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Optimizing safe and evidence-based treatment of children and adolescents

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Objectives

- Review FDA approved pediatric indications for commonly prescribed psychotropic medication (ADHD, antidepressant, and SGA medications)
- Discuss updated information on safety concerns
- Introduce a NIMH-funded study to investigate a healthy lifestyle intervention to address metabolic side effects

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Dr. Paul Ehrlich

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My Perspective

- Clinician
- Researcher
- Clinical Reviewer

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Evidence Base

Pediatric safety and efficacy data

- FDA approved pediatric indications
- Pediatric clinical trial data

Expert consensus guidelines

- Practice guidelines (e.g. AACAP, AAP)
- Federal agency reviews and guidelines (e.g. AHRQ)

Adult data

- FDA approved adult indications
- Adult clinical trial data

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ADHD Stimulant Medications

"TEAM M"
Ritalin IR/SR/LA
Methylin IR/ER
Focalin IR/XR
Metadate ER/CD
Quillivant XR
Quillichew ER
Concerta
Daytrana

"TEAM A"
Adderall IR/XR
Evekeo
Dexedrine IR/SR
Dextrostat
Procentra
Zenzedi
Adzenys IR/XR
Vyvanse
Dyanavel XR

*Summarized in Brown et al., 2017

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Non-Stimulant ADHD Medication

Medication	Drug Class	Age
atomoxetine (Strattera)	Norepinephrine reuptake inhibitor	6-17 yrs old
clonidine extended release (Kapvay)*	Alpha 2 agonist	6-17 yrs old
guanfacine extended release (Intuniv)*	Alpha 2 agonist	6-17 yrs old

*Approved for monotherapy and adjunctive to stimulant treatment

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Selecting a treatment

Clinician: consider patient age, ADHD severity, comorbidity

Patient/Family: consider efficacy expectations, feasibility, preferences

Caye et al. 2018

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General Med Recommendations

- First med: stimulant, generally long acting are preferred
- Second med: if poor efficacy, switch to other class of stimulant
- Third med: If poor efficacy or tolerability challenges, consider a non-stimulant med

Brown et al., 2018

- **Advantage of combined treatment (med + therapy) over med only treatment is may have lower doses

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Special Populations

- Pre-schoolers
- Youth vulnerable to side effects (e.g. underweight, co-occurring tic disorders)
- Co-occurring substance abuse (youth or household)

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Safety considerations

Consider consultation with PCP at baseline or over maintenance treatment for:

- Growth (monitor BMI%)
- Elevated bp or suspected hypertension

Consultation:

- Clearance for stimulant use
- Guidance on monitoring plan

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AAP 2017 screening BP that require further evaluation

Age (yrs)	M SBP	M DBP	F SBP	F DBP
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

*Flynn et al., 2017

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Antidepressant Medications with Pediatric FDA approval

Medication	Pediatric age & indication
fluoxetine (Prozac)	OCD (7-17 yrs old); MDD (8-17 yrs old)
escitalopram (Lexapro)	MDD (12-17 yrs old)
sertraline (Zoloft)	OCD (6-17 yrs old)
fluvoxamine (Luvox)	OCD (8-17 yrs old)
duloxetine (Cymbalta)	GAD (7-17 yrs old)
clomipramine (Anafranil)	OCD (10-17 yrs old)

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Systematic Review and Meta-analysis

Comparative effectiveness/safety of CBT and pharmacotherapy for childhood anxiety disorders

- Participant age: Mean age 9.2 years old (5.4 – 16.1 yr old)
- Diagnoses – Panic disorder, social anxiety (avoidant disorder*), specific phobias, separation anxiety, generalized anxiety (overanxious disorder*)
- Excluded – OCD and PTSD
- SSRI's – sertraline, fluoxetine, fluvoxamine, paroxetine
- SNRI's – atomoxetine, duloxetine, venlafaxine
- Triclyclics – imipramine, clomipramine
- Benzodiazepine – clonazepam

Wang et al JAMA Pediatrics 2017

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Treatment response

Monotherapy (CBT or SSRI): response/remission

- CBT > waitlist or no treatment
- SSRI > placebo

Combined tx vs monotherapy: symptom improvement/treatment response

- Combined tx > CBT only (2 studies)
- Combined tx > med only (1 study)

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Positive treatment response (X) by rater compared to placebo

