ADHD e psicofarmacoterapia dell’eta’ evolutiva

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Disclosures:
• I have no financial relationships with pharmaceutical companies or other competing interests
• I work at the NIMH/NIH, but the views here presented should not be construed as official statements of the NIMH/NIH
Aims

• To provide an update on pharmacotherapy of ADHD in children and adolescents

with focus on:
  ➢ Stimulant medications
  ➢ Long-term effects
  ➢ Safety

Attention deficit/hyperactivity disorder

◆ Developmentally inappropriate
  ■ Inattention
  ■ Hyperactivity
  ■ Impulsivity

◆ That impairs functioning in school and other social context
Frequency Distribution of Total Scores of ADHD Rating Scale for Teachers (SDAI) (N=1,887) [Donfrancesco et al., 2015]

Cortical development in ADHD (N=234) vs. normal (N=231) children (Shaw et al., 2012)
Kaplan–Meier curves illustrating the proportion of cortical points that had attained peak thickness at each age for all cerebral cortical points (Left) and the prefrontal cortex (Right).

Shaw P et al. PNAS 2007;104:19649-19654

Brain maturation in ADHD
(Shaw et al., 2007)
Developmental trajectories for the striatal and globus pallidus volumes and total surface areas in ADHD (N=270) and normals (N=270). (Shaw et al., 2014)

**ADHD: evidence-based treatments**

- **Psychosocial interventions**
- **Pharmacotherapy:**
  - stimulants: methylphenidate, amphetamines
  - Atomoxetine
  - alpha-2 agonists: clonidine, guanfacine
- Others: bupropion, desipramine
Pharmacotherapy for ADHD:
How effective?

Average effect size (vs. placebo)

- Stimulants 0.8
  - If autism or intellectual disability 0.5
- Atomoxetine 0.6
- Alpha-2 agonists 0.6

Annual use in 6-17 year olds (Olson et al. 2015)
Methylphenidate (Ritalin)

Amphetamine
From: Striatal Dopamine Transporter Alterations in ADHD: A Meta-Analysis (Fusar-Poli et al. 2012)

**Presynaptic radiotracers**
- $[^{15}N]DOPA$, $[^{3}H]DOPA$
- $[^{3}H]DBZ$
- $[^{15}F]FDG$

**Postsynaptic radiotracers**
- $[^{11}C]BMZ$, $[^{11}C]Raclopride$, $[^{11}C]Haloperidol$

<table>
<thead>
<tr>
<th>TH</th>
<th>Tyrosine hydroxylase</th>
<th>DOPA</th>
<th>Dihydroxyphenylalanine</th>
<th>AAADC</th>
<th>Aromatic l-amino acid decarboxylase</th>
</tr>
</thead>
</table>

**Diagram**: Dopamine D2/D3 receptors in the striatum over 1-year treatment with methylphenidate (Gill et al., 2012)

**Neuropsychopharmacology**
Averaged DA D2/D3 receptor availability (BPND) images for the [11C]raclopride scans done after intravenous placebo and after intravenous MP (iv-MP) for the treatment-naive and long-term treatment conditions.


©2012 by Society for Neuroscience

Averaged dopamine transporter availability images.

Baseline visit

Follow up visit

ADHD subjects

High

After 12 months oral MP

Low

Control subjects

Repeat 12 months (no medication)


http://www.plosone.org/article/info:doi/10.1371/journal.pone.0063023
Striatal Dopamine Transporter Alterations in ADHD: Pathophysiology or Adaptation to
Psychostimulants? A Meta-Analysis (Fusar-Poli et al., 2012)

Circle size reflects the weight a study obtained in the meta-regression. Lower effect sizes were detected in studies involving drug-naive ADHD patients ($\beta=-1.61$, 95% CI=$-2.19$ to $-1.03$, z=$-5.45$, p<0.001).

Mean daily dose of methylphenidate during treatment maintenance in the MTA study (Vitiello et al., 2001)
MPH Dosage in PATS (mg/kg/day)

Average Monthly Maintenance Dose

Stimulants

- Increase alertness, attention
- Decrease fatigue
- Decrease unfocused motor activity
- Increase saliency of a task (motivation)
- Increase goal-oriented activities
- Improve performance
- Decrease appetite, sleep
- Can cause euphoria and be abused
Methylphenidate effects on cognition in children: a meta-analysis of 60 studies (Coghill et al. 2014)

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive memory</td>
<td>0.26</td>
</tr>
<tr>
<td>Non-executive memory</td>
<td>0.60</td>
</tr>
<tr>
<td>Reaction time</td>
<td>0.24</td>
</tr>
<tr>
<td>Reaction time variability</td>
<td>0.62</td>
</tr>
<tr>
<td>Response inhibition</td>
<td>0.41</td>
</tr>
</tbody>
</table>

