Milano, 10 novembre 2015

RICERCA-AZIONE IN NEUROPSICHIATRIA DELL'ETÀ EVOLUTIVA (IL CASO DELL'ADHD)

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ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

Azienda Ospedaliera SPEDALI CIVILI BRESCIA

Università degli Studi di Cagliari

Percorsi Diagnostico-terapeutici condivisi per l'ADHD
Una risposta alle criticità e ai bisogni inevasi
Milano, 9-10 Novembre 2015

Ricerca-Azione in Neuropsichiatria dell'età evolutiva (il caso dell'ADHD)

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- Vifor
- Roche
- EU 7 Framework Program (PERS, STOP, ADDUCE, MATRICS)
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- Assessorato Sanità Regione Sardegna

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Giunti.OS, Oxford University Press

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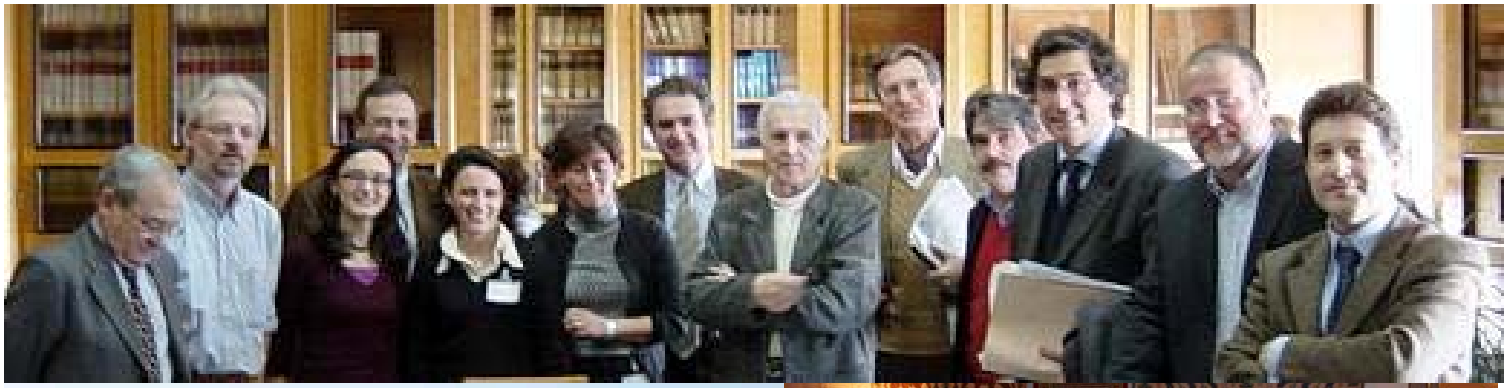
Member of Data Safety Monitory Boards

Otsuka, Lundbek,



2003

2011

Outline

- L'ADHD è un disturbo eterogeneo le cui presentazione clinica si modifica nel corso della vita*: interventi terapeutici differenziati?*
- Diversa e specifica efficacia delle terapie farmacologiche rispetto agli interventi non-farmacologici: *chi valuta che cosa?*
- Sicurezza dei farmaci per l'ADHD: *quale rapporto costo-benefici?*
- *Take home message*

L'ADHD è un disturbo eterogeneo

Clinical Presentations

- *Inattentive*
- *Hyperactive/Impulsive*
- *Combined*

Neuropsychology Models

Executive Dysfunction

Motivational Dysfunction

Time percetion

Delay Aversion

Response Variability

Speed in Cognition & Arausal

DSM-5 ADHD

vs ***ICD-10 (11?) Hyperkinetic Dis***.

Comorbidities

Developmental: Specific Learning Disorders

Motor D. (Tics & Tourette S.)

Autism spectrum disorder

Social(Pragmatic) Communication D.

Disruptive behaviours (ODD, CD)

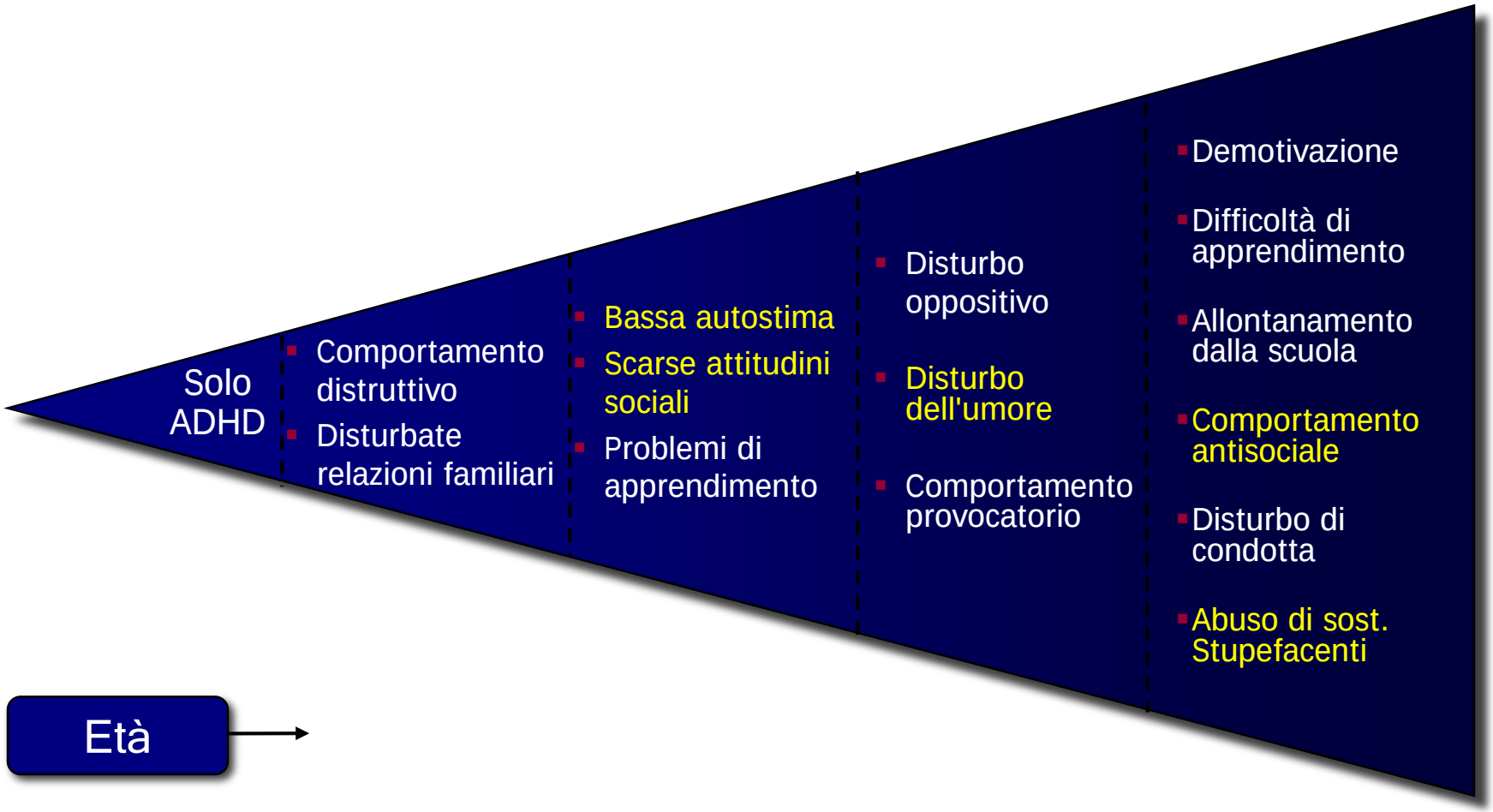
Anxiety

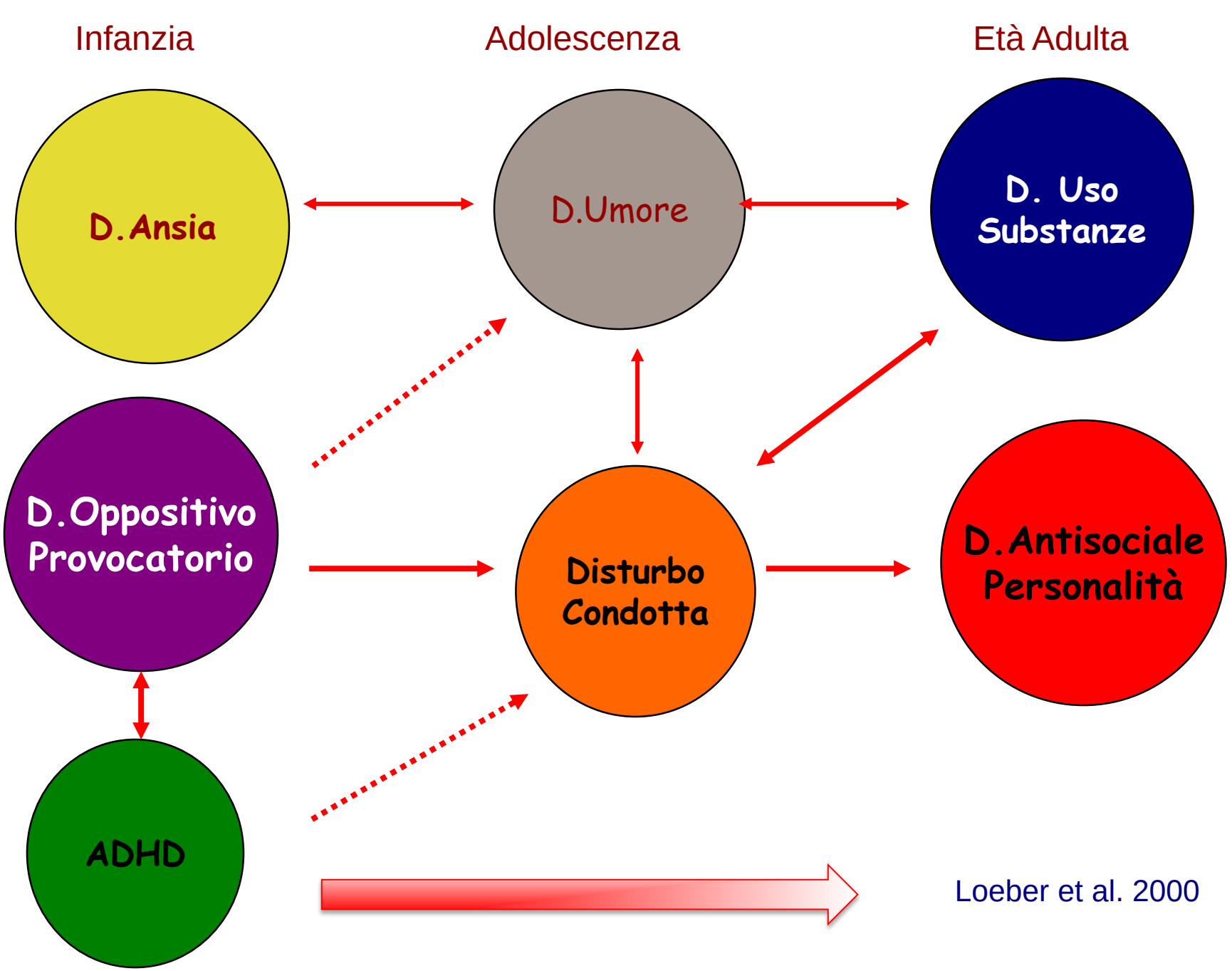
Depression

Dysruptive Mood Disregulation Disorder

Substance abuse

Decorso del Disturbo




Infanzia
Adolescenza
Età Adulta
D.Ansia
D.Umore
D. Uso Substanze
D.Oppositivo Provocatorio
Disturbo Condotta
D.Antisociale Personalità
ADHD
Loeber et al. 2000

Disturbo Oppositivo Provocatorio (DSM 5)

Almeno 4 dei seguenti sintomi (significativamente più frequenti che nei coetanei) negli ultimi 6 mesi

Angry/Irritable Mood

1. Scoppi d'ira (*Loses temper*)
2. Permaloso e infastidito dagli altri.
3. Irritabile e risentito

Defiant/Headstrong Behavior

4. Polemico con gli adulti
5. Sfida o rifiuta attivamente di seguire le indicazioni
6. Disturba volutamente gli altri
7. Scarica sugli altrui i propri errori o responsabilità

Vindictiveness / Hurtfull

8. Dispettoso e vendicativo

Significativa compromissione funzionale (sociale, accademica, lavorativa**)**
Se >18 aa. escludere Dist. Antisociale di Personalita'

Developmental Continuity of Oppositional Defiant Disorder Subdimensions at Ages 8, 10, and 13 Years and Their Distinct Psychiatric Outcomes at Age 16 Years

Yvonne M. Whelan, M.Sc., Argyris Stringaris, M.D., Ph.D., Barbara Maughan, Ph.D., Edward D. Barker, Ph.D.

JAACAP 2013

ALSCP

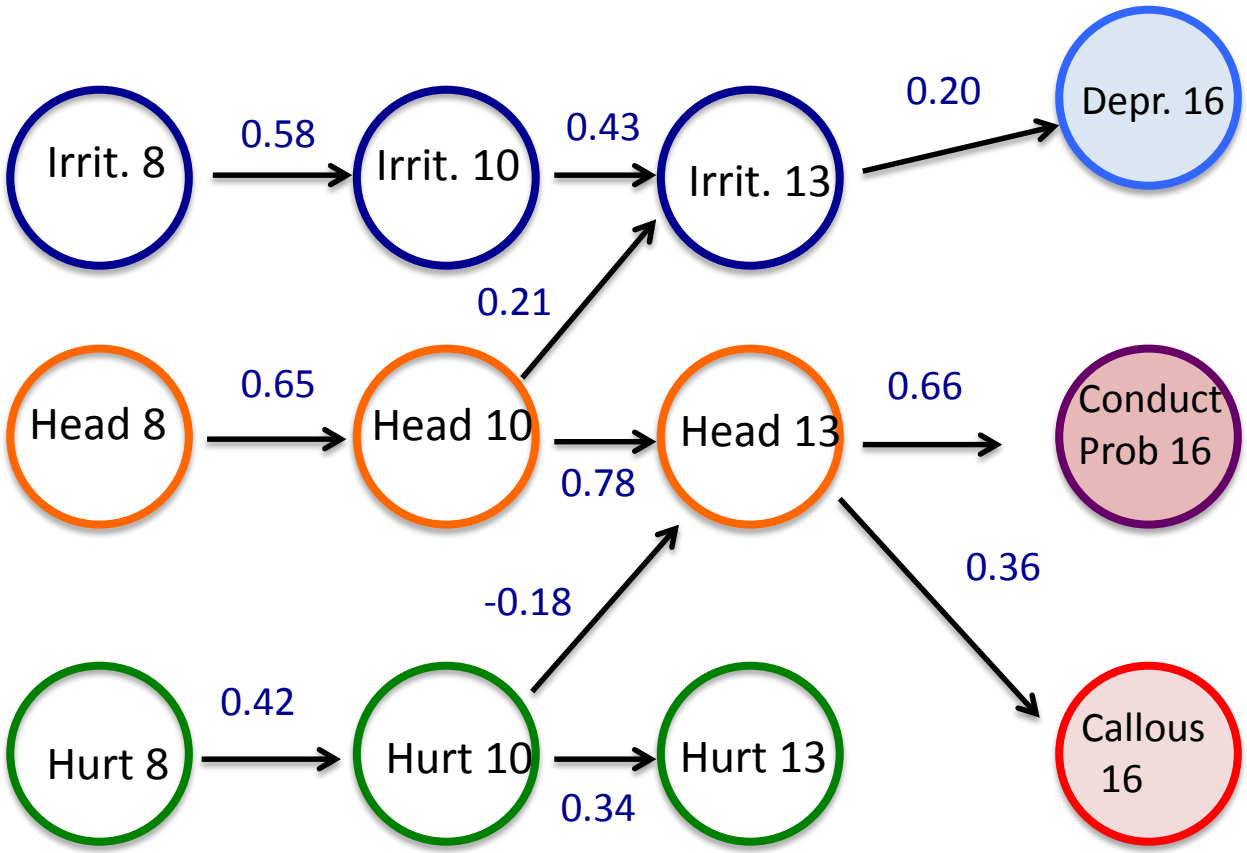
Avon Longitudinal Study of Children and Parents

13867 GRAVIDANZE
April 1991, December 1992
Follow-up 19-22 anni

DAWBA

Development and Well Being Assessment

Parent and teacher rating



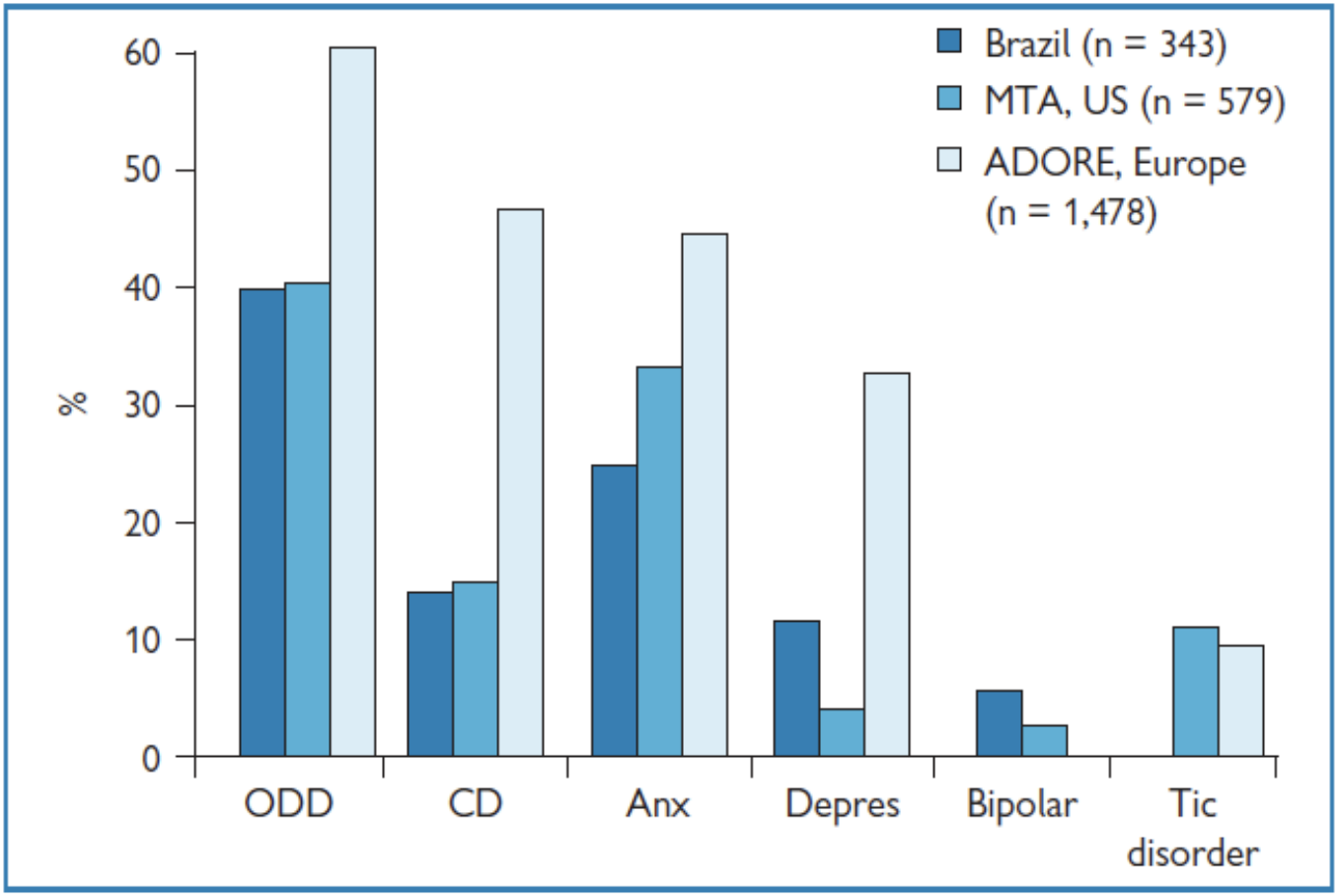
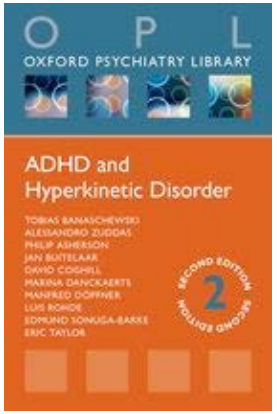


Figure 2.1 ADHD comorbid profile in three studies: The MTA (MTA Cooperative Group, 1999), the ADORE (Steinhausen *et al.*, 2006), and Souza *et al.* (2004; Brazil). Data are presented as percentages. In the Brazilian study, the comorbid profile is described only for one site (Porto Alegre) and no information is reported for tic disorders. In the MTA, only ADHD-combined type is included and several restrictions were applied to enroll patients with severe mood disorders. No information is available for bipolar disorder in the ADORE study. ODD Oppositional defiant disorder; CD conduct disorder; Anx anxiety; Depres depression



Banaschewski, Zuddas et al. 2015

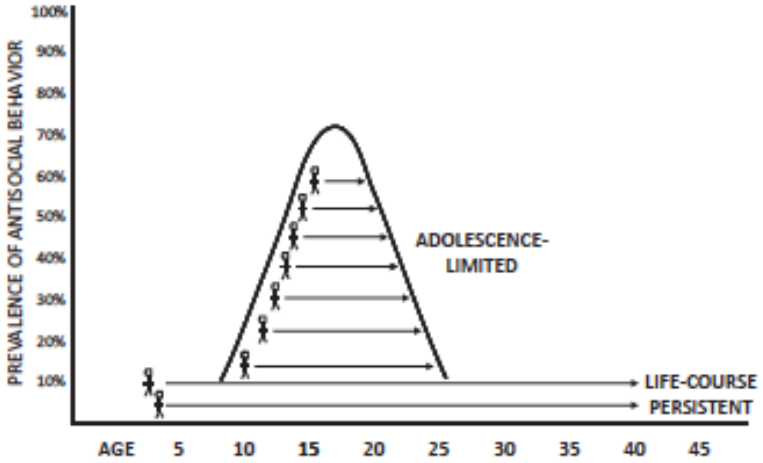
Disturbo di Condotta (DSM 5)

Modalità di comportamento ripetitiva e persistente di violazione di regole/norme appropriate per l'età o dei diritti fondamentali degli altri.

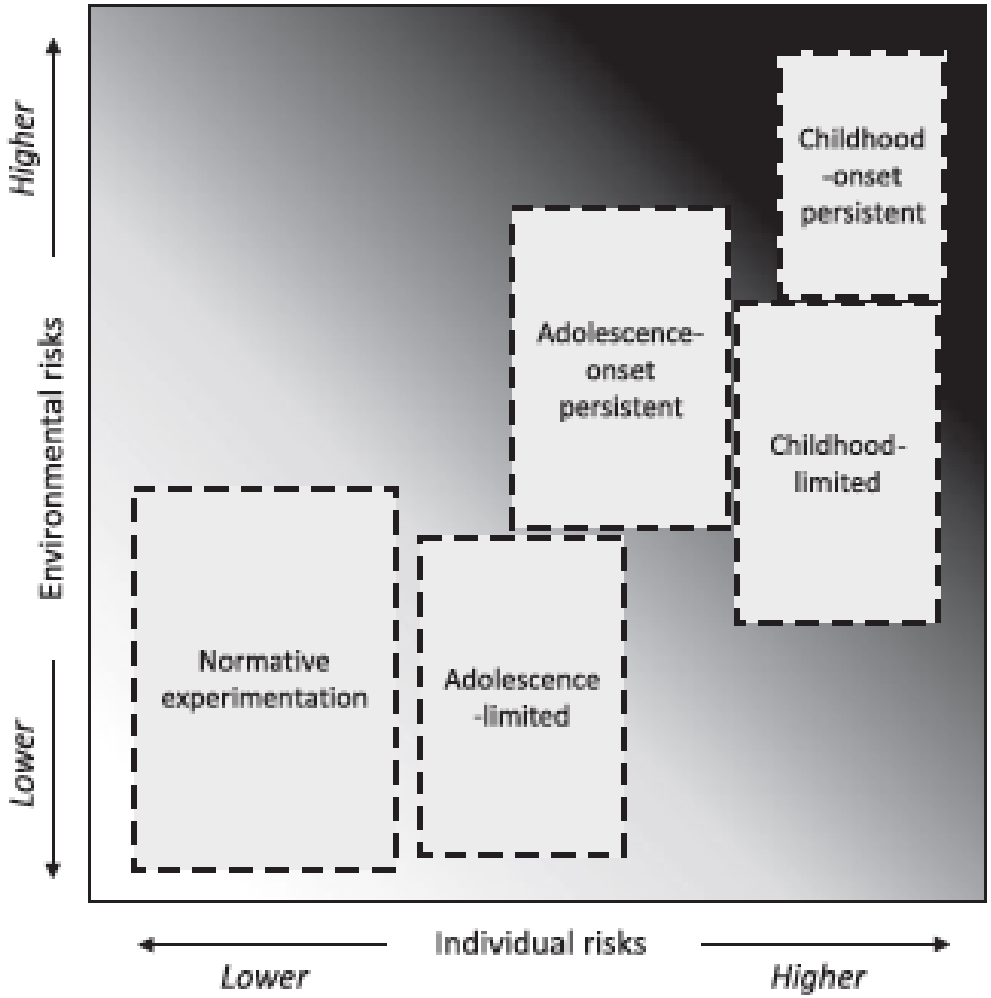
- ***Aggressione ad animali o persone***
- ***Distruzione di proprieta'***
- ***Frode o furto***
- ***Gravi violazioni di regole***

Sottostante disfunzione dell'individuo **(***Wakenfield, AJP 2002***)**

Research Review: Evaluating and reformulating the developmental taxonomic theory of antisocial behaviour

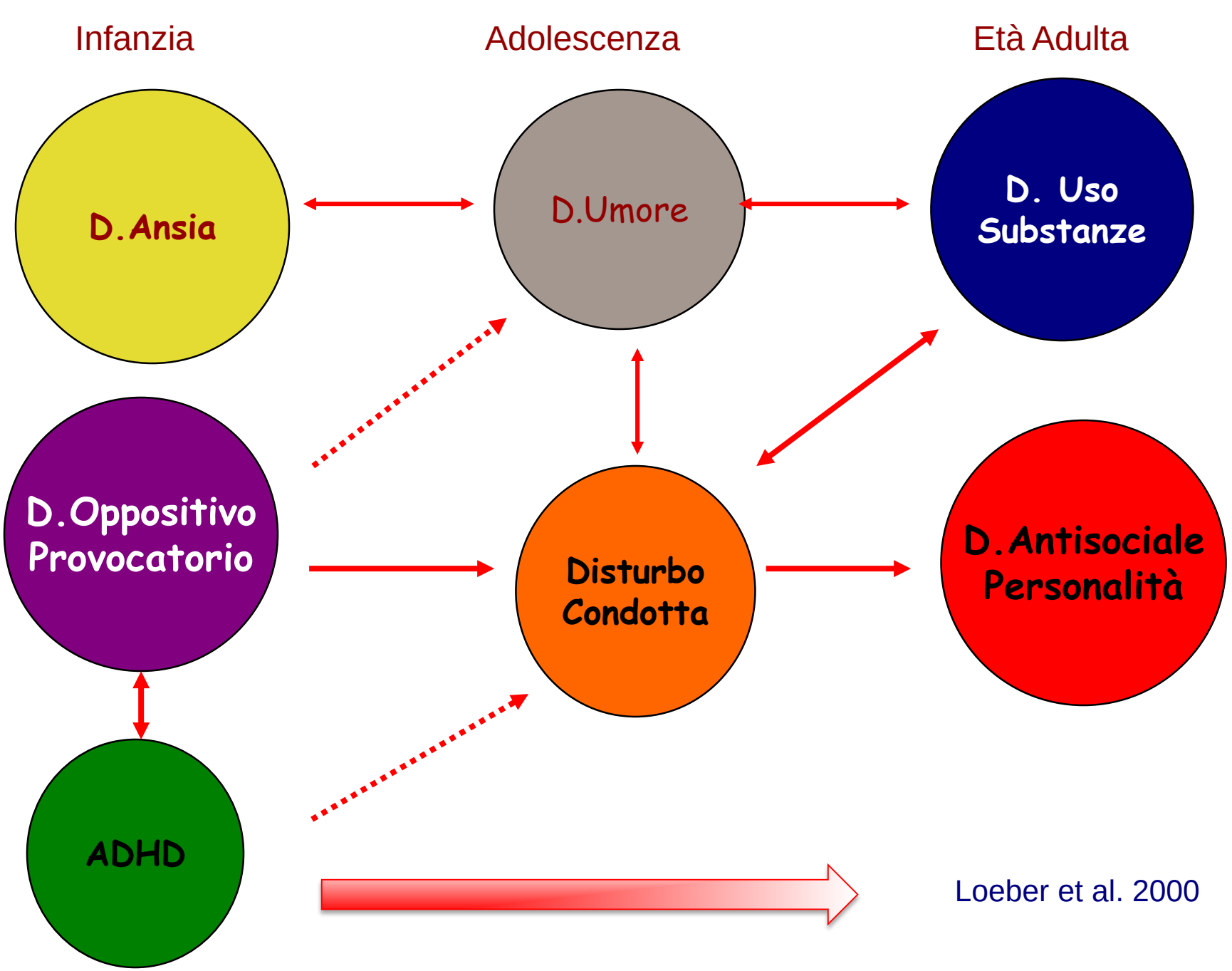


Moffit et al. 1996



Fairchild et al. JCPP 2013

CD occurs mostly in boys but can also present in girls


Infanzia
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D. Uso Substanze
D.Oppositivo Provocatorio
Disturbo Condotta
D.Antisociale Personalità
ADHD
Loeber et al. 2000

Transizione dell'ADHD dall'infanzia all'età adulta

- L'iperattività motoria diminuisce: si può manifestare come **irrequietezza psichica**

- L'inattenzione spesso persiste: si può manifestare come **difficoltà nel portare a termine i compiti** (es.: *rispettare appuntamenti, scadenze o focalizzarsi su una singola attività*).

