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

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?

Background

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.
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

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

Symptoms: Inattention

- Failure to give close attention to details
- Difficulty sustaining attention during tasks or activities
- Not listening when spoken to
- Does not finish work
- Difficulty organizing tasks
- Avoids tasks that require prolonged attention
- Loses things necessary for tasks
- Easily distracted by external stimuli
- Forgetful in daily activities

Symptoms: Hyperactivity-impulsivity

- Fidgets or taps hands or squirms in seat
- Leaves seat in situations where it is not appropriate to do so
- Often runs or climbs at inappropriate times
- Unable to play or participate quietly
- "On the go"
- Talks excessively
- Blurs out answers
- Difficulty awaiting turn
- Interrupts or intrudes on others

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

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
Stimulant Medications

- Inhibit reuptake of norepinephrine and dopamine
- Stimulate cerebral cortex and subcortical structures
- Adverse effects: insomnia, decreased appetite, tachycardia, fxs, 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?

Clinical Controversy

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?

Clinical Controversy

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

PATS (2006)

GREENHILL, ET AL.

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 6 phases
- Two double-blind, controlled phases

Inclusion Criteria
- Stimulant naïve, ages 3 to 5.5 years with DSM-IV diagnosis of ADHD based on the Diagnostic Interview Schedule for Children-IV Parent Version, 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

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
Crossover Titration | 3 weeks
Parallel Phase | 4 weeks
Open-Label Maintenance | 10 months
Discontinuation | 6 weeks
PATS Methods Cont’d

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, Kolff, Atkins, M-Flynn, and Pelham Rating Scales (SKAMP); and the Side Effect Rating Scales.

PATS Results of Crossover Phase

<table>
<thead>
<tr>
<th>Scale</th>
<th>Placebo</th>
<th>Low dose (1.25mg, n=165)</th>
<th>Mid-low dose (2.5mg, n=165)</th>
<th>Mid-high dose (5mg, n=165)</th>
<th>High dose (7.5mg, n=142)</th>
<th>Effect size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>1.28</td>
<td>1.30</td>
<td>1.19</td>
<td>1.02</td>
<td>0.99</td>
<td>0.94</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Teacher</td>
<td>1.30</td>
<td>1.20</td>
<td>1.15</td>
<td>1.02</td>
<td>0.99</td>
<td>0.94</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Parent</td>
<td>0.81</td>
<td>0.79</td>
<td>0.70</td>
<td>0.65</td>
<td>0.60</td>
<td>0.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Teacher</td>
<td>1.09</td>
<td>1.09</td>
<td>1.03</td>
<td>0.91</td>
<td>1.20</td>
<td>1.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PATS Methods Cont’d

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)

PATS Results of Parallel Phase

<table>
<thead>
<tr>
<th>Scale</th>
<th>Placebo (n=53)</th>
<th>Best dose (n=61)</th>
<th>Effect Size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent responder, N (%)</td>
<td>13 (21.7)</td>
<td>7 (13.2)</td>
<td>---</td>
<td>0.2765</td>
</tr>
<tr>
<td>Parent Teacher SNAP composite score, mean (SD)</td>
<td>17.79 (0.61)</td>
<td>1.45 (0.57)</td>
<td>0.55</td>
<td>0.0114</td>
</tr>
</tbody>
</table>

PATS Safety Outcomes

- 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
- 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)

PATS Reduction in Growth

![Graph showing reduction in growth]


PATS Reduction in Growth

Average weight in grams by expected days

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

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)
- Adverse events in study design, consistency of results across studies, directness of evidence linking intervention and outcome, and precision of effect estimate

Charach Methods Cont’d

55 reports
- 34 PBT trials – 8 “good”
- 15 stimulant trials – 1 “good”
- 6 combined PBT and school or daycare-based components
Charach Results: PBT

**Results: PBT**

- Study design

Charach Results: Stimulants

**Results: Stimulants**

- 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 Discussion: Author’s Conclusions

**Discussion: Author’s Conclusions**

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

Charach Discussion: Strengths & Limitations

**Discussion: Strengths & Limitations**

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

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

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

*FIKS, ET AL.*
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 43 primary care practices from 2008 to 2014
- Evaluated 43 months before and 33 months after

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

Fiks Results

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%)

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

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!
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?

Conclusion

Recommendation

Diagnose child with ADHD
Initiate parent behavior therapy (if no barriers)
Consider use of immediate release methylphenidate in children ≥3 with severe impairment

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

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