



## ADHD: Putting Evidence Into Practice

Patti Varley, MN, ARNP, BC  
Friday Feb. 13, 2009  
Seattle Children's


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## Genetic Study Summary


- Adult relatives of children with ADHD have elevated rates of ADHD
- Child relatives of adults with ADHD have elevated rates of ADHD
- Molecular genetic findings are similar for children and adults

Faraone SV, et al. J Consult Clin Psychol;2000;68:830-842

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## MTA Study


- 14-month, multicenter, randomized, controlled study
- 579 children, aged 7 to 10 years; ADHD/Combined
- 4 treatment groups
  - Medication management (titration followed by monthly visits)
  - Intensive behavior treatment (parent, school, and child components, with therapist involvement gradually reduced over time)
  - Combined treatment: medication management and behavioral treatment
  - Standard community care

MTA Cooperative Group. Arch Gen Psychiatry. 1999;56:1073-1086

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## MTA Study: Comorbid Disorders


- Oppositional defiant disorder – 39.9%
- Anxiety disorder – 33.5%
- Conduct disorder – 14.3%
- Tic disorder – 10.9%
- Affective disorder – 3.8%
- Mania/hypomania – 2.5%

MTA Cooperative Group. Arch Gen Psychiatry. 1999;56:1073-1086.

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## MTA Results

- All groups improved
- Combined treatment and medication management were significantly better than behavioral treatment and community care
- Combined treatment and medication management did not differ in any direct comparisons



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## MTA Results

- Combined treatment was superior to behavioral treatment and/or community care; medication management was not
- Combined treatment and medication management were better than community care; behavioral treatment was not
- Mean total methylphenidate daily dose at treatment end point
  - Medication management: 37.7 mg/d in 3 doses
  - Combined treatment: 31.2 mg/d in 3 doses
  - Community care: 22.6 mg/d in 2 doses

MTA Cooperative Group. Arch Gen Psychiatry. 1999;56:1073-1086.

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## MTA Conclusions

- Medication management was superior to behavioral treatment and routine community care for ADHD symptoms
- Combined treatment was equal to medication management for core ADHD symptoms and may have modest advantages for non-ADHD symptoms and positive functioning outcomes

MTA Cooperative Group. Arch Gen Psychiatry. 1999;56:1073-1086.

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## MTA: Parent and Teacher Satisfaction With Treatment

- Despite greater symptom reduction in the medication management group than in the behavioral treatment group, the satisfaction ratings by parents and teachers were higher for the behavioral treatment group
- Parent evaluations of the relative effectiveness of the 4 different treatments in reducing "referring problems" (vs. symptoms) were equivalent across the 4 treatment groups

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## MTA: Percent "Normalized"\* at 14-Month End Point

Treatment Group	Percent "Normalized"
Controls	88
Combined Treatment	68
Medication Management	56
Behavioral Treatment	34
Community Care	25

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## MTA: 24-Month Follow-Up

- Patients (N = 521) were allowed to change treatment groups after the 14-month treatment phase
- Four naturalistic subgroups emerged based on medication treatment
  - Med/Med
  - Med/No Med
  - No Med/Med
  - No Med/No Med
- Data on behavioral treatment were not collected

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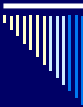
## MTA: 24-Month Results

- Groups with greatest improvement at end of treatment phase (combined and medication management) deteriorated, but the other 2 groups (behavioral and community care) did not
- Changes in medication use mediated 14- to 24-month changes in ADHD symptom ratings
  - Med/No Med showed largest deterioration
  - Med/Med and No Med/No Med showed modest deterioration
  - No Med/Med showed improvement

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## MTA: 24-Month Results

- No significant differences in 14- to 24-month growth rates among the groups
- Changes in medication use mediated growth effects
  - Med/Med showed reduced height gain (5.69 cm)
  - No Med/No Med actually grew faster than predicted by population norms (6.16 cm)

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## MTA: 24-Month Conclusions

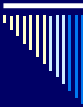
- Continued use of stimulant medication was associated with maintenance of effectiveness but continued mild growth suppression\*

\*MTA 36-month follow-up data are currently in press.

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- The follow-up of the MTA sample will continue as the participating children go through adolescence and enter adulthood.

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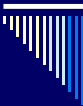
## PATS – Greenhill, et al

- Preschoolers with ADHD RCT with methylphenidate

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- "The Preschool ADHD Treatment Study, or PATS, provides us with the best information to date about treating very young children diagnosed with ADHD," said NIMH Director Thomas R. Insel, MD. "The results show that preschoolers may benefit from low doses of medication when it is closely monitored, but the positive effects are less evident and side-effects are somewhat greater than previous reports in older children."