- Può interferire significativamente con vari aspetti della vita quotidiana.

Volkow & Swanson 2013

ADHD in età adulta:

- La definizione DSM 5 di ADHD si focalizza sul deficit di attenzione, ma le manifestazioni cliniche includono una minore percezione delle gratificazioni con conseguente deficit di motivazione.

- Adulti con ADHD mostrano una ridotta le risposta alle ricompense premi e appaiono meno motivati a impegnarsi ed a portare a termine le attività.

Wolkow & Swanson *NEJM 2013*

Conseguenze dell' ADHD in età adulta

Difficoltà occupazionali e finanziarie

- frequenti cambiamenti di lavoro,
- disoccupazione
- più basso stato socioeconomico

Problemi interpersonali

disadattamento sociale
problemi coniugali

Coesistenti disturbi psichiatrici

depressione e ansia

Aumento del rischio di abuso di sostanze

tabacco , cannabis

Wolkow & Swanson *NEJM 2013*

ADHD in Età adulta

Insegnante di scuola media (31 anni) ha cercato aiuto medico perché stava avendo difficoltà a tenere il passo con i suoi compiti e le responsabilità di lavoro.

I suoi **sintomi primari** sono:

- incapacità di rimanere concentrati e di essere facilmente distratti.
- riferisce di sognare ad occhi aperti con più pensieri contemporaneamente,
- incapacità di completare in tempo i compiti assegnatili
- spesso dimentica di fare le cose al lavoro
- non riesce rimanere fermo neanche durante attività solitarie (ad esempio, guardare un film e la lettura di un libro).

Volkow & Swanson *NEJM 2013*

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ADHD in Età adulta

Insegnante di scuola media (31 anni) ha cercato aiuto medico perché stava avendo difficoltà a tenere il passo con i suoi compiti e le responsabilità di lavoro.

I suoi amici la descrivono come eccessivamente loquace, disorganizzato, impaziente e incurante.

Dall'infanzia, i suoi insegnanti hanno notato che lei era distratta e disordinata e spesso non riusciva portare a termine i compiti a casa.

Era in grado di lavorare abbastanza bene a scuola, nonostante i suoi sintomi, ma più di recente, le sue esigenze di lavoro le apparivano superiori alle sue capacità sua, tanto da considerare la possibilità di licenziarsi.

Volkow & Swanson *NEJM 2013*

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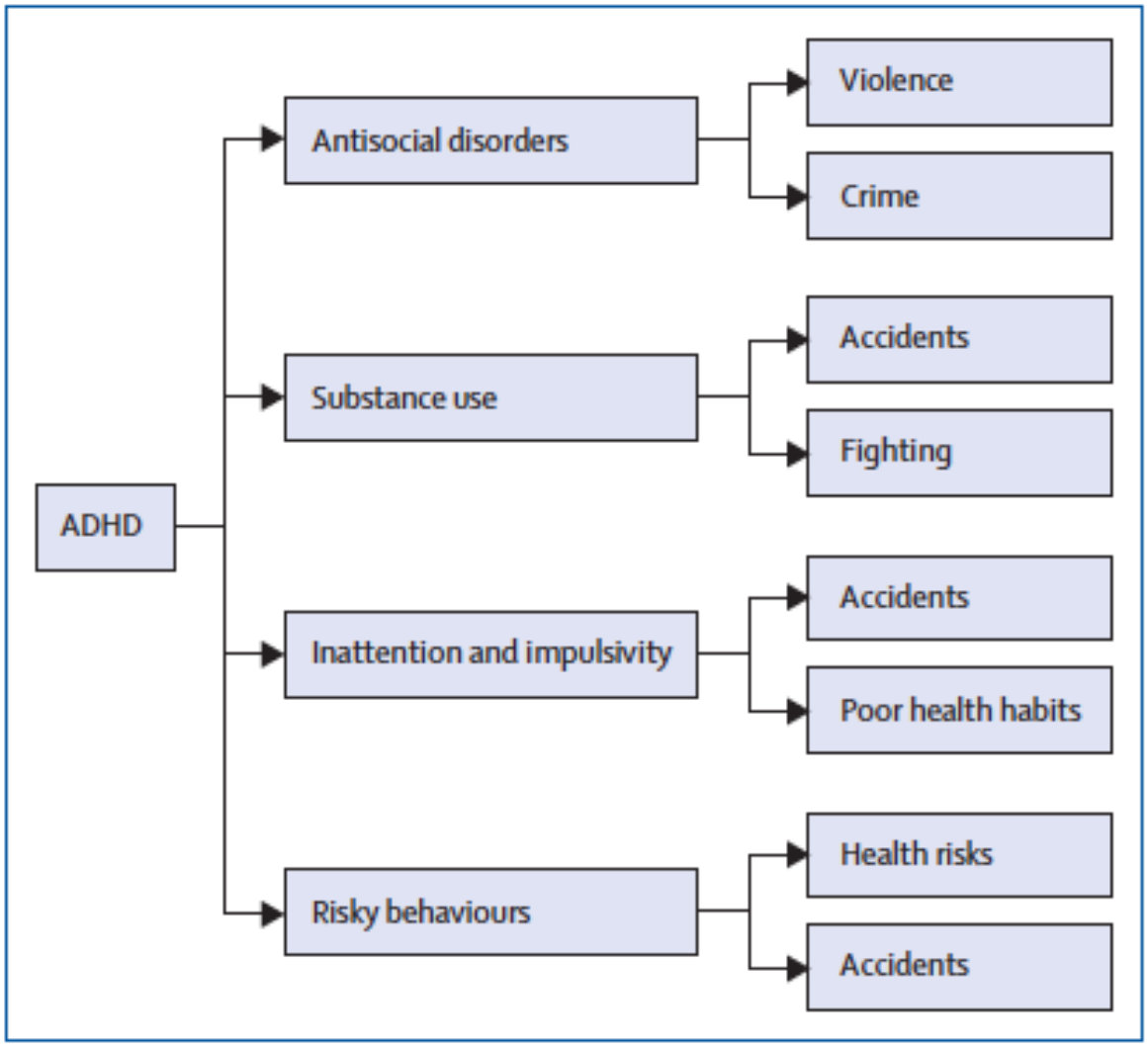
Pathways to preamture death



Faraone, *Lancet* 2015

Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study

Søren Dalsgaard, Søren Dinesen Østergaard, James F Leckman, Preben Bo Mortensen, Marianne Giørtz Pedersen

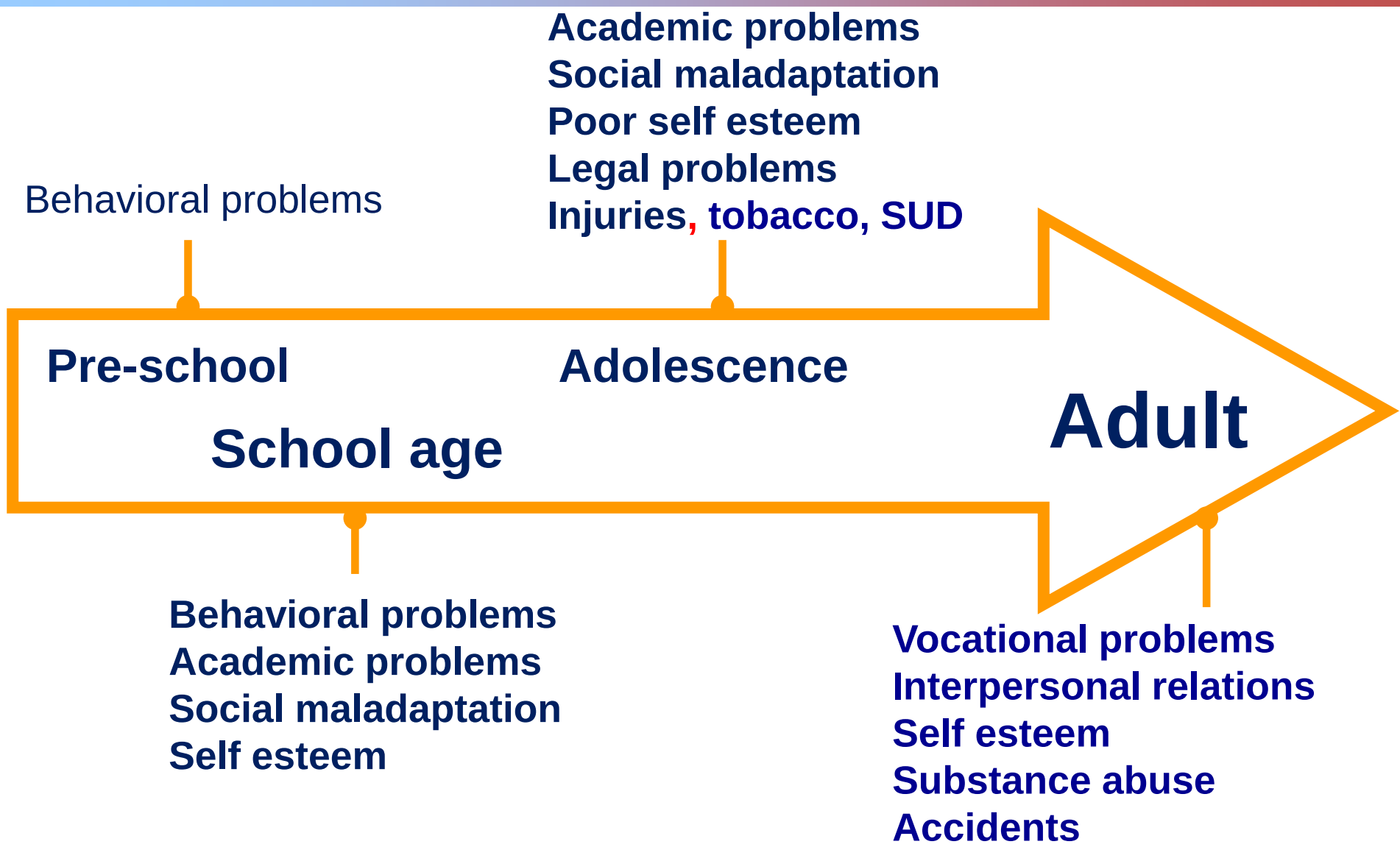
	Number of deaths	Person-years	Mortality rate per 10 000 person-years	Crude model MRR (95% CI)*	Partly adjusted model MRR (95% CI)†	Fully adjusted model MRR (95% CI)‡
Age at first ADHD-diagnosis (years)						
1–5	10	29 944	3·34	2·23 (1·11–3·91)	1·97 (0·99–3·46)	1·86 (0·93–3·27)
6–17	59	136 048	4·34	1·83 (1·40–2·35)	1·63 (1·25–2·09)	1·58 (1·21–2·03)
>17	38	17 057	22·28	5·24 (3·73–7·12)	4·46 (3·18–6·07)	4·25 (3·03–5·78)
No ADHD	5473	24 724 510	2·21	1·00 (reference)	1·00 (reference)	1·00 (reference)
p value§	..	..		p<0·0001	p<0·0001	p<0·0001
Overall cohort	5580	24 907 560	2·24	..	..	..

Cohort consisted of 1·92 million children born in 1981–2011. MRR=mortality rate ratio. ADHD=attention deficit hyperactivity disorder. ..=not applicable. *Crude model adjusted for age, calendar year, and sex. †Partly adjusted model adjusted for age, calendar year, sex, parental history of psychiatric disorders, and maternal and paternal age at time of delivery. ‡Fully adjusted model adjusted for age, calendar year, sex, parental history of psychiatric disorders, maternal and paternal age at time of delivery, parental educational, and parental employment status. §p value measures the overall effect of being diagnosed with ADHD at different ages, compared with individuals without ADHD.

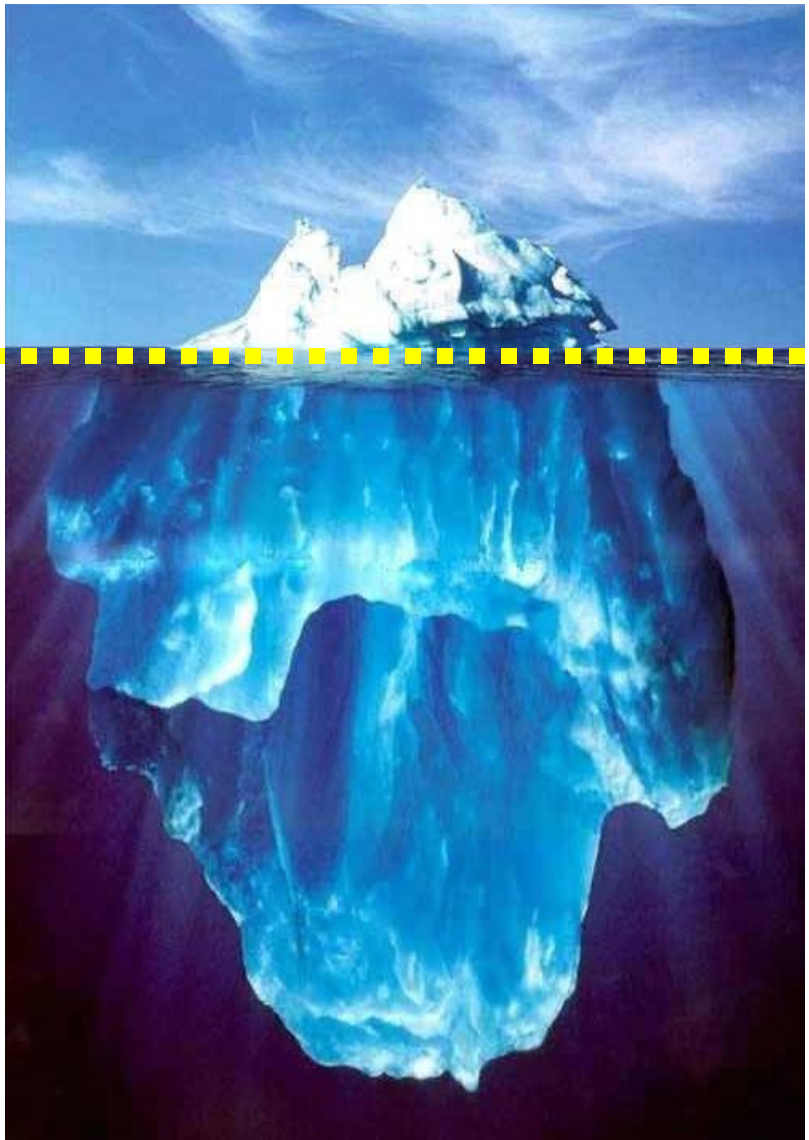
Table 2: **MRR according to age at first diagnosis of ADHD, compared with those without ADHD at same age**

Lancet 2015; 385: 2190–96

ADHD ACROSS LIFE SPAN



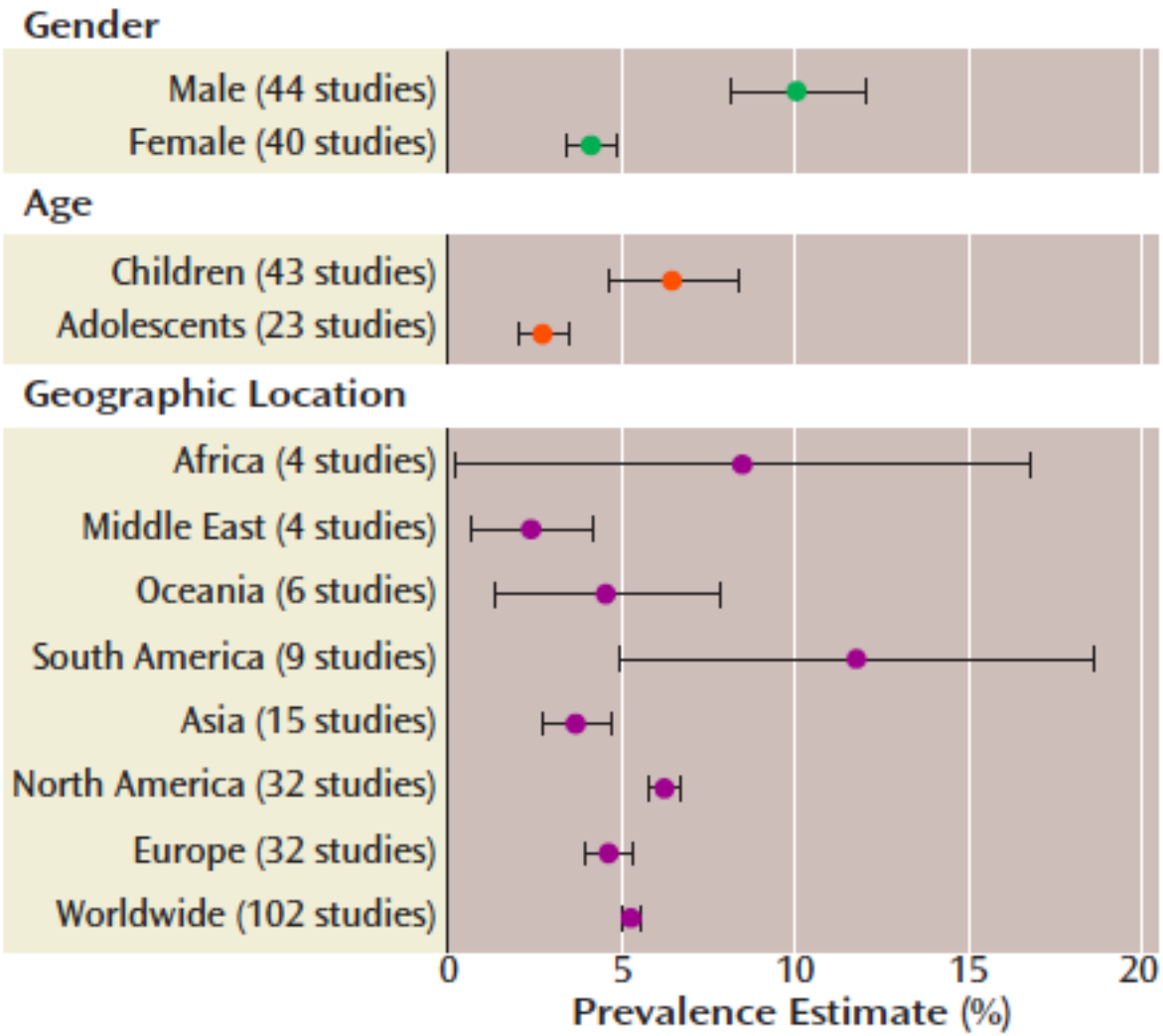
THE HIDDEN DISORDER (in adults…)



Depression
Anxiety
Personality disorder
Drug dependence

ADHD

FIGURE 2. ADHD/HD Pooled Prevalence According to Demographic Characteristics and Geographic Location



Polanczyk et al. *AJP* 2007

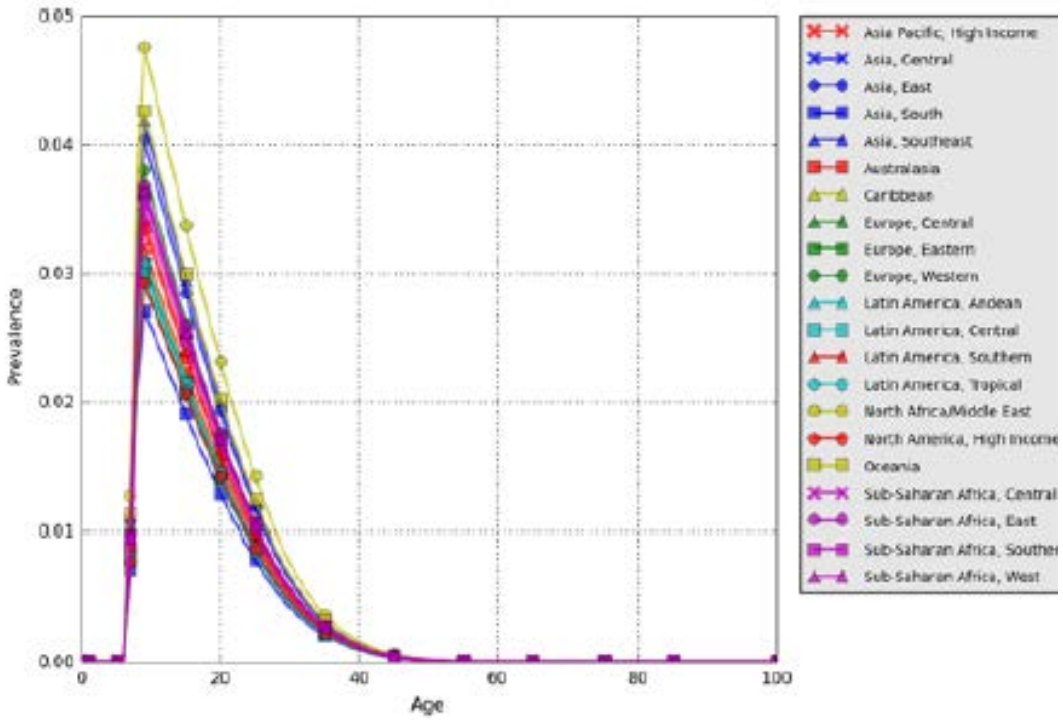
THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

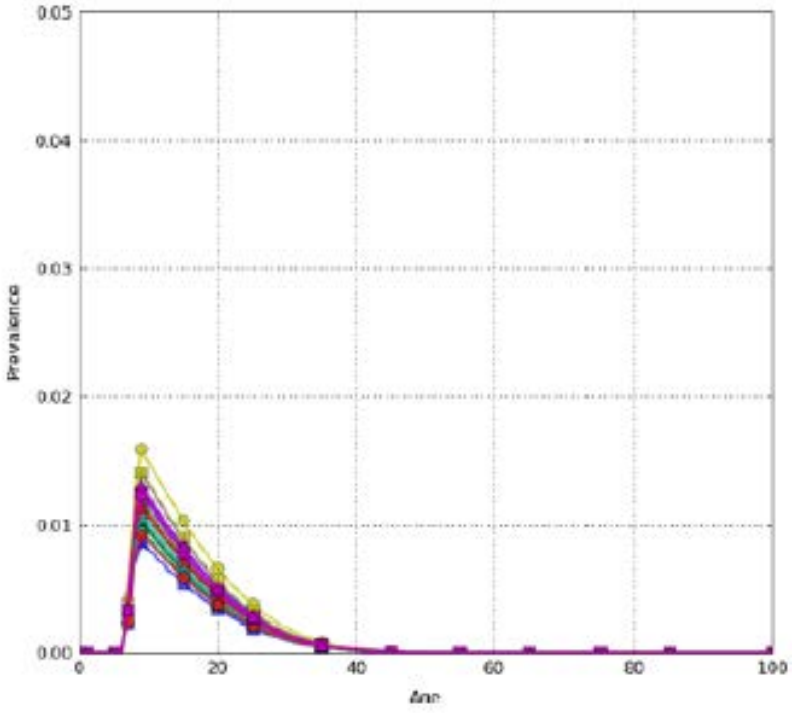
ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH

Journal of Child Psychology and Psychiatry 54:12 (2013), pp 1263–1274 doi:10.1111/jcpp.12144

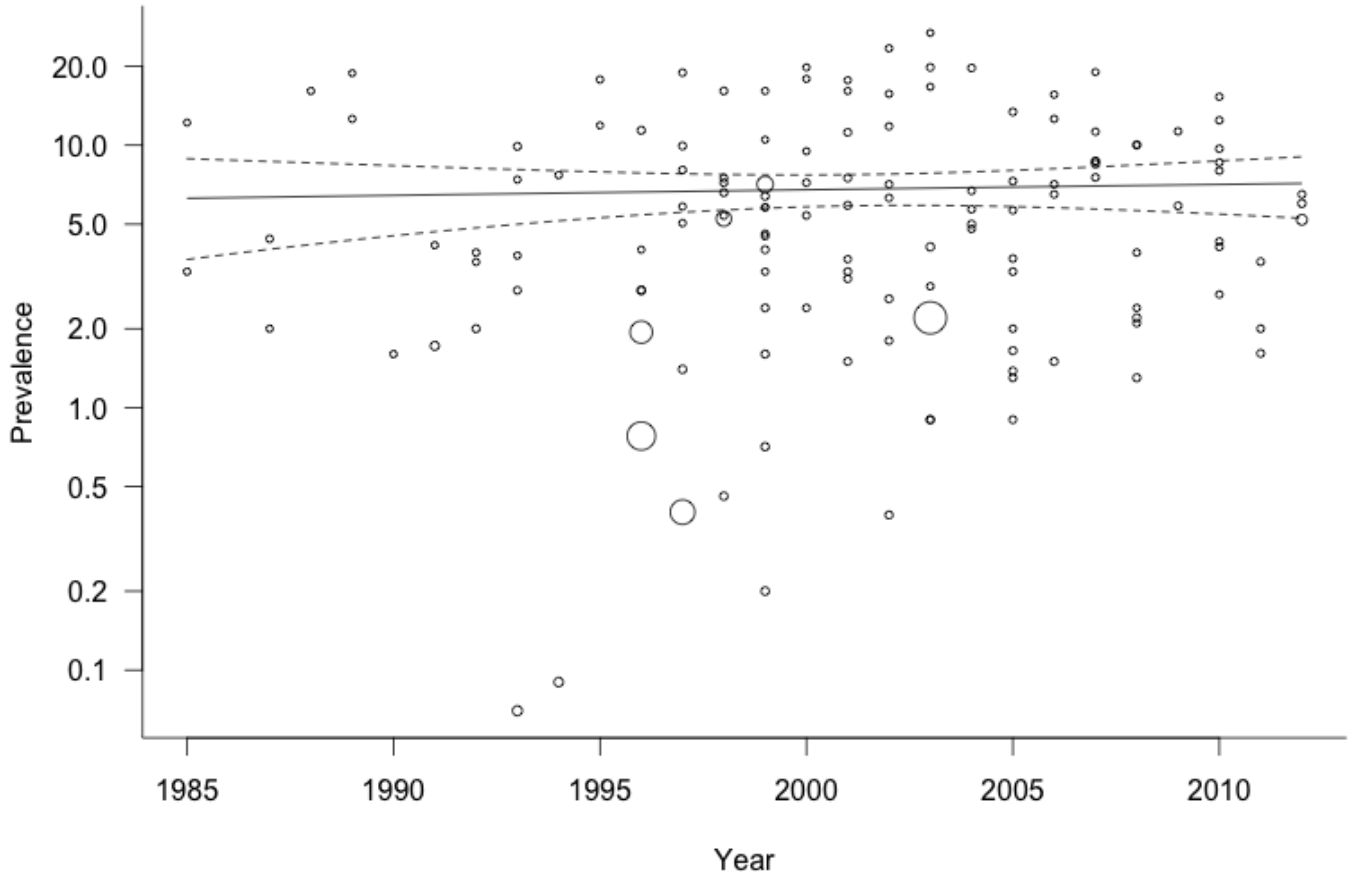
Research Review: Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010

Holly E. Erskine,[1,2] Alize J. Ferrari,[1,2] Paul Nelson,[3] Guilherme V. Polanczyk,[4,5] Abraham D. Flaxman,[6] Theo Vos,[6] Harvey A. Whiteford,[1,2] and James G. Scott[2,7,8]





ADHD prevalence estimates as a function of time



Polanczyk et al. *Int J Epidemiol* 2014;43(2):434-42

Rates of first-grade children fulfilling teacher-based diagnosis for ADHD symptoms according to different criteria

	Categorical criterion *6/9 symptoms*	*Dimensional criterion* *93th percentile*	Impairment	Impaired by ADHD symptoms	Symptoms not due to comorbidities	Symptoms not due to environment
Males	178	113	106	101	100	99
n=954	(18.6%)	(11.8%)	(11.1%)	(10.6%)	(10.5%)	(10.4%)
Females	54	54	45	38	38	36
n=937	(5.8%)	(5.8%)	(4.8%)	(4.0%)	(4.0%)	(3.8%)
Total	232	167	151	139	138	135
n=1891	(12.3%)	(8.8%)	(8.0%)	(7.3%)	(7.3%)	(7.1%)

Mugnaini et al. Eur. Psychiatry 2006

Factor structure and cultural factors of disruptive behaviour disorders symptoms in Italian children

Validation of a of the Italian Version of the *Disruptive behaviours Disorder Questionnaire* (Parent and Teachers versions; Pelham et al. 1992)

Five sites (21 primary schools; age 7-11y) located in different areas of Italy, representative of the different social and cultural contests.

