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# Stimulant Use in Preschool-Aged Children

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## Objectives

- ▶ 1. Identify signs and symptoms of attention-deficit/hyperactivity disorder (ADHD)
- ▶ 2. Explain the findings of current literature regarding ADHD treatment in preschool-aged children
- ▶ 3. Provide a recommendation on the treatment of ADHD in preschool-aged children based on available evidence

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## Case

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## Case Information

- ▶ Susie Q is a 3-year-old whose mother is concerned she may need treatment for behavioral problems
  - ▶ She has a hard time sitting still, difficulty waiting for her turn, talks excessively, leaves her seat when she should remain seated, is "on the go", and she is unable to play quietly
  - ▶ This behavior has been going on for 6 months
  - ▶ She gets in trouble at her daycare for her behavior, and her parents are bothered by her behavior
- ▶ Do you think Susie Q needs to be prescribed a stimulant?

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## Background

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## Prevalence

- ▶ National Survey of Children's Health 2011-2012
  - ▶ 237,000 children ages 2-5 diagnosed with ADHD
  - ▶ 57% higher than previous report
- ▶ Estimated 6.7/1000 expelled from preschool or child care nationally
- ▶ 1 in 3 children with ADHD is diagnosed during preschool years
- ▶ These children are at a higher risk of being in special education programs, having unintentional injuries, being disruptive, and being less liked by their peers

Daneshmandi, M. A National Profile of Attention-Deficit/Hyperactivity Disorder Diagnosis and Treatment. J Dev Behav Pediatr 2017  
 Fox AC, Ross SE. Preschool ADHD diagnosis and stimulant use before and after Pediatrics. 2013; 132(5):e1203-1209.

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## Pathophysiology

- ▶ Not yet possible to define
- ▶ Multifactorial – genetic and environmental factors believed to have a role
- ▶ Catecholamine hypothesis
  - ▶ Dopamine and norepinephrine
- ▶ Brain Systems
  - ▶ Dysregulation of the frontal cortex, subcortical structures, and networks connecting them
- ▶ Etiologic factors
  - ▶ Genetics

Figure 3V. Pathophysiology of attention-deficit/hyperactivity disorder. In: Neuropharmacology: The Fifth Generation of Progress, 2002.

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## Diagnosis

- ▶ Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV-TR)
  - ▶ Six or more symptoms of inattention and/or hyperactivity-impulsivity
  - ▶ Symptoms should be present before the age of 7, for at least 6 months, and cause impairment in at least 2 settings (social, occupational, academic)
- ▶ Assessed with checklists
  - ▶ Example: Conners Parent and Teacher Rating Scales

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington: American Psychiatric Association; 2000:85-93.

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## Symptoms: Inattention

<ul style="list-style-type: none"> <li>▶ Failure to give close attention to details</li> <li>▶ Difficulty sustaining attention during tasks or activities</li> <li>▶ Not listening when spoken to</li> <li>▶ Does not finish work</li> </ul>	<ul style="list-style-type: none"> <li>▶ Difficulty organizing tasks</li> <li>▶ Avoids tasks that require prolonged attention</li> <li>▶ Loses things necessary for tasks</li> <li>▶ Easily distracted by external stimuli</li> <li>▶ Forgetful in daily activities</li> </ul>
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American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington: American Psychiatric Association; 2000:85-93.

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## Symptoms: Hyperactivity-impulsivity

<ul style="list-style-type: none"> <li>▶ Fidgets or tap hands or squirms in seat</li> <li>▶ Leaves seat in situations where it is not appropriate to do so</li> <li>▶ Often runs or climbs at inappropriate times</li> <li>▶ Unable to play or participate quietly</li> </ul>	<ul style="list-style-type: none"> <li>▶ "On the go"</li> <li>▶ Talks excessively</li> <li>▶ Blurts out answers</li> <li>▶ Difficulty awaiting turn</li> <li>▶ Interrupts or intrudes on others</li> </ul>
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American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington: American Psychiatric Association; 2000:85-93.

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## ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

2011 ADHD PRACTICE GUIDELINES

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## 2011 ADHD Guidelines

- ▶ Defined preschool-aged as 4-5 years old
- ▶ Recommend parent behavior therapy (PBT) as first line
- ▶ Recommend methylphenidate if behavioral interventions do not improve symptoms and the child remains moderately to severely impaired
- ▶ Clinician should weigh risks and benefits

Wolach M. Subcommittee on Attention-Deficit/Hyperactivity Disorder. Steering Committee on Quality Improvement and Management. ADHD clinical practice guideline for the diagnosis. Pediatrics. 2011;128(5):1007-1022.