SMD vs. placebo

ADHD, brain circuits and stimulant treatment

- In ADHD: reduced activation and functional connectivity in fronto-parietal-cerebellar networks during selective attention

- Methylphenidate increases fronto-striato-cerebellar and parieto-temporal activation and fronto-cerebellar connectivity

[Rubia et al., 2009]
An fMRI Study of the Effects of Psychostimulants on Default-Mode Processing during Stroop Task Performance in Youths (7-18 years) with ADHD


**Default Mode Network in ADHD**

(Peterson et al., 2009)

- During the Stroop test, the brain of children with ADHD had problems deactivating the DMN

- and showed reduced connectivity between lateral prefrontal cortex & anterior cingulate cortex

- Methylphenidate → restored deactivation of the DMN and increased functional connectivity between LPFC and ACC
Teacher (n=223) vs Parent (n=253)
ADHD Ratings  
(Greenhill et al. 2001)

Drug Dosage

Placebo 5mg 10mg High Dose

Teacher Summary Score  
Parent Summary Score

Parent Summary Score

Teacher Summary Score

Mixed effects linear model: statistically significant main effect of dose (F = 6.10; P = 0.0006).

ADHD in autism spectrum
N=66, age 5-17 yrs

*Versus placebo.
Mixed effects linear model: statistically significant main effect of dose (F = 6.10; P = 0.0006).

RUPP Autism Network. Arch Gen Psychiatry 2005
Methylphenidate: long-term treatment

- The therapeutic effect is sustained
- But the dose usually needs to be increased:
  - In the MTA: from 30 mg/day to 38 mg/day (13 months later)
  - In the PATS: from 14 mg/day to 20 mg/day (10 months later)

14-Month Outcomes
Teacher SNAP-Inattention

Time x Tx: F=10.6, p<.0001
Site x Tx: F=0.9, ns
Site: F=2.7, p<.02

Comb, MedMgt > Beh, CC
**Parent SNAP-Hyperactive/Impulsive**

- Time x Tx: $F=21.5$, $p<.0001$
- Site x Tx: $F=1.3$, ns
- Site: $F=4.4$, $p<.0006$

Comb, MedMgt $>$ Beh, CC

**Teacher SNAP-Hyperactive/Impulsive**

- Time x Tx: $F=6.5$, $p<.0003$
- Site x Tx: $F=1.2$, ns
- Site: $F=4.2$, $p<.001$

Comb, MedMgt $>$ CC
Parent-Child Arguing

Time x Tx: $F=5.6$, $p<.0008$
Site x Tx: $F=1.0$, ns
Site: $F=2.8$, $p<.02$

Comb, Beh > CC

Comb > Beh, CC

Parent SSRS Internalizing Sx

Time x Tx: $F=9.2$, $p<.0001$
Site x Tx: $F=1.1$, ns
Site: $F=2.3$, $p<.05$

Comb > Beh, CC
Teacher SSRS Social Skills

Average Score vs. Assessment Point (Days)

- CC
- Beh
- MedMgt
- Comb

Time x Tx: F=6.1, p<.0004
Site x Tx: F=0.5, ns
Site: F=3.9, p<.002

Comb, MedMgt > CC

From: Effects of Group Psychotherapy, Individual Counseling, Methylphenidate, and Placebo in the Treatment of Adult Attention-Deficit/Hyperactivity Disorder: A Randomized Clinical Trial

MTA: outcomes at mean age 17 [Molina et al., 2009]

<table>
<thead>
<tr>
<th></th>
<th>MTA</th>
<th>Normative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=436</td>
<td>N=261</td>
</tr>
<tr>
<td>ADHD Inattention</td>
<td>Parent</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>Teacher</td>
<td>1.30</td>
</tr>
<tr>
<td>ADHD Hyperactive</td>
<td>Parent</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Teacher</td>
<td>0.64</td>
</tr>
<tr>
<td>ODD</td>
<td>Parent</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>Teacher</td>
<td>0.51</td>
</tr>
</tbody>
</table>
### MTA: outcomes at mean age 17 yr

(Molina et al., 2009)

<table>
<thead>
<tr>
<th></th>
<th>MTA</th>
<th>Normative</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>436</td>
<td>261</td>
</tr>
<tr>
<td>WIAT reading</td>
<td>95.7</td>
<td>102.0</td>
</tr>
<tr>
<td>WIAT math</td>
<td>94.6</td>
<td>105.4</td>
</tr>
<tr>
<td>Grade point average</td>
<td>2.75</td>
<td>3.02</td>
</tr>
<tr>
<td>Psychiatric hospital.</td>
<td>10.4%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Arrested once</td>
<td>19.8%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Arrested &gt;once</td>
<td>7.0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Car accidents/tickets</td>
<td>22.2%</td>
<td>27.6%</td>
</tr>
</tbody>
</table>

### MTA: substance abuse at mean age 15

(Molina et al., 2013)

<table>
<thead>
<tr>
<th></th>
<th>MTA</th>
<th>Normative Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>436</td>
<td>261</td>
</tr>
<tr>
<td>Alcohol/SA</td>
<td>35%</td>
<td>20%</td>
</tr>
</tbody>
</table>

No effect of stimulant treatment: it did not increase the risk, but it did not protect either
### MTA: Tobacco use at mean age 17

<table>
<thead>
<tr>
<th></th>
<th>MTA</th>
<th>Normative Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily smoking</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

No effect of stimulant treatment: it did not increase the risk, but it did not protect either.