- Bergamo (*North-West*),
- Venice (*North-East*),
- Padua (*North-East*),
- Florence (*Center*),
- Cagliari (*South*),

1575 parent's & 1085 teacher's Questionnaires

Zuddas et al. *Eur.Psychiatry* 2006

Factor structure and cultural factors of disruptive behaviour disorders symptoms in Italian children

	ADHD	ODD	CD	ADHD +ODD	ADHD +CD
Parents	2.5 %	0.7	=	0.7	0.3
Teachers	8.6	0.8	=	2.2	0.6
Parents AND Teachers	1.4	0.2	=	0.1	=

Zuddas et al. *Eur.Psychiatry* 2006

L'ADHD è un disturbo eterogeneo

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Depression

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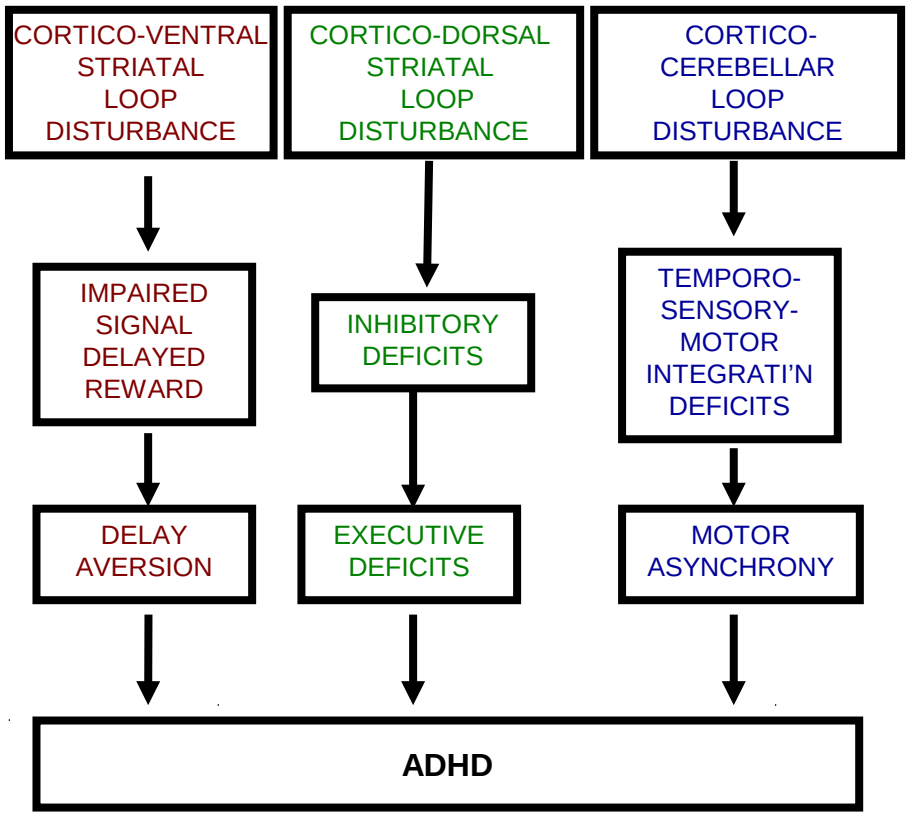
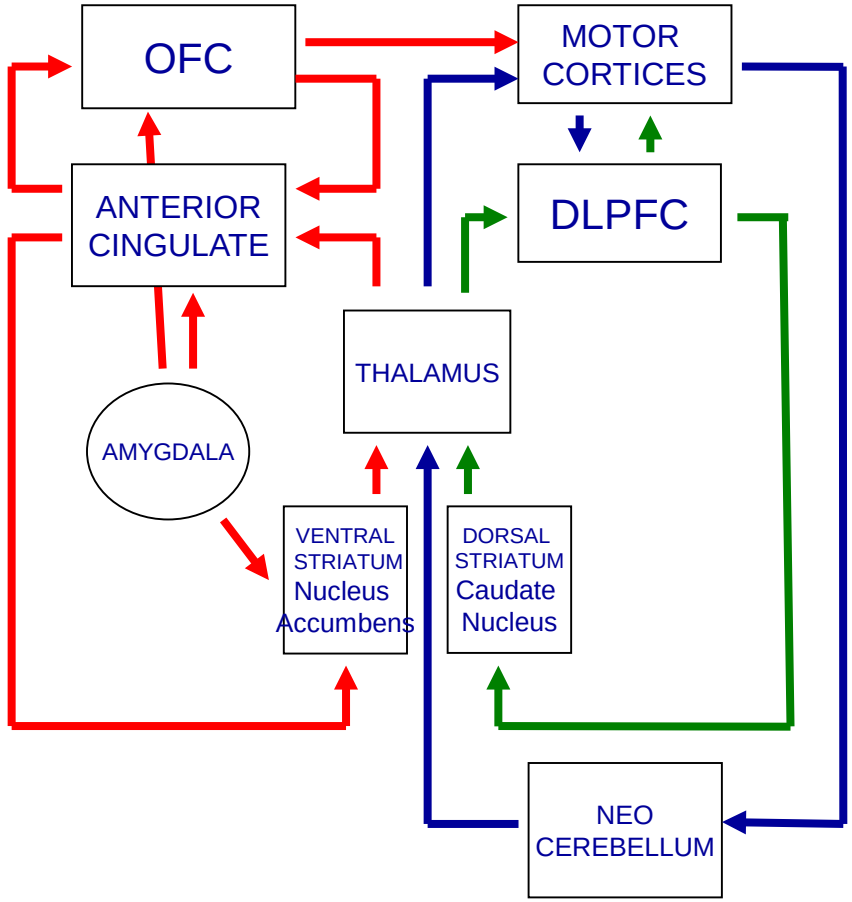
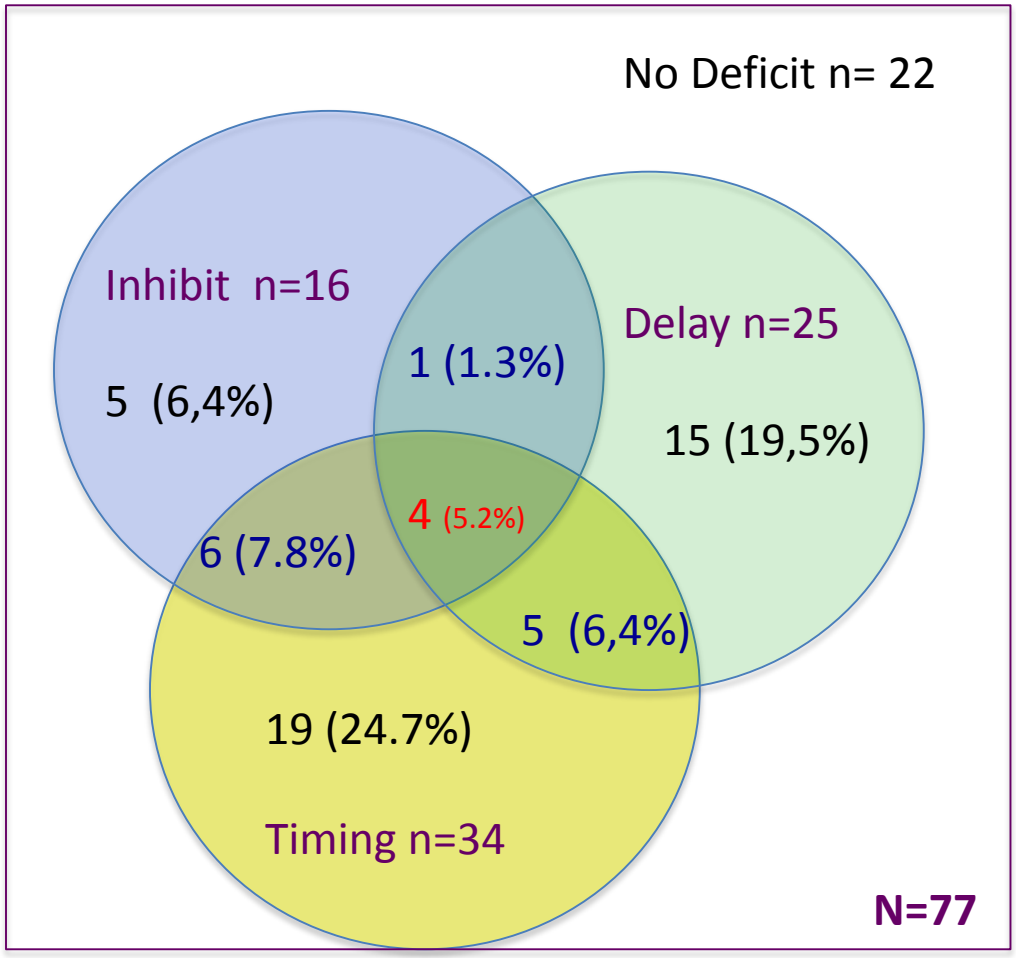
A TRIPLE PATHWAY HYPOTHESIS



SIMPLIFIED FUNCTIONAL NEUROANATOMY



Beyond the Dual Pathway Model: Evidence for the Dissociation of Timing, Inhibitory, and Delay-Related Impairments in Attention-Deficit/Hyperactivity Disorder



Familial effect for inhibition and timing less for delay

Sibling impairment intermediate between controls and probands
No evidence of cosegregation

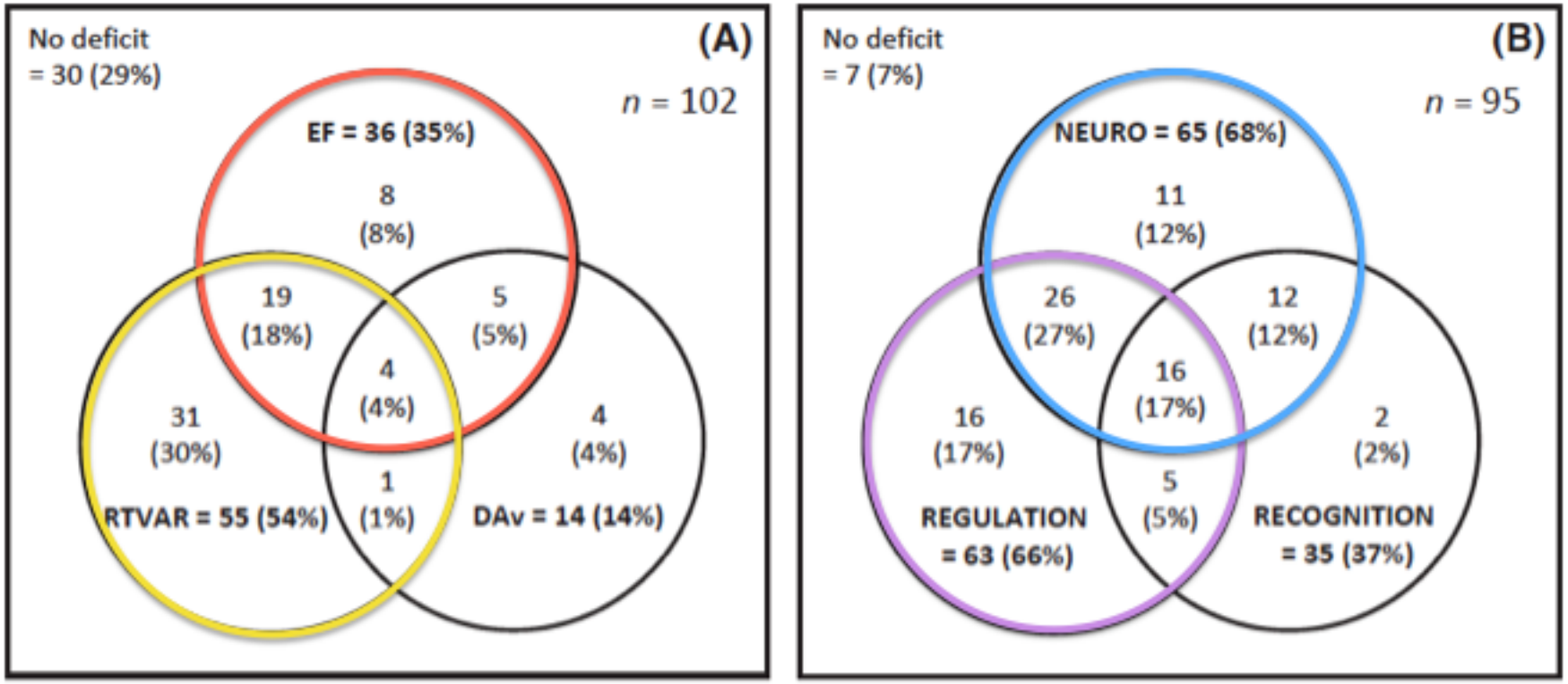
Timing associated with reading problems
Delay associated with low IQ

Sonuga-Barke et al. *JAACAP 2010*

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
Journal of Child Psychology and Psychiatry 54:6 (2013), pp 619–627

Multiple deficits in ADHD: executive dysfunction, delay aversion, reaction time variability, and emotional deficits

Douglas Sjöwall,[1] Linda Roth,[1] Sofia Lindqvist,[2] and Lisa B. Thorell[1]
[1]Department of Clinical Neuroscience and Stockholm Brain Institute, Karolinska Institutet, Stockholm, Sweden;
[2]Department of Psychology, Uppsala University, Uppsala, Sweden

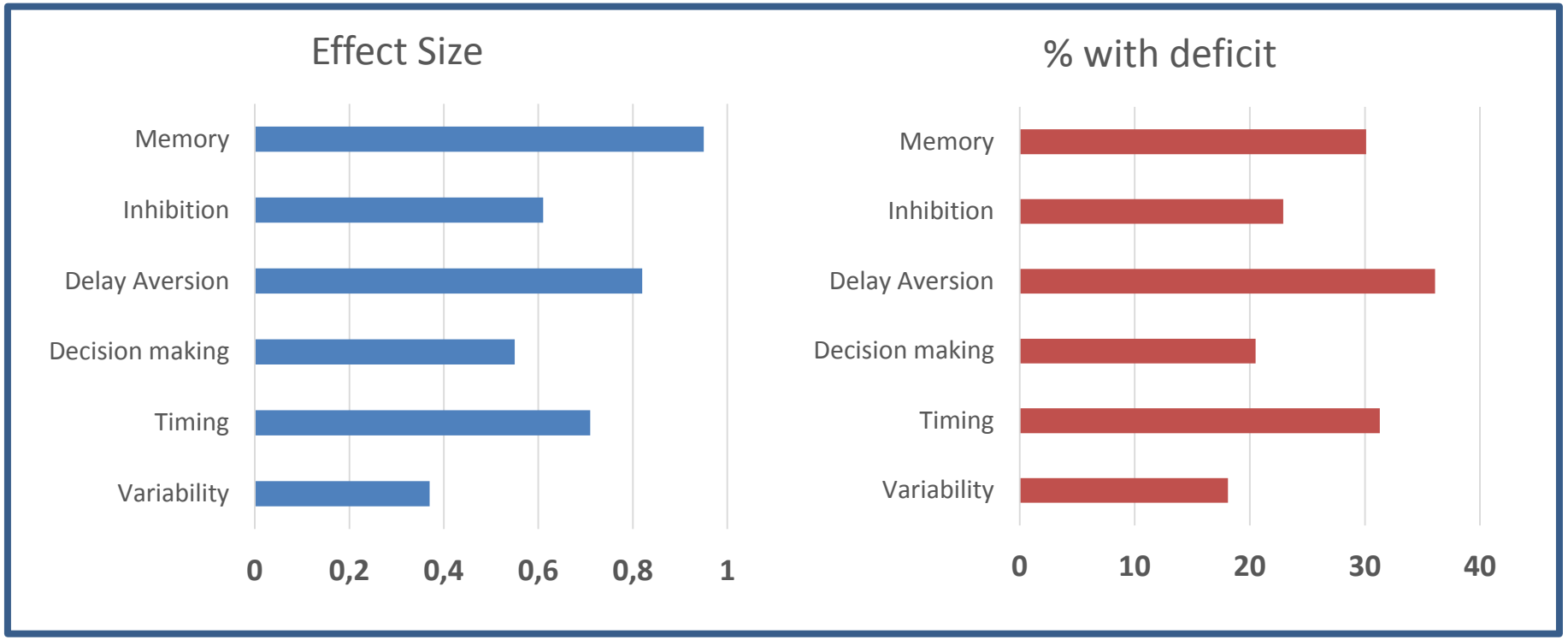


EF = Executive functioning (i.e., working memory, inhibition, shifting), RTVAR = Reaction time variability, DAv = Delay aversion, NEURO = Neuropsychological functioning, REGULATION = Emotion regulation, RECOGNITION = Emotion recognition

Proportion of ADHD cases with neuropsychological impairments (A) or impairments in neuropsychological and emotional functioning (B)

Neuropsychological Deficits in Treatment Naïve Boys with ADHD

- 83 Drug naïve boys (6 – 12 years) with DSM IV ADHD
- 66 Healthy control boys matched for age
- All completed all tasks in one session with breaks
- Tasks were counterbalanced across two orders



Coghill, Seth, Matthews, 2013

Outline

- L'ADHD è un disturbo eterogeneo le cui presentazione clinica si modifica nel corso della vita*: interventi terapeutici differenziati?*
- Diversa e specifica efficacia delle terapie farmacologiche rispetto agli interventi non-farmacologici: *chi valuta che cosa?*
- Sicurezza dei farmaci per l'ADHD: *quale rapporto costo-benefici?*
- *Take home message*

Interventi Terapeutici

- Interventi Non Farmacologici
- Farmaci

Effect Size

Differenza tra i cambiamenti dal *baseline* tra farmaco e placebo, diviso la media delle dev. standard (placebo e farmaco ad *end point)*. L'*effect size* standardizza le unità di misura nei diversi studi.

	Basaline	EndPoint
Farmaco	38.5 ± 5.8	25.5 ± 4.2
Placebo	40.4 ± 6.1	32.7 ± 5.0

$$\mathbf{d} = \frac{(38.5-25.5) - (40.4-32.7)}{(4.2+5.0)/2} = \frac{13.0 - 7.7}{4{,}6} = \mathbf{ES\ 1.1}$$

Secondo la definizione di Cohen, ES > 0.2 è considerato basso, ES > di 0.5 è considerato medio; oltre 0.8 è considerato alto

Article

Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments

Edmund J.S. Sonuga-Barke, Ph.D.
Daniel Brandeis, Ph.D.
Samuele Cortese, M.D., Ph.D.
David Daley, Ph.D.
Maite Ferrin, M.D., Ph.D.
Martin Holtmann, M.D.
Jim Stevenson, Ph.D.
Marina Danckaerts, M.D., Ph.D.
Saskia van der Oord, Ph.D.
Manfred Döpfner, Ph.D.
Ralf W. Dittmann, M.D., Ph.D.
Emily Simonoff, M.D.
Alessandro Zuddas, M.D.
Tobias Banaschewski, M.D., Ph.D.
Jan Buitelaar, M.D., Ph.D.
David Coghill, M.D.
Chris Hollis, M.D.
Eric Konofal, M.D., Ph.D.
Michel Lecendreux, M.D.
Ian C.K. Wong, Ph.D.
Joseph Sergeant, Ph.D.
European ADHD Guidelines Group

Objective: Nonpharmacological treatments are available for attention deficit hyperactivity disorder (ADHD), although their efficacy remains uncertain. The authors undertook meta-analyses of the efficacy of dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) and psychological (cognitive training, neurofeedback, and behavioral interventions) ADHD treatments.

Method: Using a common systematic search and a rigorous coding and data extraction strategy across domains, the authors searched electronic databases to identify published randomized controlled trials that involved individuals who were diagnosed with ADHD (or who met a validated cutoff on a recognized rating scale) and that included an ADHD outcome.

Results: Fifty-four of the 2,904 nonduplicate screened records were included in the analyses. Two different analyses were performed. When the outcome measure was based on ADHD assessments by raters closest to the therapeutic setting, all dietary (standardized mean differences=0.21–0.48) and psychological (standardized mean differences=0.40–0.64) treatments produced statistically significant effects. However, when the best probably blinded assessment was employed, effects remained significant for free fatty acid supplementation (standardized mean difference=0.16) and artificial food color exclusion (standardized mean difference=0.42) but were substantially attenuated to nonsignificant levels for other treatments.

Conclusions: Free fatty acid supplementation produced small but significant reductions in ADHD symptoms even with probably blinded assessments, although the clinical significance of these effects remains to be determined. Artificial food color exclusion produced larger effects but often in individuals selected for food sensitivities. Better evidence for efficacy from blinded assessments is required for behavioral interventions, neurofeedback, cognitive training, and restricted elimination diets before they can be supported as treatments for core ADHD symptoms.

(Am J Psychiatry 2013; 170:275–289)

Inclusion criteria

Age 3-18
Diagnosis ADHD (any subtype)
Symptom measured by validated rating Scale
Appropriate control group
Stable medication allowed (sensitivity analysis)
Rare comorbidity (i.e. Fragile X) excluded

Outcome measure : ADHD symptoms scale
Most proximal assessment
Probably blinding assessment

Study quality independently assessed
(Jadad et al. criteria for randomization,
blinding and missing data)

Non-pharmacological Intevention

Restricted Elimination Diet
Elimination diet, known antigenic , specific provocking foods ***vs*** Placebo or waiting list

Artificial food color exclusion
Certified food color, Feingold, KaiserPermanent diet foods ***vs*** Placebo or control diet

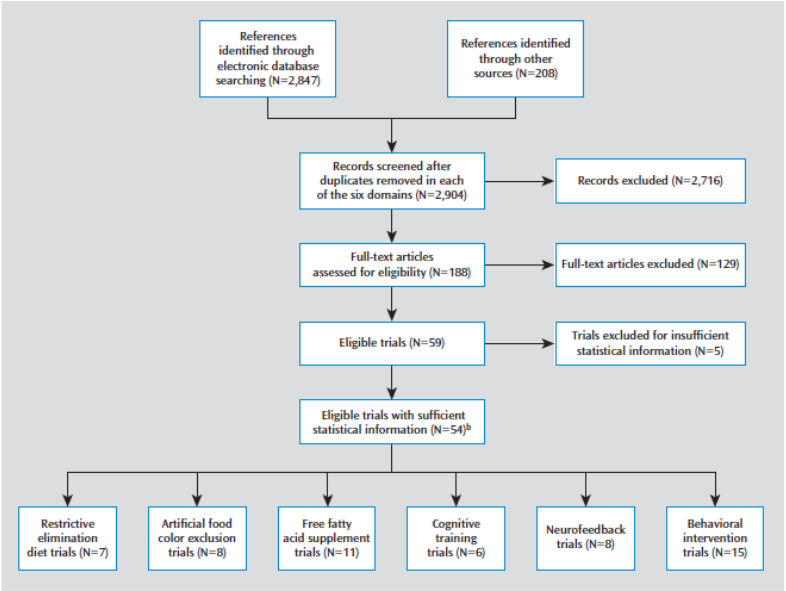
Free fatty acid supplementation
Omega 3, 6, 3+6 ***vs*** Placebo

Cognitive training
Attention or working memory training ***vs*** Waiting list, placebo, PC game, easy training

Neurofeedback
Theta-beta training, slow cortical potential training ***vs*** Waiting list, placebo, cognitive exercise

Behavioral intervention
Parent (& child/ teacher) training ***vs*** Waiting list, TAU, non directive therapy

FIGURE 1. Combined PRISMA Flow Chart for All Six Treatment Domains Systematically Reviewed[a]



[a] PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org).
[b] Data from one three-arm trial are included in both neurofeedback and cognitive training analyses.

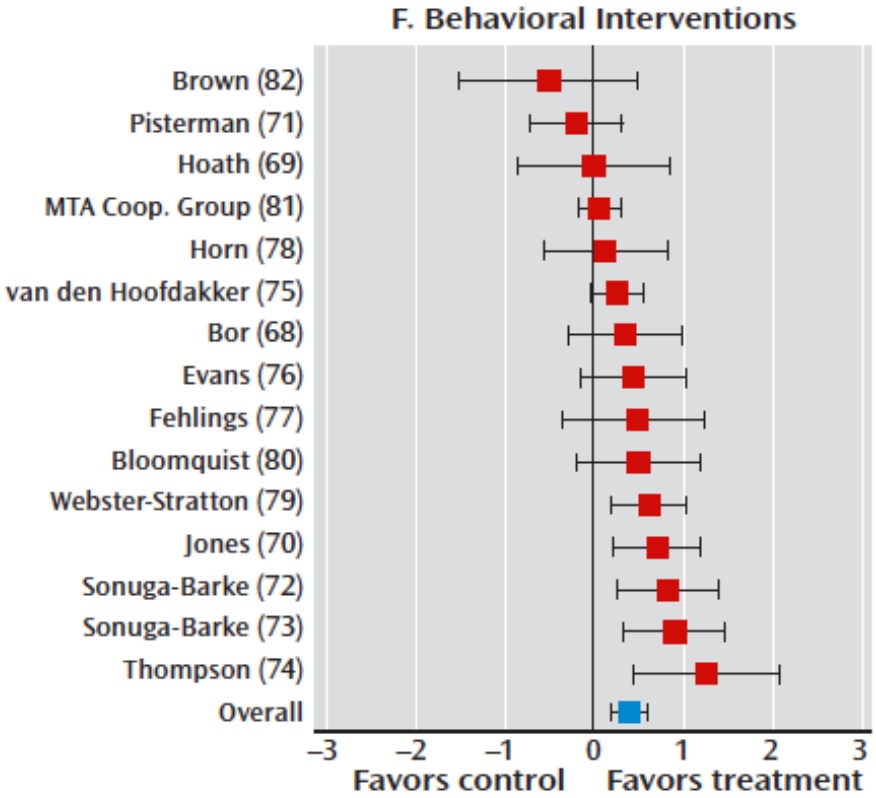
Intervention	**Most proximal assessment (SMD)**	**Probably blinding assessment (SMD)**
Restricted Elimination Diet	1.48	0.51
Artificial food color exclusion	0.32	0.42
Free fatty acid supplementation	0.21	0.16
Cognitive training	0.64	0.24
Neurofeedback	0.59	0.29
Behavioral intervention	0.40	0.02

Sonuga-Barke et al. *AJP 2013*

Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments

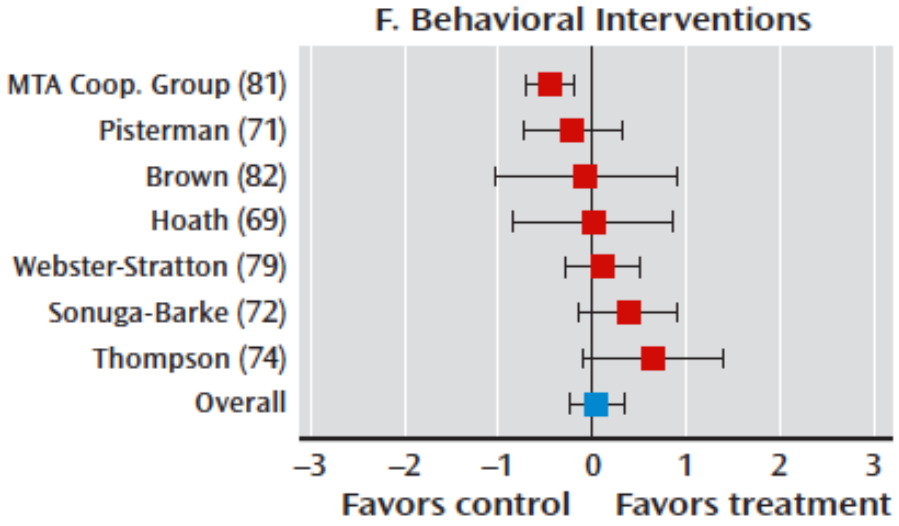
Sonuga-Barke et al. *AJP* 2013

MPROX



Overall SMD=0.40, 95% CI=0.20, 0.60
Test for overall effect: Z=3.88, p=0.0001
Heterogeneity: χ^2=30.73, df=14, p=0.006, I^2=54%

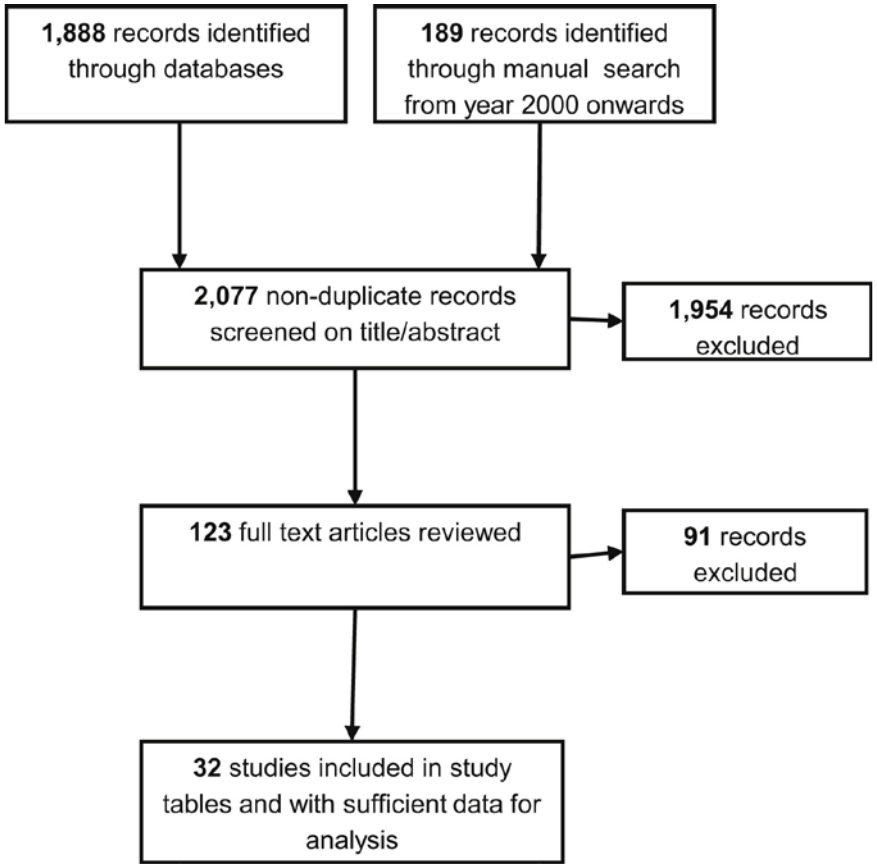
PBLIND



Overall SMD=0.02, 95% CI=–0.30, 0.34
Test for overall effect: Z=0.09, p=0.92
Heterogeneity: χ^2=15.36, df=6, p=0.02, I^2=67%

Behavioral interventions in attention-deficit/hyperactivity disorder: a meta-analysis of randomized controlled trials across multiple outcome domains.

