Basic principles of pediatric psychopharmacology

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Outline

- Setting the forum
- Kinetics, dynamics and development
- Overview of evidence base
- Thoughts for the future

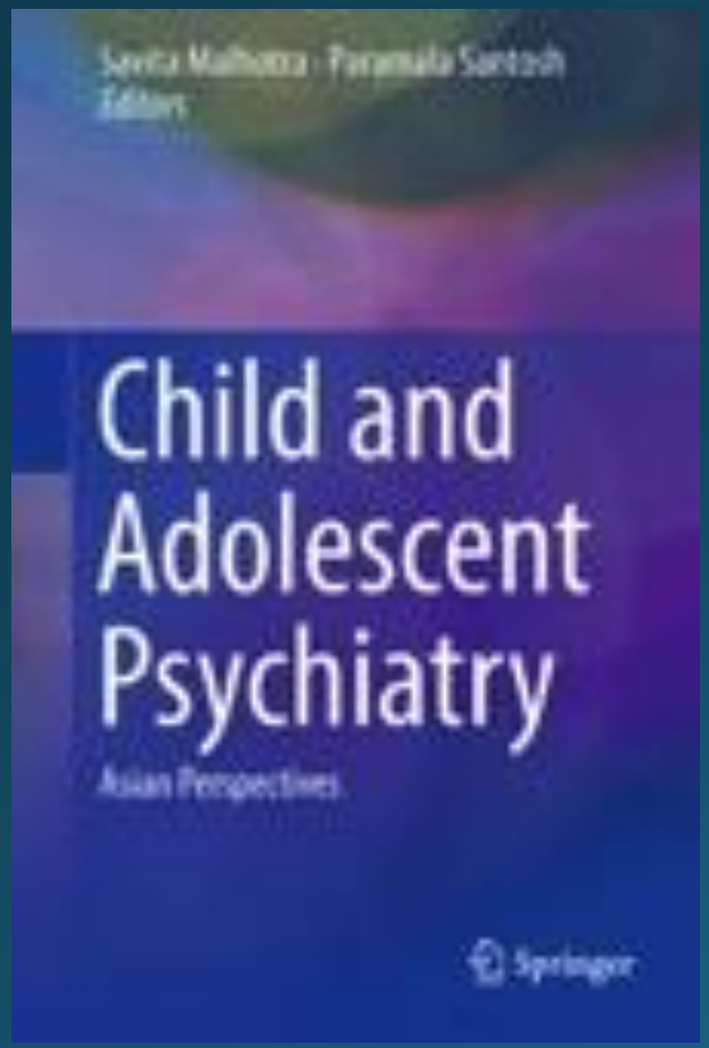
Beginnings of pediatric psychopharmacology

- 30 children with mixed emotional and behavioural symptoms
- Open label 'benzedrine'
- "*noisy, aggressive & domineering*" became "*calm & manageable*"

Bradley C, Am J Psychiatry, 1937

- 93 'juvenile delinquents'
- RCT with benzedrine
- Improvement in *learning, Motor control, Short-term memory*

Molitch & Eccles, Am J Psychiatry, 1937

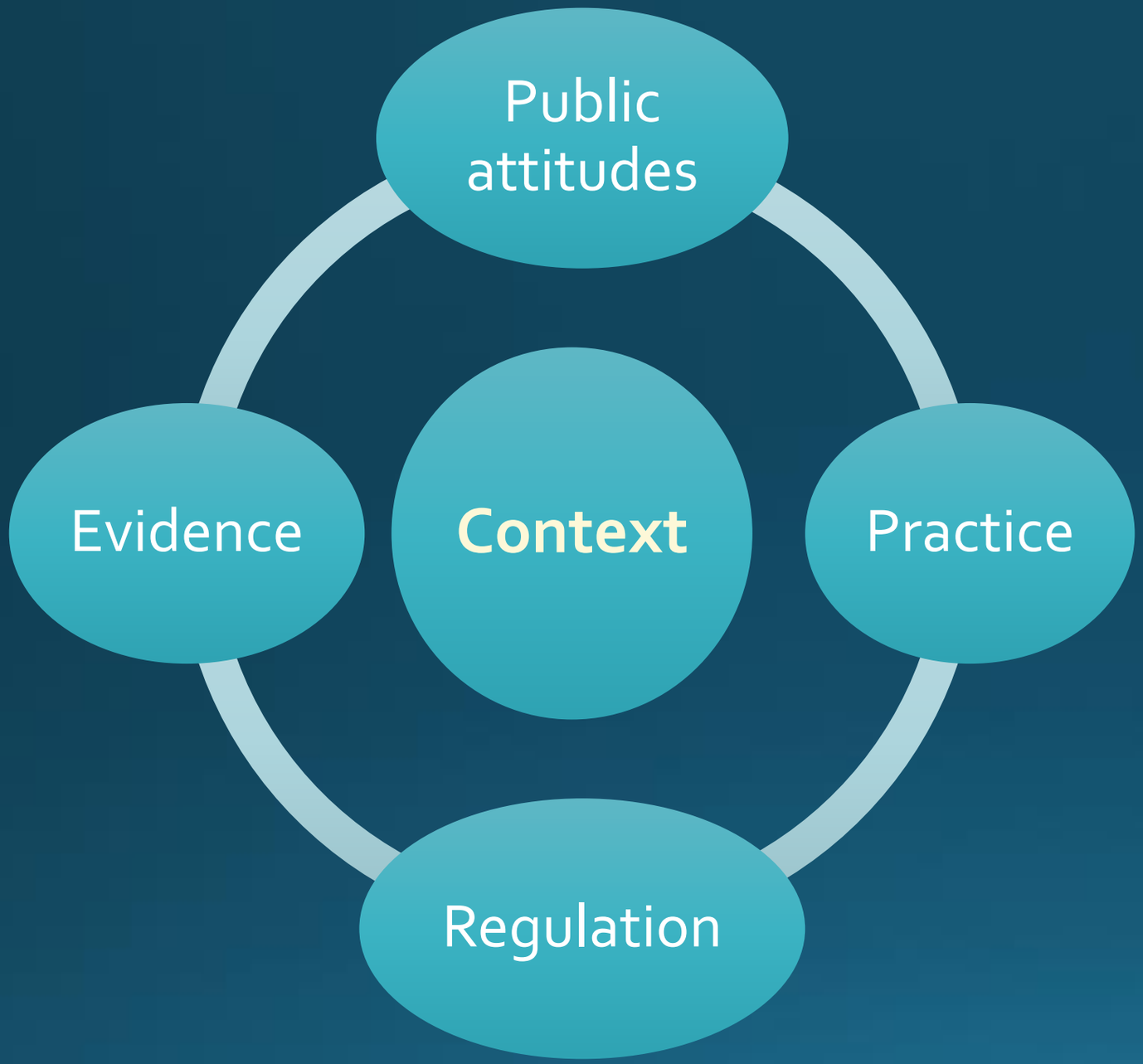


"…. the efforts of child and adolescent psychiatrists on behalf of troubled children are shaped not only by an **evolving knowledge base**, but by **public opinion**, **evolving conditions of practice**, and **regulation**. The resulting **paradigm shift revives the biopsychosocial model**, enhanced through **advances in developmental psychology and neuroscience**, with **increased understanding of the biology of attachment and developmental trauma**. *In this new paradigm focus on the child's psychosocial environment is paramount and* ***pharmacotherapy becomes adjunctive to psychosocial interventions***."

