RESEARCH SYMPOSIUM II: Multimodal Treatment Study of Children with ADHD

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NIMH, NIDA, OJJDP, and
United States Department of Education.
DISCLOSURES

- Tim Wigal has received research support from NIDA and the following pharmaceutical companies:

<table>
<thead>
<tr>
<th>Source</th>
<th>Consultant</th>
<th>Advisory Board</th>
<th>Stock Equity &gt;$10,000</th>
<th>Speaker’s Bureau</th>
<th>Research Contract</th>
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<td>UCB</td>
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</table>
MTA: It was 20 years ago today

• Early History and Original Design
• Treatment Study Results: NIMH
• Followup Study Results: NIMH and NIDA
• Followup (still in Progress): NIDA
  
  ARRA : Imaging and Qualitative
  
  Long Term Outcomes: Symptoms and Functioning

• Summary
MTA Timeline

Study

Treatments

8-yr Assessment
Mean age 16.8 yrs

12 Year Data
Molina et al (in press)

Follow-up

2002 - 6 yr follow-up
2004 - 8 year
2006 - 10 yr
2008 - 12 yr
2010 - 14 yr
2012 Follow-up (16 yr)

Feb 23, 1994 - 1st consent
1996 - Recruited 289 LNCG
1997 - Treatment Complete

1992 - 1st Study Planning Meeting

Nov 1992 - 1st Study Planning Meeting
History of MTA

- Request for Applications in February 1992
- Cooperative Agreement approval in Sept 92
  - Collaboration of 6 Sites selected (of 20) and NIMH

- Considered cooperative agreements when:
  - Public Health Importance
  - Single site approaches insufficient
  - Established treatments available

- Emphasis on collaboration
  - Planning phase resulted in cross site agreement
  - Multiple weekly phone calls
In 1994, the primary pharmacological treatment of ADHD was Ritalin (or methylphenidate) administered two or three times a day.
Evidence for Use of Stimulants

• Multiple reviews of literature by early 1990s
  – Wilens and Biederman (1992)
    • Psychiatric Clinics North America, “The Stimulants”
  – Swanson et al (1993)
    • Exceptional Children, “Review of Reviews”

• Strong empirical basis but some gaps
  – Over 50 years of clinical use
  – Over 4000 reports with many controlled trials
  – Clear evidence of short-term efficacy
  – Few controlled studies of long-term effectiveness
Evidence for the Use of Behavior Modification

  - Cognitive - Behavioral interventions
- Horn, Chatoor & Conners (1983)
  - Self control training for ADHD
- Pelham & Murphy (1986)
  - Behavioral treatment compared to psychopharmacological treatment
- Abikoff and Gittleman (1984)
  - Token reinforcement systems
  - child-focused interventions
MTA Sites

Wave 1 Sites
UC Irvine
Swanson, Cantwell, Wigal

U Pittsburgh
Pelham, Hoza, Molina

Columbia U
Greenhill, Newcorn

Wave 2 Sites
Duke U
Conners, Wells, March

LIJ/Montreal CC
Abikoff, Hetchman

UC Berkeley
Hinshaw, Elliott

NIMH/US Dept Education/Stanford
Jensen, Severe, Arnold, Richters, Vitiello, Vereen, Shiller, Kraemer
### MTA Collaborators

- Howard B. Abikoff, PhD
- L. Eugene Arnold, MD
- Dennis Cantwell, MD
- Xavier Castellanos, MD
- C. Keith Conners, PhD
- Mark Davies, MS
- Glen Elliott, PhD, MD
- Jeffrey N. Epstein, PhD
- Robert Gibbons, PhD
- Laurence Greenhill, MD
- Lily Hechtman, MD
- Kwan Hur, PhD
- Stephen Hinshaw, PhD
- Kimberly Hoagwood, PhD
- Betsy Hoza, Ph.D.
- Peter Jensen, MD
- Terry Jernigan, PhD.
- Helena Kraemer, Ph.D.
- Bo Lu, Ph.D.
- John March, M.D., M.P.H.
- Susan Marcus, M.A.
- Brooke Molina, Ph.D.
- Jeffrey Newcorn, M.D.
- William E. Pelham, Ph.D.
- Joanne Severe, M.S.
- Annamarie Stehli, M.S.
- James Swanson, Ph.D
- LeAnne Tamm, PhD.
- Benedetto Vitiello, M.D.
- Karen Wells, Ph.D.
- Tom Weisner, PhD.
- Tim Wigal, PhD.
Design of the MTA

