UPDATE IN ADHD:
FOCUS ON MEDICATION TREATMENTS
Learning Objectives

• Identify basic issues in the diagnosis of ADHD in child and adolescent patients

• Differentiate the spectrum of medication options available for use in children with ADHD
ADHD in the World

• ADHD prevalence among 8- to 15-year-olds: 8.7%
• ADHD prevalence among 18- to 44-year-olds: 4.4%
• Associated with high degrees of psychiatric comorbidity
• Associated with impairment in multiple domains
• Associated with chronic course (circa 50% persistence into adulthood)

Developmental Impact and Targets of Treatment for ADHD

Behavioral disturbance

Academic difficulties
Self-esteem issues
Legal issues
Smoking
Injuries

Preschool

School-age

Adolescent

College-age

Adult

Occupational failure
Self-esteem
Relationship problems
Injuries/accidents

Behavioral disturbance

Academic difficulties
Peer relationships
Self-esteem issues

Academic failure
Occupational difficulties
Self-esteem
Substance abuse
Injuries/accidents

**DSM-5 Criteria for ADHD:**

Inattentive Symptoms (6/9 age ≤16 years; 5/9 ≥17 years)

- Often:
  - Fails to give close attention to details
  - Has difficulty sustaining attention
  - Does not seem to listen
  - Does not follow through on instructions
  - Has difficulty organizing tasks or activities
  - Avoids tasks requiring sustained mental effort
  - Loses things necessary for tasks
  - Is easily distracted
  - Is forgetful in daily activities

**DSM-5 Criteria for ADHD:**

Hyperactive/Impulsive Symptoms (6/9 age ≤16 years; 5/9 ≥17 years)

- Often:
  - Fidgets with hands or feet or squirms in seat
  - Leaves seat in classroom inappropriately
  - Runs about or climbs excessively (or internal restlessness)
  - Has difficulty playing quietly
  - Is “on the go” or acts as if “driven by a motor”
  - Talks excessively
  - Blurts out answers before questions are completed
  - Has difficulty awaiting turn
  - Interrupts or intrudes on others

Essential Features of ADHD

Symptoms
- Inattention: 6 (5 in adults) or more developmentally inappropriate
  —and/or—
- Hyperactivity/impulsivity: 6 (5 in adults) or more developmentally inappropriate

Criteria
- Present before age 12 years
- >6 months persistence
- Not better accounted for by another disorder
- Impairment
  - Clear evidence that symptoms interfere with, or reduce the quality of, functioning
  - Several symptoms in at least 2 settings (e.g., school, social, work)
- Subtypes: combined, predominately inattentive, or hyperactive/impulsive
- Specifier: in partial remission (previous full diagnosis; now subthreshold for past 6 months)
Main Changes to ADHD DSM-5 (vs. DSM-IV)

• Similar symptoms (e.g., nine symptoms of inattention and/or hyperactive-impulsivity) – more prompts added

• Change in symptom requirements:
  • <17 years: 6/9 hyperactivity-impulsivity and/or 6/9 of inattention
  • ≥17 years: 5/9 hyperactivity-impulsivity and/or 5/9 of inattention

• Change in symptom onset: prior to age 12 years

• Change in “clinically significant impairment” to relative impairment

• Change in exclusion: diagnosis can be made in Autism Spectrum Disorder

Age-Dependent Decline of ADHD Symptoms

Brain Differences Between Persistent and Remitted ADHD

Figure 1 (A) One sample t-tests in each group showed positive functional connectivity between the posterior cingulate cortex (MNI coordinates: $x = 15$, $y = -56$, $z = 28$) and regions of the medial prefrontal cortex (MPFC) in control and remitted ADHD groups, but not in the persistent ADHD group. (B) Between-group comparisons revealed greater positive functional connectivity between posterior cingulate cortex and medial prefrontal cortex for the control group than the persistent ADHD group. (C) The remitted ADHD group also showed greater positive functional connectivity between the posterior cingulate cortex and medial prefrontal cortex than the persistent ADHD group. Statistical height threshold $P < 0.05$, FWE cluster corrected $P < 0.05$.