Harper et al, Psychopharmacology for Children and Adolescents, In: Child and Adolescent Psychiatry: Asian Perspectives, 2016

Era of easy acceptance …**2005 AD**… Era of increasing scrutiny

A paradigm shift



1990's:

Shift in approach: " least restrictive" & "lowest effective dose" to "most effective" treatment

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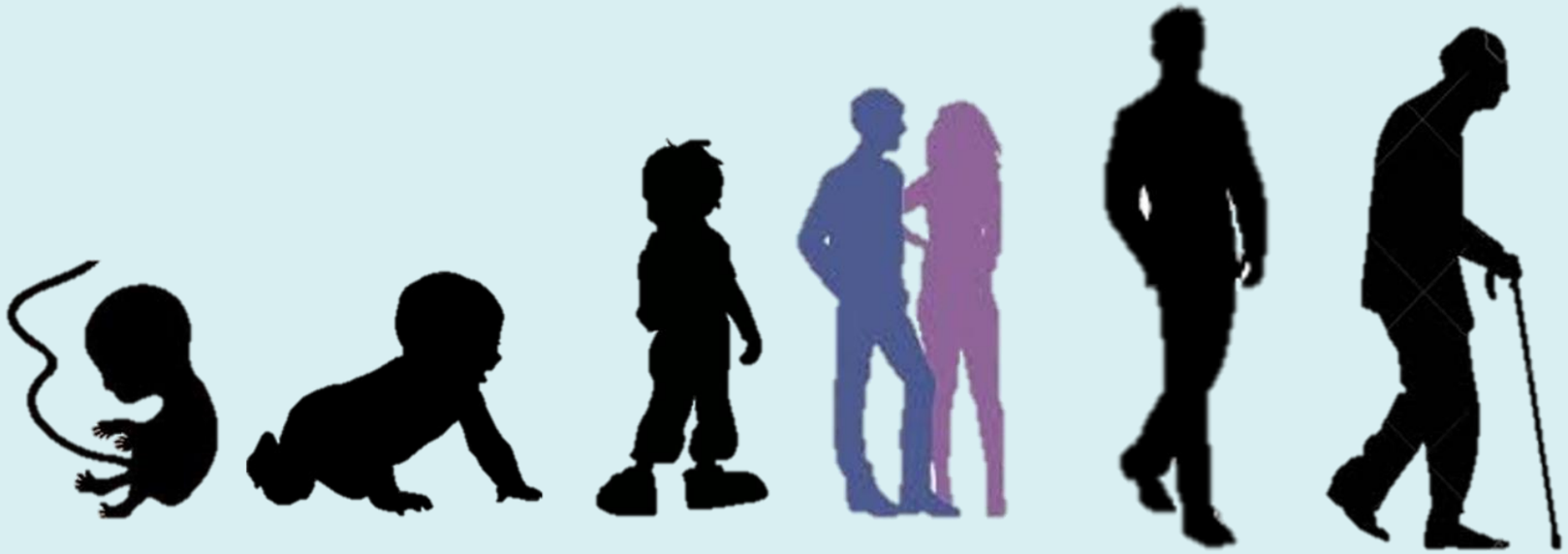


Neuronal formation

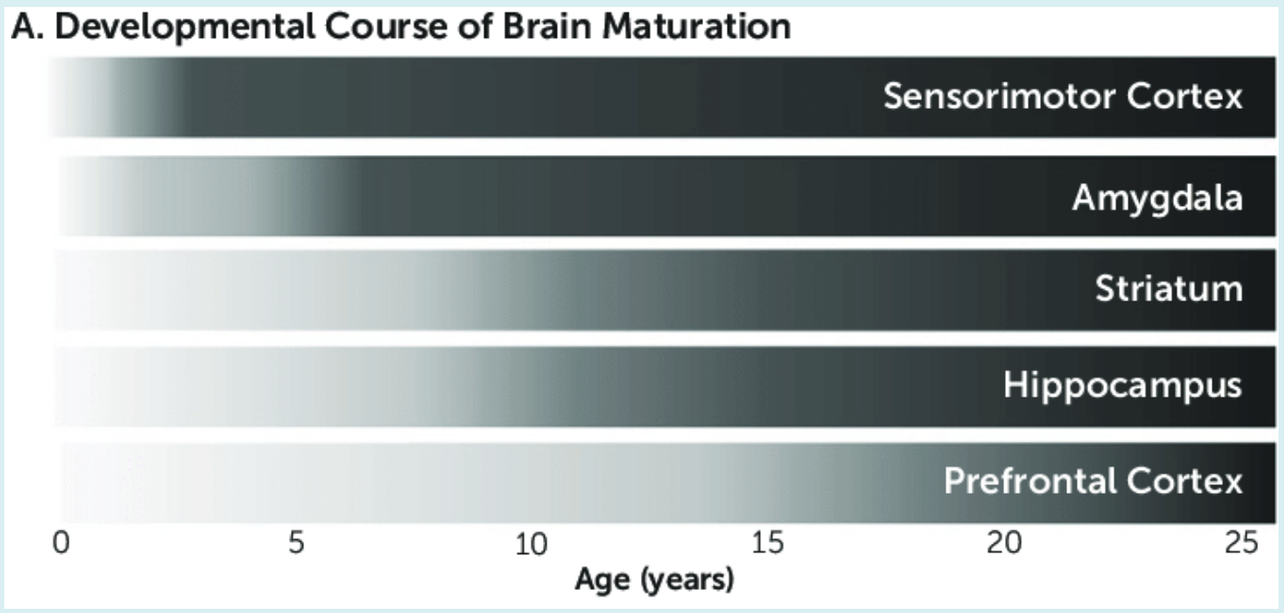
95% adult brain vol

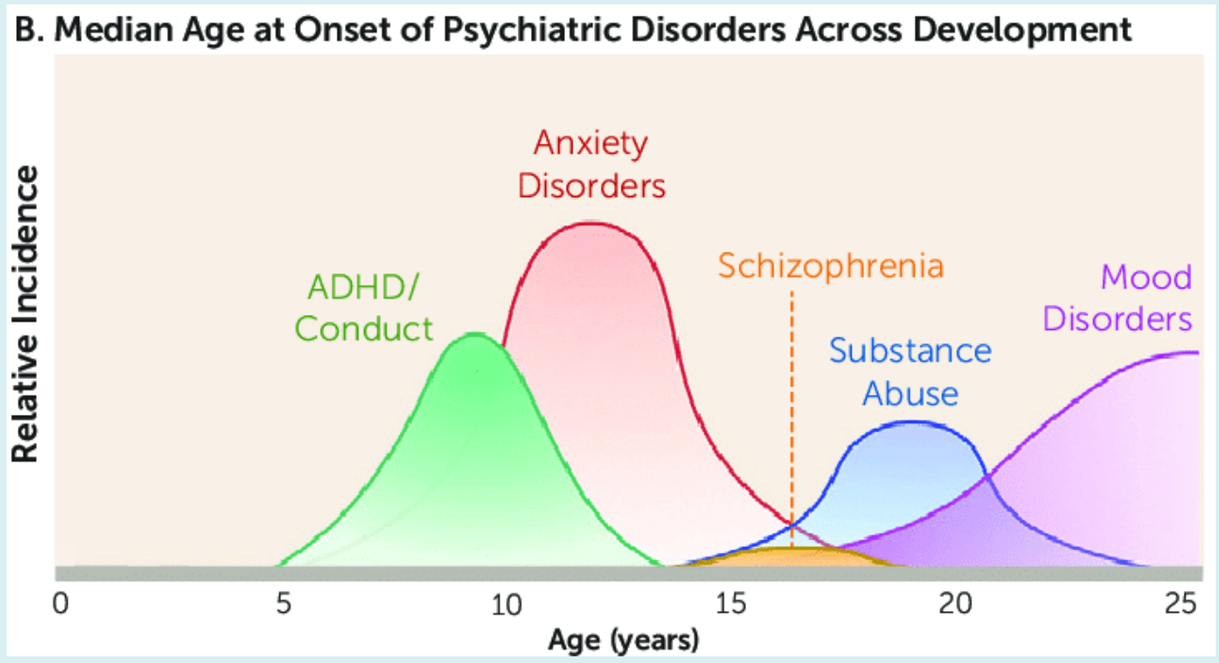
Neuronal migration

Myelination, Arborization, Pruning

Synapse formation

The Developing Brain





Meyer & Lee, Am J Psychiatry, 2019

Pharmacokinetics

Classification	Age
Preterm newborn	
Newborn	0-28 days
Infant	>28 days – 12 mnth
Toddler	>12 mnth – 23 mnth
Preschool child	2-5 yrs
School age child	6-11 yrs
Adolescents	12-18 yrs

European Medicines Agency, 2001. International Conference on Harmonization. Clinical investigation of medicinal products in the pediatric population.