- Contrast 2 established treatment modalities
  - Med management only (MedMgt)
  - Behavioral treatment only (Beh)
- Contrast each with multimodal treatment
  - Combination (Comb)
  - Include a Community Comparison Group (CC)
- Use random assignment of 579 children
- Provide intensive treatment for 14 months
- Evaluate long-term effects (> 1 year)
What Are the Long-term Effects of the MTA Algorithm for Behavior Modification?

- Parent Training (25 group and 10 individual sessions)
- Summer Treatment Program (8 weeks, 8 hours/day)
- UCI Paraprofessional Program (12 weeks, 4 hours/day)
What Are the Long-Term Effects of the MTA Algorithm for Medication Management (MedMgt)?

- **Titration Trial**: 28-days to find best dose

- **Maintenance Treatment**: monthly visits for 1 year with TID dosing
MTA Publications
(Swanson et al, 2008, J Attn Disorders)

MTA Group, 1999, Archives General Psychiatry
8 to 11 years of age

Molina et al, 2009 JAACAP (SU)
15 to 18 years of age

Swanson, Waxmonsky, Bock et al, 2010 (Ht)
17 to 20 years of age

Baseline, 7-9.9 yrs
14 Mos, 8-12 yrs
24 Mos, 9-12 yrs
36 Mos, 10-14 yrs
6 – 8 Years
10 Years
12 Years
14 Years
16 Years (in progress)

Study Treatments

LNCG (n=289) added here
MTA Group (2004, Pediatrics)

36 Month Findings (JAACAP, 2007)
Symptom Severity, Jensen et al, 2007
Substance Use, Molina et al, 2007
Growth, Swanson et al, 2007

12 Year Data
Molina et al (in press)
Comorbidity in the MTA Sample

- ADHD (31%) alone: 179
- ODD (21%) alone: 126
- TIC (11%): 15
- CONDUCT (14%): 14
- ANXIETY (34%): 58
- MOOD (4%): 5
- ODD (40%): 67
MTA Outcome Domains

- **Symptomatic**
  - Core ADHD symptoms ($\text{SNAP}_{P,T}$)
  - Aggressive behavior ($\text{SNAP}_{P,T} - \text{ODD}$)
  - Internalizing symptoms ($\text{MASC}, \text{SSRS}_{P,T}$)

- **Functional**
  - Social skills ($\text{SSRS}_T$)
  - Academic performance ($\text{WIAT}$)
  - Parent-child relations ($\text{PCR}$)
## SNAP-IV Teacher & Parent Rating Scale

James M. Swanson, Ph.D., University of California, Irvine or ADHD.net

For each item, check the column which best describes this child:

