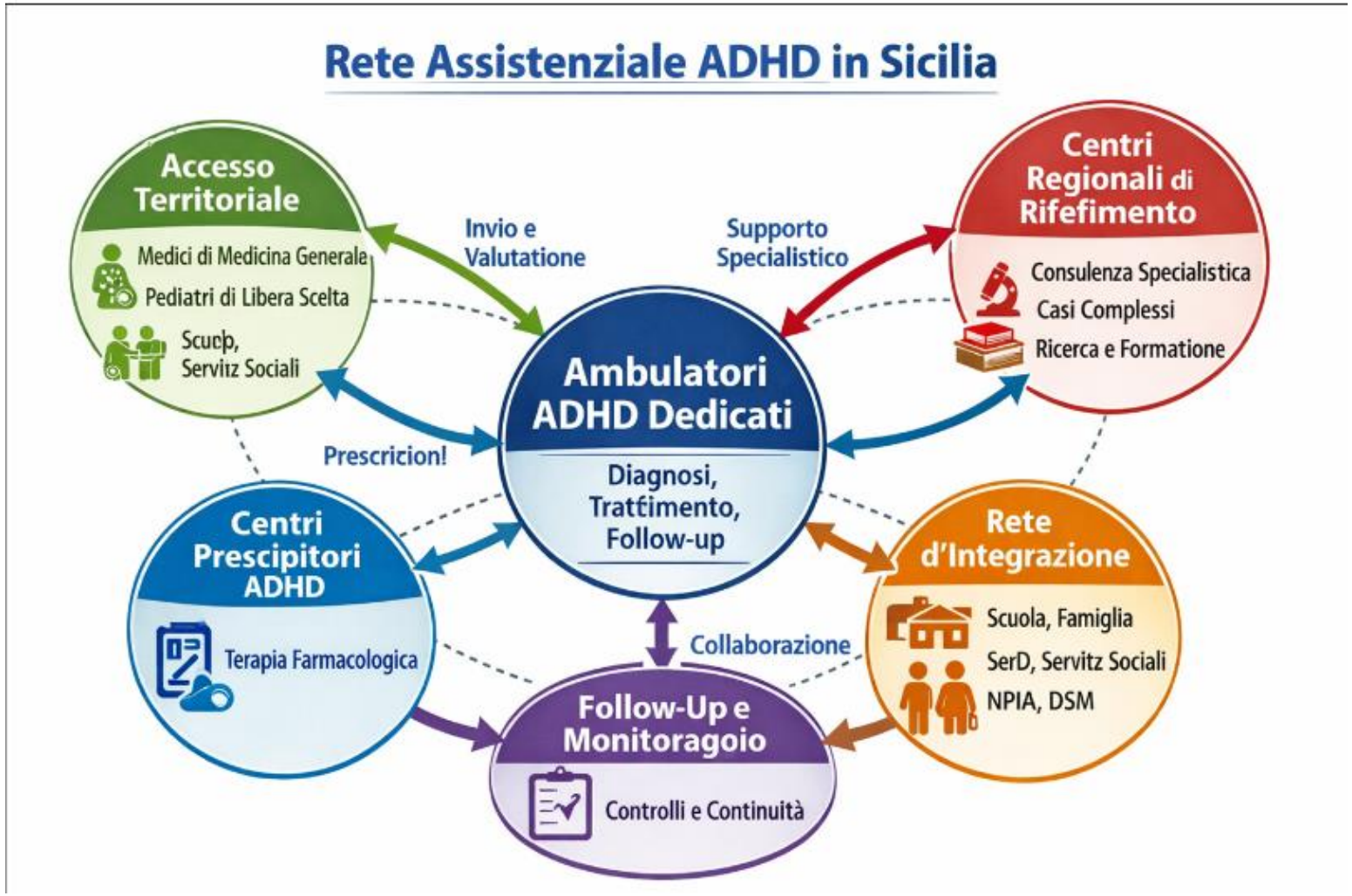
## SINPIA practical guide for the pharmacological treatment of ADHD in children and adolescents

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]

SINPIA
Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza

**PERCORSO DIAGNOSTICO TERAPEUTICO ASSISTENZIALE (PDTA) PER IL DISTURBO DA DEFICIT D'ATTENZIONE E/O IPERATTIVITA' (ADHD)**

**Gruppo Studio Regionale sui Disturbi da Deficit di attenzione e/o Iperattività (ADHD)**



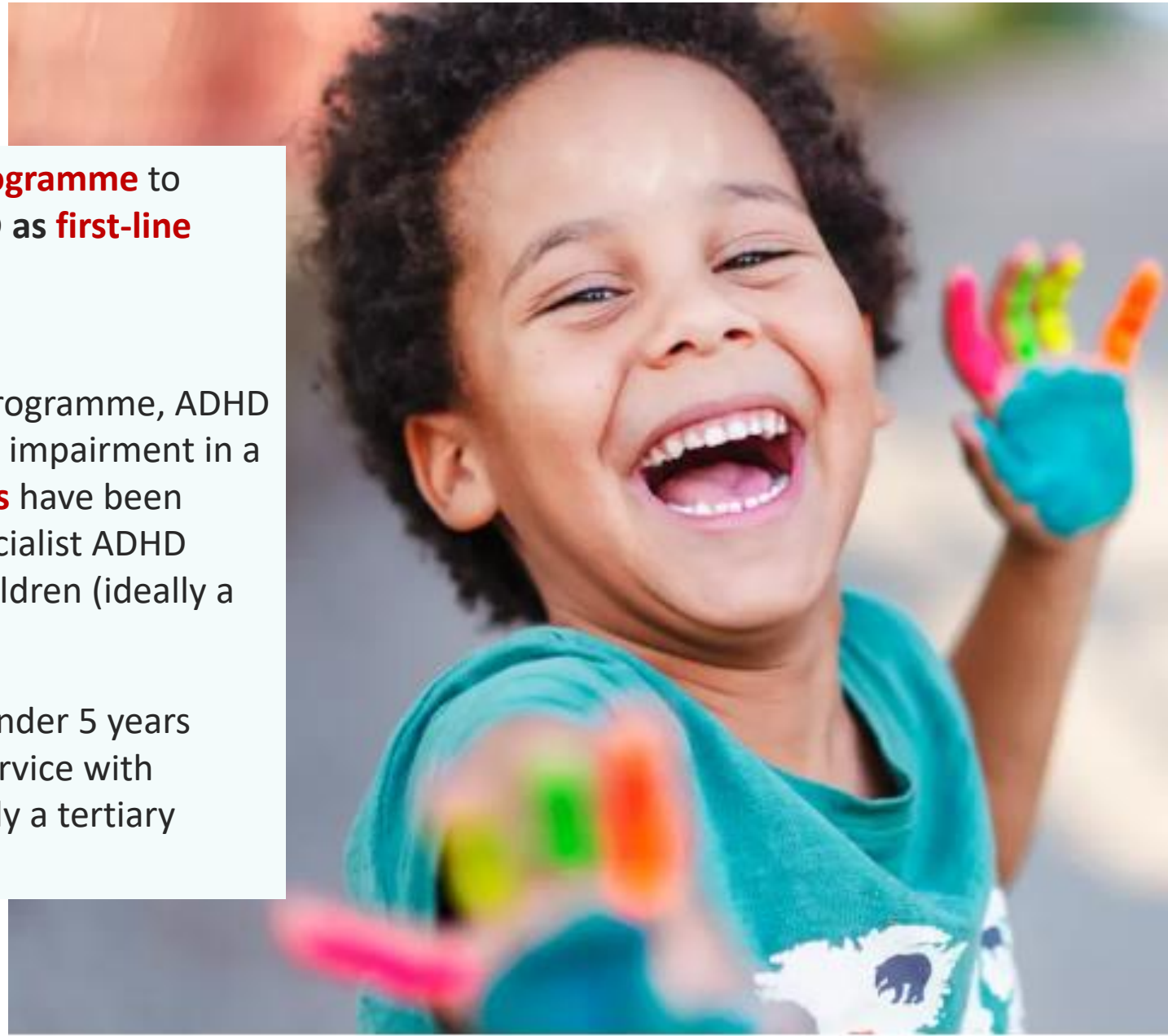
# Università Kore di Enna, 12 febbraio 2027

# Gestire l'ADHD in età evolutiva: la rete, la cura, la care

Con il contributo non condizionante di Neuraxpharma



# 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

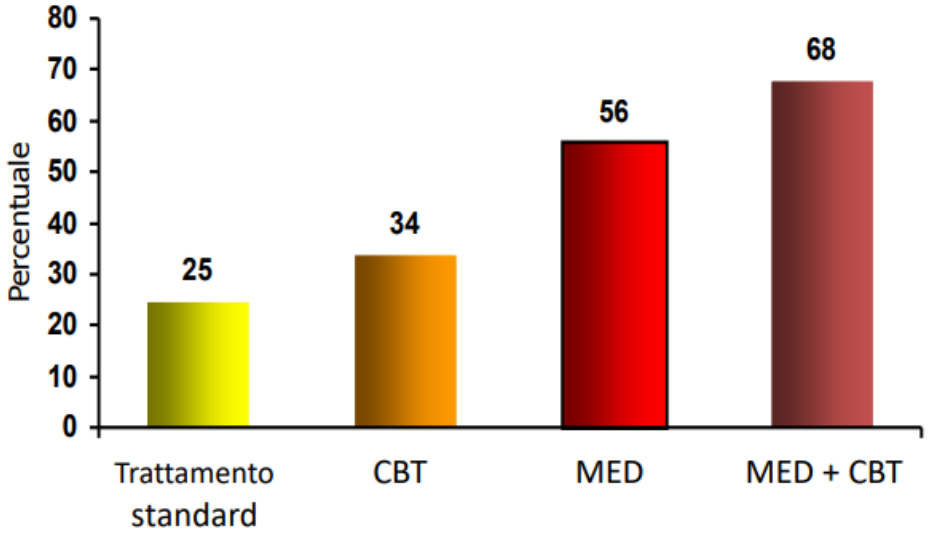
1.5.14 **Consider a course of cognitive behavioural therapy (CBT)** for young people with ADHD **who have benefited from medication but whose symptoms are still causing a significant impairment** in at least one domain, addressing the following areas:

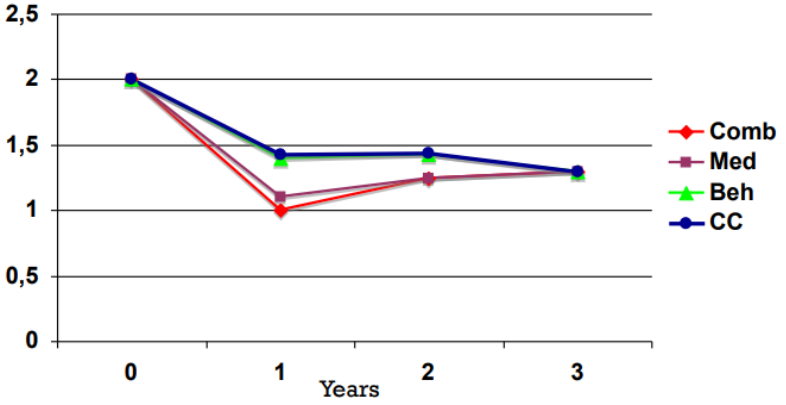
- **social skills with peers**
- **problem-solving**
- **self-control**
- **active listening skills**
- **dealing with and expressing feelings**



# 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.**

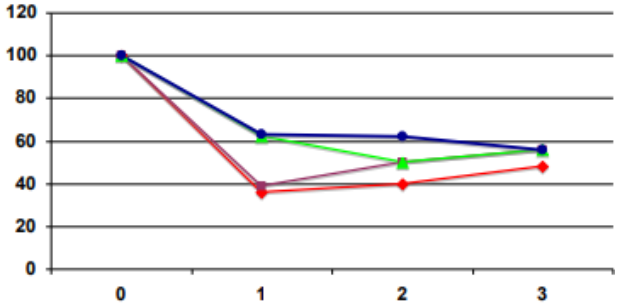


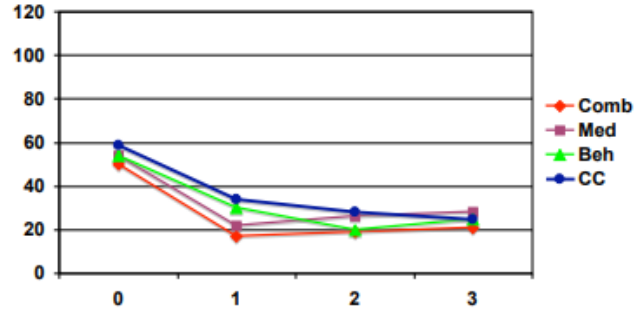

*The combined treatment also offered:*

- 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



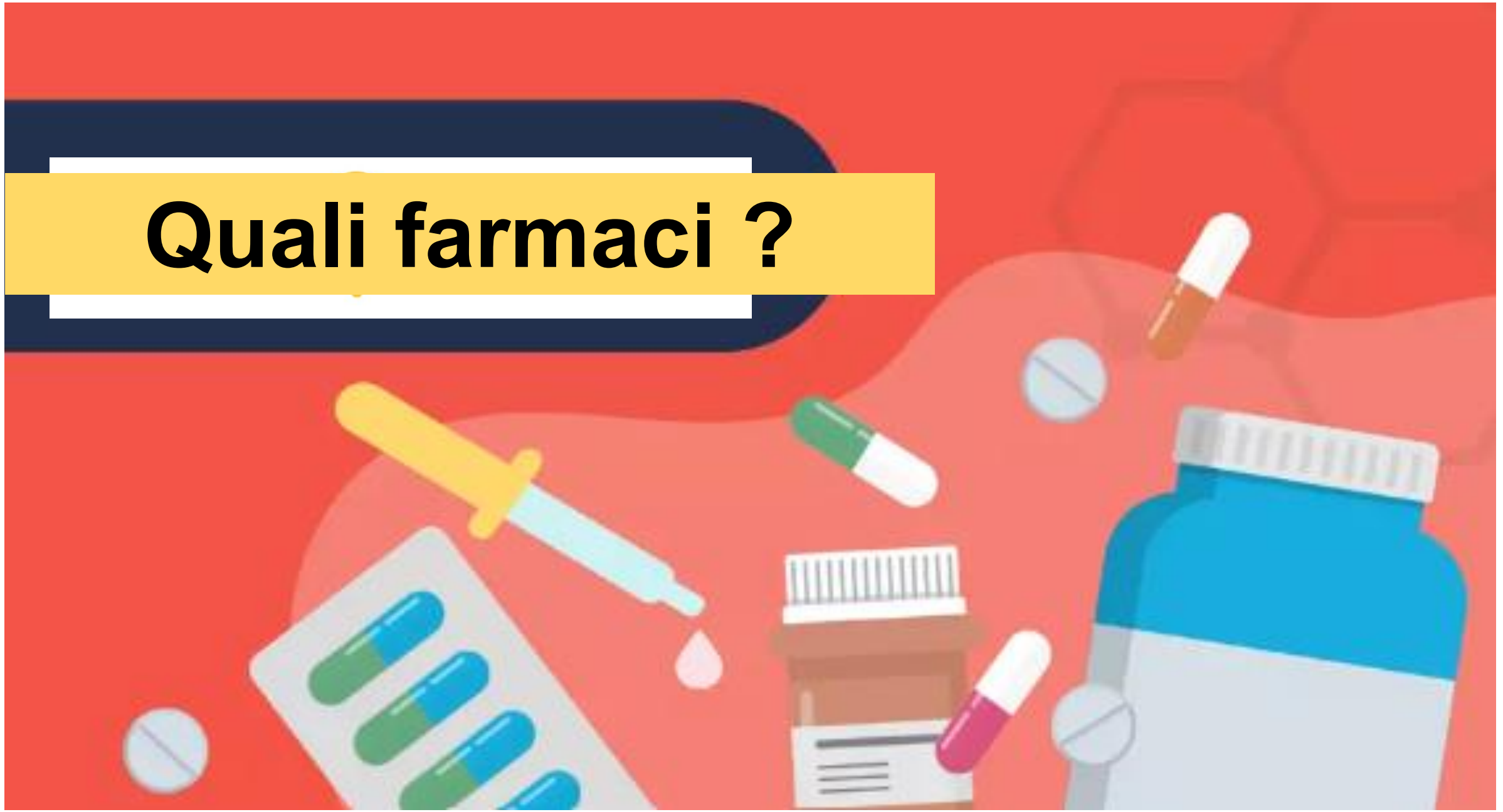

ODD



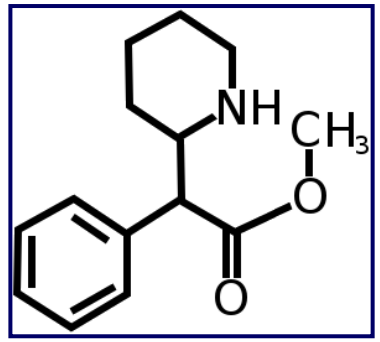


- The MTA Cooperative Group; Multimodal Treatment Study of Children with ADHD. A 14-month randomized clinical trial of treatment strategies for attentiondeficit/hyperactivity disorder. Arch Gen Psychiatry. 1999;56(12):1073–1086 140.
- Jensen PS, Hinshaw SP, Swanson JM, et al. Findings from the NIMH Multimodal 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

# Quali farmaci ?

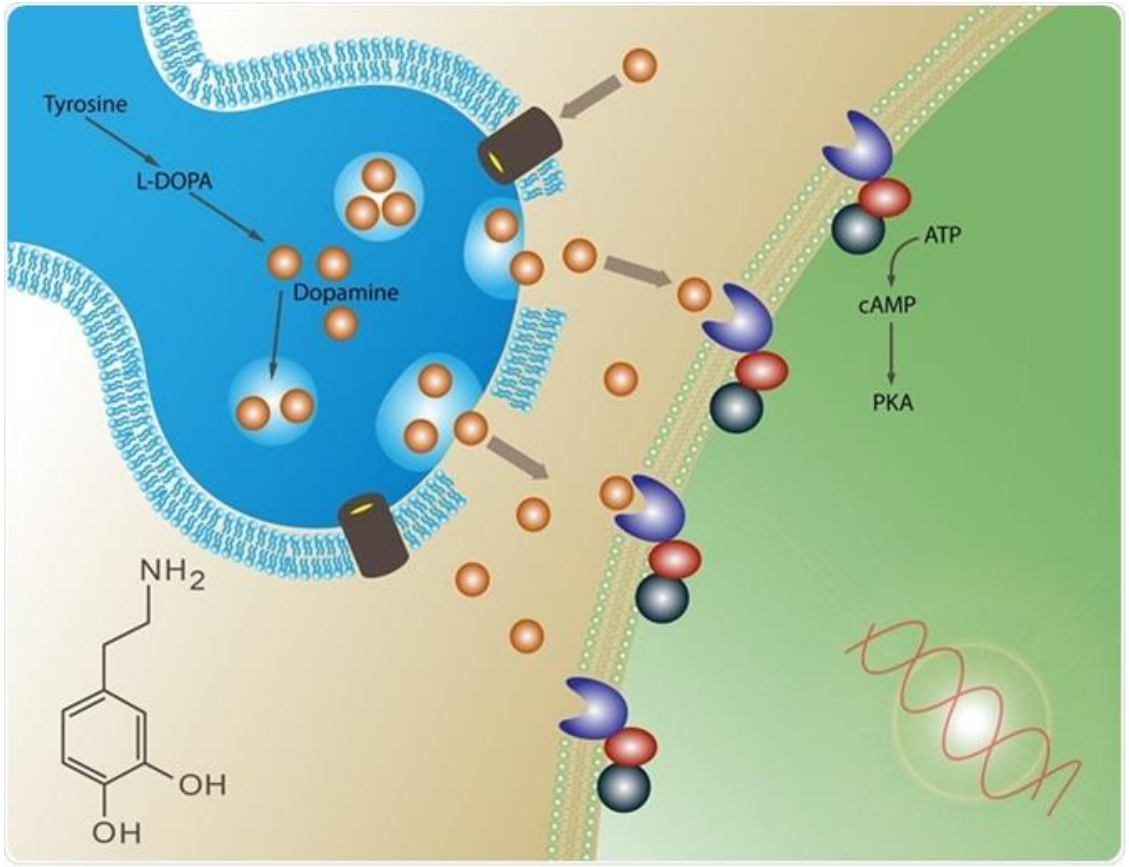


# Methylphenidate hydrochloride




**central nervous system stimulant**

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

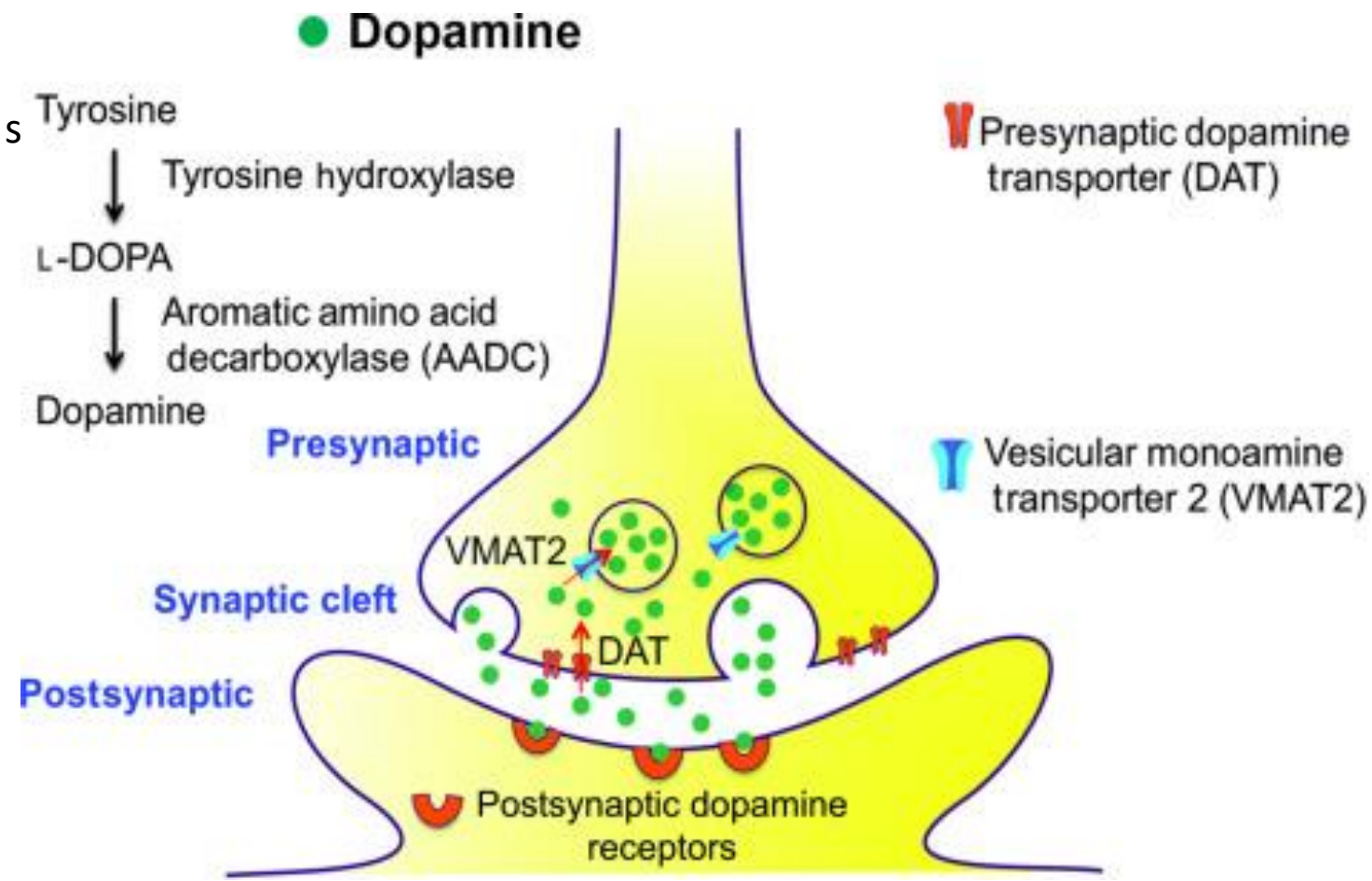



Metilfenidato: il blocco del trasportatore della dopamina induce **aumento della concentrazione della dopamina, in particolare nei gangli della base** che mostrano la più alta espressione del trasportatore

## 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]

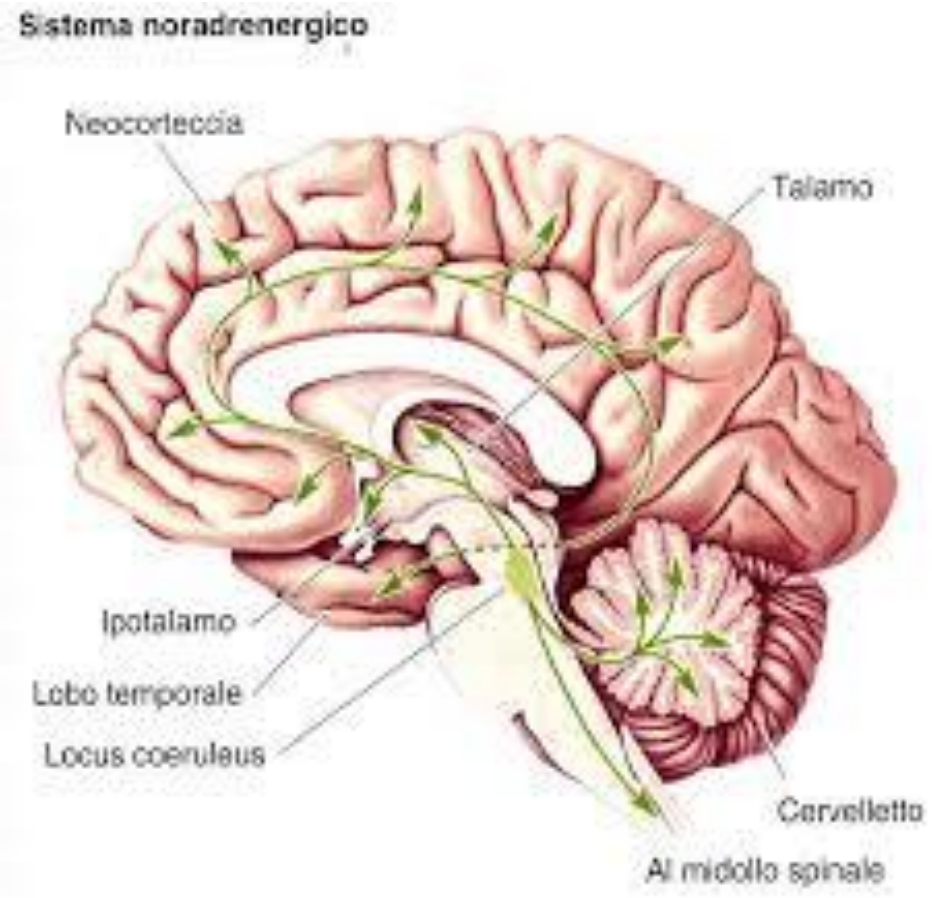
**associazione di questo insieme di geni con la gravità dei sintomi nei bambini**

[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.

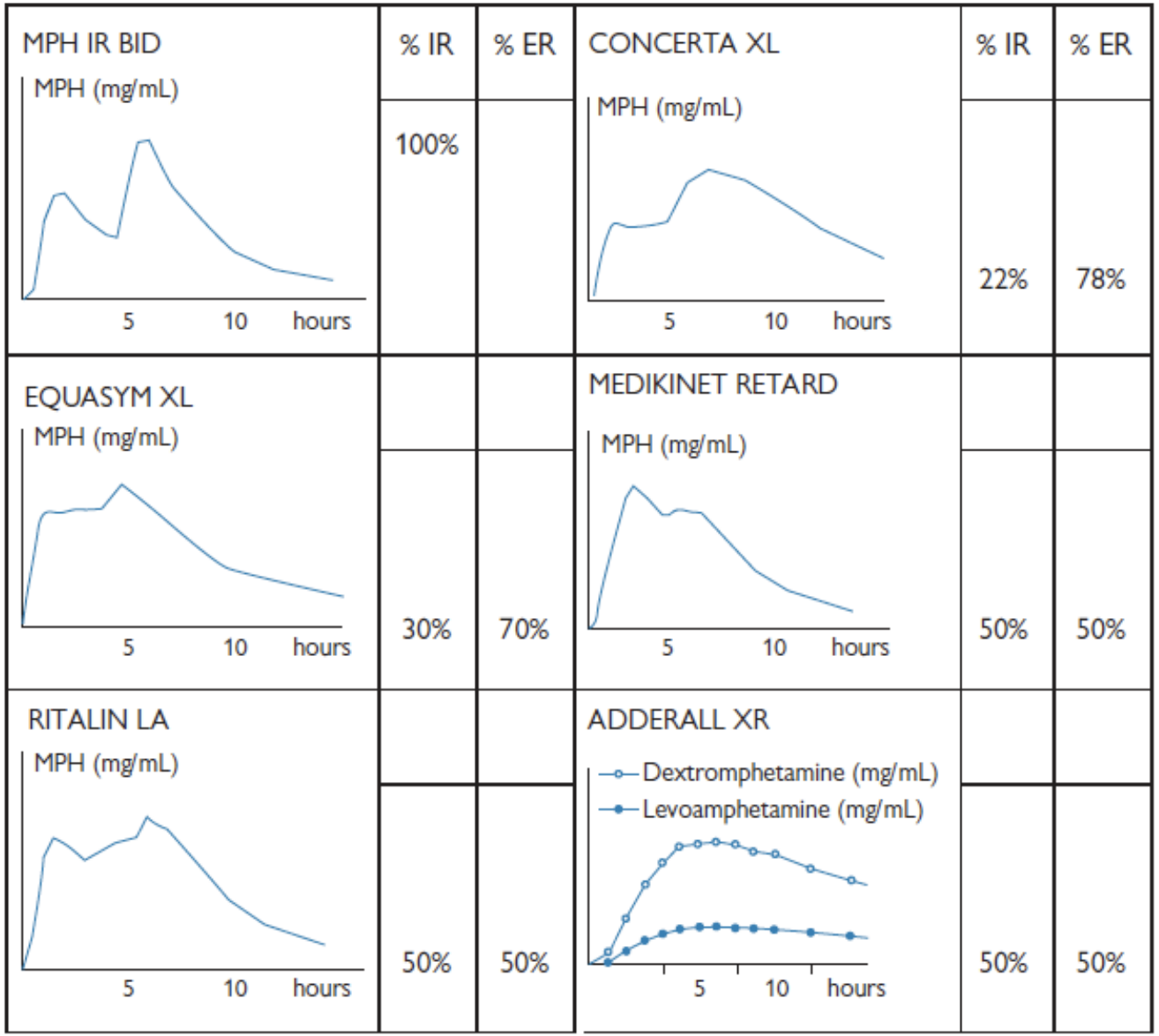
le **formulazioni a rilascio immediato** determinano delle **fluttuazioni dei picchi di concentrazione** associati ad ogni singola somministrazione:

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




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

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

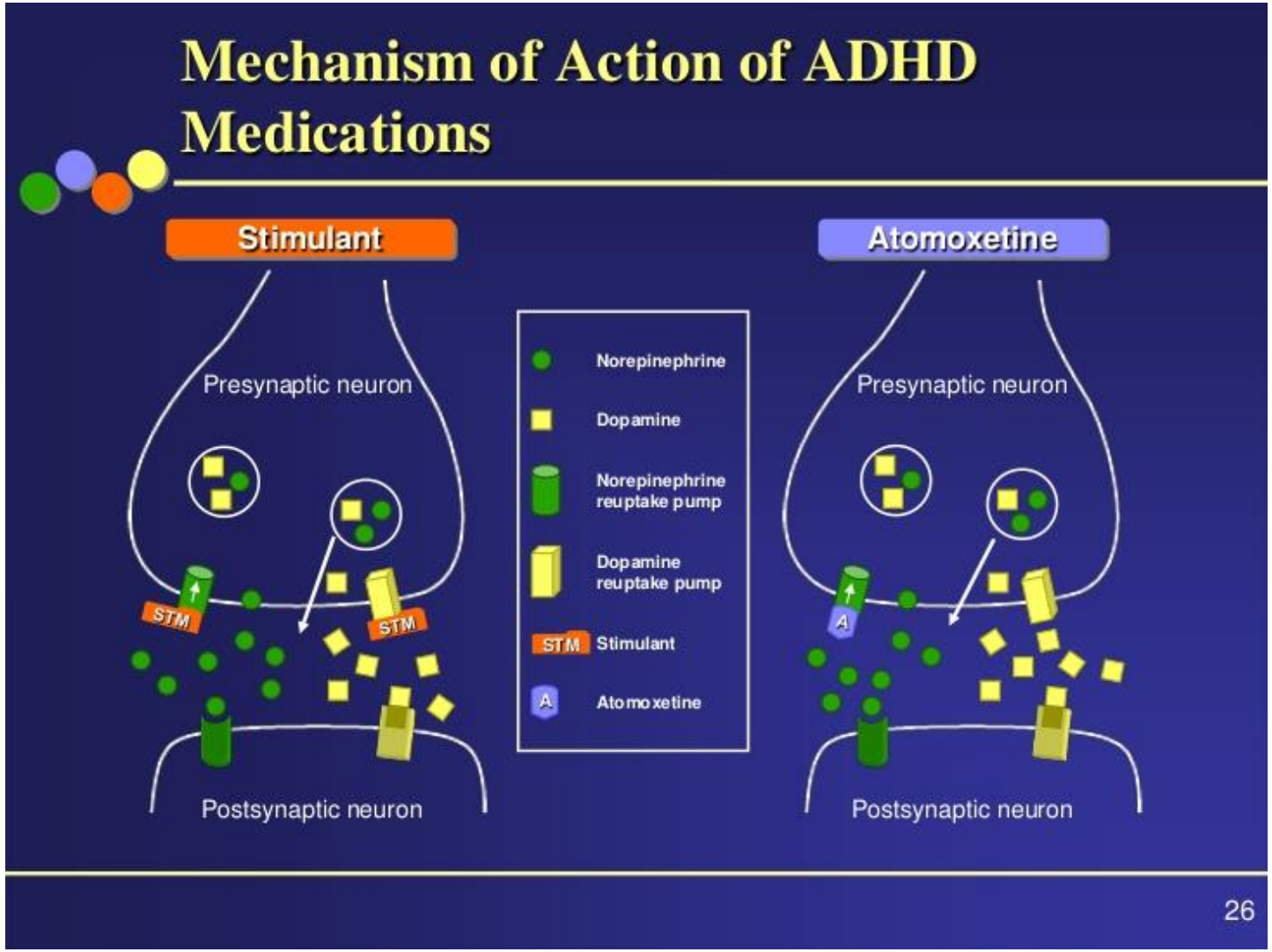
**50% IR; 50% ER**

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

Il **Ritalin Effetto Prolungato** (formulazione a rilascio modificato) è stato ufficialmente autorizzato in Italia nel 2025. Successivamente, a partire dal **30 maggio 2026**, l'AIFA ne ha approvato anche la **rimborsabilità a carico del SSN**

| 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) |

# 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.

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



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(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

# efficacy





**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.

# 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 |

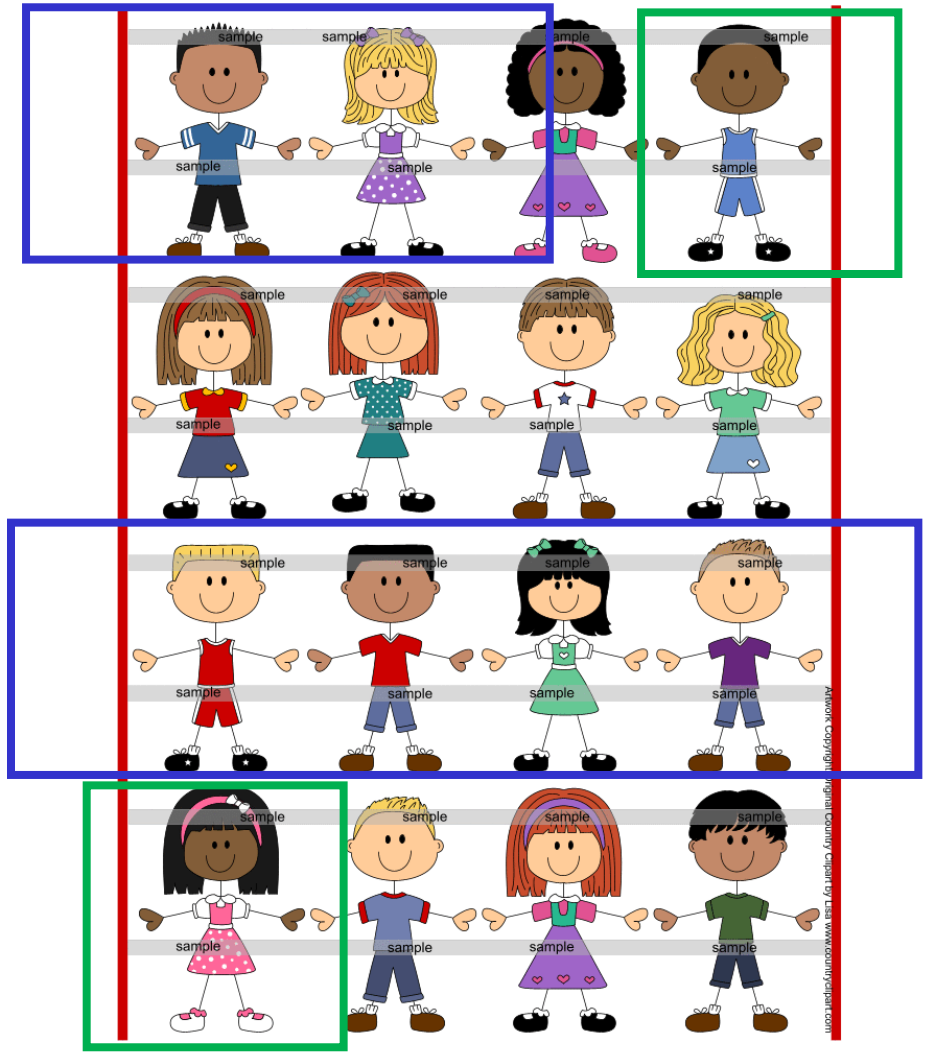
**Effect Size: MPH-IR = MPH-ER (approx 1) > ATX, Modafinil (approx 0.7)**

# **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





*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.

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

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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

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## Non-pharmacological treatment

- Whenever possible, provide psychoeducation taking a lifespan approach.
- Parents and carers of teenage girls need psychoeducation to support detection of deliberate self-harming or risky behaviour.
- Follow-up sessions are essential for support at key points of transition.
- Interventions should be tailored to needs and address difficulties and challenges faced at home, school/work and in social activities.
- Both group and individual assessments may be beneficial.
- Direct parental input into interventions is required for children. Adolescents and adults are more likely to receive direct interventions without parental/carer input.
- Programmes for all ages will benefit from focus on ADHD symptoms and associated problems, including executive functions, emotion regulation, conduct and social impairments, in an age-sensitive manner.
- Programmes should differ depending on age with issues relating to transition,
- As relevant, risk (sexual risk, substance misuse), and self-management should be addressed in adolescence, with adult interventions including employment problems, child-rearing and parenting.

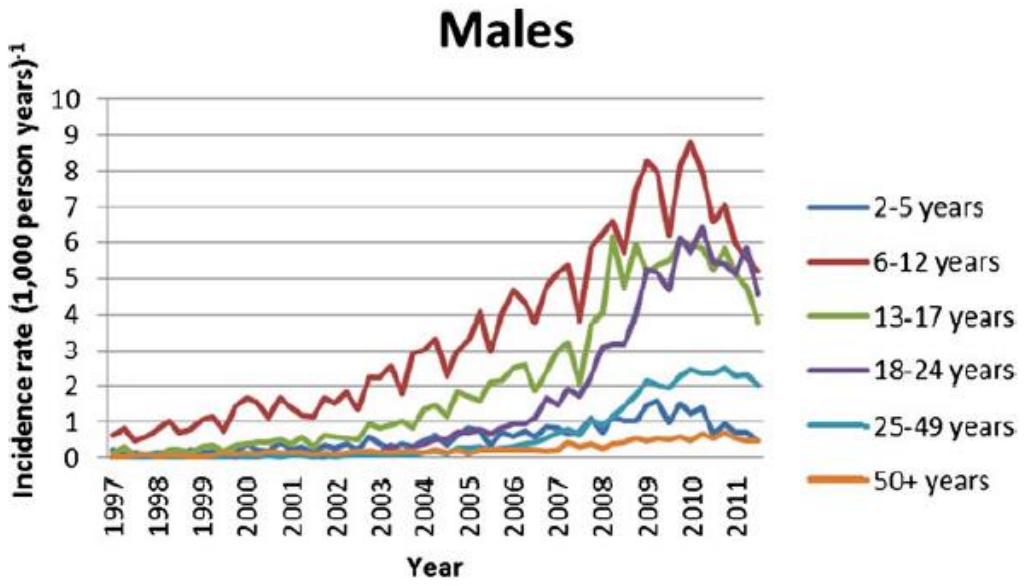
# Males are more likely to receive ADHD medication than females

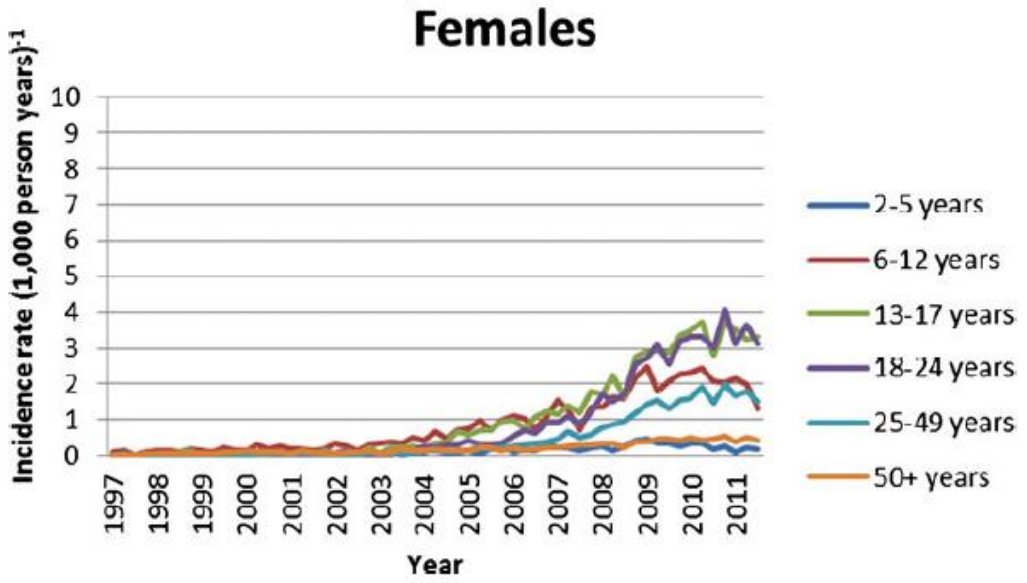

- Derks EM, Hudziak JJ, Boomsma DI (2007) Why more boys than girls with ADHD receive treatment: a study of Dutch twins. Twin Res Hum Genet 10:765–770.
- Angold A, Erkanli A, Egger HL, Costello EJ (2000) Stimulant treatment for children: a community perspective. J Am Acad Child Adolesc Psychiatry
- Pottegård 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

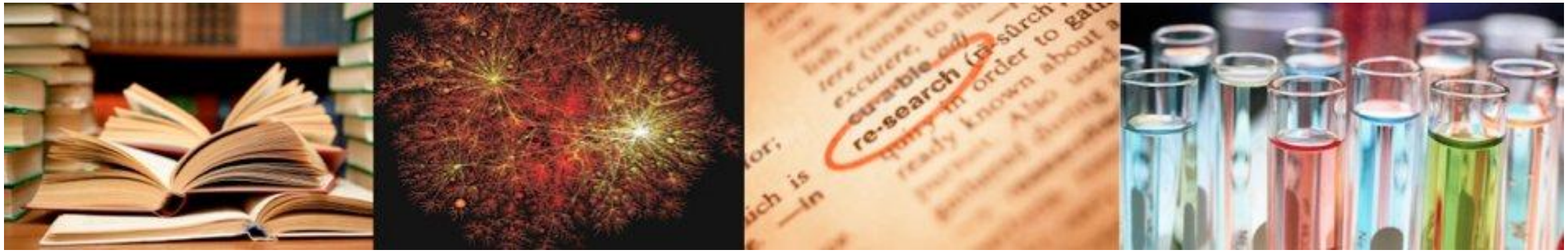

- **hyperactive symptoms** have greater influence on being prescribed pharmacological treatment
- females with ADHD are **less likely to have learning difficulties** or manifest problems at school compared to males

… females with ADHD are **often undertreated**

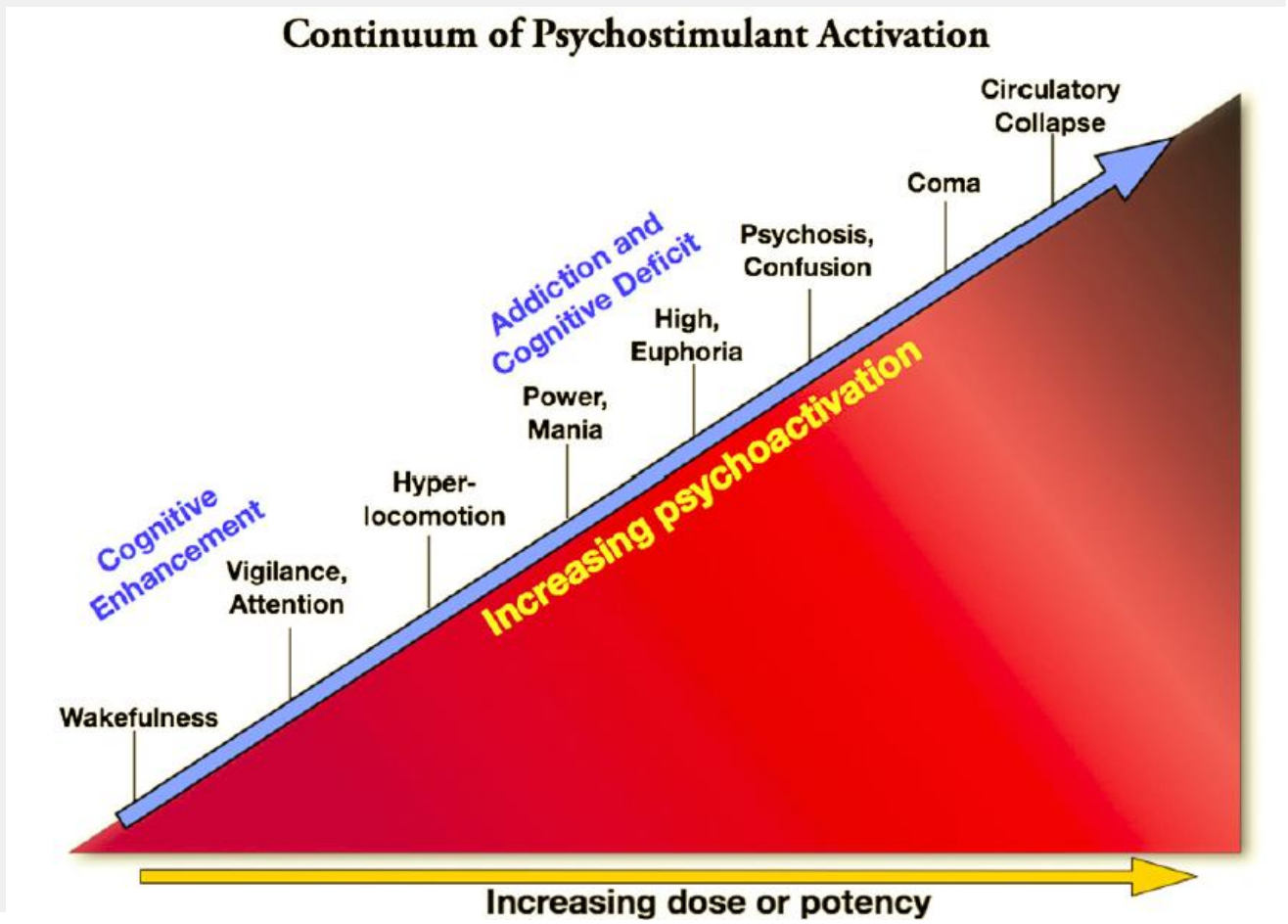







**How and what drug dosage influence the response?**




Wood et al, Pharmacol Rev 66:193–221, January 2014,

PS initially produces increased wakefulness and cognitive enhancement.
These are the desired **therapeutic effects.**

As dose increases, a sense of power and euphoria can ensue
These are the **effects addicts** seek and are accompanied by cognitive deficits.

Higher doses can result in overdose, psychosis, coma, and eventual circulatory collapse.

Methylphenidate

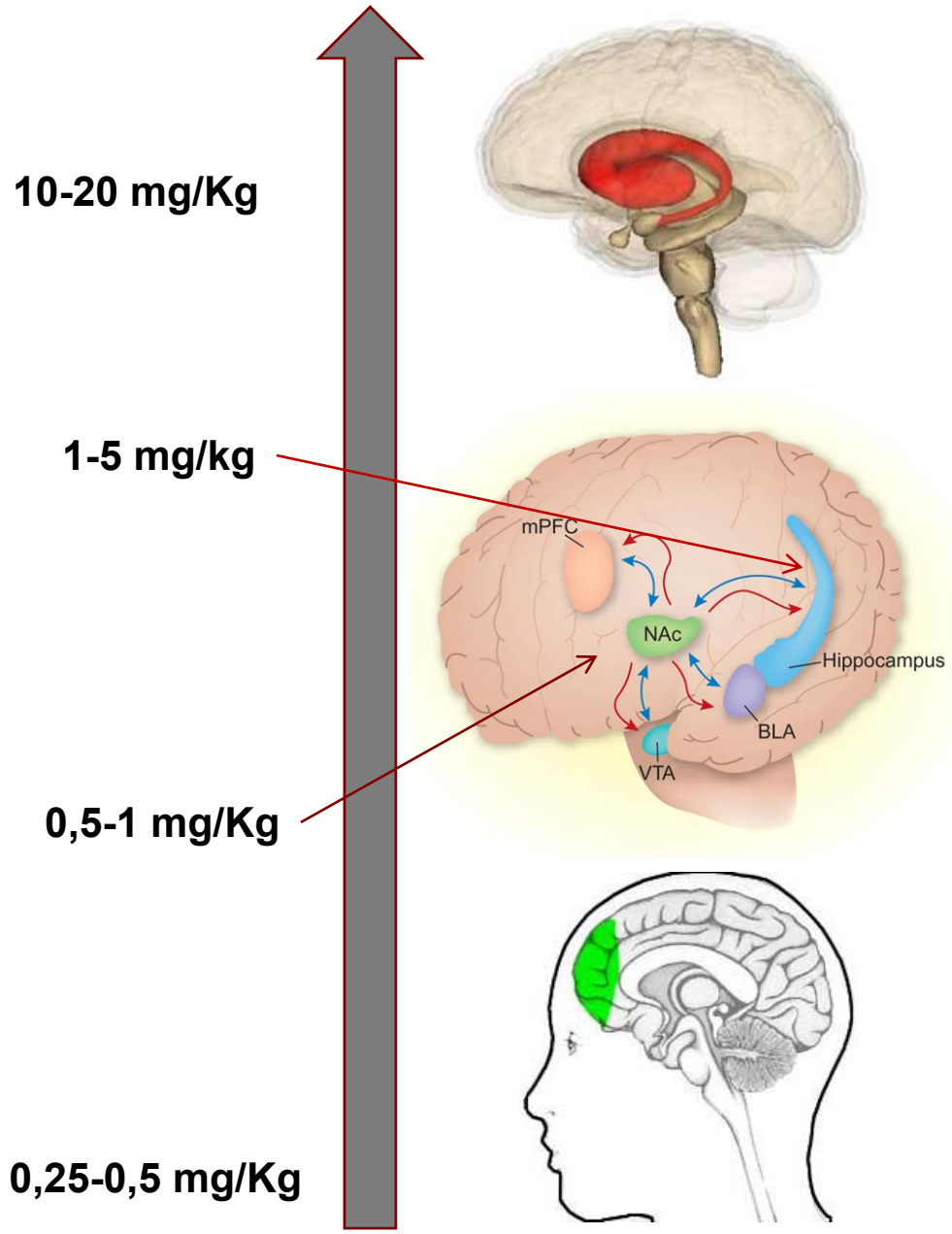
## dose-dependent effect

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.)



