

Pediatric Psychopharmacology Update With A Focus on ADHD

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Christopher K. Varley, M.D.

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Disclosures

Dr. Varley has no disclosures



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There will be discussion of off-label
utilization of psychotropic
medications in youth.



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Goals & Objectives

- Improve fidelity to evidenced based pharmacological treatment of ADHD.
- Appraise implications of prescribing trends of psychotropic medications to children and adolescents.
- Integrate FDA actions regarding antidepressant medications into your practice.



OVERVIEW

- Focus on ADHD, but will cover the waterfront
- Discussion of new developments



National Trends in Child and Adolescent Psychotropic Polypharmacy in Office-Based Practice, 1996-2007



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National Trends

- Data from National Ambulatory Medical Care surveys
- Nationally Representative sample of 3466 children
- Office-based visit in which a psychotropic medication was prescribed

Comer, 2010



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Results

- Multiclass prescription rose from 14.3% to 20%
- When a mental disorder was diagnosed, the change was from 22% to 32%



Results

Significant increase in visits for multiclass prescription in which ADHD medications, antidepressants or antipsychotics prescribed and decrease in visits with mood stabilizers prescribed



- Specific increase of ADHD medication and antipsychotics prescribed together
- Overall, 75% increase in percentage of visits mentioned a psychotropic medication



Weight Gain on Atypical Antipsychotics in Treatment Naïve Children

- 272 children ages 4-19
- 12 weeks
- Aripiprazole, Olanzapine, Quetiapine, Risperidone
- 15 patients who refused medication = Comparison group

Varley, 2010



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Results

- More than half gained more than 7% of their body weight
- Lipid and other cardiometabolic abnormalities
- Olanzapine: 8.5kg increase
- Quetiapine: 6.1kg
- Risperidone: 5.3kg
- Aripiprazole: 4.4kg



CARDIOMETABOLIC SIDE EFFECTS

Profound implications regarding
cardiometabolic risk over time in a
vulnerable population



Bias in Publication for Pediatric Antidepressants

- 4/15 SRI published studies positive
- 3 negative trials, published as positive
- Studies with negative results took twice as long to be published as compared to positive trials
- **BE CAREFUL WHAT YOU READ**



Quality of Care for Childhood Attention Deficit/ Hyperactivity Disorder in a Managed Care Medicaid Program

- Longitudinal cohort study of 350 children age 5-11 receiving ADHD care and on Medicaid
- Studied over 3 six-month intervals

Zima, 2010



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Results

- Receipt of no care 34-44% in at least 1 of the 3 six-month intervals studied
- In Primary Care 80-85% had at least one ADHD Rx – one or two visits per year



Results (cont.)

- Less than 1/3 of kids in specialty clinics were on any stimulant
- Poor refill persistence (31%-49%)



Implications

- Extraordinary failure to meet standard of care
- Enormous opportunity for improvement



Stimulant-Responsive and Stimulant-Refractory Aggressive Behavior Among Children with ADHD

- Kids 6-13 with ADHD and ODD/CD and aggression
- Insufficient response to stimulants

Blader, 2010



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Design

- Open stimulant monotherapy titration
- OROS Methylphenidate up to **90mg/day** or optimal response or intolerable side effects
- Switch option to Metadate CD or XR form of mixed salts of Amphetamine to maximum of 35mg/day



Results

- Overall reduction in aggression
- 49% considered to have responded
- Both responders and non responders had a decrease in aggression



Results (cont.)

Responder Characteristics

- Responded to OROS
- Lower doses
- Fewer behavioral sessions



Results (cont.)

OROS	Responders		Non-Responders	
	N	Mean Dose	N	Mean Dose
OROS	27	52mg	16	63mg
Metadate CD	2	40mg	4	27mg
Mixed Salts of Amphetamine	3	27mg	12	26mg



Conclusion

Optimal dosing of stimulant and behavior treatment may preclude need for polypharmacy



STIMULANTS – NEW DEVELOPMENTS

GENERIC FORM OF CONCERTA AVAILABLE IN 2011

SUPPLY PROBLEMS NATIONALLY WITH A NUMBER OF
STIMULANT PREPARATIONS IN 2011



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Lis-dexamphetamine Dimesylate

Amphetamine prodrug, dextro amphetamine bound to lysine

- Inactivity initially, converted in gut by cleaving of lysine
- FDA approval, 2-07, as a Schedule II drug
- Brand name Vyvanse
- Released July, 2007



Lis-dexamphetamine Dimesylate (cont.)

- Dose equivalence to amphetamine not clear, but probably $\sim \frac{1}{2}$ as potent, multiple dose sizes up to 70mg
- No published trials $> 70\text{mg/day}$
- Added benefit vs. Adderall XR not established
- Adderall XR is off patent
- Comparison studies underway by SHIRE



Stimulant Side Effect Issues



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American Heart Association 5/2008

Now a Class IIa recommendation that children with ADHD get a careful cardiac evaluation, including an EKG before starting stimulant, which means it is reasonable to consider an EKG, but at the physician's judgment. It is not mandatory.