ADHD Assessment

• Life history
• Self-report
• Mental status exam
• Rating scales: measuring core and broad features
• Medical history review; cardiac and neurologic status, blood pressure/pulse
• If medical history is unremarkable, laboratory or neurological testing is not indicated
• Assess for comorbidity (psychiatric, cognitive, psychosocial, medical)

Developing a Treatment Plan

- Educational/occupational evaluation and planning is critical
- Parent/individual support and guidance (referral to support groups; CHADD, ADDin)
- Cognitive behavior therapy may be recommended initially if:
  - ADHD symptoms are mild-moderate
  - Patient is in preschool
  - Pharmacotherapy is rejected
- Pharmacotherapy is typically considered first-line
- Once treatment is established, practitioner’s role:
  - Coordinating with school or college student health service regarding ADHD treatment
  - Preparing the patient (and family) for major transitions
  - Monitoring side effects
  - Monitoring progress

Activity Levels and ADHD

- Data that enhance activity improve general attentiveness and executive functioning in children
  - ABC program
  - Less use of asthma and ADHD medication
- Activity throughout day reduces hyperactivity
- Activity improves frontal lobe function (on fMRI)
- Preliminary mild improvements shown in ADHD (executive functioning Cronbach’s alpha 0.3)

ADHD, Post-Concussion, and Treatment

- Treatment of ADHD may also improve post-concussive syndrome
- Use of stimulants and modafinil for concussion and/or (traumatic) brain injury
  - Targeted symptoms: arousal, disinhibition
  - General focus and concentration
  - Enhanced processing speeds
  - Unclear effects on complex processing
- Non-specific response to stimulants
- Caveats
  - Careful with adverse effects: some indication of increased adverse effects with more “brain injury” (vs. ADHD)
  - To “return to play” faster, some players are using stimulants to improve post-concussive testing

Based on adult treatment manuals, adapted for adolescents

1. Organizing and planning (4)
2. Coping with distractibility (2)
3. Cognitive restructuring (2)
4. Parent/adolescent sessions (2)
5. Relapse prevention (1)
6. Parents included for 10 min each session
   optional
4. Application to procrastination (1)
5. Parent-only sessions (2)
MGH Randomized Controlled Trial of CBT for ADHD in Medication Treated Adolescents (N=46)
4 Month Responder Status (% responders)

30% reduction on the ADHD rating scale=categorical responder,
(Chi Sq (1) = 8.98, p=.00 for parent; Chi Sq (1) = 5.87, p=.02 for adolescent)

Telehealth is Effective for Treating ADHD: A Community-Based Randomized Controlled Trial

Abstract

OBJECTIVE: To test the effectiveness of a telehealth service delivery model for the treatment of children with attention-deficit/hyperactivity disorder (ADHD) that provided pharmacological treatment and caregiver behavior training.

METHOD: The Children’s ADHD Telemental Health Treatment Study (CATTS) was a randomized controlled trial with 223 children referred by 88 primary care providers (PCPs) in 7 communities. Children randomized to the experimental telehealth service model received 6 sessions over 22 weeks of combined pharmacotherapy, delivered by child psychiatrists through videoconferencing, and caregiver behavior training, provided in person by community therapists who were supervised remotely. Children randomized to the control service delivery model received treatment with their PCPs augmented with a telepsychiatry consultation. Outcomes were diagnostic criteria for ADHD and oppositional defiant disorder (ODD) and role performance on the Vanderbilt ADHD Rating Scale (VADRS) completed by caregivers (VADRS-Caregivers) and teachers (VADRS-Teachers) and impairment on the Columbia Impairment Scale-Parent Version (CIS-P). Measures were completed at 5 assessments over 25 weeks.

RESULTS: Children in both service models improved. Children assigned to the telehealth service model improved significantly more than children in the augmented primary care arm for VADRS-Caregiver criteria for inattention ($\chi^2(3)=19.47, p<.001$), hyperactivity ($\chi^2(3)=11.91, p=.02$), combined ADHD ($\chi^2(3)=14.90, p=.005$), ODD ($\chi^2(3)=10.05, p=.04$), and VADRS-Caregiver role performance ($\chi^2(3)=12.40, p=.01$) and CIS-P impairment ($\chi^2(3)=20.52, p<.001$). For the VADRS-Teacher diagnostic criteria, children in the telehealth service model had significantly more improvement in hyperactivity ($\chi^2(4)=11.28, p=.02$) and combined ADHD ($\chi^2(4)=9.72, p=.045$).