[Sources: Molina et al., 2013]

### Stimulant effects at population level: epidemiological analyses in Sweden

- Use of stimulants in ADHD adults was associated with:
  - Lower risk of criminal arrests in males (HR=0.63) and females (HR=0.59) (N=25,656, in 2006-09, Lichtenstein et al. 2013)
  - Lower risk of serious car accidents in males (HR=0.42). At least 40% of accidents could be averted by med (N=17,408, in 2006-09, Chang et al. 2014)
Stimulants: adverse effects

- **Common, but usually mild and transient:**
  - Decrease in appetite
  - Sleep disturbance
  - Stomach-ache

- **Less frequent:**
  - Head-ache
  - Tics
  - Stereotypies
  - Blunting of affect

**Growth in height during the 14 months of the MTA**

<table>
<thead>
<tr>
<th>Behav</th>
<th>CC</th>
<th>Comb</th>
<th>Mgt</th>
<th>(mean mg/day)</th>
<th>(mean cm/14 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>23</td>
<td>31</td>
<td>38</td>
<td>6.2</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

**Med – Behav = −1.2 cm/year**
Growth in weight during the 14 months of the MTA

<table>
<thead>
<tr>
<th>Group</th>
<th>MPH Dose (mean mg/day)</th>
<th>Weight Growth (mean kg/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behav</td>
<td>0</td>
<td>4.5</td>
</tr>
<tr>
<td>CC</td>
<td>23</td>
<td>3.1</td>
</tr>
<tr>
<td>Comb</td>
<td>31</td>
<td>2.5</td>
</tr>
<tr>
<td>Med</td>
<td>38</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Med – Behav = – 2.5 kg/year

Serum testosterone concentrations in peripubertal male rhesus monkeys chronically exposed to MPH.

Mattison et al., 2011
Effect of dose and length of treatment on mean testicular volume (± SEM) in peripubertal male rhesus monkeys chronically exposed to MPH. ANOVA indicated that testicular volume increased \( (P < 0.0001) \) over the exposure period.

Donald R. Mattison et al. PNAS 2011;108:16301-16306

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Relationship between change in gender-specific height-for-age Z scores before and after stimulant treatment and cumulative stimulant duration \((N=340)\)

Harstad et al. Pediatrics 2014
Relationship between change in gender-specific height-for-age Z scores after stimulant treatment and 24 months later and cumulative stimulant duration.

Atomoxetine and growth

Meta-analysis of 13 studies (Kratochvil et al. 2006):

- 6 to 7-year-old children
- Mean dose: 1.47/kg/day
- 2-year treatment

On average, children grew 0.9 kg and 0.44 cm less than expected.
Cardiovascular Function

Stimulants increase:

- Systolic BP: 2-4 mmHg
- Diastolic BP: 1-3 mmHg
- Heart rate: 2-6 bpm

No clinically significant effect on QTc

Atomoxetine and cardiovascular function

- Increase in heart rate: about 5-9 bpm
- Increase in diastolic BP: average 2 mmHg
Enhancement of normal function

- Stimulant medications are approved for the treatment of ADHD (and narcolepsy)
- But in fact are also used to enhance cognitive performance in “normals”
### Non-therapeutic use of ADHD medications in the U.S.

**Estimated life-time use**

- **High school students**: 5-10%
- **College students**: 5-35%

[Source: Clemow & Walker, 2014]

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### University students in UK and Ireland

*N=877 (Singh et al. 2014)*

**Have used to enhance cognitive performance:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Occasionally</th>
<th>Regularly</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH</td>
<td>2.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Adderall</td>
<td>1.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Modafinil</td>
<td>2.1%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Caffeine</td>
<td>12.4%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>
### Potential Use, Misuse and Abuse of Stimulants

<table>
<thead>
<tr>
<th>Use</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full ADHD criteria</td>
<td>Proper use</td>
</tr>
<tr>
<td>Some ADHD symptoms</td>
<td>Off-label therapeutic use</td>
</tr>
<tr>
<td>Non-ADHD symptoms</td>
<td>Use</td>
</tr>
<tr>
<td>To enhance performance</td>
<td>Non-therapeutic use</td>
</tr>
<tr>
<td>To elicit euphoria</td>
<td>Abuse</td>
</tr>
</tbody>
</table>