A **Absorption**	D **Distribution**	M **Metabolism**	E **Excretion**
Gut transit time Fluid composition Wall permeability	Fat/ water composition Protein binding	Microsomal enzymes Hepatic blood flow Gut microbial flora	Glomerular filtration rate Tubular transporters
Mature by early infancy	Pre-schoolers have larger volume of distribution – higher mg/Kg	Pre-schoolers and young children: Lower proteins + higher blood flow – net higher mg/Kg	Pre-schoolers: Higher renal clearance
		Crabamazepine *Valproic acid*	*Levetiracetam*

Batchelor & Marriott, Br J Clin Pharmacol, 2015

Pharmacodynamic insights

Table 2 Summary of Selected Studies

Study	Design	Results
Genome Wide Association Studies – Adult Subjects		
Uher et al 2013	Meta-analysis of 3 GWAS (from GENDEP, MARS, and STAR*D) with total of 2256 adults with MDD	• No genetic predicto treatment outcome • Some preliminary evidence that perhaps some patient sub-populations might improve treatment response
Combinatorial Gene Guidance – Adult Subjects		
Perez et al 2017	Subject and rater blinded RCT of PGX guided vs non-guided treatment in 316 adults with MDD	• No difference in primary outcome of sustained treatment response • PGX guided group had greater responder rate especially if subject previously had >1 drug failure
Rosenblat et al 2018	Meta-analysis of 2 RCTs and 2 open label studies of PGX guided vs non-guided treatment in 1534 adult subjects with MDD	• PGX guided treatment increased likelihood for response and remission
Greden et al 2019	Subject and rater blinded RCT of PGX guidance vs non-guided treatment in 1167 adults with MDD who had failed ≥ 1 medication trial	• No difference in primary outcome of response at 8 weeks • Increased response and remission rates in PGX guided groups on secondary analysis
Bousman et al 2019	Meta-analysis of combinatorial gene testing from 5 RCTs among 1737 adults with MDD	• Subjects with PGX guided treatment were more likely to achieve remission compared to non-guided
Gene-Medication Association – Pediatric Subjects		
Michelson et al 2007	Retrospective analysis of routine PGX testing in 894 pediatric subjects with ADHD on atomoxetine	• Poor metabolizer status in CYP2D6 was associated with more frequent adverse effects and greater reduction in mean symptom severity relative to extensive metabolizers
Brown et al 2016	Single dose atomoxetine administered in 23 pediatric subjects with ADHD who were stratified based on CYP2D6 metabolizer status	• 30-fold differences in concentrations of active drug in extensive metabolizers vs poor metabolizers
Aldrich et al 2019	Retrospective analysis of routine PGX testing in 263 pediatric subjects hospitalized with anxiety and depression treated with es/citalopram	• Metabolizer phenotype was not associated with responder rate • Faster metabolizer status of CYP2C19 associated with faster response rate • Slower CYP2C19 metabolizer status had decreased tolerability, high discontinuation rates, and longer length of stays
Poweleit et al 2019	Retrospective analysis of routing PGX testing in 369 pediatric subjects hospitalized with anxiety and depression treated with sertraline	• No association between RFAs and response dose or number of adverse effects • Slower CYP2C19 metabolizers prescribed lower maximum doses of sertraline

No clear winners!!

Namerow et al,
Current Psychiatry Reports, 2020

Pharmacogenomics??

Relevant gene polymorphisms

1. Cytochrome P450 liver enzyme systems – 2D6, 2C9, 2C19
   - Normal (extensive) metabolizers: 2 active alleles
   - Intermediate metabolizers: 1 active allele
   - Ultrarapid metabolizers: >/=3 active alleles
   - Poor metabolizers: partially/ non-functioning alleles
2. Serotonin transporter
3. Serotonin receptor
4. Catecholamine-O-methyltransferase
5. P-glycoprotein

Drugs with some evidence for pharmacogenomic considerations

CYP 2D6
- Atomoxetine
- Fluvoxamine
- Paroxetine
- Nortriptyline

CYP 2C19
- Citalopram
- Escitalopram

HLA-B HLA-A
- Carbamazepine
- Oxcarbazepine
- Phenytoin

CYP 2C9
- Phenytoin

Recommendations

- Widespread testing not recommended (APA, AACAP, ISPG)
- Role in treatment non-responders
- Start low, go slow and monitor *esp in vulnerable populations - children, elderly, ethnic groups*
- Drug-drug interactions

Namerow et al, Current Psychiatry Reports, 2020

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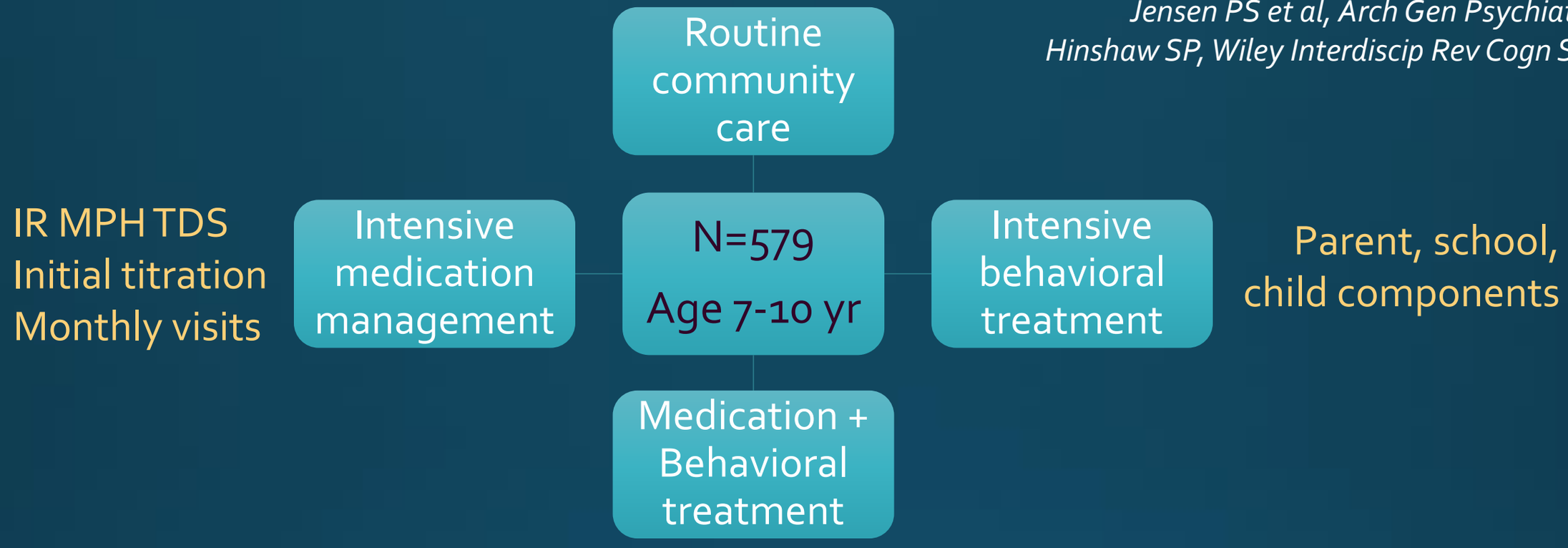
Multimodal Treatment of ADHD Study (MTA Study)

Jensen PS et al, Arch Gen Psychiatry, 1999
Hinshaw SP, Wiley Interdiscip Rev Cogn Sci , 2015



- NIMH funded, Six American sites, ADHD-Combined, RCT
- Baseline assessments (10 hours) - Systematic FU 14 mnths - Unstructured FU >15 yrs
- Outcomes: ADHD, externalizing, internalizing, academic, parent-child, social skills

Efficacy	Side effects	Moderators	Mediators
Medication/ Combination more efficacious Combination more effective with comorbid anxiety, academic issues, interpersonal distress, etc Dose of medication lower with Combination High individual variation	Severe enough to discontinue ~ 4% Loss of appetite Sleep problems Crying spells Repetitive movements Slowed growth	Anxiety Parental depression Illness severity Low IQ	Treatment acceptance/ attendance Improved parenting

Preschool ADHD Treatment Study (PATS)

- NIMH's flagship study in Preschoolers, 6-centre, 2000s,
- DSM-IV ADHD – Combined OR Predominant Hyperactive/Impulsive
- RCT, Effectiveness/Efficacy trial
- Outcome: Parent & Teacher rated

- Significant decreases in ADHD symptoms on MPH (vs Placebo)
  - Effect sizes 0.4-0.8
  - 2.5mg, 5mg, 7.5mg TDS doses; Not with 1.25mg TDS
  - Mean optimal daily dose for group – 14.2+/-8.1 mg
  - Remission 21% on *best-dose* MPH and 13% on placebo

- Side effects
  - 30% moderate-severe, spontaneously reported
  - Emotional outbursts, Difficulty falling asleep, Repetitive behaviors and thoughts, Appetite disturbances

- In follow-up (> 6 years)
  - 80% children retained diagnosis, esp those with comorbid DBDs
  - Moderate-severe symptom scores
  - Severity dropped till 3 years, not thereafter
  - Greater severity with – lower IQ, those who continued medication
  - Similar trajectories for IA and HI symptoms
  - Parent rating higher than teachers

Collins, JAACAP, 2006
March, JAACAP, 2011
Riddle, JAACAP, 2013
Vitiello, JAACAP, 2015