CONCLUSION: The CATTS trial demonstrated the effectiveness of a telehealth service model to treat ADHD in communities with limited access to specialty mental health services. Clinical trial registration Information—Children’s Attention Deficit Disorder With Hyperactivity (ADHD) Telemental Health Treatment Study; http://clinicaltrials.gov; NCT00330700.

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Medications: Attention-Deficit/Hyperactivity Disorder

Pharmacological Treatment

Stimulants
- Methylphenidate
- Amphetamines

FDA Approved

Atomoxetine

FDA Approved

Alpha Agonists
- Guanfacine (XR)
- Clonidine (XR)
- Guan XR or Clon XR + stimulants

FDA Approved

Antidepressants
- Bupropion
- Tricyclics

FDA Approved

Modafinil

Miscellaneous
fMRI in Adults With ADHD

- MGH NMR Center and Harvard-MIT CITP
- fMRI, functional magnetic resonance imaging.

Suspected Mechanism of Action of Medications for ADHD

Effect of Psychostimulants on Brain Structure and Function in ADHD: A Qualitative Literature Review of Magnetic Resonance Imaging–Based Neuroimaging Studies

Thomas J. Spencer, MD; Ariel Brown, PhD; Larry J. Seidman, PhD; Eve M. Valera, PhD; Nikos Makris, MD; Alexandra Lomedico, BA; Stephen V. Faraone, PhD; and Joseph Biederman, MD

ABSTRACT
Objective: To evaluate the impact of therapeutic oral doses of stimulants on the brains of ADHD subjects as measured by magnetic resonance imaging (MRI)-based neuroimaging studies (morphometric, functional, spectroscopy).

Data Sources: We searched PubMed and ScienceDirect through the end of calendar year 2011 using the keywords (1) psychostimulants or methylphenidate or amphetamine, and (2) neuroimaging or MRI or fMRI, and (3) ADHD or ADD or attention-deficit/hyperactivity disorder or attention deficit hyperactivity disorder.

Study Selection: We included only English language articles with new data from case-control or placebo controlled studies that examined attention-deficit/hyperactivity disorder (ADHD) subjects on and off psychostimulants as well as 5 relevant review articles.

Data Extraction: We combined details of study design and medication effects in each imaging modality.

Results: We found 29 published studies that met our criteria. These included 6 structural MRI, 20 functional MRI studies, and 3 spectroscopy studies. Methods varied widely in terms of design, analytic technique, and regions of the brain investigated. Despite heterogeneity in methods, however, results were consistent. With only a few exceptions, the data on the effect of therapeutic oral doses of stimulant medication suggest attenuation of structural and functional alterations found in unmedicated ADHD subjects relative to findings in controls.

Conclusions: Despite the inherent limitations and heterogeneity of the extant MRI literature, our review suggests that therapeutic oral doses of stimulants decrease alterations in brain structure and function in subjects with ADHD relative to unmedicated subjects and controls. These medication-associated brain effects parallel, and may underlie, the well-established clinical benefits.
Effect of Psychostimulants on Brain Structure and Function in ADHD: A Qualitative Literature Review of Magnetic Resonance Imaging–Based Neuroimaging Studies

Thomas J. Spencer, MD; Eve M. Valera, MD; and Stephen V. Faraone, MD

Conclusions: Despite the inherent limitations and heterogeneity of the extant MRI literature, our review suggests that therapeutic oral doses of stimulants decrease alterations in brain structure and function in subjects with ADHD relative to unmedicated subjects and controls. These medication-associated brain effects parallel, and may underlie, the well-established clinical benefits.
Early ADHD Treatment Reduces Marijuana Use