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## Stimulant Medications

- ▶ Inhibit reuptake of norepinephrine and dopamine
- ▶ Stimulate cerebral cortex and subcortical structures
- ▶ Adverse effects: insomnia, decreased appetite, tachycardia, tics, weight loss, growth suppression
- ▶ Dextroamphetamine
  - ▶ Indicated for children 3 and up
- ▶ Methylphenidate
  - ▶ Indicated for children 6 and up
- ▶ Why do the guidelines support methylphenidate in preschool-aged children?

Dextroamphetamine monograph, Lexi-Comp, Online™, Pediatric Lexi-Drug, Online®; 2017.  
Methylphenidate monograph, Lexi-Comp, Online™, Pediatric Lexi-Drug, Online®; 2017.

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## Clinical Controversy

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## Controversy

- ▶ Guidelines have recommendations for children ≥4, but children are being diagnosed at 2
- ▶ Are stimulants safe and effective for this population?
- ▶ Should we be treating children under the age of 4?

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## Efficacy and Safety of Immediate-Release Methylphenidate Treatment for Preschoolers with ADHD

PATS (2006)  
GREENHILL, ET AL.

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## PATS Methods

- Objective**
  - To determine safety and efficacy of immediate release methylphenidate given three times daily to children ages 3-5.5
- Methods**
  - Randomized, controlled trial with **8 phases**
  - Two double-blind, controlled phases
- Inclusion Criteria**
  - Stimulant naive, ages 3 to 5.5 years with DSM-IV diagnosis of ADHD based on the Diagnostic Interview Schedule for Children IV-Parent Version and semi-structured interview, participation in a preschool or day care group, and more
- Exclusion Criteria**
  - Current evidence of adjustment disorder, pervasive development disorder, psychosis, significant suicidality, or had another psychiatric disorder that required medication, and more

Greenhill L. Efficacy and safety of immediate release methylphenidate treatment. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284-1293.

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## PATS Methods Cont'd

Phase	Duration
Screening/Enrollment	Time varied
Parent Training	10 weeks
Baseline	2-4 weeks
Open Label Safety Lead-in	1 week
<b>Crossover Titration</b>	<b>5 weeks</b>
<b>Parallel Phase</b>	<b>4 weeks</b>
Open-Label Maintenance	10 months
Discontinuation	6 weeks

Greenhill L. Efficacy and safety of immediate release methylphenidate treatment. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284-1293.

PATS Methods Cont'd

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Crossover Titration Phase

- Randomized to 1.25, 2.5, 5, 7.5mg, or placebo tid and changed every week
- Established "best dose"
- Assessed with Conners, Loney, and Milich Rating Scales (CLAM); Swanson, Kotkin, Atkins, M-Flynn, and Pelham Rating Scales (SKAMP); and the Side Effect Rating Scales

Greenberg L. Efficacy and safety of immediate-release methylphenidate treatment. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284-1293

PATS Results of Crossover Phase

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Scale	Placebo	Low dose (1.25mg, n=165)	Mid-low dose (2.5mg, n=165)	Mid-high dose (5mg, n=165)	High Dose (7.5mg, n=142)	Effect size on best dose	P-value
Parent CLAM mixed	1.35	1.28	1.18	1.17	1.02	0.89	<0.0001
Teacher CLAM mixed	1.08	1.20	1.13	1.02	0.99	0.75	<0.0001
Parent SKAMP attention	0.94	0.89	0.74	0.73	0.64	0.74	0.0001
Teacher SKAMP attention	0.95	0.81	0.79	0.70	0.63	0.68	<0.0001
Parent-teacher composite	1.28	1.19	1.09	1.03	0.91	1.20	<0.0001

Greenberg L. Efficacy and safety of immediate-release methylphenidate treatment. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284-1293

PATS Methods Cont'd

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Placebo-Controlled Phase

- After a 24-hour washout, given their optimized dose or placebo
- Assessed using an average of parent and teacher ratings on the Swanson, Nolan, and Pelham Rating Scale, Version IV (SNAP)
- Identified as "excellent responders" (Y/N)

Greenberg L. Efficacy and safety of immediate-release methylphenidate treatment. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284-1293