Treatment of ADHD

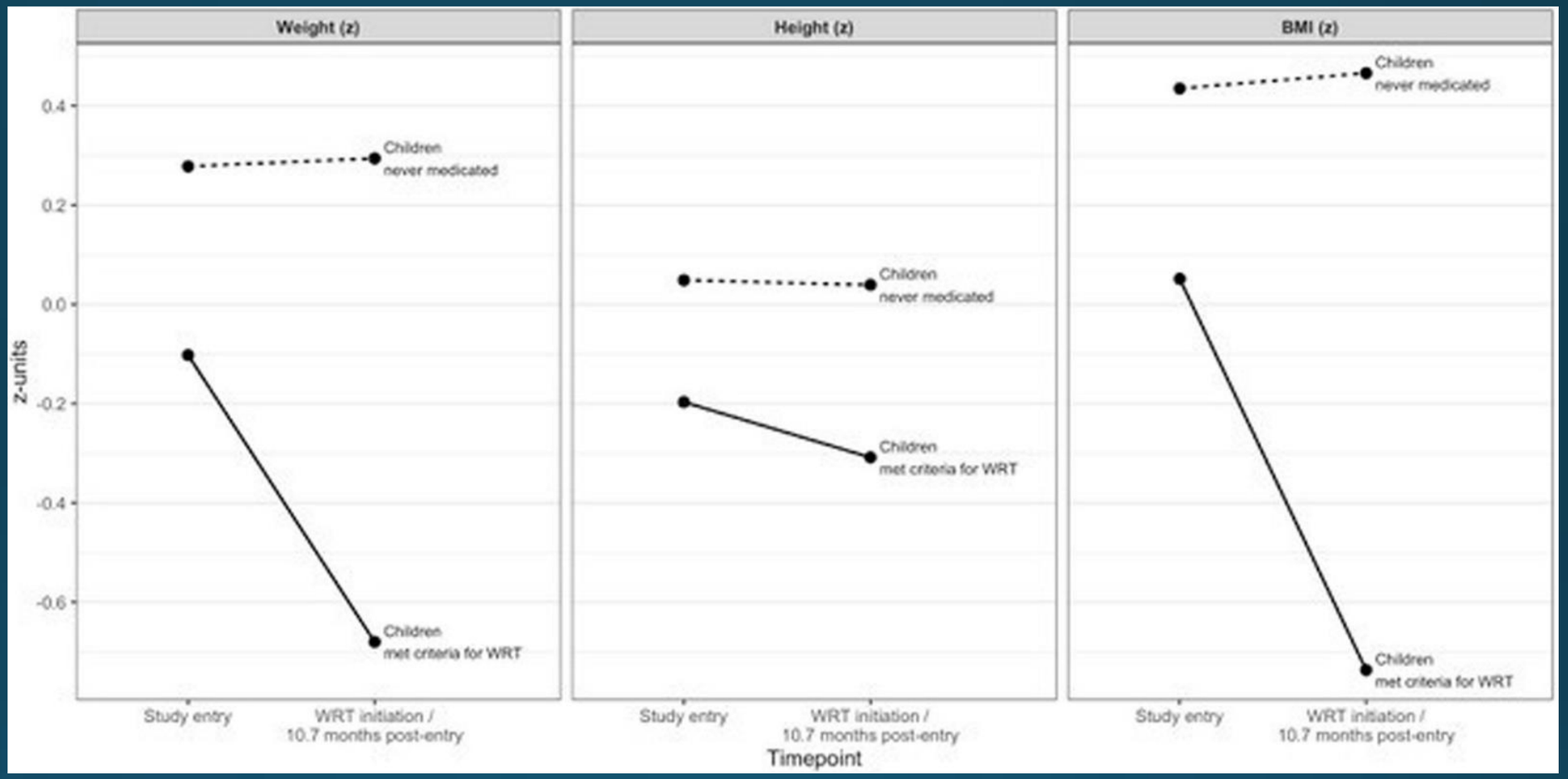
	Methylphenidate	Atomoxetine	Clonidine
Mechanism	DA/ NE transmission in PFC/ BG	NE reuptake inhibitor	Alpha-2 adrenergic agonist
Dose	0.3-0.8 mg/Kg	0.8-1.2 mg/Kg	0.05mg/d… up to 0.2-0.3 mg/d
Regimen	2-3 divided doses	Single dose	Up to 4 divided doses
Action	Within hours	4-6 weeks	Immediate and delayed
Adverse effects	1. Sleep disturbance 2. Appetite disturbance 3. Paradoxical worsening 4. Mood changes 5. Headaches 6. Rebound withdrawal effects 7. Over-focussing on details 8. Tics/ mannerisms	1. Sleep disturbance 2. Appetite disturbance 3. Paradoxical worsening 4. Mood changes 5. Headaches 6. Dyspepsia *BLACK BOX warnings* *Hepatitis, Aggression, Suicidality*	1. Sedation 2. Hypotension, dizziness 3. Dry mouth 4. Rebound withdrawal effects Irritability Hypertension
Choice	First choice	With depressive disorders	With tics

- **Major considerations in choice of treatment:**
  - **Follow-up feasibility**
  - **Side effects monitoring**
  - **Co-morbidity**
  - **Abuse potential**
  - **Objective feedback (rating scales)**

Lewis' Child & Adolescent Psychiatry, Fourth edition

Stimulant induced growth suppression
[European ADHD Guidelines Group (EAGG) update]

Significant reductions in weight & height within 11 months of therapy



- Monitor appetite, weight, height and body mass index (BMI) every 6 months.
- Differentiate between pre-treatment eating problems and medication-induced eating problems.
- Medication after meals, rather than before
- High-calorific snacks and late evening meals.
- Dose reduction or switching to an alternative class or formulation
- Drug holidays for ‘catch up’ growth
- Referral to paediatric endocrinologist/growth specialist if values below critical thresholds.

Cortese, Journal of Child Psychology and Psychiatry, 2013
Waxmonsky, J Am Acad Child Adolesc Psychiatry, 2019

Selective serotonin reuptake inhibitors in children

Most extensively used antidepressants in children; Maximum empirical support

FDA approval

- Fluvoxamine & Sertraline for OCD
- Fluoxetine for depression

Comparable with CBT for depression/ OCD

Drug	Starting dose	Increments	Dose range
Fluoxetine	2.5 - 10 mg	1-2 weeks	5 - 40 mg
Sertraline	12.5 - 25 mg	Weekly	50 - 150 mg
Fluvoxamine	12.5 - 25 mg	Weekly	50 - 200 mg
Citalopram	5 mg	1 - 2 weeks	5 - 40 mg
Paroxetine	Not recommended in children/adolescents		

Duration of treatment:

- Clinical judgment
- Relapse rates high
- Persistence of disorders like OCD into adulthood

Adverse effects:

- GI - nausea, reduced appetite, diarrhoea, heartburn
- Fatigue, headaches
- Behavioural activation
  - Early treatment/Dose increase/ Drug interaction
  - Restlessness, insomnia, impulsivity, disinhibition/ garrulosity
- Hypomania/ Mania - especially in prepubertal children
- Suicidality (??)

Lewis' Child & Adolescent Psychiatry, Fourth edition ; Rey JM, 2006
https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications

Other antidepressants

Antidepressant	Use	S/e
TCAs	1. Enuresis - Imipramine (2.5-5mg/Kg/d) 2. ADHD - Desipramine (2.5-5mg/Kg/d) 3. OCD - Clomipramine (2-3mg/Kg/d)	**Cardiac events** **Sedation** **Anticholinergic** **Seizures**
Bupropion (3-6mg/Kg/d)	**Depression** **ADHD**	Seizures (> 150mg at a time OR > 300mg/day)
Venlafaxine (1-3mg/kg/d)	**Depression**	**Suicidal ideation**
Trazodone (25-200mg/d)	**Insomnia**	**Hypotension, Sedation, Priapism**
Mirtazapine (7.5-30mg/d)	**Depression**	**Drowsiness, Increased appetite, weight gain**

ANTI-PSYCHOTICS

Antipsychotic	Studied in	Doses
Risperidone	1. Psychosis 2. Behaviour problems in autism/ ID 3. Disruptive behaviour 4. Tics & Tourette's syndrome 5. Augmentation	0.25 - 4 mg/d; OD/ BDS
Clozapine	Treatment resistant psychosis	50 - 400 mg/d; BDS/TDS
Olanzapine	1. Schizophrenia 2. Bipolar disorder 3. Aggression/hyperactivity in autism	2.5 - 10 mg/d; OD/BDS
Quetiapine	1. Bipolar disorder 2. Psychosis	100 - 600 mg/d; BDS/TDS
Ziprasidone	1. Tics/ Tourette's syndrome 2. Behavior problems in autism	40 - 160 mg/d; BDS
Aripiprazole	1. Bipolar disorder 2. Schizophrenia 3. Tics & Tourette's syndrome 4. Behaviour problems in autism/ ID 5. Augmentation	2-20 mg/d; OD/BDS
Haloperidol	1. Psychosis 2. Aggressive behavior 3. Tics 4. Behavioral problems with autism	0.75 - 10 mg/day
Chlorpromazine	Severe behavioural dyscontrol	25 - 400 mg/d; OD/BDS/TDS