10 Cohorts of senior years 2005 to 2014  (N=40,358; ca. 10% with ADHD)

Population risk

Stimulant use started prior to 9 years of age*

Stimulant use started between 10-14 years*

Stimulant use started after 15 years of age**

* > 6 years of treatment
** > 3 years of treatment

Past Year Use

p<0.001 vs. controls

ADHD Medication Reduces SUD: Within Subjects Analyses

• Study of U.S. Claims Data from 2004-2013
• Follow-up of from 1 to 120 months (median 15.5 months)
• N = 2,993,887 ADHD > 13 years old (47% female)
• Stimulants and atomoxetine (no other [adjunct use])
• Age at follow-up (median 21 years [male], 28 years [female])
• Controls: Matched 1:1 on sex, enrollment
• Examination: Main outcome within subject changed based on medication periods vs. non-medication periods, sex, age groups
• Data adjusted for confounds
• Secondary vs. non-ADHD controls
• Outcome: Substance-related events

ADHD Medication and SUD Results

• Comparison of Medicated ADHD vs. Never Medicated ADHD

• Treated males 24% < untreated males for SUD risk (3.1% vs. 4%, OR=0.76, CI 0.75-0.78)

• Treated females 6% < untreated females for SUD risk (2.6% vs. 2.8%, OR=0.94, CI 0.91-0.97)

ADHD Medication and SUD Results

• Comparison of periods of medicated vs. unmedicated ADHD individuals (primary outcome)
  
  • Males 35% lower risk: treated periods < untreated periods for SUD risk (OR=0.65, CI 0.64-0.67)
  
  • Females 31% lower risk: treated periods < untreated periods for SUD risk (OR=0.69, CI 0.67-0.71)

For first-only SUD incidents, medication was associated with 55% and 43% lower SUD events in male and females, respectively

# Methylphenidate (MPH) in ADHD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose*</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin IR®</td>
<td>5 mg QD/BID</td>
<td>2 mg/kg/day</td>
<td>4 hr /BID</td>
</tr>
<tr>
<td>Focalin®</td>
<td>2.5 mg QD/BID</td>
<td>1 mg/kg/day</td>
<td>4–5 hr / BID–TID</td>
</tr>
<tr>
<td>Focalin XR®</td>
<td>5 mg QD</td>
<td>1 mg/kg/day</td>
<td>10–12 hr QD</td>
</tr>
<tr>
<td>Daytrana®</td>
<td>10 mg</td>
<td></td>
<td>6–16 hr</td>
</tr>
<tr>
<td>Concerta®</td>
<td>18 mg QD</td>
<td>2 mg/kg/day</td>
<td>12 hr / once</td>
</tr>
<tr>
<td>Metadate CD®</td>
<td>20 mg QD</td>
<td></td>
<td>8 hr / once</td>
</tr>
<tr>
<td>Ritalin LA®</td>
<td>20 mg QD</td>
<td></td>
<td>8 hr / once</td>
</tr>
<tr>
<td>Quillivant®</td>
<td>&lt;10 mg QD</td>
<td></td>
<td>12 hr / once</td>
</tr>
<tr>
<td>Quillichew™</td>
<td>&lt;10 mg QD</td>
<td></td>
<td>8 hr /once</td>
</tr>
<tr>
<td>Contempla XR (disintegrating tab)</td>
<td>8.6 mg QD</td>
<td>51.8 mg</td>
<td>12 hr/once</td>
</tr>
<tr>
<td>Aptensio XR</td>
<td>10 mg QD</td>
<td>2 mg/kg/day</td>
<td>12 hr/once</td>
</tr>
<tr>
<td>Jornay PM</td>
<td>20 mg in PM</td>
<td>100 mg</td>
<td>Initial absorption delayed; single peak at 14 hours</td>
</tr>
</tbody>
</table>

### Amphetamine (AMPH) in ADHD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose*</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall®</td>
<td>2.5–5 mg QD</td>
<td>1.5 mg/kg/day</td>
<td>6 hr / BID</td>
</tr>
<tr>
<td>Adderall XR®</td>
<td>2.5–5 mg QD</td>
<td></td>
<td>12 hr / QD</td>
</tr>
<tr>
<td>Vyvanse®</td>
<td>30 mg QD</td>
<td></td>
<td>12–14 hr / QD</td>
</tr>
<tr>
<td>Mydayis®</td>
<td>12.5 mg QD</td>
<td>50/25 mg (adults/adol)</td>
<td>To 16 hr/QD</td>
</tr>
<tr>
<td>Dexedrine Tablets®</td>
<td>2.5–5 mg BID</td>
<td>1.5 mg/kg/day</td>
<td>3–5 hr / BID–QID</td>
</tr>
<tr>
<td>Evekeo®</td>
<td>2.5–5 mg BID</td>
<td></td>
<td>3–5 hr / BID–QID</td>
</tr>
<tr>
<td>Dexedrine Spansule®</td>
<td>5 mg QD</td>
<td></td>
<td>6 hr / QD–BID</td>
</tr>
<tr>
<td>Dyanavel XR™ (suspension)</td>
<td>2.5–5 mg QD</td>
<td>1.5 mg/kg/day</td>
<td>12 hr / QD</td>
</tr>
<tr>
<td>Adzenys XR™ (disintegrating tab)</td>
<td>6.3–12.5 mg QD</td>
<td>12.5 mg (adolescents)</td>
<td>12 hr / QD</td>
</tr>
</tbody>
</table>