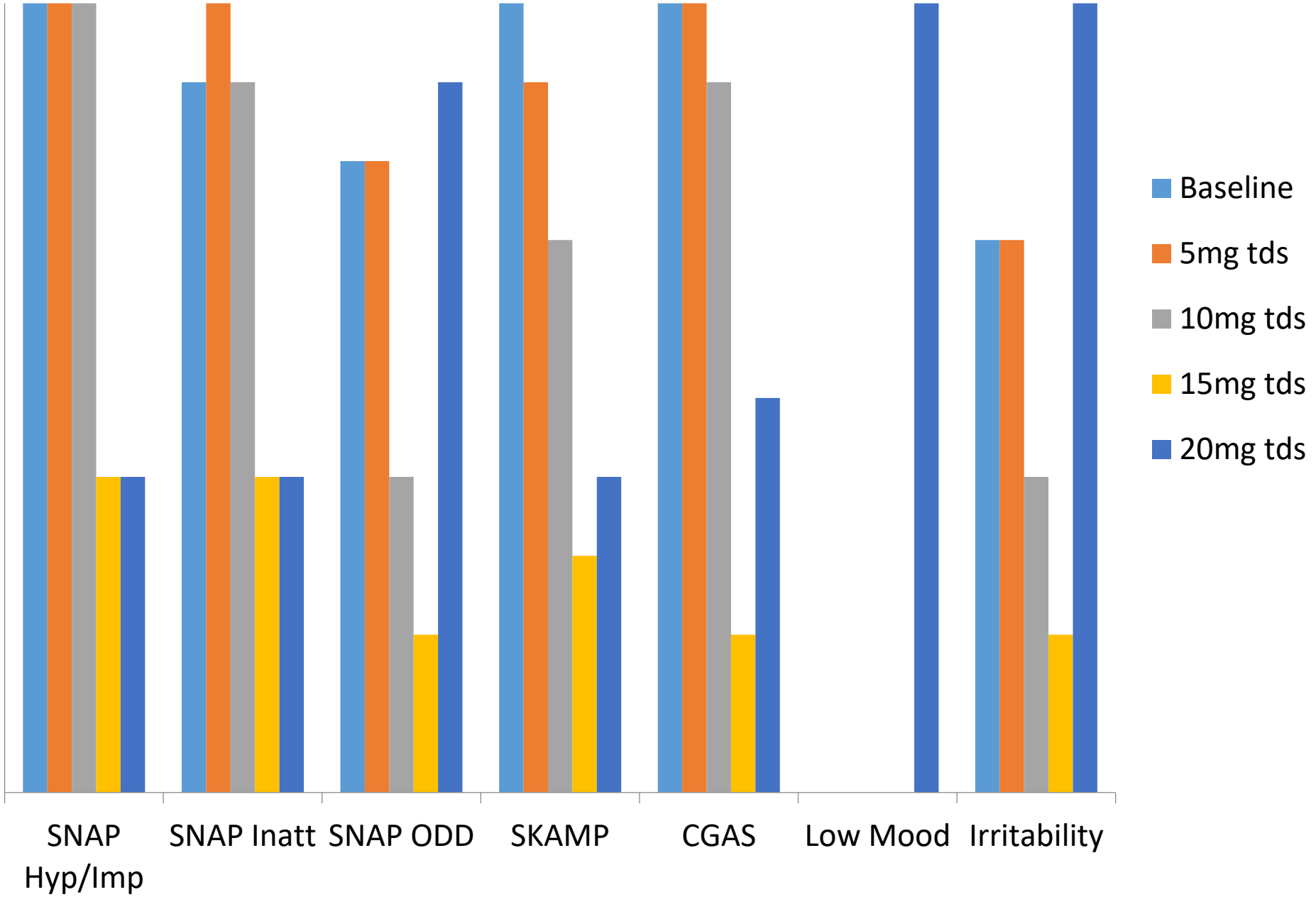

(Kuczenski and Segal, 2002, Heal et al., 2009)

# Forced Dose Titration

Coghill D, 2011

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.



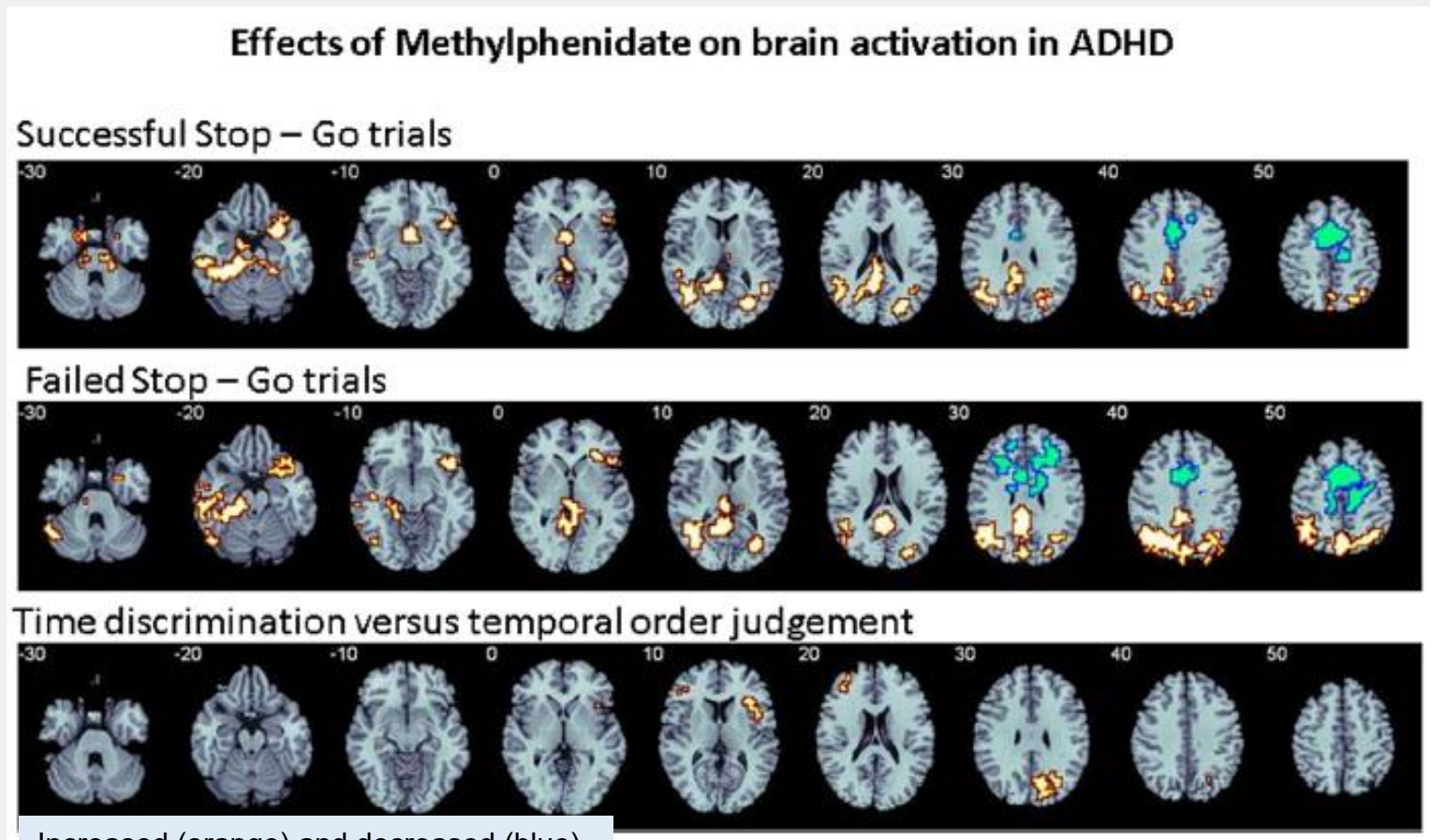



# How and what drug treatments change brain activity?

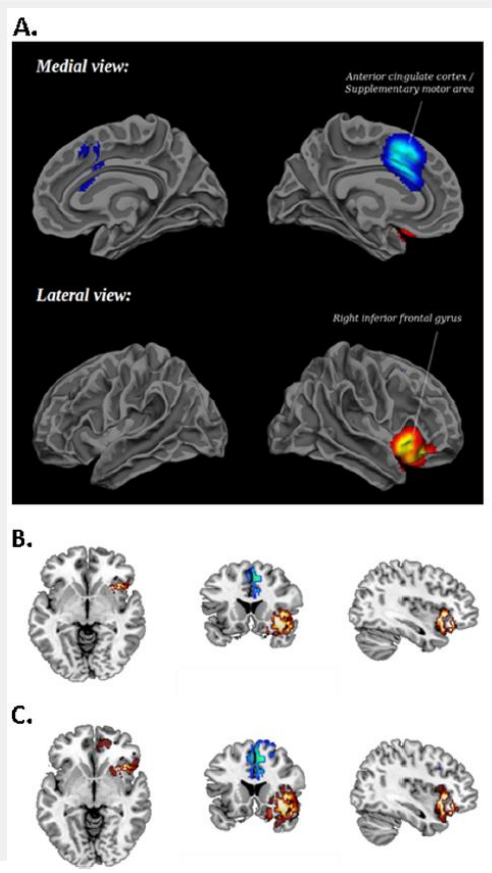
Rubia et al, BIOL PSYCHIATRY 2014;76:616–628

# fMRI study

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



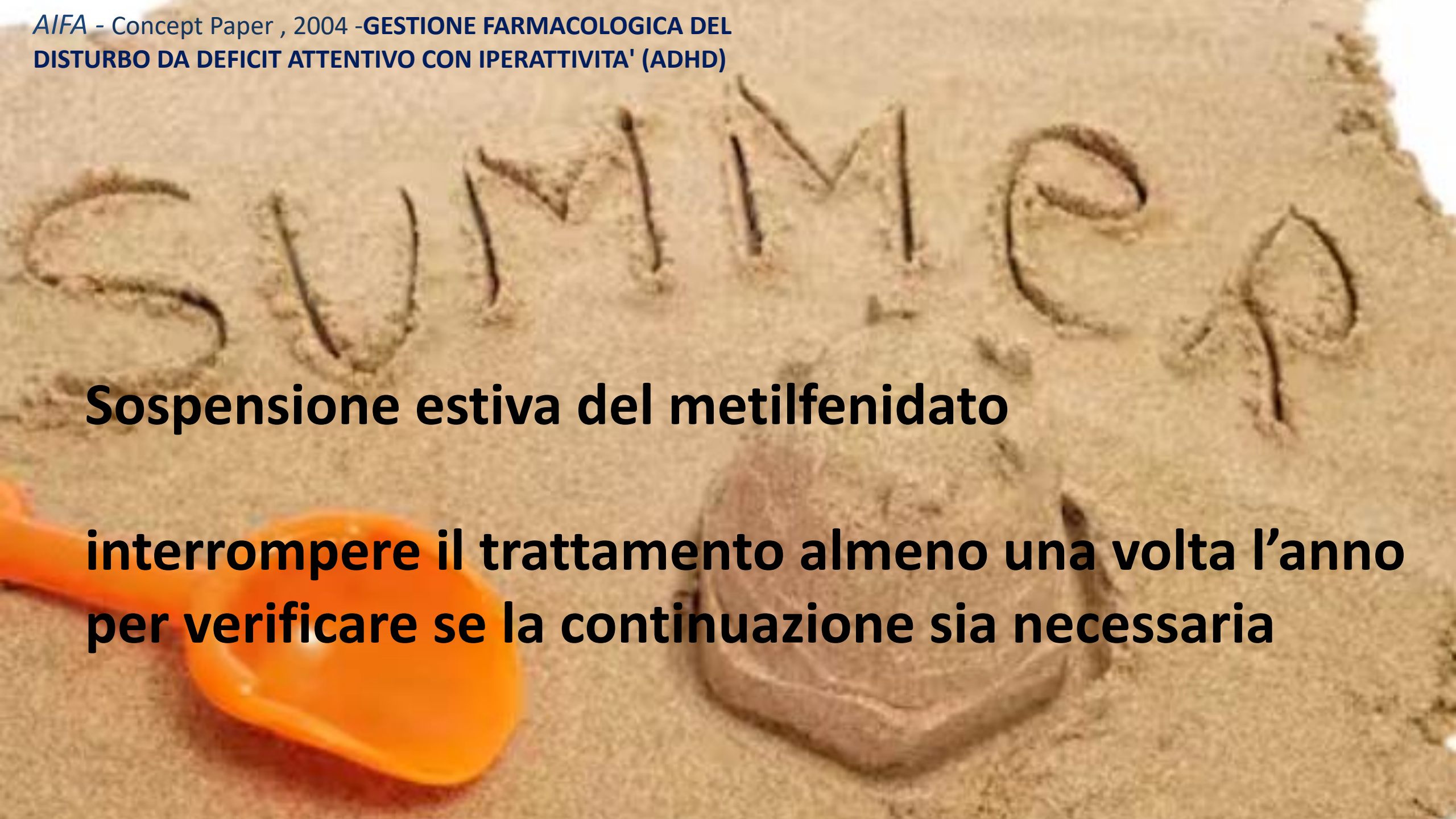

Increased (orange) and decreased (blue) activation with MPH relative to placebo




**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)**


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**

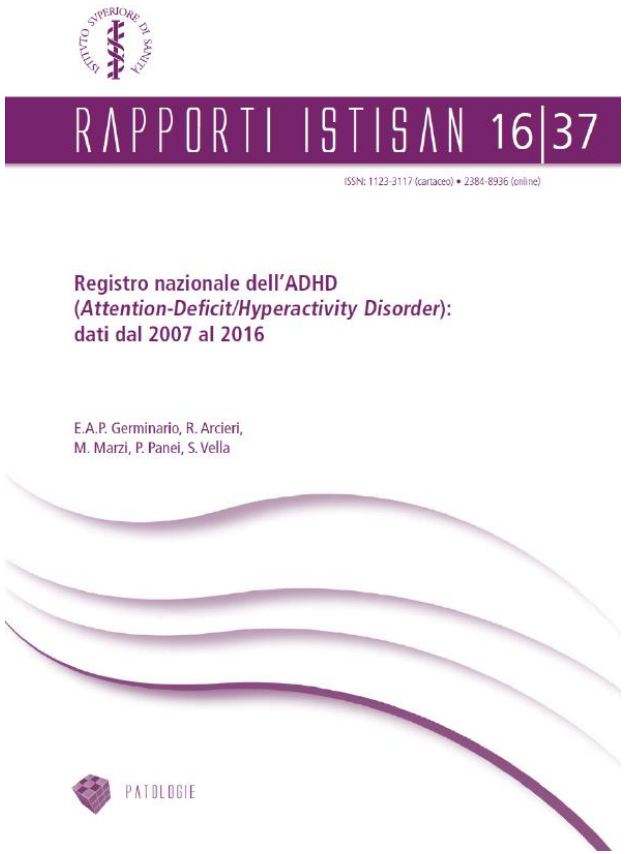



**Tabella 13. Distribuzione dei SAE per tipo di trattamento nei soggetti ADHD in età evolutiva (Registro ADHD, 2007-2016)**

| 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.

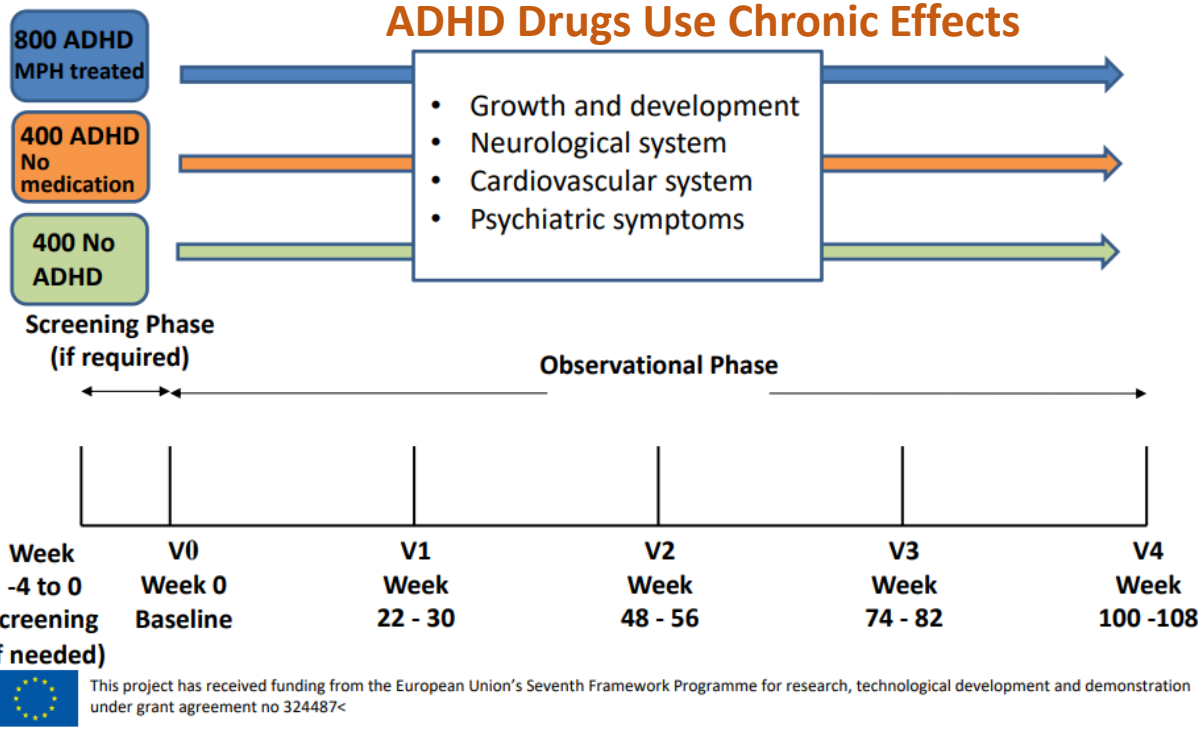
- L'uso del MPH può causare o peggiorare alcuni disturbi psichiatrici, come depressione, pensieri suicidari, ostilità, psicosi e mania. Tutti i pazienti devono essere attentamente sottoposti a delle verifiche per individuare la presenza di questi disturbi prima del trattamento e **monitorati attentamente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

# 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<br>(56-88) | 77,4 ±6,2<br>(56-88) | NS |
| Tp Te/QTc | 0,207 ±0,16<br>(0,140 - 0,235) | 0,214 ±0,19<br>(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.<br>- Misurare il peso:<br>• Ogni 3 mesi nei bambini ≤10 anni<br>• 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)<br>• Ogni 6 mesi negli adulti<br>- Se la perdita di peso è clinicamente significativa:<br>• Assumere il farmaco con o dopo i pasti<br>• Inserire pasti o spuntini extra al mattino presto o alla sera<br>• Cercare consulenza nutrizionale<br>• Consumare alimenti ad alto valore calorico e nutrizionale<br>• Considerare una pausa programmata dal trattamento o cambiare il farmaco<br>- Nei bambini con altezza inferiore al previsto: valutare pausa programmata durante le vacanze scolastiche<br>- 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<br>- 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<br>- Trattare la sindrome delle gambe senza riposo se presente<br>- Se effetto rebound da stimolante → considerare piccola dose di stimolante a breve durata la sera<br>- Se trattamnento con stimolante in corso → valutare: ridurre dose, cambiare classe/formulazione, provare atomoxetina se disponibile<br>- Se persistono problemi di sonno → considerare melatonina |
| *Tics* | - Monitorare per 3 mesi prima di modificare trattamento ADHD<br>- 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<br>- 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).<br>- Dopo la risoluzione → valutare una reintroduzione cauta, se clinicamente appropriata. |

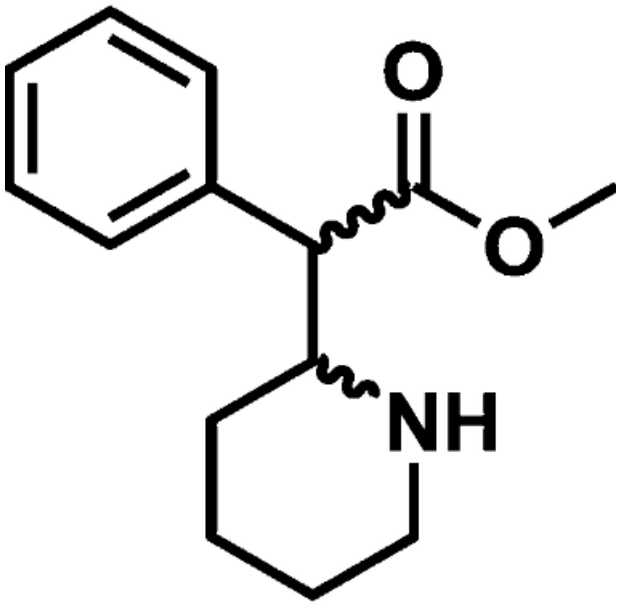
**Appendice:**

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.




Methylphenidate

The first-line treatment for ADHD

its contribution to sleep problems in ADHD is currently unclear

Becker SP, Froehlich TE, Epstein JN. Effects of Methylphenidate on Sleep Functioning in Children with Attention-Deficit/Hyperactivity Disorder. J Dev Behav Pediatr. 2016 Jun;37(5):395-404.

**effects of stimulant medication on the sleep functioning of children with ADHD and predictors of sleep problems as a side effect of taking stimulant medication.**

163 stimulant-naïve children (7-11 years)

**four-week**, randomized, double-blind, placebo-controlled trial of once-daily (**long-acting**) methylphenidate (MPH).

**10% had sleep problems prior** to the initiation of medication.

Rates of parent-rated sleep problems during MPH titration increased with increasing MPH dose

- placebo: 8%
- low dose: 18%
- medium dose: 15%
- high dose: 25%

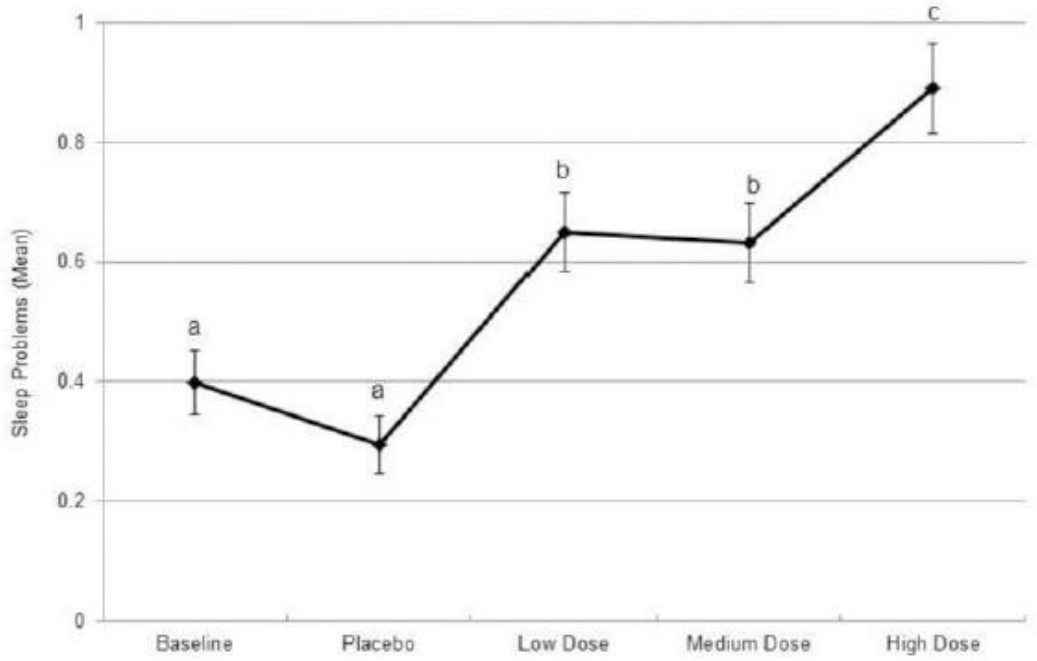



**Figure 1. Effect of methylphenidate (MPH) dose on sleep problems in children with ADHD**
*Note.* Time-points with different superscripts differ significantly ($p < .05$) in sleep problem severity such that a < b < c, while time-points with the same superscript did not differ ($p > 0.05$).

Becker SP, Froehlich TE, Epstein JN. Effects of Methylphenidate on Sleep Functioning in **Children** with Attention-Deficit/Hyperactivity Disorder. J Dev Behav Pediatr. 2016 Jun;37(5):395-404.

# studies examining the impact of MPH on sleep functioning

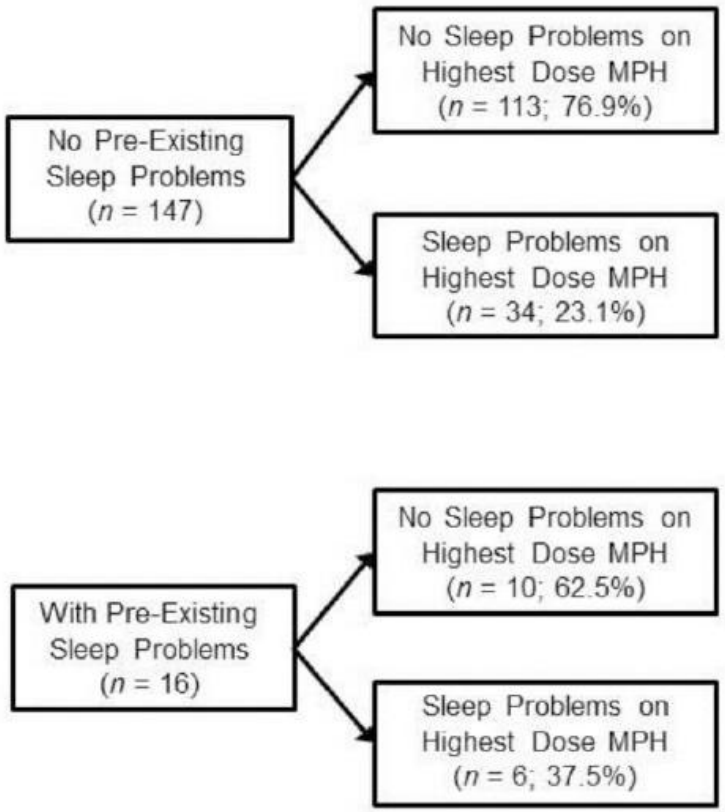



**Figure 2. Number of Children with and without Pre-Existing Sleep Problems and Sleep Problems at the High Dose of MPH**

*Note.* The presence or absence of sleep problems was determined based on parent ratings of sleep, with "none" or "mild" sleep problems classified as sleep problems absent and "moderate" or "severe" sleep problems classified as sleep problems present. MPH = methylphenidate.

Differences between children with or without pre-existing sleep problems

23% of children without pre-existing sleep problems went on to have sleep problems at the highest MPH dose

37.5% of children with pre-existing sleep problems still had sleep problems at the highest MPH dose

A substantial proportion of children with pre-existing sleep difficulties **no longer had sleep problems on the highest MPH dose**

This mixed findings suggest that **MPH dose titration should not be avoided solely on the basis of child's premorbid sleep problems**

Low et al, Effects of methylphenidate on subjective sleep parameters in **adults** with ADHD: a prospective, non-randomized, non-blinded 6-week trialClinical Trial Nord J Psychiatry 2023 Jan;77(1):102-107.

subjective sleep disturbances in a group of initially stimulant medication-naïve adults with ADHD

**changes in sleep problems after 6 weeks of methylphenidate treatment**



- marked improvement in patients after methylphenidate medication
- largest improvement for patients with the poorest reported sleep at baseline

treatment with methylphenidate increases subjective sleep quality for at least some adults with ADHD



*La terapia con Metilfenidato migliora le funzioni esecutive?*



## Il Metilfenidato migliora le funzioni esecutive




*I'm usually too busy listening to my own thoughts race to listen to my teachers...*

*Paul, 14 yeas old*

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

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

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

**Figure 2: Forest Plot with Standardized Mean Difference, Effect Size, and Homogeneity Statistics for Meta-Analysis Comparing the Effects of Methylphenidate and Placebo on Executive Aspects of Memory**

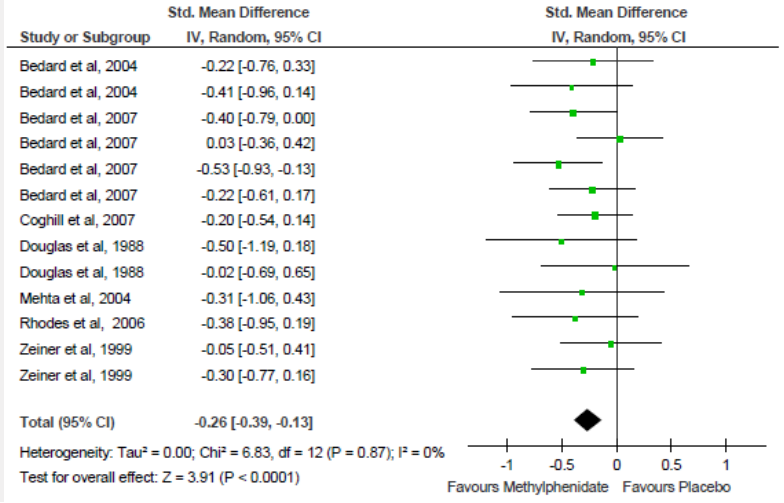



**Figure 3: Forest Plot with Standardized Mean Difference, Effect Size, and Homogeneity Statistics for Meta-Analysis Comparing the Effects of Methylphenidate and Placebo on Non-Executive Aspects of Memory**

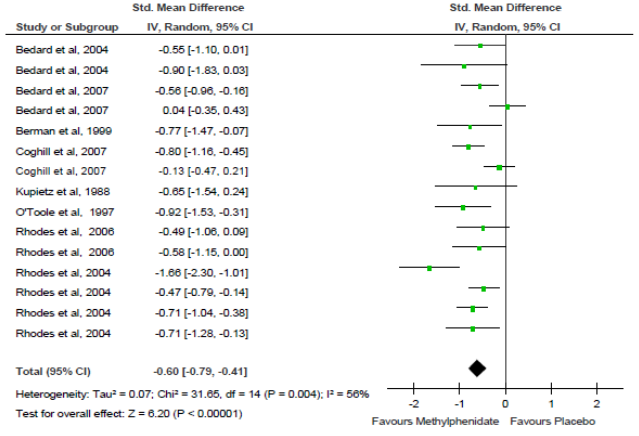



**Figure 4: Forest Plot with Standardized Mean Difference, Effect Size, and Homogeneity Statistics for Meta-Analysis Comparing the Effects of Methylphenidate and Placebo on Reaction Time**

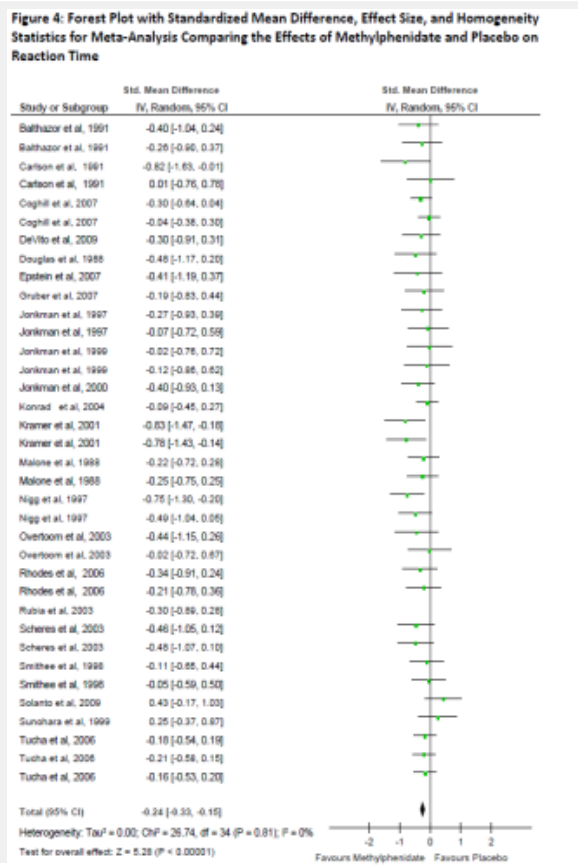



**Figure 5: Forest Plot with Standardized Mean Difference, Effect Size, and Homogeneity Statistics for Meta-Analysis Comparing the Effects of Methylphenidate and Placebo on Reaction Time Variability**

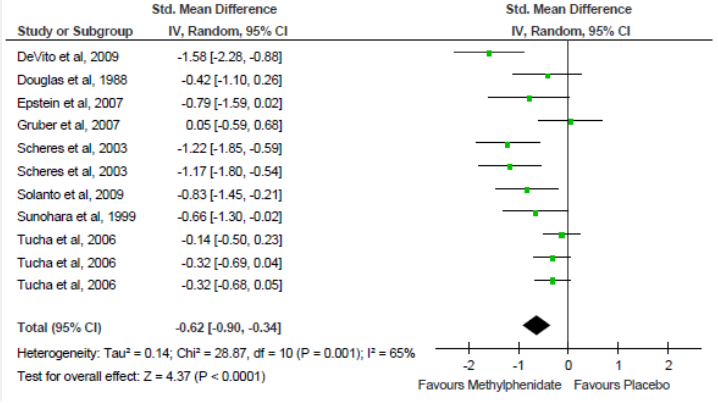
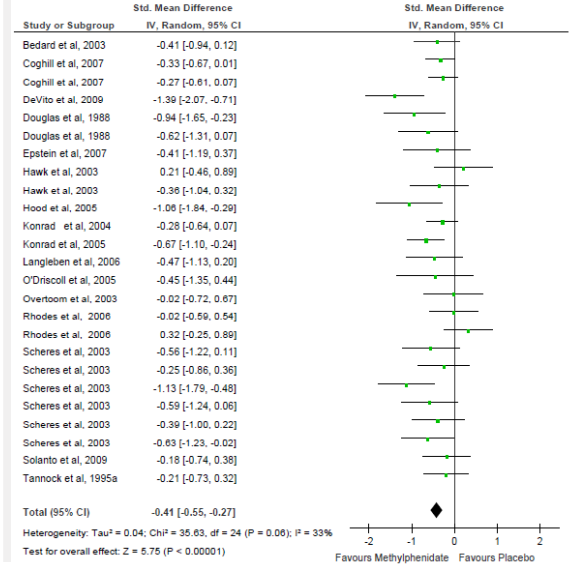
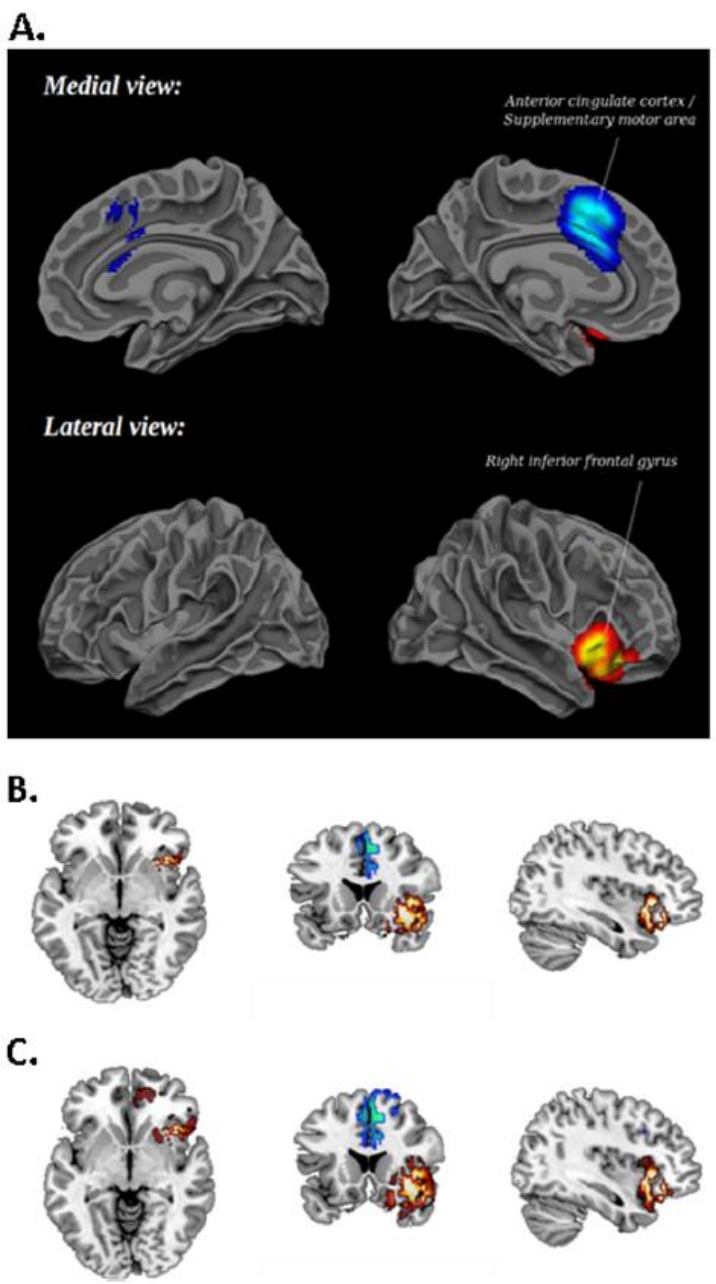



**Figure 6: Forest Plot with Standardized Mean Difference, Effect Size, and Homogeneity Statistics for Meta-Analysis Comparing the Effects of Methylphenidate and Placebo on Response Inhibition**






Rubia et al, Effects of Stimulants on Brain Function in ADHD: A Systematic Review and Meta-Analysis BIOL PSYCHIATRY 2014;76:616–628

**meta-analysis**

Psychostimulants most consistently increase **right IFC** and **insula** activation

These are

- key areas of cognitive control
- the most replicated neurocognitive dysfunctional regions in ADHD

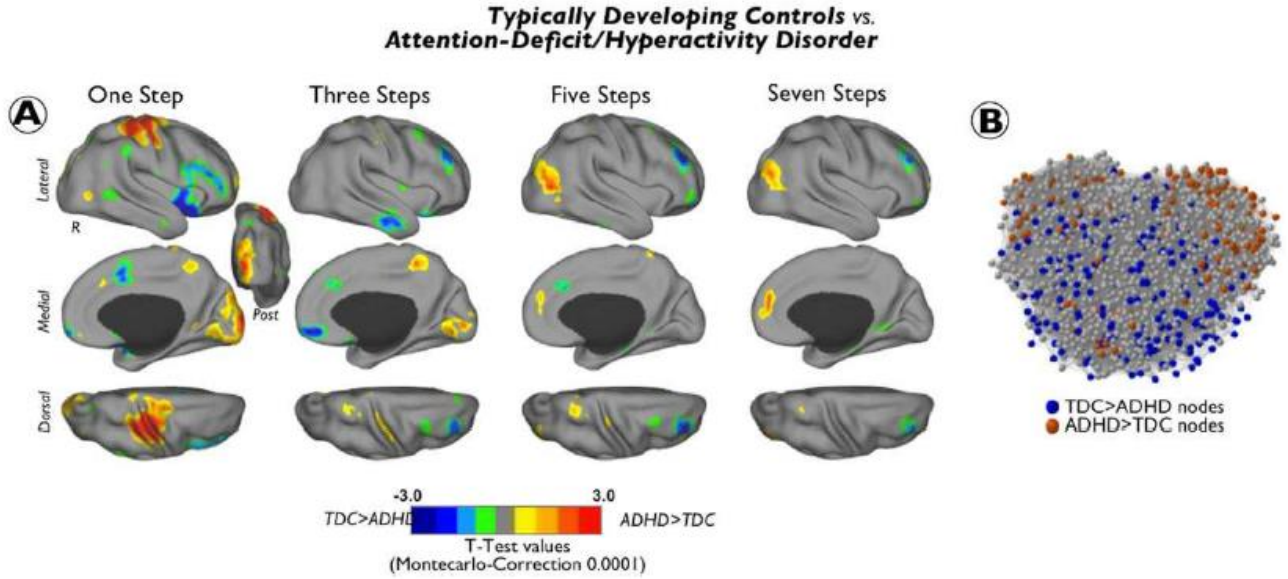
These neurocognitive effects may underlie their positive clinical effects

increased (red/orange) and decreased (blue) activation after a single dose of stimulant medication

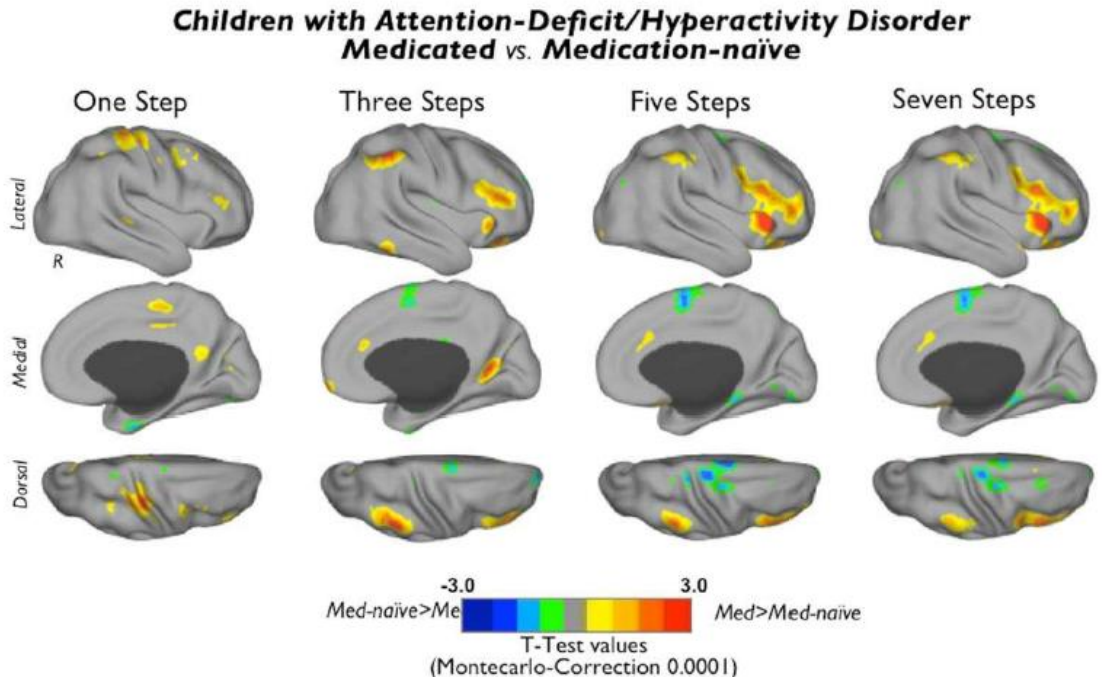
# **functional connectivity streams** that link sensory, attentional, and higher-order cognitive circuits is atypical in ADHD

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**

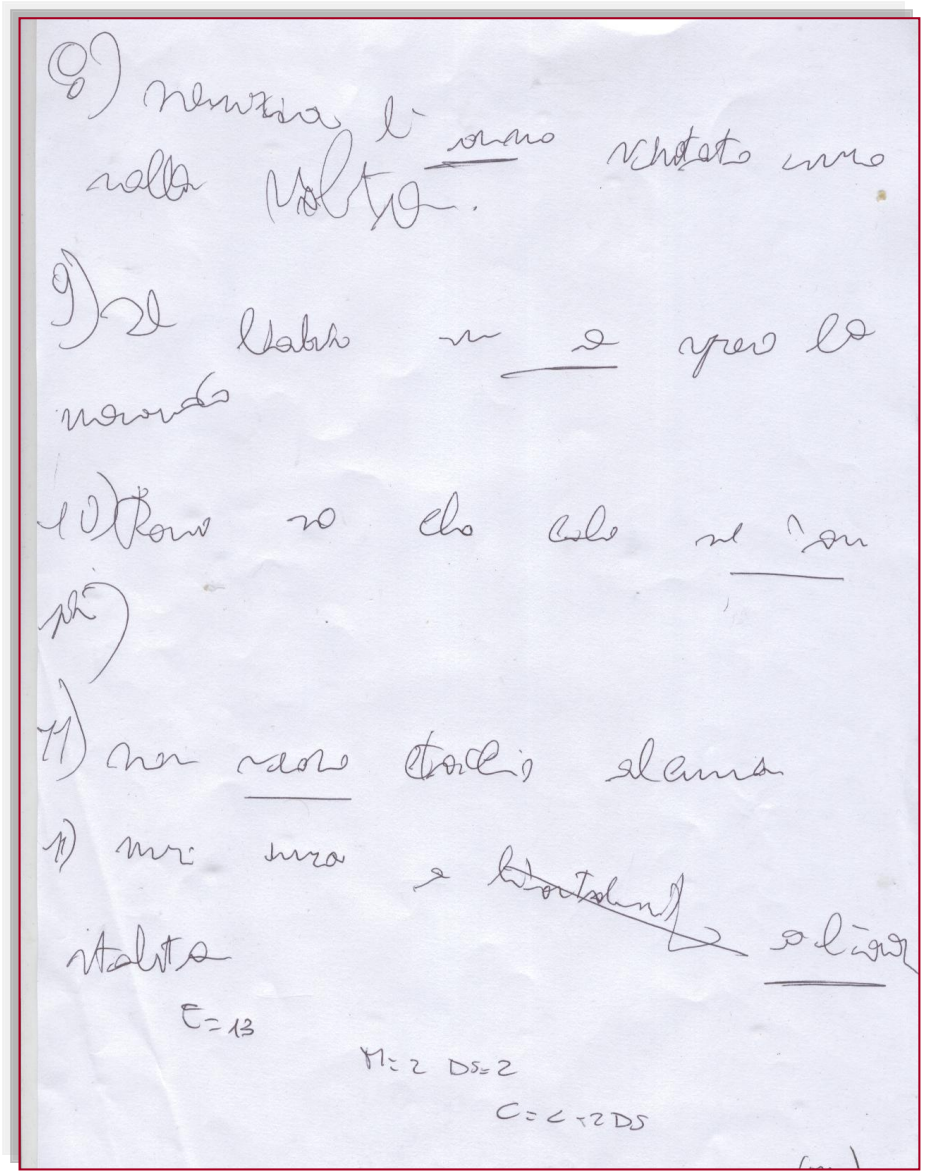



**psychostimulants improve the functional connectivity** streams with higher degree of connectivity to regions subserving attentional and executive processes

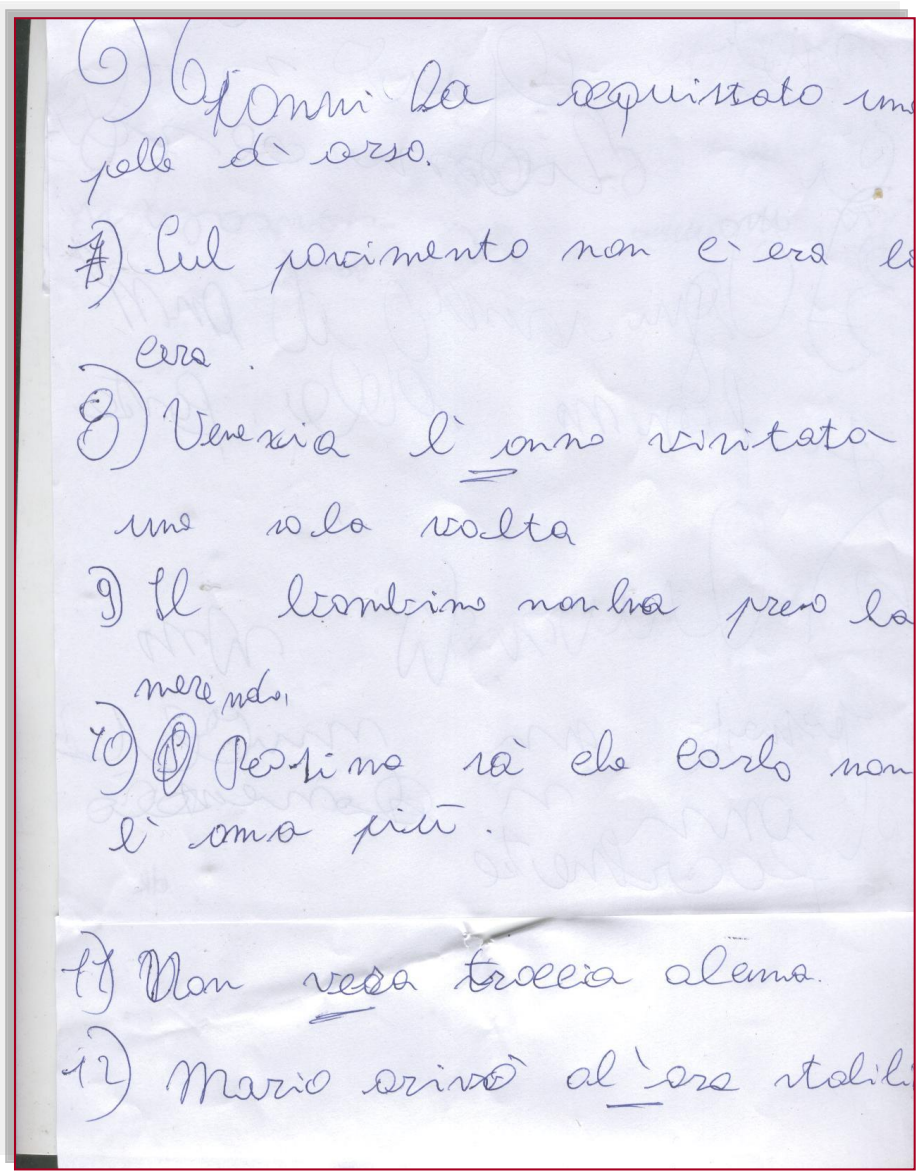


*La terapia con Metilfenidato migliora le performance scolastiche dei ragazzini ADHD ?*

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



**Baseline**



**1.5 hours later**

Tannock R, Frijters JC, Martinussen R, White EJ, Ickowicz A, Benson NJ, Lovett MW. **Combined Modality Intervention for ADHD With Comorbid Reading Disorders**: *A Proof of Concept Study*. J Learn Disabil. 2018 Jan/Feb;51(1):55-72.



**65 ADHD+RD children (7–11 years)**

## Efficacia di programmi rieducativi per la lettura in presenza o assenza di terapia con MPH

I partecipanti sono stati assegnatirandomly a uno dei 3 programmi accademici intensivi di recupero

1. **Training fonologico e strategie di lettura**
2. **Strategie accademiche convenzionali**
3. **Social skills training**

**in combinazione con metilfenidato a rilascio immediato o placebo**

**I programmi di lettura** generavano progressi nella lettura e nelle competenze accademiche **indipendentemente dalla terapia farmacologica**

Froehlich et al, **Using ADHD Medications to Treat Coexisting ADHD and Reading Disorders: A Systematic Review**. Clin Pharmacol Ther. 2018 Oct;104(4):619-637.

- Il trattamento con MPH e ATX porta a miglioramento dei sintomi ADHD e di **alcuni risultati scolastici**
- Le evidenze di efficacia per ATX si basano sulle valutazioni dei sintomi in ambiente domestico, mentre gli effetti benefici del MPH sono stati osservati anche nella valutazione dei sintomi da parte degli insegnanti
- **i farmaci hanno avuto effetto sui sintomi ADHD più che sulle performance accademiche**



**academic outcomes**
**MPH è efficace nel migliorare le prestazioni di calcolo matematico nei bambini con ADHD+RD**

**reading outcomes**
**evidenza debole di miglioramento con MPH e ATX (risultati incoerenti tra gli studi)**

**select neuropsychological measures**
**Il MPH migliora le prestazioni.**
**Nessuna evidenza per ATX**

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

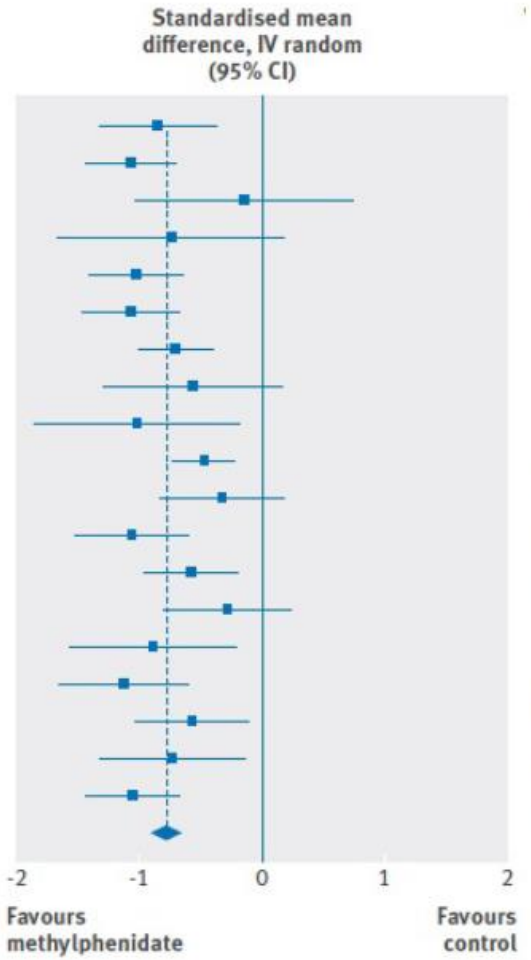



Fig 2 | Teacher rated symptoms of attention-deficit/hyperactivity disorder in parallel group trials.

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

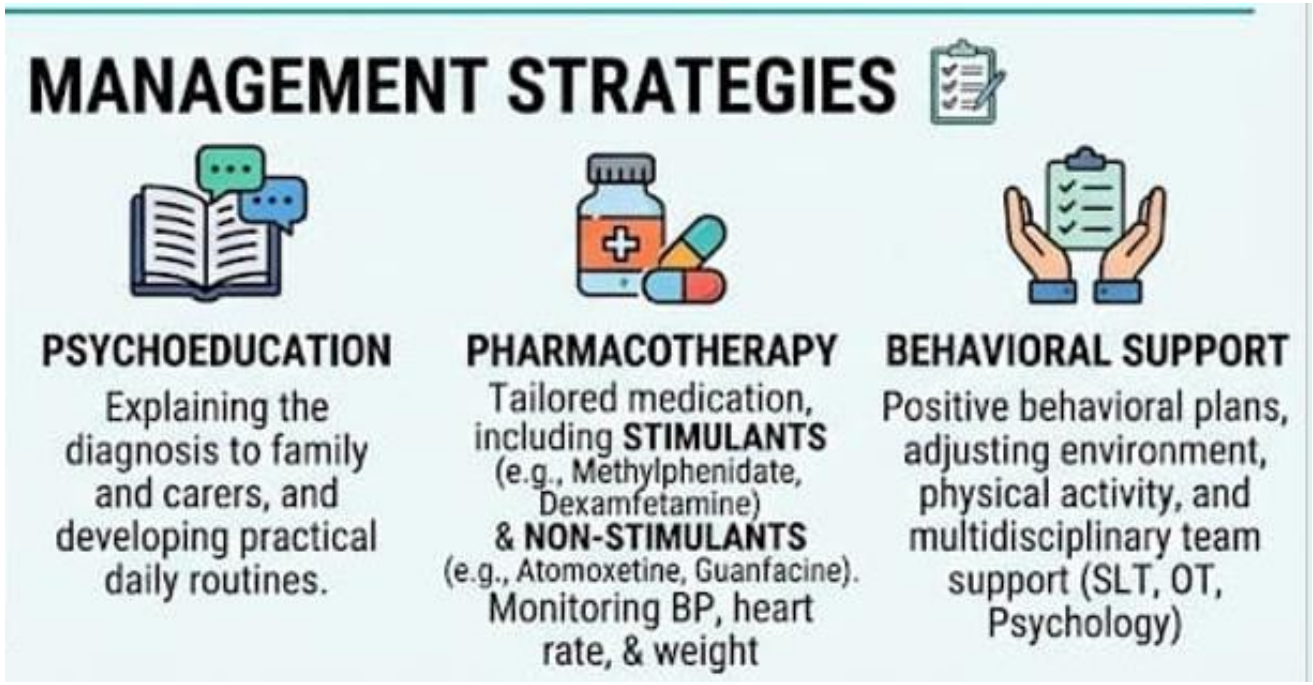
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BJPsych Advances (2022), vol. 28, 363–370 doi: 10.1192/bja.2022.23

# Assessing and managing attention-deficit hyperactivity disorder in people with intellectual disability

ARTICLE

Bhathika Perera, Jane McCarthy & Ken Courtenay




Sätilä H, Jolma LM, Meriläinen-Nipuli M, Koivu-Jolma M. Challenges and neuropsychological functioning in children and adolescents with borderline intellectual functioning. Children (Basel) 2022; 9:1847.