Antipsychotic side effects in children

- Weight gain, metabolic disturbances
- Cognitive blunting
- Dysphoria
- Elevated prolactin

  Gynecomastia in boys and galactorrhea/ amenorrhoea in girls
- Extrapyramidal side effects (Dyskinesias less common in children)

Anticholinergic agents (Trihexphenidyl)

- If possible, avoid OR time-limited use
- Long-term use (esp in younger children) - Sjogren syndrome

Treatment of pediatric bipolar disorder

Table 1
Medications approved by the Food and Drug Administration for the treatment of pediatric bipolar disorder

Medication	Phase of Bipolar Disorder	Age, y	Daily Dose Range, mg/d
Lithium	Mixed/manic	12–17	300–2400 Upto 1.4 meq/L
Risperidone	Mixed/manic	10–17	0.25–2.5
Olanzapine	Mixed/manic	13–17	2.5–20
Aripiprazole	Mixed/manic	10–17	2–30
Quetiapine	Mixed/manic	10–17	50–600
Olanzapine/fluoxetine combination	Depressive episode	10–17	3/25–12/50

Initial monotherapy preferable when treating an acute mixed or manic state
Atypical antipsychotics show higher response rates when compared with lithium or anticonvulsants
Limited data on long-term safety and effectiveness

Stepanova & Findling, Psychiatr Clin N America, 2017

Pharmacological options for ASD

- Allow children and adolescents to maximize their benefits from behavioral and psychoeducational interventions
- Interindividual variability present in ASD also spans clinical response to psychoactive drugs and side effect sensitivity.
- No drug directly ameliorates core autism symptoms
- Target symptoms
  - Hyperactivity, impulsivity
  - Agitation, temper outbursts
  - Aggression towards self or others
  - Repetitive behaviors (anxiety and obsessive-compulsive symptoms)
  - Sleep problems

Persico et al, Prog Neuropsychol Biol Psychiatry, 2021
Thom et al, Curr Psychiatry Rep. 2021

Pharmacotherapy for aggression

- A common clinical concern
- Almost all medications tested in RCTs
  - Stimulants
  - Atomoxetine
  - Antipsychotics - typical & atypical
  - Alpha-2 agonists
  - Beta blockers
  - Mood stabilisers
  - Antidepressants
- Effect sizes range between 0.3 - 0.7
- Choice of drug:
  - ABC analysis
  - Functional behavioural analysis
  - "Impulsive (hot)" v/s "Predatory (cold)" aggression

Pappadopulos E, 2006

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Effects on developing brain

- Intervention, overall, appears to have a ‘normalizing’ effect
- Lithium normalizes amygdala and hippocampal volumes
- Neuro-cognitive functions are ‘corrected’ by stimulants, antidepressants, mood stabilisers
- Several gaps in knowledge:
  - Is there a critical window period for beneficial effects?
  - What actually mediates the brain changes and clinical benefits?
  - How do trajectories differ in children on long-term treatment?

- **Neuronal/neurochemical imprinting:**
  - Long-term effects of drug exposure are delayed and come to expression once the vulnerable system reaches maturation (during adulthood)
  - Occurs when the effects of the drug outlast the drug itself

Singh MK, 2012; Bottelier MA, 2014

ePOD study: effects of Psychotropic drugs on developing brain

Objectives

1. Short-term age-dependency (pharmacological MRI)
   a) MPH on developing DA system
   b) Fluoxetine on developing 5HT system
2. Long-term effects of these drugs

Outcome measures:

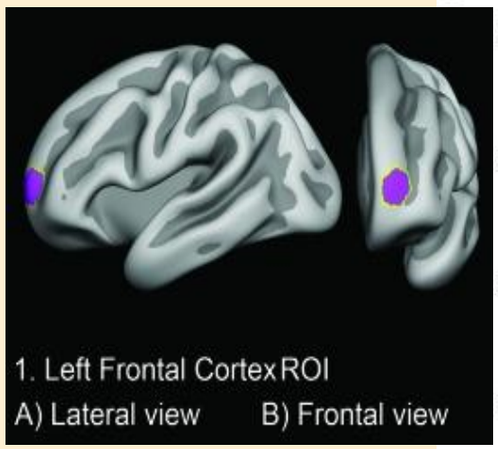
1. Neuroimaging: fMRI, DTI
2. Neuropsychology
3. Cortisol measurements
4. Sleep study

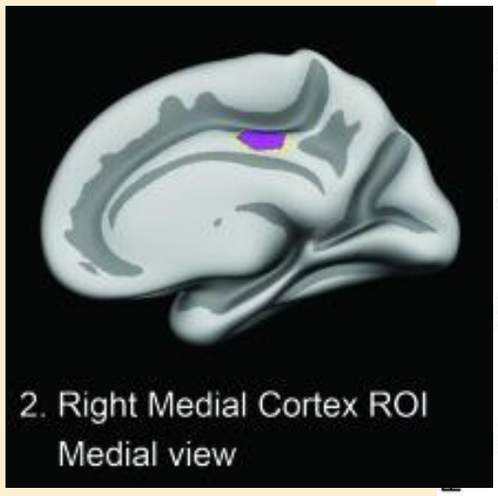
Participants:

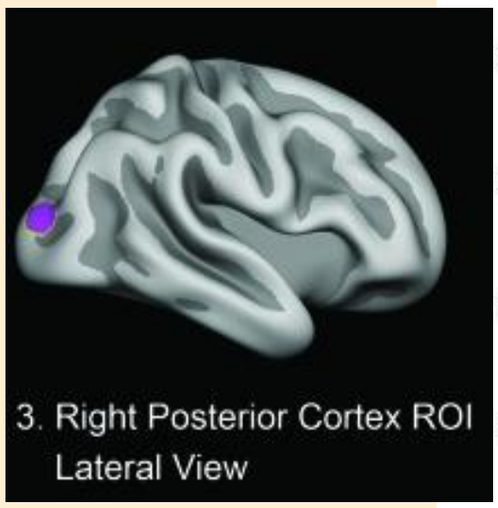
- 50 stimulant treatment–naive boys (10–12 years old)
- 49 stimulant treatment–naive men (23–40 years old)