PATS Results of Parallel Phase

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Scale	Placebo (n=53)	Best dose (n=61)	Effect Size	P-value
Excellent responder, N (%)	13 (24.7)	7 (13.2)	---	0.2765
Parent-Teacher SNAP composite score, mean (SD)	17.79(0.61)	1.46(0.57)	0.55	0.0114

Greenberg L. Efficacy and safety of immediate-release methylphenidate treatment. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1284-1293

PATS Safety Outcomes

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- ▶ Crossover titration
  - ▶ High blood pressure reported on 8 occasions, and tachycardia on 1 occasion
- ▶ 36 patients left before completing parallel phase
  - ▶ 33 behavioral deterioration
  - ▶ 2 declined participation
  - ▶ 1 side effect
- ▶ 5 side effects occurred more frequently on high dose
  - ▶ Appetite loss, trouble sleeping, stomachache, social withdrawal, lethargy
- ▶ Children who remained on therapy had significant decreases in annual growth (-20.3% for height and -55.2% for weight)

Swanson J, Greenberg L. Weight loss and stimulant-related reductions. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1304-1313

PATS Reduction in Growth

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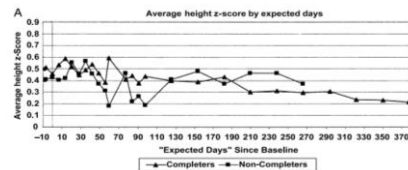


Fig. 2 Group means across the assessment times (expected number of days from baseline). (A) Height for completers and non-completers. (B) Weight for completers and non-completers. Swanson J, Greenberg L. Weight loss and stimulant-related reductions. J Am Acad Child Adolesc Psychiatry. 2006;45(11):1304-1313

### PATS Reduction in Growth

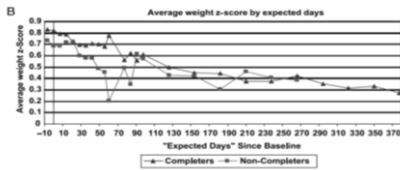


Fig. 2 Group means across the assessment times (expected number of days from baseline). (A) Height for completers and non-completers. (B) Weight for completers and non-completers

Swanson, J., Greenberg, L., Wigton, T., et al. Stimulant-related reductions. *J Am Acad Child Adolesc Psychiatry*. 2004;43(11):1304-1313.

### PATS Discussion: Author's Conclusions

- ▶ Mean optimal dose is 14.22 ± 8.1 mg/day
- ▶ Methylphenidate is safe and effective in this population
- ▶ Effect sizes not as large as those seen in the study involving older children
- ▶ Risks should be balanced with benefit

Greenberg, L. Efficacy and safety of immediate-release methylphenidate treatment. *J Am Acad Child Adolesc Psychiatry*. 2004;43(11):1294-1295

### PATS Discussion: Limitations

- ▶ Study design
- ▶ Parents may have been more nervous
- ▶ Attrition rate
- ▶ Severity of symptoms may have led to insignificant findings (all-or-nothing categorical outcome for controlled parallel phase)

### Interventions for Preschool Children at High Risk for ADHD: A Comparative Effectiveness Review

2013  
CHARACH, ET AL.

### Charach Methods

- Objective**
  - To review literature on ADHD in preschool-aged children
- Methods**
  - Searched databases from 1980 through November 2011
- Inclusion Criteria**
  - Published in English, investigated interventions for children <6 with significant disruptive behavior or diagnosis of ADHD (reliable and valid), oppositional disorder or defiant disorder
- Strength of Evidence (SOE)**
  - Internal validity, study design, consistency of results across studies, directness of evidence linking intervention and outcome, and precision of effect estimate

Charach A. Interventions for Preschool Children at High Risk for ADHD. Pediatrics. 2013

### Charach Methods Cont'd



Charach A. Interventions for Preschool Children at High Risk for ADHD. Pediatrics. 2013

### Charach Results: PBT

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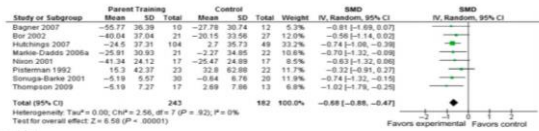


FIGURE 4 Effect of PBT on disruptive behavior in preschool-aged children (good studies). \*Includes RCTs rated as good quality (assumes correlation between post- and pre-score of 0.3). Means are post/pre differences, SMD reflects difference of these differences.