**metanalisi di studi randomizzati e controllati sull'efficacia del metilfenidato nei bambini e negli adolescenti con FIL e ADHD**

miglioramento significativo sia della componente inattentiva sia di quella iperattiva-impulsiva, con un profilo di tollerabilità sovrapponibile a quello osservato nei soggetti con sviluppo cognitivo tipico

Sun CK, Tseng PT, Wu CK, Li DJ, Chen TY, Stubbs B, Carvalho AF, Chen YW, Lin PY, Cheng YS, Wu MK. Therapeutic effects of methylphenidate for attention-deficit/hyperactivity disorder in children with borderline intellectual functioning or intellectual disability: A systematic review and meta-analysis. Sci Rep. 2019 Nov 4;9(1):15908.

alcuni studi riportano percentuali di risposta lievemente inferiori rispetto ai soggetti con ADHD e QI adeguato

**gli psicostimolanti rappresentano un'opzione terapeutica appropriata anche in presenza di un basso IQ**

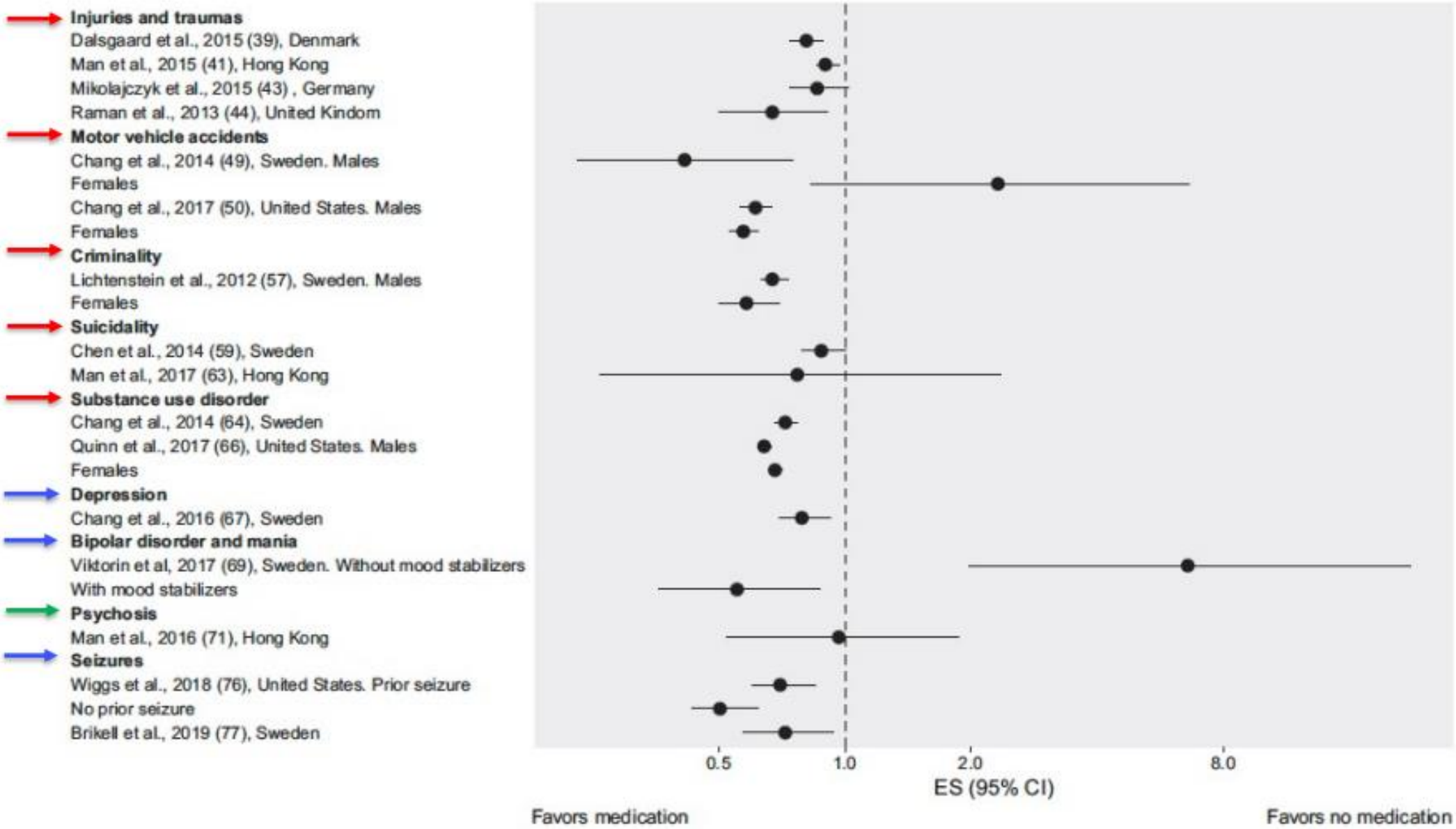


*La terapia con MPH protegge dagli outcome sfavorevoli?*

**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

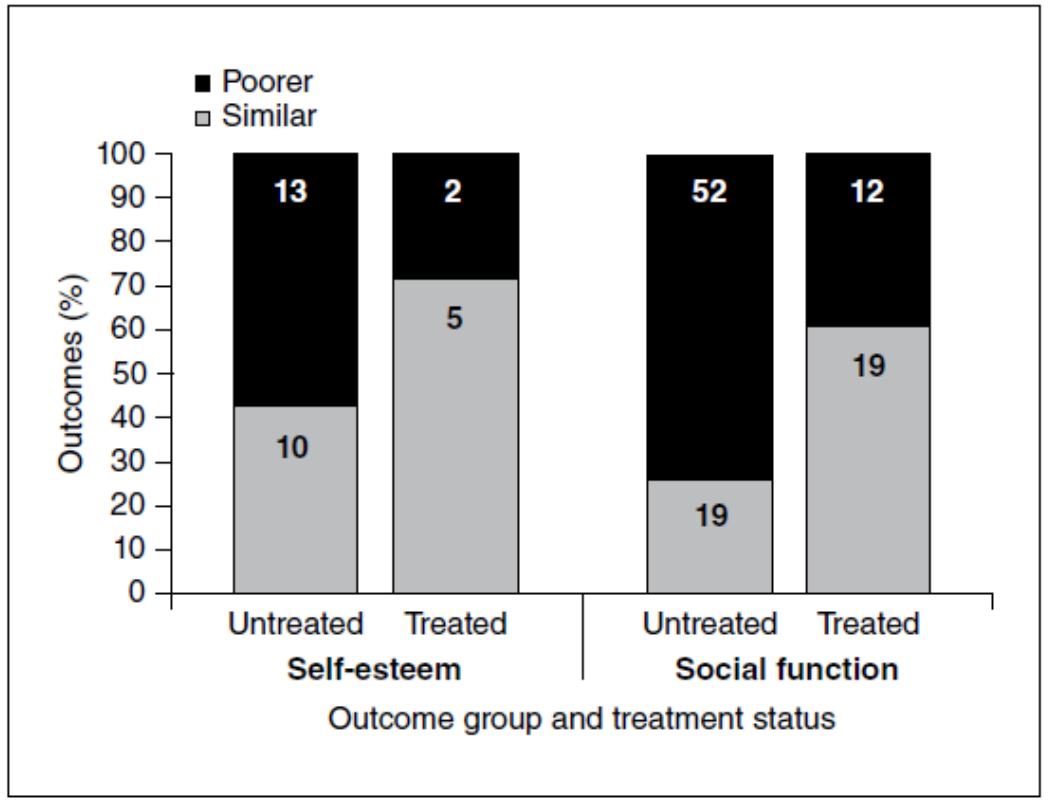


Harpin V, Mazzone L, Raynaud JP, Kahle J, Hodgkins P. Long-Term Outcomes of ADHD: A Systematic Review of Self-Esteem and Social Function. J Atten Disord. 2016 Apr;20(4):295-305.

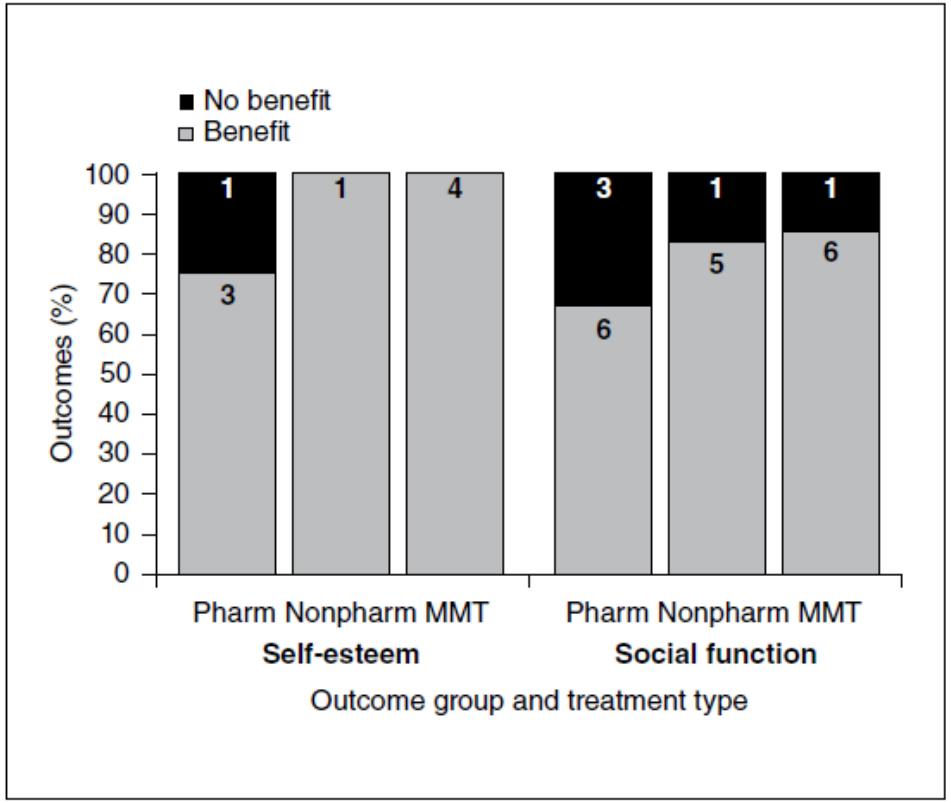
127 studies on **long-term self-esteem and social function outcomes** of individuals with **untreated and treated** ADHD across childhood, adolescence, and adulthood.

**Most outcomes were poorer in individuals with untreated ADHD vs treated ADHD**

**Self-esteem and social function** outcomes for individuals with **untreated and treated ADHD vs non-ADHD controls**




Benefit of treatment by **treatment type** for self-esteem and social function outcomes, nonpharm = nonpharmacological treatment; pharm = pharmacological treatment; MMT = multimodal treatment



*Pharmacological treatment of ADHD is **also** associated with*:

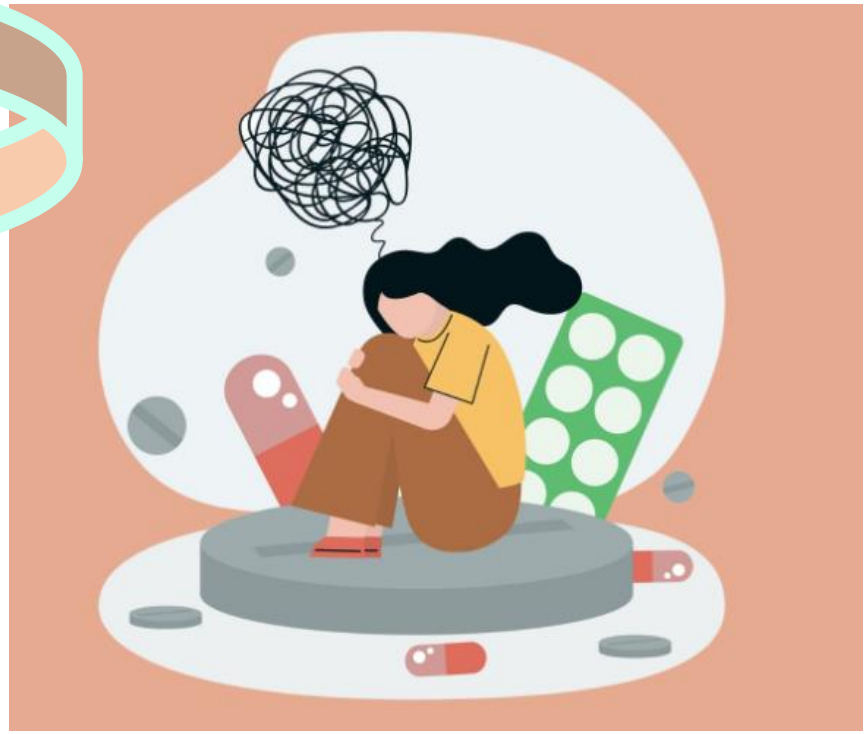
- improved **educational** and occupational outcomes
- reduced rates of **criminality**
- less percentage of **substance use** disorders
- protective effect for **obesity**

**Treatment recommendations do not differ by sex**

**The response to stimulants appears comparable in females and males…**

***…but…***

…girls are **less likely to be prescribed** stimulant treatment than boys and are likely to **start treatment at an older age**




- Sharp WS, Walter JM, Marsh WL,, Castellanos FX. ADHD in girls: Clinical comparability of a research sample. J Am Acad Child Adolesc Psychiatry. 1999;38:40–7.
- Polanczyk G, Faraone SV, Bau CHD, Victor MM, Becker K, Pelz R, et al. The impact of individual and methodological factors in the variability of response to methylphenidate in ADHD pharmacogenetic studies from four different continents. Am J Med Genet Part B Neuropsychiatr Genet. 2008; 147:1419–24.
- Dalsgaard S, Leckman JF, Nielsen HS, Simonsen M. Gender and injuries predict stimulant medication use. J Child Adolesc Psychopharmacol. 2014; 24:253–9.
- Biederman J, et aDo stimulants have a protective effect on the development of psychiatric disorders in youth with ADHD? A ten-year follow-up study. Pediatrics. 2009; 124:71–8.
- Quinn PD, Chang Z, Hur K, Gibbons RD, Lahey BB, Rickert ME, et al. ADHD medication and substance-related problems. Am J Psychiatry. 2017;174:877–85.

**Association Between Medication Use for Attention-Deficit/Hyperactivity Disorder and Risk of Motor Vehicle Crashes** (Chang et al. JAMA Psychiatry 2017)

Table 2. Concurrent Associations Between Attention-Deficit/Hyperactivity Disorder Medication Use and Motor Vehicle Crash (MVC) Events

| Variable | No. of Person-months at Risk | No. of MVC Events | Odds Ratio (95% CI) | |
|---|---|---|---|---|
| | | | Population Level | Within Individual |
| Men | | | | |
| Medicated | 11 538 041 | 2250 | 0.88 (0.84-0.93) | 0.62 (0.56-0.67) |
| Unmedicated | 12 945 705 | 3151 | 1 [Reference] | 1 [Reference] |
| Women | | | | |
| Medicated | 14 045 478 | 2960 | 0.86 (0.82-0.90) | 0.58 (0.53-0.62) |
| Unmedicated | 12 138 441 | 3134 | 1 [Reference] | 1 [Reference] |

Estimate

Up to **22.1% of the traffic accidents of patients with ADHD could have been avoided if they had received medication all the time**

Wilens TE, Woodward DW, Ko JD, Berger AF, Burke C, Yule AM. **The Impact of Pharmacotherapy of Childhood-Onset Psychiatric Disorders on the Development of Substance Use Disorders**. J Child Adolesc Psychopharmacol. 2022 May;32(4):200-214.

Child- and adolescent-onset psychopathology increases the risk for developing substance use and substance use disorders (SUDs)

**21 studies on the impact of pharmacotherapy and later SUD in ADHD**, 2 on Major Depressive Disorder, and 3 on psychotic disorders.

*these studies reported:*

- ❑ reductions in SUD (N=14)
- ❑ no effects (N=10)
- ❑ enhanced rates of SUD (N=2)




**pharmacological treatments** for ADHD and psychiatric disorders appear to **mitigate the development of SUD,** especially when treatment is initiated **early and for longer durations**

Within-subject analyses of population data

- **Use of stimulants in ADHD adults** is associated with:

  - N=25,656, in 2006-09. **Lower risk of criminal arrests in males** (HR=0.63) and females (HR=0.59)

  - N=17,408, in 2006-09. **Lower risk of serious car accidents in males** (HR=0.42).

(Lichtenstein et al. 2013)



Boland H, DiSalvo M, Fried R, Woodworth KY, Wilens T, Faraone SV, Biederman J. A literature review and meta-analysis on the effects of ADHD medications on functional outcomes. J Psychiatr Res. **2020 Apr**;123:21-30.

the meta-analyses (40 articles were included) demonstrated a protective effect of **medication treatment on academic outcomes, accidents and injuries, and mood disorders**

- ADHD medication use is associated with decreased risk of outcomes including motor vehicle crashes and depression.
- Early diagnosis and treatment of ADHD may help alleviate the risk of these harmful outcomes.
- There were variable but largely positive findings associated with lowered rates of mood disorders, substance use disorders, criminality, suicidality, traumatic brain injuries, motor vehicle crashes, injuries, and academic outcomes and ADHD medication use



REVIEW

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

# 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**

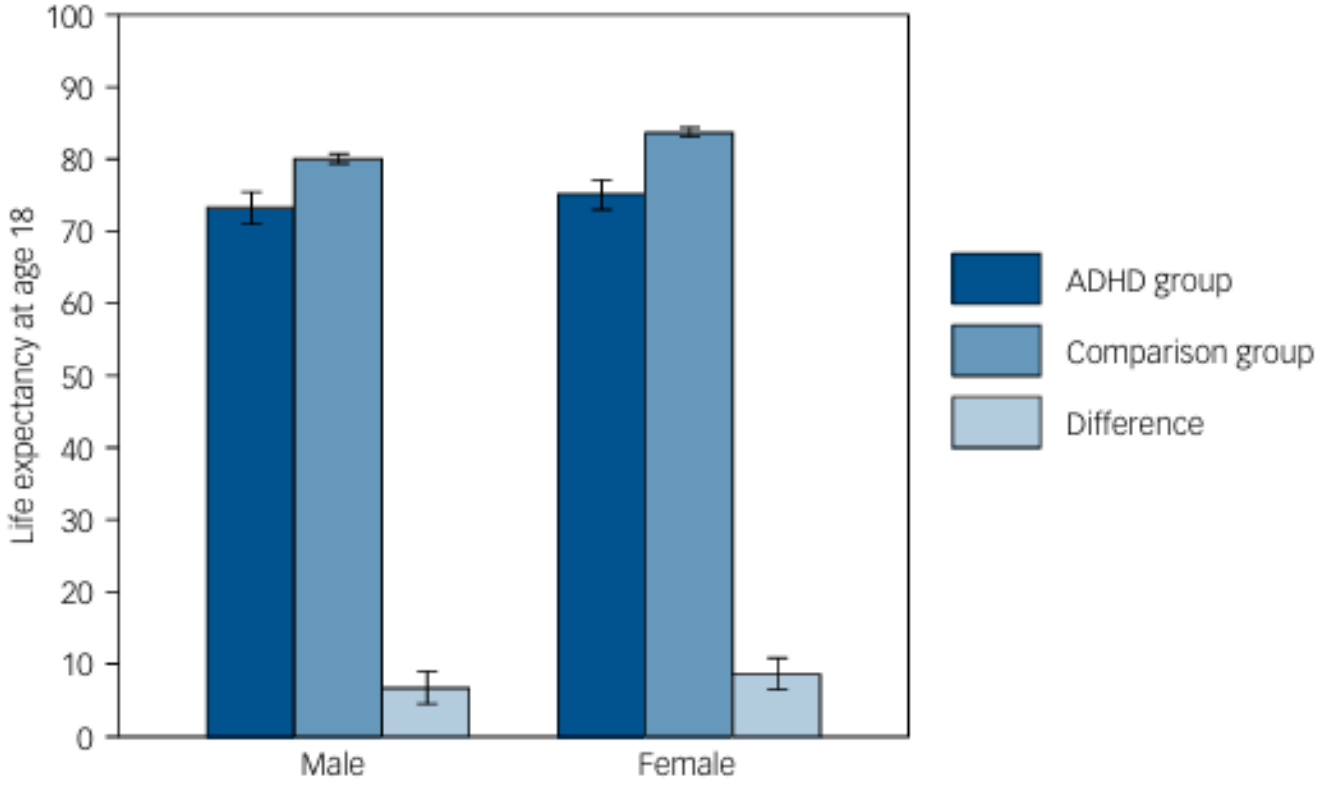
**❑comorbidity, especially with disruptive behavior disorders**




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

Credit: Illustration by Laura Porter for Verywell Health

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**

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*:<br>2 internet addiction<br>1 gambling<br>8 substance/ alcohol<br>4 gaming<br>1 mixed | 2 reviews showed an association with internet addiction.<br>1 shows a positive association with gambling<br>8 reviews showed a positive association between ADHD and various forms of substance/alcohol addiction (including substance misuse, alcohol and cigarettes)<br>4 reviews showed a positive association between ADHD and gaming issues.<br>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<br>1 OCD<br>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.<br>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<br>4 eating disorders<br>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<br>Two reviews showed a link with asthma<br>One with some vision impairments<br>Two with restless leg syndrome<br>One on chronic pain<br>One on vision<br>One on type 2 diabetes<br>One on the allergic diseases<br>One on neurodegenerative diseases<br>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<br>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…

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

# Adults



1.5.15 Offer medication to adults with ADHD if their ADHD symptoms are still causing a significant impairment in at least one domain after environmental modifications have been implemented and reviewed.

1.5.16 Consider non-pharmacological treatment for adults with ADHD who have:

- made an informed choice not to have medication
- difficulty adhering to medication
- found medication to be ineffective or cannot tolerate it.

1.5.17 Consider non-pharmacological treatment in combination with medication for adults with ADHD who have benefited from medication but whose symptoms are still causing a significant impairment in at least one domain.

1.5.18 When non-pharmacological treatment is indicated for adults with ADHD, offer the following as a minimum:

- a structured supportive psychological intervention focused on ADHD
- regular follow-up either in person or by phone. Treatment may involve elements of or a full course of CBT.

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*Scotland*

**2/3** of children diagnosed with ADHD continue to have the full syndrome or are in partial remission beyond the age of 18 (Faraone *et al*, 2006).



# ADHD in adults: good practice guidelines

Historically, such adults were often not referred because of **lack of recognition of need, and lack of service provision**.

It follows that **referrals from this group will increase disproportionately as awareness increases.**

Management of ADHD is **proactively planned in collaboration with the patient**. From the very start, the clinician should explicitly use an approach aimed at **developing the patient's own ability to self-manage over a lifelong period**. Management involves a combination of **pharmacological, psychological, educational and skills-based interventions**

# Psychoactive Medications

| | Methylphenidate | Dexafetamine | Atomoxitine |
|---|---|---|---|
| **Preparations** | **Immediate release**<br>• **Ritalin/Medikinet**: 4h duration of action; b.d. or t.d.s.; 5, 10, 20mg tablets, max. 100mg/day<br>**Modified release**<br>• **Concerta XL:** 22% IR: 78% MR); 10–12h duration of action; o.d.; 18mg tablets; max. 108mg/day<br>• **Equasym XL:** (30% IR, 70% MR) 8h duration of action; o.d.; 10mg tablets; max. 100mg/day<br>• **Medikinet XL** (50% IR: 50% MR): 8h duration of action; o.d.; 10mg tablets; max. 100mg/day | **Short-acting**<br>• **Dexamfetamine:** effect 4h; b.d. or t.d.s.; 5mg tablets; max. 60mg/day<br>**Long-acting**<br>• **Lisdexamfetamine:** effect 12–13h; o.d.; 30, 50, 70mg tablets; max. 70mg/day | • **Strattera:** o.d.; 10, 18, 25, 40, 60, 80, 100mg tablets; usual dose 80mg; max. 120mg/day |
| **Side-effects** | Reduced appetite, insomnia, depressed mood, anxiety, headache, irritability, tachycardia, tics, seizures, psychosis | Reduced appetite, insomnia, tachycardia, increased blood pressure, headache, depressed mood, anxiety, irritability, nasopharyngitis, tics, seizures | Reduced appetite, nausea, depressed mood, tachycardia, increased blood pressure, insomnia, dizziness, GI disturbance, sweating, sexual dysfunction, seizures, hepatitis |
| **Contraindications**[a] | Cardiac disease, cerebrovascular disease, hyperthyroidism, phaeochromocytoma, vasculitis, some mental disorders (weigh risks *v.* benefits) | Cardiovascular disease, hypertension, arteriosclerosis, hyperthyroidism, history of drug or alcohol misuse | Phaeochromocytoma |

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# Psychological treatments

the evidence base for the effectiveness of individual psychological therapies for ADHD in adults is **insufficiently robust** at present for NICE to make any specific recommendations.

Nevertheless, **approaches utilising cognitive–behavioural therapy and coaching strategies** can be useful in practice as adjuncts to medication and in cases where medication is contraindicated or not tolerated.

**Group-based interventions** using these techniques have been developed, e.g. the **Young–Bramham programme** (Young & Bramham, 2012).

Many patients with ADHD could potentially benefit from the **practical and emotional support** offered to other patients by multidisciplinary mental health teams.

The input of **occupational therapists** can be very useful in terms of helping patients to structure their time and improve organisational skills, and in assisting with access to further education and/or employment.

# ADHD nell'adulto

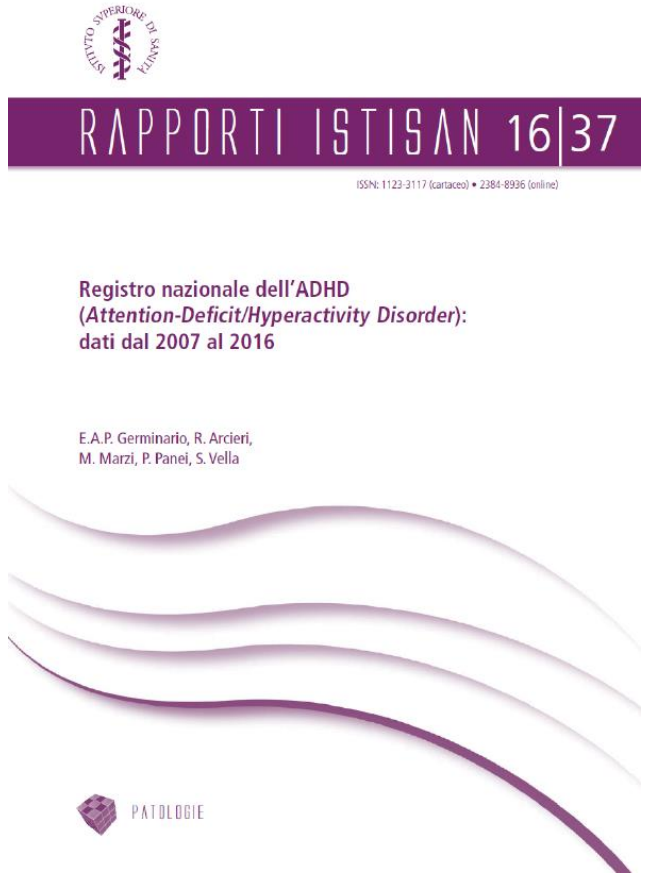
Nella *Gazzetta Ufficiale* n. 275 del **26 novembre 2014 è stato autorizzato l'uso dell'ATX (Strattera®) negli adulti.**

La Determina n. 1291/2014 indica l'ATX per il trattamento del ADHD nei bambini a partire dai 6 anni di età, negli adolescenti e negli adulti come parte di un programma di trattamento multimodale.

Negli adulti la diagnosi deve essere effettuata secondo i criteri stabiliti dal "Manuale di diagnostica e statistica dei disordini mentali", V edizione (*Diagnostic and Statistical Manual of Mental Disorders 5th edition*, DSM-5) e deve basarsi sulla **presenza di sintomi dell'ADHD già in età infantile.**

Nella ***Gazzetta Ufficiale* n. 107 dell'11 maggio 2015 è stato autorizzato l'uso del MPH (Ritalin®) negli adulti**.

La Determina n. 488/2015 ammette l'uso del MPH per il trattamento del disturbo da ADHD **negli adulti già in trattamento farmacologico con questo farmaco, prima del compimento del diciottesimo anno di età.**



L'autorizzazione all'uso del **Medikinet** (metilfenidato a rilascio modificato) negli adulti con ADHD in Italia è avvenuta in due fasi distinte:

**5 novembre 2021:** È stato autorizzato in regime di rimborsabilità SSN esclusivamente per gli **adulti già trattati prima dei 18 anni** (in continuità terapeutica).

**19 ottobre 2023:** L'Agenzia Italiana del Farmaco (AIFA) ha esteso ufficialmente l'indicazione terapeutica e la rimborsabilità anche agli **adulti con nuova diagnosi** (soggetti diagnosticati dopo il compimento del 18° anno di età). La decisione è legata alla determina AIFA pubblicata in Gazzetta Ufficiale il 18 ottobre 2023 ed è entrata in vigore il giorno successivo.

Da ottobre 2023 il farmaco non è quindi più considerato un trattamento off-label per la prima diagnosi in età adulta.

## 1. I criteri di prescrizione del Piano Terapeutico AIFA

L'avvio e la gestione della terapia con metilfenidato per gli adulti (sia in continuità sia per nuova diagnosi) avvengono tramite una **specifica piattaforma informatizzata** gestita dall'Agenzia Italiana del Farmaco (AIFA).

- **Chi può diagnosticare e prescrivere:** Il trattamento non può essere prescritto dal medico di base o da uno psichiatra privato qualunque. La diagnosi differenziale e la redazione del **Piano Terapeutico (PT) web-based** devono essere effettuate esclusivamente da **Centri di riferimento pubblici** (o accreditati) per l'ADHD dell'adulto, individuati dalle singole Regioni.

- **Il Piano Terapeutico:** Il PT certifica la diagnosi clinica, definisce la posologia, monitora l'efficacia del trattamento ed esclude eventuali controindicazioni (come disturbi cardiovascolari gravi o specifiche comorbidità psichiatriche). Ha generalmente una validità massima di 6 o 12 mesi, al termine dei quali il paziente deve effettuare una visita di controllo per il rinnovo.

- **Tipo di ricetta:** Oltre al Piano Terapeutico, per il ritiro in farmacia è necessaria la **Ricetta Ministeriale a Ricalco (RMR)**, poiché il metilfenidato rientra nella tabella dei medicinali stupefacenti.

**Le differenze normative tra Medikinet e Ritalin**

| Caratteristica | Medikinet (Rilascio Modificato) | Ritalin (Rilascio Immediato da 10 mg) |
|---|---|---|
| **Profilo di rilascio** | **50% immediato e 50% prolungato**. Copre circa 6-8 ore e va assunto tassativamente con o subito dopo i pasti per garantire il corretto rilascio. | **100% immediato**. Ha un effetto rapido ma breve (circa 3-4 ore), richiedendo spesso più assunzioni giornaliere. |
| **Nuova diagnosi in età adulta** | **Autorizzato e Rimborsato** dal SSN tramite Piano Terapeutico. | **Non autorizzato** da scheda tecnica (RCP) per l'inizio della terapia da adulti. |
| **Continuità terapeutica (diagnosi pre-18 anni)** | **Autorizzato e Rimborsato** dal SSN. | **Rimborsato** dal SSN solo in regime di continuità assistenziale grazie all'inserimento nelle liste della **Legge 648/96**. |

# Substance misuse

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Substance misuse, mostly involving **alcohol and cannabis**, **may be twice** as common among individuals with ADHD as in the general population and tends to begin earlier

(Breyer *et al*, 2014)

- **Individuals with untreated ADHD may describe self-medicating with illicit substances** (some patients report paradoxical calming effects from stimulant drugs such as cocaine and amphetamines)
- there is **little evidence of patients becoming dependent**
- treating ADHD may **reduce the lifetime risk** of developing a substance use disorder (Biederman, 2003; Dalsgaard et al, 2014)
- Where there is a risk of recreational use of non-prescribed stimulants such as cocaine, amphetamines and some novel psychoactive substances, the patient should be **warned of potential dangerous interactions** with prescribed medication.
- **Risk for diversion** of therapeutic stimulants is significantly **reduced with the use of slow-release preparations**
- Particularly long-acting formulations, appear to have **limited street value**, possibly owing to their pharmacokinetic properties (being slow to reach peak blood levels, they are not very effective at producing a 'buzz')
- Clinicians should be mindful of the use of these medications as **cognitive enhancers** in student populations (Wilens et al, 2016)

# 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***

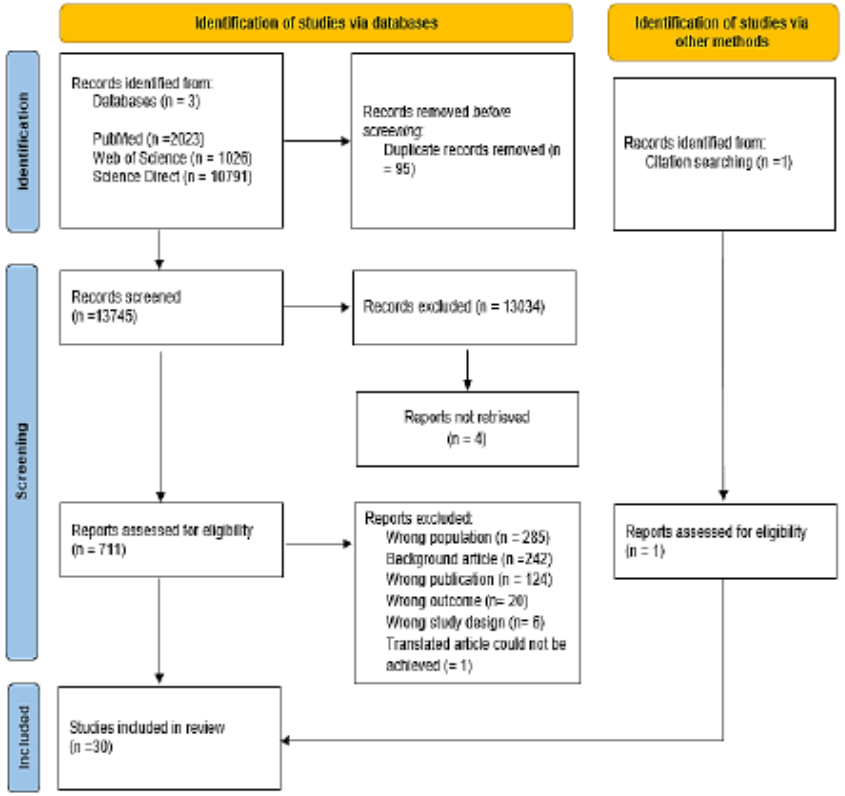



Studiare efficacia e sicurezza dei trattamenti per i sintomi ADHD nella popolazione pediatrica con ASD, con l'obiettivo di dare un contributo alla definizione di un algoritmo di intervento

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**

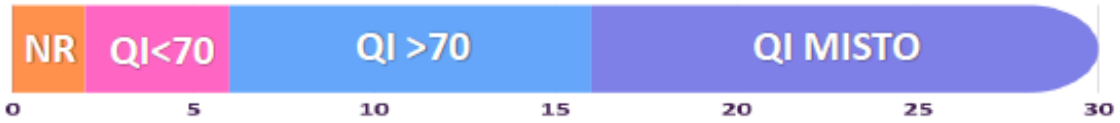



**Fig.2- Studi Inclusi**

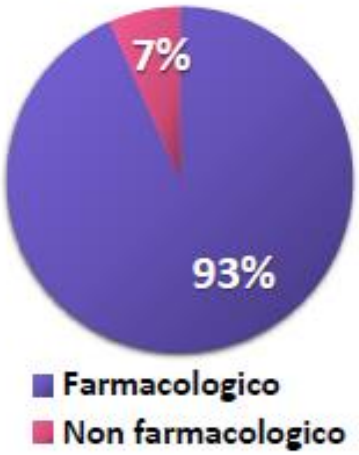
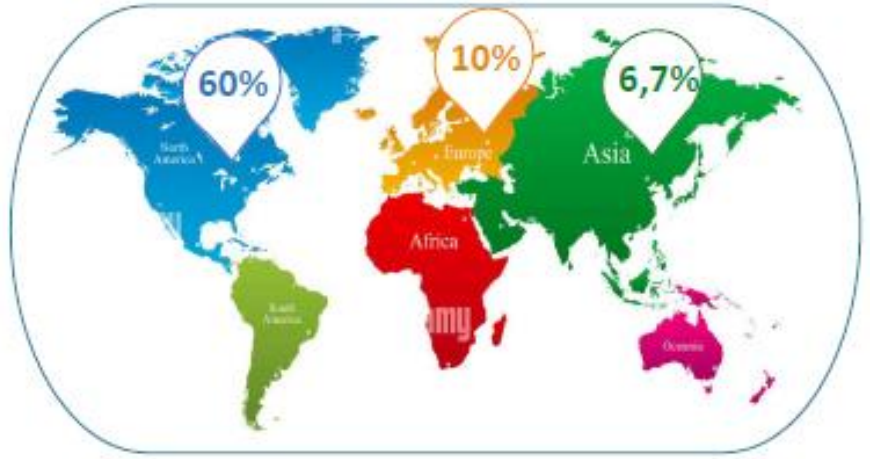
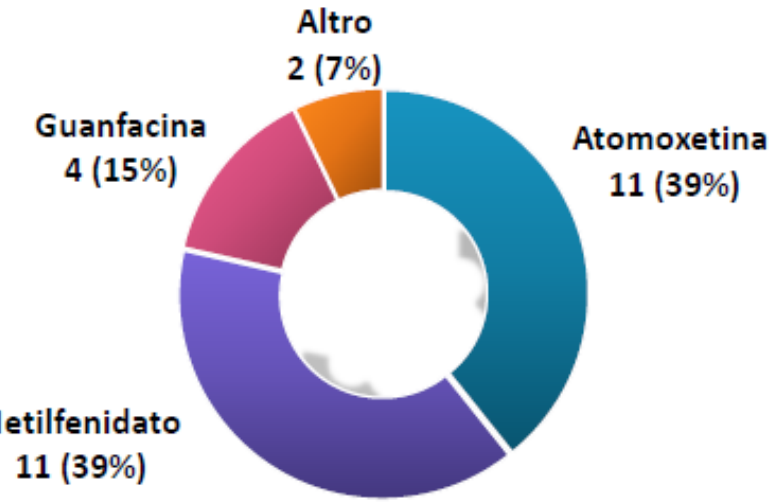



**Fig.3 – Distribuzione geografica**

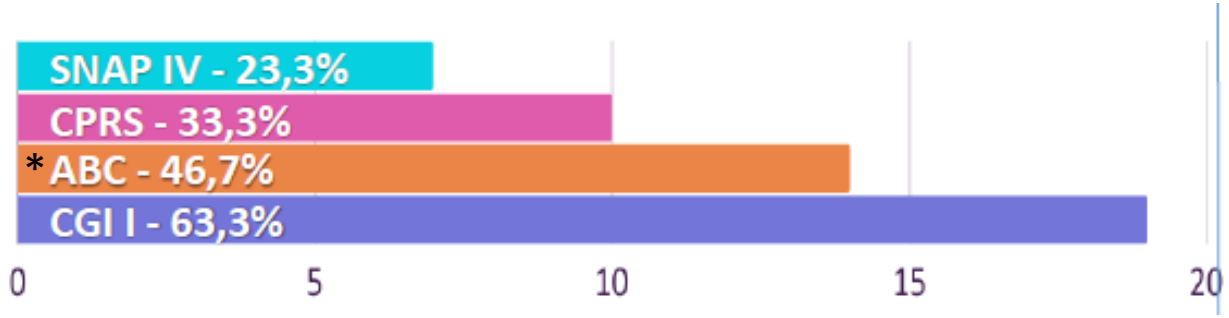



**Registrazione su PROSPERO (CRD42024526157) ricerca sistematica secondo linee guida PRISMA**

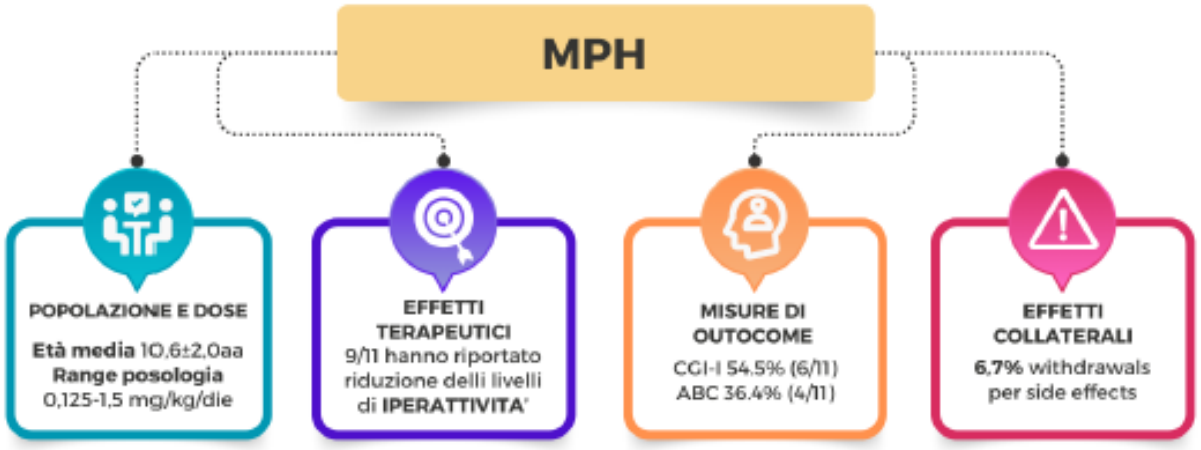
**Fig.3 – Studi su interventi farmacologici**



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.

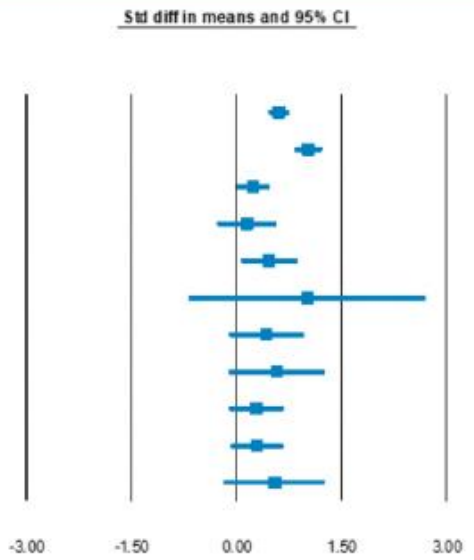
Two classes of drugs resulted significantly better than placebo in improving emotional dysregulation and irritability :

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

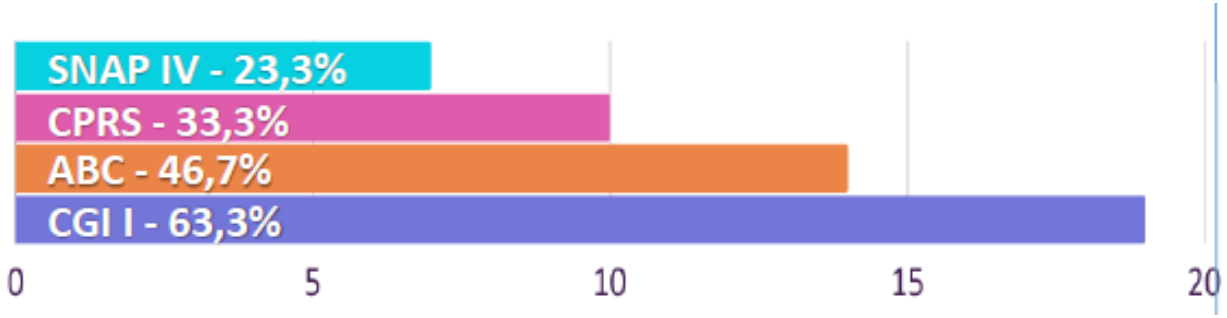
| Study name | Std diff in means | Standard error | Variance | Lower limit | Upper limit | z | p |
|---|---|---|---|---|---|---|---|
| Any pharmacological group | 0.611 | 0.078 | 0.006 | 0.458 | 0.764 | 7.830 | 0.000 |
| Antipsychotics | 1.028 | 0.104 | 0.011 | 0.824 | 1.232 | 9.885 | 0.000 |
| Antidepressants | 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.

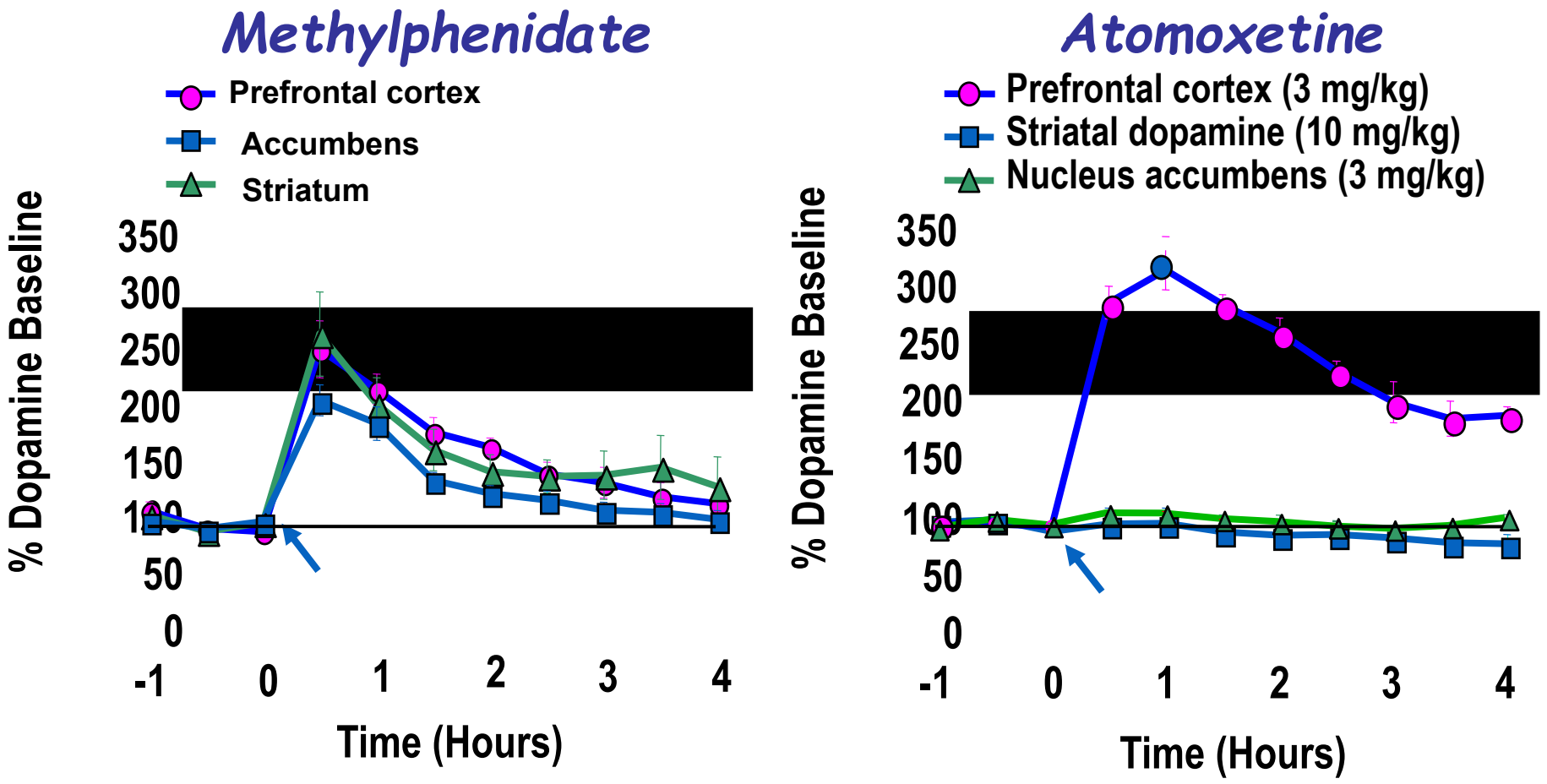
Fig.2: A proposal for a possible pharmachological treatment algorithm targeting the ADHD symptoms in the ASD population

# Confronto tra farmaci

# Atomoxetine vs Methylphenidate:

## Effects on Extracellular Dopamine

### in Rat Prefrontal Cortex, Nucleus Accumbens, and Striatum



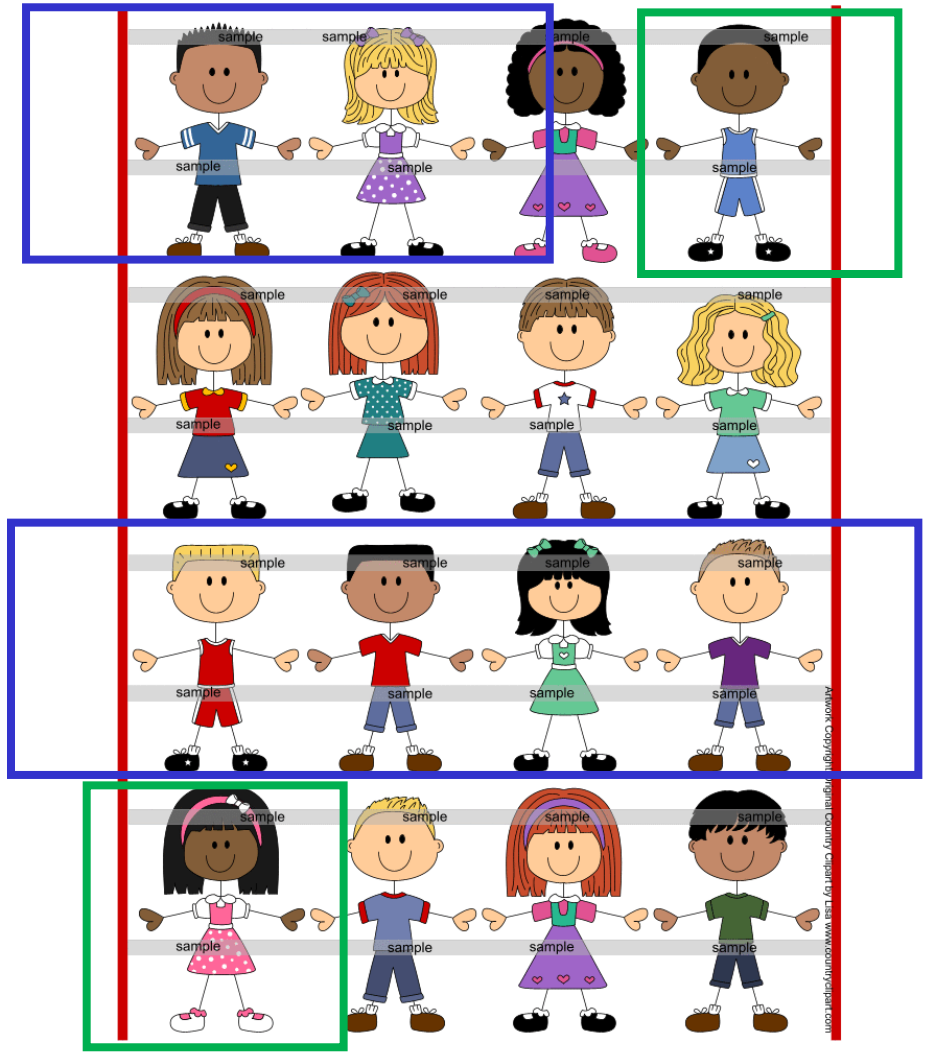

Bymaster FP, et al. *Neuropsychopharmacology* 2002; 27( 5): 699–711.