*May exceed FDA approved dose (eg, > 20 to 30 mg/day).

Previous MPH Exposure Influences Outcomes

![Graph showing mean change in ADHD-RS-IV score from baseline for different conditions and groups.](image)

Mean change from baseline in ADHD-RS-IV total score by treatment for prior MPH or stimulant-naive subgroups at endpoint (full-analysis set).

**Notes:** *P<0.05; **P<0.001 versus placebo. Nominal statistical differences based on ANCOVA of placebo-adjusted LS means in the RCT only. Statistics not performed for RWS. Not all patients had ADHD-RS-IV total score data available at end point.

**Abbreviations:** ADHD-RS-IV, ADHD Rating Scale version IV; ANCOVA, analysis of covariance; ATX, atomoxetine; GXR, guanfacine extended release; LOCF, last observation carried forward; LS, least squares; MPH, methylphenidate; RCT, randomized controlled trial; RWS, randomized-withdrawal study.

Huss et al., Neuropsychiatric Disease Tx, 2016: 12; 1085-1101.
Pharmacotherapy for ADHD

- Stimulants (FDA approved)
  - Methylphenidate
  - Amphetamine compounds
- Atomoxetine (FDA-approved)
- Alpha agonists (FDA-approved)
  - Guanfacine extended-release
  - Clonidine extended-release
- Combination therapy (FDA-approved)
- Antidepressants
  - Bupropion
  - Tricyclics
- Modafinil
- Research

Guanfacine Extended-Release in ADHD

(N=324 [51 sites];
6 weeks active*,
Mean Age 11±3 years)

Effect size:
0.41-0.89

*, + P < .05

*3 weeks titration
3 weeks maintenance (endpoint)
3 weeks taper

Extended-Release Guanfacine Has Similar Efficacy With AM or PM Administration

**FIGURE 2**  Mean change from baseline in attention-deficit/hyperactivity disorder (ADHD) Rating Scale–IV (ADHD-RS-IV) scores by visit. Note: (A) Total score, (B) Hyperactivity/Impulsivity subscale, (C) Inattention subscale. All p values are based on type III sum of squares from an analysis of covariance (ANCOVA) model. GXR = guanfacine extended release; LOCF = last observation carried forward; SE = standard error of the mean. *p < .05 versus placebo based on change from baseline (visit 2). **p < .01 versus placebo based on change from baseline (visit 2). ***p < .001 versus placebo based on change from baseline (visit 2).
Guanfacine XR in Adolescent ADHD

Percentage of responders (full analysis set). Response was defined as a percentage reduction from the baseline visit in the ADHD RS IV total score of ≥30% and a Clinical Global Impressions–Improvement of 1 or 2.

# Guanfacine XR in Adolescent ADHD

Guanfacine XR in Adolescent ADHD

\(^a\)Includes biracial, more than 1 race, Ethiopian and unknown.

| Table 2. Summary of TEAEs (≥10% of Subjects; Safety Population) |
|-------------------|------------------|
|                  | GXR (N = 157)    | Placebo (N = 155) |
| Preferred term   |                  |                  |
| Any TEAE         | 147 (93.6)       | 120 (77.4)       |
| Somnolence       | 69 (43.9)        | 33 (21.3)        |
| Headache         | 42 (26.8)        | 28 (18.1)        |
| Fatigue          | 35 (22.3)        | 19 (12.3)        |
| Dizziness        | 25 (15.9)        | 16 (10.3)        |
| Decreased appetite | 23 (14.6)    | 21 (13.5)        |
| Nausea           | 19 (12.1)        | 21 (13.5)        |
| Nasopharyngitis  | 18 (11.5)        | 9 (5.8)          |
| Sedation         | 18 (11.5)        | 3 (1.9)          |

TEAE, treatment-emergent adverse event; GXR, guanfacine extended-release.