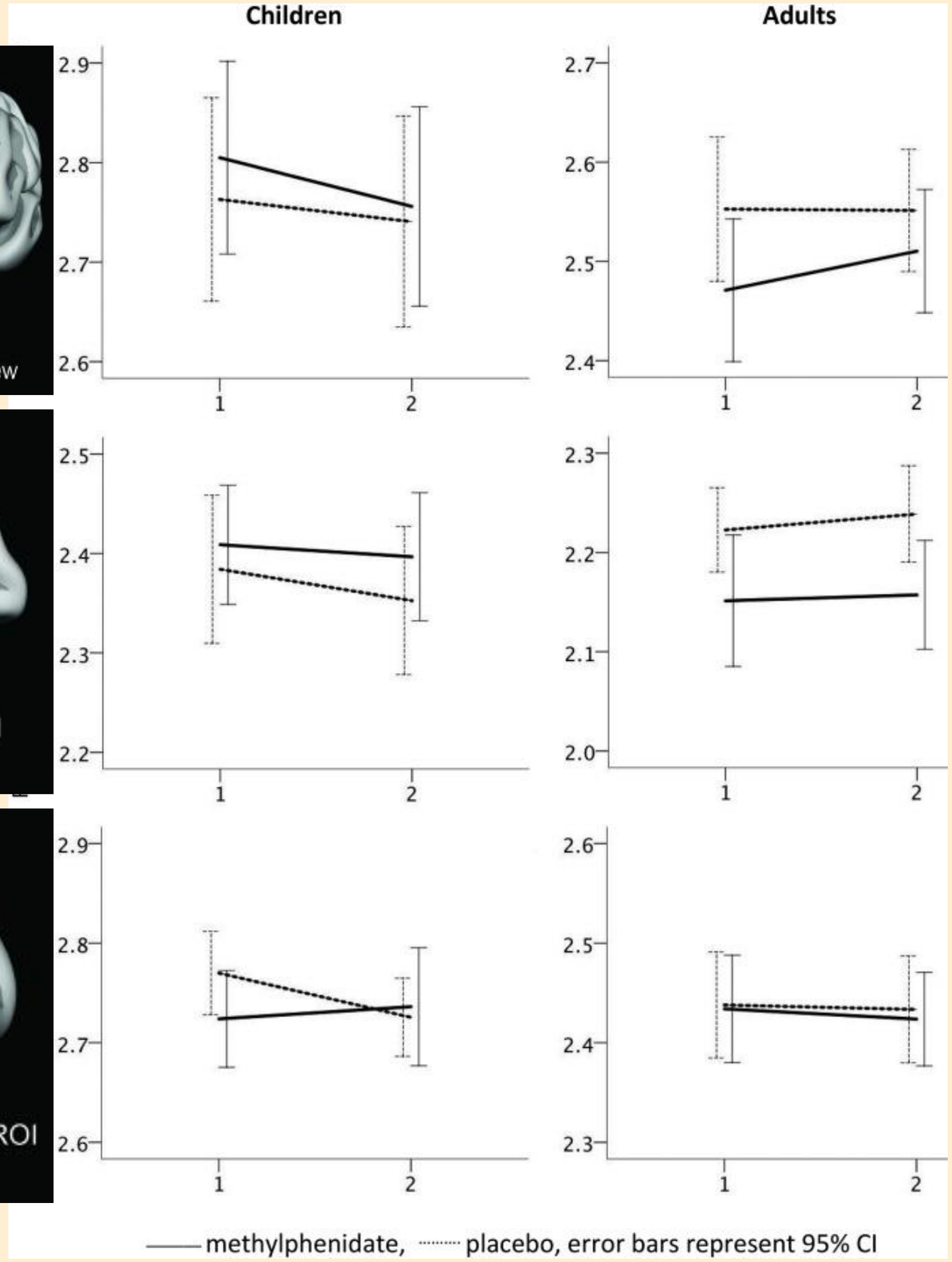
Bottelier MA, 2014

Methylphenidate effects on cortical thickness in children & adults with ADHD









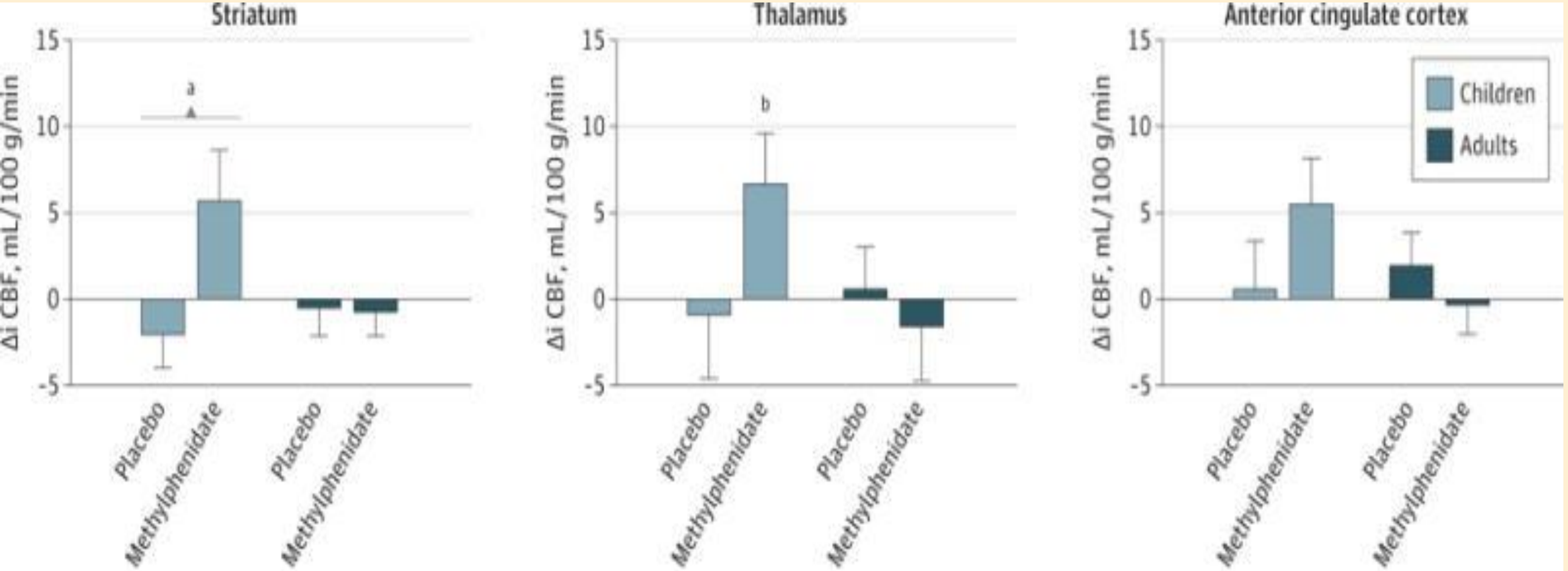
Right medial cortex

Time × medication × age interaction

MPH treatment … less cortical thinning in children, not in adults or placebo

Walhovd et al 2020, Am J Neuroradiol

Age-dependent effects of MPH on dopaminergic system in patients with ADHD

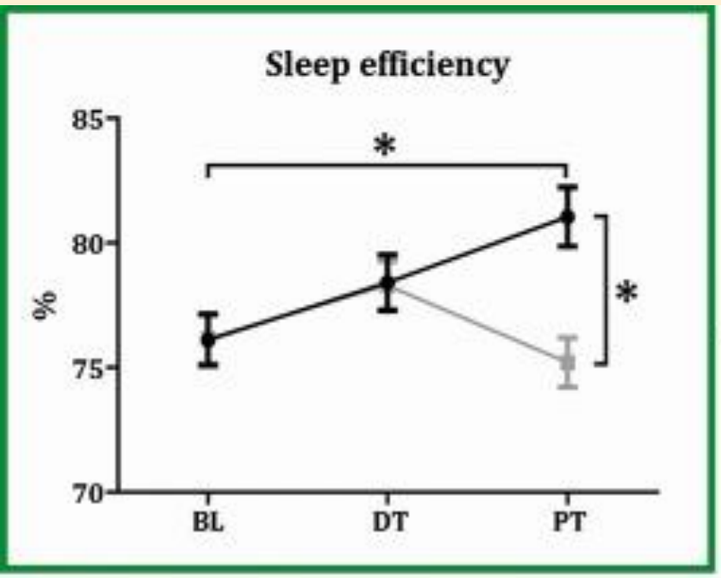


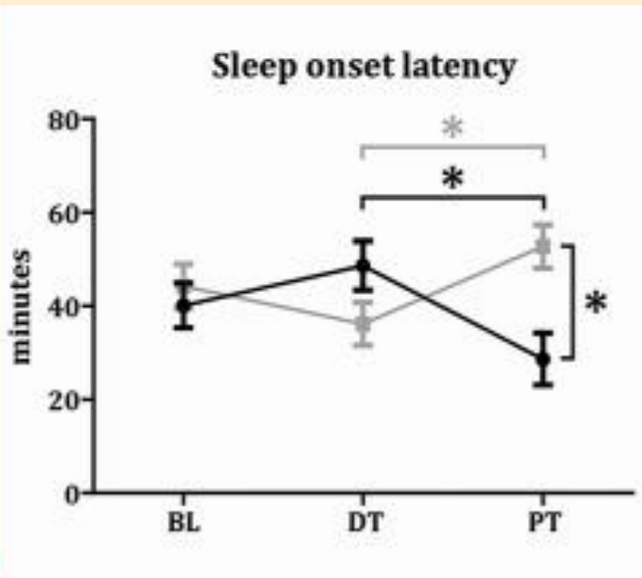
4 months of MPH –

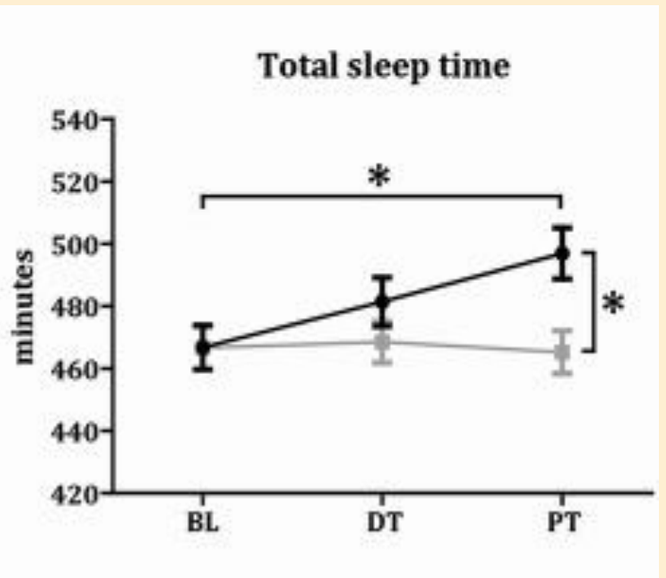
- Significant increases in CBF - striatum & thalamus 1-week post-trial
- Increased DA neurotransmission due to neurochemical imprinting by methylphenidate??
- Short term… alterations do not induce major benefits or harm in clinical improvement
- Long-term consequences remain to be established