# **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

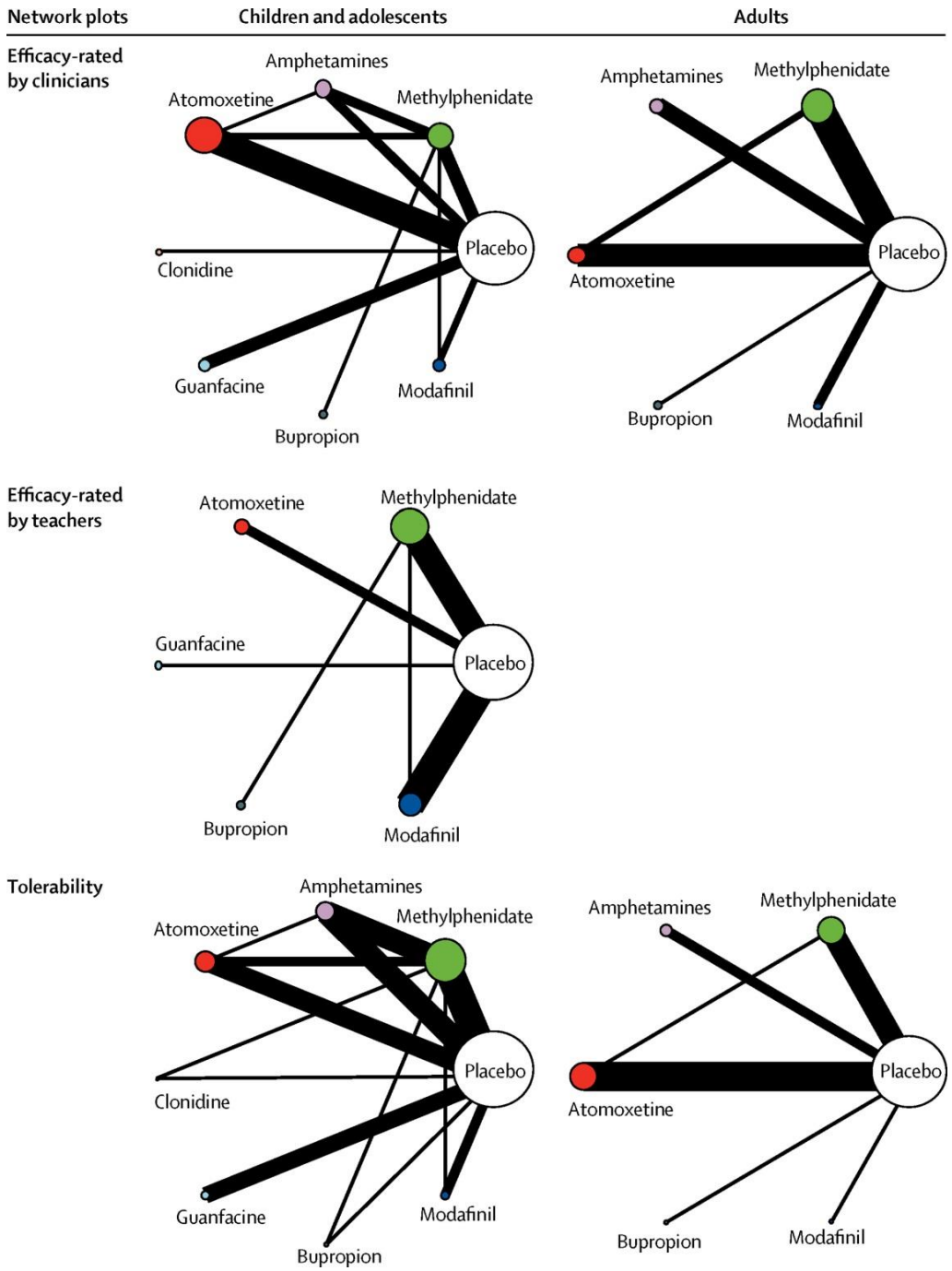


# Efficacia (*Effect Size*)

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)**




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

le **anfetamine** erano inferiori al placebo sia in bambini e adolescenti (odds ratio [OR] 2.30, IC 95% 1.36-3.89) che negli adulti (3.26, 1.54-6.92);

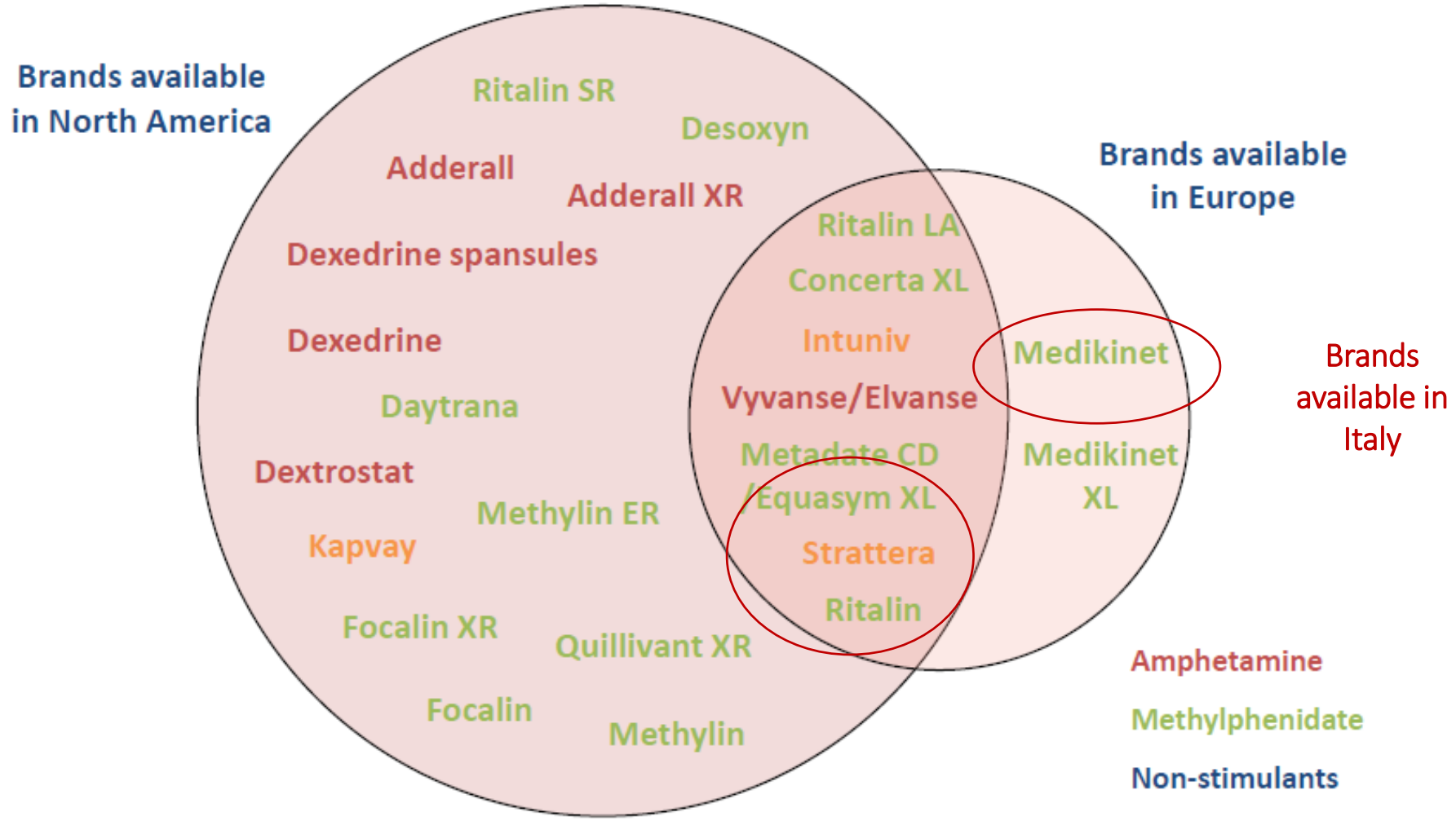
**atomoxetina** (2.33, 1.28-4.25), **metilfenidato** (2.39, 1.40-4.08) e **modafinil** (4.01, 1.42-11.33) erano meno tollerati del placebo solo negli adulti.

**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**




# More pharmacological options

# More pharmacological treatment options are available in North America than in Europe



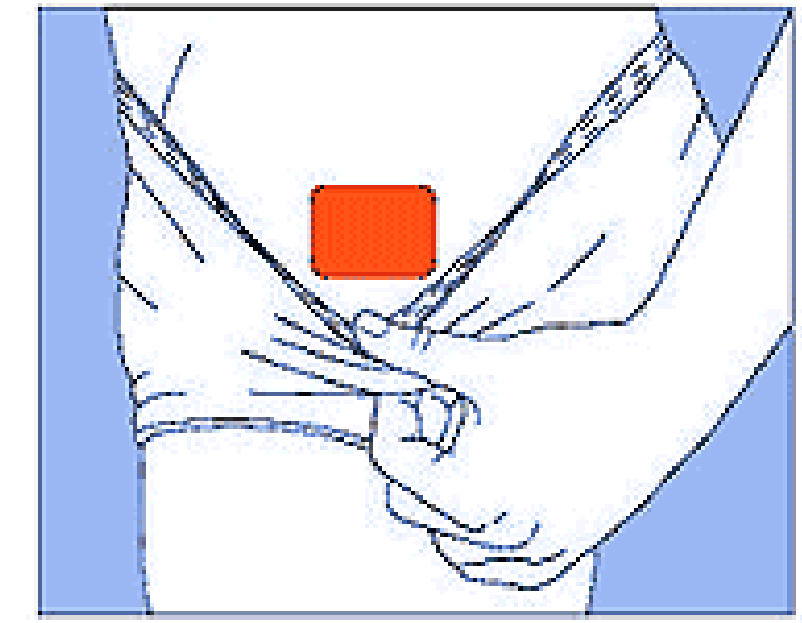

Generic dexamphetamine is available in Europe

Zuddas, 2016

In addition to long-duration stimulant formulations, the

# methylphenidate transdermal system **(Daytrana patch)**

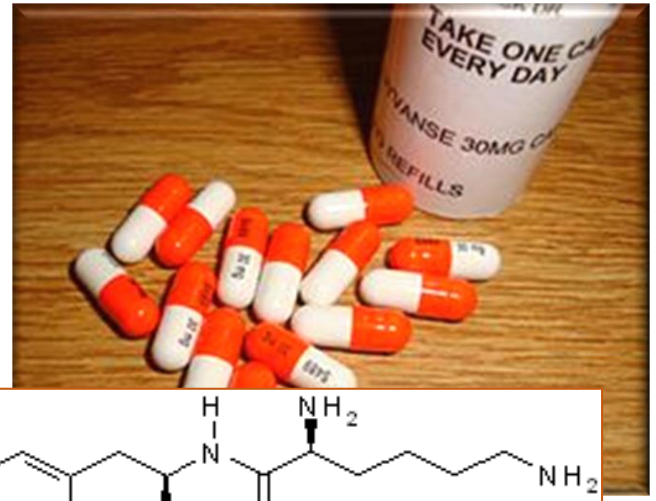
have been found to be
efficacious and tolerable






Findling RL, Bukstein OG, Melmed RD, et al. A randomized, double-blind, placebocontrolled, parallel-group study of methylphenidate transdermal system in pediatric patients with ADHD, J Clin Psychiatry. 2008;69(1):149-159.

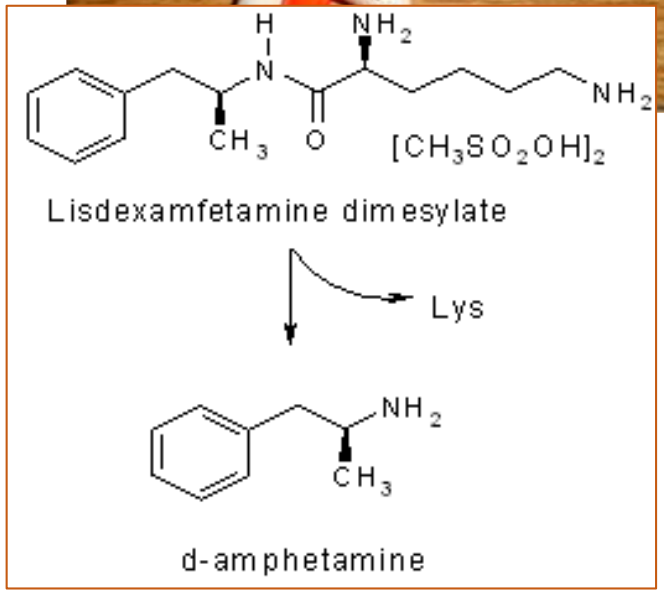
# Vyvanse (lisdexamfetamine)




Faraone SV, Expert Opin Pharmacother. 2008 Jun;9(9):1565-74.

**pro-drug of dextroamphetamine**
it needs to be absorbed in the GI-tract
to be converted to its active form

- **A once-daily, optimized, morning dose of LDX is effective**




- difficult to abuse via snorting

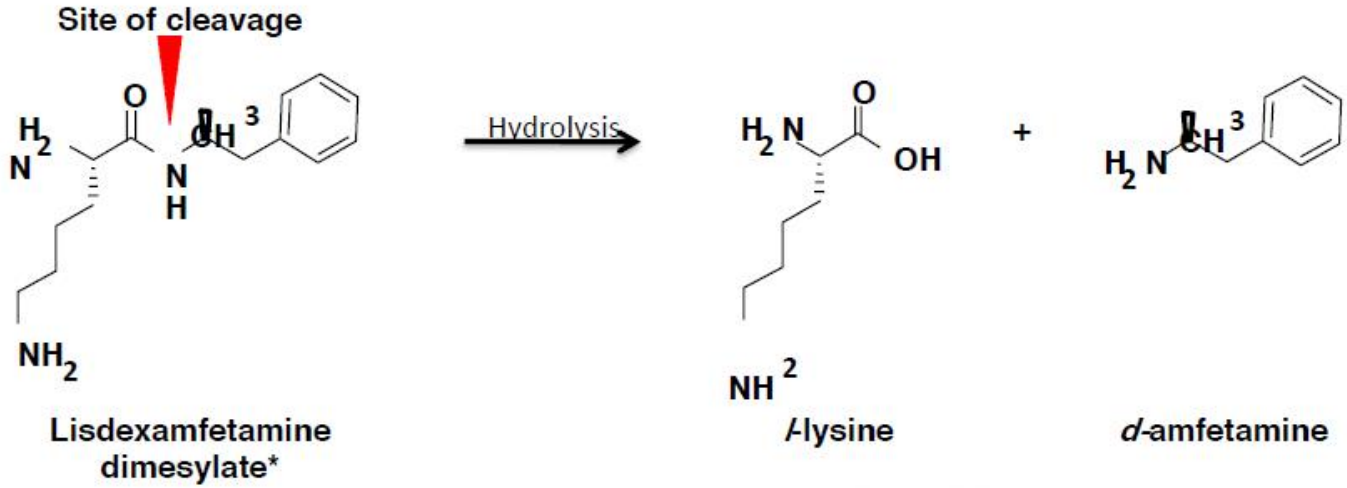
(but it doesn't prevent it from being abused orally)

- longest-acting stimulant
- onset smoother
- less interpatient variability in its duration of action
- generally well tolerated and displayed a safety profile

# Lisdexamfetamine dimesylate (LDX)

Lisdexamfetamine dimesylate (LDX): prodrug

After hydrolysis: active *d*-amphetamine and l-lysine



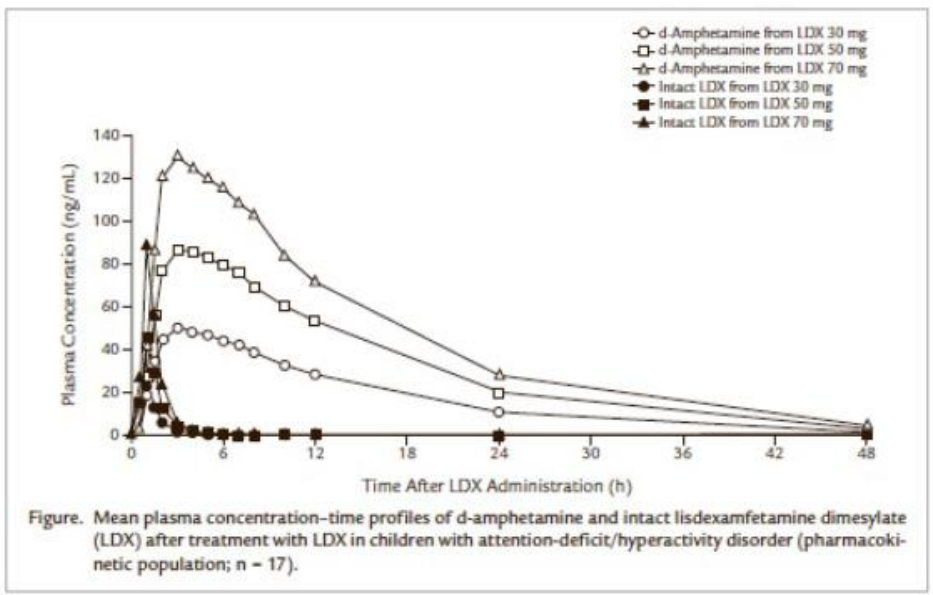




Figure. Mean plasma concentration–time profiles of d-amphetamine and intact lisdexamfetamine dimesylate (LDX) after treatment with LDX in children with attention-deficit/hyperactivity disorder (pharmacokinetic population; n = 17).

European Neuropsychopharmacology

ELSEVIER

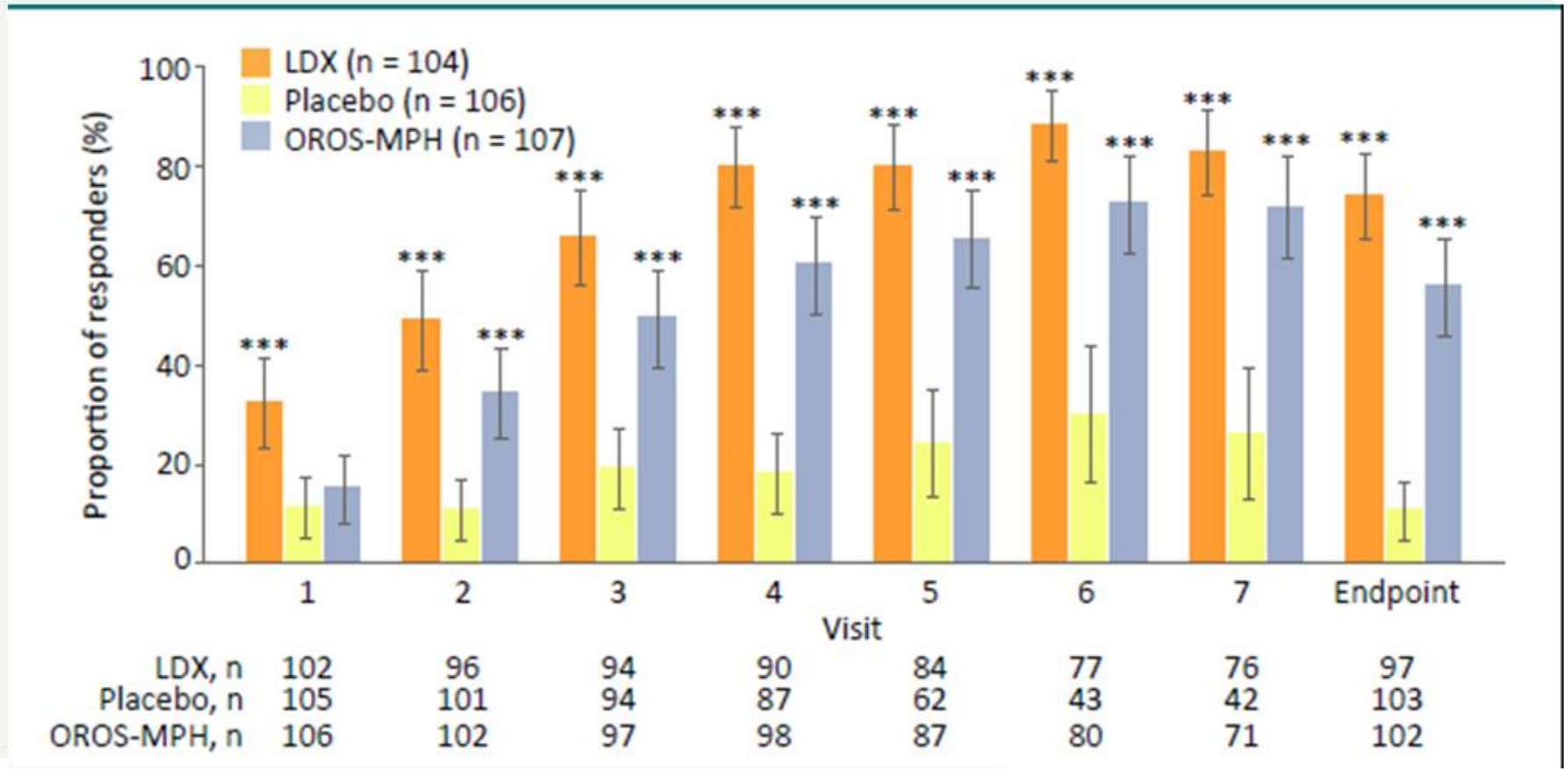
www.elsevier.com/locate/euroneuro

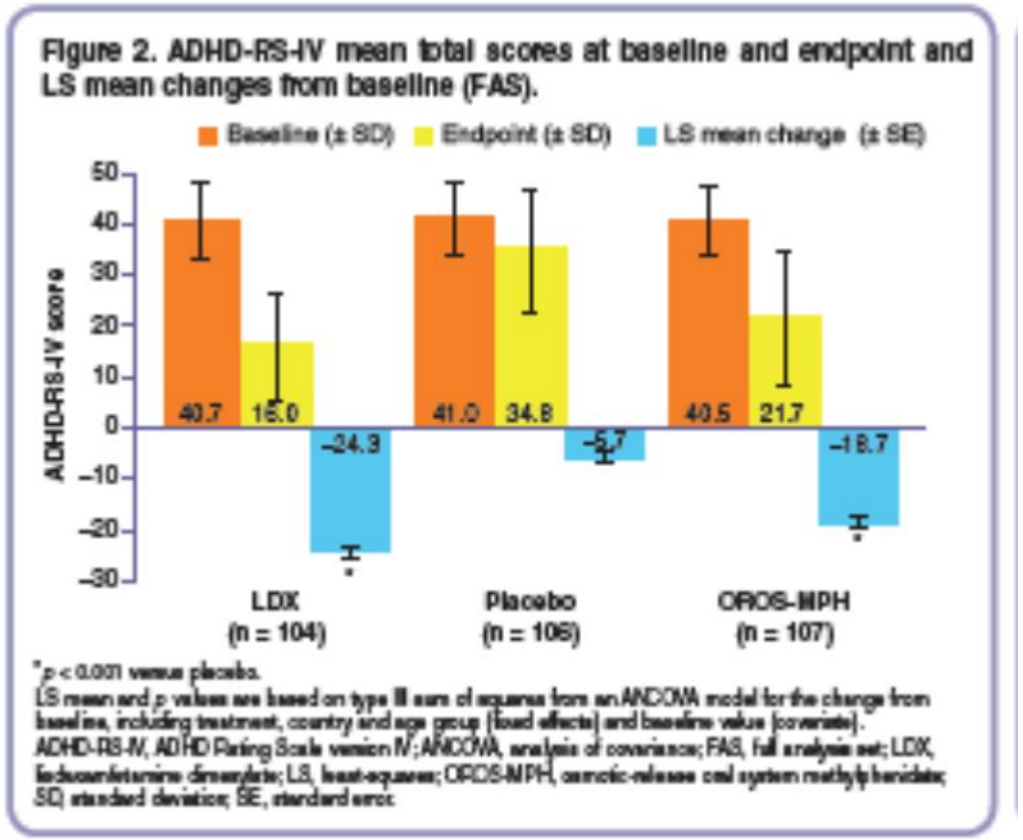
# European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder

David Coghill[a,*], Tobias Banaschewski[b], Michel Lecendreux[c], Cesar Soutullo[d], Mats Johnson[e], Alessandro Zuddas[f], Colleen Anderson[g], Richard Civil[g], Nicholas Higgins[g], Andrew Lyne[h], Liza Squires[g]

*LDX was developed with 2 goals*

1. providing a long duration of effect
2. less abuse-related liking









- **A once-daily, optimized, morning dose of LDX was effective in children and adolescents with ADHD of at least moderate severity**

- **LDX was generally well tolerated and displayed a safety profile consistent with the known effects of long-acting stimulant use and the results from previous LDX trials.**

European Neuropsychopharmacology (2013) 23, 1208-1218



www.elsevier.com/locate/euroneuro



# European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/ hyperactivity disorder

David Coghill[a,*], Tobias Banaschewski[b], Michel Lecendreux[c], Cesar Soutullo[d], Mats Johnson[e], Alessandro Zuddas[f], Colleen Anderson[g], Richard Civil[g], Nicholas Higgins[g], Andrew Lyne[h], Liza Squires[g]

CNS Drugs (2013) 27:829–840
DOI 10.1007/s40263-013-0095-5

ORIGINAL RESEARCH ARTICLE

# Health-Related Quality of Life and Functional Outcomes from a Randomized, Controlled Study of Lisdexamfetamine Dimesylate in Children and Adolescents with Attention Deficit Hyperactivity Disorder

Tobias Banaschewski · César Soutullo · Michel Lecendreux · Mats Johnson · Alessandro Zuddas · Paul Hodgkins · Ben Adeyi · Liza A. Squires · David Coghill

# Maintenance of Efficacy of Lisdexamfetamine Dimesylate in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Randomized-Withdrawal Study Design

David R. Coghill, MD, FRCPsych, MBChB, Tobias Banaschewski, MD, Michel Lecendreux, MD, Mats Johnson, MD, Alessandro Zuddas, MD, Colleen S. Anderson, MEd, Richard Civil, MD, Matthew Dauphin, MS, Nicholas Higgins, BS, Andrew Lyne, MSc, CStat, Maria Gasior, MD, PhD, Liza A. Squires, MD

JAACAP 2014

CNS Drugs (2013) 27:743–751
DOI 10.1007/s40263-013-0086-6

ORIGINAL RESEARCH ARTICLE

# A Post Hoc Comparison of the Effects of Lisdexamfetamine Dimesylate and Osmotic-Release Oral System Methylphenidate on Symptoms of Attention-Deficit Hyperactivity Disorder in Children and Adolescents

César Soutullo · Tobias Banaschewski · Michel Lecendreux · Mats Johnson · Alessandro Zuddas · Colleen Anderson · Richard Civil · Nicholas Higgins · Ralph Bloomfield · Liza A. Squires · David R. Coghill

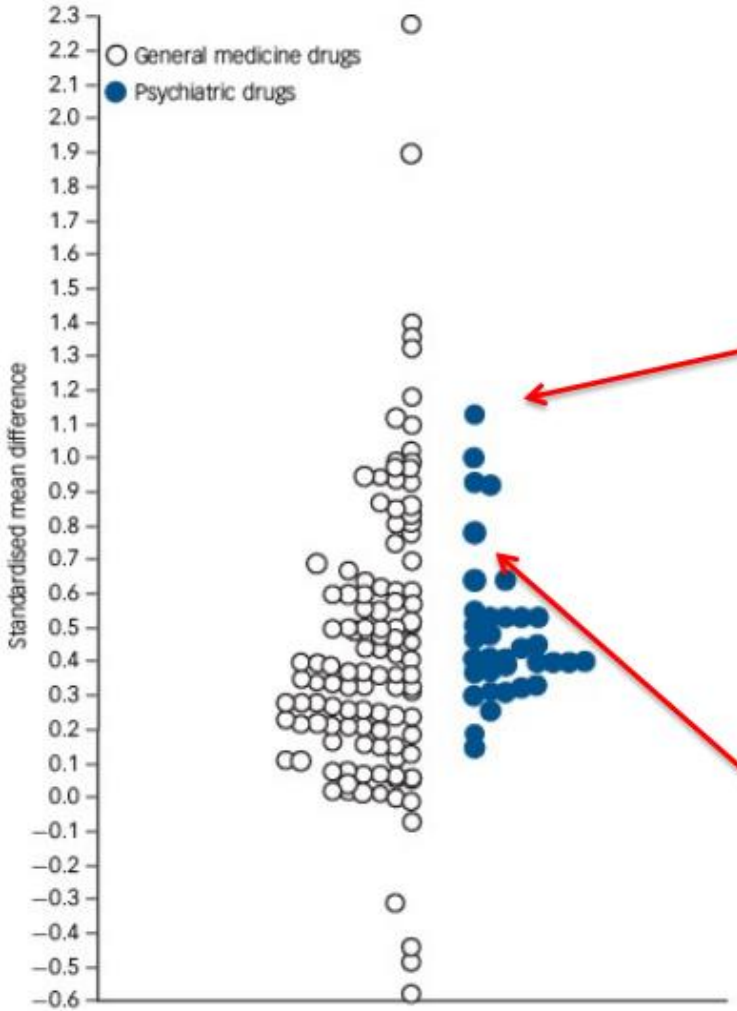



**Fig. 1** Summary of effect sizes.

All effect sizes in online Tables DS3 and DS4 are presented except for duplicates (e.g. effect size on dichotomous response and continuous reduction of severity in schizophrenia). Online Fig. DS25 identifies which dot corresponds to which result, and Figs DS26–29 present the results of dichotomous outcomes as relative and absolute risk/responder differences. Data on older meta-analyses from Table DS1 are not included. Effect sizes of dichotomous outcomes were converted to standardised mean differences expressed as Hedges' *g*. Effect sizes of general medicine medication are presented on the left-hand side (median 0.37, mean 0.45, 95% CI 0.37–0.53) and psychiatric drugs on the right-hand side (median 0.41, mean 0.49, 95% CI 0.41–0.57).

European Neuropsychopharmacology (2013) 23, 1208–1218

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## European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/ hyperactivity disorder

David Coghill[a,*], Tobias Banaschewski[b], Michel Lecendreux[c], Cesar Soutullo[d], Mats Johnson[e], Alessandro Zuddas[f], Colleen Anderson[g], Richard Civil[g], Nicholas Higgins[g], Andrew Lyne[h], Liza Squires[g]

## Relapse Prevention in Pediatric Patients With ADHD Treated With Atomoxetine: A Randomized, Double-Blind, Placebo-Controlled Study

DAVID MICHELSON, M.D., JAN K. BUITELAAR, M.D., PH.D., MARINA DANCKAERTS, M.D., PH.D., CHRISTOPHER GILLBERG, M.D., PH.D., THOMAS J. SPENCER, M.D., ALESSANDRO ZUDDAS, M.D., DOUGLAS E. FARIES, PH.D., SHUYU ZHANG, M.S., AND JOSEPH BIEDERMAN, M.D.

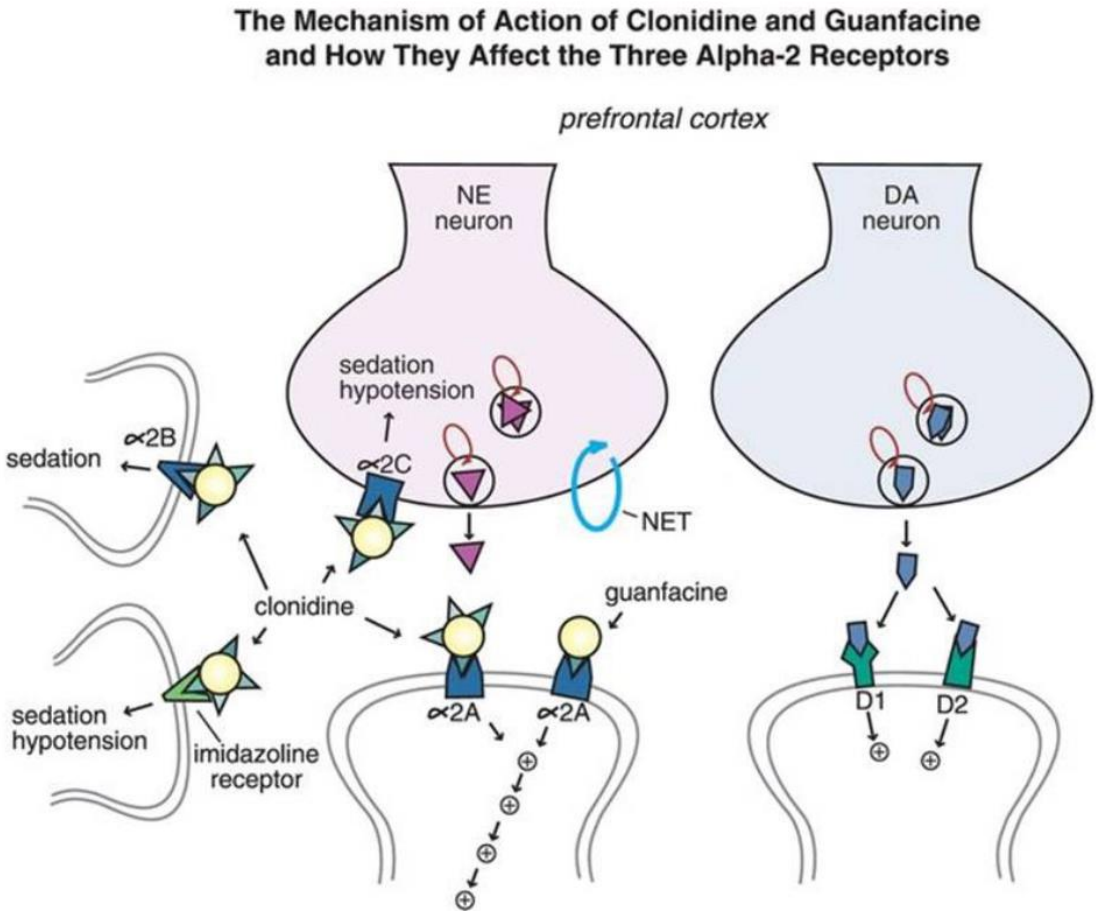
*J. Am. Acad. Child Adolesc. Psychiatry*, 2004;43(7):896–904.

J Child Adolesc Psychopharmacol. 2013 Jun;23(5):308-19, **A review of the rationale and clinical utilization of α2-adrenoceptor agonists for the treatment of attention-deficit/hyperactivity and related disorders.** Sallee F, Connor DF, Newcorn JH.

# Food and Drug Administration approved clinical use of α2-adrenoceptor agonists clonidine and guanfacine in the treatment of ADHD

Large, randomized, placebo-controlled clinical trials support the efficacy and safety of α2-adrenoceptor agonists as

- monotherapy
- adjunctive therapy with psychostimulants



Clin Ther. 2013 Nov;35(11):1778-93. **Guanfacine extended release: a novel treatment for attention-deficit/hyperactivity disorder in children and adolescents.** Faraone SV, McBurnett K, Sallee FR, Steeber J, López FA.

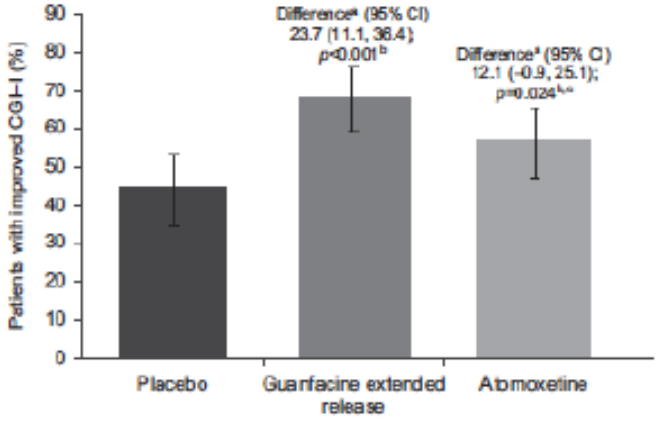
**Guanfacine** extended release (GXR) is efficacy as once-daily monotherapy as well as adjunctive therapy to psychostimulants for ADHD in short-term trials

The safety profile of GXR is consistent with that of a centrally acting α2A-adrenoceptor agonist



Somnolence, sedation, and hypersomnia adverse events (AEs), although frequent, are typically mild to moderate and tend to diminish with continued treatment.

# Efficacy and safety of extended-release guanfacine hydrochloride in children and adolescents with attention-deficit/ hyperactivity disorder: A randomized, controlled, Phase III trial




**Guanfacine:**

a selective $\alpha_{2A}$ receptor antagonist

$\alpha_{2A}$ are highly expressed in the prefrontal cortex and In the locus coeruleus

**Table 2** ADHD-RS-IV total scores (A) and ADHD-RS-IV total score by GXR weight-adjusted dose (B) (full analysis set).

| A | GXR ($n=114$) | ATX ($n=112$) | Placebo ($n=111$) |
|---|---|---|---|
| Baseline mean (SD) score | 43.1 (5.47) | 43.7 (5.86) | 43.2 (5.60) |
| Visit 15 LOCF mean (SD) score | 19.2 (11.85) | 25.0 (12.97) | 28.1 (14.13) |
| Mean (SD) change from baseline to Visit 15 LOCF | −23.9 (12.41) | −18.6 (11.91) | −15.0 (13.07) |
| Comparison to placebo[a] | | | |
| LS mean | −23.9 | −18.8 | −15.0 |
| Difference (95% CI) in LS means[b] | −8.9 (−11.9, −5.8) | −3.8 (−6.8, −0.7) | |
| Effect size | 0.76 | 0.32 | |
| *p*-Value | <0.001 | 0.017[c] | |

| B | GXR (0.01-0.04 mg/kg) $n=13$ | GXR (0.05-0.08 mg/kg) $n=40$ | GXR (0.09-0.12 mg/kg) $n=47$ | GXR (0.13-0.16 mg/kg) $n=12$ |
|---|---|---|---|---|
| Visit 15 LOCF mean (SD)[d] score | 20.2 (14.49) | 19.3 (12.35) | 17.9 (9.76) | 22.5 (15.08) |
| Mean (SD) change from baseline to Visit 15 LOCF | −23.1 (15.99) | −22.3 (12.03) | −26.2 (11.24) | −21.2 (13.90) |

Hervas et al. ENP 2014

# Un nuovo farmaco per l'ADHD: cosa sappiamo su centanafadine

*1R,5S*)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane

luglio 2026 la Food and Drug Administration (FDA) ha approvato il farmaco, commercializzato con il nome **SIMTRIYO®**, per il trattamento dell'ADHD nei pazienti pediatrici (dai 6 anni e con peso maggiore di 20 kg) e negli adulti, in una formulazione a rilascio prolungato da assumere una volta al giorno.
(mean elimination half-life of 5.2 h; it readily crosses the blood–brain barrier)

**E' un triplo inibitore della ricaptazione di noradrenalina, dopamina e serotonina (NDSRI)**

Agisce bloccando contemporaneamente i trasportatori responsabili della ricaptazione di questi tre neurotrasmettitori, con un'attività maggiore sul trasportatore della noradrenalina (NET), seguita da quello della dopamina (DAT) e, in misura minore, da quello della serotonina (SERT), senza indurre direttamente il rilascio dei neurotrasmettitori.

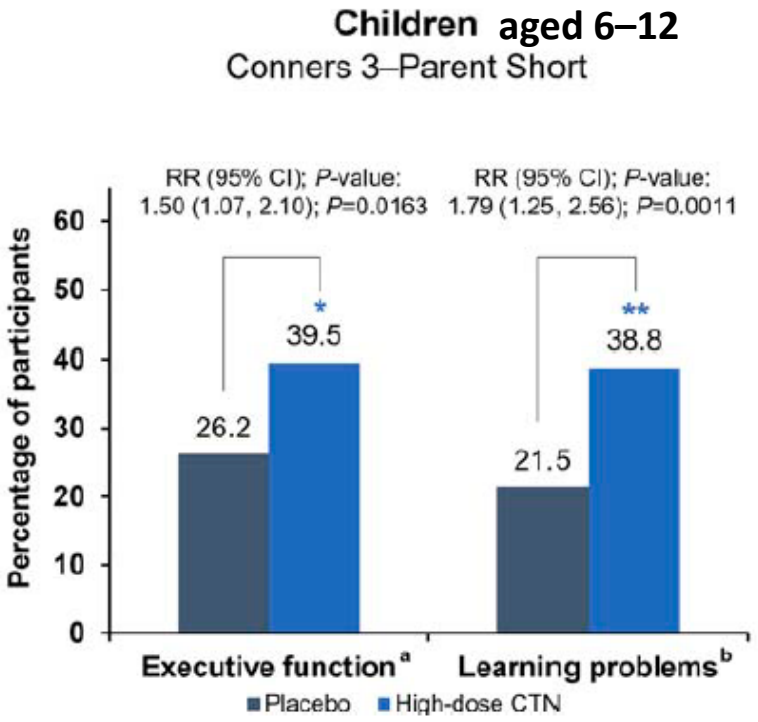
L'approvazione di centanafadine si basa sui risultati di quattro studi clinici di fase 3, randomizzati, in doppio cieco e controllati con placebo, condotti sia su adulti sia su bambini e adolescenti ADHD.

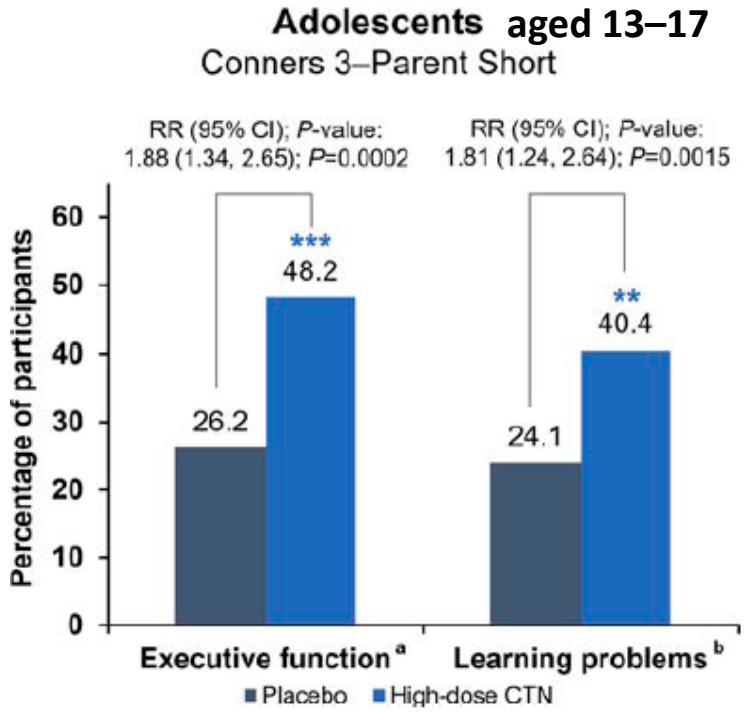

- Hu L. Centanafadine (Simtriyo®): a first-in-class triple reuptake inhibitor approved for attention-deficit/hyperactivity disorder (ADHD). Med Chem Res. 2026 Sep;35(9):1548-1552.
- Schein J, Cloutier M, Gauthier-Loiselle M, Catillon M, Xu C, Qu A, Childress A. Assessment of centanafadine in adults with ADHD: a matching adjusted indirect comparison versus methylphenidate hydrochloride extended release (Concerta). Curr Med Res Opin. 2024 Aug;40(8):1397-1406.

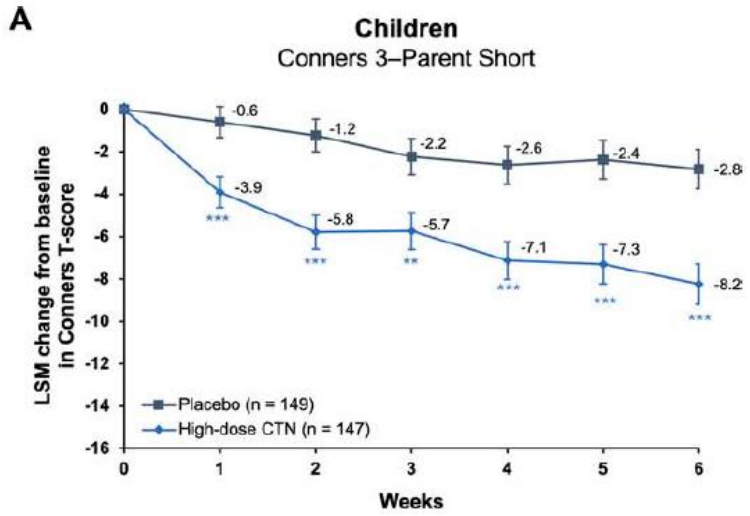
Wilens et al **Efficacy of Centanafadine for Executive Functioning and Learning Problems in Children and Adolescents with ADHD**
J Child Adolesc Psychopharmacol. 2026 Jun;36(5):266-277.

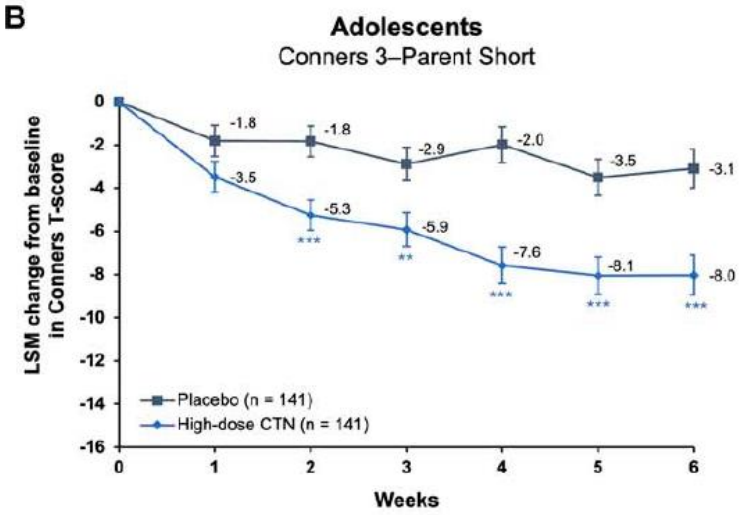
*centanafadine vs placebo for 6 weeks*

- **50% (bambini) e 88% (adolescenti)** in più di probabilità di sperimentare un cambiamento clinicamente significativo nelle **funzioni esecutive**
- **79% (bambini) and 81% (adolescenti)** in più di probabilità di sperimentare un cambiamento clinicamente significativo nei **problemi di apprendimento**




**Oltre al suo impatto sui sintomi core dell'ADHD, la centanafadina ha migliorato le funzioni esecutive, i problemi di apprendimento e il funzionamento nelle attività quotidiane in bambini e adolescenti ADHD**

***Quale classe di farmaci per Francesco……?***

disregolazione emozionale





# La disregolazione emozionale

# Disregolazione emozionale

fattore transnografico di vulnerabilità, presente già in età evolutiva, in diversi fenotipi psichiatrici, avente aspetti comuni nelle diverse categorie diagnostiche e **tendenza ad influenzare l'outcome a lungo termine** e a persistere in età adulta

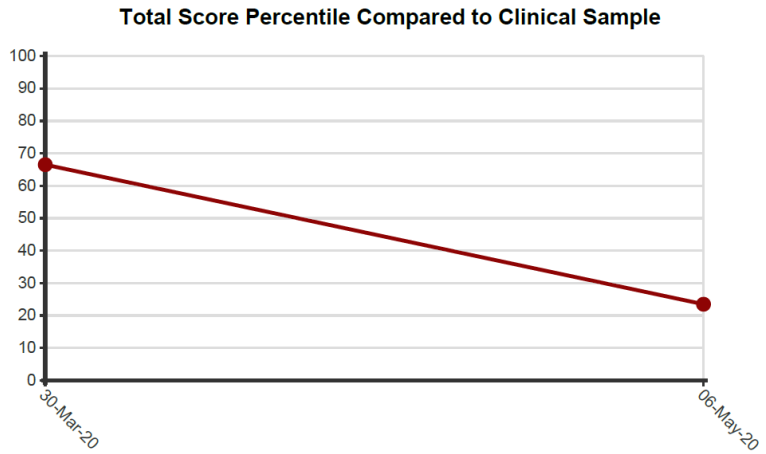

- Gratz KL,WeissNH,McDermottMJ,Dilillo D,Messman-Moore T, TullMT. Emotion dysregulation mediates the relation between borderline personality disorder symptoms and later physical health symptoms. *J Pers Disord.* (2017)31:433–48..
- Pat-Horenczyk R, Cohen S, Ziv Y, AchituvM, Asulin-Peretz L, Blanchard TR, et al. Emotion regulation in mothers and young children faced with trauma. *Infant Ment Health J.* (2015) 36:337–48.
- Biederman J, Petty CR, Day H, Goldin RL, Spencer T, Faraone SV, et al. Severity of the aggression/anxiety-depression/attention child behavior checklist profile discriminates between different levels of deficits in emotional regulation in youth with attention-deficit hyperactivity disorder. *J Dev Behav Pediatrics.* (2012) 33:236–43.

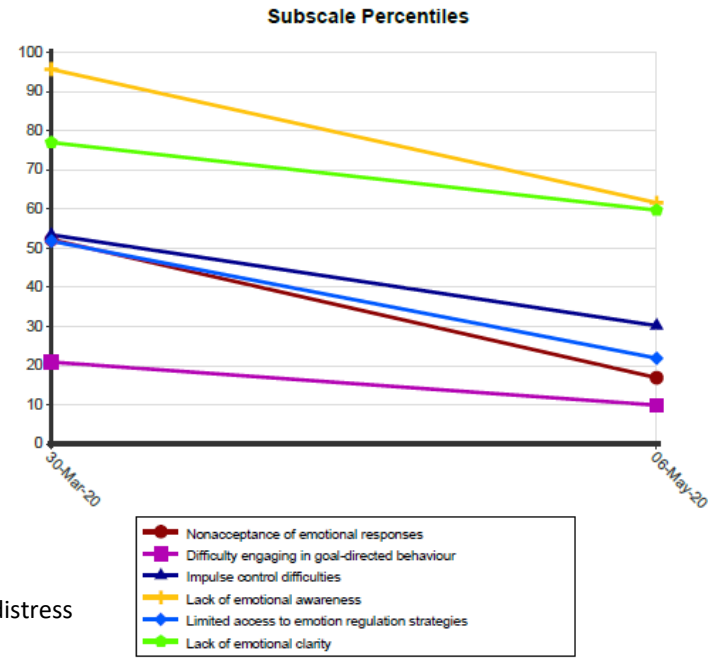
Emotion Dysregulation (ED) reflects a **limited set of strategies** for understanding, accepting and dealing with one's own emotional states



Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. J Psychopathol Behav Assess. (2004) 26:41–54.

# Difficulties in Emotion Regulation Scale (DERS) 36 items self-report scale - Ages 18+




SUBSCALES:

**Nonacceptance of emotional responses**: 11, 12, 21, 23, 25, 29
Tendency to have a negative secondary or non accepting reaction to one's own distress

**Difficulty engaging in goal-directed behaviour**: 13, 18, 20R, 26, 33
Difficulty in concentrating and/or accomplishing tasks when experiencing negative emotions

**Impulse control difficulties**: 3, 14, 19, 24R, 27, 32
Difficulty remaining in control of one's behaviour when experiencing negative emotions

**Lack of emotional awareness**: 2R, 6R, 8R, 10R, 17R, 34R
Reflects a lack of awareness or inattention to emotional responses

**Limited access to emotion regulation strategies**: 15, 16, 22R, 28, 30, 31, 35, 36
Reflects the belief that there is little one can do to regulate oneself once upset

**Lack of emotional clarity**: 1R, 4, 5, 7R, 9
Reflects the extent to which an individual knows and is clear about his or her emotions



higher scores are also **predictive of bigger treatment gains from CBT**

This suggests that emotion regulation is a **key skill** that **can be learnt** during therapy and mastering these skills is a an important mechanism for symptom reduction in successful treatment


Hallion, L. S., Steinman, S. A., Tolin, D. F., & Diefenbach, G. J. (2018). Psychometric properties of the Difficulties in Emotion Regulation Scale (DERS) and its short forms in adults with emotional disorders. Frontiers in psychology, 9, 539.
Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. J psychopath and behav assessment, 26(1), 41-54.

SLEEPJ, 2019, 1–12

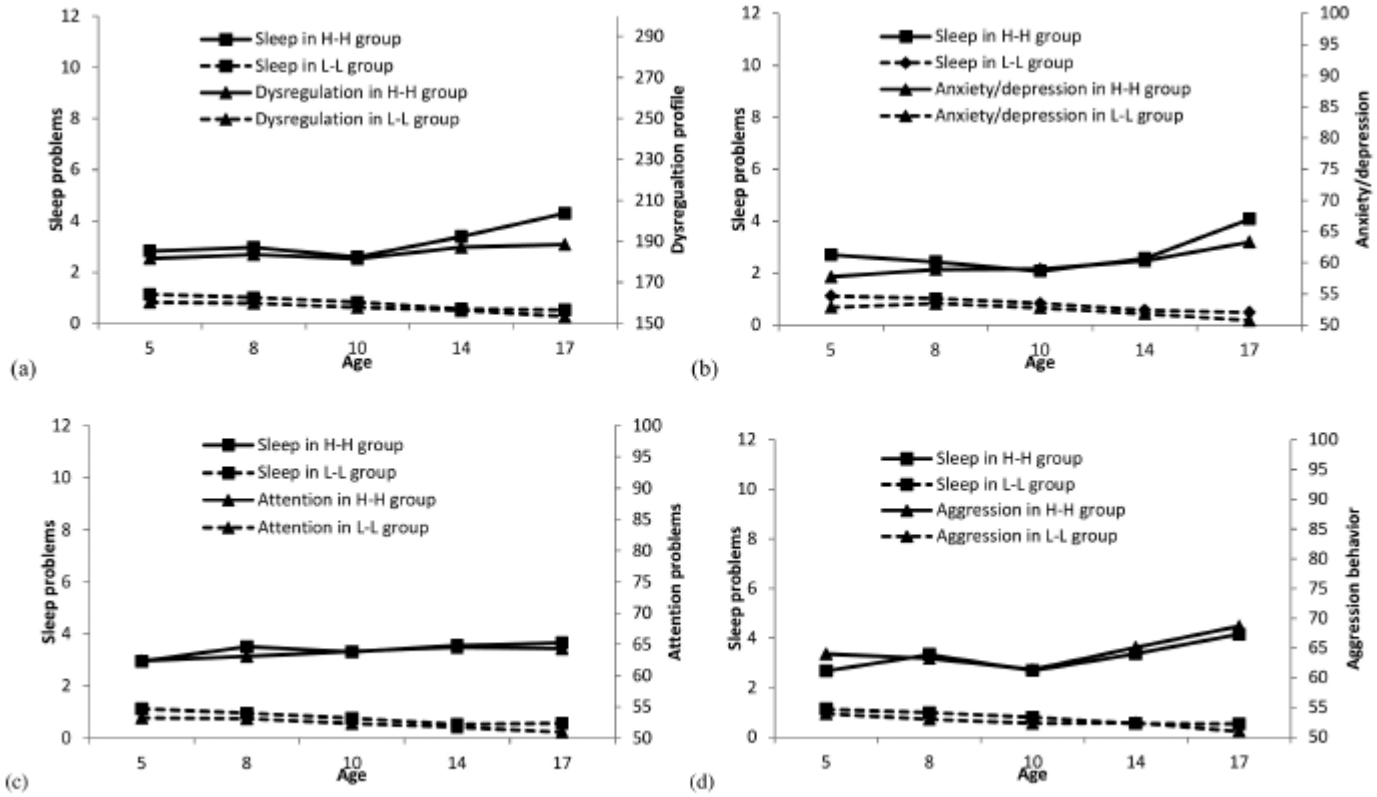
doi: 10.1093/sleep/zsy243
Advance Access Publication Date: 6 December 2018
Original Article

ORIGINAL ARTICLE

**Concurrent developmental course of sleep problems and emotional/behavioral problems in childhood and adolescence as reflected by the dysregulation profile**

Biyao Wang[1,*], Peter R. Eastwood[2,o], Andreas Becker[1], Corinna Isensee[1], Janice WY. Wong[3,4,5], Rae-Chi Huang[4], Kevin C. Runions[3,4], Richard M. Stewart[3], Thomas Meyer[6], L. G. Brüni[7], Aribert Rothenberger[1,†] and Florian D. Zepf[3,4,8,†]

The course and relationships (over time) of **sleep problems** and "**dysregulation profile",** as dimensional condition common to **anxiety, depression, attention deficiency, and aggressive behaviors**




*Note*. H-H = High-High group; L-L = Low-Low group. The former H/L indicate the class of sleep problems, the latter H/L indicate the class of dysregulation.