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Not At All</th>
<th>Just a Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Often fails to give close attention to details or makes careless mistakes in schoolwork or tasks</td>
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<td>2.</td>
<td>Often has difficulty sustaining attention in tasks or play activities</td>
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<td>3.</td>
<td>Often does not seem to listen when spoken to directly</td>
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<td>4.</td>
<td>Often does not follow through on instructions and fails to finish schoolwork, chores, or duties</td>
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<td>5.</td>
<td>Often has difficulty organizing tasks and activities</td>
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<td>6.</td>
<td>Often avoids, dislikes, or reluctantly engages in tasks requiring sustained mental effort</td>
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<td>7.</td>
<td>Often loses things necessary for activities (e.g., toys, school assignments, pencils, or books)</td>
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<td>8.</td>
<td>Often is distracted by extraneous stimuli</td>
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<td>9.</td>
<td>Often is forgetful in daily activities</td>
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<td>10.</td>
<td>Often fidgets with hands or feet or squirms in seat</td>
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<td>11.</td>
<td>Often leaves seat in classroom or in other situations in which remaining seated is expected</td>
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<td>12.</td>
<td>Often runs about or climbs excessively in situations in which it is inappropriate</td>
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<td>13.</td>
<td>Often has difficulty playing or engaging in leisure activities quietly</td>
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<td>14.</td>
<td>Often is &quot;on the go&quot; or often acts as if &quot;driven by a motor&quot;</td>
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<td>15.</td>
<td>Often talks excessively</td>
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<td>16.</td>
<td>Often blurts out answers before questions have been completed</td>
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<td>17.</td>
<td>Often has difficulty awaiting turn</td>
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<td>18.</td>
<td>Often interrupts or intrudes on others (e.g., butts into conversations/games)</td>
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<td>19.</td>
<td>Often loses temper</td>
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<td>20.</td>
<td>Often argues with adults</td>
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<td>21.</td>
<td>Often actively defies or refuses adult requests or rules</td>
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<td>22.</td>
<td>Often deliberately does things that annoy other people</td>
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<td>23.</td>
<td>Often blames others for his or her mistakes or misbehavior</td>
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<td>24.</td>
<td>Often touchy or easily annoyed by others</td>
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<tr>
<td>25.</td>
<td>Often is angry and resentful</td>
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<tr>
<td>26.</td>
<td>Often is spiteful or vindictive</td>
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Percent “Normalized” at 14 months

- Controls: 88%
- Comb: 68%
- MedMgt: 56%
- Beh: 34%
- CC: 25%
Summary: MTA Group Outcomes at 14 Months on Symptoms

• Combination ~ MedMgt > Behavioral ~ Community Care
  – Comb & MedMgt both better than Beh & CC
  – 85% of children responded well to either MPH or AMP

• Comb and MedMgt not statistically different
  – but Comb group on 20% less medication
  – Multimodality treatment superiority was small and variable across domains

• Behavioral and Community Care not statistically different
  – even though most (70%) in CC on stimulant medications
Follow Up Assessments:

in childhood: 24 and 36 months

in adolescence: 6, 8, and 10 yr

into adulthood: 12, 14, and 16 yr

(NIDA support)
Convergence of Symptoms by 3 Years

Randomized Clinical Trial at 14-month assessment: Transition to Naturalistic Follow-up at the 24-month & 36-month Assessment
ADHD Symptom-severity at 14-m, 36-m, and 8-y MTA Assessments

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


Molina et al, 2009, J Am Acad Child Adolesc Psychiatry. 48; 484-500
SCAPI Developed for the MTA

The Services for Children and Adolescents–Parent Interview: Development and Performance Characteristics

PETER S. JENSEN, M.D., KIMBERLY EATON HOAGWOOD, Ph.D., MARGARET ROPER, M.S., L. EUGENE ARNOLD, M.D., CAROL ODBERT, B.S. MAURA CROWE, B.A., BROOKE S.G. MOLINA, Ph.D., LILY HECHTMAN, M.D., STEPHEN P. HINSHAW, Ph.D., BETSY HOZA, Ph.D., JEFFREY NEWCORN, Ph.D., JAMES SWANSON, Ph.D., AND KAREN WELLS, Ph.D.

J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 43:11, NOVEMBER 2004

Objective: To date, no instrument has been developed that captures children's services use across primary care, specialty mental health, and other settings, including setting, treatment type, provider discipline, and length and intensity of specific interventions over varying follow-up periods. The authors developed a highly structured services assessment measure [Services for Children and Adolescents–Parent Interview (SCAPI)] for use in the National Institute of Mental Health Multimodal Treatment Study of Children With Attention Deficit Hyperactivity Disorder (MTA). Method: After
Percentage of Medication Use Over Time by Treatment

% Med Use

Month

Comb Med Beh CC
## Table 3: Co-linearity of Assigned Treatment and Pattern of High Medication Use