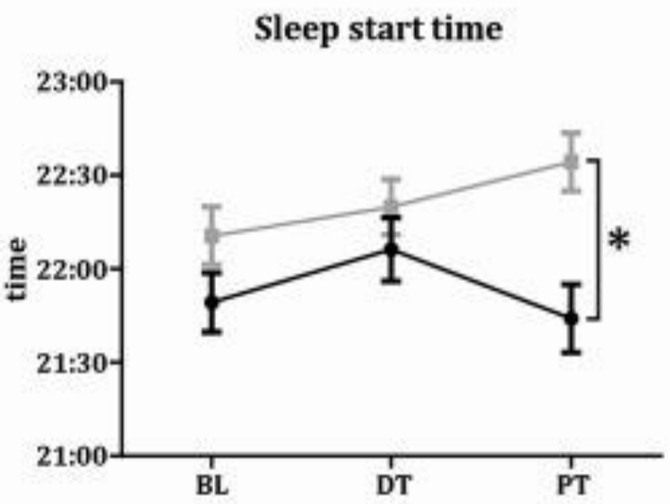
Schrantee et al 2017, Front Psychiatry

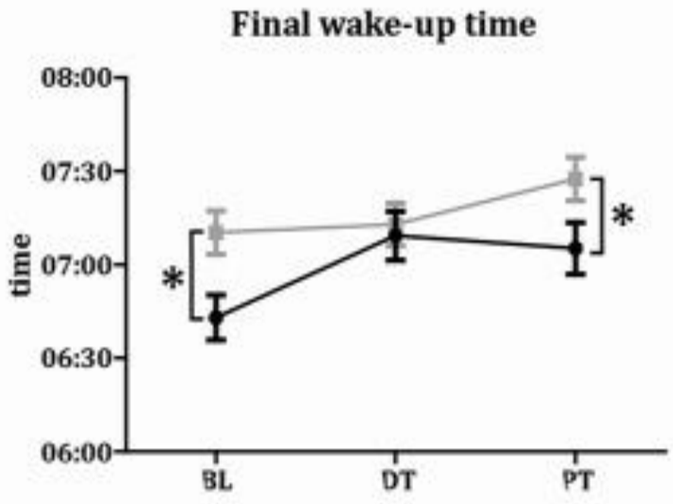
Effects of MPH on actigraph-assessed sleep measures in children with ADHD

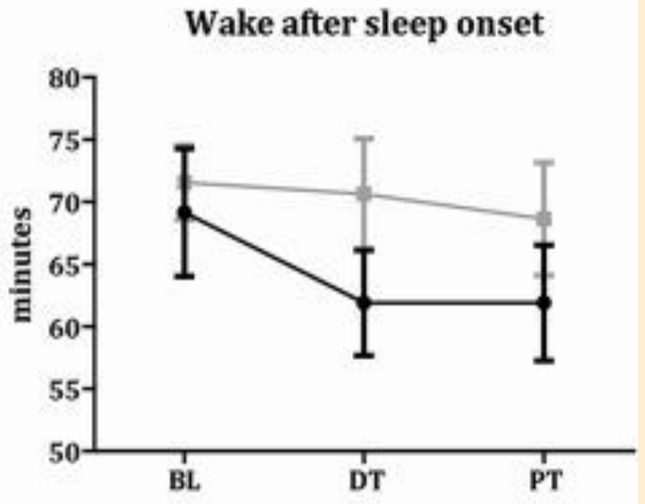


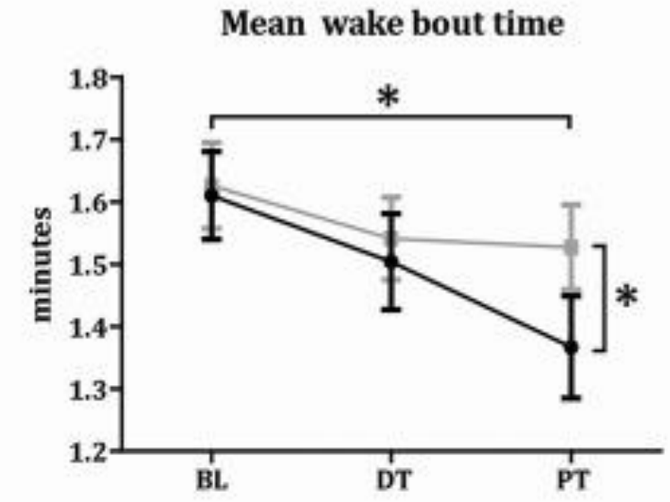


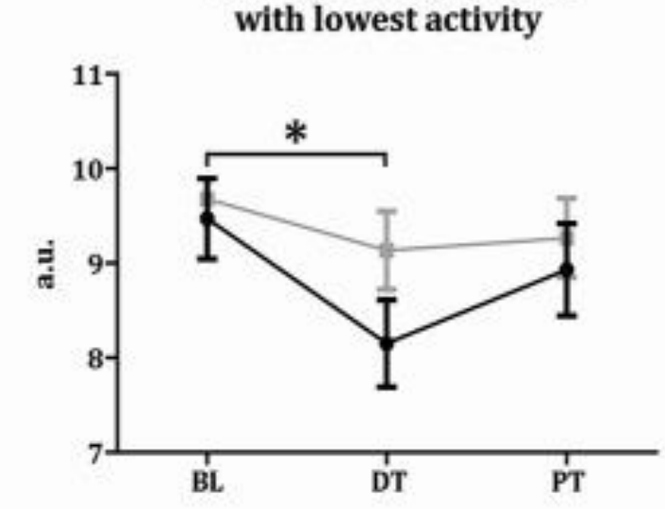


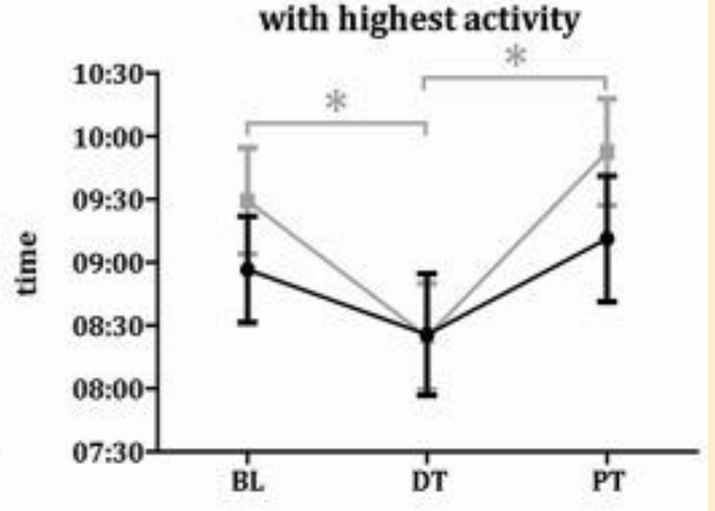












Benefits:
? Rebound
? Long-term

Solleveld et al
Front Psychiatry, 2020

A summary of considerations…

Difficult diagnosis - Treating diagnosis or **symptoms**??
Developmental process
Empirical support minimal in disorders like autism
Conducting trials and generating evidence is challenging
Limited number of studies (especially from LAMIC)
Medication overuse for lack of trained professionals
Pharmacodynamic & pharmacokinetic considerations
Duration of treatment
Long-term efficacy

Primacy of and greater advocacy for non-pharmacological methods
Combination treatment *'gold standard'*
Important to set clear 'therapeutic targets'

Rohde LA, 2013, Sareen H, 2013, Rapoport JL, 2013

Twenty years of progress in pediatric psychopharmacology

Table 1 Randomised clinical trials in paediatric psychopharmacology for common medication groups and therapeutic indications*