Having **persistent sleep problems** over time was associated with an increased risk of having **regulatory difficulties** by approximately **10 times and vice versa**

strong mutual association between sleep problems and difficulties of **dysregulation with emotion, cognition, and aggression**

# *Quale classe di farmaci per l'ED?*

Second Generation Antipsychotic Medications

Depression & Anxiety Medications

Mood Stabilizer Medications

ADHD Medications

Sleep Medications

# 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.

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.

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 28, Number 5, 2018
© Mary Ann Liebert, Inc.
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**

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**

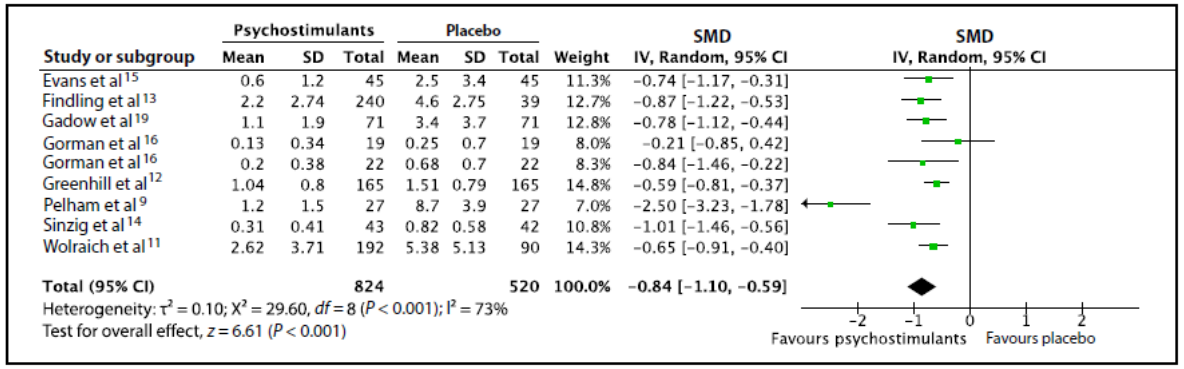
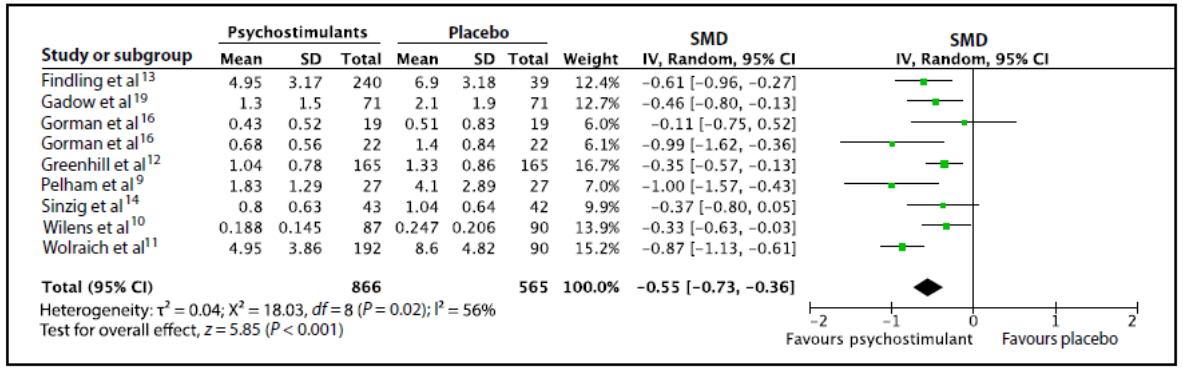



**Figure 1b Psychostimulants, compared with placebo, for aggression, oppositional behaviour, and conduct problems as measured by parents in youth with attention-deficit hyperactivity disorder, with and without oppositional defiant disorder, and conduct disorder**




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

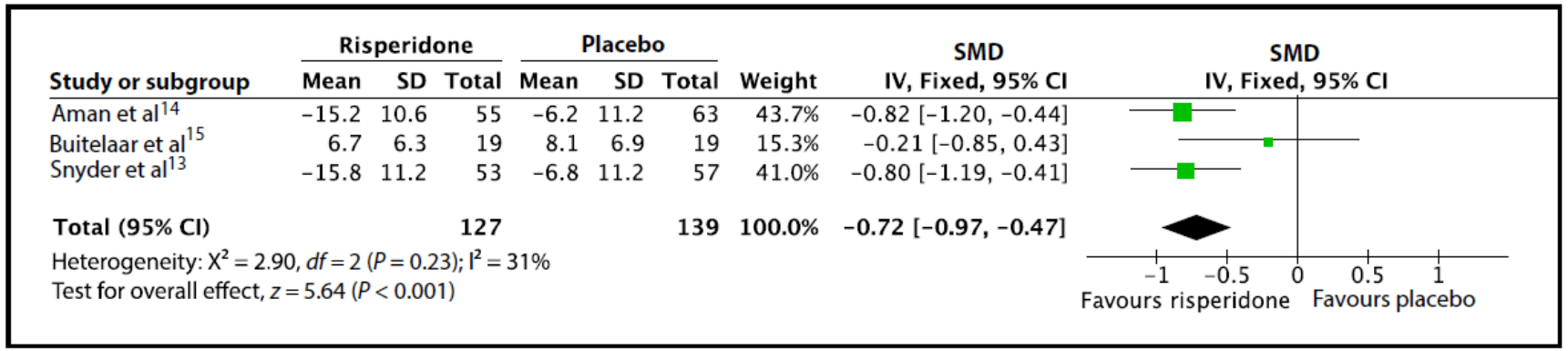
There is **moderate-quality evidence** that **guanfacine** has a small-to-moderate effect on oppositional behaviour in youth with ADHD, with and without ODD.

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**

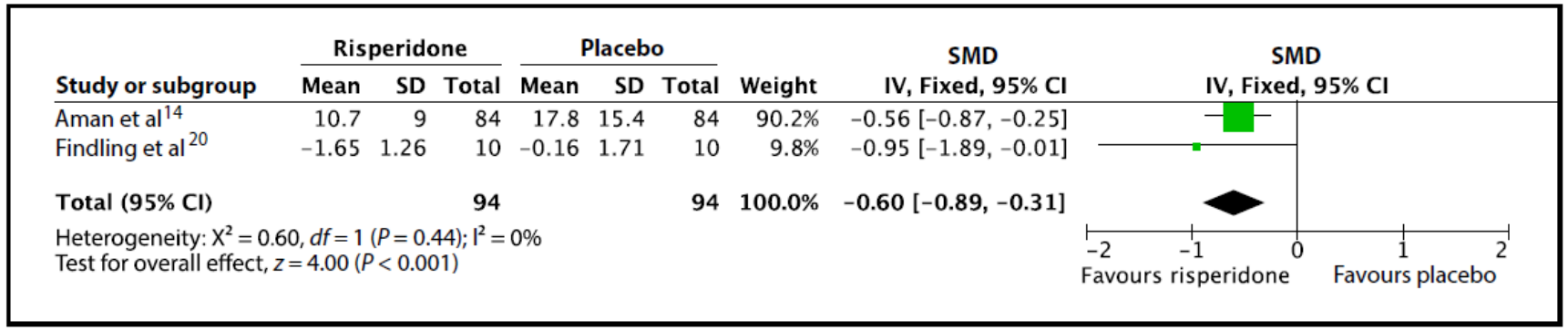
Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and **adolescents** with ADHD, ODD and CD: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry.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

**Figure 1 Risperidone, compared with placebo, for conduct problems and aggression in youth with subaverage or low IQ and oppositional defiant disorder, conduct disorder, or disruptive behaviour disorder not otherwise specified, with and without attention-deficit hyperactivity disorder**




risperidone has a **moderate-to-large effect** on conduct problems and aggression in youth with **subaverage IQ** and ODD, CD, or disruptive behaviour disorder not otherwise specified, **with and without ADHD,**

**Figure 2 Risperidone, compared with placebo, for disruptive behaviour and aggression in youth with oppositional defiant disorder or conduct disorder, with and without attention-deficit hyperactivity disorder**




risperidone has a **moderate effect** on disruptive and aggressive behaviour in youth with **average IQ** and ODD or CD, **with and without ADHD**

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<br>5 RCTs;<br>398 patients;<br>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:<br>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<br>4 RCTs;<br>429 patients;<br>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:<br>0.60 (95% CI 0.31 to 0.89) | High |
| Quetiapine for conduct problems in youth with CD, with and without ADHD | | | | | | | | |
| Conduct problems<br>One RCT;<br>19 patients;<br>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<br>One RCT;<br>61 patients;<br>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<br>One RCT;<br>30 patients;<br>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 no different from placebo for the management of aggression in youth with CD.

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.

Seven studies investigated the efficacy of risperidone and one study used quetiapine.

The analysis suggested that **risperidone** led to a reduction of aggression and conduct problems to some extent after **six weeks** of treatment and that the medication appeared safe during the study period.

**Analysis 1.1. Comparison 1 Medication vs. placebo, Outcome 1 Aggression.**

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

Comparison: 1 Medication vs. placebo

Outcome: 1 Aggression

| 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 (ABC irritability) | | | | | | | |
| Aman 2002 | 52 | -10 (9.3) | 63 | -4.4 (8.9) | | 47.3 % | -5.60 [ -8.95, -2.25 ] |
| Snyder 2002 | 53 | -10.9 (8.5) | 57 | -4.2 (9.8) | | 45.3 % | -6.70 [ -10.12, -3.28 ] |
| Van Bellinghen 2001 | 6 | -10.8 (6.05) | 7 | 0.1 (9.4) | | 7.4 % | -10.90 [ -19.38, -2.42 ] |
| **Subtotal (95% CI)** | **111** | | **127** | | | **100.0 %** | **-6.49 [ -8.79, -4.19 ]** |

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.32$, df = 2 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 5.52 (P < 0.00001)

Test for subgroup differences: Not applicable



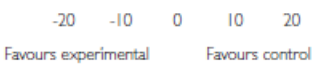

**Analysis 1.4. Comparison 1 Medication vs. placebo, Outcome 4 Conduct problems.**

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

Comparison: 1 Medication vs. placebo

Outcome: 4 Conduct problems

| 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 NCBRF-CP | | | | | | | |
| Aman 2002 | 52 | -15.2 (10.6) | 63 | -6.2 (11.2) | | 51.9 % | -9.00 [ -12.99, -5.01 ] |
| Snyder 2002 | 53 | 17.6 (11.24) | 57 | 25.8 (10.91) | | 48.1 % | -8.20 [ -12.34, -4.06 ] |
| **Subtotal (95% CI)** | **105** | | **120** | | | **100.0 %** | **-8.61 [ -11.49, -5.74 ]** |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.07$, df = 1 (P = 0.79); $I^2 = 0.0\%$ | | | | | | | |
| Test for overall effect: Z = 5.87 (P < 0.00001) | | | | | | | |
| 2 CPRS-CP | | | | | | | |
| Connor 2008 | 9 | 11.3 (7.7) | 10 | 12.2 (4.4) | | 53.6 % | -0.90 [ -6.62, 4.82 ] |
| Findling 2000 | 8 | -28 (13.86) | 9 | -1.75 (16.5) | | 46.4 % | -26.25 [ -40.69, -11.81 ] |
| **Subtotal (95% CI)** | **17** | | **19** | | | **100.0 %** | **-12.67 [ -37.45, 12.11 ]** |
| Heterogeneity: $Tau^2 = 289.92$; $Chi^2 = 10.24$, df = 1 (P = 0.001); $I^2 = 90\%$ | | | | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | | | | |



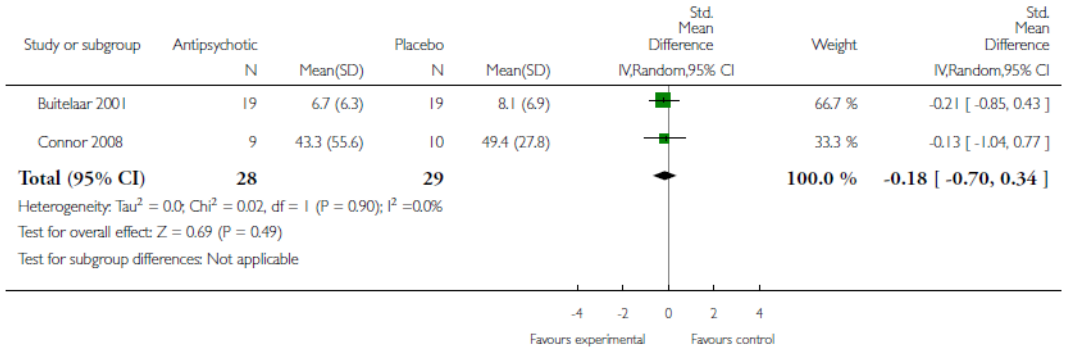
Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Database Syst Rev. 2017 Aug 9;8(8):CD008559.

**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)

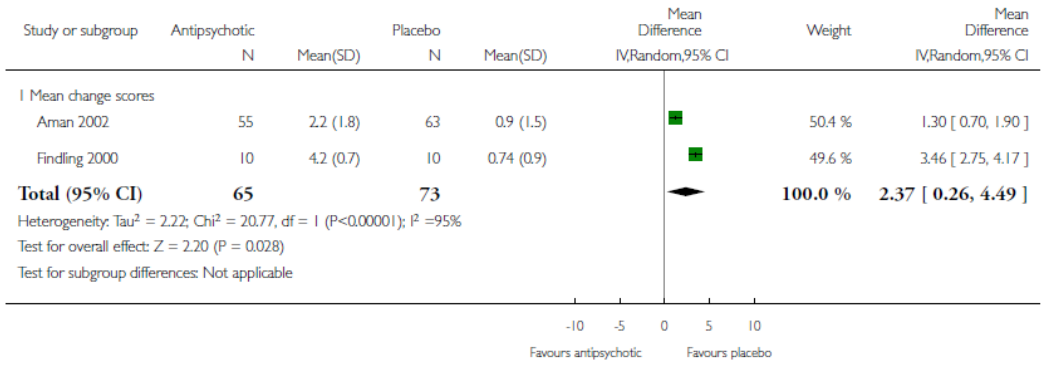



**Analysis 1.3. Comparison 1 Medication vs. placebo, Outcome 3 Weight gain.**

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

Comparison: 1 Medication vs. placebo

Outcome: 3 Weight gain





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The second meta-analysis on aggression included two different outcome measures (Overt Aggression Scale (modified) (OAS-M) and OAS, respectively). Results was statistically non-significant

Use of medication was associated with significant **weight gain**

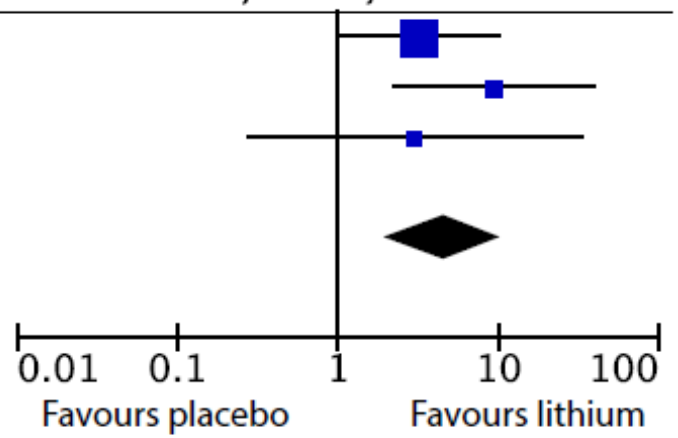
Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD and CD: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry. 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, $z = 3.55$ ($P < 0.001$)



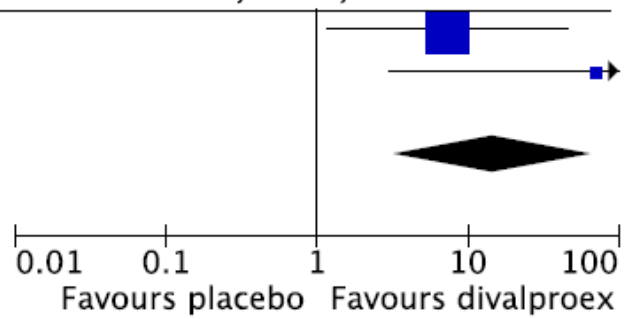
Pringsheim T, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD and CD: a systematic review and meta-analysis. Part 2: antipsychotics and traditional mood stabilizers. Can J Psychiatry.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

# 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.

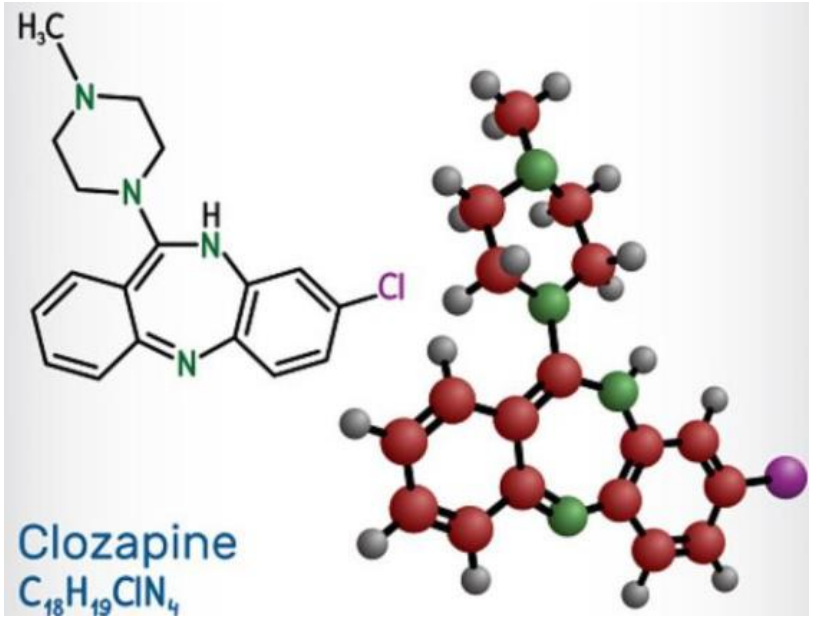


# effectiveness and tolerability of Clozapine in the treatment of aggression in youth with Neurodevelopmental Disorders

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**

**In children and adolescents**, **low dosages of Clozapine** has been shown to be effective for aggression, suicidal behaviors, conduct disorder, bipolar disorder obsessive–compulsive disorder, and autism spectrum disorder, **even without concurrent schizophrenia diagnoses**…


- Patel NC, Crismon ML, Hoagwood K, et al. Unanswered questions regarding atypical antipsychotic use in aggressive children and adolescents. J Child Adolesc Psychopharmacol. 2005;15:270–284.
- Teixeira EH, Celeri EV, Jacintho AC, et al. Clozapine in severe conduct disorder. J Child Adolesc Psychopharmacol. 2013;23:44–48.
- Teixeira EH, Jacintho A, Celeri HV, et al. Atypical antipsychotics in the treatment of pathological aggression in children and adolescents: literature review and clinical recommendations. Trends Psychiatry Psychother. 2013;35: 151–159.
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- Frogley C, Taylor D, Dickens G, et al. A systematic review of the evidence of clozapine's anti-aggressive effects. Int J Neuropsychopharmacol. 2012;15:1351–1371.
- Kranzler H, Roofeh D, Gerbino-Rosen G, et al. Clozapine: its impact on aggressive behavior among children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry. 2005;44:55–63.
- Wink LK, Badran I, Pedapati EV, et al. Clozapine for drug-refractory irritability in individuals with developmental disability. J Child Adolesc Psychopharmacol. 2016; 26:843–846.


American Journal of Therapeutics 26, e406–e416 (2019)

## Off-Label Use of Clozapine in Children and Adolescents—A Literature Review

Vivekananda Rachamallu, MD,[1,2]* Benjamin W. Elberson, PhD,[3]
Emily Vutam, MD,[3] and Manish Aligeti, MD, MHA[1]

Documented efficacy of clozapine for the management of **refractory psychotic and nonpsychotic symptoms** in the pediatric population.

**The risk of unmanaged** early-onset schizophrenia, aggressive or suicidal behavior, and severe nonpsychotic pathology should be underline

Despite the **lack of FDA guidelines**, clozapine continues to be used in young patients…

Indications for prescription of clozapine **should be revisited**

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.

CME

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.

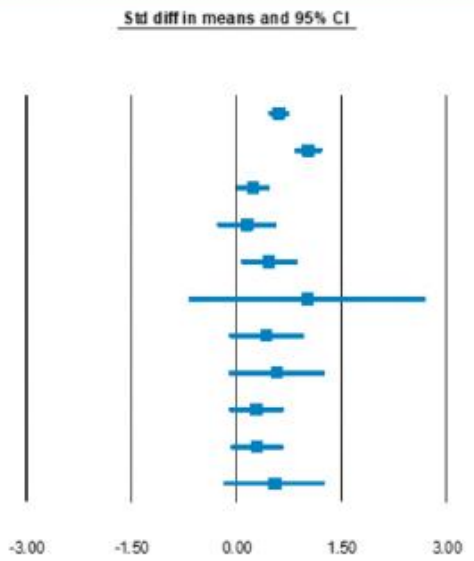
Two classes of drugs resulted significantly better than placebo in improving emotional dysregulation and irritability :

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)

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

***Quale classe di farmaci per Francesco……?***

Ideazione suicidaria



# Il suicidio



# worldwide public health crisis : 800,000* deaths per year

* 400.000 per l'influenza (OMS); 1.350.000 per incidenti (WHO)

**Suicide is the second leading cause of death among individuals between the ages of 10 and 34**

**The rate of suicidal behavior has climbed steadily over the past two decades**




- Kochanek KD, Xu JQ, Arias E. Mortality in the United States, 2019. NCHS Data Brief, no 395. Hyattsville, MD: National Center for Health Statistics; 2020.
- Centers for Disease Control and Prevention. WISQARS. Ten leading causes of death by age group.
- Hedegaard H, Curtin SC, Warner M. Increase in suicide mortality in the United States, 1999–2018. NCHS Data Brief, no 362. Hyattsville, MD: National Center for Health Statistics; 2020.
- Pettrone K, Curtin SC. Urban–rural differences in suicide rates, by sex and three leading methods: United States, 2000–2018. NCHS Data Brief, no 373. Hyattsville, MD: National Center for Health Statistics; 2020.
- Curtin SC, Heron M. Death rates due to suicide and homicide among persons aged 10–24: United States, 2000–2017. NCHS Data Brief, no 352. Hyattsville, MD:National Center for Health Statistics; 2019.

MEDICINA / NEUROPSICHIATRIA / SOCIETÀ

# Nel 2022 un suicidio ogni 16 ore in Italia. Incidenza grave tra i giovani

DI INSALUTENEWS.IT · 9 SETTEMBRE 2022

BRF
BRAIN RESEARCH FONDAZIONE ONLUS
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**In Europa è la seconda causa di morte tra gli adolescenti dai 10 ai 19 anni**

Rapporto Unicef

**Nel mondo 46.000** ragazzi tra i 10 e i 19 anni si tolgono la vita ogni anno (uno ogni 11 minuti circa )

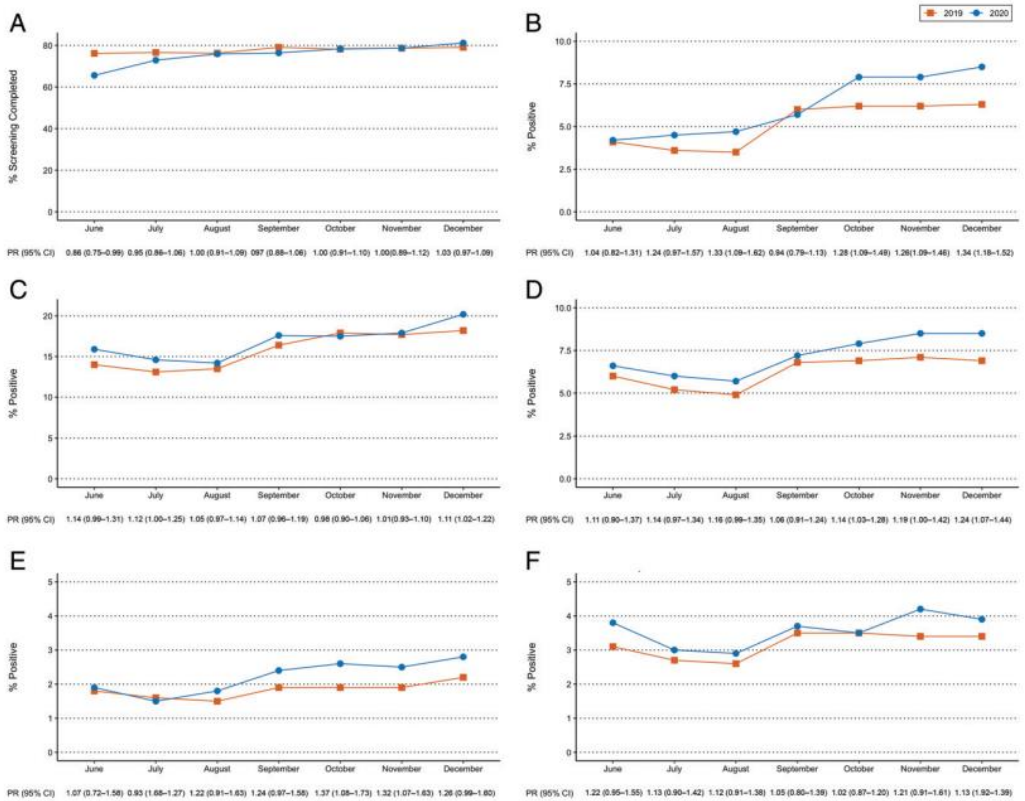
l'età media è di circa 15 anni

**negli ultimi due anni i tentativi sono aumentati del +75%**

Mayne SL, Hannan C, Davis M, et al. COVID-19 and Adolescent Depression and Suicide Risk Screening Outcomes. Pediatrics. 2**021**;148(3):e2021

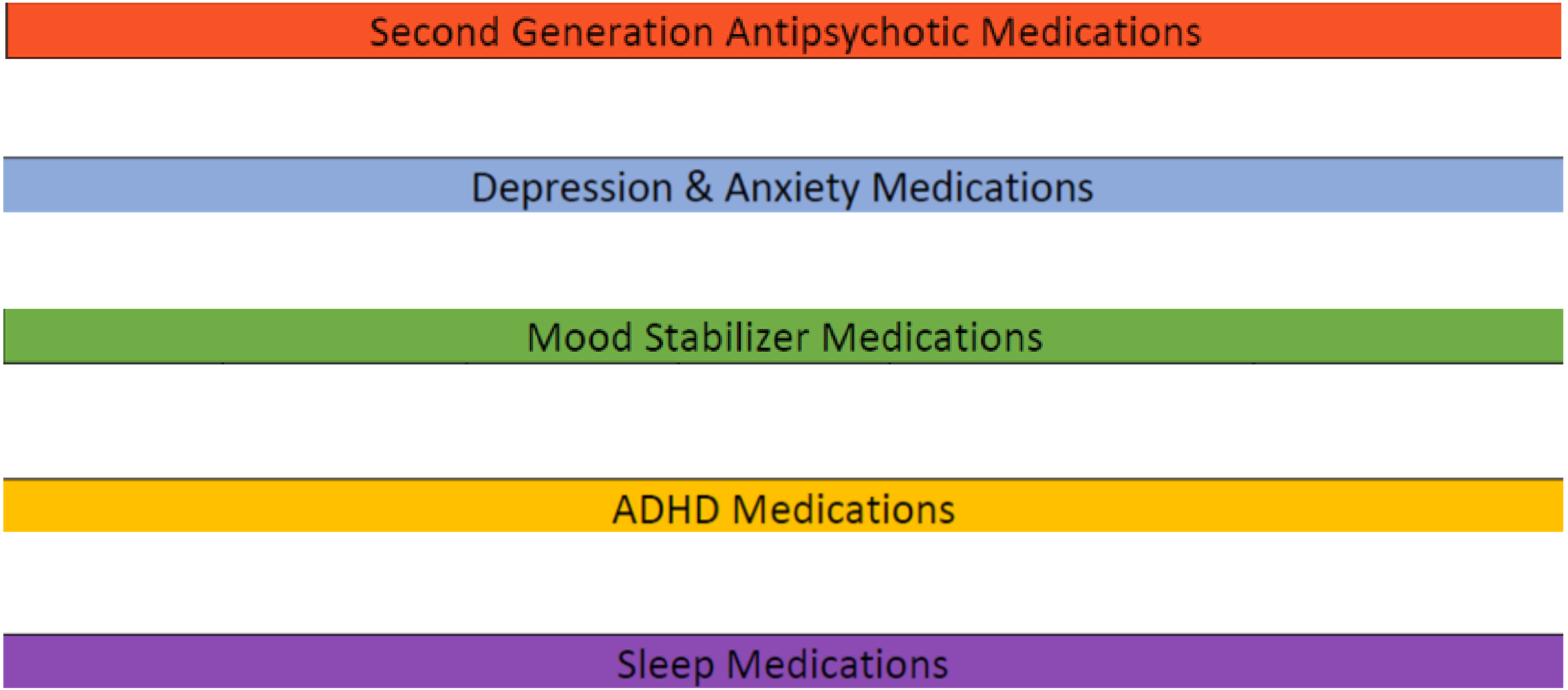
The percentage of adolescents screening positive for depressive symptoms increased **from 5.0% to 6.2%** (PR: 1.24, 95% CI: 1.15–1.34),
(greater increases among female)

**Positive suicide risk screens increased from 6.1% to 7.1%** (PR: 1.16, 95% CI: 1.08–1.26),
34% relative increase in reporting recent suicidal thoughts among female adolescents (PR: 1.34, 95% CI: 1.18–1.52).




depression and suicide concerns have increased during the pandemic, especially among female adolescents

*Quale classe di farmaci per il suicidio?*





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.*

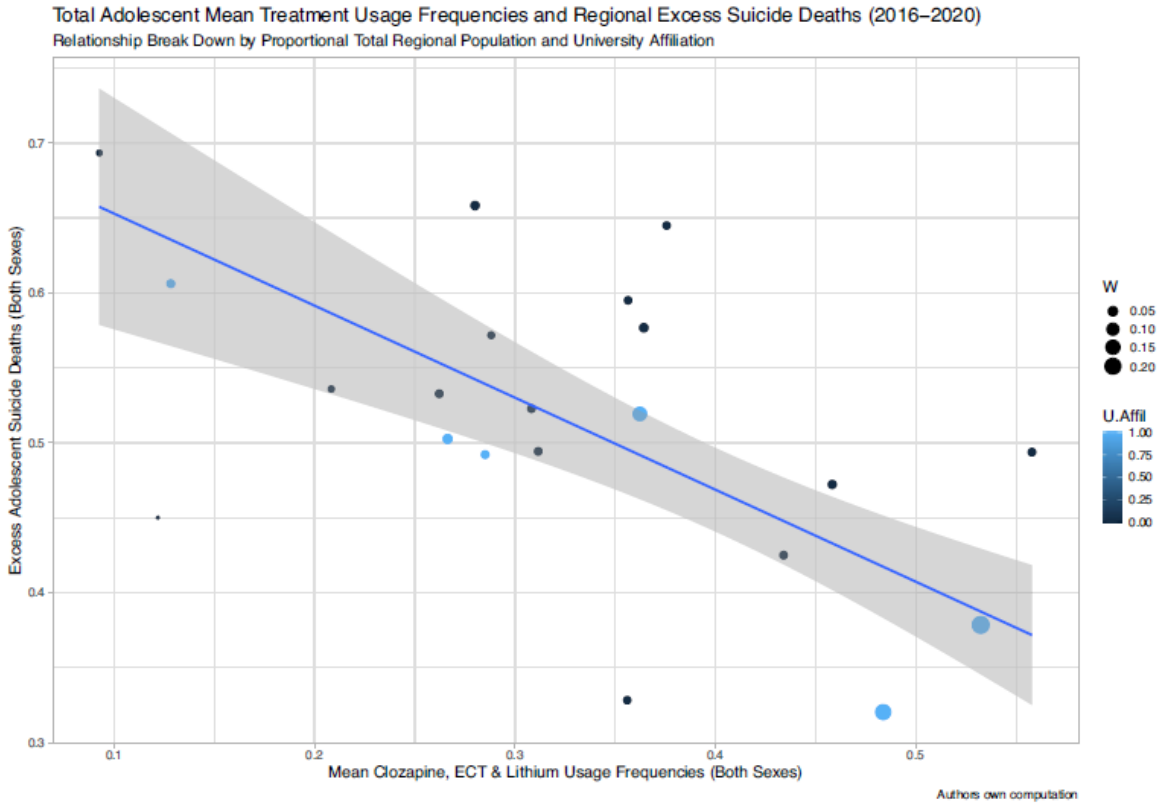
*Innov Clin Neurosci.* 2018;15(11–12):30–32

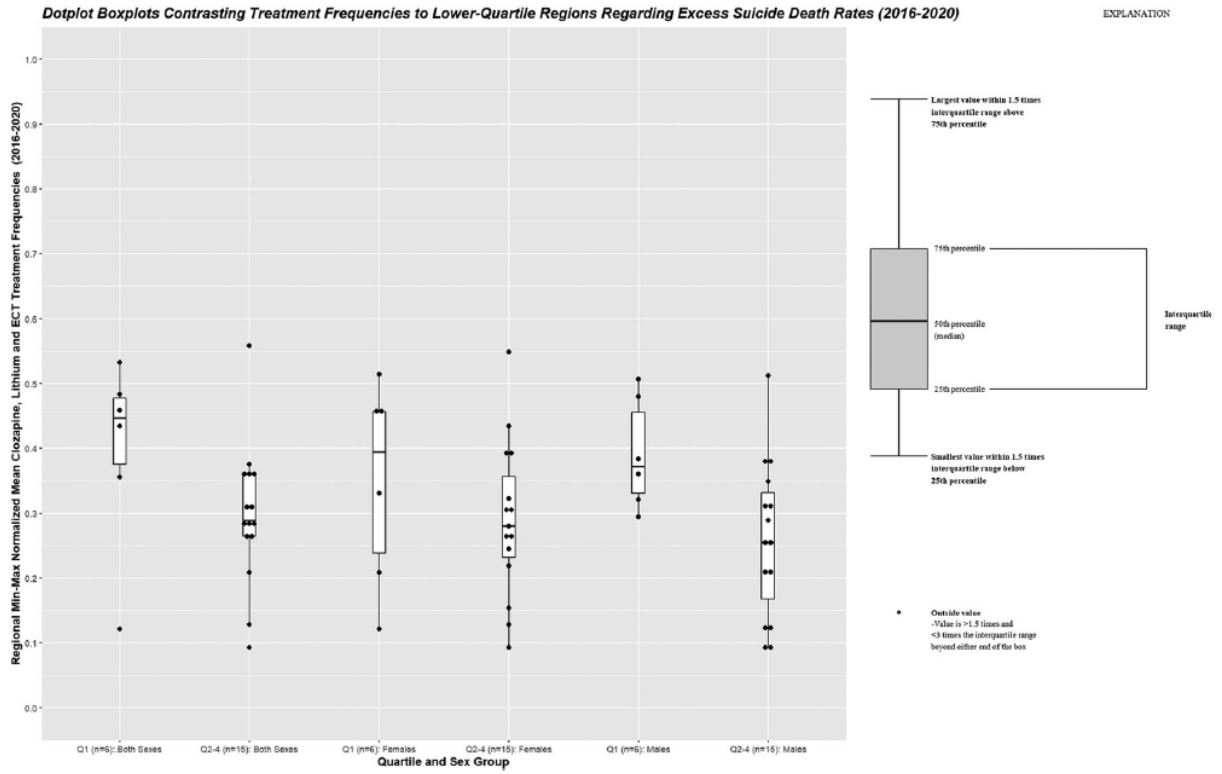
**Use of lithium is thought to reduce risk for suicidality, even if mood stabilization is not achieved and serum concentration is lower than the conventionally accepted therapeutic blood level ranges.**

**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.

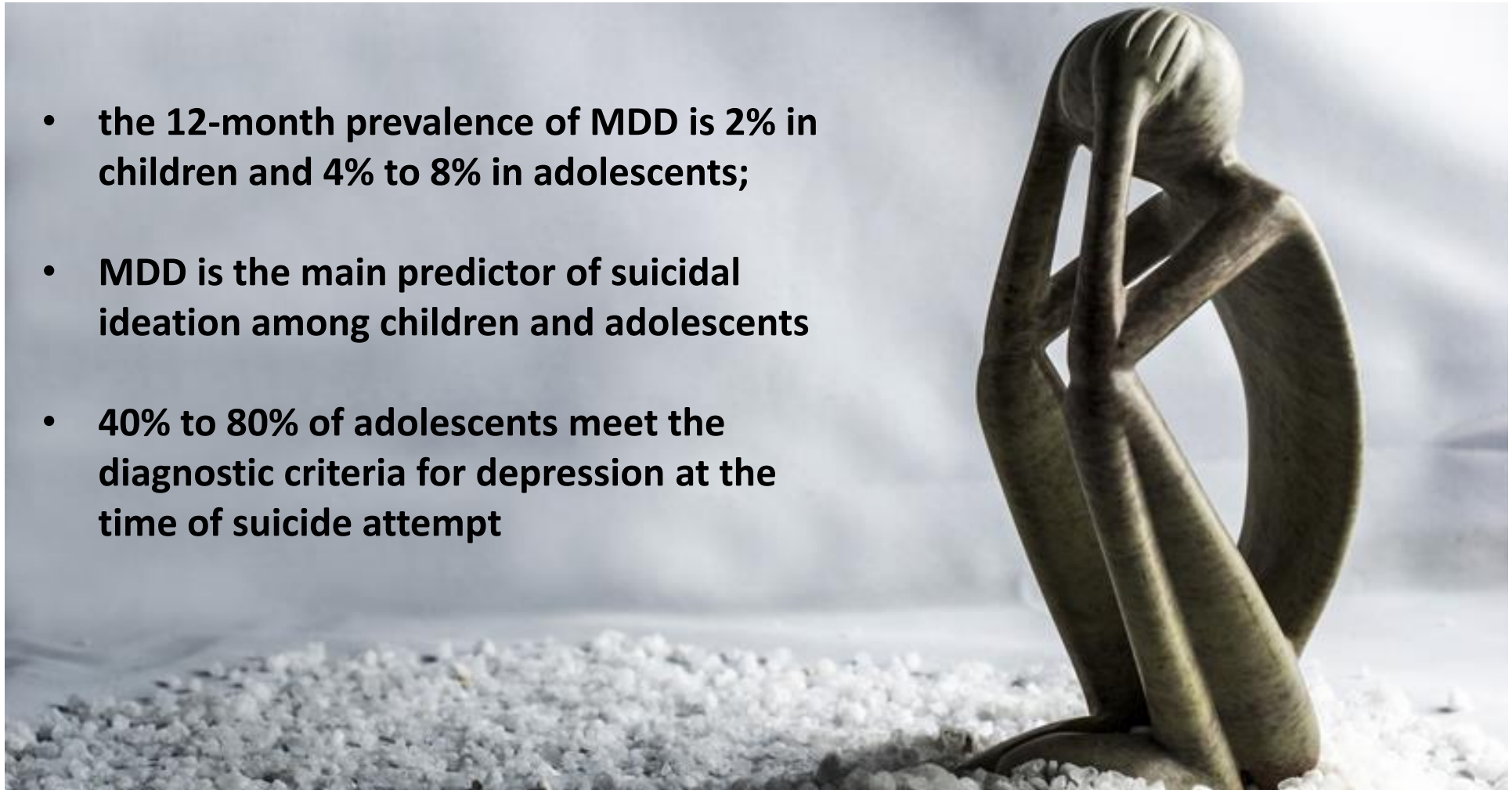


*Medicina delle 4 P*

1. **Personalizzata**
2. **Preventiva**
3. **Predittiva**
4. **Partecipativa**

necessità di assumere una **prospettiva di genere** anche in psichiatria dell'età evolutiva, con approcci e terapie che tengano conto delle **attuali** differenze tra maschi e femmine

# 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

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

**Suicidal ideation** decreased less with fluoxetine therapy than with **combination therapy or CBT alone**



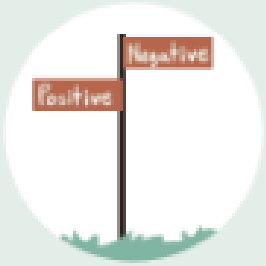
## Suicidal events

**14.7%** fluoxetine
**8.4%** combination therapy
**6.3%** CBT

**Table 4. Patients With Suicidal Events[a]**

| Treatment | No. of Patients | No. (%) of Patients | |
|---|---|---|---|
| | | ITT Population | 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) |

# Benefits of CBT for Teens



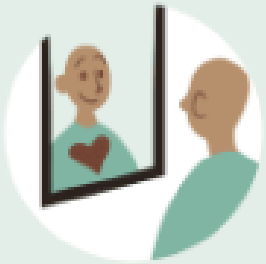

Reroutes negative thought patterns



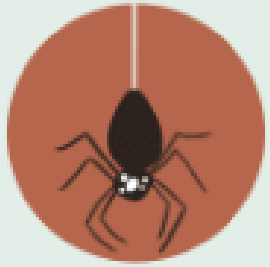
Improves communication skills



Uncovers positive stress responses



Enhances self-esteem



Reduces fears and phobias



# 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*

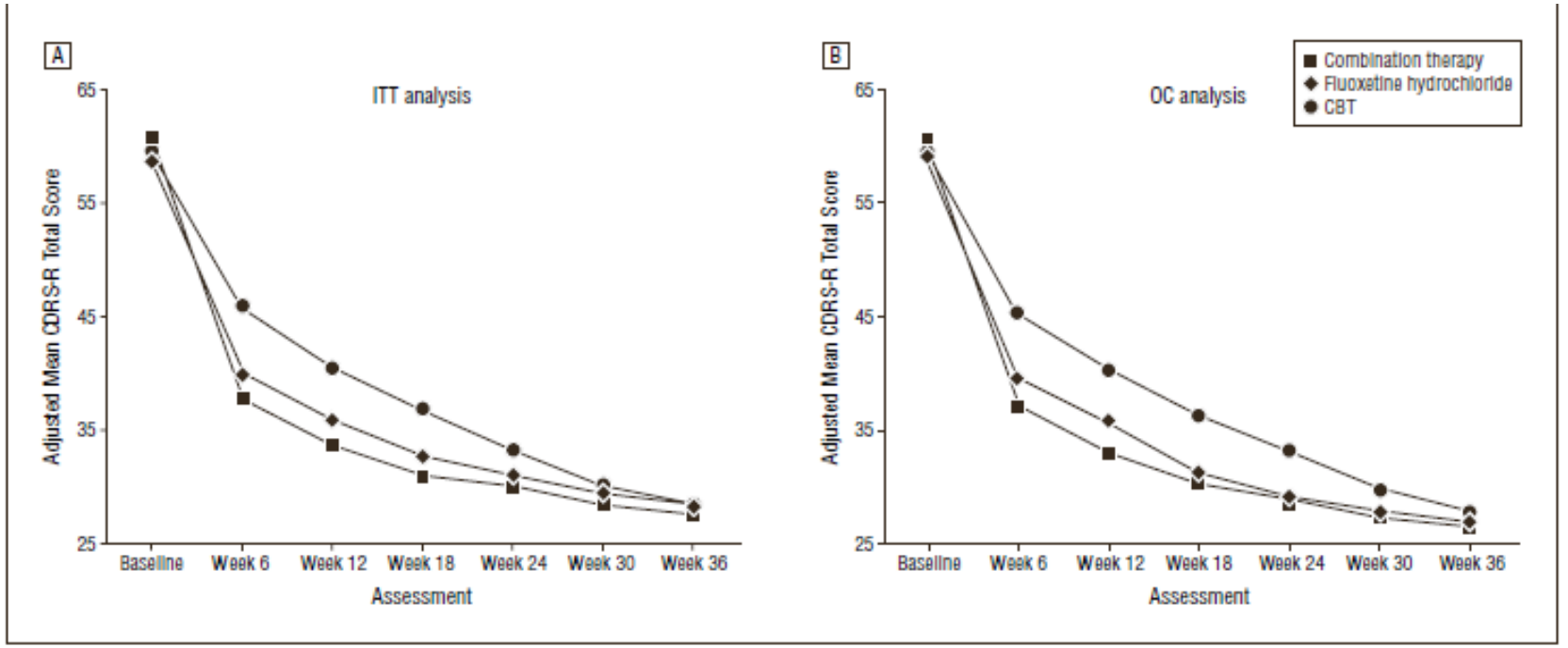
**327 patients aged 12 to 17 years**

**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.

**titolazione lenta**

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

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.

**Suicidal ideations and behaviors is about 4% for youth receiving antidepressants compared with 2% on placebo**

"**Dose iniziale 10 mg**, eventualmente 20 mg dopo 1-2 settimane; valutazione per almeno 9 settimane"

# I benefici dell'uso di fluoxetina superano i rischi

all'aumento degli SSRI corrisponde una riduzione di suicidi completati, sia negli adulti (Gibbons, 2005) che negli adolescenti Isacsson et al. (2005)

(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)

# Troppi o troppo pochi antidepressivi?

***Quale classe di farmaci per Francesco……?***



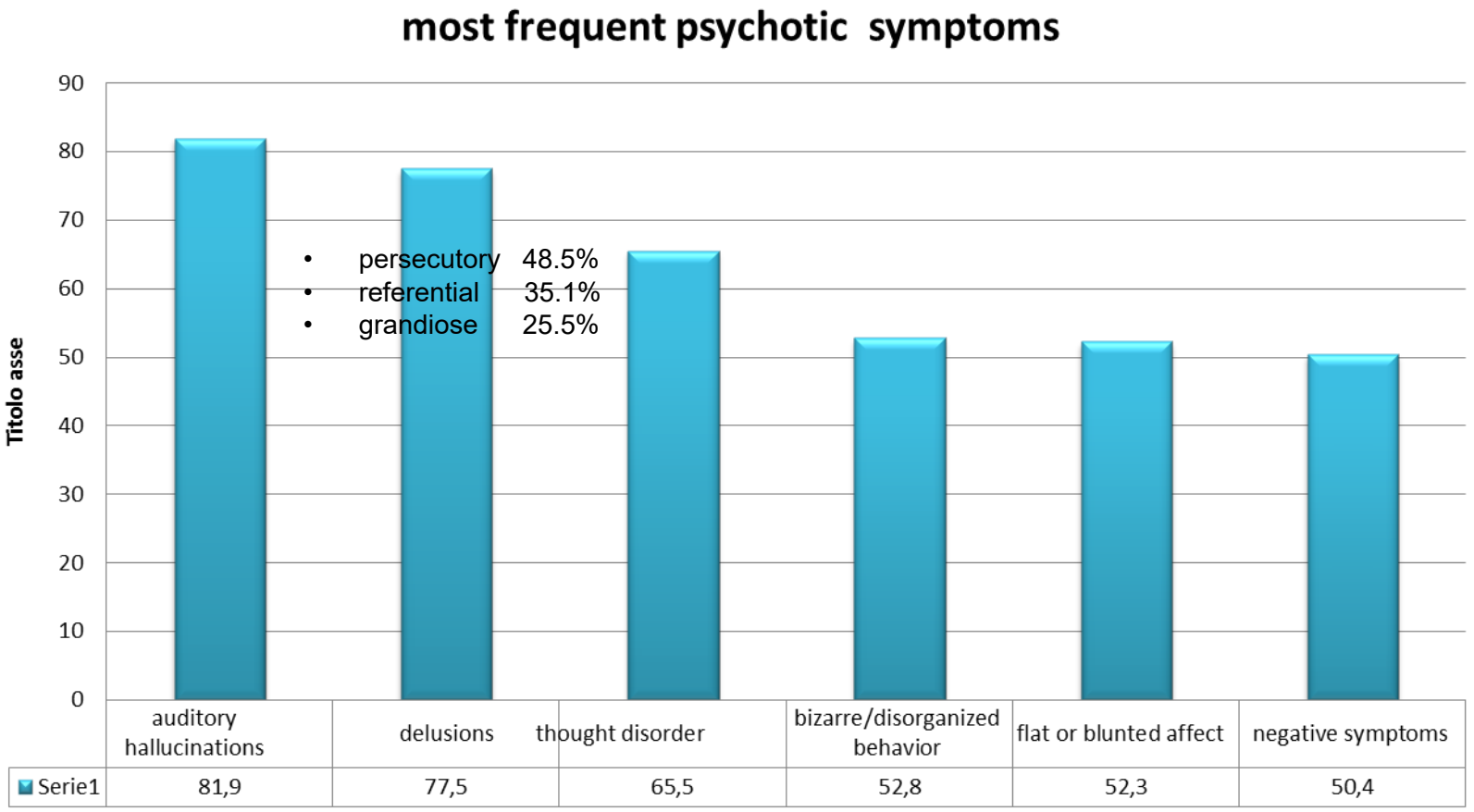
Depersonalizzazione
e derealizzazione

# I SINTOMI PSICOTICI



# 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**

# **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

***rischio di transizione***

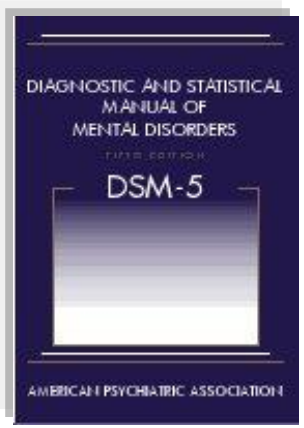
- **18% a sei mesi**
- **40% dopo tre anni**

**sintomi psicotici attenuati in individui asintomatici nel 5% nella popolazione generale**




- 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.

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




**la diagnosi aggiuntiva di Schizofrenia può 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" siano presenti da almeno un mese



*Quale classe di farmaci per i sintomi psicotici?*

Second Generation Antipsychotic Medications

Depression & Anxiety Medications

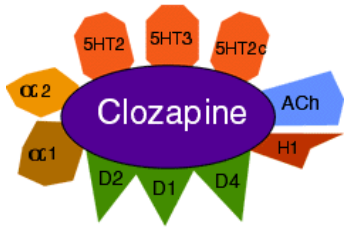
Mood Stabilizer Medications

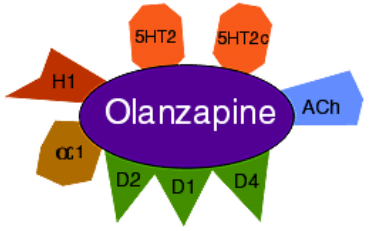
ADHD Medications

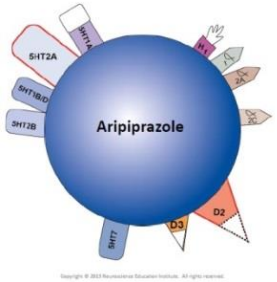
Sleep Medications

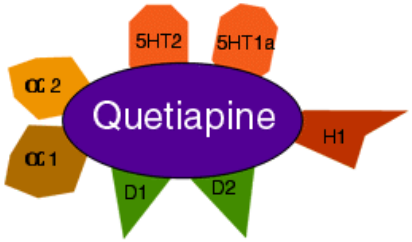
Cochrane Database Syst Rev. 2013 Oct 15;10:. **Atypical antipsychotics for psychosis in adolescents.** Kumar A[1], Datta SS, Wright SD, Furtado VA, Russell PS.