Daley et al. *JAACAP 2014*

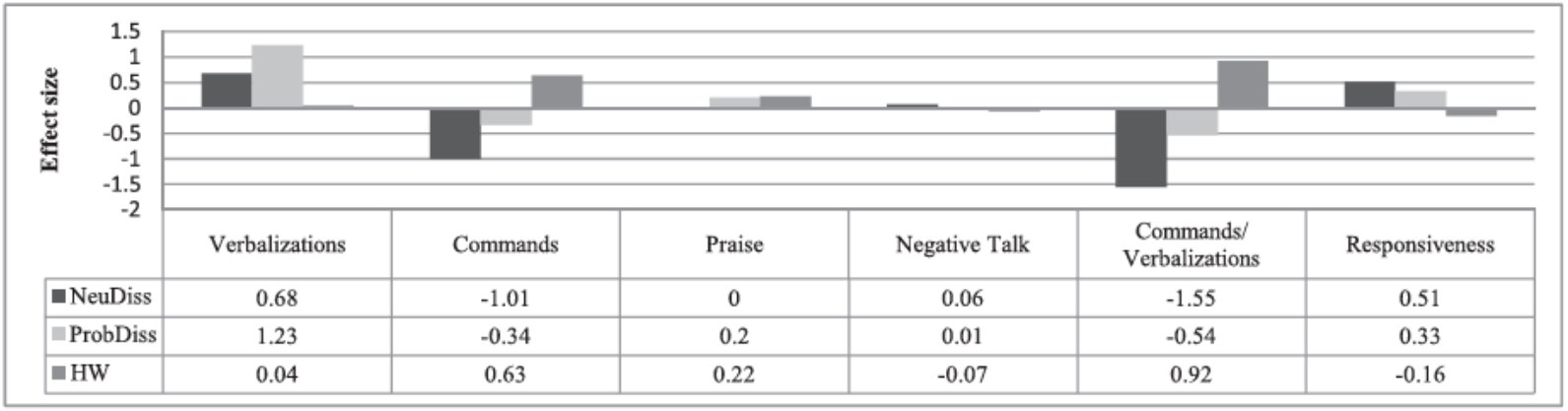


Dimension	MPROX	PBLIND
ADHD	0.35	0.02
Conduct problem	0.26	0.31
Social skills	0.47	
Academic Achievement	0.28	

Dimension	MPROX	PBLIND
Positive parenting	0.68	0.63
Negative parenting	0.57	0.43
Parental self-concept	0.37	
Parental Mental Health	0.09	

A Pilot Study of Stimulant Medication for Adults with Attention-Deficit/Hyperactivity Disorder (ADHD) Who Are Parents of Adolescents with ADHD: The Acute Effects of Stimulant Medication on Observed Parent–Adolescent Interactions

Babinski et al. *JCAP* 2014



	Verbalizations	Commands	Praise	Negative Talk	Commands/ Verbalizations	Responsiveness
NeuDiss	0.68	-1.01	0	0.06	-1.55	0.51
ProbDiss	1.23	-0.34	0.2	0.01	-0.54	0.33
HW	0.04	0.63	0.22	-0.07	0.92	-0.16

	Verbalizations	Commands	Praise	Negative Talk	Commands/ Verbalizations	Responsiveness
NeuDiss						
LDX	133.20 (25.79)	8.40 (5.41)	0.01 (0.01)	0.05 (0.06)	0.06 (0.03)	0.70 (0.45)
Placebo	118.00 (17.93)	16.00 (9.19)	0.01 (0.01)	0.05 (0.06)	0.13 (0.06)	0.47 (0.46)
ProbDiss						
LDX	142.00 (6.73)	17.50 (7.14)	0.01 (0.01)	0.03 (0.03)	0.13 (0.05)	0.58 (0.38)
Placebo	130.00 (12.06)	20.25 (9.03)	0.00 (0.00)	0.03 (0.04)	0.16 (0.07)	0.69 (0.25)
HW						
LDX	43.20 (20.39	9.20 (6.02)	0.01 (0.04)	0.03 (0.03)	0.25 (0.18)	0.88 (0.18)
Placebo	44.0 (30.13)	6.00 (3.94)	0.02 (0.01)	0.03 (0.05)	0.13 (0.05)	0.90 (0.14)

FIG. 1. Medication effect sizes of observed parenting behaviors. Bars in the top half represent medication effects (i.e., mean standard differences) by task. Parent behavior codes are based on the coding scheme used for reporting results in the trial of parents of children with attention-deficit/hyperactivity disorder (ADHD) (Waxmonsky et al. 2014). Values in the bottom half represent means, and standard deviations are presented in parentheses. Verbalizations and commands represent total frequency counts, whereas all remaining parent behaviors are calculated as a percentage score. NeuDiss, neutral discussion; ProbDiss, problem discussion; HW, homework.

Cognitive Training for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials

Samuele Cortese, MD, PhD, Maite Ferrin, MD, PhD, Daniel Brandeis, PhD, Jan Buitelaar, MD, PhD, David Daley, PhD, Ralf W. Dittmann, MD, PhD, Martin Holtmann, MD, Paramala Santosh, MD, PhD, Jim Stevenson, PhD, Argyris Stringaris, MD, PhD, MRCPsych, Alessandro Zuddas, MD, Edmund J.S. Sonuga-Barke, PhD, on behalf of the European ADHD Guidelines Group (EAGG)

Objective: The authors performed meta-analyses of randomized controlled trials to examine the effects of cognitive training on attention-deficit/hyperactivity disorder (ADHD) symptoms, neuropsychological deficits, and academic skills in children/adolescents with ADHD.

Method: The authors searched Pubmed, Ovid, Web of Science, ERIC, and CINAHAL databases through May 18, 2014. Data were aggregated using random-effects models. Studies were evaluated with the Co

Results: Sixteen of 695 nondup analyzed (759 children with ADHI training were considered together, effects on total ADHD (standardi [SMD] = 0.37, 95% CI = 0.09– symptoms (SMD = 0.47, 95% CI = by raters most proximal to the t typically unblinded). These figure tially when the outcomes were p blinded raters (ADHD total: SMD = 0.40; inattention: SMD = 0.32, 95% CI = −0.01 to 0.66). Effects on hyperactivity/impulsivity symptoms were not significant. There were significant effects on laboratory tests of working memory (verbal: SMD = 0.52, 95% CI = 0.24–0.80; visual: SMD = 0.47, 95% CI = 0.23–0.70) and parent ratings of executive function (SMD = 0.35, 95% CI = 0.08–0.61). Effects on academic performance were not statistically significant. There were no effects of working memory training, specifically on ADHD symptoms. Interventions targeting multiple neuropsychological deficits had large effects on ADHD symptoms rated by most

Conclusion: Despite improving working memory performance, cognitive training had limited effects on ADHD symptoms according to assessments based on blinded measures. Approaches targeting multiple neuropsychological processes may optimize the transfer of effects from cognitive deficits to clinical symptoms.

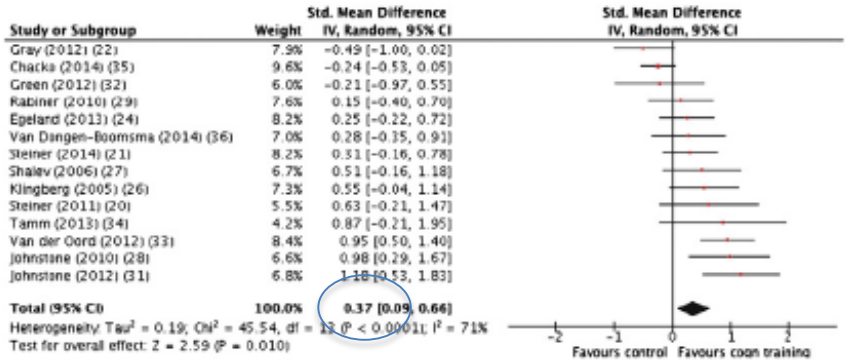
J Am Acad Child Adolesc Psychiatry 2015;54(3):164–174.

Cognitive Training for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials

Cortese et al. *JAACAP* 2015

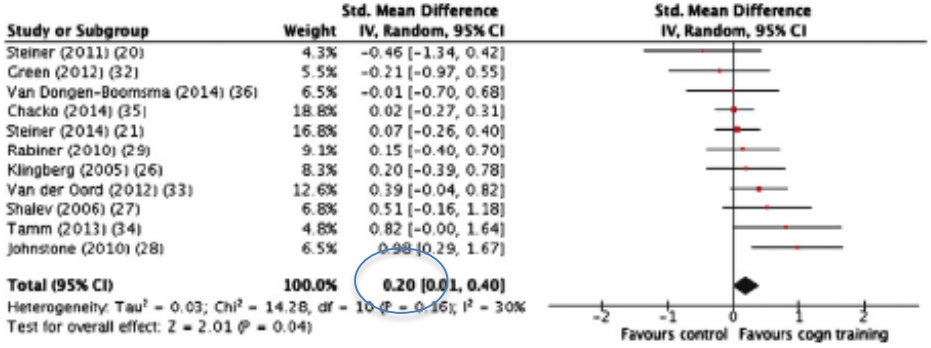
a **Most proximal measures**

Inattention plus hyperactivity/impulsivity symptoms



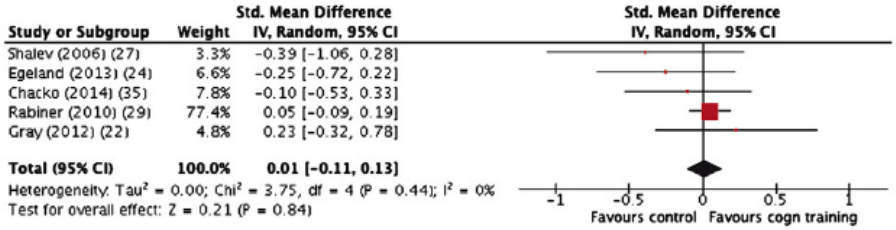
b **Probably blinded measures**

Inattention plus hyperactivity/impulsivity symptoms

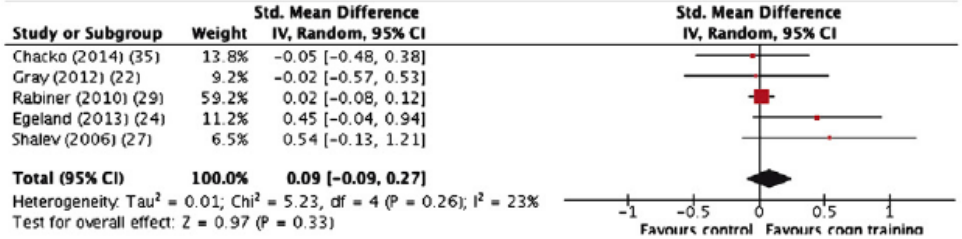


b **Academic outcomes**

Math



Reading



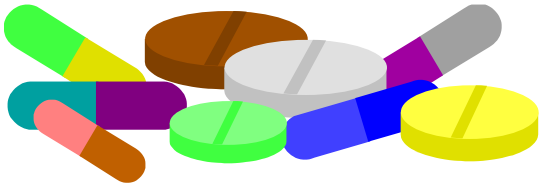
Pharmacotherapy of ADHD

Stimulants

- Methylphenidate
- Amphetamine compounds
- Lys-dexamphetamine (pro-drug)

Atomoxetine

Guanfacine



Antihypertensive

- Clonidine

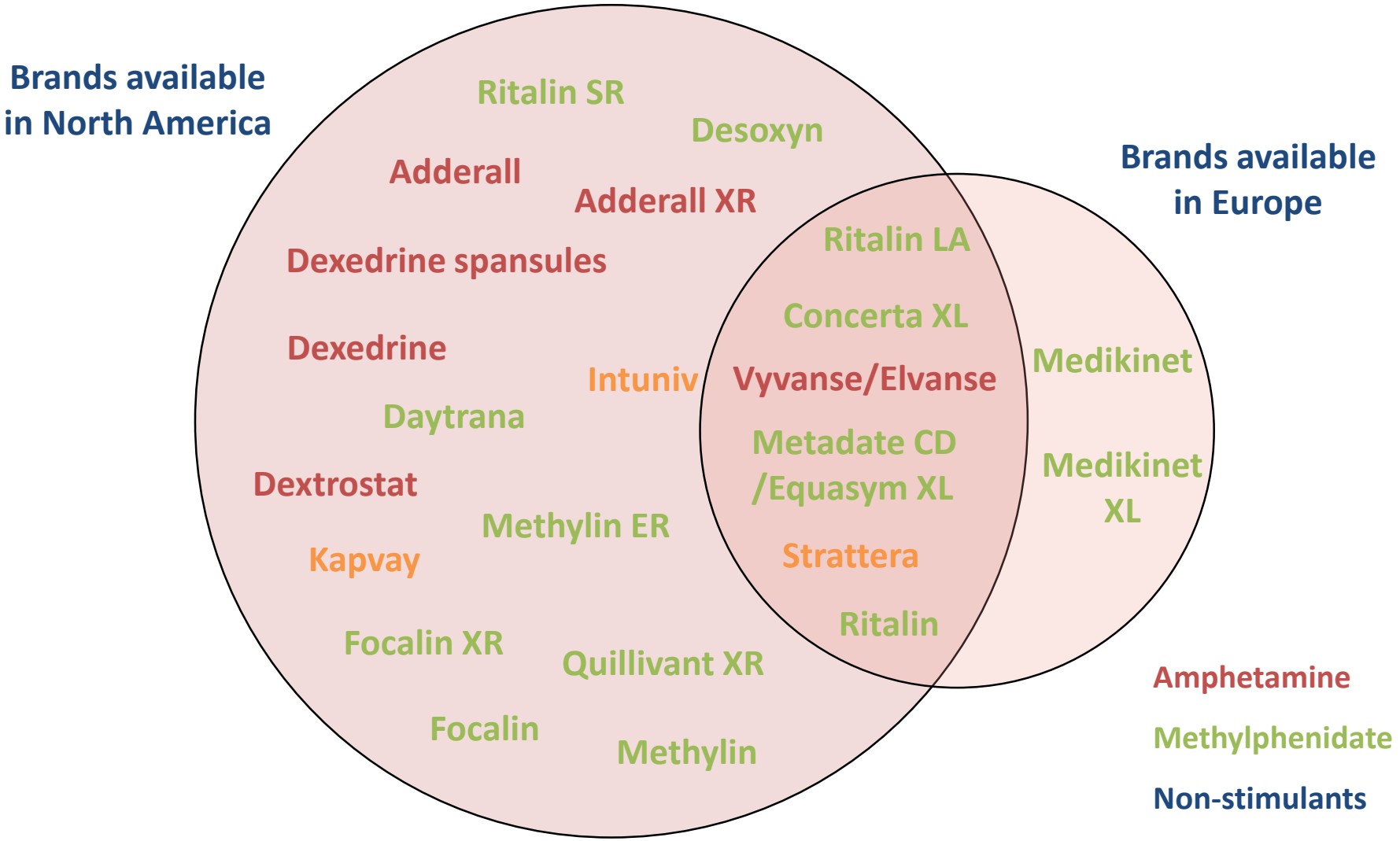
Antidepressant

- Tricyclics
- Bupropion

Investigational

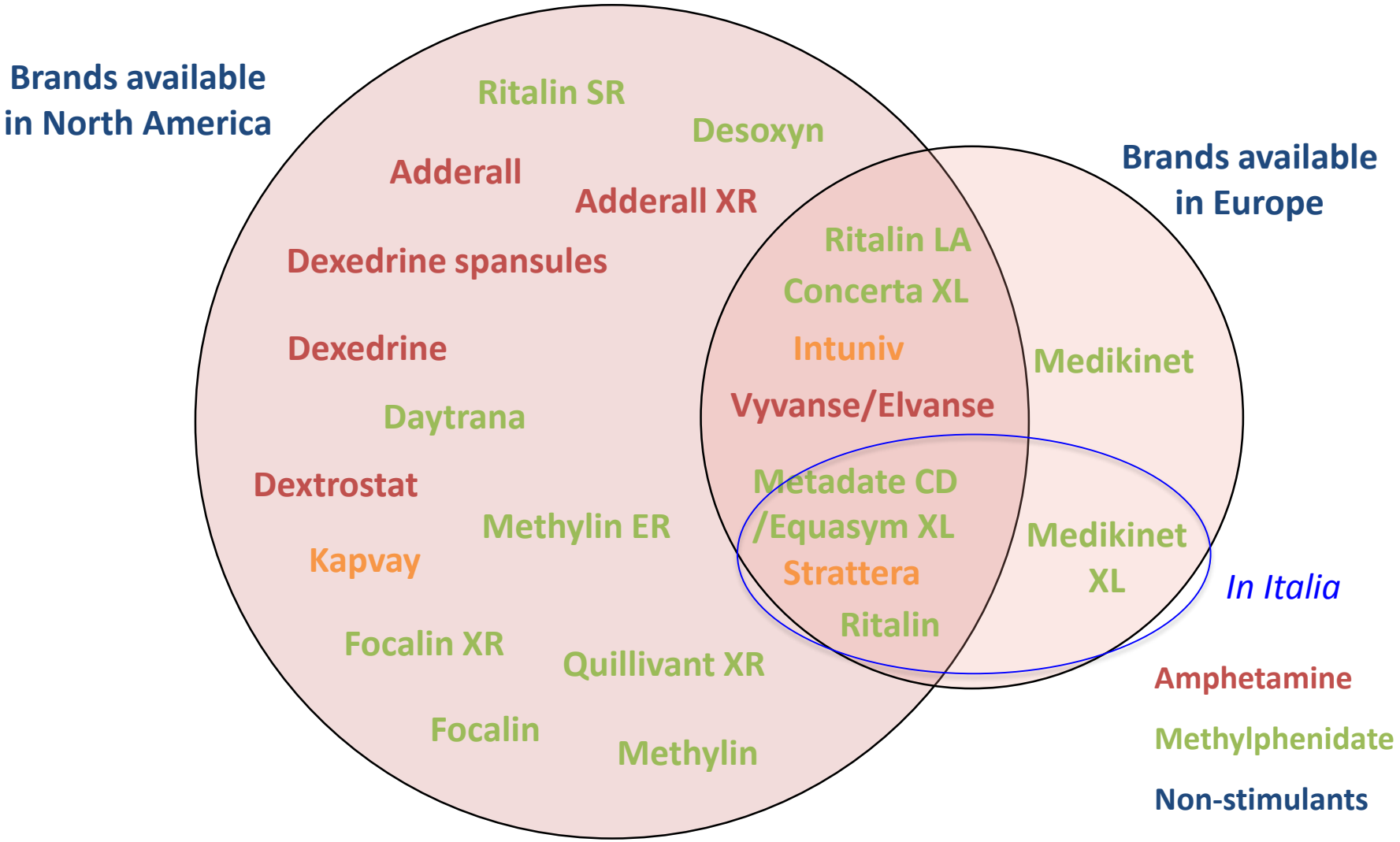
- AcethylCholine (Nicotine) (Chan NPF 2007)
- Glutamate: Ampakine
- Histamine: H3 antagonists (Esbenshade BJF 2008)
- Serotonine: 5HT 7 Agonists
- (Omega 3/6)

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



Generic dexamphetamine is available in Europe

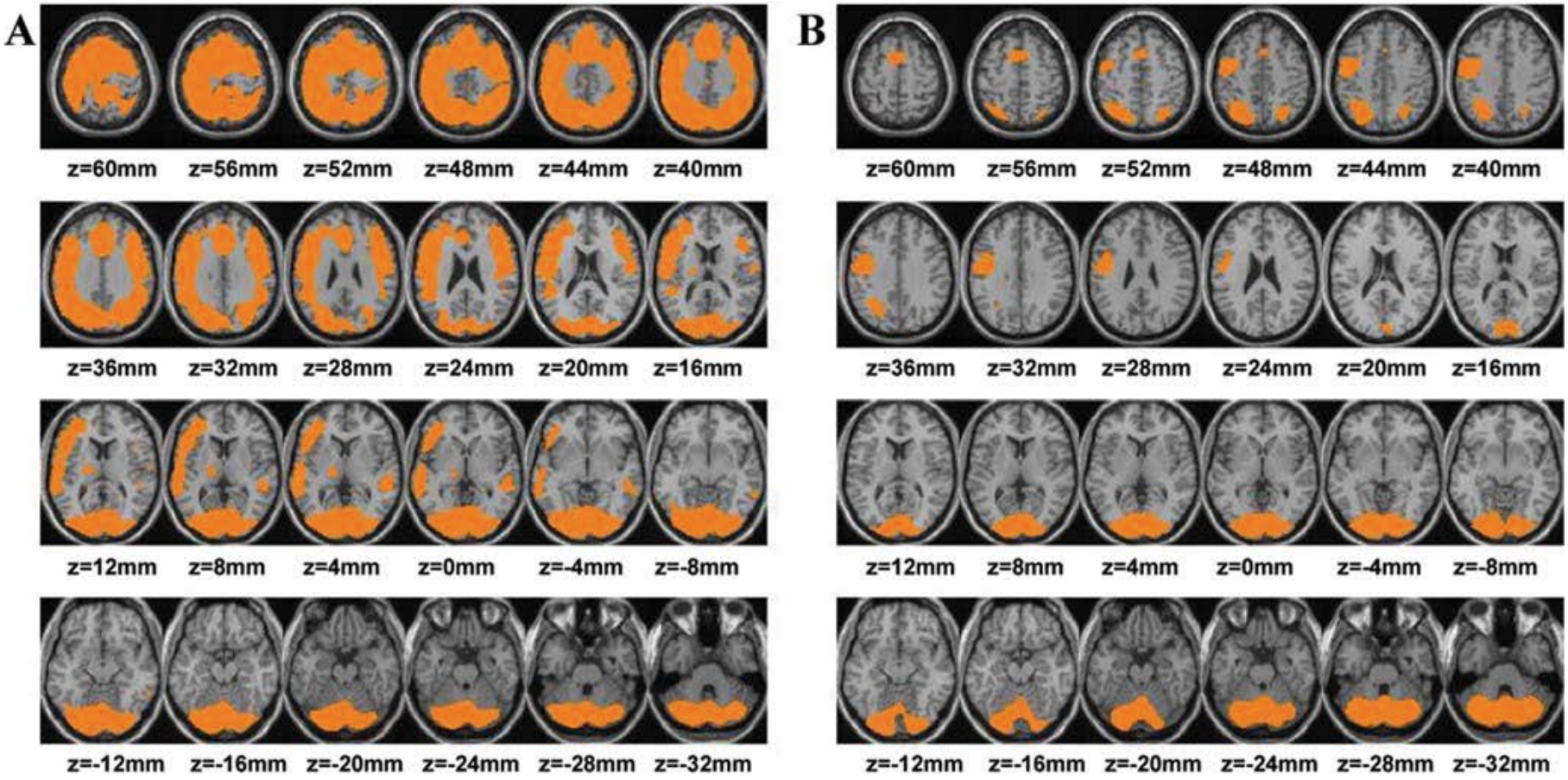
More pharmacological treatment options are available in North America than in Europe



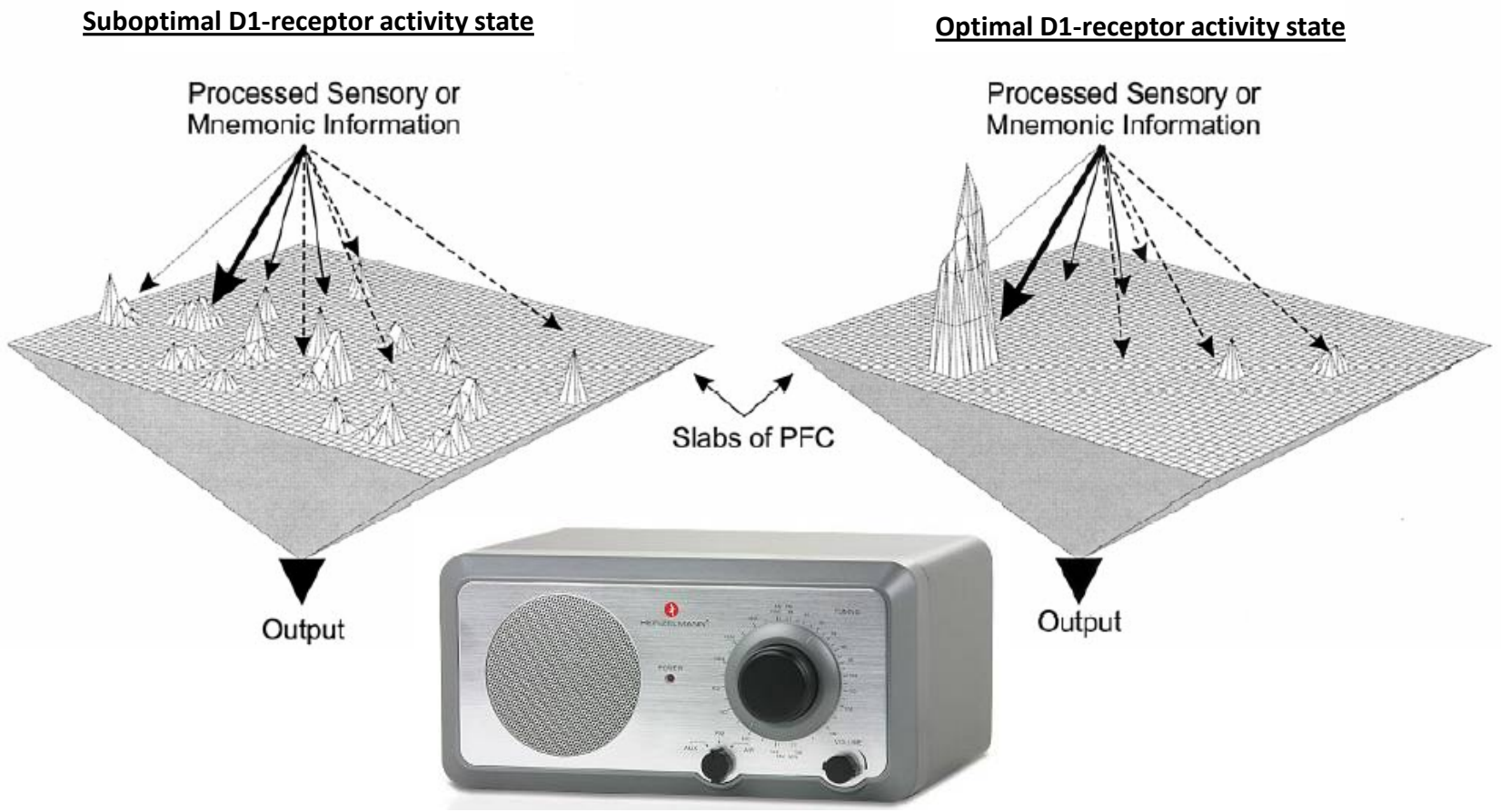
Generic dexamphetamine is available in Europe

Methylphenidate Decreased the Amount of Glucose Needed by the Brain to Perform a Cognitive Task

Volkow *et al., 2008*



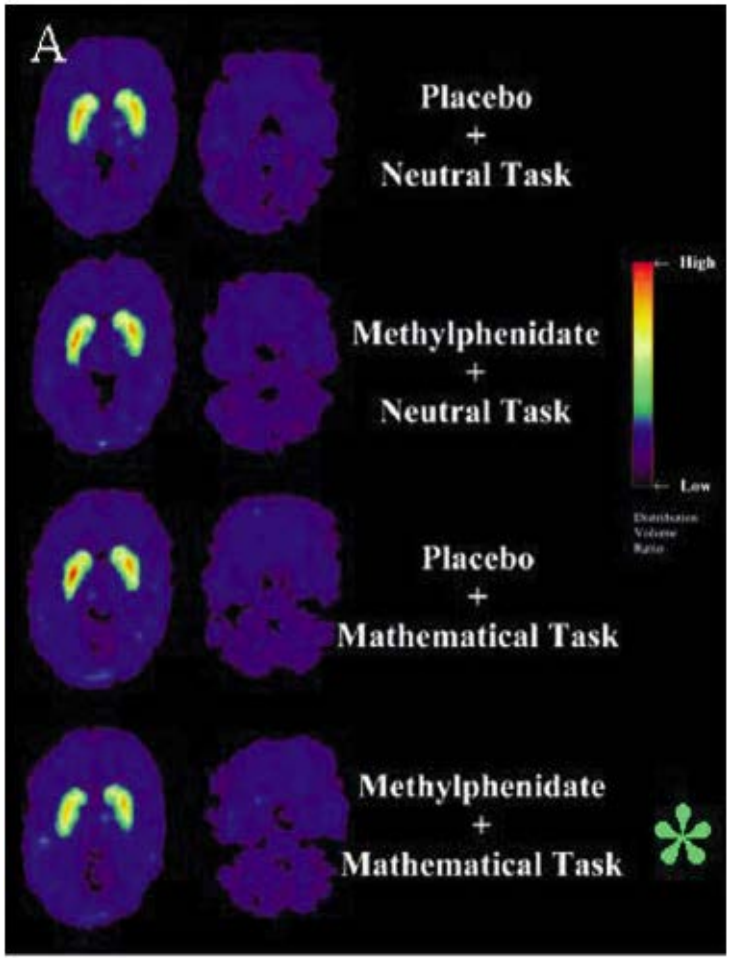
What is the action of dopamine on prefrontal cortex ?