Atomoxetine Improves Anxiety and ADHD in Youth With ADHD & Anxiety Disorders

Dose of ATMX = 1.26 mg/kg/day

Effect size = 1.0

Effect size = 0.5

** p=.011

* p<.001

Atomoxetine Improves Anxiety and ADHD in Youth With ADHD & Anxiety Disorders

Atomoxetine: When to Use

• Monotherapy (higher likelihood of response as first start)
• Stimulant nonresponders
• Stimulant partial responders (monotherapy, adjunctive therapy - no drug interactions with stimulants)
• Adverse effects to stimulants
• Concerns of stimulant diversion
• Executive dysfunction (?)
• Comorbid ADHD plus:
  • Oppositional disorder
  • Anxiety
  • Tics
  • Substance abuse
Combination of Atomoxetine Plus Stimulants in the Treatment of ADHD

• Qualitative analysis of existing studies

• N=3 prospective (1RCT) + 7 retrospective reports

• Predominately children/adolescents with inadequate response to stimulants

• Most often used stimulant = methylphenidate

• Conclusions:
  
  • Small sample sizes
  
  • “Existing evidence suggests, but does not confirm, that this drug combination may benefit some, but not all, patients who have tried several ADHD medications without success.”

Combination of Guanfacine XR Plus Stimulants in the Treatment of ADHD (n=455)

Figure 2. GXR PM dosing plus psychostimulant group: change in ADHD-RS-IV total score from baseline by visit (FAS).

*P<0.05 vs placebo, based on Dunnett's test.
Effect size at endpoint was 0.447.
Endpoint is the last valid assessment obtained after baseline and before dose taper.
Effect of Extended-Release Guanfacine on Parent-Rated Before School Functioning Questionnaire

*\(p < .02\) + psychostimulant

Wilens et al., J Att Disorders, 2013.
Combination of Clonidine XR Plus Stimulants for ADHD

Study of clonidine XR coadministration to partial responders on stimulants (≥ADHD RS 26 score)
- Dosing to 0.4 mg daily (in 0.2 mg BID dosing)
- Duration: 5 weeks (then taper)
RCT on Guanfacine (GUAN), D-Methylphenidate (D-MPH), or the Combination (COMB) on ADHD in Children

*M Denotes LS mean end point changes versus baseline

Age: 7 – 14 years
Sample Size: Guan (N=68), D-MPH (N=69), COMB (N=70)
Dosing:
  Guan (1-3 mg/day)
  D-MPH (5-20 mg/day)

Baseline: 21.1 21.3 20.4
Baseline: 36.8 35.6 35.6

P<.0001 P=.0024 P<.0001
P<.0001 P=.0029 P<.0001
F=.02  F=.01

Med Group p<0.0001; Visit p=0.0002

Alpha Agonists: When to Use

• Monotherapy
• Stimulant or nonstimulant nonresponders
• Medication partial responders (adjunctive therapy)
  • Studied with stimulant coadministration (N=5 studies)
• Adverse effects to stimulants or nonstimulants
• Comorbid ADHD plus
  • Oppositional disorder
  • Anxiety
  • Tics
  • “Emotional dysregulation” (needs to be studied)
• Potentially younger children (needs to be studied)
Medications: Attention-Deficit/Hyperactivity Disorder

Stimulants
- Methylphenidate
- Amphetamines

Atomoxetine

Alpha Agonists
- Guanfacine (XR)
- Clonidine (XR)
- Guan XR or Clon XR + stimulants

Antidepressants
- Bupropion
- Tricyclics

Modafinil

Miscellaneous

FDA Approved

Tricyclic Antidepressants in ADHD

• Effective in children with ADHD
  • Use as monotherapy and adjunctly
  • Trials predominately of imipramine, desipramine, nortriptyline
  • Dosing generally to 4 mg/kg/day (2 mg/kg/day with nortriptyline)
  • Use in ADHD, ADHD plus tics/TS