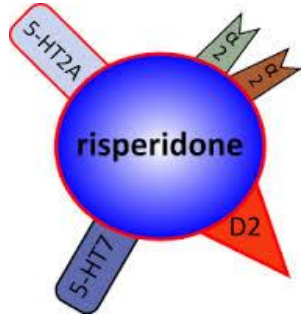
**Second generation of antipsychotic medications** may be more acceptable to young people because fewer symptomatic adverse effects



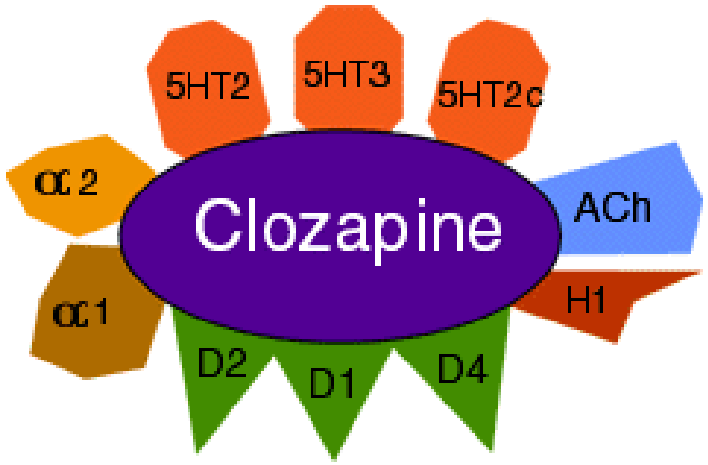




Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications

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.

.




**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**

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…

# Clozapina è **più efficace degli altri antipsicotici**

short term double-blind studies of 6 and 8 weeks

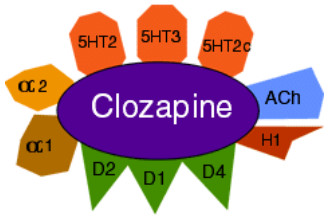



TABLE 1. CLOZAPINE VERSUS ACTIVE TREATMENT STUDIES FOR ADULT-AND EARLY-ONSET SCHIZOPHRENIA, EARLY-ONSET SCHIZOPHRENIA STUDIES

| *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<br>Range: 6–18 | Typical: Haldoperidol<br>16±8 | Clozapine<br>176±149 | 21 | SANS: 1.156<br>SAPS: 0.675<br>BPRS: 0.258<br>CGAS: 1.370 | 0.002<br>0.01<br>0.04<br>0.01 |
| Shaw et al. (2006) | Parallel randomized DB | 8 | Mean: 12.3<br>Range: 7–16 | Atypical: Olanzapine<br>18.1±4.3 | Clozapine<br>327±113 | 25 | SANS: 0.7<br>SAPS: 0.4<br>BPRS: 1<br>CGI-S: 0.6 | 0.08<br>0.14<br>0.12<br>0.39 |
| Kumra et al. (2008) | Parallel randomized DB | 12 | Mean: 15.6±2.1[a]<br>Range: 10–18 | Atypical: Olanzapine<br>26.2±6.5 | Clozapine<br>403.1±201.8 | 39 | SANS: 0.92<br>BPRS: 0.29<br>CGI-S: 0.4<br>CGI-Improvement: 0.59 | 0.02<br>0.78<br>0.8<br>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)

## 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**

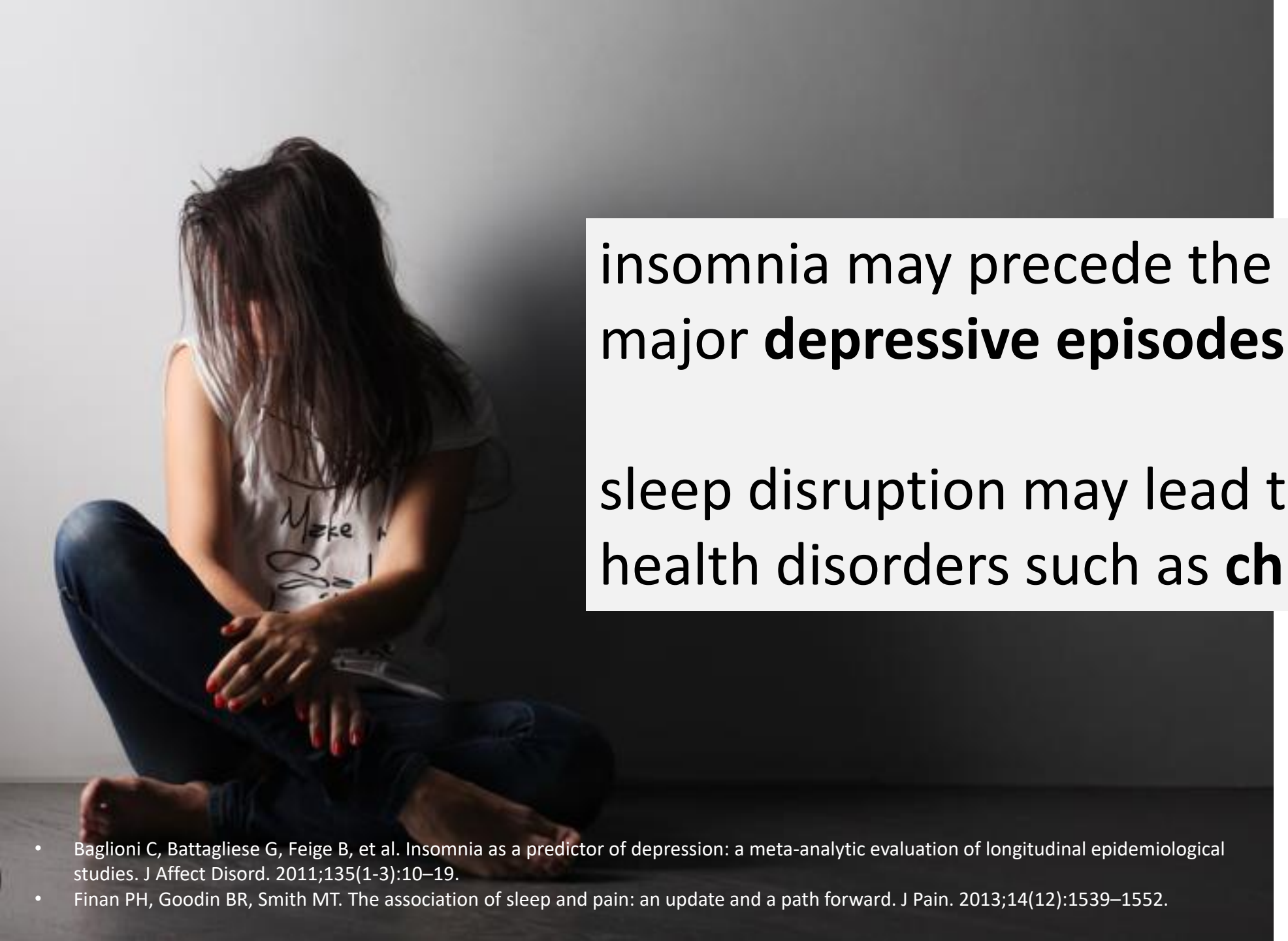
**Side effects of LAIs among youth appear are similar to oral preparations.**

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.**

***Quale classe di farmaci per Francesco……?***

Insonnia





insomnia may precede the onset of major **depressive episodes**…

sleep disruption may lead to physical health disorders such as **chronic pain**


- Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord. 2011;135(1-3):10–19.
- Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain. 2013;14(12):1539–1552.

Freeman D, Sheaves B, Waite F, Harvey AG, Harrison PJ. Sleep disturbance and psychiatric disorders. Lancet Psychiatry. 2020 Jul;7(7):628-637

## Many of the effects of sleep loss are likely to increase susceptibility to mental health conditions, such as:

- ❑ increased state anxiety
- ❑ decreased positive mood and depression
- ❑ poor emotion regulation
- ❑ negative perception of neutral stimuli
- ❑ increased perception of pain
- ❑ poor response inhibition
- ❑ working memory impairment
- ❑ poor problem solving

Babson KA, Trainor CD, Feldner MT, Blumenthal H. A test of the effects of acute sleep deprivation on general and specific self-reported anxiety and depressive symptoms: an experimental extension. J Behav Ther Exp Psychiatry 2010; 41: 297–303
.

Talbot LS, McGlinchey EL, Kaplan KA, Dahl RE, Harvey AG. Sleep deprivation in adolescents and adults: changes in affect. Emotion 2010; 10: 831–41.

Palmer CA, Alfano CA. Sleep and emotion regulation: an organizing, integrative review. Sleep Med Rev 2017; 31: 6–16.

Tempesta D, Couyoumdjian A, Curcio G, et al. Lack of sleep affects the evaluation of emotional stimuli. Brain Res Bull 2010; 82: 104–08..

Schrimpf M, Liegl G, Boeckle M, Leitner A, Geisler P, Pieh C. The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis. Sleep Med 2015; 16: 1313–20.

Drummond SP, Paulus MP, Tapert SF. Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. J Sleep Res 2006; 15: 261–65. .

Reeve S, Emsley R, Sheaves B, Freeman D. Disrupting sleep: the effects of sleep loss on psychotic experiences tested in an experimental study with mediation analysis. Schizophr Bull 2018; 44: 662–71.
.

Lewis PA, Knoblich G, Poe G. How memory replay in sleep boosts creative problem-solving. Trends Cogn Sci 2018; 22: 491–503

Review

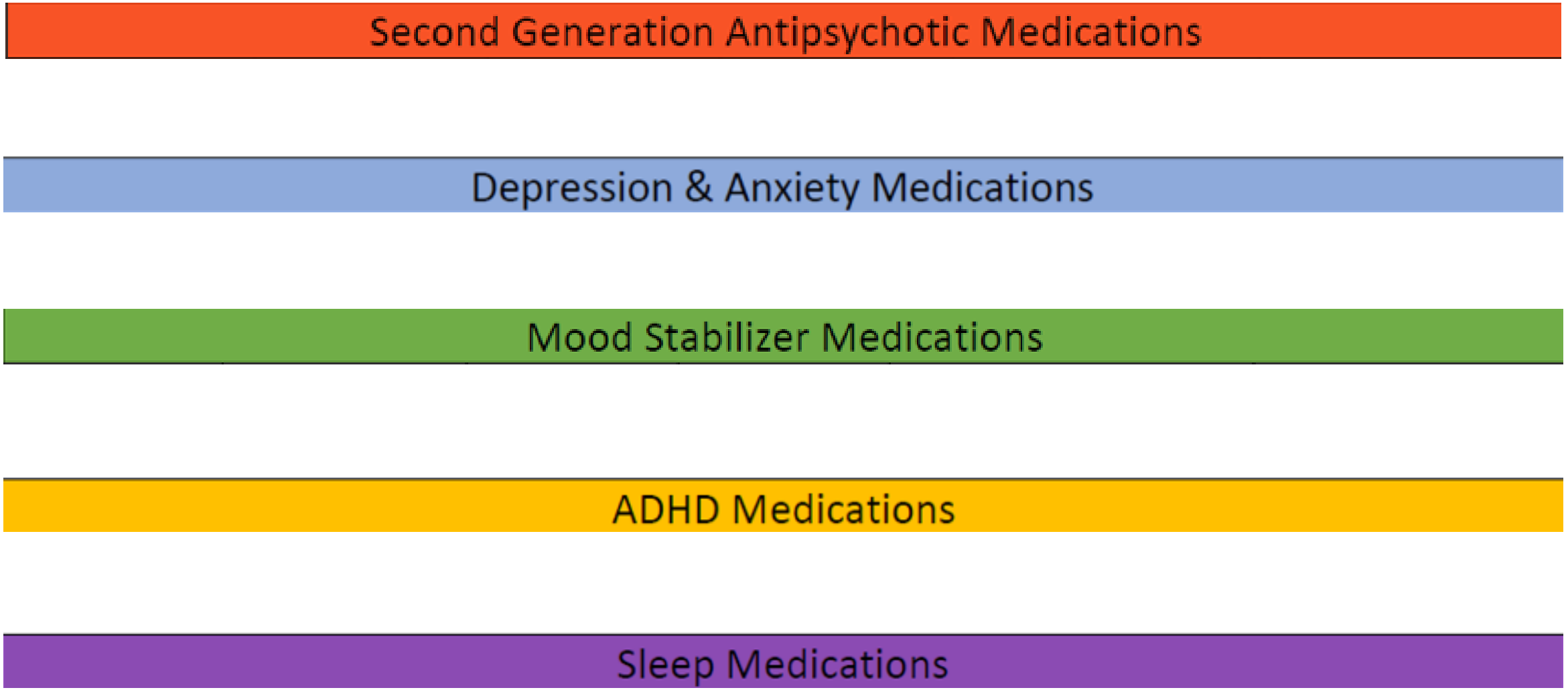
*Lancet Psychiatry* 2020;
7: 628–37

# Sleep disturbance and psychiatric disorders

*Daniel Freeman, Bryony Sheaves, Felicity Waite, Allison G Harvey, Paul J Harrison*

- **adolescents presenting with sleep problems should be screened for mental health symptoms, particularly depression, anxiety, and ADHD**
- **Treating insomnia lessens other mental health problems**
- **Intervening on sleep at an early stage might be a preventive strategy for the onset of mental health disorders**

*Quale classe di farmaci per il sonno?*

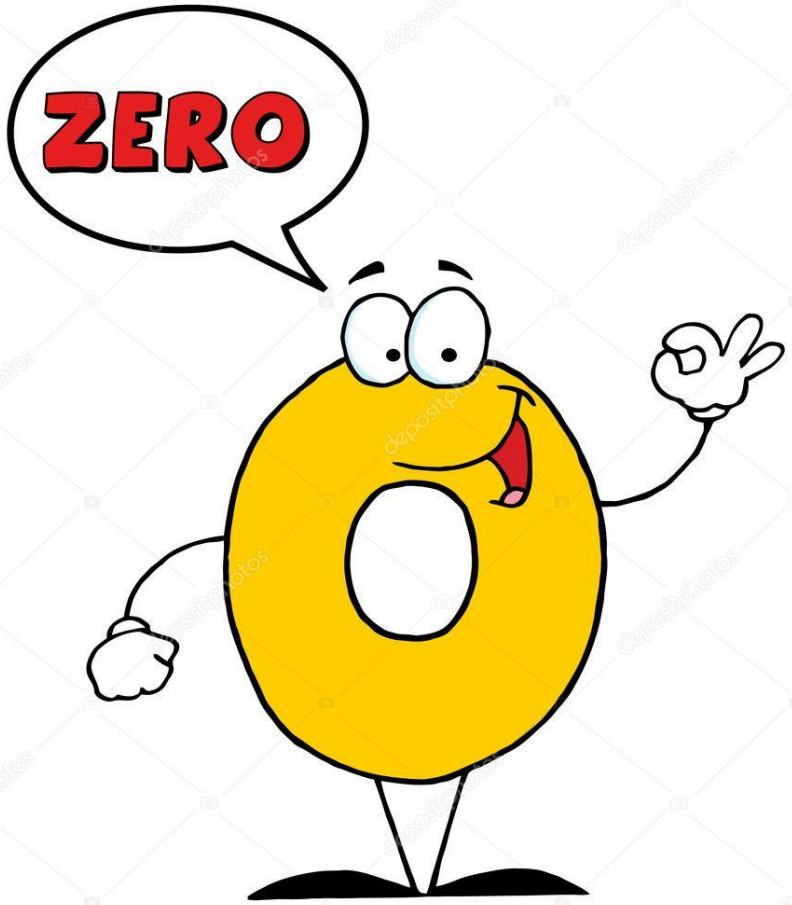


# Treatment

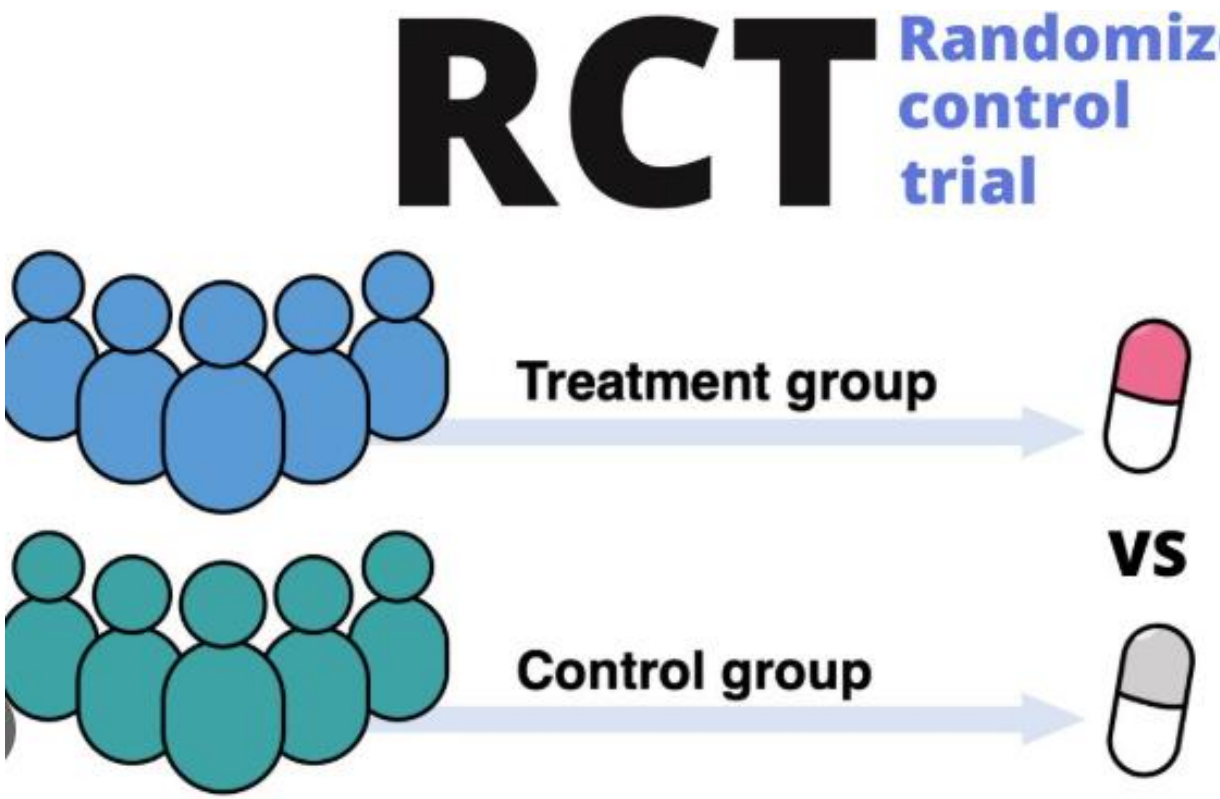




**How many drugs are approved* for sleep disorders in childhood ?**




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


RCT
Randomized control trial
Treatment group
VS
Control group



***Quanti ?***

Larsson I, Aili K, Lönn M, Svedberg P, Nygren JM, Ivarsson A, Johansson P. **Sleep interventions for children with ADHD**: **A systematic literature review**. Sleep Med. **2023 Feb**;102:64-75

The systematic literature **search identified 7710 records, but only 7 papers** were included

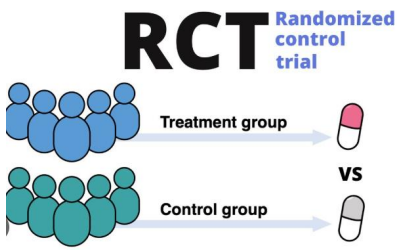
*Parameters:*

- increasing sleep
- quality of life (QoL)
- ADHD symptoms

*The studies included:*

- **behavioral sleep interventions**
- **melatonin**
- **eszopiclone**

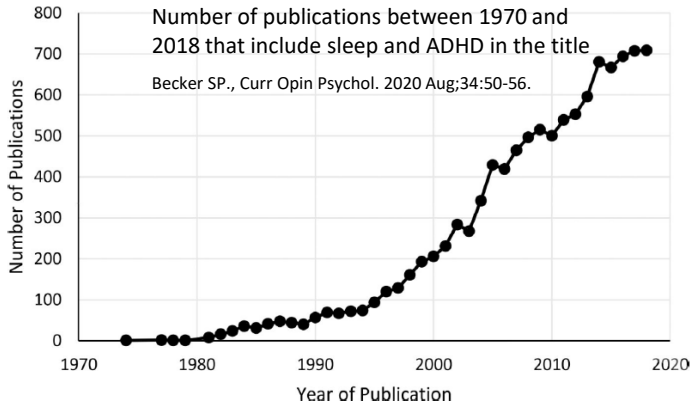
Eszopiclone is classified as a nonbenzodiazepine or Z-drug and a sedative and hypnotic of the cyclopyrrolone group. It is the S-stereoisomer of zopiclone.

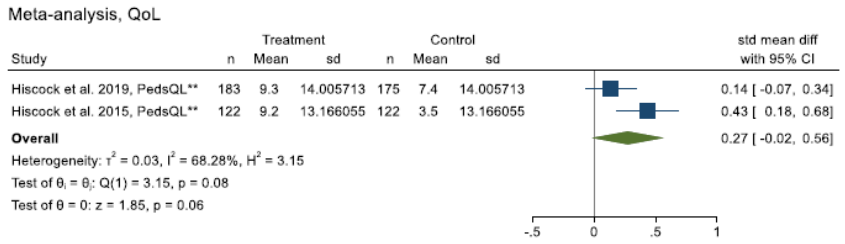


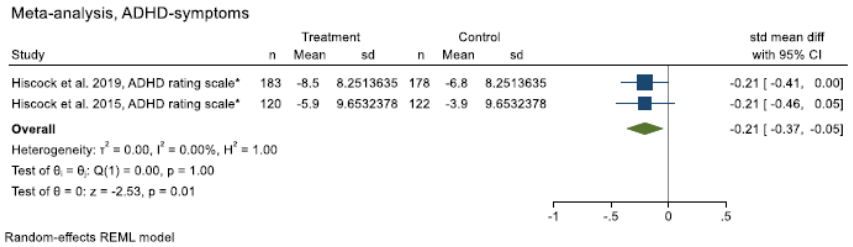

**results**

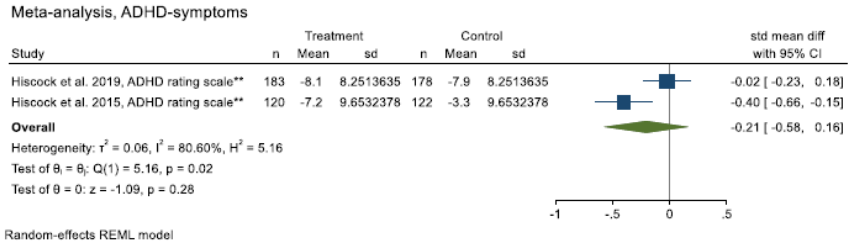
**In 6/7: ES was small to moderate and certainty of the evidence was low**

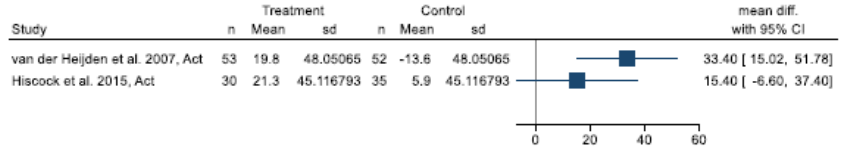
**In 1/7 (on behavioral intervention):**
**ES was moderate** (0.49 SMD; 95% CI 0.65;-0.33) **and the certainty of evidence was moderate** in children aged 5-13 years



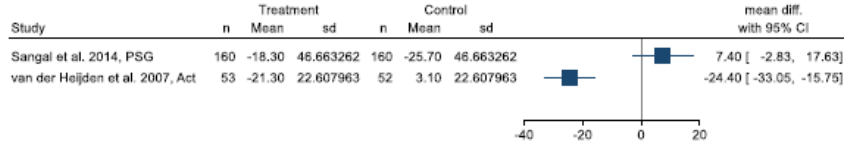



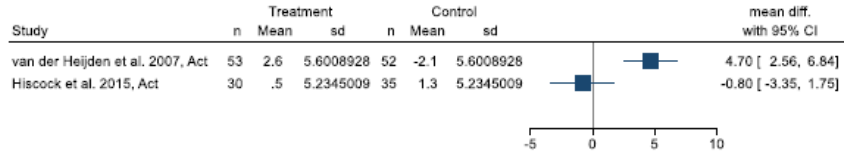



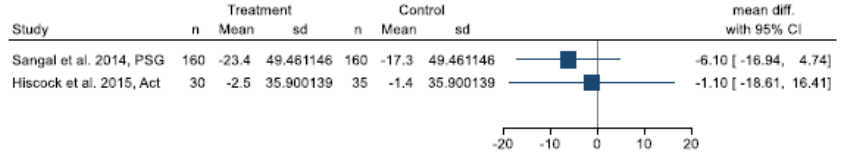

SOL



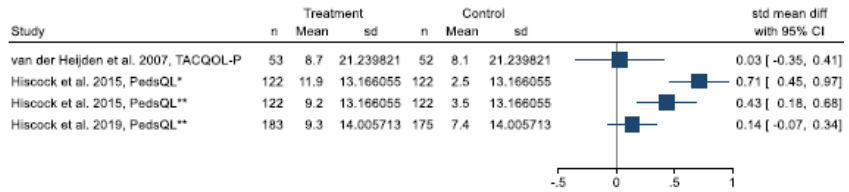

SE



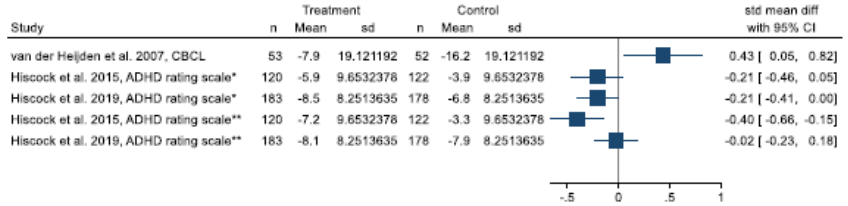

WASO




QoL




ADHD-symptoms



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

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REVIEW

OPEN ACCESS Check for updates

# 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.

Cortese S, Fusetto Veronesi G, Gabellone A, Margari A, Marzulli L, Matera E, Petruzelli MG, Piarulli FM, Tarantino F, Bellato A, Parlatini V, Rietz ED, Larsson H, Hornsey S, Hill C, Margari L. The management of sleep disturbances in children with attention-deficit/hyperactivity disorder (ADHD): an update of the literature. Expert Rev Neurother. 2024 Jun;24(6):585-596.

# **Pharmacological treatments in children** (8 RCTs in total; 6/8 in children and adolescents)

**2 positive** (i.e. with significant results in the primary outcomes favoring the active treatment)
RCTs of **melatonin immediate release** (rather than extended)

- der Heijden KB V, Smits MG, Van Someren EJ, et al. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry. 2007;46 (2):233–241.
- Weiss MD, Wasdell MB, Bomben MM, et al. Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. J Am Acad Child Adolesc Psychiatry. 2006;45 (5):512–519.

1 trial in children found **L-dopa** improved Restless Legs Syndrome/Periodic Limb Movements in Sleep (RLS/PLMS) symptoms severity compared with placebo, but had no significant effect on other sleep parameters

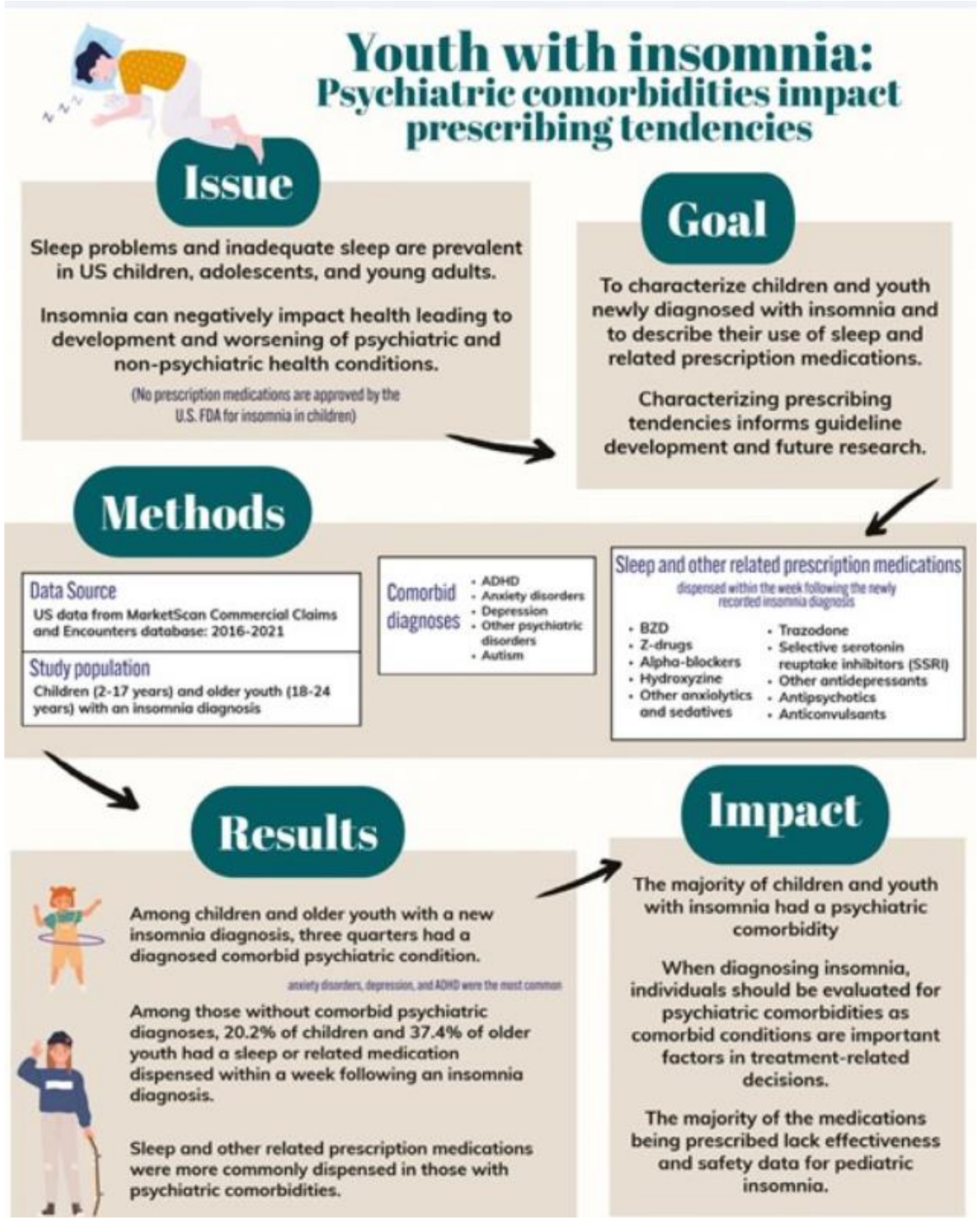
England SJ, Picchietti DL, Couvadelli BV, et al. L-Dopa improves restless legs syndrome and periodic limb movements in sleep but not attention-deficit-hyperactivity disorder in a double-blind trial in children. Sleep Med. 2011;12(5):471–477.

1 RCT in children found a significant trend toward better sleep quality with **longer patch wear times of methylphenidate**

Ashkenasi A. Effect of transdermal methylphenidate wear times on sleep in children with attention deficit hyperactivity disorder. Pediatr Neurol. 2011;45(6):381–386.

**2 negative** (i.e. with negative results on the primary outcome)
RCTs in children on the primary outcome, for **eszopiclone and zolpidem**, both in terms of reduction in latency to persistent sleep measured by polysomnography

- Sangal RB, Blumer JL, Lankford DA, et al. Eszopiclone for insomnia associated with attention-deficit/hyperactivity disorder. Pediatrics. 2014;134(4):e1095–103.
- Blumer JL, Findling RL, Shih WJ, et al. Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention- deficit/hyperactivity disorder in children 6 to 17 years of age. Pediatrics. 2009;123(5):e770–6.



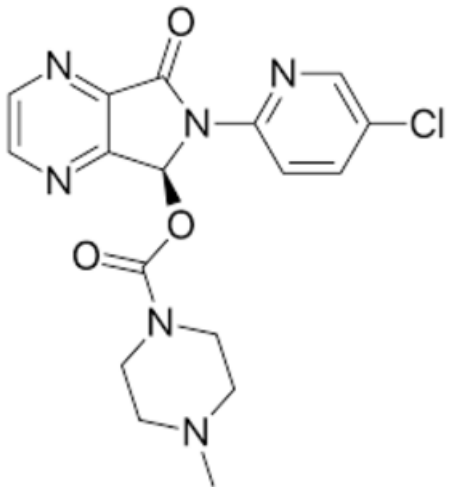

Greta Bushnell, Anna Ivanenko, Daniel B Horton, Jessica R Lunsford-Avery, Jonathan Posner, Tobias Gerhard, Elizabeth Suarez, Mark Olfson, Psychiatric comorbidities and prescribing tendencies of sleep medications and related medications in young people with insomnia: a United States commercial claims-based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









**Ricetta:** RR - medicinali soggetti a prescrizione medica
**Classe:** CN
**Principio attivo:** Eszopiclone
**Gruppo terapeutico:** Ipnotici e sedativi benzodiazepinici

*Popolazione pediatrica*

Eszopiclone **non deve essere utilizzato in bambini e adolescenti al di sotto dei 18 anni**

La sicurezza e l'efficacia di eszopiclone in bambini e adolescenti non sono state stabilite.

# 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*

### References

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

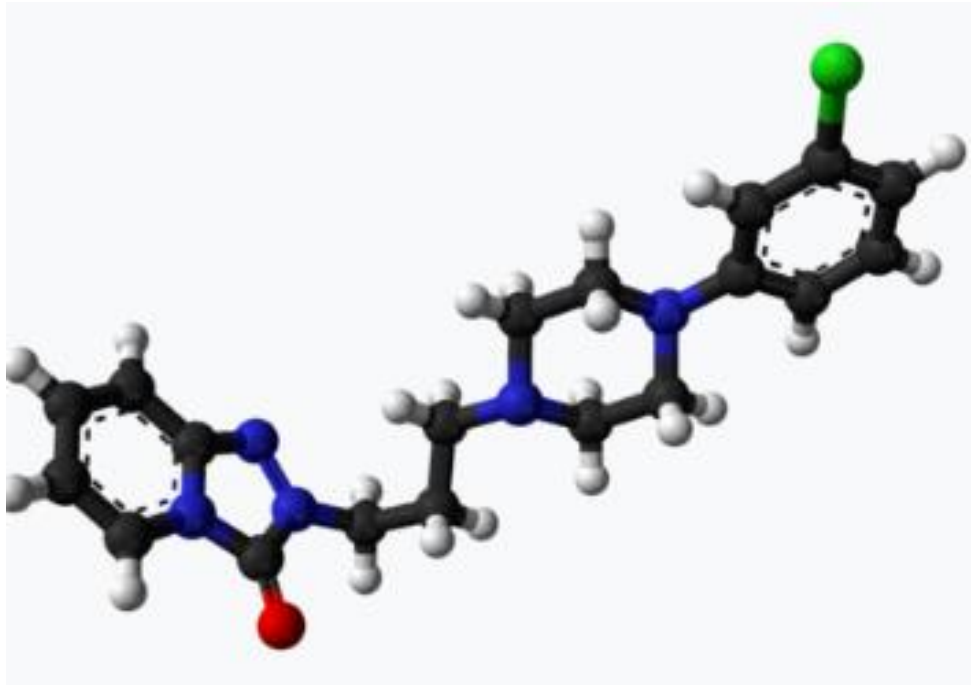
**proprietà antidepressive, ansiolitiche e ipnotiche**

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

(piperazine e  triazolopiridine, antidepressivo di seconda generazione)

## Warning

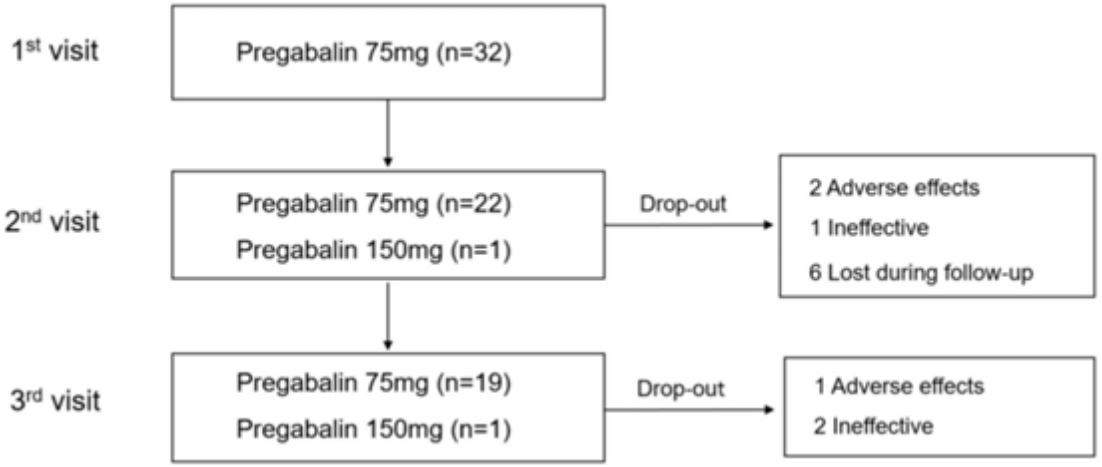
- Drugs like this one have raised the chance of suicidal thoughts or actions in children and young adults. The risk may be greater in people who have had these thoughts or actions in the past. All people who take this drug need to be watched closely. Call the doctor right away if signs like depression, 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

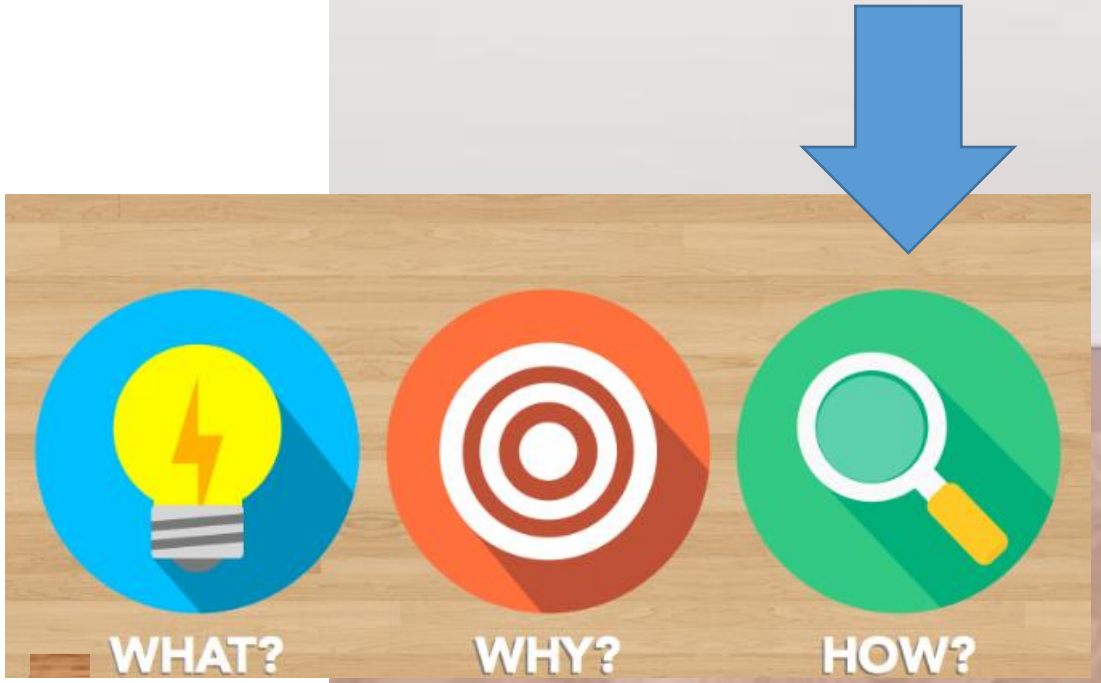
efficacy and safety of pregabalin as add-on therapy in RLS patients already taking dopamine agonists (DA) but still in need of further management.

**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.*

# melatonina...

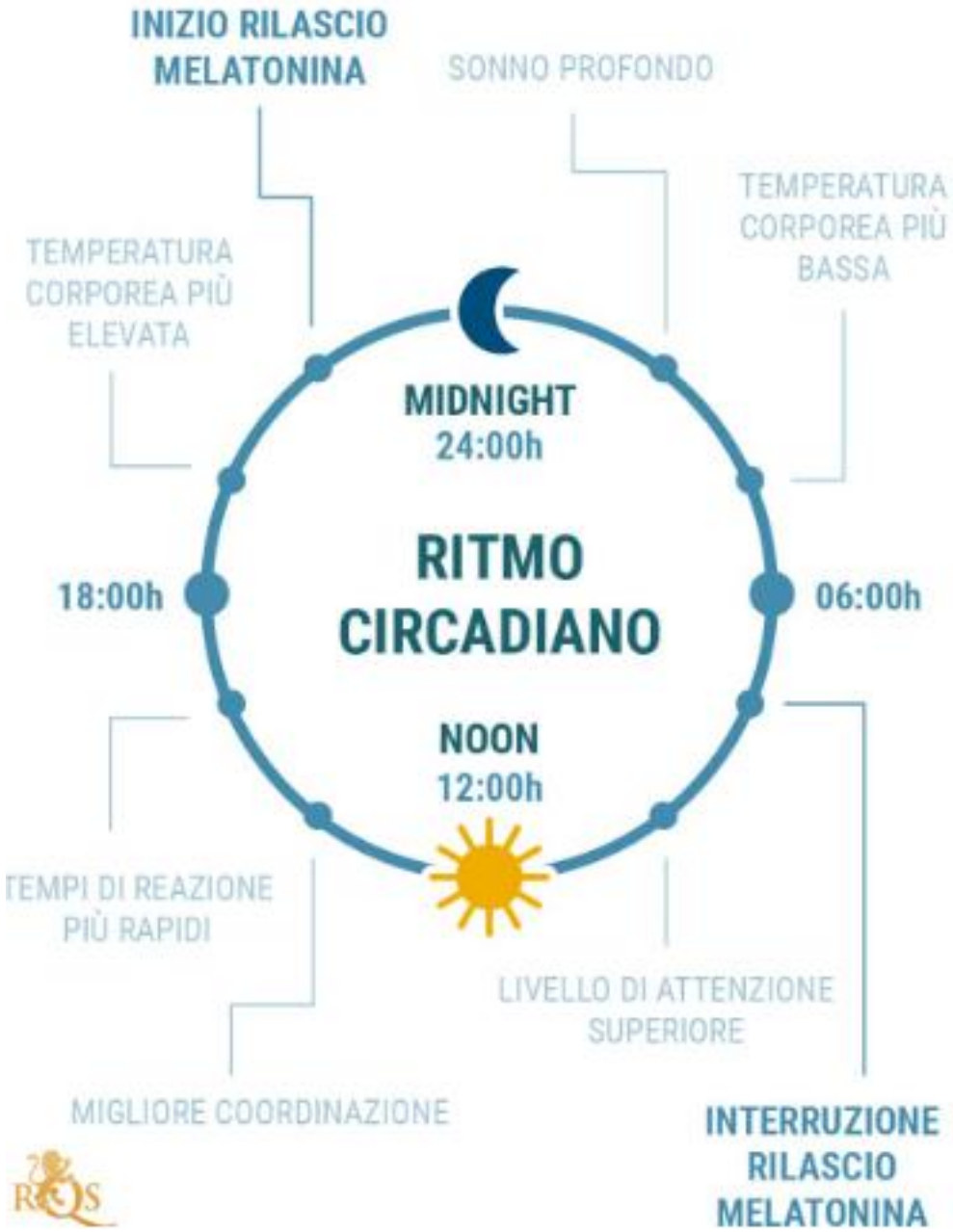


Melatonin is **the second most popular natural product** used by children in the United States (second only to fish oil)

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



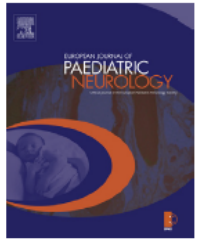


- Brzezinski A, Vangel MG, Wurtman RJ, et al. Effects of exogenous melatonin on sleep: a meta-analysis. Sleep Med Rev. 2005;9(1):41–50

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 *)<br>When DLMO cannot be measured: administer melatonin 3–4 h before actual sleep onset time<br>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<br>If no response after 1 week: increase dose by 1 mg every week until effect appears<br>When 1 mg is effective: try lower dose<br>Maximum dose: <40 Kg: 3 mg; >40 Kg: 5 mg<br>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<br>Treatment can be withdrawn just before puberty (age around 12 yrs) or shortly after puberty (18–24 yrs)<br>Stopping successful treatment too early (i.e. 4 weeks after its start) may results in reappearance of insomnia<br>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%.





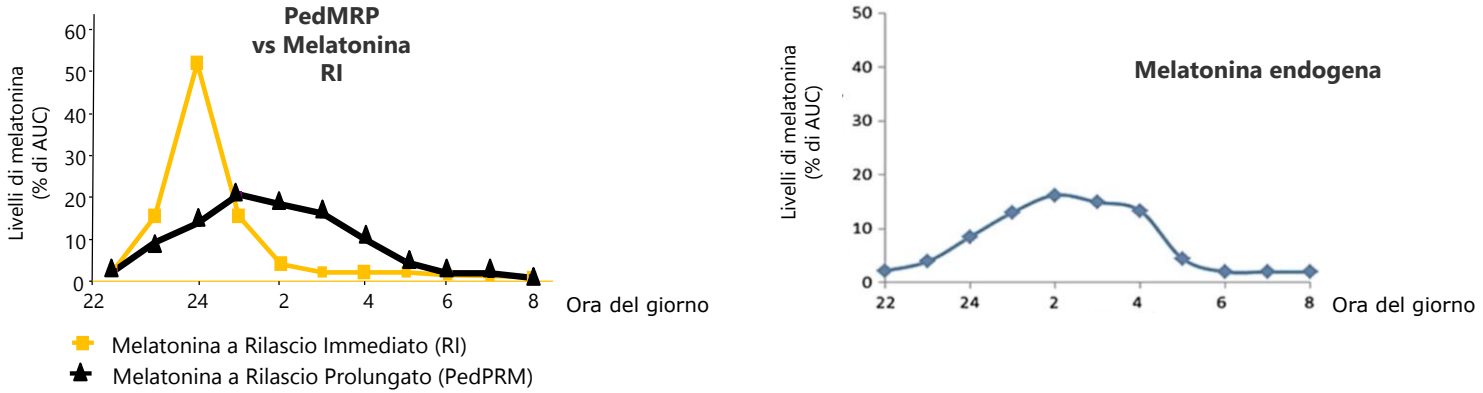
- Grigg-Damberger MM, Ianakieva D. Poor Quality Control of Over-the-Counter Melatonin: What They Say Is Often Not What You Get. J Clin Sleep Med. 2017 Feb 15;13(2):163-165
- Erland LA, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin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

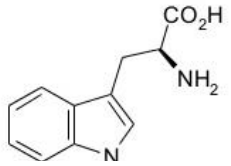

**1.** Zisapel N. Melatonin and sleep. The Open Neuroendocrinology Journal, 2010, 3: 85-95

**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

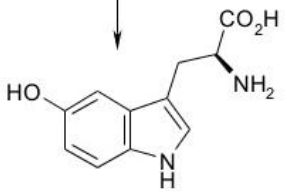




**L-tryptophan**

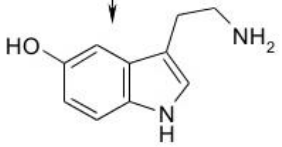
*Triptofano idrossilasi* [O]

**1%**



**5-OH-tryptophan**

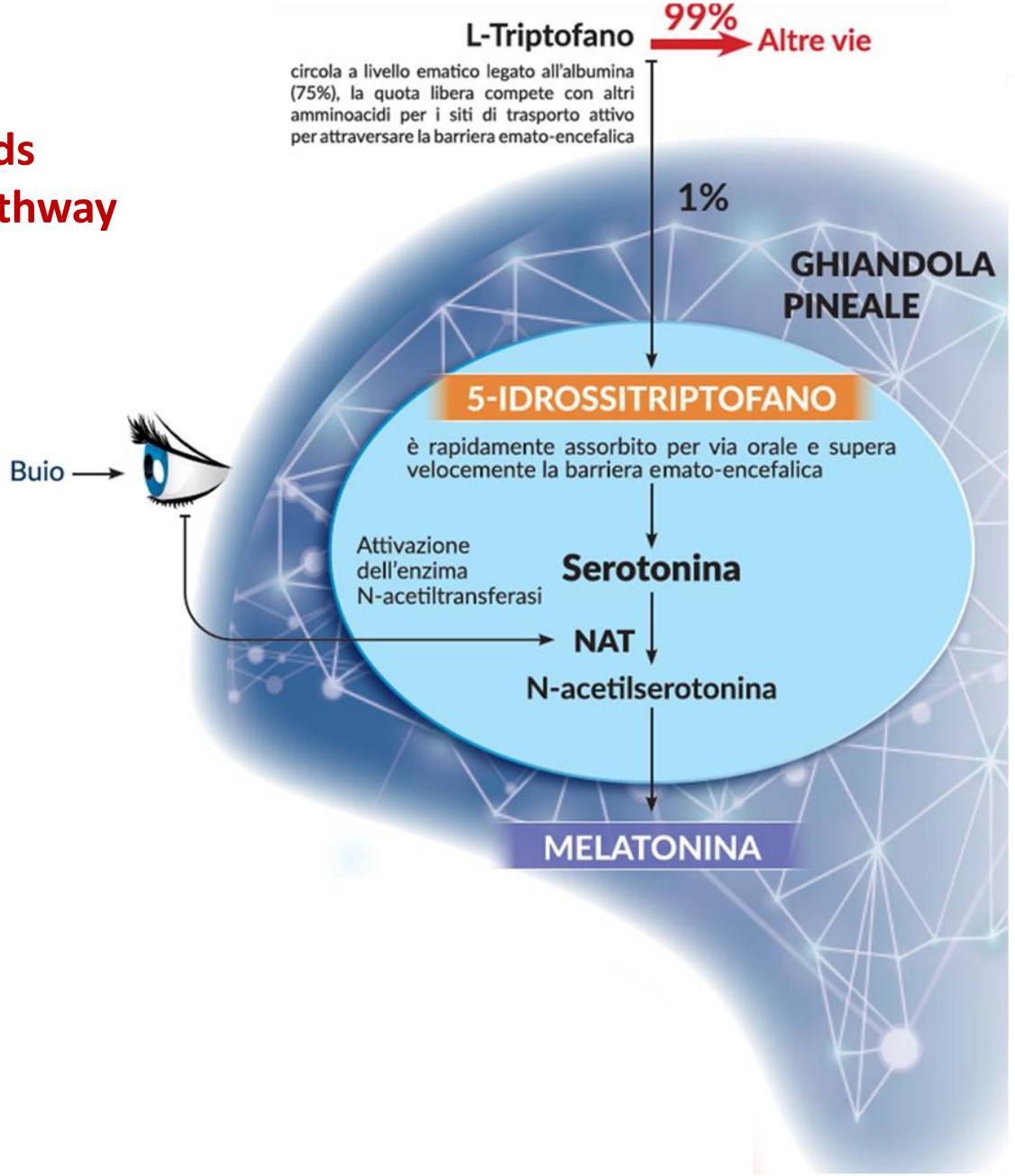
*5-idrossitriptofano decarbossilasi* $-CO_2$



5-idrossitriptammina
Serotonina

**serotonin**

**99% towards chinurenine pathway**



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

# fitoterapici e nutraceutici…





# **Il modello allostatico** ha un obiettivo terapeutico diverso

**la risposta è multisistemica e i sistemi periferici coinvolti sono molteplici**

**La regolazione dei diversi sistemi si basa su segnali provenienti dal cervello che organizza dall'alto la risposta in previsione dei bisogni**

**Ripristinare la flessibilità della risposta preservando la capacità di adattamento  e normalizzando le richieste**

Differentemente dal modello omeostatico che modula farmacologicamente uno dei mediatori della trasmissione nervosa, riducendone la fluttuazione in funzione delle richieste



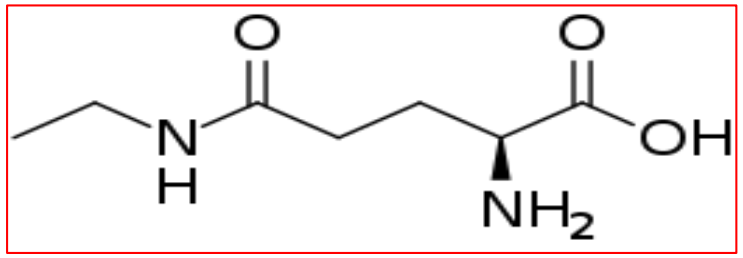
Es. la L-teanina, presente nel tè verde(Camellia sinensis) è un fitochimico che ha il potenziale per diventare un nutraceutico utile nel mitigare gli effetti dello stress

**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




La L-Teanina assorbita a livello gastroenterico esercita i suoi effetti a livello cerebrale perché

- **attraversa la barriera ematoencefalica**
- è trasportata a livello cerebrale in **modo dose dipendente**.