Charach A. Interventions for Preschool Children of High Risk for ADHD. Pediatrics. 2013

### Charach Results: PBT

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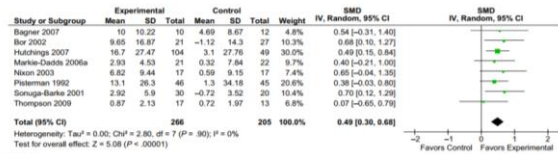


FIGURE 5 Effect of PBT on parenting skills (good studies). \*Includes RCTs rated as good quality (assumes correlation between post- and pre-score of 0.3). Means are post/pre differences, SMD reflects difference of these differences.

Charach A. Interventions for Preschool Children of High Risk for ADHD. Pediatrics. 2013

### Charach Results: Stimulants

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- ▶ Only study with good SOE was PATS trial
- ▶ Methylphenidate has many adverse effects, PBT does not
- ▶ Not enough evidence to support methylphenidate as first line

Charach A. Interventions for Preschool Children of High Risk for ADHD. Pediatrics. 2013

### Charach Discussion: Author's Conclusions

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- ▶ PBT has high SOE for improving behavior
- ▶ Methylphenidate has low SOE
- ▶ Mixed parent and school components shows inconsistent results

Charach A. Interventions for Preschool Children of High Risk for ADHD. Pediatrics. 2013

### Charach Discussion: Strengths & Limitations

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- ▶ Strengths
  - ▶ Study design
- ▶ Limitations
  - ▶ Study design – small sample sizes, only 1 good study of methylphenidate

Charach A. Interventions for Preschool Children of High Risk for ADHD. Pediatrics. 2013

### Preschool ADHD Diagnosis and Stimulant Use Before and After the 2011 AAP Guidelines

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2016  
FKS, ET AL.

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## Fiks Methods

**Objective**

- To evaluate the change in the diagnosis of ADHD and prescribing of stimulants to children 4-5 years old before and after 2011 guidelines

**Methods**

- Electronic health records extracted from 63 primary care practices from 2008 to 2014
- Evaluated 45 months before and 33 months after

**Inclusion**

- Children ages 48-72 months (4-5 years) old during preventative primary care visits

Fik AG, Ross ME. Preschool ADHD diagnosis and stimulant use before and after. *Pediatrics*. 2013;131(5):e2011-2025

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## Fiks Results

FIGURE 2  
ADHD diagnosis and stimulant prescriptions before and after release of the AAP guideline for ADHD management in 48 to 72-month-old children (October 2011). Values were derived from logistic regression spline models with splines reflecting practice clustering.

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## Fiks Author's Conclusions

- ▶ Pre-guideline diagnosis 0.7%, post-guideline 0.9%
- ▶ Individual practices varied
- ▶ There was a pre-guideline increase in ADHD diagnosis that stabilized post-guideline
- ▶ Stimulant prescribing remained the same (0.4%)

Fik AG, Ross ME. Preschool ADHD diagnosis and stimulant use before and after. *Pediatrics*. 2013;131(5):e2011-2025

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## Fiks Limitations

- ▶ Limitations
  - ▶ Cannot assess causality
  - ▶ Cannot assess outside providers
  - ▶ Lacked data on actual patient use

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## Case

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## Case Information

- ▶ Susie Q is a 3-year-old whose mother is concerned she may need treatment for behavioral problems
  - ▶ She has a hard time sitting still, difficulty waiting for her turn, talks excessively, leaves her seat when she should remain seated, is "on the go", and she is unable to play quietly
  - ▶ This behavior has been going on for 6 months
  - ▶ She is getting in trouble at her daycare for her behavior, and her parents are bothered by her behavior
- ▶ Do you think Susie Q needs to be prescribed a stimulant?

No! PBT first!

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## Case Information Update

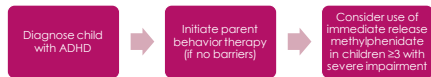
- ▶ Susie Q and her parents have completed 10 weeks of group parent behavior therapy
- ▶ She still has severe impairment
- ▶ Do you think Susie Q should be prescribed methylphenidate now?

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## Conclusion

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## Recommendation



More studies need to be done to further assess safety and efficacy of methylphenidate

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## Acknowledgements

- ▶ Evaluator
  - ▶ Dr. Leslie Getchell, PharmD
- ▶ Preceptors
  - ▶ Dr. Allison Rowland, PharmD

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