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## PATS Results

- Largest Study To-Date
- Positive Response
- Lower Doses
- Higher Side Effects

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## FDA Warning (Not BLACKBOX) August 2006

Followed Advisory Panel 2-9-2006 recommendations

- 8-7 vote for the FDA to display a BLACK BOX warning about possible cardiovascular risks though - "We didn't find the sudden death data very persuasive"
- 15-0 for FDA to create "Medication Guides" explaining possible risk
  - Possible Cardiovascular risks
  - Psychiatric side effects, including psychosis

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## EKG Monitoring

- Recommendation to routinely do baseline EKG made 5-6-08 by the AHA
- Changed shortly thereafter to a class IIB recommendation, by clinician choice

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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.

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## ADHD Motor Vehicle Driving

Study of 16 to 22 year olds  
-35 with ADHD (*not on medication*)  
-36 controls



- Significantly more drivers with ADHD
- drove without a license
  - had licenses revoked or suspended
  - had multiple crashes (2+)
  - had multiple traffic citations (3+), especially for speeding

Subgroups of ADHD with co morbid oppositional defiant or conduct disorder were at highest risk

Barkley et al. Pediatrics 1993;92:212

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## Trials Suggest Improved Driving on Methylphenidate

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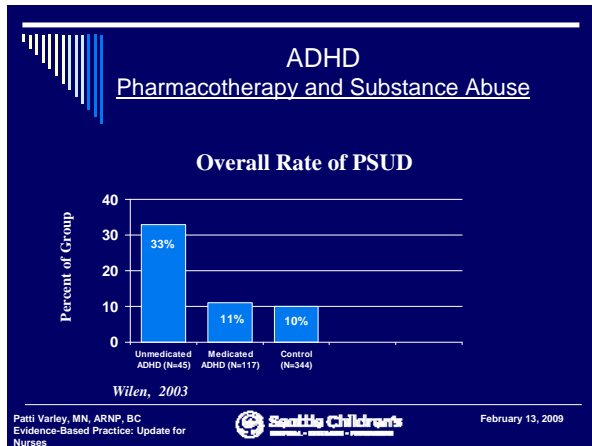
## ADHD and Psychoactive Substance Use Disorders (PSUD)

- 4-year follow-up of a clinically referred sample of boys 6 to 17 years old at baseline (ADHD N=140; control N=120)
  - no difference in the rate of alcohol or drug abuse between groups (15% vs. 15%), mean age-early adolescence
  - Risk for PSUD mediated by conduct disorder and bipolar disorder with or without ADHD

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- Adults with ADHD (N=139) vs. controls (N=268)
    - significantly greater lifetime rate of PSUD than controls (55% vs. 27%)
    - Age of onset of PSUD in subjects with ADHD averaged 3 years earlier than controls (late adolescence/early adulthood)
    - ADHD was a significant risk factor independent of co morbid diagnoses
- Biederman et al., JAACAP 1997:36:21  
Biederman et al., BioPsychiatry 1998:44:269
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- ## Medication for ADHD
- ### I. Primary - Stimulants
- a) Methylphenidate (Ritalin\*\*, Metadate ER\*\*, CD\*\*, Concerta\*\*, Methylin\*\*)
  - b) Dextroamphetamine (Dexedrine\*\*\*, Dextrostat\*\*\*)
  - c) Amphetamine/Dextroamphetamine (Adderall\*\*\*)
  - d) Dexmethylphenidate (Focalin\*\*)
  - e) Daytrana patch\*\*
  - f) Vyvanse\*\*
- \* non FDA approved to Rx ADHD  
\*\* FDA approval to Rx ADHD for children 6 and over  
\*\*\* FDA approval to Rx ADHD for children 3 and over*
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- ## Medication for ADHD
- ### II. Secondary
- a) Atomoxetine (Strattera)
  - b) Alpha - 2 Agonists
    - 1) Clonidine (Catapres<sup>®</sup>)
    - 2) Guanfacine (Tenex<sup>®</sup>)
  - c) Other Antidepressants
    - 1) Bupropion (Wellbutrin<sup>®</sup>)
    - 2) Venlafaxine (Effexor<sup>®</sup>)
  - d) Tricyclic Antidepressants
    - 1) Imipramine (Tofranil<sup>®</sup>)
    - 2) Nortriptyline (Pamelor<sup>®</sup>)
    - 3) Desipramine (Norpramin<sup>®</sup>)
  - e) Stimulant
    - 1) Pemoline (Cylert<sup>®</sup>)\*\* (taken off the market)
  - f) Other
    - 1) Modafinil (Provigil<sup>®</sup>)
- \* non FDA approved to Rx ADHD  
\*\* FDA approval to Rx ADHD for children 6 and over  
\*\*\* FDA approval to Rx ADHD for children 3 and over*
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## Comparison Studies Have All Been Industry Sponsored