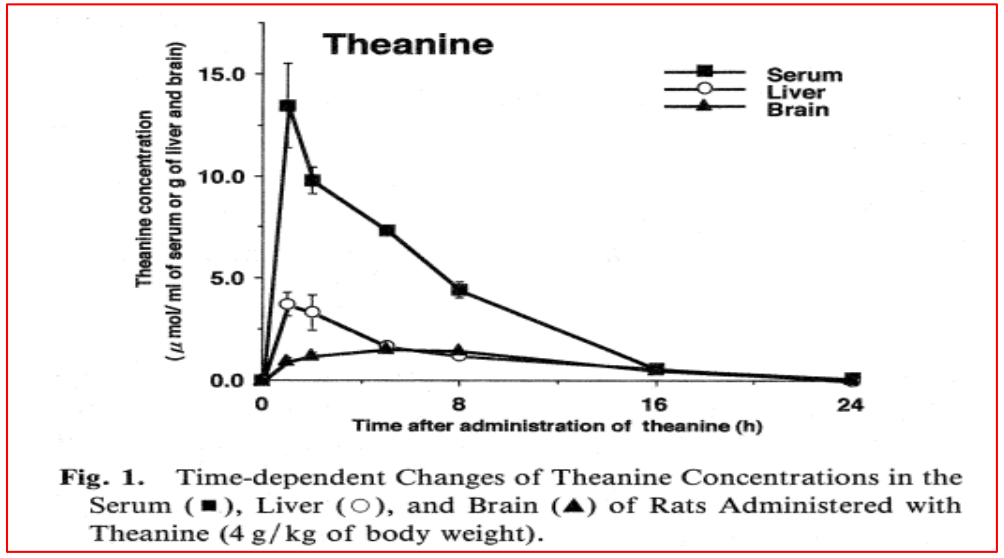
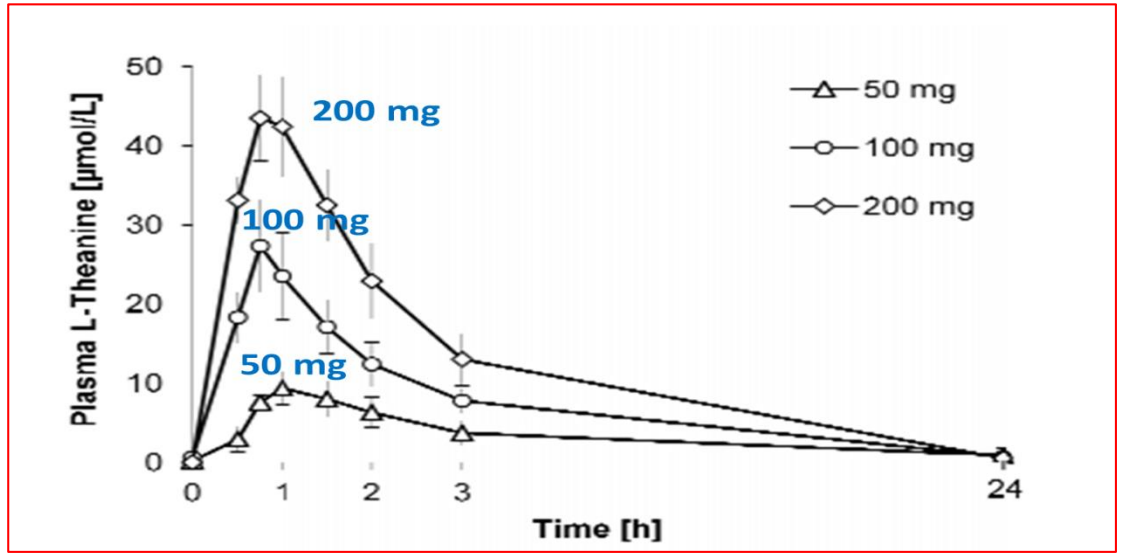



**Fig. 1.** Time-dependent Changes of Theanine Concentrations in the Serum (■), Liver (○), and Brain (▲) of Rats Administered with Theanine (4 g/kg of body weight).



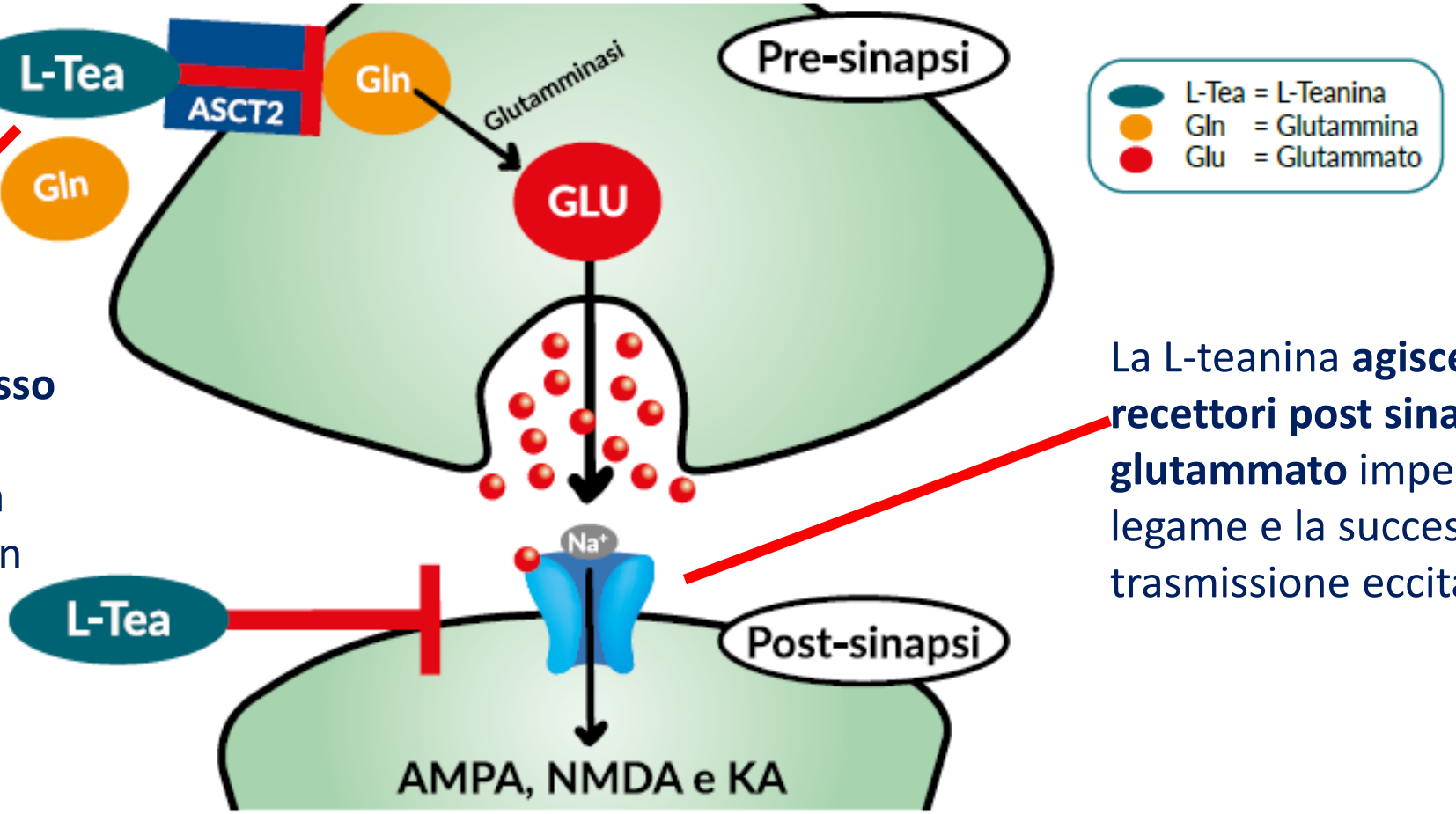

Scheid el al. Kinetics of L-Theanine Uptake and Metabolism in Healthy Participants - J. Nutr. 142: 2091–2096, 2012

TERASHIMA, Jun TAKIDO & Hidehiko YOKOGOSHI (1999) Timedependent Changes of Amino Acids in the Serum, Liver, Brain and Urine of Rats Administered withTheanine, Bioscience, Biotechnology, and Biochemistry, 63:4, 615-618

# 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)

# 200-400 mg / die di L-THE possono aiutare a ridurre lo stress e l'ansia nelle persone esposte a condizioni stressanti.

Plant Foods for Human Nutrition
https://doi.org/10.1007/s11130-019-00771-5

REVIEW ARTICLE

## The Effects of Green Tea Amino Acid L-Theanine Consumption on the Ability to Manage Stress and Anxiety Levels: a Systematic Review

Jackson L. Williams[1,2] · Julian M. Everett[1] · Nathan M. D'Cunha[1,2] · Domenico Sergi[3] · Ekavi N. Georgousopoulou[4,5] · Richard J. Keegan[1,6] · Andrew J. McKune[1,2,6,7] · Duane D. Mellor[2,8] · Nicola Anstice[1,2] · Nenad Naumovski[1,2]

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**L'utilizzo di una dose di 400 mg di L-teanina per 4-8 settimane è risultata efficace e sicura**



Journal of the American College of Nutrition

ISSN: 0731-5724 (Print) 1541-1087 (Online) Journal homepage: www.tandfonline.com/journals/uacn20

# In Search of a Safe Natural Sleep Aid

Theertham P. Rao, Motoko Ozeki & Lekh R. Juneja

**To cite this article:** Theertham P. Rao, Motoko Ozeki & Lekh R. Juneja (2015) In Search of a Safe Natural Sleep Aid, Journal of the American College of Nutrition, 34:5, 436-447, DOI: 10.1080/07315724.2014.926153

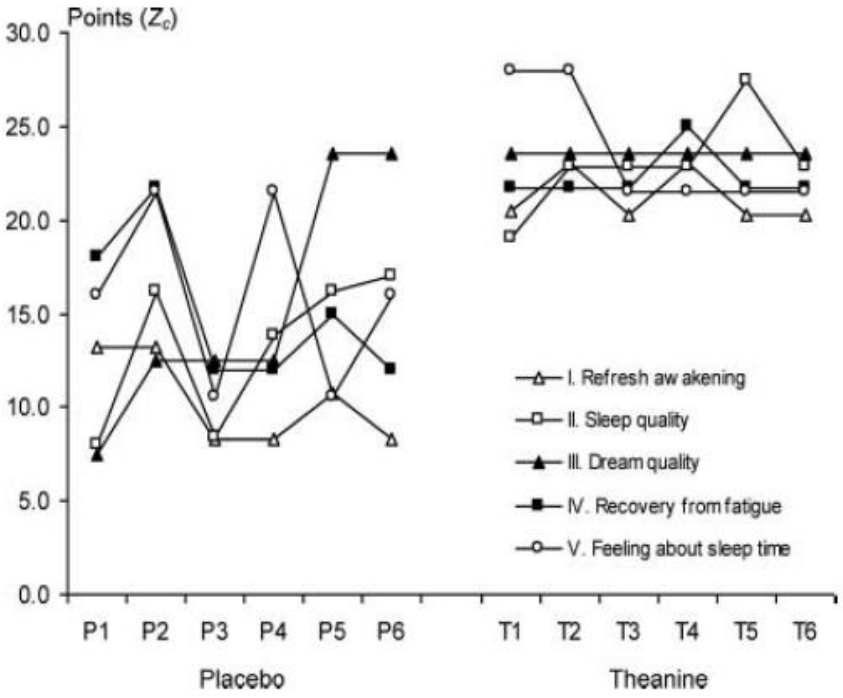
**To link to this article:** https://doi.org/10.1080/07315724.2014.926153

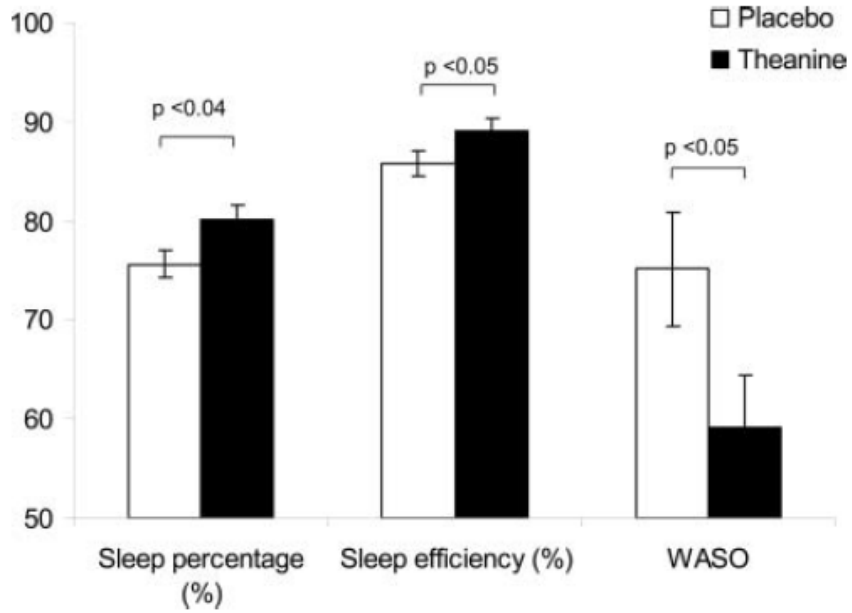
Published online: 11 Mar 2015.

the administration of 200 mg of L-theanine before bed may support improved sleep quality not by sedation but through anxiolysis.

Because L-theanine does not induce daytime drowsiness, it may be useful at any time of the day.

The no observable adverse effect level (NOAEL) for the oral administration of L-theanine was determined to be above 2000 mg/kg bw/day in adults



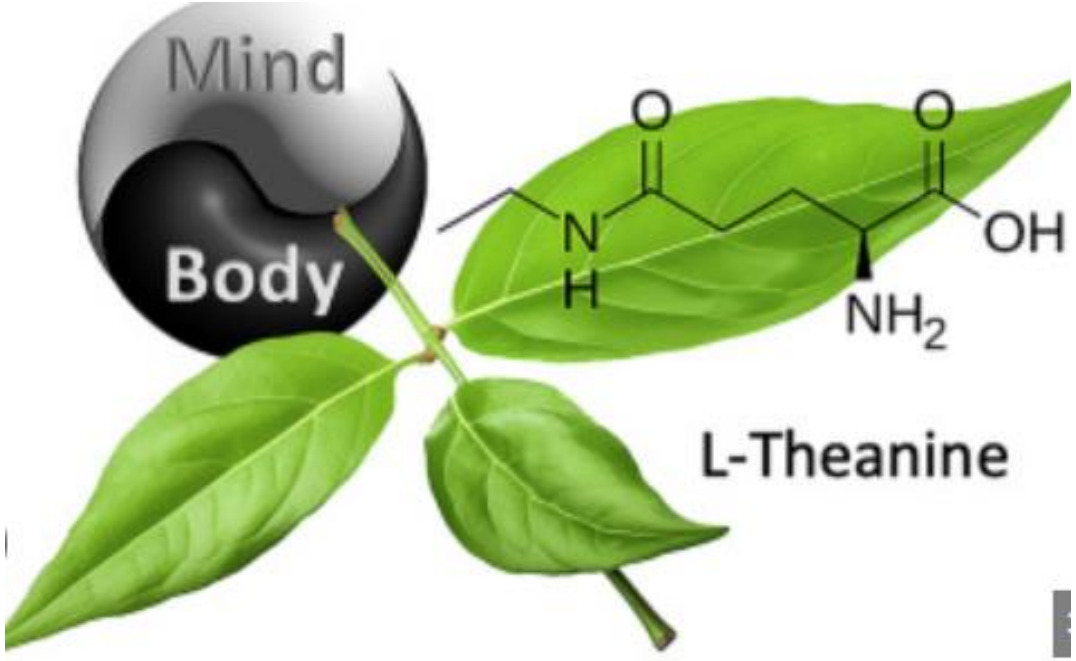



Bulman, A.; D'Cunha, N.; Marx,W.; Turner, M.; McKune, A.;Naumovski, N. The Effects of **L-Theanine Supplementation on Quality of Sleep: A Systematic Review**. Proceedings **2023**, 91, 32.

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)

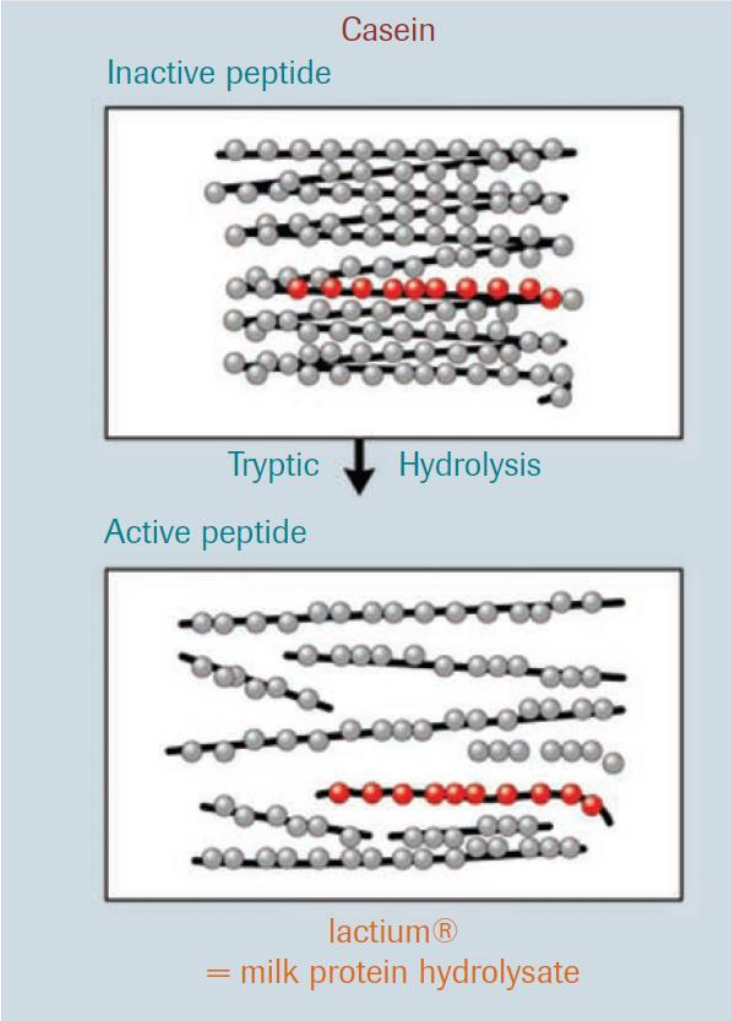
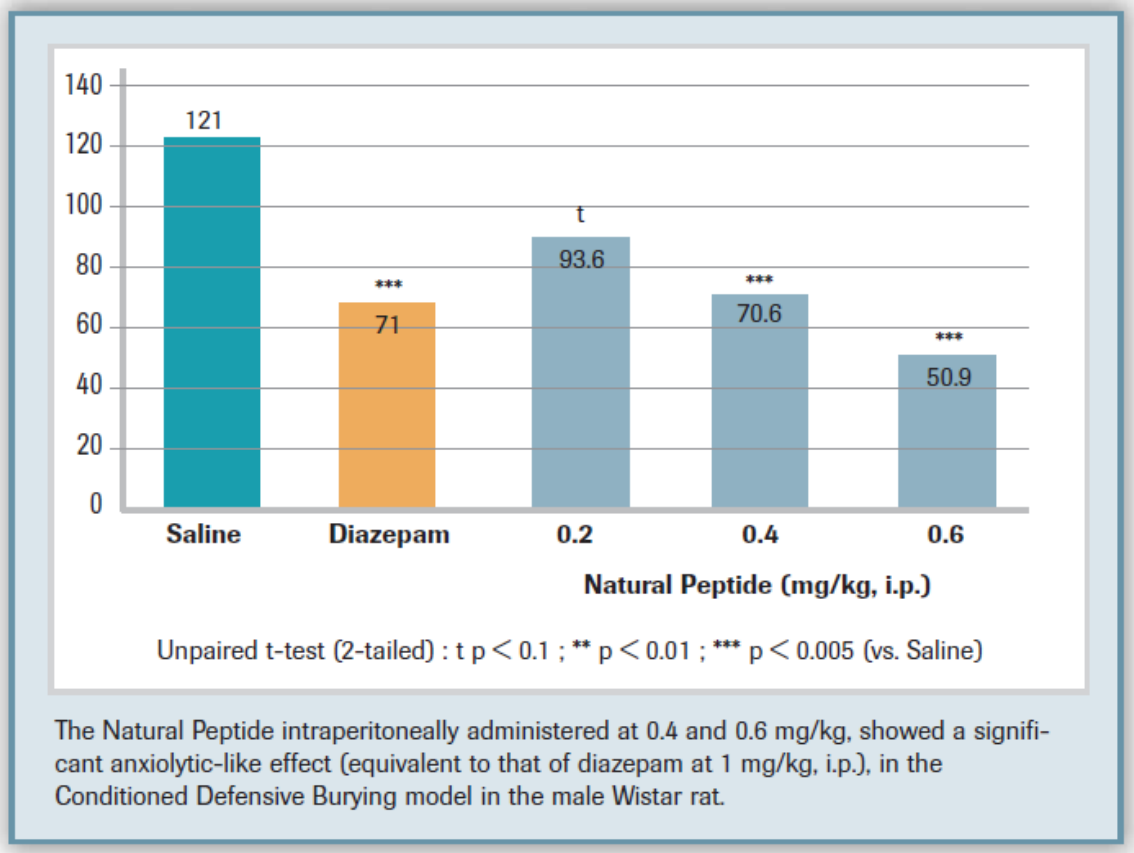



**Figure 1** — **Anxiety Global**




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.

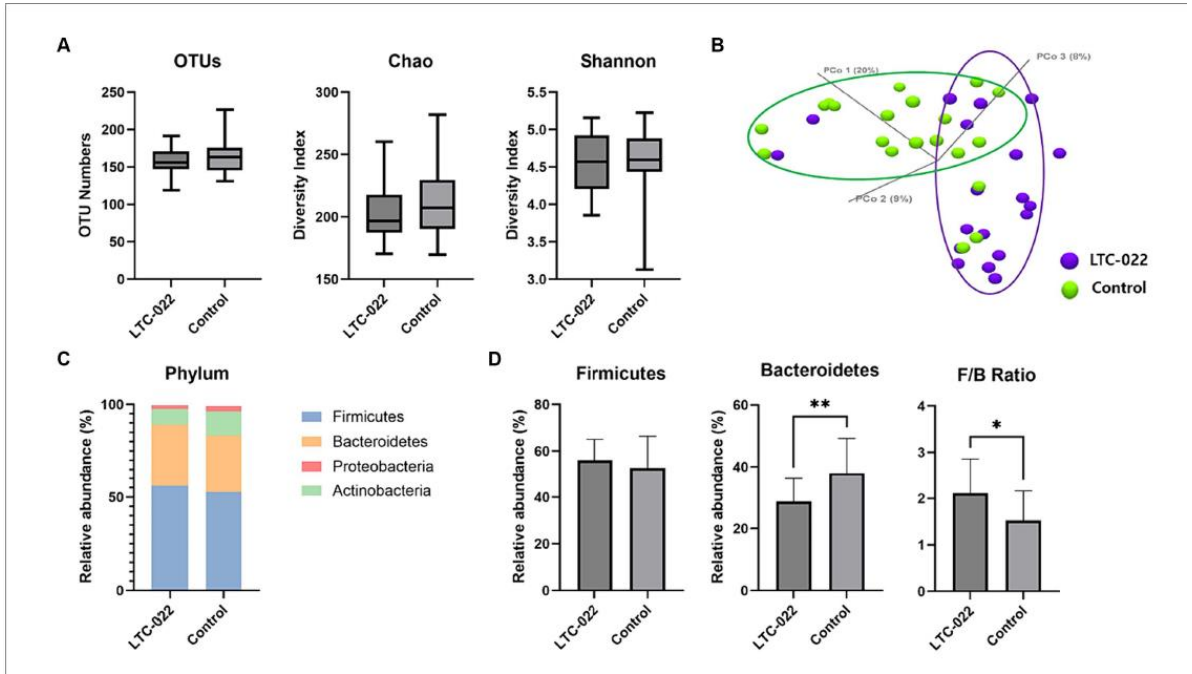
| Variables | Weekday | | | | Weekend | | | |
|---|---|---|---|---|---|---|---|---|
| | LTC-022 | Control | *p*-value | p-interaction† | LTC-022 | Control | *p*-value | p-interaction† |
| **TIB (min)** | | | | | | | | |
| Baseline | 456.70 (57.70) | 455.35 (72.05) | 0.949[a] | 0.864 | 453.88 (57.50) | 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



Nutrients 2017, 9, 154; doi:10.3390/nu9020154

nutrients

MDPI

Article

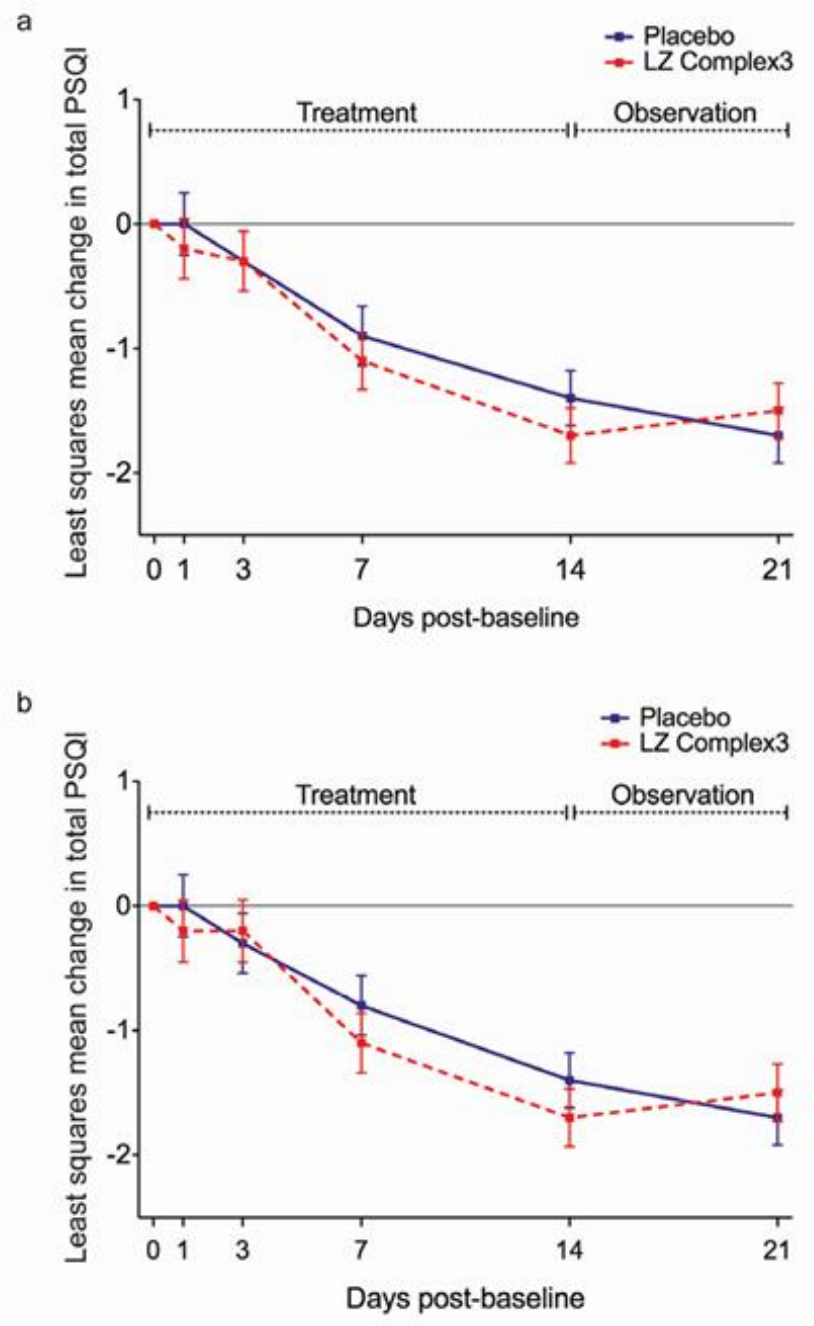
# Exploring the Effect of Lactium™ and *Zizyphus* Complex on Sleep Quality: A Double-Blind, Randomized Placebo-Controlled Trial

Andrew Scholey [1,*], Sarah Benson [1], Amy Gibbs [1], Naomi Perry [1], Jerome Sarris [1,2] and Greg Murray [3]

Results revealed that sleep quality measured by change in Pittsburgh Sleep Quality Index (PSQI) score improved in both the LZComplex3 and placebo groups.

**There were no significant between group differences between baseline and endpoint on the primary and secondary outcome**.

It currently cannot be concluded that administration of LZComplex3 for 2 weeks improves sleep quality, however, a marked placebo response (despite placebo run-in) and/or short duration of treatment may have masked a potential beneficial effect on sleep quality.






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..

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<br>Striatal transferrin receptors<br>Striatal dopamine levels<br>Striatal D1 receptor levels<br>Tyrosine hydroxylase levels | Ventral midbrain iron<br>Nucleus accumbens iron<br>Striatal D2 receptor levels<br>Striatal A1 receptor levels<br>REM sleep<br>Sleep onset |
|  | Transferrin levels<br>D1 receptor levels<br>Spinal cord excitability<br>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.

# Algoritmi per il  trattamento



**Appunti di Neuropsichiatria**

Medico e Bambino 2024;43(1):37-42. doi: 10.53126/MEB43037

# L'insonnia nei disturbi del neurosviluppo: ADHD e ASD

FRANCESCA BANDITELLI[1], LAURA PISANU[1], ANTONELLA GAGLIANO[2]

[1]*Scuola di Specializzazione in Neuropsichiatria Infantile, Università di Cagliari*
[2]*Azienda Ospedaliero-Universitaria Policlinico "Gaetano Martino" Università di Messina*

**Il disturbo più frequente è l'insonnia** che può aggravare il quadro sintomatologico e causare un peggioramento del funzionamento globale durante le ore di veglia, insieme a una riduzione della qualità di vita dei bambini e delle loro famiglie.

**I genitori di questi bambini manifestano alti livelli di stress** che si ripercuotono sia sulla gestione familiare che sull'attività lavorativa individuale[6].

Modificata da
Bruni O, Ottaviano S, Guidetti V, et al., The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. Journal of Sleep Research 1996,5:251-61

**SCALA PER LA VALUTAZIONE DEI DISTURBI DEL SONNO**

**Istruzioni** Questo questionario permetterà di comprendere meglio il ritmo sonno-veglia del vostro bambino e valutare se esistono problemi a questo riguardo. Cercate di rispondere a ogni domanda. Nel rispondere considerate ogni domanda relativamente agli ultimi 6 mesi di vita del bambino. Rispondere barrando il numero da 1 a 5.

NOME _____ Sesso M F

Età _____ Peso _____ Altezza _____

| | | | | | |
|---|---|---|---|---|---|
| 1. Quante ore dorme il bambino durante la notte | 1 (9-11 ore) | 2 (8-9 ore) | 3 (7-8 ore) | 4 (5-7 ore) | 5 (meno di 5 ore) |
| 2. Quanto tempo impiega il bambino ad addormentarsi | 1 (meno di 15') | 2 (15-30') | 3 (30-45') | 4 (45-60') | 5 (più di 60') |

**1** Mai
**2** Occasionalmente (1 o 2 volte al mese o meno)
**3** Qualche volta (1 o 2 volte a settimana)
**4** Spesso (4 o 5 volte a settimana)
**5** Sempre (tutti i giorni)

| | | | | | |
|---|---|---|---|---|---|
| 3. Non vuole andare a letto per dormire | 1 | 2 | 3 | 4 | 5 |
| 4. Ha difficoltà ad addormentarsi | 1 | 2 | 3 | 4 | 5 |
| 5. All'addormentamento è agitato, ansioso o ha paura | 1 | 2 | 3 | 4 | 5 |
| 6. Presenta "scatti" o sussulti all'addormentamento | 1 | 2 | 3 | 4 | 5 |
| 7. Fa movimenti ritmici o si dondola per addormentarsi | 1 | 2 | 3 | 4 | 5 |
| 8. Dice di vedere "cose strane" poco prima di addormentarsi | 1 | 2 | 3 | 4 | 5 |
| 9. Suda molto all'addormentamento | 1 | 2 | 3 | 4 | 5 |
| 10. Si sveglia più di due volte durante la notte | 1 | 2 | 3 | 4 | 5 |
| 11. Se si sveglia la notte ha difficoltà a riaddormentarsi | 1 | 2 | 3 | 4 | 5 |
| 12. Si muove continuamente durante il sonno | 1 | 2 | 3 | 4 | 5 |
| 13. Non respira bene durante il sonno | 1 | 2 | 3 | 4 | 5 |
| 14. Smette di respirare per qualche momento durante il sonno | 1 | 2 | 3 | 4 | 5 |
| 15. Russa | 1 | 2 | 3 | 4 | 5 |
| 16. Suda molto durante la notte | 1 | 2 | 3 | 4 | 5 |
| 17. Si alza e si siede sul letto o cammina mentre dorme | 1 | 2 | 3 | 4 | 5 |
| 18. Parla durante il sonno | 1 | 2 | 3 | 4 | 5 |
| 19. Digrigna i denti nel sonno | 1 | 2 | 3 | 4 | 5 |
| 20. Durante il sonno urla angosciato senza riuscire a svegliarsi | 1 | 2 | 3 | 4 | 5 |
| 21. Ha degli incubi che non ricorda il giorno dopo | 1 | 2 | 3 | 4 | 5 |
| 22. Ha difficoltà a svegliarsi la mattina | 1 | 2 | 3 | 4 | 5 |
| 23. La mattina si sveglia stanco | 1 | 2 | 3 | 4 | 5 |
| 24. Al risveglio è incapace di muoversi o è come paralizzato per pochi minuti | 1 | 2 | 3 | 4 | 5 |
| 25. È sonnolento durante il giorno | 1 | 2 | 3 | 4 | 5 |
| 26. Si addormenta improvvisamente e senza preavviso durante il giorno | 1 | 2 | 3 | 4 | 5 |

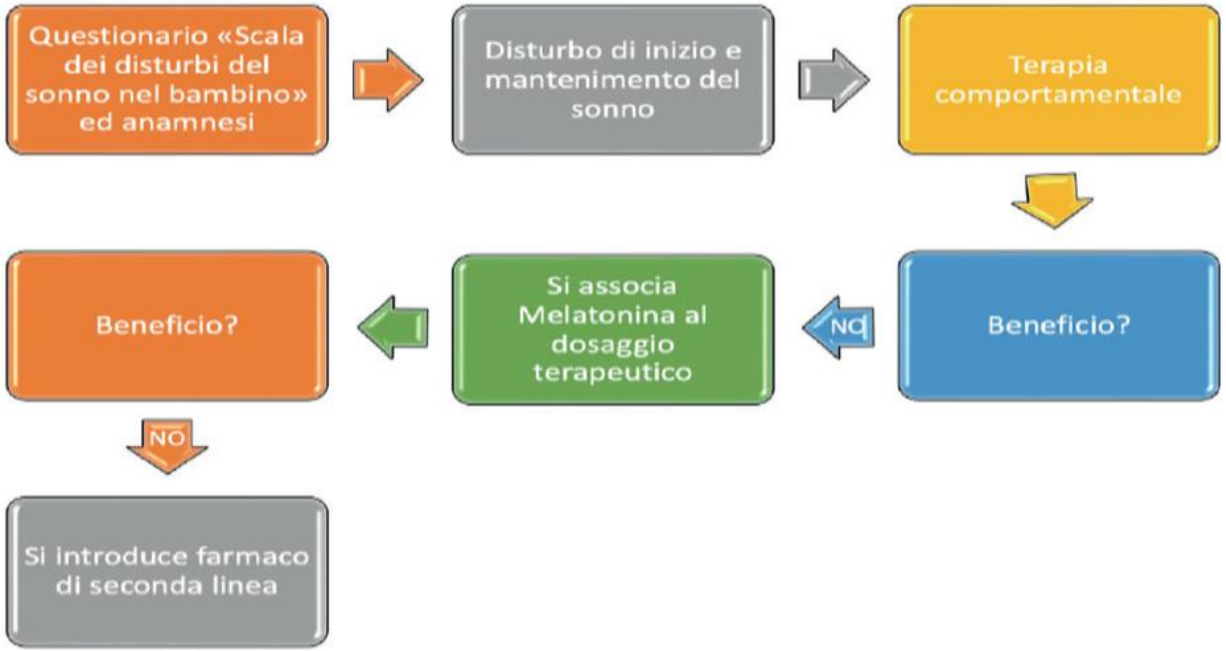
| | |
|---|---|
| **DIMS** | *Disturbi di inizio e mantenimento del sonno (sommare i punteggi delle risposte 1, 2, 3, 4, 5, 10, 11)* |
| **DRS** | *Disturbi respiratori in sonno (sommare i punteggi delle risposte 13, 14, 15)* |
| **DA** | *Disturbi dell'arousal (sommare i punteggi delle risposte 17, 20, 21)* |
| **DTVS** | *Disturbi della transizione veglia-sonno (sommare i punteggi delle risposte 6, 7, 8, 12, 18, 19)* |
| **DES** | *Disturbi da eccessiva sonnolenza (sommare i punteggi delle risposte 22, 23, 24, 25, 26)* |
| **IPN** | *Iperidrosi notturna (sommare i punteggi delle risposte 9, 16)* |
| **TOTALE** | *Punteggio totale (sommare i punteggi delle sei scale precedenti)* |

Medico e Bambino 2024;43(1):37-42. doi: 10.53126/MEB43037

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**SECONDA LINEA DI TRATTAMENTO DELL'INSONNIA**

| Disturbi del neurosviluppo | Classe di farmaci | Molecole | Meccanismo di azione | Effetti avversi |
|---|---|---|---|---|
| ADHD | Antagonista recettore alfa2 adrenergici | Clonidina Guanfacina | Recettori pre-sinaptici alfa2 del SNC | Tachicardia, tremore, iperidrosi, irritabilità |
| ASD | D2 bloccanti | Risperidone Aripiprazolo Quetiapina Olanzapina | Modulazione trasmissione dopaminergica | Iperfagia. allungamento QT, ipotensione |
| Disabilità intellettiva | Antistaminici | Niaprazina Difenidramina Idrossizina | Azione sui recettori H1 del SNC | Sonnolenza. xerostomia, vertigini, tachicardia |
| Carenza marziale in tutti i disturbi del neurosviluppo | Terapia marziale | Sali ferrosi eventualmente associati a vitamina C | Replezione dei depositi corporei di ferro | Vomito, algie addominali, diarrea |

# I comportamenti ripetitivi



*Quale classe di farmaci per i comportamenti ripetitivi?*

Second Generation Antipsychotic Medications

Depression & Anxiety Medications

Mood Stabilizer Medications

ADHD Medications

Sleep Medications

Farmer et al, Pharmacotherapy for the Core Symptoms in Autistic Disorder: Current Status of the Research Drugs. 2013 March ; 73(4): 303–314.

| Agent | Ref | Sample | Study Design | Target Symptoms | Study Results (Relevant to Core Symptoms Only) | Reported Serious AEs[1] |
|---|---|---|---|---|---|---|
| Risperidone | 33 | N = 101. Autism. Children. Recruited for irritability. | 8-week, R, DB, PBO, PG. | Irritability. | Moderate effect of RIS on ABC Stereotypy. N.S. effect on ABC Social Withdrawal and Inappropriate Speech. CY-BOCS NR. | None. |
| | 36 | N = 79. ASD. Children. | 8-week, R, DB, PBO, PG. | Behavioral symptoms. | Moderate effects of RIS on ABC Inappropriate Speech, Social Withdrawal, and Stereotypy. | No serious AEs reported. |
| Paliperidone | 41 | N = 25. Autism. Children & adults. Recruited for irritability. | 8-week, prospective, OL. | Irritability. | Large pre-post effects on ABC Social Withdrawal, Stereotypy, Inappropriate Speech; SRS Total score, CY-BOCS. | None. |
| Aripiprazole | 42, 43, 44 | N = 218 [42]; N = 164 [43]; N = 330 [44]. Children. Recruited for irritability. | 8-week, DB, PBO, PG [42, 43]. Fixed-dose [42], flexible-dose [43]. 52-week, OL [44]. | Irritability | ARI superior to PBO on ABC Stereotypy, Inappropriate Speech, CY-BOCS Compulsions [42, 43]. Pre-post improvements on these subscales in OL [44]. | Presyncope and agitation [42]. Aggression, impulsivity, acute otitis media, pharyngotonsillitis, sinusitis, dysphagia, cholecystitis, cholelithiasis, athsma, suicidal ideation, skin infection, convulsion [44]. |

AAPS: Most studies have recruited children specifically for irritability

no study has evaluated the core symptoms as a primary outcome

modest potential improvement in the core symptoms

## L’efficacia degli SSRI sul DOC pediatrico è da tempo documentata

**Sertraline** (March, Biederman et al, J Am Med Ass, 1998)
**Fluvoxamine** (Riddle et al, JAACAP, 2001)
**Fluoxetine** (Geller et al, JAACAP, 2001)
**Paroxetine** (Geller et al, JAACAP, 2004)

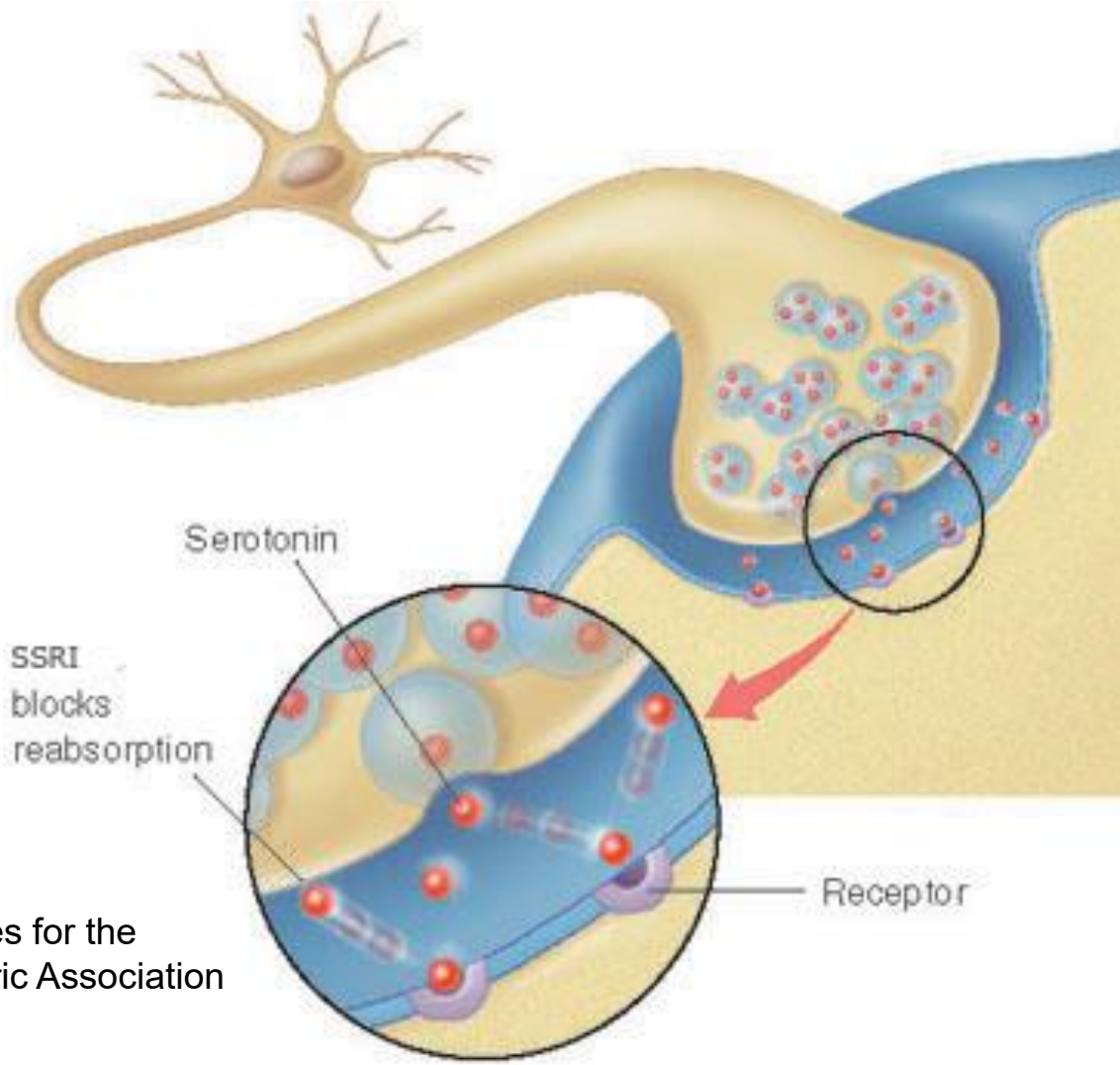
*First line*

**•CBT**

**•SSRIs o clomipramina**

*No responders*

**trattamento combinato**




Koran LM, Simpson HB**: Guideline Watch (March 2013):** Practice Guidelines for the treatment of patients with obsessive-compulsive disorder. American Psychiatric Association Practice Guidelines, March 2013

# superiorità statistica del trattamento combinato rispetto alla sola CBT (P = .008) ed alla sola sertralina (P = .006).

**POTS study**, randomized, controlled 12-week study
112 patients with OCD (7-17 years)

•Solo CBT (CBT)
•Solo Sertralina alone (S)
•CBT + Sertralina (CBT+ S)
•Placebo

1. **Tutte superiori al placebo**
2. **CBT= S**
3. **Il trattamento combinato superiore sia a CBT che a Sertralina**

Percentuale di remissione
**combinato= CBT e > di S**

First line: **solo CBT o trattamento combinato (SSRI)**



**Pediatric OCD Treatment Study (POTS)** Team. (2004), Cognitive-behavior therapy, sertraline, and their combination in children and adolescents with obsessive-compulsive disorder: Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA 292:1969–1976

**Nordic Long-Term OCD Treatment Study (NordLOTS)**

bambini e adolescenti con DOC **che non avevano risposto** ad un primo ciclo di psicoterapia

sertralina vs nuovo ciclo di CBT

- **sertralina 45.4 %**
- **CBT 50.0%**

**Prolungare la CBT aumenta la percentuale di responders**

Skarphedinsson G1, Weidle B, Thomsen PH, Dahl K, Torp NC, Nissen JB, Melin KH, Hybel K, Valderhaug R, Wentzel-Larsen T, Compton SN, Ivarsson T. Continued cognitive-behavior therapy versus sertraline for children and adolescents with obsessive-compulsive disorder that were non-responders to cognitive-behavior therapy: a randomized controlled trial: Eur Child Adolesc Psychiatry. **2015**, May;24(5):591-602..

Metanalisi di 12 trials randomizzati, controllati (1044 children with OCD)

# Differenza significativa rispetto al placebo per tutti gli SSRI

Geller DA, Biederman J, Stewart SE, et al. Which SSRI? **A meta-analysis of pharmacotherapy trials in pediatric obsessive-compulsive disorder.** Am J Psychiatry 2003; 160:1919-28

Alcuni studi meta-analitici (Watson e Rees, 2008) ridimensionano l'efficacia del trattamento farmacologico rispetto alla CBT e rilevano una significativa differenza tra gli Effect Sides

Farmacoterapia: EF 0.48

CBT: EF 1.45

Altra Metanalisi

- farmacoterapia 0.7
- CBT 1.2
- terapia combinata 1.7

Sánchez-Meca J, Rosa-Alcázar AI, Iniesta-Sepúlveda M, Rosa-Alcázar A: Differential efficacy of cognitive-behavioral therapy and pharmacological treatments for pediatric obsessive-compulsive disorder: a meta-analysis. J Anxiety Disord 2014, Jan;28(1):31-44.

In sintesi…

la terapia farmacologica da sola ha un’efficacia leggermente minore della sola CBT

La farmacoterapia rimane la terapia di prima scelta per i casi severi

il trattamento farmacoterapico ha un ruolo fondamentale anche in casi di moderata intensità perchè, associato  alla CBT, ne potenzia significativamente l’efficacia

# Augmentation

## Aripiprazolo
## dosi non elevate (comprese tra 2 e 10 mg/die)

Masi G, et al: J Psychiatr Res 2013, 47(8): 1007-12.

Masi G, et al, Journal of Clinical Psychopharmacology 2010, 30: 688-93.

Ercan ES, et al: J Child Adolesc Psychopharmacol. 2015,  Sep;25(7):580-4.

## **Risperidone** (efficacia sovrapponibile)
## dosi comprese tra 1 e 2.5 mg/die

Fitzgerald et al, Journal of Child and Adolescent Psychopharmacology 1999, 9: 115-23.
Thomsen H , Annals of Clinical Psychiatry 2004, 16: 201-7.

Masi G, et al, . J Psychiatr Res 2013, 47(8): 1007-12**.**

Masi et al, Aripiprazole augmentation in 39 adolescents with medication-resistant obsessive-compulsive disorder. J Clin Psychopharmacol. 2010 Dec;30(6):688-93

**aripiprazole augmentation of serotonin reuptake inhibitor (SRI) treatment**

39 **adolescents with OCD** (28 M- 11F; 12-18 anni)
no reponders dopo 2 tentativi con SRI in monoterapia

**aripiprazole augmentation**

Dose finale media di aripiprazole 12.2 ± 3.4 mg/d.

**27 responders (59.0%)**

**CGI-Improvement** :1 or 2 (very much or much improved)
Nei responder passa da 39.2 ± 5.8 a 49.8 ± 9.0 (P < 0.0001)

.

**CGI-severity**:non superiore a 3
Nei responder passa da 6.0 ± 0.9 (baseline) a 3.5 ± 1.0 (endpoint) (P < 0.0001)

# *E quando ci sono anche i tic?*

Both cognitive behavioral therapy and SSRIs are less effective in OCD with tics than in OCD with no tics

(Garcia, Sapyta, & Moore, 2010; The Pediatric OCD Treatment Study (POTS) Team, 2004).



The current expert consensus is that the pharmacological treatment of choice for OCD with TS **is the same** as for OCD without TS: SSRIs, or clomipramine.

**A better outcome however may be achieved with concurrent CBT**

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

*Se si associano i tics…*

## la risposta agli SSRI è più bassa

(McDougle et al 2000; Miguel et al 2003)

optimal therapy for patients with ***compultics*** * involves the combination of **anti-obsessional and tic-suppressing treatments**

Palumbo and Kurlan, Neuropsychiatric Disease and Treatment 2007:3(5) 687–693

* Tourette patients that are virtually impossible to classify as a tic or a compulsion and have features of both.

## Tics Induced by SSRIs

Rua and Damasio, Movement Disorders Clinical Practice, Volume 1, Issue 3, pages 243–244, September 2014

To better account for TOCD holistically when considering the best treatment, **clinicians should consider their condition as a case of comorbid OCD and tics disorder rather than a tic-related subtype of OCD**

Mansueto CS, Keuler DJ. Tic or compulsion?: it's Tourettic OCD. Behav Modif (2005) 29:784–99. doi: 10.1177/0145445505279261

# First line agents differ between CTD and OCD




Katz TC, Bui TH, Worhach J, Bogut G, Tomczak KK. **Tourettic OCD**: Current understanding and treatment **challenges of a unique endophenotype**. Front Psychiatry. 2022 Jul 27;13:929526.

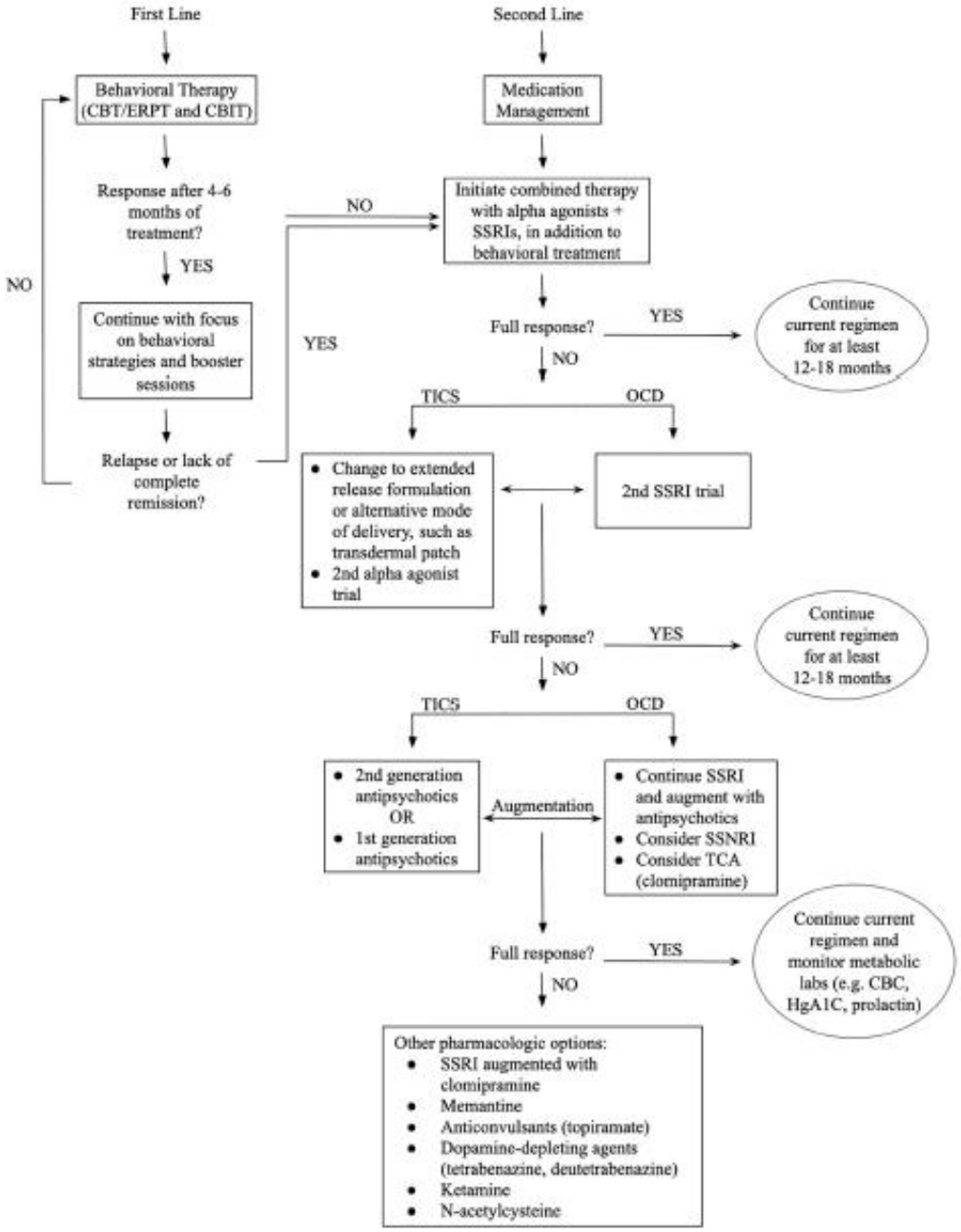



FIGURE 2
Proposed treatment algorithm for patients with TOCD.

