ADHD in the Preschool Aged Child

The Preschool ADHD Treatment Study (PATS)
11/2/2013
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The Preschool ADHD Treatment Study (PATS)

- National Institute of Mental Health study
- First papers published in 2006 after 1-2 years of study
  - J.Am.Acad.Child Adolesc.Psychiatry, 45:11, Nov 2006
- Developed to fill the gap in limited knowledge of the course of moderate-severe ADHD beginning in young childhood
- Six year follow-up study published in 2013
  - J.Am.Acad.Child Adolesc.Psychiatry, 52:3, Mar 2013

Preschool ADHD

- Emily
  - 4.5 years old
  - Former 27 week preemie
  - Prolonged, rocky NICU course
    - Meningitis
    - anemia
  - Older parents
  - Now severely hyperactive/inattentive w/ very delayed language
  - Unable to make gains in speech and OT due to hyperactivity/inattention

The Preschool ADHD Treatment Study (PATS)

- 303 preschoolers with severe ADHD
- Multi-center study with rigorous diagnostic process using cross-site consensus and data collected from parents and teachers (SKAMP and CLAMS and SNAP)
- 261 completed 10-week parent management training
- 165 still met the ADHD severity criteria and were eligible to enter and begin medication treatment
- 147 completed the double blind phase
- 140 enrolled in open label maintenance

PATS Efficacy and Safety of Immediate-Release Methylphenidate

Greenhill et al 1284-1293

- 6 Center randomized controlled trial over 70weeks
- Immediate release MPH given tid (MPH-IR)
- Ages 3-5.5yrs with ADHD
- Demographics:
  - Average age 4.4years
  - 63% white, 19% black, 16% Latino, 2% Asian, 1% Native Am
  - 73% male
  - DAS General Ability Score mean 97 (SD 16)
  - 52% ODD/CD
  - 22% Communication Disorder
  - 16% Anxiety Disorder
  - 8% Elimination Disorder
  - 97% Mom and dad HS graduates; 76% 2 parent households

PATS Efficacy and Safety of Immediate-Release Methylphenidate

Greenhill et al 1284-1293

- Safety and Tolerability
  - 92% tolerated MPH in the open label lead in study
  - 1 seizure was thought to relate to the medication
- Efficacy Compared w/ placebo
  - Mean optimal daily dose was 14.2 +/- 8.1
  - Initiated at low doses, but in some higher doses were needed for maintenance
  - 21% treated with optimum dose of MPH-IR met the criteria for remission of ADHD, 13% on placebo
  - Significant decrease in ADHD symptoms at MPH-IR dose
    - 2.5mg tid (.01), 5mg tid (.001) and 7.5mg (.001) tid
  - Preschoolers with ADHD do benefit from treatment
    - Emily is able to pay attention and makes dramatic gains in speech and OT

PATS Safety and Tolerability of MPH-IR

Wigal et al 1294-1303

- 183 children entered
  - multiple phases to the placebo controlled study
- Measured
  - Pulse, BP, adverse events, parent and teacher ratings
- 30% of parents reported moderate to severe AEs
  - Emotional outbursts
  - Sleep difficulty
  - Decreased appetite
  - Repetitive behaviors/thoughts
  - Irritability

PATS Safety and Tolerability of MPH-IR

Wigal et al 1294-1303

- 21/183 discontinued tx because of AEs (11%)
  - 11 in open lead-in phase
  - 3 in titration phase
  - 7 in maintenance phase
- The higher the dose, the greater the likelihood of AEs
  - Total 15-20% AE compared to placebo
  - 19-24% with 2.5mg tid
  - 25-30% with 5mg tid
  - 25-30% with 7.5mg tid
- A higher dose was needed to maintain gains of treatment during the maintenance phase
  - Emily developed tachycardia, MaryBeth Hourihan found no ECG or cardiac abnormalities but mother chose to stop meds
  - She maintained the gains made but school was a major challenge

PATS Safety and Tolerability of MPH-IR

Wigal et al 1294-1303

- 21/183 discontinued tx because of AEs (11%)
  - Anorexia
  - Irritability/Emotionality
  - Tics
  - Weight loss
  - Depression
  - Anxiety
  - Social isolation
  - 1 seizure
  - Formication (skin crawling)
  - No cardiovascular AEs were reported

PATS MPH-IR Related Reduction of Growth Rate

Swanson et al 1304-1313

- 2002 American Academy of Child and Adolescent Psychiatry Guidelines recommended regular monitoring growth of children treated with stimulants
- Theories
  - Growth rebound hypothesis (Safer 1975 and Satterfield 1979)
    - Initial growth reduction would be offset by rebound w/ med stopped
    - Others proposed that rebound would occur even during treatment
  - Delayed maturation hypothesis (Spencer 1996)
    - Disorder related delay in maturation in children w/ADHD
      - Mistaken as stimulant related growth delay
    - Late maturation results in catch up growth (constitutional growth delay)
      - Even if treated with stimulants

PATS MPH-IR Related Reduction of Growth Rate

Swanson et al 1304-1313

- This study designed to describe short term effects of stimulant medication of growth in preschool children
  - Average age 4.77 years
  - Children were larger than expected average size (2cm taller and 1.78kg heavier) and mean BMI 86th percentile
  - Greater average height was maintained over time before initiating MPH-IR
  - Reduction in growth rate for those completing treatment resulted in reduced but still larger than expected height and weight, average BMI decreased to the 71st percentile