- Have to consider results in that context

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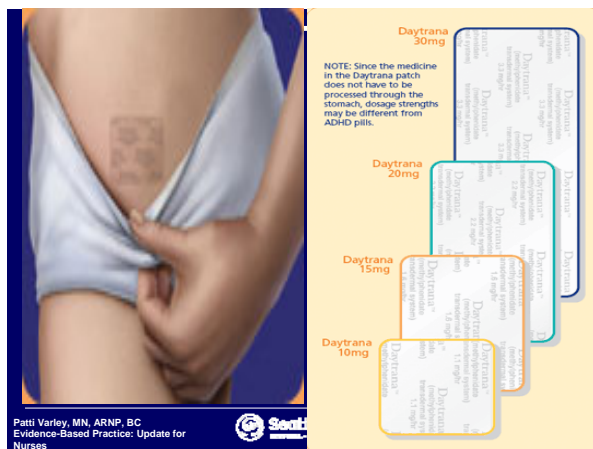
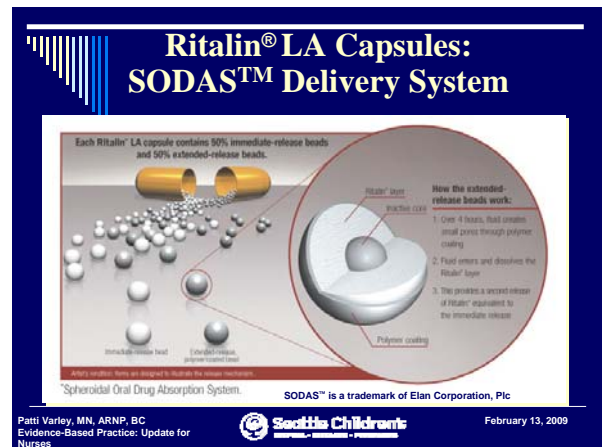
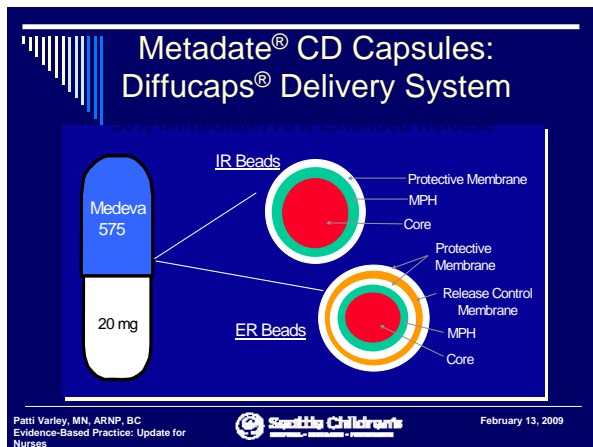
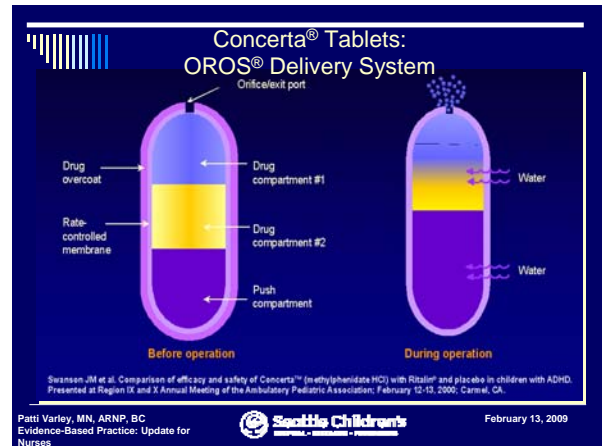
- Recent Trials Indicate Benefit of Combining Stimulant and Atomoxetine
  - Should be reserved for cases with failure to respond to single agents
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### Long-acting Oral MPH Medications

Products	Concerta®	Metadate® CD	Ritalin® LA
Formulation Technology	OROS®	Diffucaps®	SODAS™
Dose mg	18mg/27 mg/36 mg/54 mg	10,20,30 mg	20mg/30 mg/40 mg
Immediate Release	22% 4 mg/6 mg/8 mg/12 mg	30% 6 mg	50% 10 mg/15 mg/20 mg
Sustained/2 <sup>nd</sup> release	78% 14 mg/21 mg/28 mg/42 mg	70% 14 mg	50% 10 mg/15 mg/20 mg

Concerta® (package insert). Menlo Park, CA, Alza Corporation; 2001. OROS® is a registered trademark of ALZA Corporation.  
Metadate® CD (package insert). Rochester, NY, Cellego Pharmaceuticals, Inc; 2002. Diffucaps® is a registered trademark of Euran.  
Ritalin® LA (package insert). East Hanover, NJ, Novartis Pharmaceuticals Corporation; 2002. SODAS™ is a trademark of Elan Corporation, Plc.