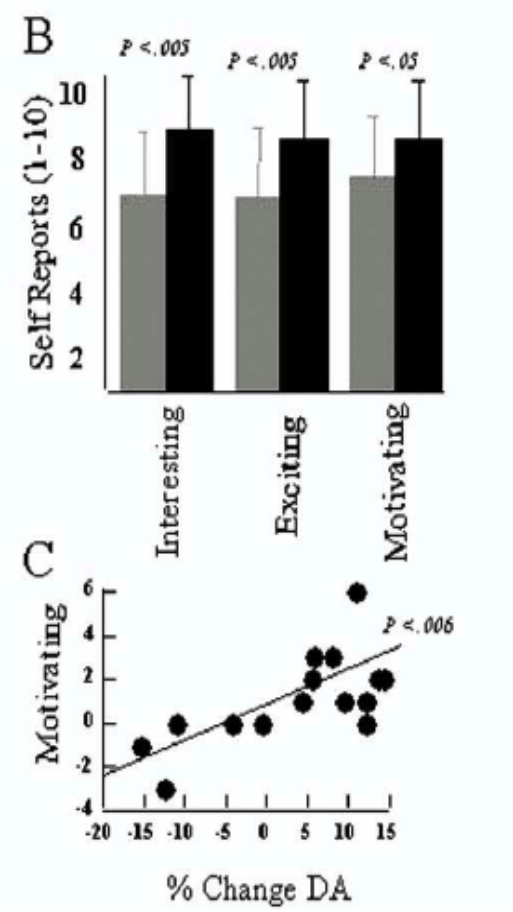


Optimal signal-to-noise ratio
in interaction with other neurotransmitter systems

Nach Seamans et al. J Neurosci 2001

Effect of MPH on cognitive tasks

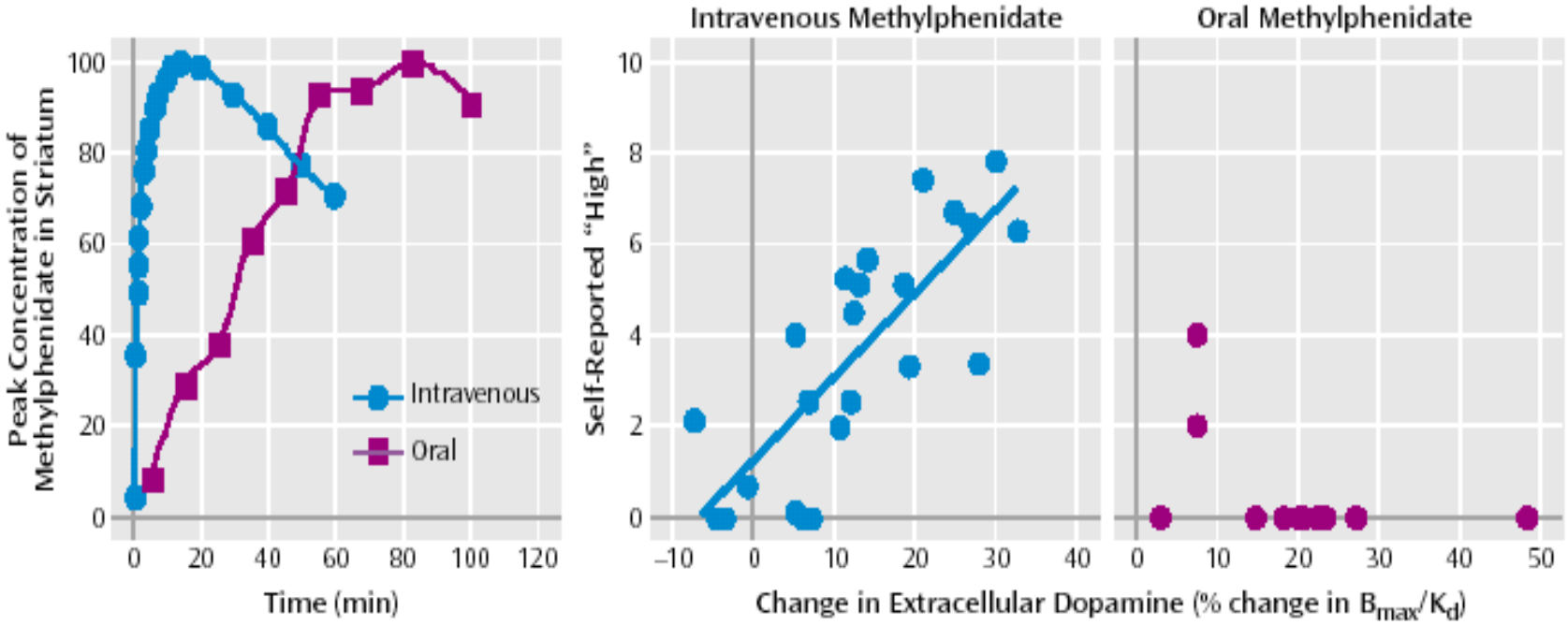




Volkow et al. 2004

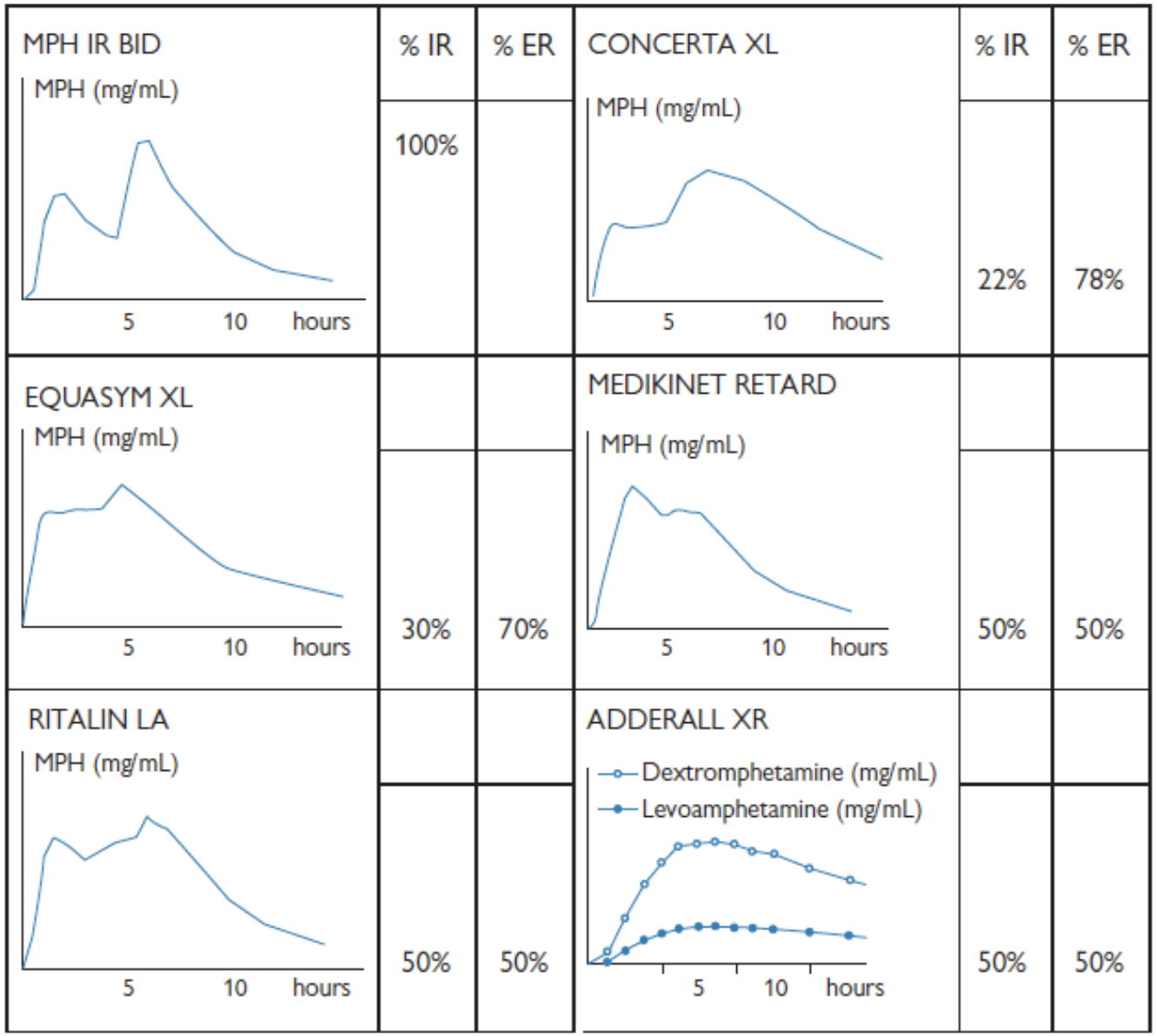
Variables That Affect the Clinical Use and Abuse of Methylphenidate in the Treatment of ADHD

FIGURE 4. Striatal Uptake and the Relationship Between Changes in Extracellular Dopamine and Self-Reports of Being "High" After Intravenous or Oral Administration of Methylphenidate[a]



Volkow & Swanson AJP 2003

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



I farmaci per l'ADHD
sono tra i farmaci più efficaci in psichiatria
(e forse in medicina)

Eur Child Adolesc Psychiatry (2006)
xx:1–20 DOI 10.1007/s00787-006-0549-0

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Eric Taylor

Long-acting medications for the hyperkinetic disorders

A systematic review and European treatment guideline

Efficacia

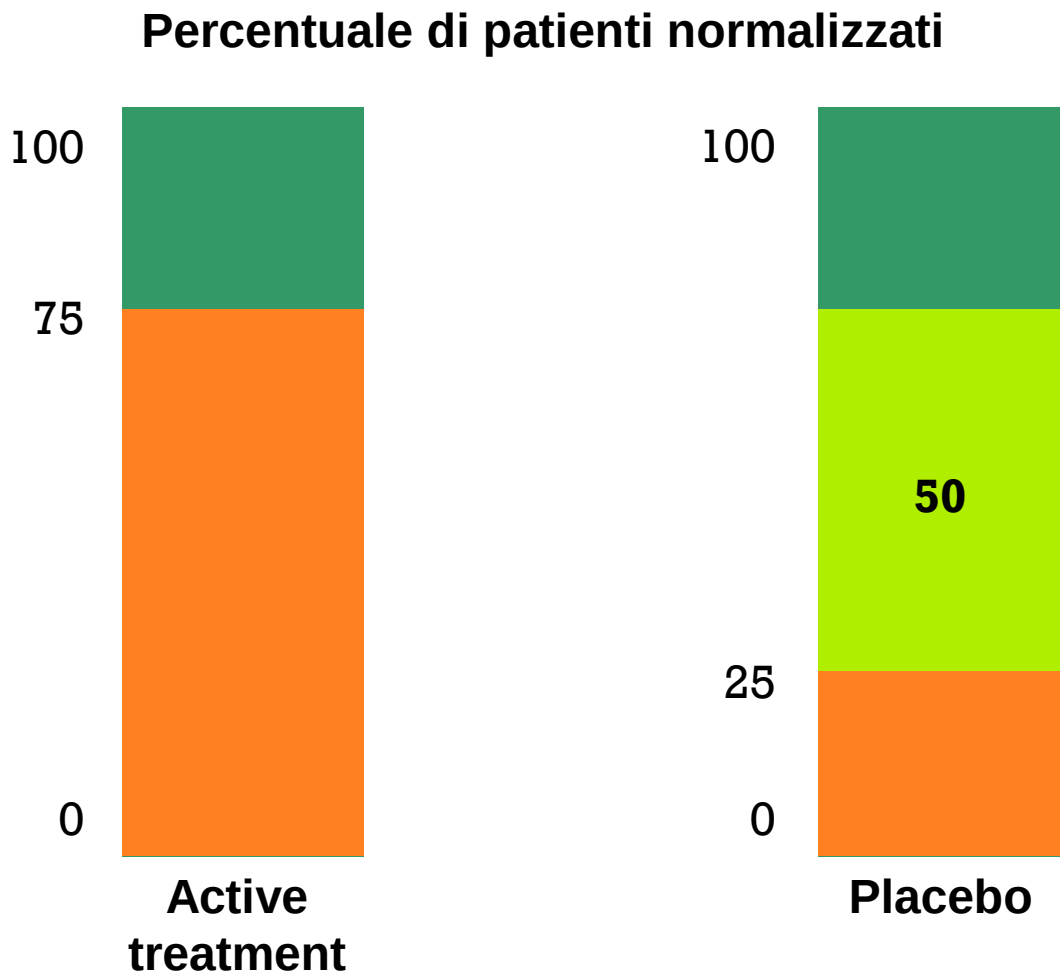
Effect Sizes sui sintomi di ADHD

	Parent		Teacher		Clinician		References
	SMD	No. of studies (rating scales used)	SMD	No. of studies (rating scales used)	SMD	No. of studies (rating scales used)	
▪ 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 = difference in outcome scores between drug and placebo groups divided by the pooled standard deviation
- Caveat: Effect size might be influenced by design features (e.g., different types of rater, durations of studies, dosing regimens)

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

Efficacia: Number Needed to Treat (NNT)



Numbers needed to treat = 100% / (% migliorato col farmaco – % i migliorato con Placebo)

Esempio:
Numbers Needed to Treat
= 100 / (75 – 25)
= 100 / 50
= 2

Maggiore la differenza, minore il numero

Efficacia (*Numbers Needed to Treat*)

Medication	% normalised active med	% normalised placebo	Number needed to treat (95% CI)
MPH IR	41	20	**4.8** (±0.15)
Adderall XR	51	25	**3.8** (±0.14)
Concerta XL *	66	14	**1.9** (±0.20)
Equasym XL	39	20	**5.3** (±0.15)
Medikinet retard	49	12	**2.7** (±0.18)
Atomoxetine	42.3	18.5	**4.2** (±0.07)

NNT: MPH-IR = MPH-ER = ATX (c. 3–5)

*Caveat: Normalisation data may be influenced by an inadequate study design (e.g. Concerta data)

I farmaci per l'ADHD sono tra i farmaci più efficaci in psichiatria

Efficacia dei Farmaci per l'ADHD

- *Effect sizes* (misura di cambiamento): **0.7-1.0**
  → MPH IR = MPH ER > ATX
- *Numbers needed to treat* (misura di *outcome*) **3-5**
  → MPH IR = MPH ER = ATX

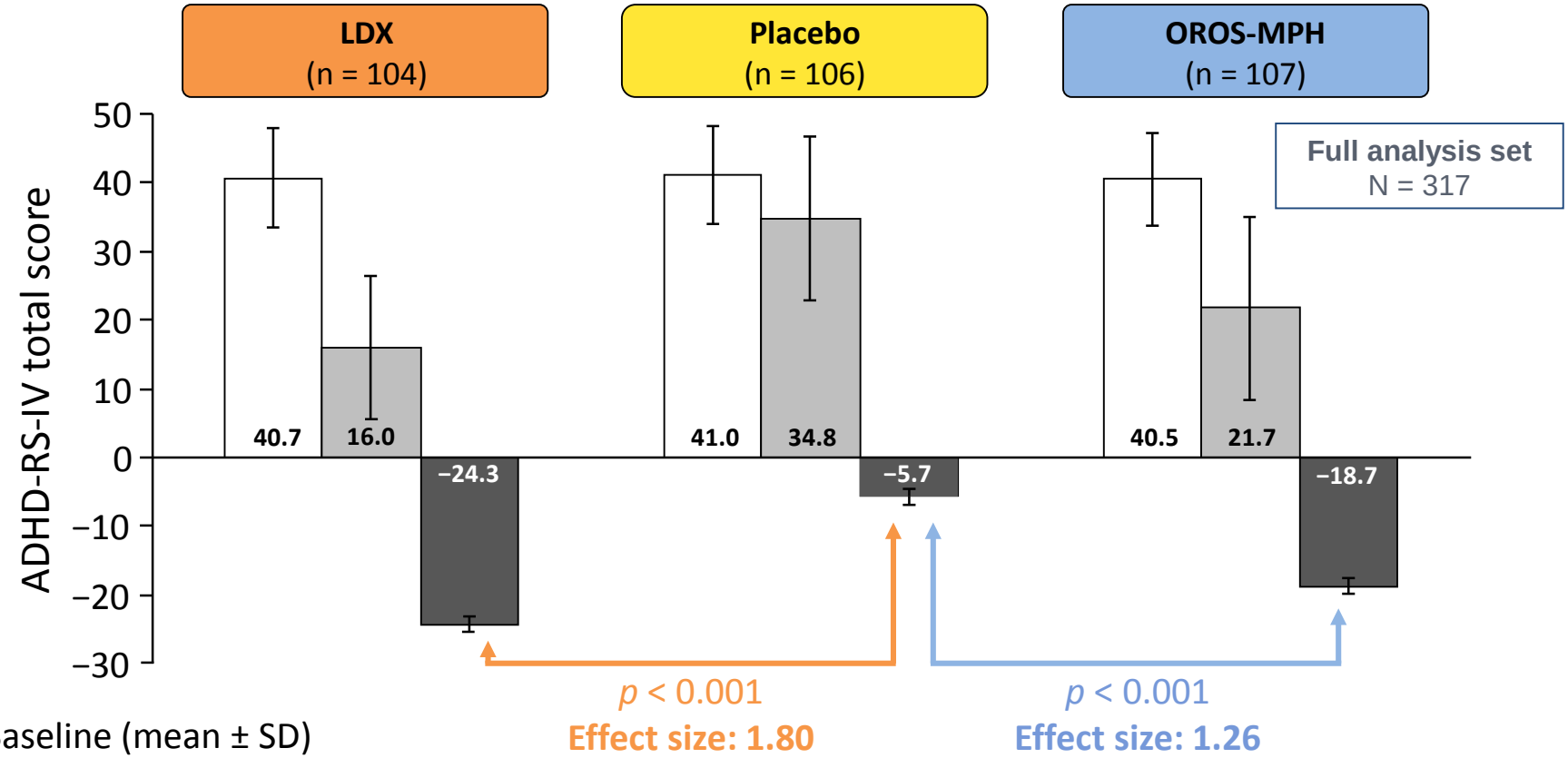
→ *Effect sizes* e *NNTs* dei farmaci per l'ADHD risultano significativamente migliori di quelli di altri farmaci psichiatrici

- **0.5** and **9** per antidepressivi per depressione or OCD dell'adulto
- **0.25** and **10-20** antipsicotici nella terapia della schizofrenia

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

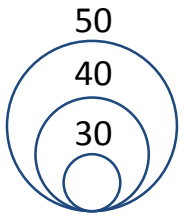
David Coghill[a,*], Tobias Banaschewski[b], Michel Lecendreux[c], Cesar Soutullo[d], Mats Johnson[e], Alessandro Zuddas[f], Colleen Anderson[g], Richard Civil[g], Nicholas Higgins[g], Andrew Lyne[h], Liza Squires[g]

European Neuropsychopharmacology (2013) 23, 1208-1218



p-values and effect sizes are from an ANCOVA model of the change in ADHD-RS-IV total score from baseline to endpoint. ANCOVA, analysis of covariance; SD, standard deviation

Pretreatment mean domain T-scores in three ADHD study populations and controls



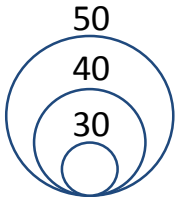
	Study SPD489-326	ADORE study	Pooled ATX studies	Diabetes	Control
Achievement	30.2	30.2	30.5	49.7	48.6
Risk Avoidance	32.3	29.9	30.2	50.0	50.5
Resilience	36.8	36.0	36.0	45.3	44.6
Satisfaction	35.5	32.8	34.4	45.5	42.8
Comfort	44.5	42.5	43.7	50.8	53.5

No statistical comparisons between these studies have been performed, ATX, atomoxetine

Health-Related Quality of Life and Functional Outcomes from a Randomized-Withdrawal Study of Long-Term Lisdexamfetamine Dimesylate Treatment in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

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

CNS Drugs 2014



Open label (≤ 26 weeks)

Randomized withdrawal (6 weeks)

	LDX (n = 262)		**LDX** (n = 76)		**Placebo** (n = 77)	
	Baseline	**Endpoint**	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**
Achievement	30.2	38.9	39.6	40.1	41.2	35.3
Risk Avoidance	32.3	44.1	45.8	47.5	46.8	41.3
Resilience	36.8	40.5	42.0	43.3	42.6	40.2
Satisfaction	35.5	40.3	41.9	44.9	43.3	39.3
Comfort	44.5	49.4	51.0	51.1	51.1	48.5

Guanfacine for attention deficit and hyperactivity disorder in pediatrics: A systematic review and meta-analysis

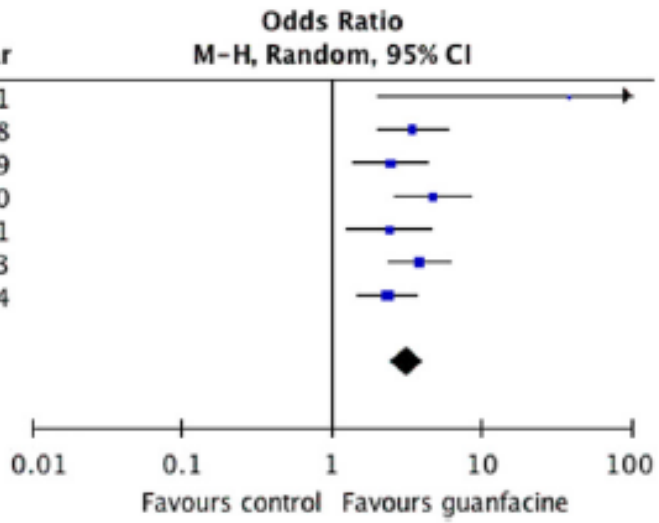
Simona Ruggiero[a], Antonio Clavenna[b,*], Laura Reale[b], Annalisa Capuano[a], Francesco Rossi[a], Maurizio Bonati[b]

ENP 2014

Study or Subgroup	Guanfacine Events	Guanfacine Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Scahill 2001	9	17	0	17	0.8%	39.12 [2.03, 754.53]	2001
Biederman 2008	141	259	22	86	16.6%	3.48 [2.02, 5.98]	2008
Salee 2009	134	258	20	66	15.1%	2.49 [1.39, 4.43]	2009
Connor 2010	93	138	24	79	14.4%	4.74 [2.61, 8.61]	2010
Kollins 2011	69	121	20	57	12.6%	2.45 [1.28, 4.71]	2011
Newcorn 2013	144	227	35	113	19.5%	3.87 [2.39, 6.26]	2013
NCT01081132	104	157	71	157	20.9%	2.38 [1.51, 3.75]	2014
Total (95% CI)		**1177**		**575**	**100.0%**	**3.18 [2.44, 4.13]**	
Total events	694		192				

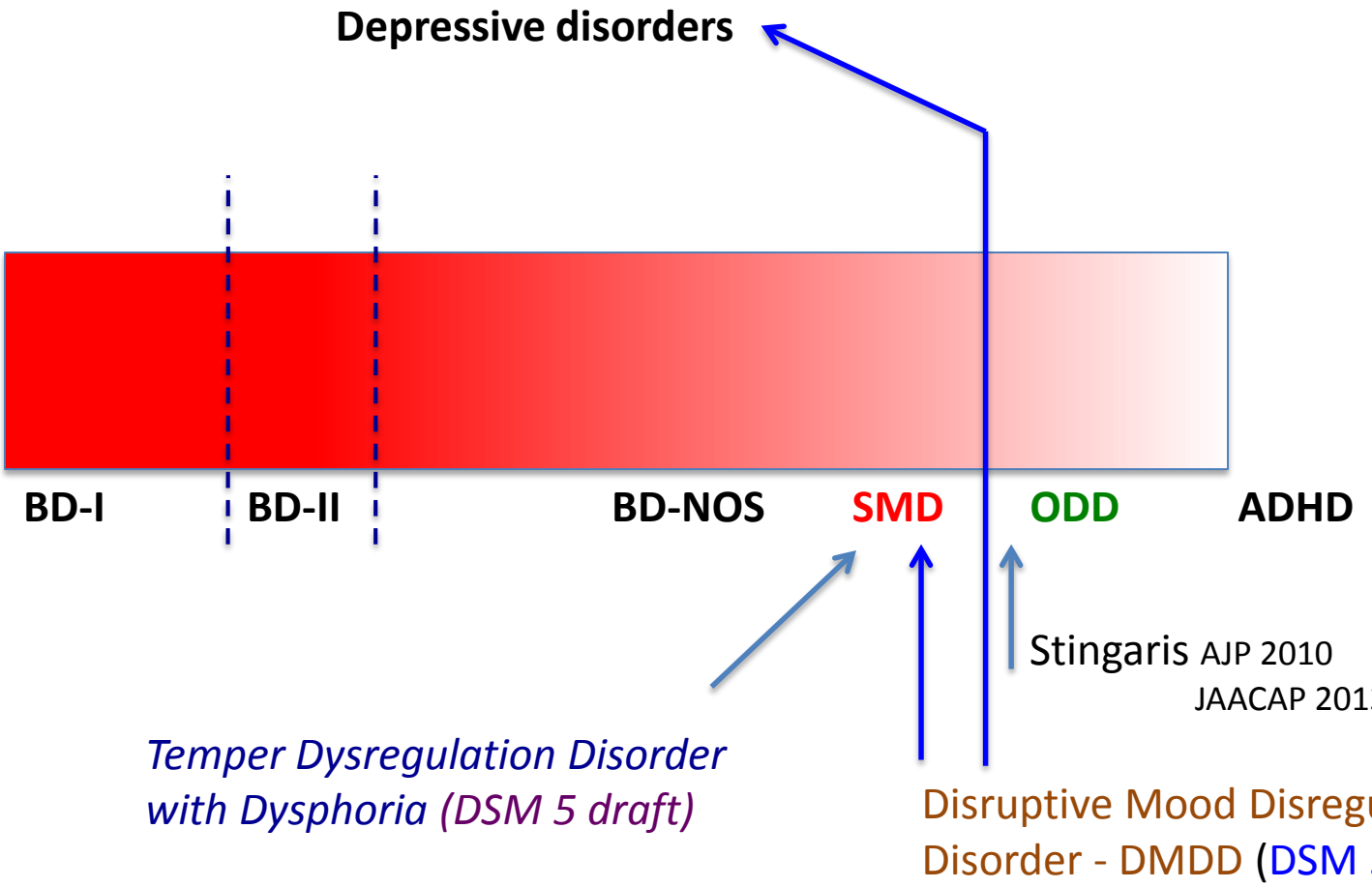
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.08$, df = 6 (P = 0.23); $I^2 = 26\%$

Test for overall effect: Z = 8.62 (P < 0.00001)