<table>
<thead>
<tr>
<th>Assigned Treatment (n = 568)</th>
<th>Pattern of High Medication Use (subgroup size; % of assigned groups)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Never (n=142; 25.0%)</td>
</tr>
<tr>
<td>BEH (n=138)</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>47.80%</td>
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<tr>
<td></td>
<td>2,051 mg</td>
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<tr>
<td>CC (n=144)</td>
<td>43</td>
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<tr>
<td></td>
<td>29.90%</td>
</tr>
<tr>
<td></td>
<td>800 mg</td>
</tr>
<tr>
<td>COMB (n=144)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>11.80%</td>
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<tr>
<td></td>
<td>3,576 mg</td>
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<tr>
<td>MED (n = 142)</td>
<td>16</td>
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<tr>
<td></td>
<td>11.30%</td>
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<td>2,217 mg</td>
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Follow-Up to 8 Yrs: Outcome on SNAP (ADHD symptom-severity) rating as well as Columbia Impairment Scale, with ITT analysis of the Randomized Controlled Trial (RCT) of Assigned Treatment

MTA worse than LNCG on 91% of outcome variables; mdm to large effect sizes

JAACAP, May 2009
ARRA funded projects

• Substance Use

• Turning Points
Substance Use in Early Adolescence

- Gateway theory of substance use (Denise Kandel)
  - Nicotine and alcohol → marijuana → illicit drug use

- Precocious substance use (experimenting at particularly early age) robustly associated with later problems with substance use

- Does early exposure to medication for the condition of ADHD predispose to later Substance Use?
Substance Use for MTA Adjusted for Age-Specificity

(recall that at 12 years, youth are 19-22)

- **Alcohol**: drank alcohol (more than just a sip) more than 5 times in life or became drunk at least once
- **Tobacco**: smoked cigarettes or tried chewing tobacco more than a few times
- **Marijuana**: more than once
- **Other Drugs**: inhalants, hallucinogens, cocaine, or amphetamines/stimulants, barbiturates/sedatives, opioids/narcotics (without a prescription or used more than prescribed)
Acceptance and integration of ADHD diagnosis as turning point
Turning Points

• Caregivers refer to specific events more than youth do
• Youth build turning points into a turning pathway narrative
  – Includes several events
  – Includes perceptions of ADHD as a diagnosis
  – Includes only indirectly the influence of ADHD
• General major life events typically described by youth as turning points
  – Parental death or illness
  – Divorce
  – Financial setbacks
  – Leaving school
• SU history or desistance described as turning points
• ADHD generally described as “just who I am,” or “everyone has some of these traits,” or “it gives me energy and gets me going.” …Not often described as a currently negative feature or turning point
• Romantic relationships that require attention and commitment now emerge as “turning points”
I realized I was not crazy

• I think the ADHD is a lot of my personality I guess. . . . . . . what it is, is when I realized like I said everyone kind of realized I had ADHD, but when I got the diagnosis it was like I said it wasn't a surprise, but it's nice to know that there are reasons or there is for some of my behaviors. It's nice to know that like I'm not crazy or something like that, because my brain is running like a motor. Or that I can't keep track of my keys. It's nice to know that it's not that I don't have any responsibility for it, but it's nice to know because then I can also combat it, you know .... And so it's nice to know that some of my problems or shortcomings are that there's an explanation for it or somewhat of an explanation, so that I'm more aware of it and so that I can combat the negative aspects of it. I mean ... I lost the question again. ...
36 Month Outcomes (Comorbidity)

- Residually impaired children were more likely to be suffering from Major Depression or Dysthymia both at baseline (8.7 vs. 3.6%, $X^2 = 5.1, p < .05$) and at 14-, 24-, and 36-month follow-up (6.1% vs. 0.6%, $X^2 = 14.6, p < .001$).

- Of 264 children who had ODD/CD at baseline, fewer than ½ (n=122) had ODD/CD at 36-month follow-up
  - However, more than 2/3rds of these children (n=79, 68.7%) remained severely impaired according to parents’ ratings.
36 Month Outcomes
Implications

• Many/most children with ADHD show substantial improvement in functioning by 3 years
  – less than one-fourth of children remain severely impaired.

• Residually impaired children were
  – more severely impaired at baseline
  – characterized by higher initial levels of oppositionality and irritability according to both parents and teachers
Conclusions

• No Effect of Treatment on Substance Use – it is neither predisposing or protective.

• No longterm benefit from meds on either measurements of impairment or symptom reduction

• No increase in comorbididiites