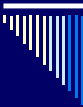
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### Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

Focus, June 1, 2008; 6(3): 401 - 426.  
[\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

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The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit hyperactivity disorder. *Archives of General Psychiatry*, 1999; 56:1073-1086.



□ MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics*.2003; 113 :762 –769



## Clinical Practice Guidelines American Academy of Pediatrics:


Committee on Quality Improvement, Subcommittee on Attention-Deficit/Hyperactivity Disorder

1) *Pediatrics* Vol. 105 No. 5 May 2000, pp 1158-1170  
Clinical Practice Guideline: Diagnosis and Evaluation of the Child With Attention-Deficit/Hyperactivity Disorder


2) *Pediatrics* 2001 108: 1033-1044  
Clinical Practice Guideline: Treatment of the School-Aged Child With Attention-Deficit/Hyperactivity Disorder



□ J. Swanson, L. E. Arnold, H. Kraemer, L. Hechtman, B. Molina, S. Hinshaw, B. Vitiello, P. Jensen, K. Steinhoff, M. Lerner, *et al.*  
**Evidence, Interpretation, and Qualification From Multiple Reports of Long-Term Outcomes in the Multimodal Treatment Study of Children With ADHD (MTA): Part I: Executive Summary**  
*J Atten Disord*, July 1, 2008; 12(1): 4 - 14.  
[\[Abstract\]](#) [\[PDF\]](#)



□ J. Swanson, L. E. Arnold, H. Kraemer, L. Hechtman, B. Molina, S. Hinshaw, B. Vitiello, P. Jensen, K. Steinhoff, M. Lerner, *et al.*  
**Evidence, Interpretation, and Qualification From Multiple Reports of Long-Term Outcomes in the Multimodal Treatment Study of Children With ADHD (MTA): Part II: Supporting Details**  
*J Atten Disord*, July 1, 2008; 12(1): 15 - 43.  
[\[Abstract\]](#) [\[PDF\]](#)




□ Press Release  
October 16, 2006

□ **Preschoolers with ADHD Improve with Low Doses of Medication**

□ The first long-term, large-scale study designed to determine the safety and effectiveness of treating preschoolers who have attention deficit/hyperactivity disorder (ADHD) with methylphenidate (Ritalin) has found that overall, low doses of this medication are effective and safe. However, the study found that children this age are more sensitive than older children to the medication's side effects and therefore should be closely monitored. The 70-week, six-site study was funded by the National Institutes of Health's National Institute of Mental Health (NIMH) and was described in several articles in the November 2006 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry*.

□ V. L. Vetter, J. Elia, C. Erickson, S. Berger, N. Blum, K. Uzark, and C. L. Webb  
**Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Medications for Attention Deficit/Hyperactivity Disorder: A Scientific Statement From the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing**  
 Circulation, May 6, 2008; 117(18): 2407 - 2423.  
[\[Full Text\]](#) [\[PDF\]](#)

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□ **Reference**

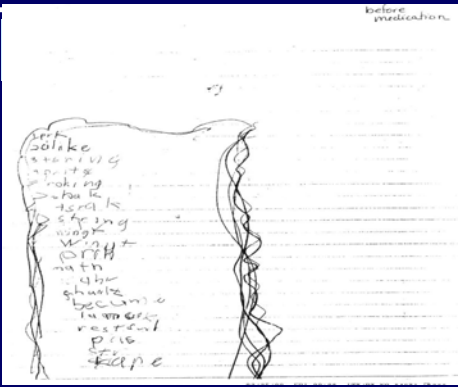
□ Langberg JM, Epstein JN, Altaye M, Molina BSG, Arnold LE, Vitiello B. The transition to middle school is associated with changes in the developmental trajectory of ADHD symptomatology in young adolescents with ADHD. *Journal of Clinical Child and Adolescent Psychology*. 2008; 37(3): 651-663.

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before medication



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after medication

February 7 1991

phonics test

1) prak	1) arch
2) alike	2) math
3) string	3) night
4) prity	4) hawk
5) roking	5) became
6) shak	6) almost
7) srak	7) restful
8) shab	8) prsh
9) wingk	9) store
10) wiageb	10) carry

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Inside of me  
 there is creativity  
 running through my body  
 like a river,  
 flowing into a lake.

Inside of me  
 is a purring cat  
 happy to be petted,  
 playful and curious.

Inside of me  
 is a castle on a hill  
 surrounded by trees.


Sometimes at war with an army of  
 knights,  
 sometimes in peace with the enemy.

Inside of me  
 a tree grows unharmed,  
 branches reaching out as far as they  
 can,  
 roots growing down to good soil.

Inside of me  
 a key waits  
 for someone to unlock the chest  
 and free the treasure.

Mike Uhrich  
 Grade 6

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