In both disorders, antipsychotics can be used for augmentation or as primary agents for children who do not respond or cannot tolerate first line agents.

TOCD often warrants combined treatment as well as higher dosing regimens due to overlapping symptomatology

Katz TC, Bui TH, Worhach J, Bogut G, Tomczak KK. **Tourettic OCD**: Current understanding and treatment **challenges of a unique endophenotype**. Front Psychiatry. 2022 Jul 27;13:929526.

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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Besides a dysfunction in the dopaminergic system…

*imbalances in other neurotransmitter systems*

- Serotonergic
- Noradrenergic
- Glutamatergic
- GABAergic
- Cholinergic
- Histaminergic
- Endocannabinoid
- Opioid systems

These findings give some rationale to use substances other than dopamine blocking drugs particularly for the treatment of tics resistant to dopamine-modulating agents.

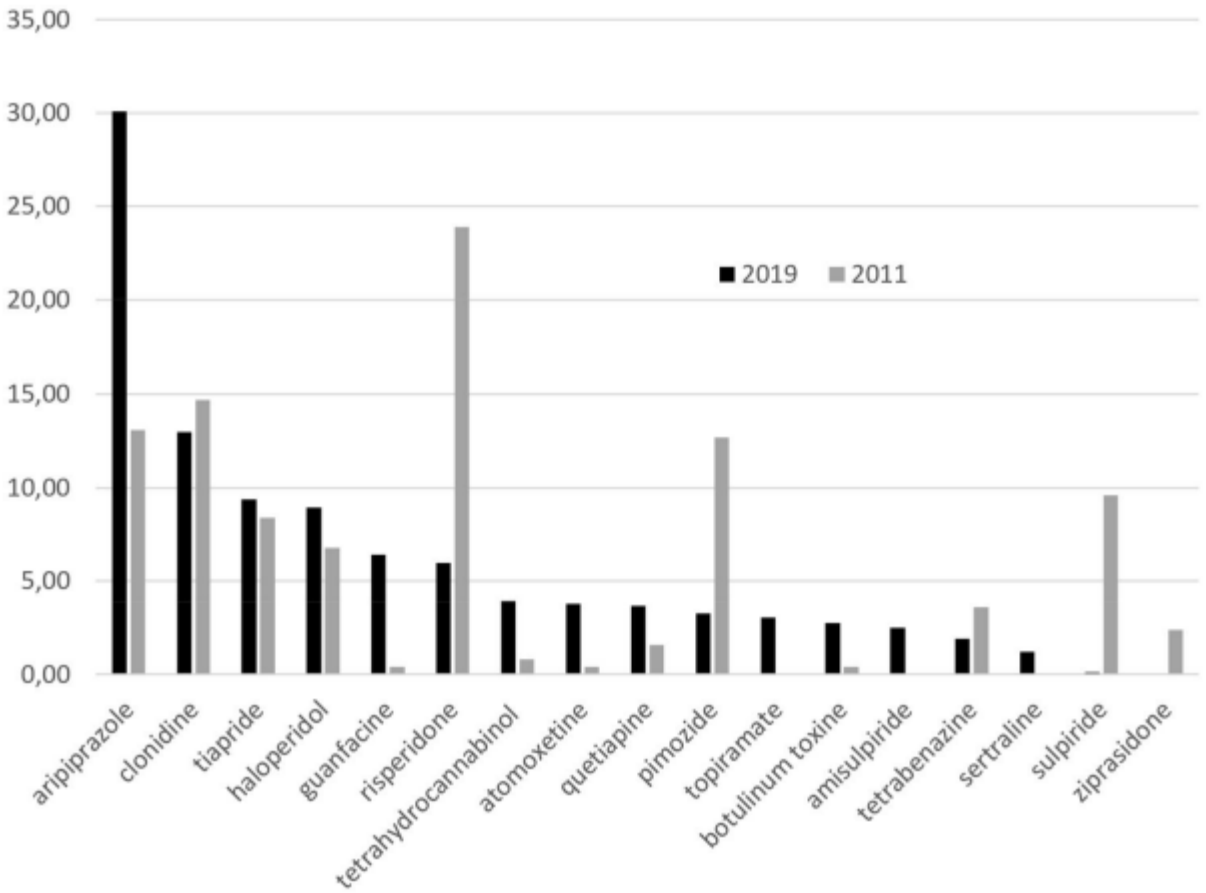
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**The largest amount of evidence supports the use of dopamine blocking agents**, **preferably aripiprazole because of a more favorable profle of adverse events** than frst- and second-generation antipsychotics.

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

European Child & Adolescent Psychiatry (2022) 31:425–441
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In treatment resistant cases, treatment with agents with either a limited evidence base or risk of extrapyramidal adverse efects might be considered, including **pimozide, haloperidol, topiramate, cannabis-based agents, and botulinum toxin injections**.

Overall, treatment of TS should be individualized, and decisions based on the patient's needs and preferences, **presence of co-existing conditions**, latest scientifc fndings as well as on the physician's preferences, experience, and local regulatory requirements.

**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<br>Motor tics: 50–75 U | 1–2.5<br>75–250 | 1.27 (0.51–2.03) [4] | Moderate | Weakness of the injected muscles | |

The dopamine agonists, **pergolide and ropinirole**, prescribed at lower doses than used in treating Parkinson's disease, have been beneficial, but ergot-containing medications should be avoided because of side effects

Anca MH, Giladi N, Korczyn AD. Ropinirole in Gilles de la Tourette syndrome. Neurology. 2004;62(9):1626–1627.

Gilbert DL, Dure L, Sethuraman G, Raab D, Lane J, Sallee FR. Tic reduction with pergolide in a randomized controlled trial in children. Neurology. 2003 Feb 25;60(4):606-11.

**Botulinum toxin** (Botox), a focal chemodenervator has a beneficial effect on both dystonic motor and vocal tics as well as reducing the premonitory sensory component.

Kwak C, Jankovic J. Tics in Tourette syndrome and botulinum toxin. J Child Neurol. 2000;15(9):631–634.

# A new D1-receptor antagonist, **ecopipam,** has been shown to be beneficial for thetreatment of tics in adults

Gilbert DL, Budman CL, Singer HS, Kurlan R, Chipkin RE. A D1 Receptor Antagonist, Ecopipam, for Treatment of Tics in Tourette Syndrome. Clinical neuropharmacology. 2014;37(1):26–30.

**'Ecopipam Treatment of Tourette's Syndrome in Subjects 7-17 Years (PSY302)',** double-blind, randomized, placebo-controlled crossover study conducted to assess the efficacy and safety of ecopipam in children with Tourette's Syndrome.

**Ecopipam is a first-in-class drug that selectively blocks the actions of the Dopamine "D1 receptors."**

Gilbert DL, Murphy TK, Jankovic J, Budman CL, Black KJ, Kurlan RM, Coffman KA, McCracken JT, Juncos J, Grant JE, Chipkin RE. **Ecopipam, a D1 receptor antagonist, for treatment of tourette syndrome in children**: A randomized, placebo-controlled crossover study. Mov Disord. 2018 Aug;33(8):1272-1280.

Relative to changes in placebo, **reduction in total tic score** was greater for ecopipam **at 16 days** (mean difference, -3.7; 95% CI, -6.5 to -0.9; P = 0.011) and 30 days (mean difference, -3.2; 95% CI, -6.1 to -0.3; P = 0.033).

There were no weight gain, drug-induced dyskinesias, or changes in laboratory tests, electrocardiograms, vital signs, or comorbid symptoms. Dropout rate was 5% (2 of 40). **Adverse events reported for both treatments were rated predominantly mild to moderate,** with only 5 rated severe (2 for ecopipam and 3 for placebo).

**Tetrabenazine** depletes presynaptic dopamine and serotonin stores and blocks postsynaptic dopamine receptors.

effective in a wide range of hyperkinetic movement disorders and in TD

Kenney CJ, Hunter CB, Mejia NI, Jankovic J. Tetrabenazine in the treatment of Tourette syndrome. Journal of Pediatric Neurology. 2007;5(1):9–13.

Porta M, Sassi M, Cavallazzi M, Fornari M, Brambilla A, Servello D. Tourette's syndrome and role of tetrabenazine:
review and personal experience. Clin Drug Investig. 2008;28(7):443–459. 286. Anca MH, Giladi N, Korczyn AD. Ropinirole in Gilles de la Tourette syndrome. Neurology.

patients with TS (n = 77; mean age ≈15 years) showed that 2 years' treatment with tetrabenazine resulted in an improvement in functioning and TS-related symptoms in over 80% of patients

Jankovic J, Coffey B, Claassen DO, Jimenez-Shahed J, Gertz BJ, Garofalo EA, Stamler DA, Wieman M, Savola JM, Gordon MF, Alexander J, Barkay H, Harary E. **Safety and Efficacy of Flexible-Dose Deutetrabenazine in Children and Adolescents With Tourette Syndrome: A Randomized Clinical Trial.** JAMA Netw Open. 2021 Oct 1;4(10):e2128204.

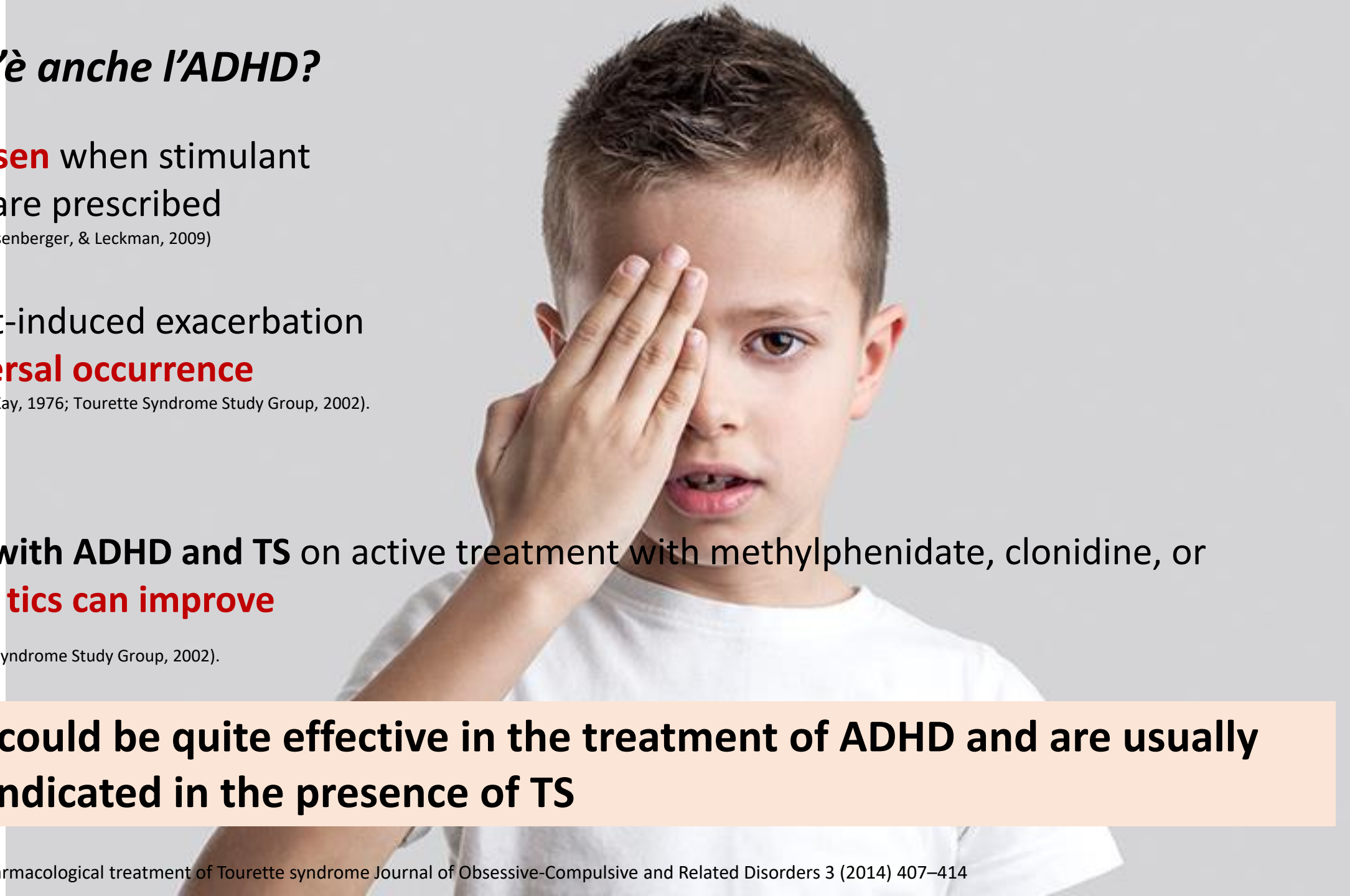
At week 12, the difference in YGTSS-TTS score **was not significant between deutetrabenazine and placebo** (least squares mean difference, -0.7; 95% CI, -4.1 to 2.8; P = .69; Cohen d, -0.07). There were no nominally significant differences between groups for key secondary end points.

Treatment-emergent adverse events were reported for 38 patients (66%) and 33 patients (56%) receiving deutetrabenazine and placebo, respectively, and were generally mild or moderate.

# *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

**dysregulated dopaminergic system**

**dopamine antagonists, or synthesis blockers or depletion drugs**

**Improvements**

**dopaminergic stimulants**

**Exacerbation**

***Non solo….***

(Singer, 2010)

# ADHD is the most common condition associated with TS, with a comorbidity of **60–80 %** between the two entities

Robertson MM, Eapen V, Cavanna AE (2009) The international prevalence, epidemiology, and clinical phenomenology of Tourette syndrome: a cross cultural perspective. J PsychosomRes 67:475–83
Rizzo R, GulisanoM, Calì PV, Curatolo P (2012) Long term clinical course of Tourette syndrome. Brain Dev 34(8):667–73. doi:10. 1016/j.braindev.2011.11.006

# children with ADHD have an increased risk to develop tic disorder in their early school years

Steinhausen HC, Nøvik TS, Baldursson G, Curatolo P, Lorenzo MJ, Rodrigues Pereira R, Ralston SJ, Rothenberger A, ADORE Study Group (2006) Co-existing psychiatric problems in ADHD in the ADORE cohort. Eur Child Adolesc Psychiatry 15(Suppl 1):I25–9

**Table 1** Pre-perinatal risk factors implicated in the pathogenesis of TS and ADHD

| Pre-perinatal risk factors | TS | ADHD | Ref. |
|---|---|---|---|
| Alcohol during pregnancy | + | + | [78] |
| Smoking during pregnancy | + | + | [9, 53] |
| Prematurity | + | + | [36] |
| Low birth weight | + | + | [41] |

El Malhany N, Gulisano M, Rizzo R, Curatolo P. Tourette syndrome and comorbid ADHD: causes and consequences. Eur J Pediatr. 2015 Mar;174(3):279-88.

**Table 3** Main brain regions implicated in the pathogenesis of TS and ADHD

| Brain areas | TS | ADHD | Ref. |
|---|---|---|---|
| Prefrontal areas | + | + | [19, 29, 56] |
| Inferior frontal gyrus | + | + | [100] |
| Sensorimotor areas | + | + | [19, 29, 55] |
| Anterior cingulated cortex | + | + | [19, 29, 55] |
| Posterior cingulated cortex | + | + | [91] |
| Basal ganglia | +/– | + | [19, 29, 73] |
| Cerebellum | – | + | [29] |

(+) implicated region, (–) not implicated region, (+/–) findings contradictory

**Table 2** Candidate genes implicated in the pathogenesis of TS and ADHD

| Genes | Gene functions | TS | ADHD | Ref. |
|---|---|---|---|---|
| Dopamine receptors | | | | |
| DRD1 (dopamine D1 receptor gene) | Encodes the D1 subtype of the dopamine receptor. D1 receptors regulate neuronal growth and development, mediate some behavioral responses, and modulate dopamine receptor D2-mediated events | − | − | [61, 67, 95] |
| DRD3 (dopamine D3 receptor gene) | Encodes the D3 subtype of the dopamine receptor. This receptor is localized to the limbic areas of the brain, which are associated with cognitive, emotional, and endocrine functions | − | − | [61, 67] |
| DRD4 (dopamine D4 receptor gene) | Encodes the D4 subtype of the dopamine receptor. Mutations in this gene have been associated with various behavioral phenotypes, including autonomic nervous system dysfunction, attention deficit/hyperactivity disorder, and the personality trait of novelty seeking | +/− | + | [61, 67, 25] |
| Dopamine-associated transporter | | | | |
| SCL6A3/DAT1 (dopamine-associated transporter) | This gene encodes a dopamine transporter which is a member of the sodium- and chloride-dependent neurotransmitter transporter family. Variation in the number of repeats is associated with idiopathic epilepsy, attention deficit hyperactivity disorder, dependence on alcohol and cocaine, susceptibility to Parkinson disease, and protection against nicotine dependence | +/− | + | [61, 67, 104] |
| Catecholamine transporter | | | | |
| COMT (catechol-*O*-methyltranferase) | Catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. This *O*-methylation results in one of the major degradative pathways of the catecholamine transmitters | − | − | [61, 67, 95] |
| SLC6A2/NET (norepinephrine transporter) | Encodes a member of the sodium: neurotransmitter symporter family. This member is a multi-pass membrane protein, which is responsible for reuptake of norepinephrine into pre-synaptic nerve terminals and is a regulator of norepinephrine homeostasis | − | − | [61, 67, 95] |
| MAOA (monoamine oxidase A) | Is one of two neighboring gene family members that encode mitochondrial enzymes which catalyze the oxidative deamination of amines, such as dopamine, norepinephrine, and serotonin. This gene has also been associated with a variety of other psychiatric disorders, including antisocial behavior | + | − | [61, 67, 95] |

El Malhany N, Gulisano M, Rizzo R, Curatolo P. Tourette syndrome and comorbid ADHD: causes and consequences. Eur J Pediatr. 2015 Mar;174(3):279-88.

**Table 4** Therapeutic options for TS and ADHD

| Therapeutic options | TS | ADHD | Ref. |
|---|---|---|---|
| Non-pharmacological therapeutic options | | | |
| Cognitive-behavior | + | + | [49, 65, 83] |
| Psychoeducational | + | + | [49, 65, 83, 86] |
| rTMS | +/− | +/− | [44, 50, 57, 68, 69] |
| Pharmacological therapeutic options | | | |
| Alpha-2 agonists (clonidine/guanfacine) | + | + | [27, 83] |
| Psychostimulants (methylphenidate) | + | + | [27, 83] |
| Alpha-2 agonists and psychostimulants | + | + | [27, 83] |
| Aripiprazole | + | +/− | [27, 83] |

(+) positive effect of therapeutic option, (+/−) findings contradictory

El Malhany N, Gulisano M, Rizzo R, Curatolo P. Tourette syndrome and comorbid ADHD: causes and consequences. Eur J Pediatr. 2015 Mar;174(3):279-88.

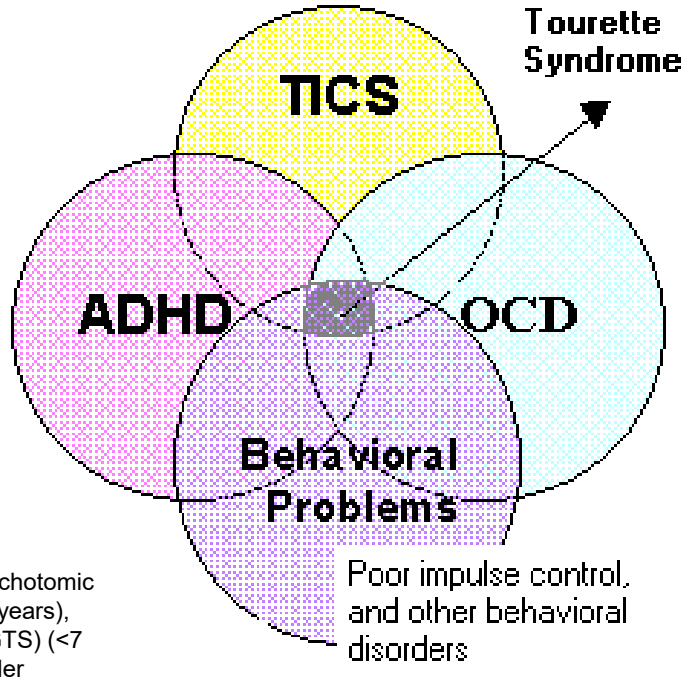
Masi G, Gagliano A, et al,J Child Adolesc Psychopharmacol. 2012 Apr

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

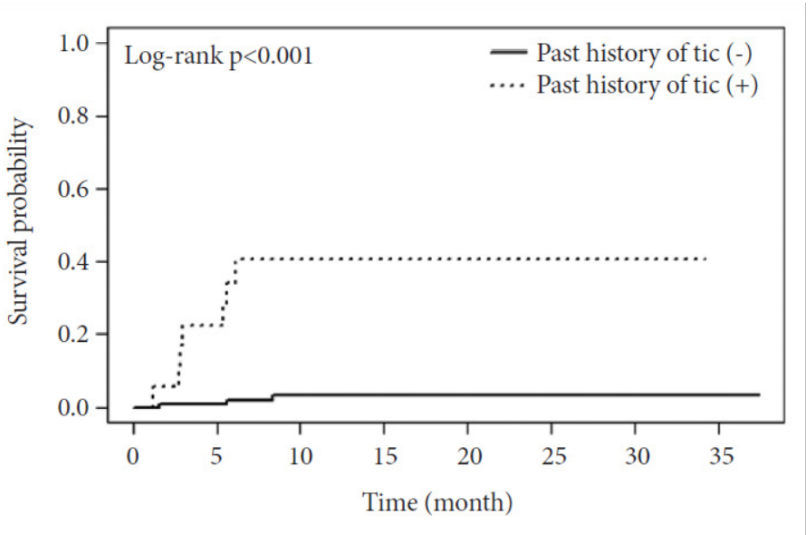
Cha JY, Joung YS, Oh S, Kim BW, Song IM, Ahn BM. Association Between Tic Aggravation and Methylphenidate in Youth With Attention-Deficit/Hyperactivity Disorder. Psychiatry Investig. 2021 Sep;18(9):818-824.

Tic aggravation event rates **without a past history of tics were 2.9%** with MPH treatment in ADHD.

tic aggravation with MPH appeared within approximately eight months but for subjects with a past history of tic, aggravation showed within approximately six months (p<0.001)

| | Hazard ratio (95% CI)* | p-value |
|---|---|---|
| Age | 0.78 (0.66–0.92) | 0.004 |
| Male† | >999.999 | <0.001 |
| Methylphenidate dosage | | |
| Total dosage | 0.94 (0.90–0.99) | 0.014 |
| mg/kg | 0.22 (0.03–1.74) | 0.152 |
| Psychiatric family history | 0.64 (0.08–4.89) | 0.667 |
| Comorbidity | 2.63 (0.75–9.20) | 0.131 |
| Past history of tics | 16.03 (4.20–61.20) | <0.001 |
| FSIQ | 1.01 (0.98–1.04) | 0.444 |
| K-ARS | | |
| Total score | 1.00 (0.95–1.06) | 0.968 |
| Inattention | 0.95 (0.86–1.05) | 0.316 |
| Hyperactivity/impulsivity | 1.07 (0.98–1.17) | 0.114 |

| | Hazard ratio (95% CI)* | p-value |
|---|---|---|
| Age | 0.79 (0.64–0.97) | 0.021 |
| Methylphenidate total dosage | 0.94 (0.89–0.99) | 0.023 |
| Past history of tics | 21.46 (5.02–91.85) | <0.001 |

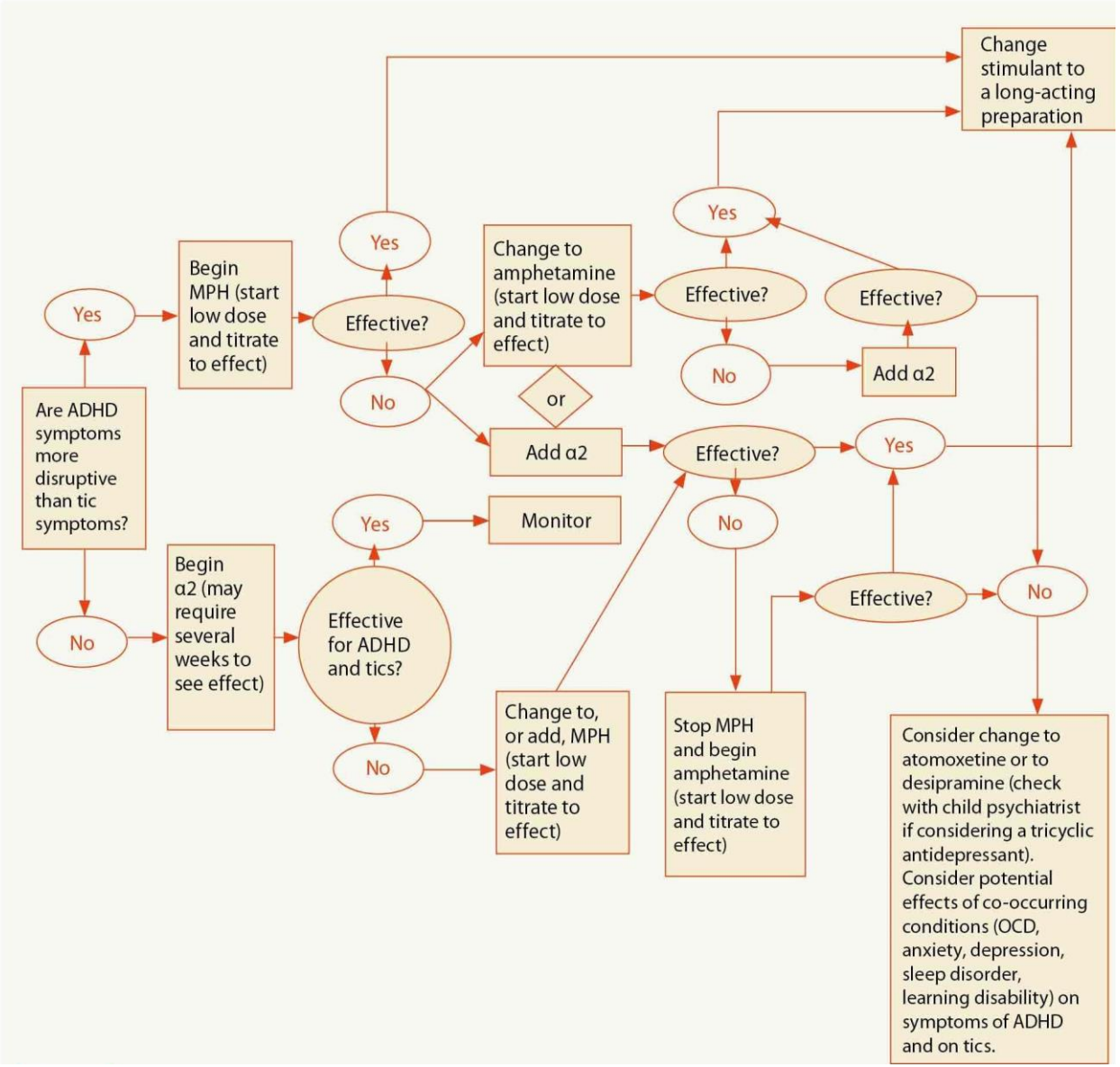



**Past history of tics total MPH dosage and age** were the factors associated with tic aggravation

**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.

## Pay attention  diagnostic misclassification of both inattention and hyperactivity symptoms

The individual with TS, instead of paying attention to what is salient, may attend to attend to internal premonitory tic urges, poorly filtered sensations, obsessions, ruminations, or areas of special interest.




## Treat the tics first and add a stimulant later

treatment with a stimulant may increase the child's internally directed focus (like zombie effect) and, therefore, tics…



# La neuroflogosi






**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.**

**Translational Psychiatry (2022) 12:5 ;**
**https://doi.org/10.1038/s41398-021-01700-4**

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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?

Dominique Endres[1,2✉], Thomas A. Pollak[3], Karl Bechter[4], Dominik Denzel[2], Karoline Pitsch[2], Kathrin Nickel[1,2], Kimon Runge[1,2], Benjamin Pankratz[2], David Klatzmann[5,6], Ryad Tamouza[7], Luc Mallet[7], Marion Leboyer[7], Harald Prüss[8,9], Ulrich Voderholzer[10,11], Janet L. Cunningham[12], ECNP Network Immuno-NeuroPsychiatry, Katharina Domschke[2,13,14], Ludger Tebartz van Elst[1,2,14] and Miriam A. Schiele[2,14]




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**

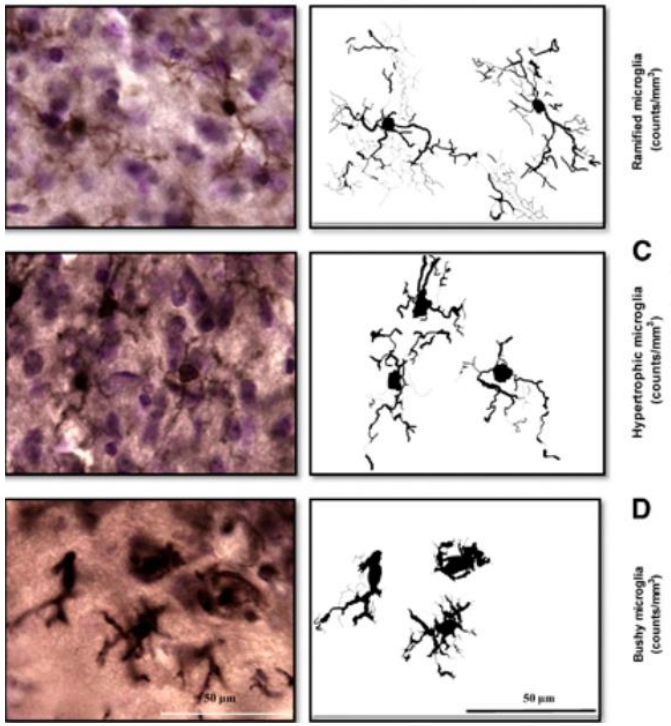
www.thelancet.com/psychiatry Published online October 24, 2019
https://doi.org/10.1016/S2215-0366(19)30290-1

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**


- Trepanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol Psychiatry 2016; 21: 1009–26
- van Kesteren CF, Gremmels H, de Witte LD, et al. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl Psychiatry 2017; 7: e1075.



# early and aggressive immunotherapy improves outcomes

# In contrast, spontaneous clinical improvement is infrequent

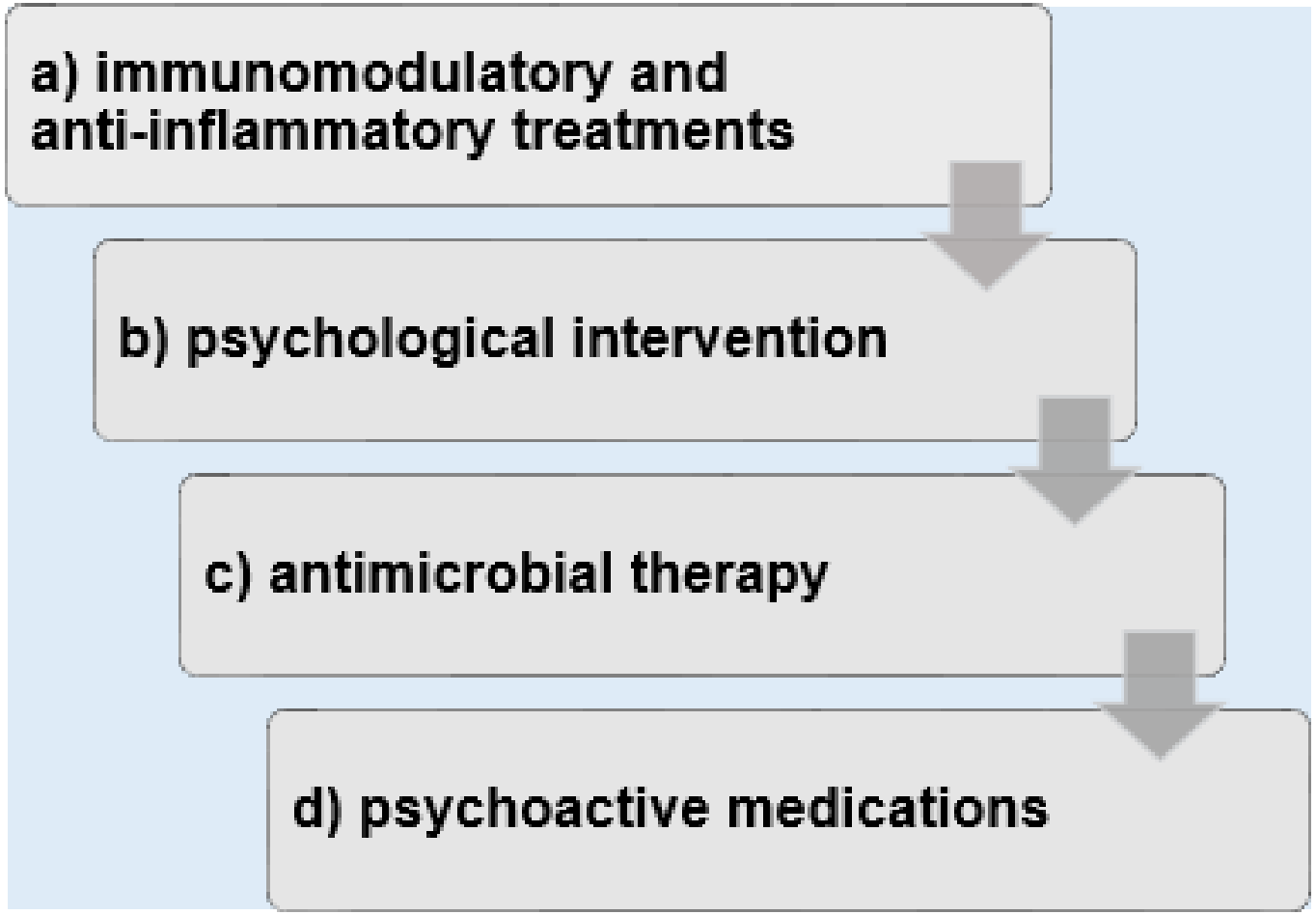

- Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody associated encephalopathy: a potentially immunotherapyresponsive form of limbic encephalitis. Brain 2004;127:701–712.
- Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74.
- Irani SR, Stagg CJ, Schott JM, et al. Faciobrachial dystonic seizures: the influence of immunotherapy on seizure control and prevention of cognitive impairment in a broadening phenotype. Brain 2013;136:3151–3162
- Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–165

**Table 4.** Therapeutic options of autoimmune encephalitis [13,122–124,128].

| Immunomodulator | Dosing Regimen |
|---|---|
| **First line immunomodulators** | |
| 1. Pulsed methylprednisolone | 1000 mg IV daily for 5 consecutive days |
| 2. IVIG | 2 g/kg bodyweight IV infusion typically divided over 5 days |
| 3. Plasmapheresis | 1 session every other day for an average of 5–7 sessions, based on response and tolerance |
| **Second line immunomodulators** | |
| 1. Rituximab | Two 1000 mg doses separated by 2 weeks or weekly 375 mg/m$^2$ infusions for 4 weeks |
| 2. Cyclophosphamide | 750–800 mg/m$^2$ monthly for 3–6 months |
| **Third line immunomodulators** | |
| 1. Tocilizumab | Initially 4 mg/kg, followed by an increase to 8 mg/kg monthly based on clinical response (maximum dose: 800 mg) |
| 2. Intrathecal methotrexate | 10–12 mg weekly for 3–4 weeks |
| **Maintenance therapy** | |
| 1. IVIG | (Doses, frequency, and duration of treatment vary based on the symptom's severity, relapse risk, and tolerance) |
| 2. Pulsed methylprednisolone | |
| 3. Oral prednisone | |
| 4. Azathioprine | |
| 5. Mycophenolate | |


- Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013; 12: 157-65
- Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother 2015; 15: 1391-419.
- Pham HP, Daniel-Johnson JA, Stotler BA, et al. Therapeutic plasma exchange for the treatment of anti-NMDA receptor encephalitis. J Clin Apher 2011;26:320–325.
- Ehrlich S, Fassbender CM, Blaes C, et al. Therapeutic apheresis for autoimmune encephalitis: a nationwide data collection [in German]. Nervenarzt 2013;84:498–507.

**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

***Quale classe di farmaci per Francesco……?***

Dice di sentirsi meglio se si fa le canne

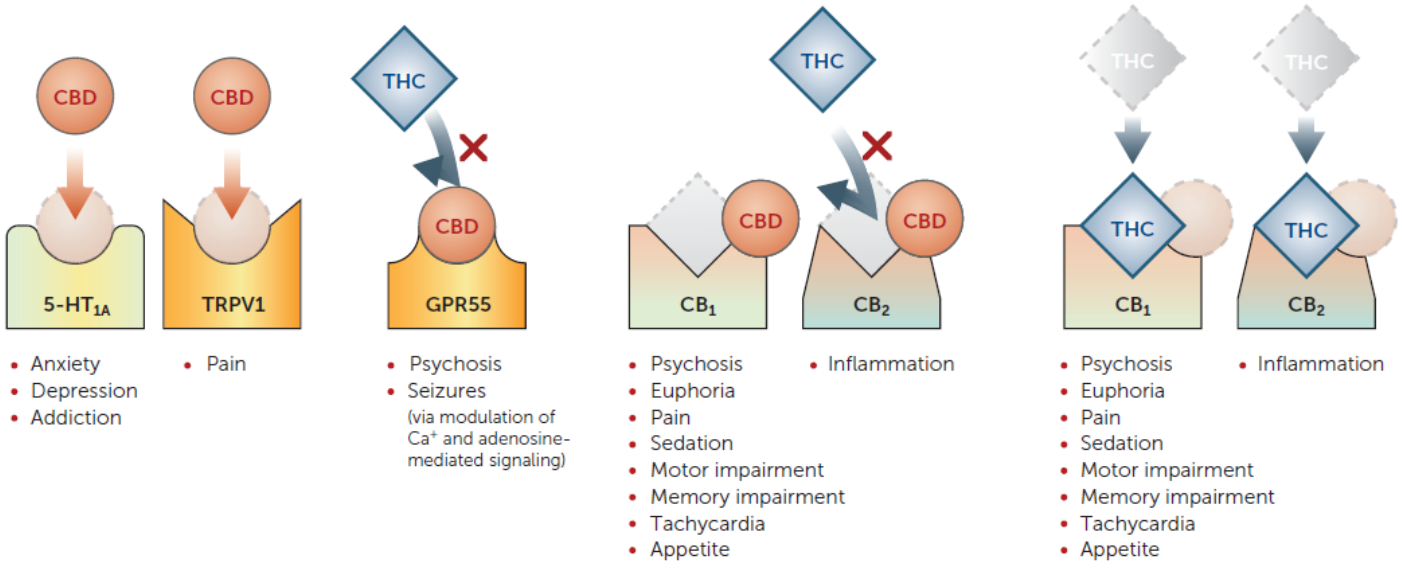


Am J Psychiatry 2022; 179:98–109; doi: 10.1176/appi.ajp.2021.21030320

# 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

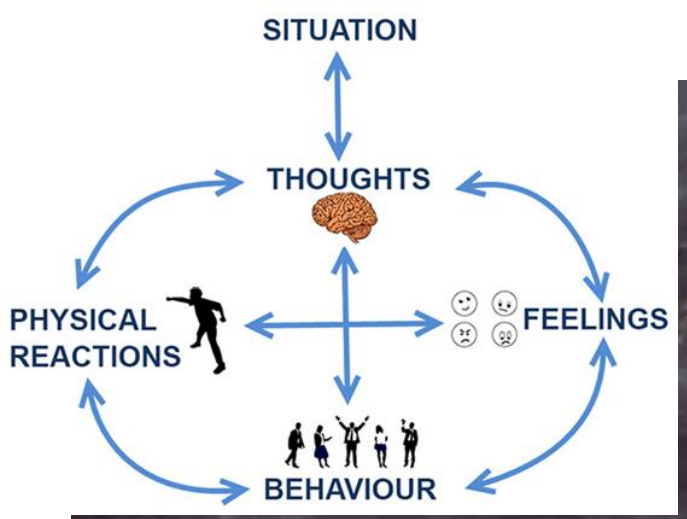
Watkins PB, Church RJ, Li J, Knappertz V: Cannabidiol and abnormal liver chemistries in healthy adults: results of a phase I clinical trial. Clinical Pharm Ther 2021; 109:1224–1231

***Quale classe di farmaci per Francesco……?***

Sostiene che la psicoterapia non gli serve



# *Mai solo farmaci…*












tema attuale della ricerca

# La “fragilità adulta”

Genitori e adulti della comunità educante fragili, confusi, che inviano messaggi contraddittori….

modelli culturali che permeano gli stili educativi, tipici delle società occidentali

**Disorientamento** dei bambini e degli adolescenti per assenza di modelli e di punti di riferimento solidi



VIEWPOINT

# Addressing the Mental Health Crisis in Youth—Sick Individuals or Sick Societies?

Published Online: June 21, 2023. doi:10.1001/jamapsychiatry.2023.1298

In addition to an increase in anxiety and depression symptoms, there has been a **drastic increase in the suicide** rate among US youth, with an increase of **57% for those aged 10 to 24** years from 2007 to 2018.

Curtin SC. State suicide rates among adolescents and young adults aged 10-24: United States, 2000-2018. Natl Vital Stat Rep. 2020;69(11):1-10.

Enhanced awareness of social determinants of mental health

Substantial increases in normal distress at the population level would also likely accompany increases in states of psychopathology…

clinical interventions could have a limited role to play in addressing problems that are primarily consequences of a sick society…

…but

…the fact that **social forces have contributed to distress and suicidality among youth** neither takes away the urgency of clinical care nor eliminates the importance of social reform.

**Figure A.7.2 General approach to pharmacotherapy in child psychiatry**

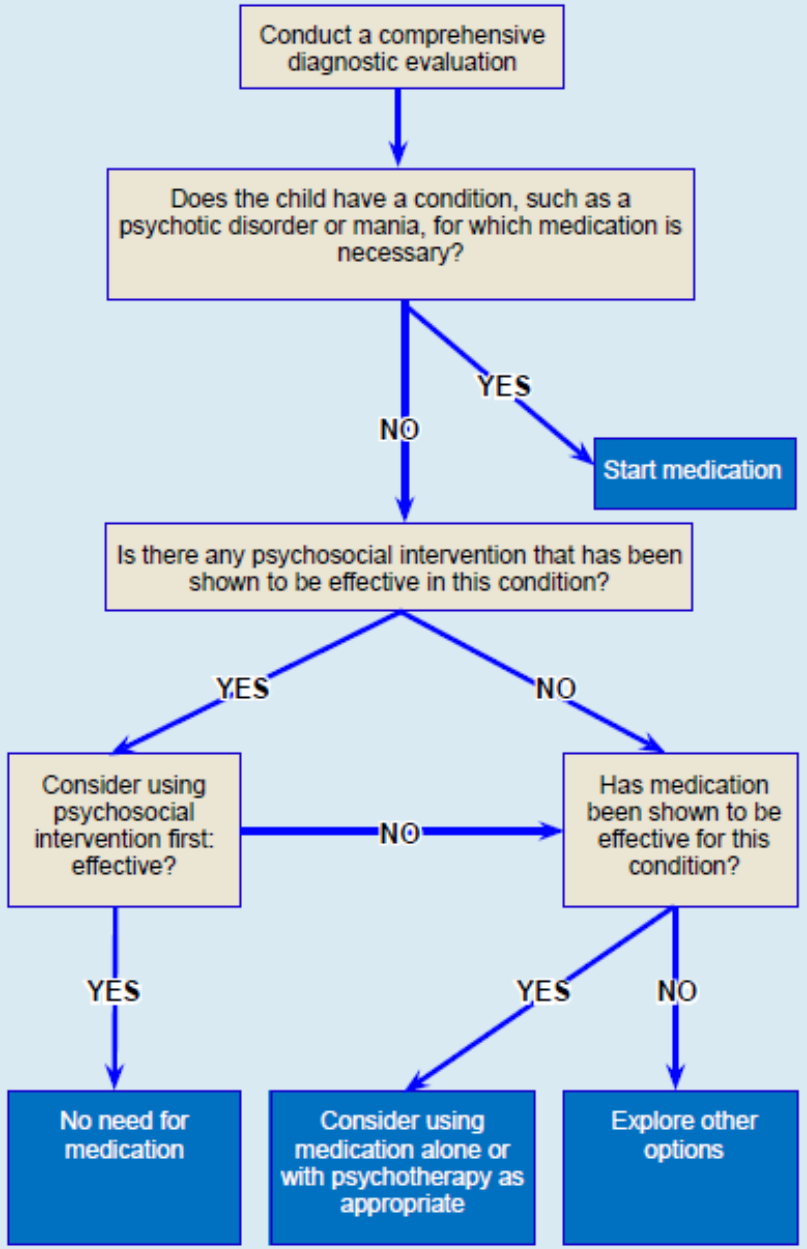



**Table A.7.7 Key steps in implementing pharmacotherapy in child and adolescent psychiatry**

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**

***Quale classe di farmaci per Francesco……?***



tra 10 giorni farà 18 anni
ma non vuole festeggiare…

# Transition: la terapia psicofarmacologica

# **i 10 comandamenti**



1. Non avrai principio più importante di: “primum non nocere”
2. Il calcolo del rapporto costo/beneficio deve sempre dare un numero inferiore a 1
3. Se c’è stato un disturbo del neurosviluppo, tienilo in considerazione perché non è sparito
4. La monoterapia è la regola, la politerapia l’eccezione
5. I farmaci stimolanti sono la prima scelta, le benzodiazepine l’ultima
6. Ricorda che il Carbolithium è spesso la prima scelta e che gli antiepilettici sono soprattutto antiepilettici
7. A prescindere dalla “generazione” (I° o II°), ricorda che gli antipsicotici sono sempre D2 bloccanti
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



*“It is easier to build a strong child than to repair broken men”*

***Frederick Douglass***

# Normative legali



# USO OFF-LABEL IN ETA' PEDIATRICA

Nella Comunità Europea dal **50 al 90%** dei farmaci utilizzati in età evolutiva nei vari ambiti della pediatria non sono stati testati in tale fascia di età, e sono usati off-label.

Tale situazioni è trasversale nelle varie aree pediatriche, inclusa la psichiatria infantile.

**Riluttanza dell'industria ad effettuare studi pediatrici**: mercato ridotto, studi complessi per metodologia, necessità di lunghi follow-up (effetti sullo sviluppo).

# Legge n. 648 del 23.12.1996

L'articolo 1, comma 4 della Legge 648 del 23.12.1996 prevede che, "qualora non esista valida alternativa terapeutica, sono erogabili a totale **carico del Servizio Sanitario Nazionale**, a partire dal 1 gennaio 1997, i medicinali innovativi la cui commercializzazione è autorizzata in altri Stati ma non sul territorio nazionale, i medicinali non ancora autorizzati ma sottoposti a sperimentazione clinica e i medicinali da impiegare per un'indicazione terapeutica diversa da quella autorizzata, inseriti in apposito elenco predisposto e periodicamente aggiornato dall'Agenzia Italiana del Farmaco (AIFA)".

In altri termini il medico può, in singoli casi, utilizzare un farmaco rispettando i seguenti requisiti:

- Mancanza di valida alternativa terapeutica da dati documentabili
- Consenso informato del paziente
- Assunzione di responsabilità del medico
- Pubblicazioni scientifiche accreditate in campo internazionale
- Non disponibilità alla cessione per "uso compassionevole" da parte della ditta produttrice

# Legge n. 94 del 08.04.98 (Legge Di Bella)

- L'articolo 3 comma 2 della L. 94/1998 dispone che **in singoli casi** il medico possa, **sotto sua diretta responsabilità** e **previa acquisizione del consenso informato** del paziente, impiegare un medicinale prodotto industrialmente per una indicazione, via o modalità di somministrazione diversa da quella autorizzata, qualora il medico stesso **ritenga su basi documentabili,** che un paziente non possa essere trattato con medicinali già approvati
- che tale impiego sia conforme a **lavori apparsi su pubblicazioni scientifiche accreditate in campo internazionale**
- **Questo tipo di prescrizione è sempre a totale carico del cittadino**

# CODICE DEONTOLOGICO

- Il medico agisce secondo il principio di efficacia delle cure nel rispetto dell'autonomia della persona tenendo conto dell'uso appropriato delle risorse. (art. 6)

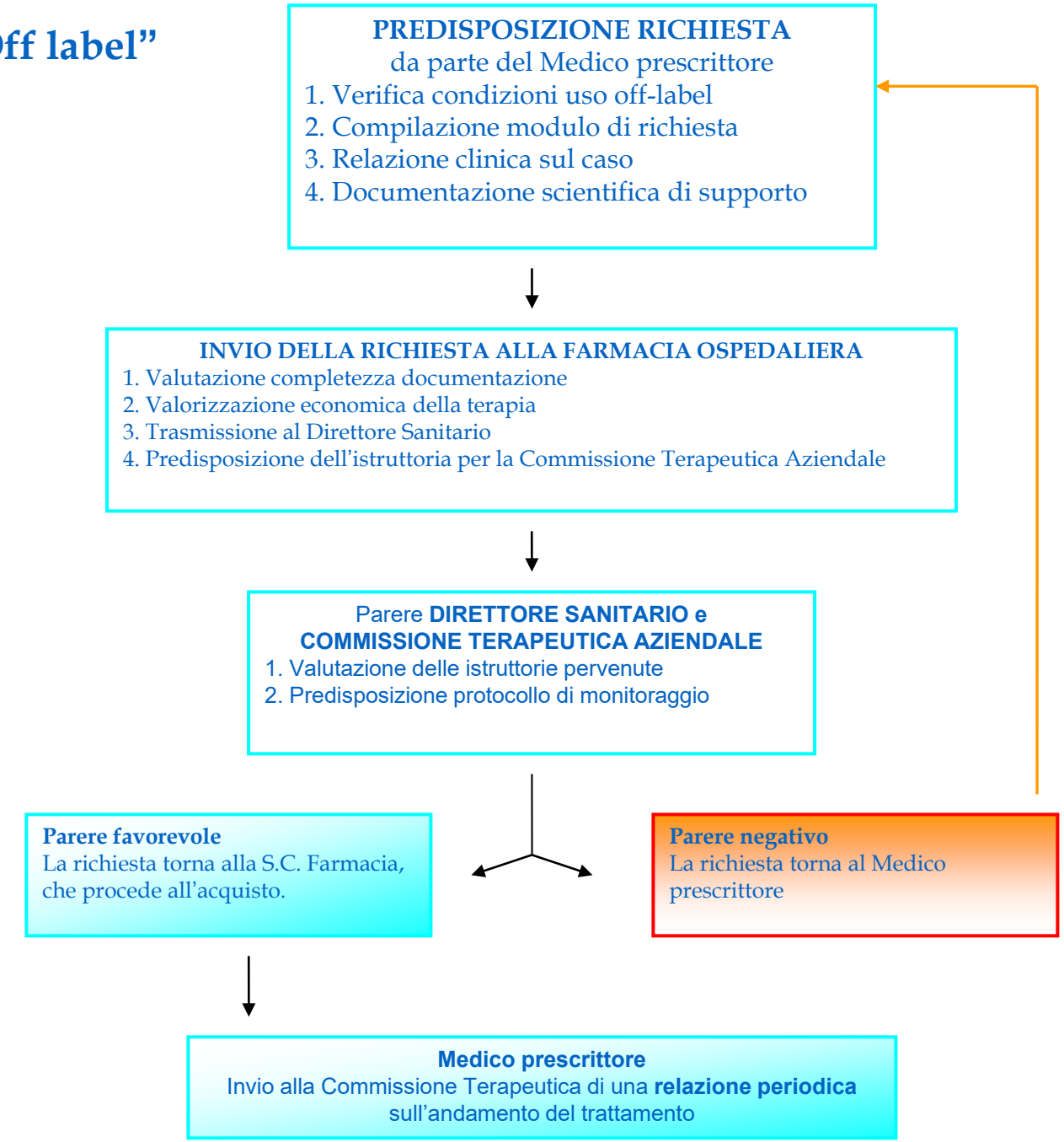
- Le prescrizioni e i trattamenti devono essere ispirati ad aggiornate e sperimentate acquisizioni scientifiche tenuto conto dell'uso appropriato delle risorse, sempre perseguendo il beneficio del paziente secondo criteri di equità. (art. 13)

- Le prescrizioni di farmaci, sia per indicazioni non previste dalla scheda tecnica sia non ancora autorizzati al commercio, è consentita purchè la loro efficacia e tollerabilità sia scientificamente documentata. In tali casi, acquisito il consenso scritto del paziente debitamente informato, il medico si assume la responsabilità della cura ed è tenuto a monitorarne gli effetti. (art. 13)

# Modello di Consenso Informato

- Generalita' del paziente;
- nome e qualifica del medico prescrittore;
- recapito cui fare riferimento in caso di emergenza;
- impegno da parte del medico ad informare il paziente di eventuali nuovi dati relativi alla terapia;
- nome del medicinale o specialità medicinale, modalita' di somministrazione,
- dosaggio, durata del trattamento;
- trattasi di medicinale autorizzato alla commercializzazione in Italia per indicazione terapeutica diversa;
- la incompletezza dei dati relativi alla sicurezza ed efficacia del medicinale per l'indicazione terapeutica corrispondente alla patologia del paziente;
- i potenziali benefici ed i rischi prevedibili.

# Percorso richiesta uso “Off label”



# 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.**