PATS MPH-IR Related Reduction of Growth Rate

Swanson et al 1304-1313

- Neto 2002 and Volkow 2002
  - Clinical doses of MPH-IR block >50% of the dopamine transporter (DAT) in the striatum and increase dopamine levels in that region of the brain
  - Also increases dopamine in other regions of the brain
- Animal studies show that DAT blockade in the hypothalamus affects pituitary function and causes growth retardation
- Caron 2004 suggested that a dopamine deficit in stimulant naïve children with ADHD may contribute to the greater than expected growth rate
- Risks of reduced growth rate should be balanced against expected benefits when preschool children are treated with stimulant medications

PATS Pharmacogenetics of MPH-IR Response Rate

McGough et al 1314-1322

- ADHD is thought to be a complex, polygenic syndrome with 70-80% heritability
- This study looked at potential genetic moderators of variability in both medication response and side effects, the hope is to eventually choose medications with higher likelihood of success while minimizing risk of side effects for an individual
- 81 of 165 agreed to take part in the study
- Appetite suppression was predicted by dose alone across all genotypes
- DRD4 Genetic variations predicted dose response differences
- Specific genotypes were associated with particular side effects
  - Irritability
  - Motor tics
  - Oral movements
  - Skin picking
  - Social withdrawal

The Preschool ADHD Treatment Study (PATS) 6-year Follow-up

Riddle et al 264-278

- Worldwide ADHD prevalence estimated to be 5.3%
- ADHD follows a chronic course
- USA 4-17 year olds current 7.2%
  - Core symptom cluster unchanged over the last 30 years
    - Inattention
    - Impulsivity
    - Hyperactivity
  - Symptoms decrease with age
    - Severity
    - Impulsivity
    - Hyperactivity

The Preschool ADHD Treatment Study (PATS) 6-year Follow-up

Riddle et al 264-278

- To describe the longitudinal clinical course of ADHD symptom severity and diagnosis from age 3-5 up to age 9-12 after the original PATS
- Parents and teachers rated symptom severity
- Clinicians established psychiatric diagnoses
- Baseline mean age 4.4 years
- Follow-up at 3 points
  - Year 3 mean age 7.4 years
  - Year 4 mean age 8.3 years
  - Year 6 mean age 10.4 years

The Preschool ADHD Treatment Study (PATS) 6-year Follow-up

Riddle et al 264-278

- Demographics
  - 207 children (68% of the original 303)
    - 75% Male
    - 75% 2 parent caregivers
    - 10% Public assistance
    - 70% College or more degree
  - Ethnicity
    - 75% White
    - 21% Black
    - 19% Latino
    - 7% Native American
    - 1% Asian

The Preschool ADHD Treatment Study (PATS) 6-year Follow-up

Riddle et al 264-278

- Outcomes
  - Does the child still meet criteria for the diagnosis
  - Symptom severity
- 10 Classes of Medication
  - Stimulants (MPH or amphetamines)
  - Norepinephrine reuptake inhibitors (NRI-Atamoxetine)
  - Alpha 2 adrenergic agonists
  - Non SSRI antidepressants (buproprion)
  - Antipsychotics
  - Non antipsychotic mood stabilizers
  - SSRIs
  - Anxiolytics
  - Miscellaneous (propranalol)
  - Sleepers (melatonin, diphenhydramine)

The Preschool ADHD Treatment Study (PATS) 6-year Follow-up

Riddle et al 264-278

- Outcomes
  - At year 6, almost 90% still met criteria for ADHD
  - Symptom severity declined by year 3 but was stable thereafter
  - Co morbid dx of ODD/CD strongest predictor of dx at 6yrs
  - Female sex predicted:
    - Worse hyperactivity (teacher report)
    - Worse inattention (parent and teacher report)
  - The pattern of change of symptom severity was the same for hyperactivity/impulsivity and inattention (different from the pattern described in older kids)
  - No evidence of symptom decline in either domain after age 7
  - Parent ratings showed higher symptoms than teachers at year 3, 4 & 6

The Preschool ADHD Treatment Study (PATS) 6-year Follow-up

Riddle et al 264-278

- Outcomes
  - Age
    - Little change in sx severity after the 3rd year of the study (7.4-10.4yrs)
    - Increased use of other psychotropic medication and stimulants
  - Sex
    - Girls were more symptomatic relative to non ADHD girls than boys
  - IQ
    - Lower IQ a/w higher teacher rated inattention
  - Diagnosis
    - The initial dx of ADHD persisted throughout the 6 years for most

The Preschool ADHD Treatment Study (PATS) 6-year Follow-up

Riddle et al 264-278

- Outcomes
  - Medications
    - Year 3: 59% stimulants, 11% NRIs, 8% antipsychotics, 3% SSRIs
    - Year 6: 63% stimulants, 13% antipsychotics, 9% SSRIs, 6% NRIs
  - Most participants taking medication still met ADHD criteria
  - Parent-teacher severity rating s were no different for children taking meds compared with no meds
- Study limitations
  - No comparison group
  - Treatment was not controlled
  - Naturalistic follow-up
  - High severity requirement for initial diagnosis
  - Demographics not representative of most populations

The Preschool ADHD Treatment Study (PATS) 6-year Follow-up

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- Conclusions
  - Dx moderately severe ADHD is stable in preschoolers over time
  - ODD/CD in this sample was common (52%)
  - Short term medication was helpful
  - Long term treatment did not lead to significant benefit
  - Future studies should look at characteristics that increase the risk of long term ADHD
  - More comprehensive and intensive treatments are needed for this population of children