Medication class	Parent	Clinician	Child
SSRI	X	X	--
SNRI	--	X	--
Benzodiazepines & Tricyclics	--	--	--

NOTE:

- Duloxetine trials excluded 1) comorbid MDD; 2) co-treatment with stimulant

AE's except suicidality were not systematically assessed (Strawn et al., 2015)

*2 pediatric trials of busprione (Buspar) are unpublished (Hussain et al., 2016)

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Off-label treatment

"Ironically, the best researched medications are off-label for childhood anxiety treatment (excluding OCD) with US FDA approval only for duloxetine"

Asarnow et al., 2017 *JAMA Pediatrics*

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OCD (POTS study)

12 week RCT remission outcomes:

- Combined 53.6%
- CBT 39.3%
- Sertraline 21.4%
- Placebo 3.6%

Conclusions:

- First line treatment: CBT or combined treatment
- Sertraline was superior to placebo but med only treatment is less effective

POTS Study Team 2004

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MDD Treatment

- Fluoxetine (Prozac) and escitalopram (Lexapro) are recommended first line treatment
- These two SSRI's are more effective in adults than pediatric patients
- No changes in FDA recommendation for pediatric MDD treatment >10 yrs

Neavin et al., 2018

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Benefits of combined tx of MDD

TADS study: Fluoxetine/CBT vs. Fluoxetine only

- Time to remission is quicker
- Lower risk of suicidality

March et al. 2004

Safety concerns: suicidality

- 2004 FDA issued black box warning about risk of suicidality as a side effect of treatment
- JAMA Pediatrics 2017 Update on Medical Overuse "Antidepressant Medications increase suicidality and aggression in children"
- Consider strategies for prospective, daily mood ratings

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Second Generation Antipsychotics

Antipsychotic	Irritability due to autism	Bipolar I	Schizophrenia
aripiprazole (Abilify)*	X	X	X
risperidone (Risperdal)	X	X	X
olanzapine (Zyprexa)		X	X
quetiapine (Seroquel)		X	X
asenapine (Saphris)		X	
paliperidone (Invega)			X
lurasidone (Latuda)			X

*Also has indication for treatment of Tourette's Disorder

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"Off-label treatment"

- Treatment refractory conditions
- Diagnoses that don't have FDA approved pediatric treatments: PTSD, DMDD, ODD/CD
- Target symptoms: irritability & aggression (not due to autism), insomnia

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Treatment Refractory

- Dose and duration of treatment
- Consider: was dosing too high or too low?
- At least two first line agents tried
- Baseline and outcome measurement

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Adherence

- Reinforce accurate reporting over compliance
- Track at each medication follow up visit
- Anticipate challenges (e.g. child living in more than one household over the week)