• Effective in adults with ADHD
  • Use as monotherapy
  • Studies largely in desipramine

• Effect size ca 0.7-0.8 (est) < Stimulants

• Need to monitor serum level, ECG (?), side effects, OD risk

Modafinil: When to Use

• Weak stimulant effects (Spencer et al.)
• Stimulant or nonstimulant partial or non-partial responders (monotherapy, adjunctive therapy - no drug interactions with stimulants)
• Adverse effects to medications
• Concerns of diversion or misuse of stimulants
• Need for renewable agent
• Cardiovascular risk factors (still cautionary in PI)
• Predominately cognitive deficits (e.g., motivation, arousal of attention)
Risperidone + Stimulants in ADHD + Aggression (TOSCA Study)

- Study of severely aggressive children (mean age 9 years) receiving stimulant (ADHD + Oppositional or Conduct disorder); age 9 years
- 9-week trial (N = 84/group) followed by 52-week follow-up
- Parent training (3 weeks) + stimulant + risperidone versus placebo
- 9-week findings: Risperidone > placebo for multiple behavioral ratings
- Few differences in adverse effects
- 52-week outcomes: <50% still on treatment; slight advantage to risperidone vs. placebo
- Recommendations: Parent training for 1 month, then stimulants, then risperidone (SGA)

Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments

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Samuele Cortese, M.D., Ph.D.
David Daley, Ph.D.
Maite Ferrin, M.D., Ph.D.
Martin Holtmann, M.D.
Jim Stevenson, Ph.D.
Marina Danckaerts, M.D., Ph.D.
Saskia van der Oord, Ph.D.
Manfred Döpfner, Ph.D.
Ralf W. Dittmann, M.D., Ph.D.
Emily Simonoff, M.D.
Alessandro Zuddas, M.D.
Tobias Banaschewski, M.D., Ph.D.
Jan Buitelaar, M.D., Ph.D.
David Coghill, M.D.
Chris Hollis, M.D.
Eric Konofal, M.D., Ph.D.
Michel Lecendreux, M.D.
Ian C.K. Wong, Ph.D.
Joseph Sergeant, Ph.D.

European ADHD Guidelines Group

Objective: Nonpharmacological treatments are available for attention deficit hyperactivity disorder (ADHD), although their efficacy remains uncertain. The authors undertook meta-analyses of the efficacy of dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) and psychological (cognitive training, neurofeedback, and behavioral interventions) ADHD treatments.

Method: Using a common systematic search and a rigorous coding and data extraction strategy across domains, the authors searched electronic databases to identify published randomized controlled trials that involved individuals who were diagnosed with ADHD (or who met a validated cutoff on a recognized rating scale) and that included an ADHD outcome.

Results: Fifty-four of the 2,404 nonduplicate screened records were included in the analyses. Two different analyses were performed. When the outcome measure was based on ADHD assessments by raters closest to the therapeutic setting, all dietary (standardized mean differences=0.21-0.48) and psychological (standardized mean differences=0.40-0.64) treatments produced statistically significant effects. However, when the best probably blinded assessment was employed, effects remained significant for free fatty acid supplementation (standardized mean difference=0.16) and artificial food color exclusion (standardized mean difference=0.42) but were substantially attenuated to nonsignificant levels for other treatments.

Conclusions: Free fatty acid supplementation produced small but significant reductions in ADHD symptoms even with probably blinded assessments, although the clinical significance of these effects remains to be determined. Artificial food color exclusion produced larger effects but often in individuals selected for food sensitivities. Better evidence for efficacy from blinded assessments is required for behavioral interventions, neurofeedback, cognitive training, and restricted elimination diets before they can be supported as treatments for core ADHD symptoms.