Early onset bipolar "spectrum"

a tentative "clinical" nosology

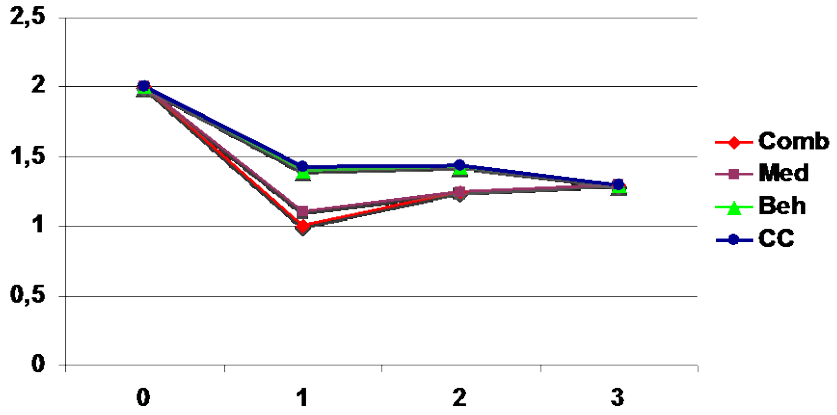


MTA study follow up

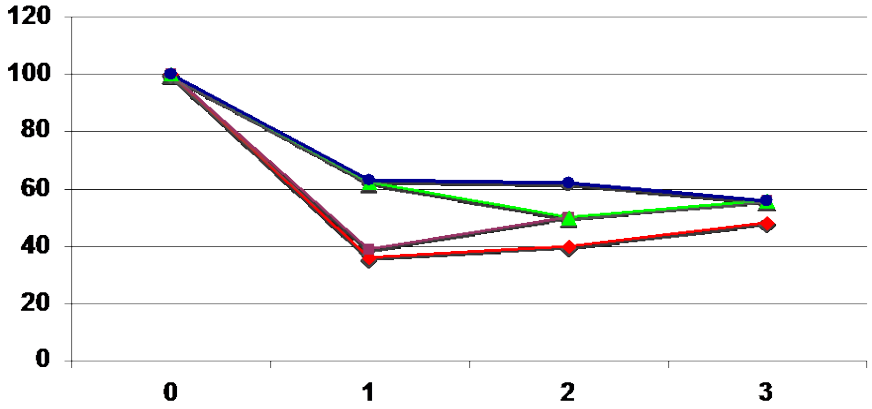
Jensen et al. *JAACAP* 2007

ADHD

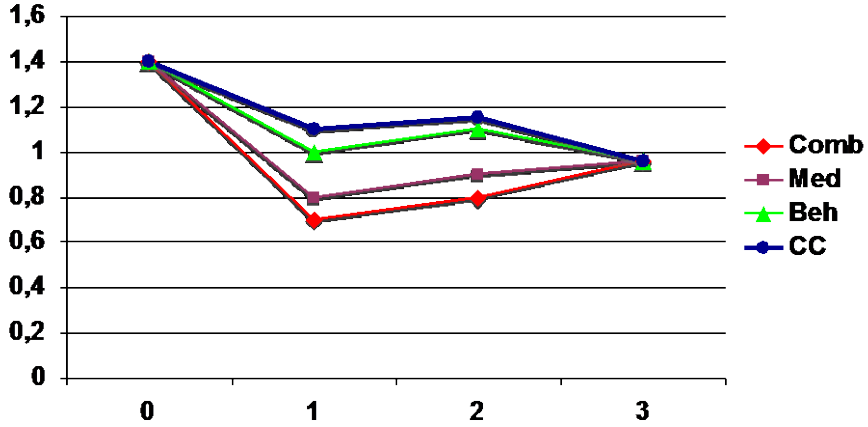
Symtoms

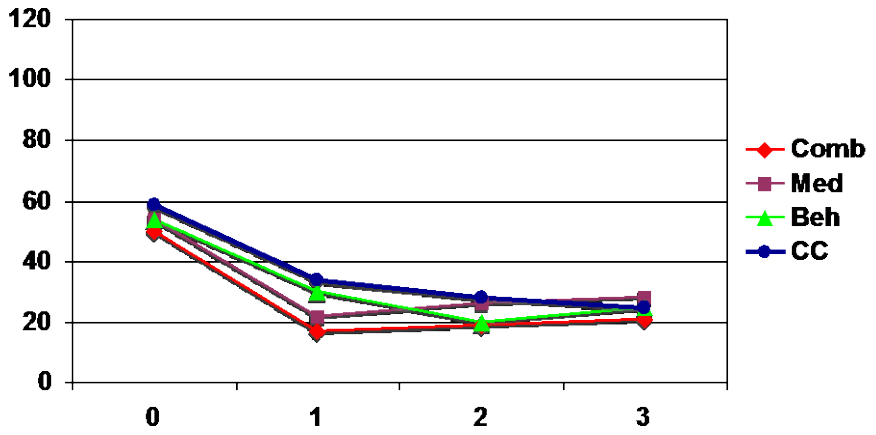


Diagnostic status



ODD





Percentuale di bambini che assumevano farmaci nelle diverse fasi dello studio MTA

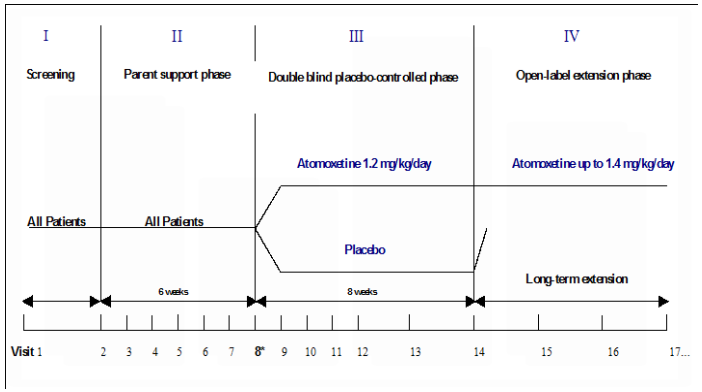
Years / Treatment	0	1	2	3
Comb	20	90	70	71
Med	22	90	70	71
Beh	19	14	35	43
CC	20	60	62	62

Jensen et al. *JAACAP* 2007

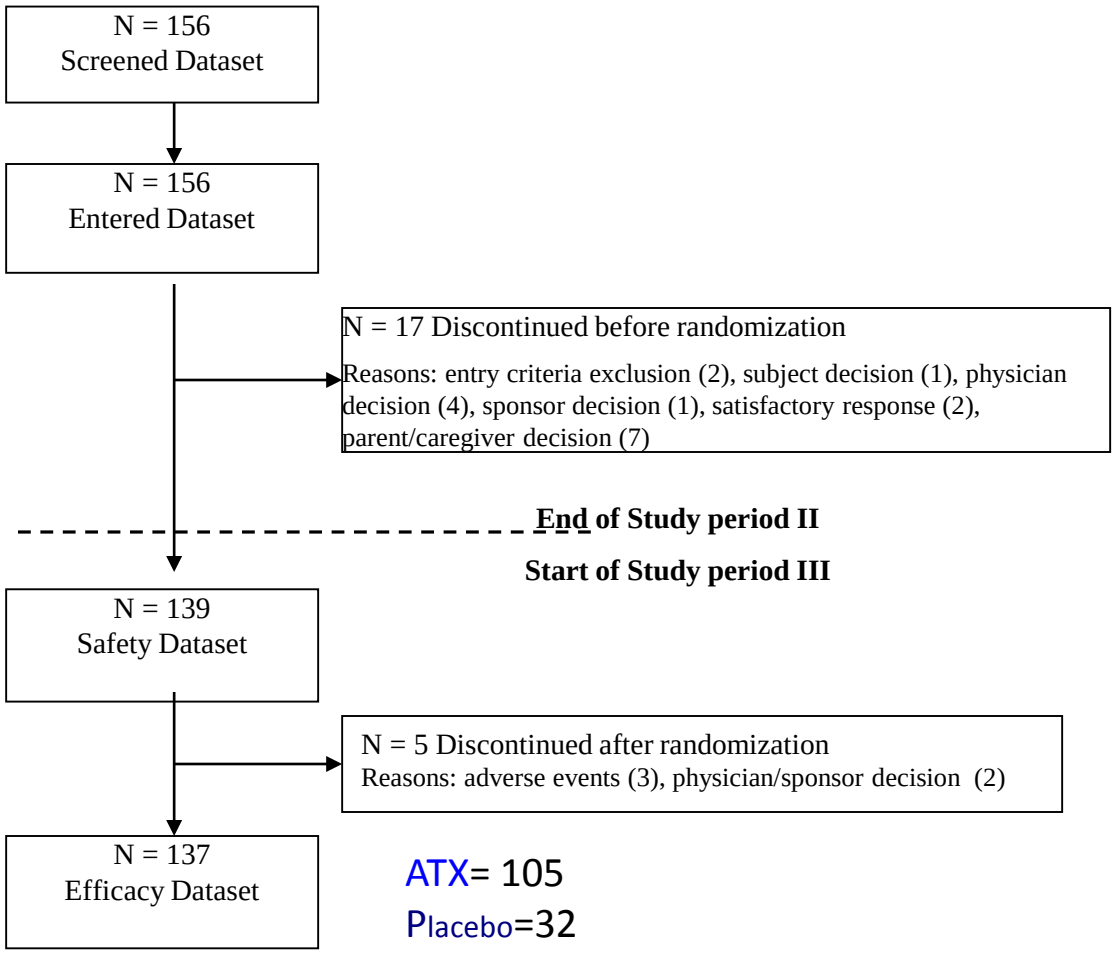
Atomoxetine hydrochloride in the treatment of children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: A placebo-controlled Italian study

Grazia Dell'Agnello [a], Dino Maschietto [b], Carmela Bravaccio [c], Filippo Calamoneri [d], Gabriele Masi [e], Paolo Curatolo [f], Dante Besana [g], Francesca Mancini [a], Andrea Rossi [a], Lynne Poole [h], Rodrigo Escobar [i], Alessandro Zuddas [j,*]

European Neuropsychopharmacology 2009



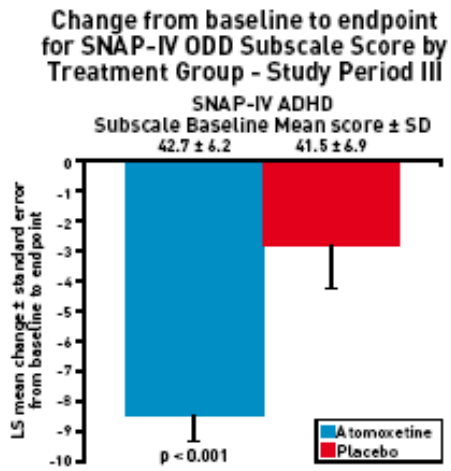
Age 6-15
ADHD+ODD (DSM-IV criteria)
SNAP-ADHD >1.5 SD
SNAP-ODD >15
IQ >70

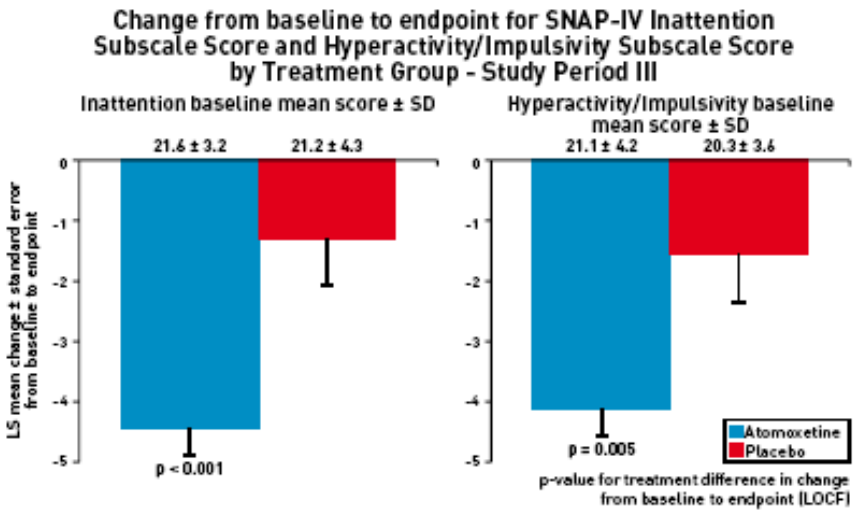


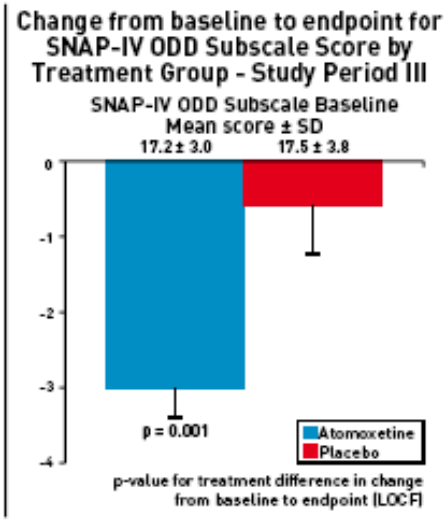
ATX= 105
Placebo=32

Atomoxetine hydrochloride in the treatment of children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: A placebo-controlled Italian study

Grazia Dell'Agnello [a], Dino Maschietto [b], Carmela Bravaccio [c], Filippo Calamoneri [d], Gabriele Masi [e], Paolo Curatolo [f], Dante Besana [g], Francesca Mancini [a], Andrea Rossi [a], Lynne Poole [h], Rodrigo Escobar [i], Alessandro Zuddas [j,*]







Age of Methylphenidate Treatment Initiation in Children With ADHD and Later Substance Abuse: Prospective Follow-Up Into Adulthood

Mannuzza et al. *AJP* 2008

Effect of Age

	Age of medication onset
subst. use disorder (No-alcohol) (n=65)	**9.10**+1.74
Absence of subst. use disorder (n=111)	**8.52**+1.55

t=2.31; df=174, p=0.02

***Rate of* subst. use disorder (No-alcohol):**

Starting before age 8 **27**%
Starting after age 8 **47**% **p=0.02**

Control non ADHD group **29**% **p=0.10**

No effect of ADHD duration per se

Risperidone Added to Parent Training and Stimulant Medication: Effects on Attention-Deficit/ Hyperactivity Disorder, Oppositional Defiant Disorder, Conduct Disorder, and Peer Aggression

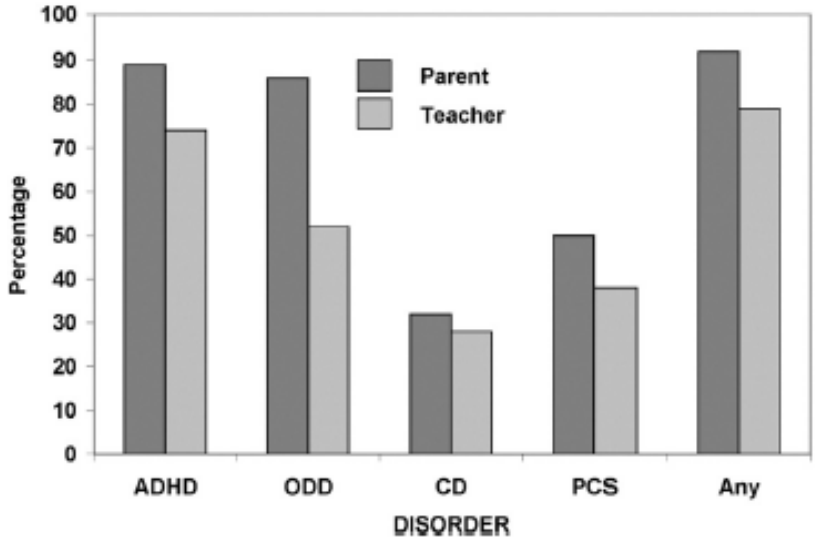
Kenneth D. Gadow, PhD, L. Eugene Arnold, MEd, MD, Brooke S.G. Molina, PhD, Robert L. Findling, MD, MBA, Oscar G. Bukstein, MD, MPH, Nicole V. Brown, MS, Nora K. McNamara, MD, E. Victoria Rundberg-Rivera, MD, Xiaobai Li, PhD, Heidi L. Kipp, MEd, LPC, Jayne Schneider, PhD, Cristan A. Farmer, PhD, Jennifer L. Baker, MA, Joyce Sprafkin, PhD, Robert R. Rice, Jr., PhD, Srihari S. Bangalore, MD, MPH, Eric M. Butter, PhD, Kristin A. Buchan-Page, BA, Elizabeth A. Hurt, PhD, Adrienne B. Austin, BA, Sabrina N. Grondhuis, MA, Michael G. Aman, PhD

JAACAP 2014

- 168 children, 6-12; 8.9 + 2.0 years
- Boys 77%, mean, IQ 97.1I
- 53% whites, 53% working parents,

Basic: MPH (45 mg/day) + parent training

Augmented : Basic + risperidone (1.9 mg/day)



Symptoms	Baseline n	Baseline Mean (SD)	Week 3 n	Week 3 Mean (SD)	Week 9 n	Week 9 Mean (SD)	p^a	p^b	Estimate (CI)[b]	ES[c]
Parent Ratings										
ADHD							.051	.129	0.15 (−0.04, 0.34)	0.13
Basic	84	2.4 (0.5)	82	1.3 (0.8)	71	1.0 (0.7)				
Augmented	84	2.3 (0.6)	75	1.3 (0.7)	66	0.8 (0.5)				
ODD							.002	.014	0.27 (0.06, 0.49)	0.27
Basic	84	2.4 (0.5)	82	1.4 (0.9)	71	1.1 (0.8)				
Augmented	84	2.3 (0.6)	75	1.5 (0.8)	66	0.8 (0.6)				
CD[d]							NA	.145*	0.06 (−0.02, 0.13)	0.09
Basic	84	0.6 (0.4)	NA	NA	77	0.2 (0.2)				
Augmented	84	0.5 (0.4)			73	0.1 (0.2)				
Peer Conflict Scale							.175	.022*	0.14 (0.02, 0.26)	0.32
Basic	84	1.5 (0.9)	82	0.8 (0.8)	71	0.6 (0.7)				
Augmented	83	1.5 (0.9)	75	0.8 (0.8)	66	0.3 (0.4)				
Teacher Ratings										
ADHD							NA	.021	0.35 (0.05, 0.65)	0.61
Basic	46	1.6 (0.6)	39	0.8 (0.7)	48	0.8 (0.6)				
Augmented	40	1.8 (0.8)	34	0.9 (0.7)	38	0.6 (0.5)				
ODD							NA	.120*	0.17 (−0.04, 0.38)	0.34
Basic	46	1.2 (1.0)	38	0.4 (0.6)	48	0.4 (0.6)				
Augmented	40	1.5 (1.1)	34	0.6 (0.8)	38	0.4 (0.6)				
CD[d]							NA	.087*	0.14 (−0.02, 0.31)	0.14
Basic	45	0.4 (0.4)	NA	NA	39	0.1 (0.2)				
Augmented	37	0.6 (0.6)			30	0.1 (0.3)				
Peer Conflict Scale							NA	.163*	0.15 (−0.10, 0.40)	0.29
Basic	46	0.7 (0.8)	38	0.2 (0.5)	48	0.2 (0.3)				
Augmented	40	0.9 (0.9)	34	0.3 (0.6)	38	0.2 (0.4)				

Symptoms	Baseline n	Baseline Mean (SD)	Week 3 n	Week 3 Mean (SD)	Week 9 n	Week 9 Mean (SD)	p^a	p^b	Estimate (CI)[b]	ES[c]
Parent Ratings										
ADHD							.051	.129	0.15 (−0.04, 0.34)	0.13
Basic	84	2.4 (0.5)	82	1.3 (0.8)	71	1.0 (0.7)				
Augmented	84	2.3 (0.6)	75	1.3 (0.7)	66	0.8 (0.5)				
ODD							.002	.014	0.27 (0.06, 0.49)	0.27
Basic	84	2.4 (0.5)	82	1.4 (0.9)	71	1.1 (0.8)				
Augmented	84	2.3 (0.6)	75	1.5 (0.8)	66	0.8 (0.6)				
CD[d]							NA	.145*	0.06 (−0.02, 0.13)	0.09
Basic	84	0.6 (0.4)	NA	NA	77	0.2 (0.2)				
Augmented	84	0.5 (0.4)			73	0.1 (0.2)				
Peer Conflict Scale							.175	.022*	0.14 (0.02, 0.26)	0.32
Basic	84	1.5 (0.9)	82	0.8 (0.8)	71	0.6 (0.7)				
Augmented	83	1.5 (0.9)	75	0.8 (0.8)	66	0.3 (0.4)				
Teacher Ratings										
ADHD							NA	.021	0.35 (0.05, 0.65)	0.61
Basic	46	1.6 (0.6)	39	0.8 (0.7)	48	0.8 (0.6)				
Augmented	40	1.8 (0.8)	34	0.9 (0.7)	38	0.6 (0.5)				
ODD							NA	.120*	0.17 (−0.04, 0.38)	0.34
Basic	46	1.2 (1.0)	38	0.4 (0.6)	48	0.4 (0.6)				
Augmented	40	1.5 (1.1)	34	0.6 (0.8)	38	0.4 (0.6)				
CD[d]							NA	.087*	0.14 (−0.02, 0.31)	0.14
Basic	45	0.4 (0.4)	NA	NA	39	0.1 (0.2)				
Augmented	37	0.6 (0.6)			30	0.1 (0.3)				
Peer Conflict Scale							NA	.163*	0.15 (−0.10, 0.40)	0.29
Basic	46	0.7 (0.8)	38	0.2 (0.5)	48	0.2 (0.3)				
Augmented	40	0.9 (0.9)	34	0.3 (0.6)	38	0.2 (0.4)				

Disorder	Baseline n	Baseline Mean (SD)	Week 3 n	Week 3 Mean (SD)	Week 9 n	Week 9 Mean (SD)	p^a	p^b	Estimate (CI)[b]	ES[c]
Parent Ratings										
ADHD										
Attention							.034	.156	0.15 (-0.06, 0.36)	0.11
Basic	84	2.5 (0.6)	82	1.4 (0.8)	71	1.1 (0.7)				
Augmented	84	2.4 (0.6)	75	1.4 (0.8)	66	0.9 (0.6)				
Hyperactivity							.329	.237	0.13 (-0.08, 0.33)	0.15
Basic	84	2.3 (0.8)	82	1.2 (0.9)	71	0.8 (0.8)				
Augmented	84	2.2 (0.8)	75	1.2 (0.9)	66	0.6 (0.6)				
Impulsivity							.475	.243	0.14 (-0.10, 0.39)	0.08
Basic	84	2.3 (0.7)	82	1.4 (0.9)	71	1.1 (0.9)				
Augmented	84	2.1 (0.9)	75	1.3 (0.8)	66	0.8 (0.7)				
ODD										
Anger/irritability							.001	.026	0.27 (0.03, 0.50)	0.19
Basic	84	2.3 (0.7)	82	1.4 (0.9)	71	1.1 (0.9)				
Augmented	84	2.2 (0.7)	75	1.4 (0.8)	66	0.7 (0.6)				
Noncompliance							.005	.015	0.28 (0.05, 0.50)	0.30
Basic	84	2.4 (0.5)	82	1.4 (0.9)	71	1.1 (0.8)				
Augmented	84	2.3 (0.6)	75	1.5 (0.8)	66	0.8 (0.6)				
Teacher Ratings										
ADHD										
Inattention							NA	.060	0.33 (-0.01, 0.68)	0.38
Basic	46	1.8 (0.8)	39	1.0 (0.8)	48	1.0 (0.7)				
Augmented	40	2.0 (0.8)	34	1.1 (0.8)	38	0.8 (0.6)				
Hyperactivity							NA	.218	0.24 (-0.15, 0.63)	0.30
Basic	46	1.3 (0.8)	38	0.5 (0.7)	48	0.4 (0.5)				
Augmented	40	1.5 (1.0)	34	0.7 (0.8)	38	0.5 (0.6)				
Impulsivity							NA	.011*	0.29 (0.07, 0.51)	0.75
Basic	46	1.4 (0.9)	38	0.7 (0.9)	48	0.7 (0.8)				
Augmented	40	1.7 (1.0)	34	0.9 (0.9)	38	0.5 (0.6)				
ODD							NA			
Anger/irritability								.317	0.19 (-0.19, 0.57)	0.17
Basic	46	1.2 (1.0)	38	0.4 (0.7)	48	0.5 (0.7)				
Augmented	40	1.4 (1.2)	34	0.6 (0.9)	38	0.4 (0.7)				
Noncompliance							NA	.175	0.29 (-0.13, 0.70)	0.23
Basic	46	1.2 (1.0)	38	0.4 (0.6)	48	0.4 (0.7)				
Augmented	40	1.5 (1.2)	34	0.6 (0.8)	38	0.4 (0.6)				

Outline

- L'ADHD è un disturbo eterogeneo le cui presentazione clinica si modifica nel corso della vita*: interventi terapeutici differenziati?*
- Diversa e specifica efficacia delle terapie farmacologiche rispetto agli interventi non-farmacologici: *chi valuta che cosa?*
- Sicurezza dei farmaci per l'ADHD: *quale rapporto costo-benefici?*
- *Take home message*

Approach to Common Adverse Events during Stimulant Treatment

Adverse event	***Possible Approach***
Loss of Appetite (es. No food intake at lunch)	1. If early in treatment, look for possible tolerance over time to this side effect 2. Decrease dose, if clinically possible 3. Increase caloric intake at breakfast and dinner. 4. Monitor weight
Loss of weight	1. Decrease dose (unless child is overweight). 2. Increase caloric intake at breakfast and dinner; allow late evening meals; add caloric snacks in between. 3. Consider lower dose or no medication during weekend 4. Monitor weight: tolerance to this effect often develops.
Early insomnia (difficulty falling asleep)	1. If immediate release prep.: allow no dosing after 3 pm. 2. If extended release prep.: a. reduce dosing, b. change formulation or c. start treatment early in the morning and give medication before breakfast (more rapid absorption). 3. Be sure that there is an appropriate bedtime routine (e.g., reading). 4. Add evening dose covering bedtime. 5. Consider atomoxetine.
Blunted affect (“zombie”-like appearance)	1. Decrease dose, if possible. 2. Try different preparation 3. Consider atomoxetine
Tics (new onset)	1. Discontinue treatment and see if tics go away. 2. Restart treatment and see if tics come back. 3. Consider atomoxetine

Eur Child Adolesc Psychiatry
DOI 10.1007/s00787-010-0140-6

ORIGINAL CONTRIBUTION

European guidelines on managing adverse effects of medication for ADHD

J. Graham · T. Banaschewski · J. Buitelaar · D. Coghill · M. Danckaerts · R. W. Dittmann · M. Döpfner · R. Hamilton · C. Hollis · M. Holtmann · M. Hulpke-Wette · M. Lecendreux · E. Rosenthal · A. Rothenberger · P. Santosh · J. Sergeant · E. Simonoff · E. Sonuga-Barke · I. C. K. Wong · A. Zuddas · H.-C. Steinhausen · E. Taylor · (for the European Guidelines Group)

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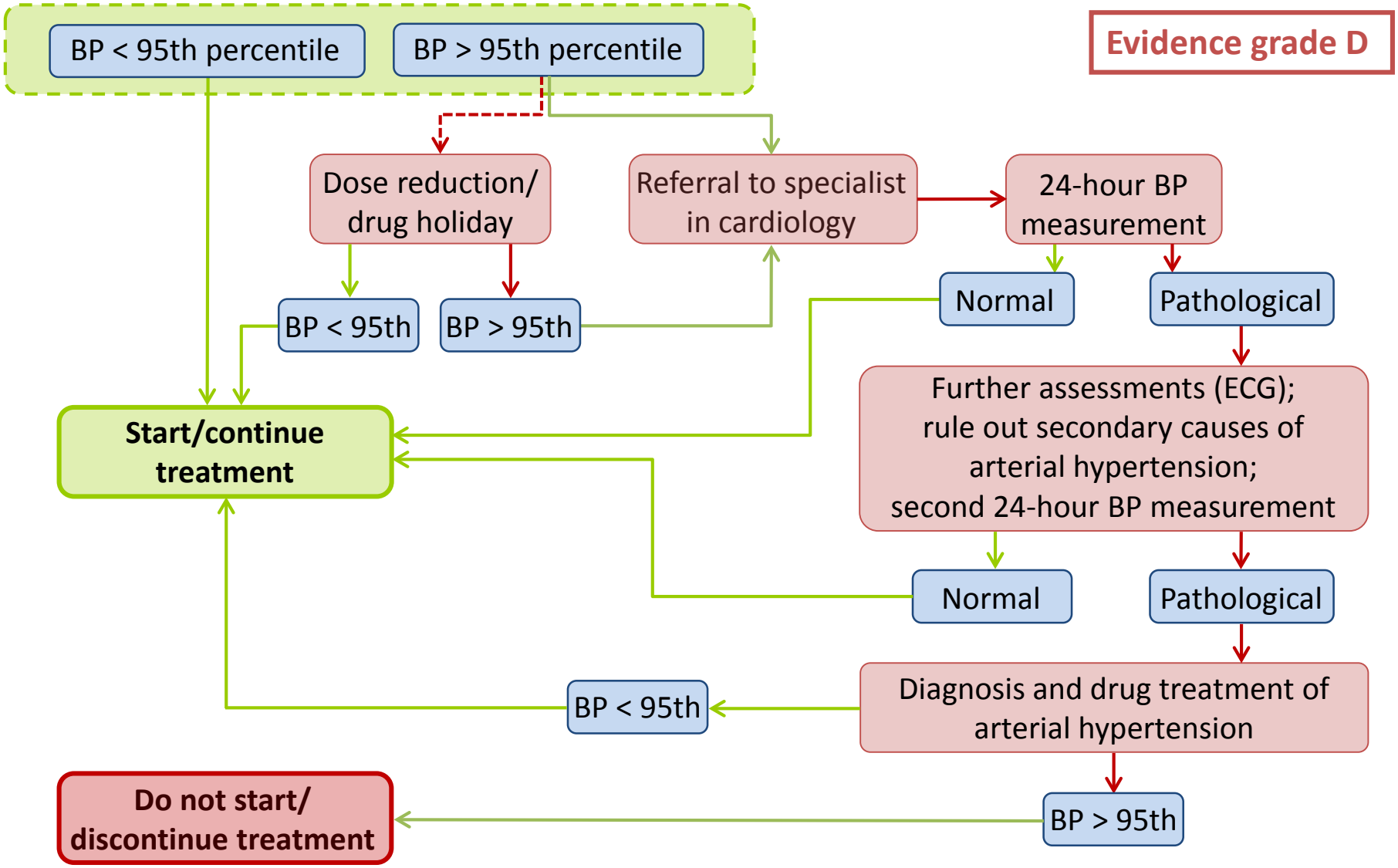
ACAMH
Journal of Child Psychology and Psychiatry 54:3 (2013), pp 227–246
doi:10.1111/jcpp.12036

Practitioner Review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents

Samuele Cortese,[1,2,3,*] Martin Holtmann,[4,*] Tobias Banaschewski,[5] Jan Buitelaar,[6] David Coghill,[7] Marina Danckaerts,[8] Ralf W. Dittmann,[5] John Graham,[9] Eric Taylor,[10] Joseph Sergeant,[11] on behalf of the European ADHD Guidelines Group†

How should I manage cardiovascular risk during treatment with ADHD drugs?