		Through 1998				1999–June 2018†			
		RCTs (N)	Patients randomised (N)			RCTs (N)	Patients randomised (N)		
Medication group	Indication		Total‡	To medication	To placebo		Total	To medication	To placebo
Stimulants	ADHD	66§	2306	2276	2190	130¶ *(2.0)*	12 239 *(5.3)*	9838 *(4.3)*	7838 *(3.6)*
Antidepressants	MDD	10	462	230	232	24 *(2.4)*	4956 *(13.1)*	2561 *(11.1)*	1937 *(8.3)*
	OCD	6**	357	208	138	6 *(1.0)*	636 *(1.8)*	336 *(1.6)*	268 *(1.9)*
	Anxiety disorders	1	15	6	9	12 *(12.0)*	2091 *(139.4)*	1064 *(171.2)*	855 *(95.0)*
	Other††	7‡‡	260	192	142	10§§ *(1.4)*	451 *(1.7)*	298 *(1.6)*	281 *(2.0)*
Antipsychotics	Schizophrenia spectrum	6	211	196	15	18 *(3.0)*	2764 *(13.1)*	2099 *(10.7)*	665 *(44.3)*
	Bipolar	0				12	2522	1591	931
	Aggression and other conduct disturbances	7	242	139	66	26 *(3.1)*	2113 *(8.7)*	1202 *(8.6)*	866 *(13.1)*
	Tic disorders	3¶¶	118	118	118	7***	317	201	43
Lithium	Bipolar disorder					5	496	208	61
	Aggression and other conduct disturbances	3***	118	52	52	1	40 *(0.3)*	20 *(0.4)*	20 *(0.4)*
	Mood dysregulation					1	25	14	11
Anticonvulsants	Bipolar disorder	0				8	791	339	245
	Aggression and other conduct disturbances†††	4§§	115	88	84	9*** *(2.2)*	285 *(2.5)*	175 *(2.0)*	129 *(1.5)*

Accomplishments

1. Comparative effectiveness (not just v/s placebo)
2. Safety assessments:
   Cardiac events with stimulants, Risk of abuse with stimulants, Cardiometabolic side effects with antipsychotics, Suicidality with antidepressants

Unmet needs

1. Clinical trials in practice settings
   a. Real world outcomes
   b. v/s psychosocial interventions
2. Disease-modifying interventions (not just symptom control)
3. Targeting dimensions of psychopathology
4. Neuroscience-informed psychopharmacology

Vitiello & Davico, Evidence based mental health, 2018

Principles of prescribing in CAP (Maudsley 14th)

Target symptoms, not diagnoses
Begin with less, go slow, monitor efficacy and adverse reactions
Multiple medications often required for the severely ill
Allow time for an adequate trial of treatment
Where possible, change one drug at a time
Monitor outcome in more than one setting
Patient and family medication education is essential

"Psychopharmacology requires a sense of humor. Sometimes, the best use of EBM is to remember how little evidence we have."

TA Kramer, MD (Chicago Illinois)

Table 2 Selection of randomised comparative effectiveness clinical trials in paediatric psychopharmacology

Study	Main research question	Sample	Setting	Randomisation to	Main findings
Multimodal Treatment Study of Children with ADHD[24]	How do different treatment strategies (pharmacological, behavioural and combined) compare with usual community care for decreasing ADHD symptoms and improving functioning?	n=579 Aged 7–9 years, with ADHD combined type	Outpatient university clinics	Medication (stimulant) management, behaviour therapy, their combination or usual care, for 14 months, followed by a 10-year naturalistic follow-up.	Greater improvement with medication management, either alone or in combination, with no difference between these two. Dissipation of treatment differences during naturalistic treatment.
Paediatric OCD Treatment Study[25]	Is SSRI combined with CBT more effective than either monotherapy in childhood OCD?	n=112 Aged 7–17 years, with OCD	Outpatient university clinics	Sertraline, CBT, their combination or placebo, for 12 weeks.	Combined treatment was more effective than monotherapy, which was better than placebo.
Treatment for Adolescents with Depression Study[27 28]	Is SSRI combined with CBT more effective than either monotherapy adolescent MDD?	n=439 Aged 12–17 years, with MDD	Outpatient university and community clinics	Fluoxetine, CBT, their combination or placebo for 12 months, followed by unblinded maintenance treatment for 6 months.	Fluoxetine, either alone or combined with CBT, was better than CBT, or placebo, in improving mood. Fluoxetine as monotherapy, but not when combined with CBT, increased the risk of suicidal events. No distal differences in outcome 6 months after randomisation.
Adolescent Depression Antidepressant and Psychotherapy Trial[29]	Is combined CBT and SSRI treatment more effective than SSRI monotherapy for adolescent depression?	n=208 Aged 11–17 years, with MDD	Outpatient practice settings	SSRI+routine care or CBT+SSRI+ routine care, for 12 weeks.	No difference between combined treatment and monotherapy.
Treatment of Resistant Depression in Adolescents[30]	After an unsuccessful treatment with SSRI, is switching to another antidepressant plus adding CBT more effective than switching to another antidepressant monotherapy?	n=326 Aged 12–18 years	Outpatient university clinics	SSRI or venlafaxine with or without CBT for 12 weeks.	Combined treatment was more effective than monotherapy.
Treatment of Early Onset Schizophrenia Spectrum Disorders[59]	Are second-generation antipsychotics superior to first-generation antipsychotic in the treatment of early onset schizophrenia?	n=119 Aged 8–19 years, with schizophrenia or schizoaffective disorder	Outpatient university clinics	Risperidone, olanzapine or molindone for 8 weeks (acute treatment) followed by 10-month maintenance treatment.	No difference among medications in efficacy, but with important differences in safety outcomes. Most patients discontinued the randomly assigned treatment after a few months.
Child-Adolescent Anxiety Multimodal Study[26]	Is SSRI combined with CBT more effective than monotherapy in childhood anxiety disorders?	n=488 Aged 7–17 years, with separation anxiety disorder, generalised anxiety disorder or social phobia	Outpatient university clinics	Sertraline, CBT, their combination or placebo, for 12 weeks.	Combined treatment was the most effective intervention. Monotherapy with sertraline or CBT was better than placebo.
Treatment of Early Age Mania[60]	How effective are antidopaminergic vs anticonvulsant medications vs lithium for acute mania stabilisation in children?	n=290 Aged 6–15 years	Outpatient university clinics	Valproate, lithium or risperidone for 8 weeks.	Risperidone was the most effective intervention, with no significant difference between lithium and valproate.
Treatment of Serious Behaviour Problems in PDD[61]	Does the addition of parent training to pharmacotherapy result in better outcomes in PDD?	n=124 Aged 4–13 years, with PDD	Outpatient university clinics	Risperidone, as monotherapy or combined with behaviour therapy, for 24 weeks.	Medication plus parent training was more effective than medication alone at decreasing maladaptive behaviours.

Vitiello & Davico, Evidence based mental health, 2018

Generic *(Registered®)* Drug Names	CYP 2C9	CYP 2C19	CYP 2D6
ANTIDEPRESSANTS			
Bupropion* *(Wellbutrin®)*	□	-	□
Citalopram* *(Celexa®)*	-	■	□
Desvenlafaxine *(Pristiq®)* ◊	-	-	-
Duloxetine *(Cymbalta®)*	-	-	■
Escitalopram* *(Lexapro®)*	-	■	-
Fluoxetine* *(Prozac®)* ╥	■	□	■
Fluvoxamine *(Luvox®)* ╥	-	-	■
Levomilnacipran *(Fetzima®)*	-	□	□
Paroxetine *(Paxil®)* ╥	-	-	■
Reboxetine *(Edronax®)* ◊	-	-	-
Sertraline* *(Zoloft®)*	■	■	□
Venlafaxine* *(Effexor®)*	□	□	■
Vilazodone *(Viibryd®)*	-	□	□
Vortioxetine *(Brintellix®)*	□	□	■
STIMULANTS, ADHD			
Amphetamine *(Adderall®)*	-	-	■
Atomoxetine* *(Strattera®)*	-	□	■
Clonidine *(Kapvay®, Catapres®)*	-	-	■
Dexmethylphenidate *(Focalin®)* ◊	-	-	-
Dextroamphetamine *(Dexedrine®)*	-	-	■
Guanfacine *(Intuniv®, Tenex®)* ◊	-	-	-
Lisdexamfetamine§ *(Vyvanse®)* ◊	-	-	-
Methamphetamine *(Desoxyn®)*	-	-	■
Methylphenidate* *(Concerta®, Ritalin®)*	-	-	□

■ Major, □ Minor, Drug substrate for metabolism by CYP2C9, CYP2C19, CYP2D6 isoenzyme(s)
◊ Drug not metabolized by CYP2C9, CYP2C19, CYP2D6 isoenzymes
* Drug with pharmacologically active metabolites
§ Prodrug of [d-amphetamine]
╥ DRUG INTERACTIONS: Drug metabolism inhibitor ╥ of CYP2C9, CYP2C19 and/or CYP2D6

Namerow et al, Current Psychiatry Reports, 2020