ADHD is significantly associated
with Adolescent and Adult
substance use disorder



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ADHD and SUBSTANCE ABUSE

Rates of lifetime disorder:

- 45% any substance use disorder
- 28% alcohol use disorder
- 37% non-alcohol use disorder
- 24% stimulant use disorder



- Early age of MPH initiation does not increase risk of negative outcomes

AND

- Early MPH initiation may be protective



Substance Abuse

In controlled settings, evidence of benefit with stimulants when substance abuse is present



Do need to be aware of diversion
and abuse potential



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If concerns re substance abuse
by patient/parent or diversion
options:

- Atomoxetine
- Vyvanse
- Daytrana



Risk of Psychosis

- 1.5 per 100 patient years of exposure (*Pediatrics, January 2009*)
- Risk present but low risk



Stimulants and Growth

Results of a meta-analysis:

- Decreases in height and weight
- Impact of **0.5-1” over lifetime**
- Attenuation over time
- Seem to be dose dependent
- MPH and d-amphetamine are similar
- Discontinuation can lead to normal growth
- Do kids with ADHD have different patterns of growth?



Recommendations

- Treat one patient at a time regarding appetite/growth decisions
- Measure height and weight regularly
- Unusual to have to stop or change medication as a result of decreases in growth velocity
- Remember other problems can explain decrease in growth velocity



Guanfacine (Intuniv)

- Long-acting preparation
- Two positive industry sponsored RCTs



Intuniv vs. Immediate Release Guanfacine

- No comparison trial
- Greater T max and AUC on equal number of milligrams with IR guanfacine



Guanfacine (INTUNIV)

- Approved initially as monotherapy
- FDA approved in 2009
- Approved in 2011 as adjunctive



Long Acting Guanfacine

- Effect size similar to stimulants in controlled trial
- **NO** comparison studies



Guanfacine

- Off patent in two years



Guanfacine

- Seldom used as monotherapy



Long Acting Guanfacine + Stimulants

- Suboptimal ADHD response with a stimulant
- 3 Treatment Arms
 - Stimulant + Placebo
 - Stimulant + AM Guanfacine
 - Stimulant + HS Guanfacine
- Not yet published but presentation by Wilens at 2010 APA



Long Acting Guanfacine + Stimulant Results

- Both AM and PM Guanfacine Superior to Placebo
- No Difference Between AM and PM Guanfacine



Clonidine

1. Long acting preparation – KAPVAY
2. FDA Indication for both monotherapy and add-on to stimulant
3. Administered BID
4. Released January, 2011



Clonidine Extended-Release Tablets for Pediatric Patients with Attention-Deficit/Hyperactivity Disorder

- 236 patients with ADHD, 6-17
- Placebo, 0.2mg/day, 0.4mg/day for 8 weeks
- Forced titration of 0.1mg/day increase each week
- Tapering began at week 5



Results

- Significant improvement by week 2 and maintained to week 5. LOCF
- Effect size 0.7 no difference between 0.2mg and 0.4mg
- Similar to Guanfacine ER and non stimulants



- Discontinuation from lack of efficacy
 - Placebo 32%
 - 0.2mg 9%
 - 0.4mg 11%



Adverse Events

- Main side effect: somnolence
- Discontinuation rate from side effects
 - Placebo 1%
 - 0.2mg 7%
 - 0.4 19%



Clonidine (Kapvay) Combination with a Stimulant

- Children 6-17
- Stable stimulant dose
- Clonidine dose begun at 0.1 mg/day and titrated up to 0.4 mg/kg
- **75% were on 0.4 mg/day as optimal dose**



Anxiety and ADHD Controlled Trials

- Benefit with stimulants
- Benefit with atomoxetine



ADHD Symptoms in Autistic Spectrum Disorders

- Emerging evidence for some benefit with:
 - Methylphenidate
 - Guanfacine
 - Atomoxetine
- Degree of response is attenuated vs. children without Autism



Combination Rx

- Benefit of combining stimulant and atomoxetine in trials
- Should be reserved for cases with failure to respond to single agents



CBT, Sertraline, or a Combination, in Childhood Anxiety (CAMS)

- MOST IMPORTANT ANXIETY DISORDER STUDY
- Study of Separation Anxiety Disorder, Generalized Anxiety Disorder, Social Phobia
- Similar to TADS and POTS as a multisite RCT, funded by NIMH



CAMS Design

- 3 active treatment groups (sertraline, CTB, combined) and placebo IN A 2:2:2:1 ratio
- CBT – Coping Cat (Kendall)
- 12 weeks of active treatment
- 6 month follow-up



CAMS Results at 12 weeks:

	% Responders
Combined	81%
CBT	60%
Sertraline	55%
Placebo	24%



CAMS

- Mean Doses (mg/day)
 - Combined 131
 - Sertraline 141
 - Placebo 171



Escitalopram

- 3/2009 FDA indication to prescribe major depressive disorder in adolescents 12-17



Based on 2 Studies

- 1) Study of children and adolescents with no efficacy overall and a trend toward greater efficacy in adolescents.
- 2) 8 week, Phase III RCT in Adolescent



Study Design

- Diagnosis of MDD (mean duration 1.3 years)
- Escitalopram 10-20mg/day or placebo
 - 10 mg x 3 weeks
 - Could then go to 20mg
- CDRS –R = primary efficacy indicator



Results

- At week 8, decrease in CDRS-S
- Change noted at week 4



16 Week Extension Study

Effects Endured



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Side Effects

- No difference in suicidal ideation (1%)



Summary

- Essentially no new medications
- What does change are preparations
- Stay tuned, as information is always coming out



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