European Medicines Agency
Press office

London, 22 January 2009
Doc. Ref. EMEA/22315/2009

A seguito dell'analisi dei dati disponibili, il CHMP ha stabilito che:

non è necessaria alcuna restrizione urgente dell'uso dei medicinali a base di metilfenidato,

Al fine di massimizzare l'uso sicuro di tali medicinali siano necessarie nuove raccomandazioni per:

- la prescrizione,
- lo screening dei pazienti prima del trattamento
- il monitoraggio durante la terapia.

European Medicines Agency
Press office

London, 22 January 2009
Doc. Ref. EMEA/22315/2009

Il CHMP ha deciso che in tutti gli stati membri dell'UE, l'informazione in essi contenuta debba riportare i seguenti elementi in tutti gli stati membri dell'UE:

1. Prima del trattamento, tutti i pazienti devono essere controllati per verificare se abbiano alterazioni della **pressione arteriosa** o del **ritmo cardiaco**.

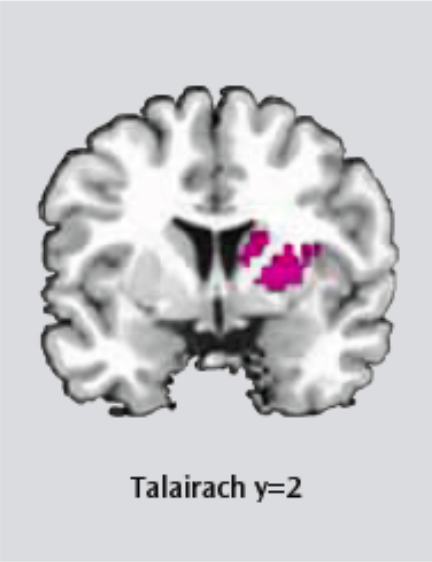
Deve essere verificato anche se vi sia una **storia familiare di patologie cardiovascolari**.

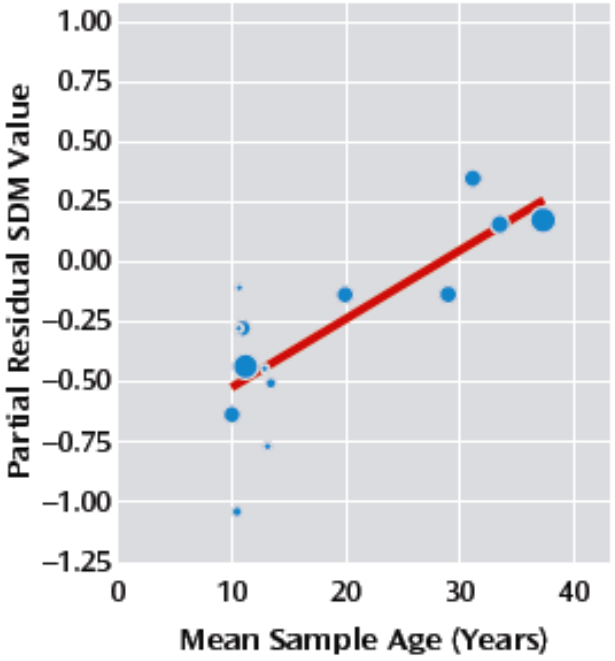
I pazienti che presentano tali problematiche non devono essere trattati senza che sia stata condotta una valutazione specialistica;

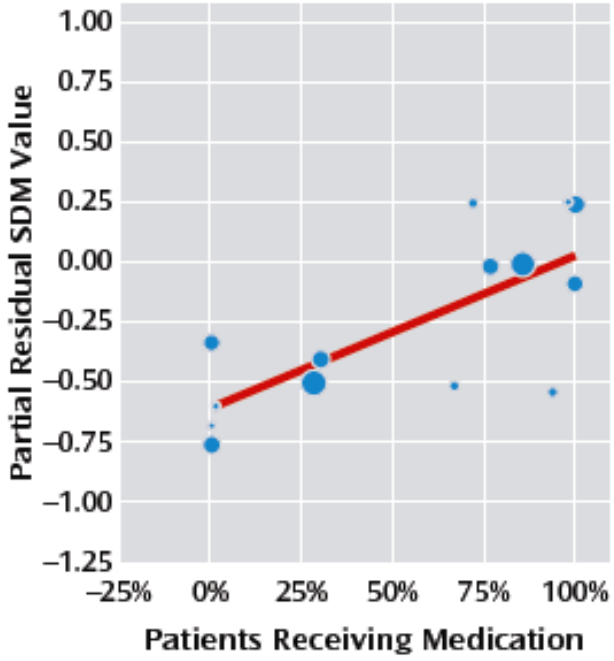
2. **Durante il trattamento**, la pressione arteriosa ed il ritmo cardiaco devono essere monitorati regolarmente. Se dovessero insorgere problemi, questi vanno immediatamente approfonditi;

Gray Matter Volume Abnormalities in ADHD: Voxel-Based Meta-Analysis Exploring the Effects of Age and Stimulant Medication

FIGURE 2. Results of the Metaregression Analysis Showing Independent Associations of Mean Age and Percentage of Patients Receiving Stimulant Medication With More Normal Gray Matter Volumes in the Right Basal Ganglia[a]







[a] In the graphs, each study is represented as a dot, with dot size reflecting sample size: large dots indicate samples with over 40 patients; medium dots, samples with 20–40 patients; and small dots, samples with under 20 patients. The regression line (metaregression signed differential mapping slope) is presented as a straight line. SDM refers to the signed differential mapping meta-analytic method (www.sdmproject.com).

Nakao et al. *AJP* 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Medication for Attention Deficit–Hyperactivity Disorder and Criminality

Paul Lichtenstein, Ph.D., Linda Halldner, M.D., Ph.D., Johan Zetterqvist, M.Ed., Arvid Sjölander, Ph.D., Eva Serlachius, M.D., Ph.D., Seena Fazel, M.B., Ch.B., M.D., Niklas Långström, M.D., Ph.D., and Henrik Larsson, M.D., Ph.D.

November 22, 2012 Vol. 367 No. 21

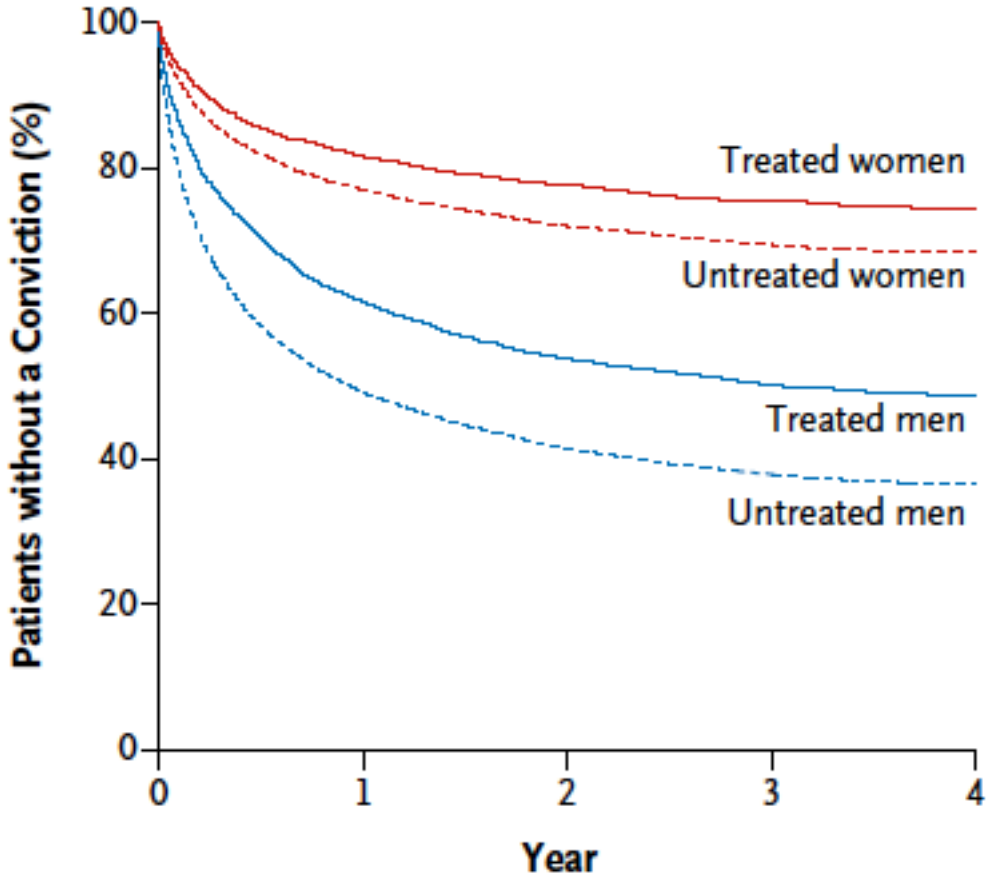


Figure 1. Extended Kaplan–Meier Curves for Patients in the Swedish Patient Register with a Diagnosis of ADHD Who Were Born No Later Than 1990, According to Sex and Medication Status.

Serious Transport Accidents in Adults With Attention-Deficit/Hyperactivity Disorder and the Effect of Medication

A Population-Based Study

Zheng Chang, PhD; Paul Lichtenstein, PhD; Brian M. D'Onofrio, PhD; Arvid Sjölander, PhD; Henrik Larsson, PhD

JAMA 2014

Table 2. Association Between ADHD and Serious Transport Accidents in Swedish Adults

Characteristic	Person-years at Risk	No. of Accidents	HR (95% CI)	
			Crude Association	Adjusted Association
Men				
ADHD	41 793	897	2.45 (2.27-2.65)	1.47 (1.32-1.63)
Non-ADHD	415 662	3217	1 [Reference]	1 [Reference]
Women				
ADHD	27 399	330	2.10 (1.86-2.38)	1.45 (1.24-1.71)
Non-ADHD	271 866	1417	1 [Reference]	1 [Reference]

Table 3. Rate of Serious Transport Accidents During Medication Periods Compared With Nonmedication Periods Among Swedish Adult Patients With ADHD

Characteristic	Person-years at Risk	No. of Accidents	HR (95% CI)	
			Between Individual	Within Individual
Men				
Medicated	8377	144	0.71 (0.57-0.89)	0.42 (0.23-0.75)
Nonmedicated	33 416	753	1 [Reference]	1 [Reference]
Women				
Medicated	6195	67	0.92 (0.78-1.23)	2.35 (0.83-6.64)
Nonmedicated	21 204	263	1 [Reference]	1 [Reference]

Linee-guida Europee
Raccomandazioni generali

Prima della prescrizione

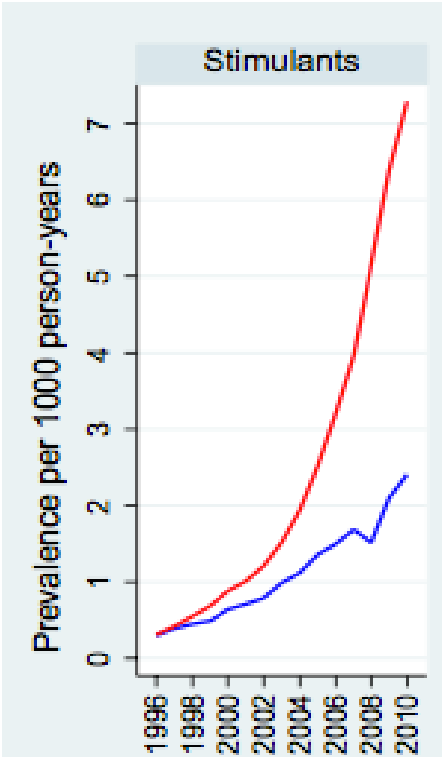
- Esame Fisico (visita medica)
- Anamnesi accurata (anche *familiare*) per convulsioni / epilessia
- Valutazione basale di ogni possibile comorbidità psichiatrica.
- Considerare ***sempre*** il rischio cardiovascolare
  - Anomalie strutturali cardiache (***talvolta difficili da identificare...*****)**
  - Storia familiare di cardiopatie precoci
  - Indagare sempre su sincope da esercizio
    (consultare il cardiologo).

Linee-guida Europee
Raccomandazioni generali

Durante il monitoraggio indagare sempre su:

- terapie associate
- convulsioni,
- irregolarità ritmo cardiaco
- segni di danno epatico (sub-ittero, urine scure, sintomi simil-influenzali)
- Irritabilità & ideazione o comportamenti suicidari

Denmark



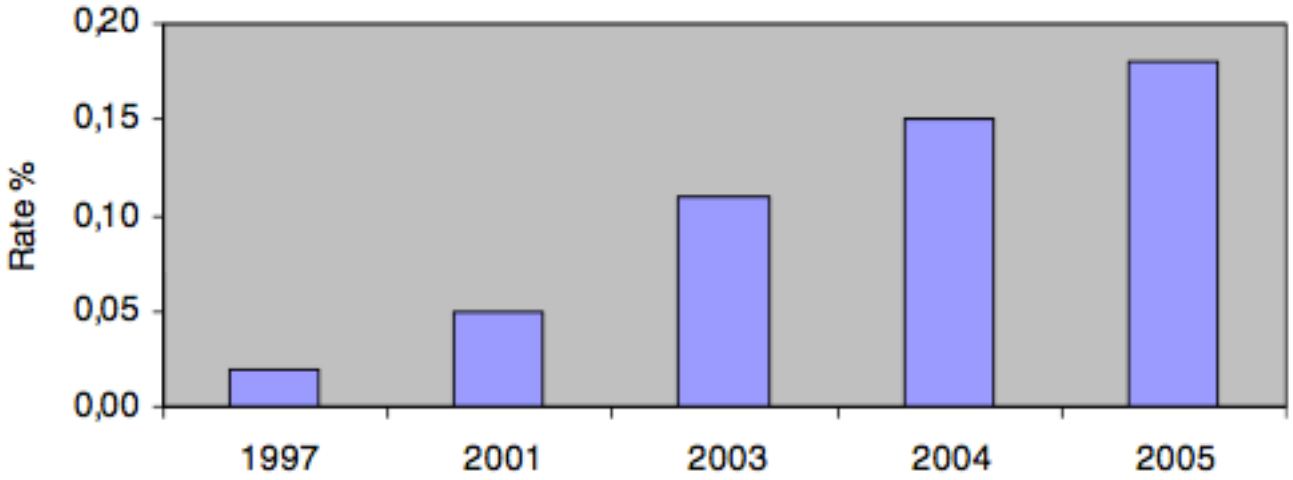
Steinhausen et al.,

Acta Psych Scand, 2014

Non-adjusted prevalence rate

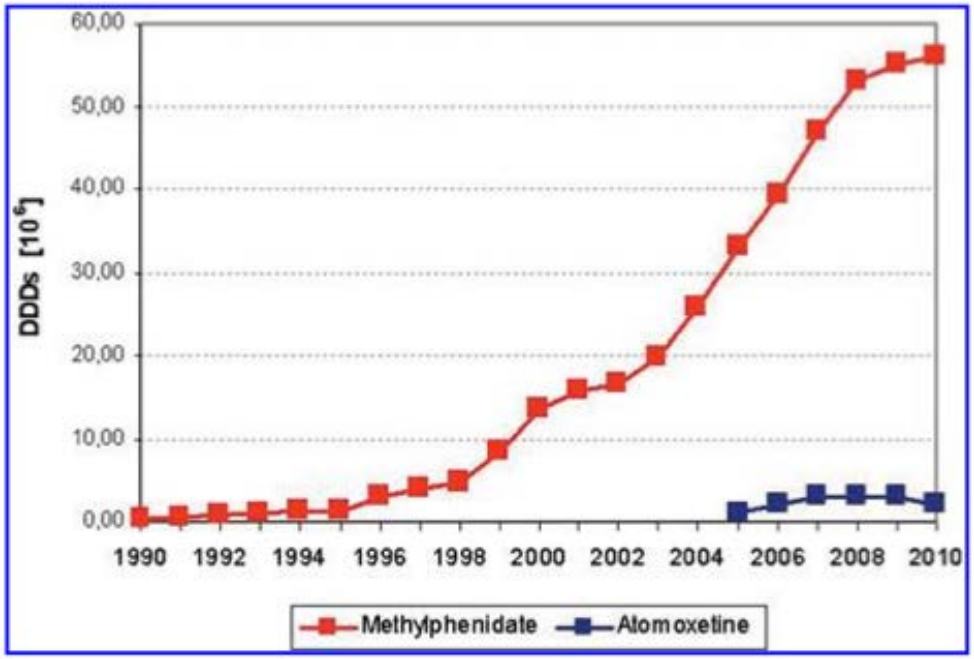
Adjusted prevalence rate

France



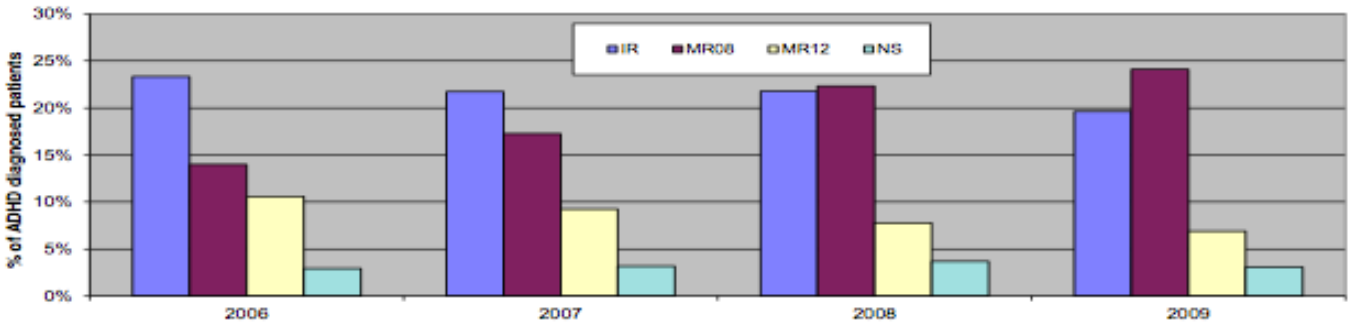
Knellwolf et al.,
Eur J Clin Pharmacol
2008

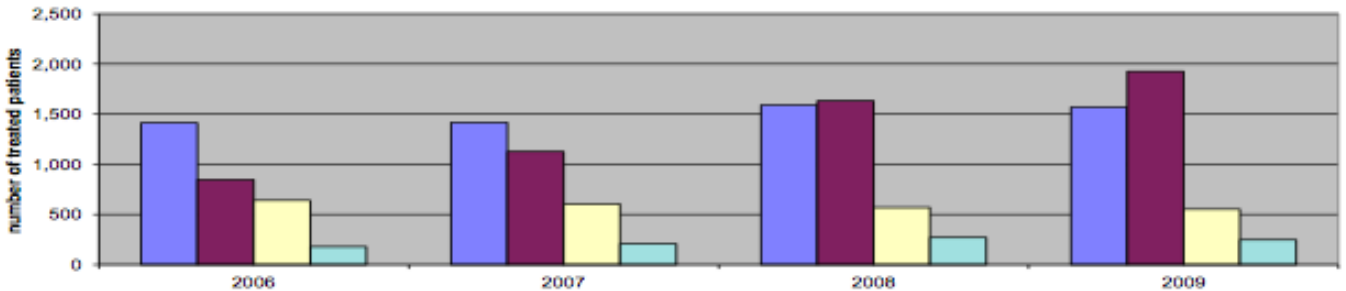
Germany



Million defined daily doses (DDDs)

Garbe et al., *JCAP* 2012



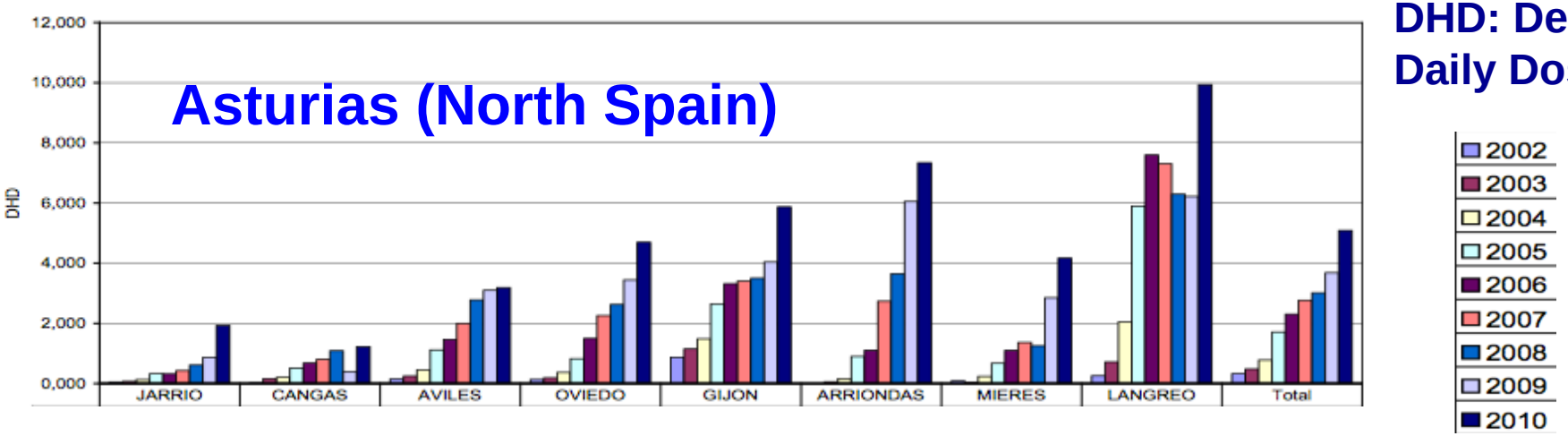


Norbaden (South Germany)

Schlander et al., *ISPOR*, 2011

Spain

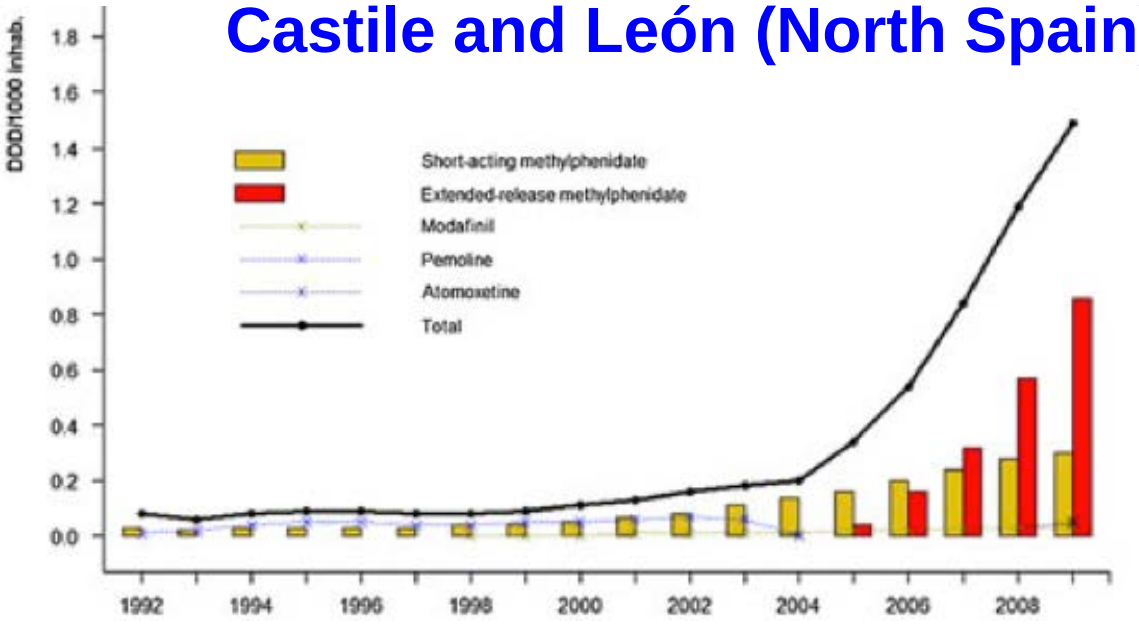
Asturias (North Spain)



DHD: Defined Daily Doses

Fernández Pérez & Carbajo, *Rev Psyq Inf*, 2012

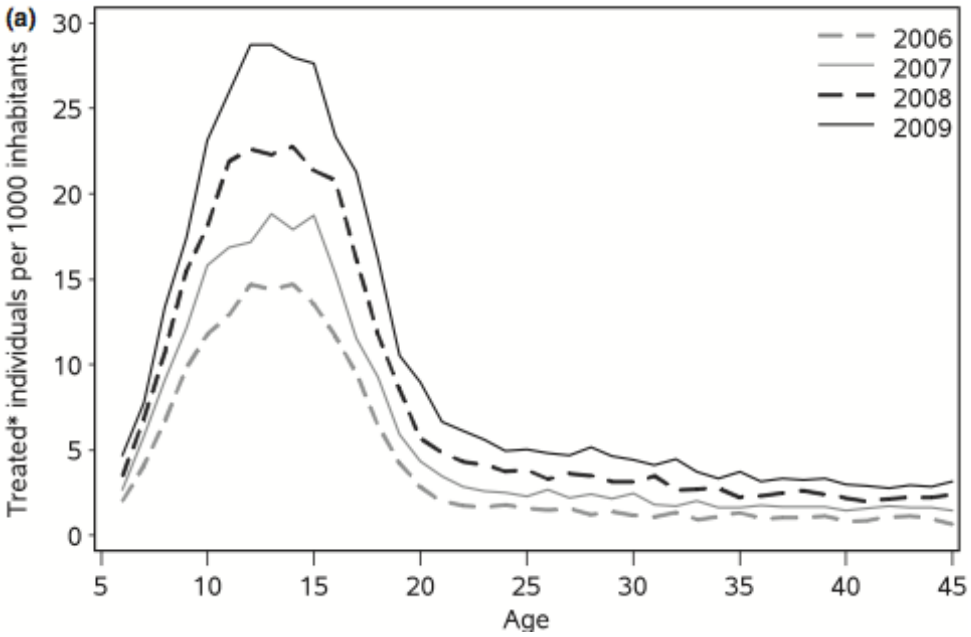
Castile and León (North Spain)