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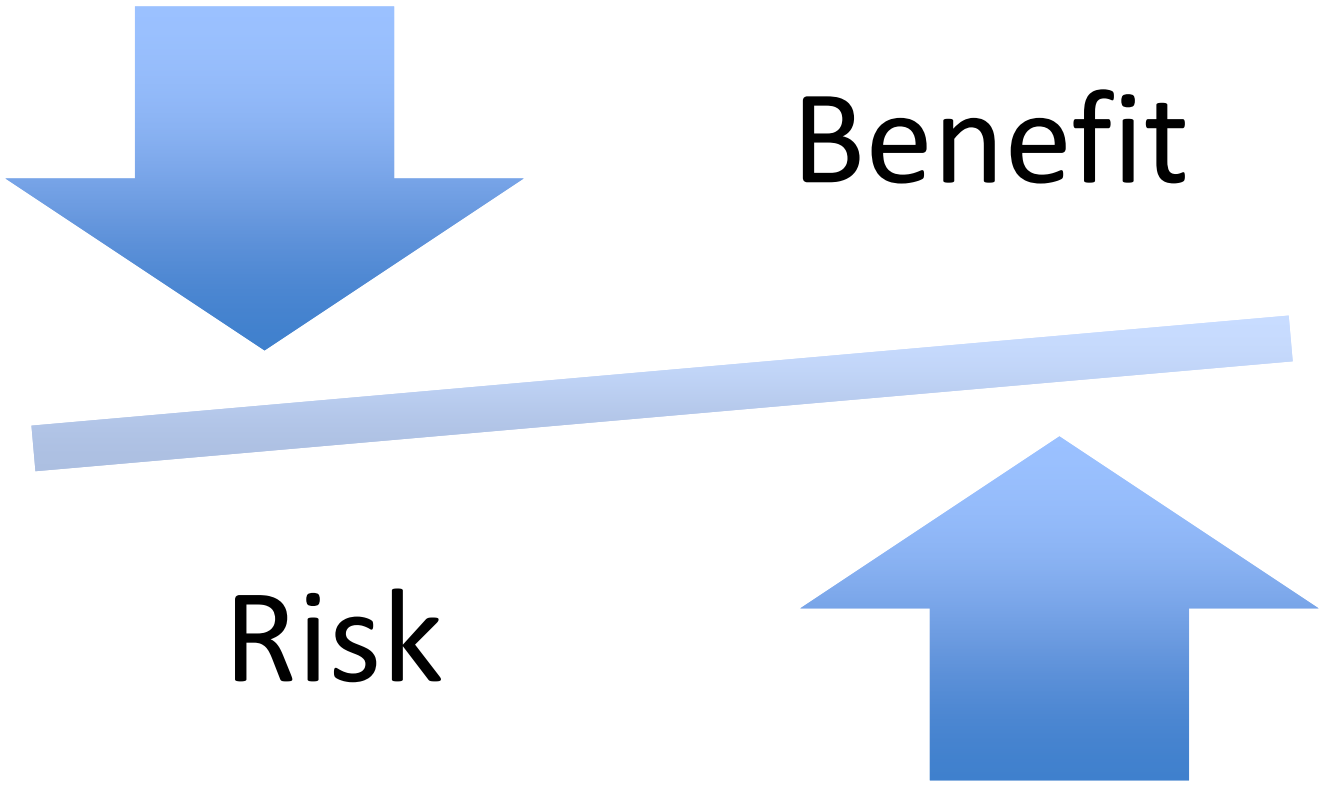
"Off-label" treatment



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2015 AHRQ Review

Inclusion:

- Pharmacologic treatment of disruptive behavior disorders
- Head-to-head or placebo comparison group
- ADHD studies only included if all youth had ODD/CD

Exclusion:

- Studies where disruptive behavior is secondary to autism, intellectual disability, or substance abuse
- Studies published prior to 1994

Epstein et al., 2015

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Key Findings

- 13 studies identified
- Study duration: most studies 4-10 wks (1 study with 6 month maintenance treatment)
- Funding: only 1 federally-funded; remainder industry sponsored
- Participants: mostly male; mostly ADHD plus ODD/CD
- Medications: antipsychotics, mood stabilizers, ADHD stimulant and non-stimulant meds
- Only 3 drugs were studied in >1 trial (atomoxetine, depakote, risperidone)

Conclusion

"…very few studies supporting effectiveness of pharmacologic interventions, but small studies of antipsychotics and stimulants reported positive effect in short term ."

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Strategies

- Family engagement critical
- Ongoing screening for violence exposure
- Optimize first line evidence-base psychosocial and pharmacologic treatment
- Conservative dosing
- Have clear plan to re-assess risk:benefit ratio

Reeves, Wehring, and Riddle 2018

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A word about cost

Average retail monthly cost (reported by Good Rx)

Vraylar: $1444

Latuda: $1489

Rexulti: $1355

Aripiprazole: $745

Risperidone: $77

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Metabolic side effects SGA

- Obesity
- Elevated blood sugar
- New onset diabetes
- Abnormal cholesterol/lipids

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Side effect management

- Baseline and ongoing assessment
- Consultation with PCP: clearance and monitoring schedule
- Monitor “silent side effects”
- Treat needle phobia

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Metabolic side effects SGA

- NIMH-funded R01 study (PI – Reeves)
- Parent-youth dyads
- Medicaid-insured youth recently started on an antipsychotic medication
- 6 month intervention

Diet

Activity

Parent health coaching/goal setting

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Make it easy

- Home-based (no office visits)
- Diet: reduce sugary beverage intake
- Activity: incremental improvement in child activity (pedometer) and activity monitoring by parent
- Health coaching: telephone-delivered, family navigator services

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Outcomes

- Sugary beverage intake (parent and child)
- Weight, height, blood pressure (parent and child)
- Physical activity (child)
- Fasting glucose and triglyceride (child)