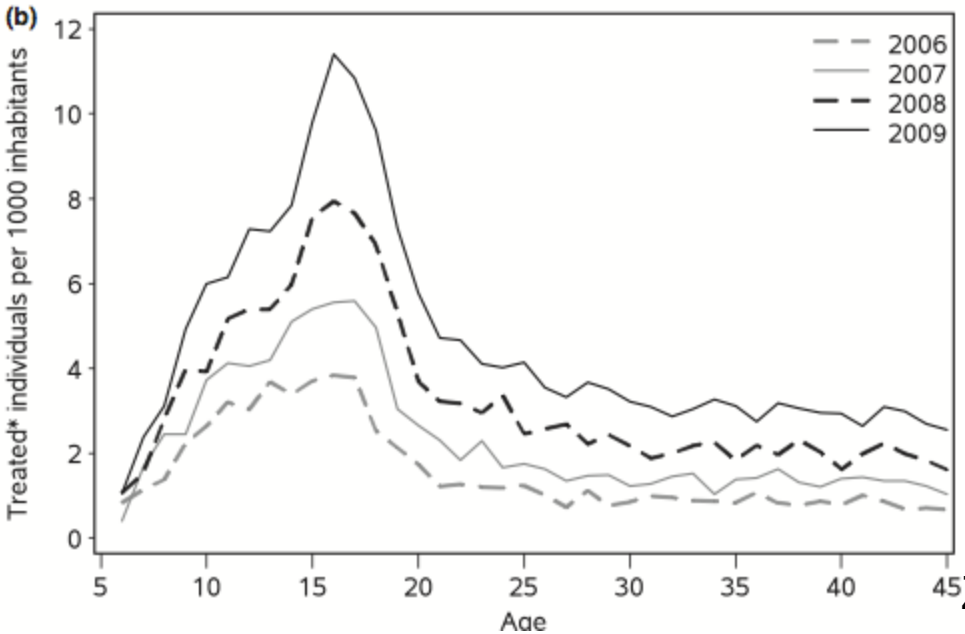
Defined daily doses per 1000 inhabitants

Treceño et al., *Pharmacoepid And Drug Safety*, 2012

Sweden



Males



Females

Zetterqvist et al., *Acta Psych Scan*, 2013

UK

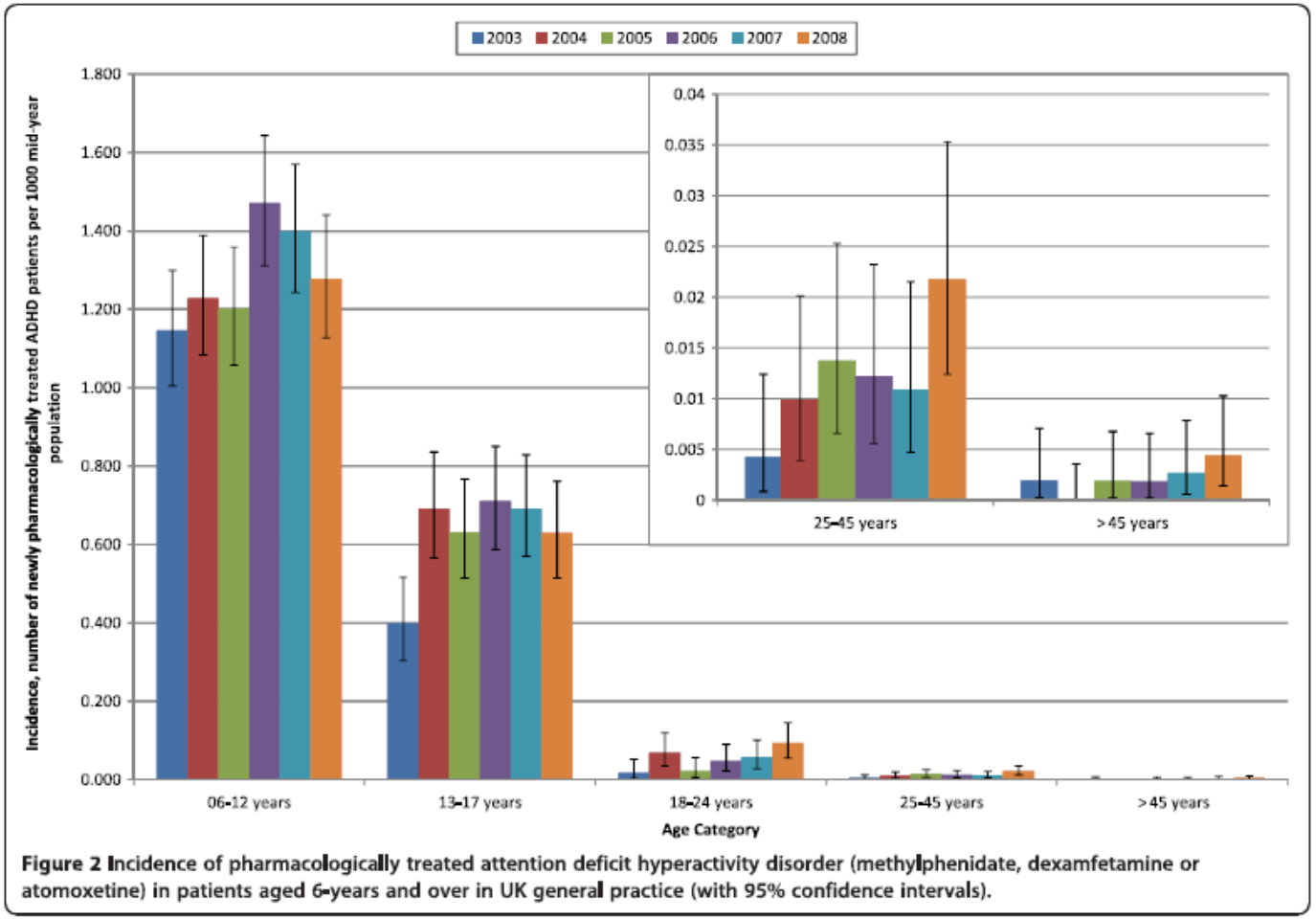


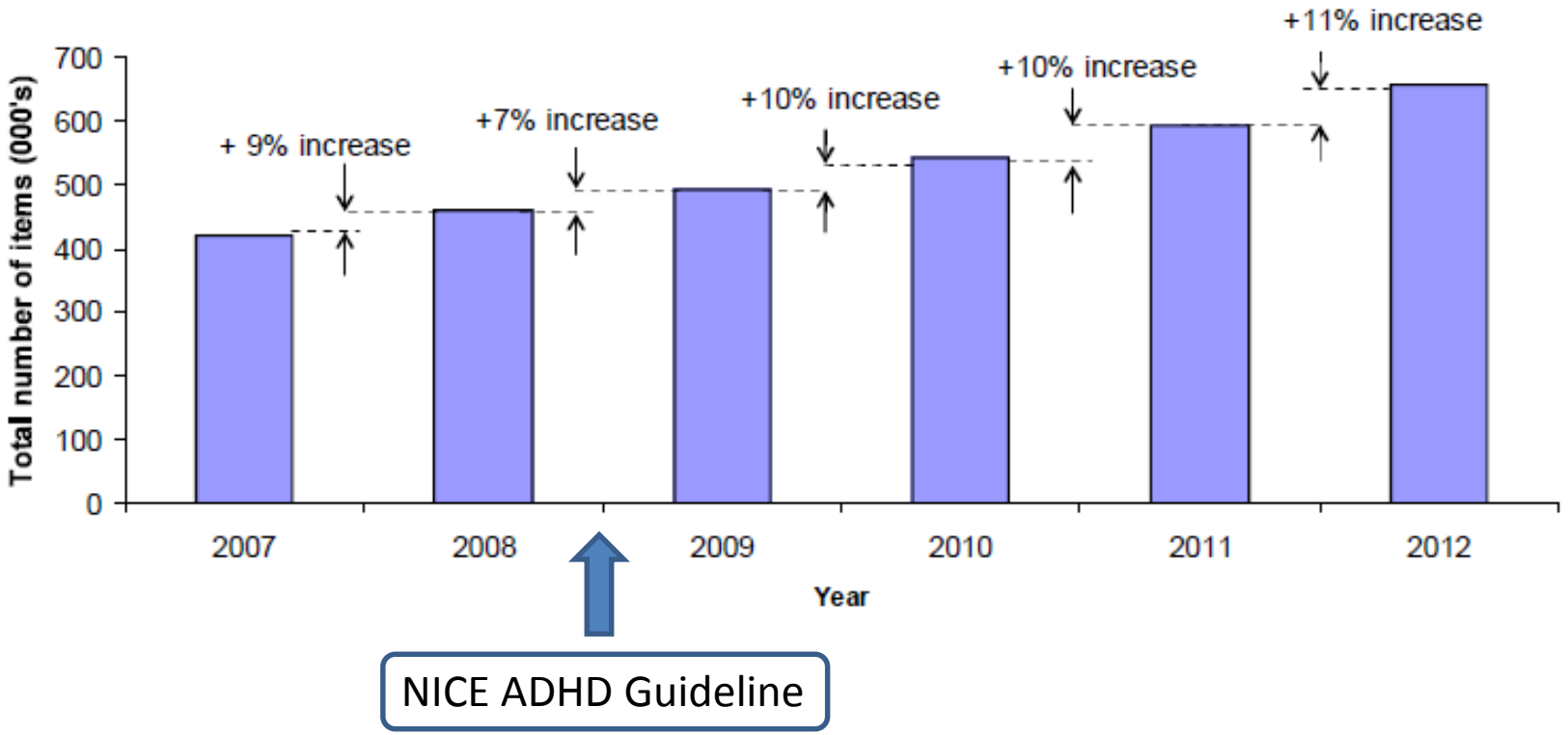
Figure 2 Incidence of pharmacologically treated attention deficit hyperactivity disorder (methylphenidate, dexamfetamine or atomoxetine) in patients aged 6-years and over in UK general practice (with 95% confidence intervals).

McCarthy et al. *BMC Pediatrics 2012*

	2003	2004	2005	2006	2007	2008	Total
Total Number of Prescriptions	11,441	14,763	17,906	22,108	26,205	26,506	118,929
Methylphenidate (n, % of total prescriptions)	11,053 (96.6)	14,233 (96.4)	16,058 (89.7)	19,710 (89.2)	23,255 (88.7)	23,476 (88.6)	107,785 (90.6)
Dexamfetamine (n, % of total prescriptions)	388 (3.4)	352 (2.4)	433 (2.4)	487 (2.2)	494 (1.9)	484 (1.8)	2,638 (2.2)
Atomoxetine (n, % of total prescriptions)	N/A*	178 (1.2)	1,415 (7.9)	1,911 (8.6)	2,456 (9.4)	2,546 (9.6)	8506 (7.2)

Total number of methyphenidate items prescribed in NHS primary care 2007-11

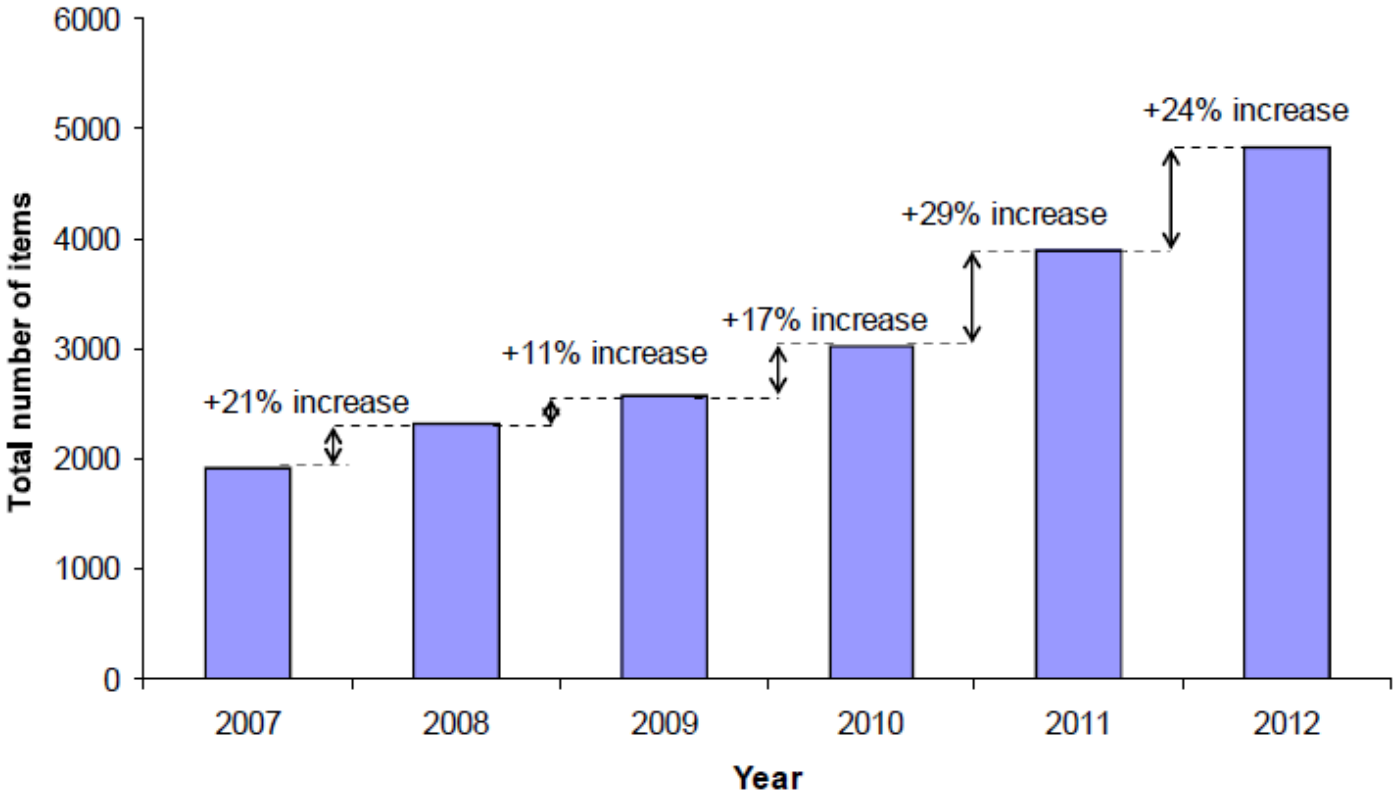
UK



The safer management of controlled drugs: Care Quality Commission; Annual Report 2012

Total numbers of methylphenidate items privately prescribed in England 2007-11

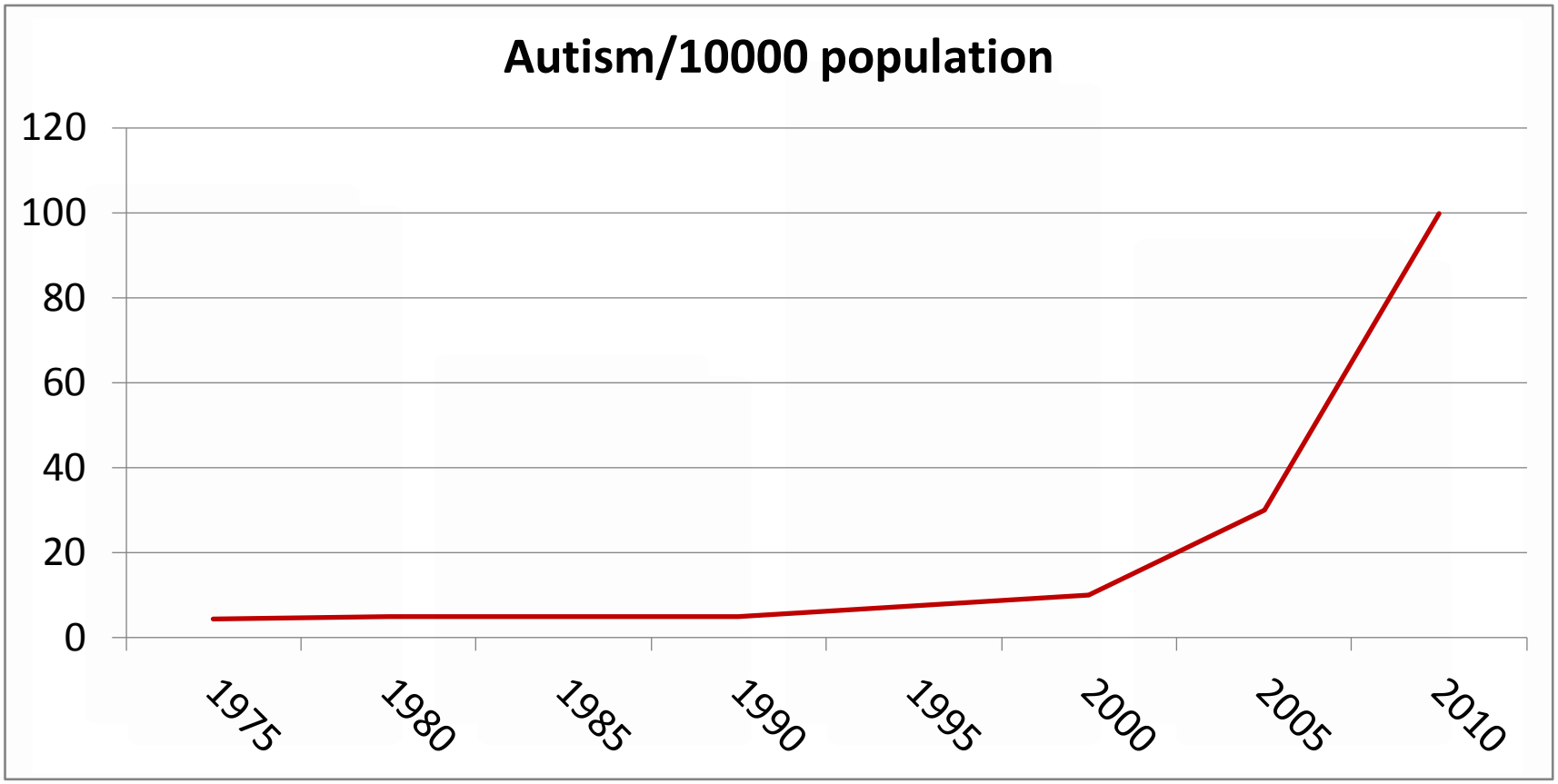
UK



The safer management of controlled drugs: Care Quality Commission; Annual Report 2012

UK

Secular Trends in Autism Prevalence

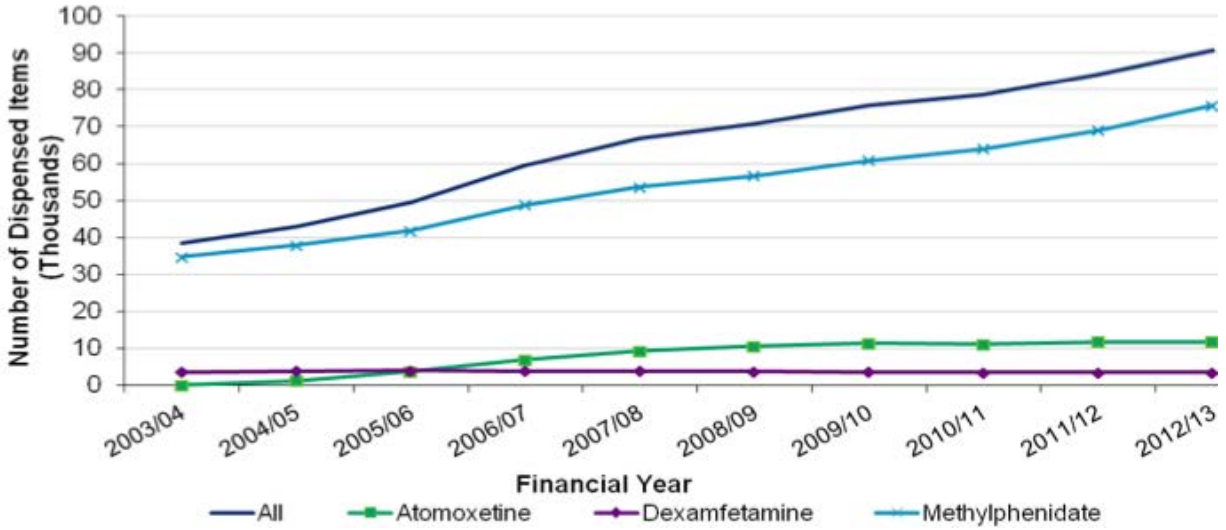


Causes of increased prevalence in autism

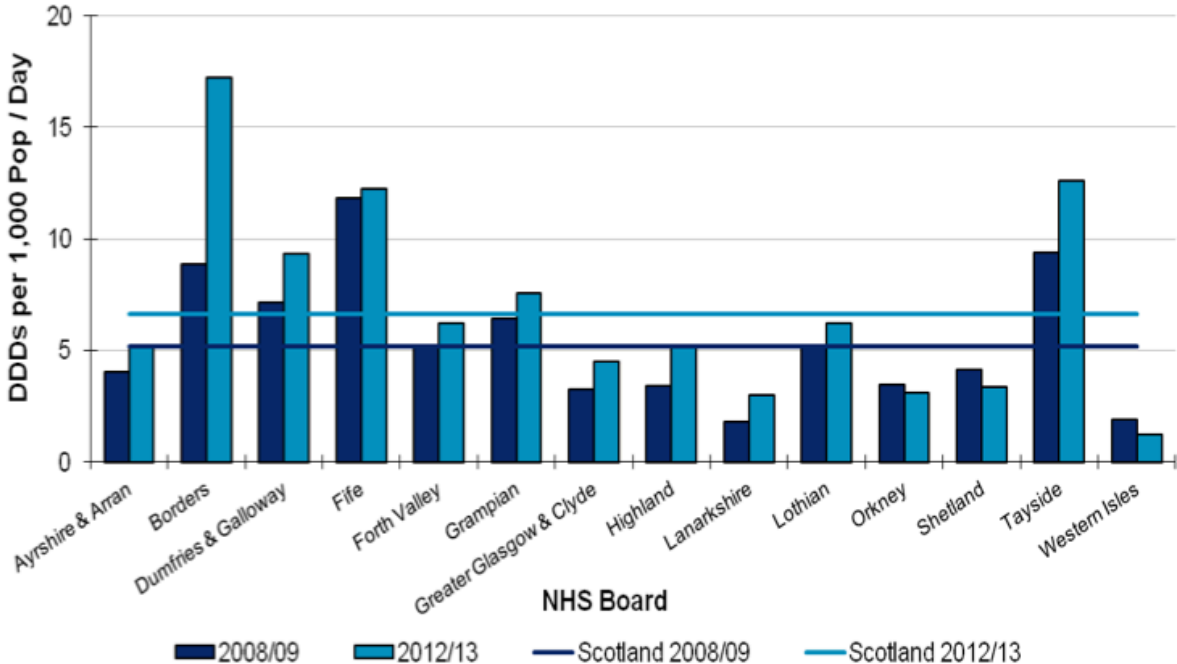
- Increased recognition
  - Implementation of standardized assessments
- Broadening of diagnostic concept
- Diagnostic substitution
  - Autism for ID
- True increase in autism **??**
- Increase request for diagnosis by parents because of service implications

Scotland

Total number of itmes dispensed (thousands)
ADHD drugs
2003/04 to 2012/13



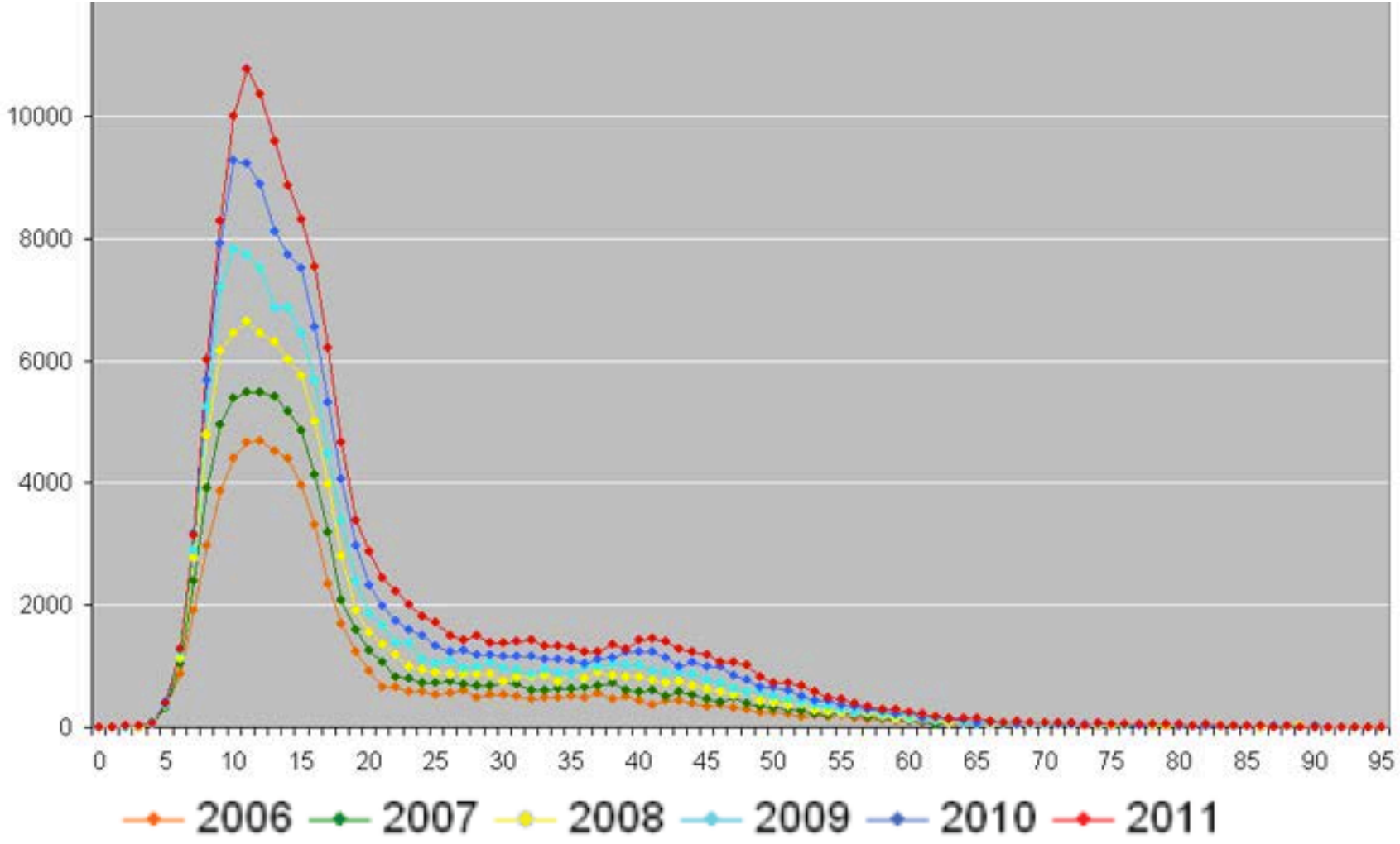
Number of Defined Daily Doses per 1,000 Population (aged 0-19) per Day
ADHD Drugs
2008/09 and 2012/13



*Medicines for Mental Health, Scotland**, 2013***

Netherlands

Use of methylphenidate and atomoxetine in the years 2006-2011



Source: Stichting Farmaceutische Kengetallen http://www.sfk.nl/nieuws-publicaties/PW/2011/meer-dan-1-miljoen-adhd-voorschriften

To summarize

- Prescription of psychotropic/ADHD medications vary substantially between countries: US consumption >80% of the world use

- **US:** parent report Hx of diagnosis increase 42% (7.8%-11%) between 2003-2011 [22% increase 2003-2007; 16% increase 2007-2011]. Medicated children increased 28% (4.8%-6.1%) between 2007-2011

- **Europe :** continuing and steady increase year on year across all countries. Although base rates between countries differ, rate of increase across countries broadly similar

- **UK** data shows falling incidence (in 6-17 yr olds) from a peak in 2006; prescribing incidence continued to increase in adult population and might be due to the role of media, governmental rules, provision of services, Primary Care and private prescriptions. Preferences of families and clinicians

- **Undertreatment might be a bigger problem**: 30% children with ADHD not receiving any treatment (6.1/8.8%)

Consumo di farmaci nel Sud Europa

Numero confezioni vendute nell'anno **2012**

Metilfenidato

Paese	n. abitanti	n. Confezioni (dato ufficiale)	tempo	n. pazienti in terapia (stima)
Italia	60.000.000	22.330	anno	< 2.500
Francia	64.000.00	383.577	anno	
Spagna	47.000.000	135.585	*mese*	110.000

Atomoxetina

Paese	n. Confezioni (dato ufficiale)	tempo
Italia	6030	anno
Spagna	8654	*mese*

Take home message

- I farmaci per l'ADHD sono molto efficaci e relativamente sicuri nelle diverse età della vita

- Esistono solo limitate evidenze di efficacia degli attuali interventi non-farmacologici nel ridurre I sintomi *core* dell'ADHD, ma possono avere un ruolo importante nella gestione dei sintomi e disturbi associati.

- I farmaci per l'ADHD possono prevenire (o almeno modularne la comparsa) della psicopatologia associata all'ADHD.

- Non usare farmaci efficaci per l'ADHD dovrebbe essere considerato NON ETICO come non usare gli antibiotici o i vaccini nella terapia/prevenzione delle infezioni

- La gestione della terapia farmacologica per l'ADHD richiede le abilità cliniche proprie di ogni neuropsichiatra infantile

Congresso SINPIA

Alghero, 7-9 Ottobre 2016

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Grazie per l'attenzione

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