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Omega-3/Omega-6 Fatty Acids for ADHD

• Meta-analysis of 10 studies; N = 699 children
  • Examined EPA, DHA (omega-3), and g-linoleic acid (omega-6)
  • Indicating mild improvement in ADHD overall with good tolerability (ES = 0.28 monotherapy; 0.18 adjunct)
  • Potential dose response effect of EPA (omega-3)

• Dosing
  • High EPA to DHA (docohexaenoic acid) or g-linoleic acid (omega-6)
  • < 1000 mg/day
  • Preparations, brands vary dramatically

MGH Open Study: Fish Oils Reduce Emotional Dysregulation in Med-Treated ADHD Children (N=10)

75% of Patients Improved

More improvement

Dosing to 975 mg EPA/day
Effect noted by week 2

*P<0.0001

Wilens et al., J Child Adoles Psychopharm 2017.
New Representative ADHD Meds in Development

Stimulants:
- Abuse deterrence
- Novel delivery systems
- Various isomeric preparations

Nonstimulants:
- Dasatroline (NET>DAT uptake inhibitor)
- Centanafadine (DAT>NET>5HT uptake inhibitor (triamine))
- Mazandole (potentially regulating the orexins)
- Eltoprazine (5-HT1A/1B partial agonist)
- SPN-810 (Molindone HCl; indole-derivative; D2 receptor selective antagonist)
- AR-08 (Adrenergic receptor agonist)
Stimulant Misuse and Diversion

• N=21 studies (N>113,000 participants); mostly survey studies in college students (80%)\textsuperscript{1}
• 10% to 20% prevalence of non-medical use of stimulants
• 65% to 85% of stimulants diverted from “friends”
  • Majority not “scamming” local docs
  • Not seen as potentially dangerous
• Motivation typically for concentration and alertness more so than getting “high”
• Appears to be occurring in substance (ab)users during academic decline
• Immediate release > > extended release stimulants
• Recent increase in IR mixed amphetamine salts misuse

Misuse Peaks at Age 21, With 10% of the Population Reporting Lifetime Misuse of Stimulants

Stimulants are Frequently Diverted


1 Drug diversion = Transfer of legally prescribed controlled substance to another person by selling, trading, or giving away
Misuse by Alternative Routes is Common: Snorting is Frequently Reported

Method of Stimulant Misuse by College Students (n=1,025)

- Snort: 55%
- Swallow: 40%
- Other: 4%

White et al, Stimulant Medication Use, Misuse, and Abuse in an Undergraduate and Graduate Student Sample, JRN of Am College Health, 2006; Random sample: anonymous surveys at the University of New Hampshire administered via email and paper, 1,025 received out of 5,000 distributed, 6.6% diagnosed with ADHD, over 16% of students abuse stimulants
ADHD Rates* and Neuropsychological Dysfunction Are Higher in College Students Who Misuse Stimulants (N=300)

*full and subthreshold dx

Adolescents’ Prescription Stimulant Use and Adult Functional Outcomes: A National Prospective Study

Sean Esteban McCabe, PhD, Philip Veliz, PhD, Timothy E. Wilens, MD, John E. Schulenberg, PhD

Objective: To assess the prospective 17-year relationship between the medical and nonmedical use of prescription stimulants during adolescence (age 18 years) and educational attainment and substance use disorder (SUD) symptoms in adulthood (age 35 years).

Method: A survey was self-administered by nationally representative probability samples of US high school seniors from the Monitoring the Future study; 8,362 of these individuals were followed longitudinally from adolescence (age 18, high school senior years 1976–1996) to adulthood (age 35, 1993–2013).

Results: An estimated 8.1% reported medical use of prescription stimulants, and 16.7% reported nonmedical use of prescription stimulants by age 18 years. Approximately 43% of adolescent medical users of prescription stimulants had also engaged in nonmedical use of prescription stimulants during adolescence. Among past-year adolescent nonmedical users of prescription stimulants, 97.3% had used at least one other substance during the past year. Medical users of prescription stimulants without any history of nonmedical use during adolescence did not differ significantly from population controls (i.e., non-attention-deficit/hyperactivity disorder [ADHD] and non-stimulant-mediated ADHD during adolescence) in educational attainment and SUD symptoms in adulthood. In contrast, adolescent nonmedical users of prescription stimulants (with or without medical use) had lower educational attainment and more SUD symptoms in adulthood, compared to population controls and medical users of prescription stimulants without nonmedical use during adolescence.

Conclusion: Nonmedical use of prescription stimulants is common among adolescents prescribed these medications. The findings indicate youth should be carefully monitored for nonmedical use because this behavior is associated with lower educational attainment and more SUD symptoms in adulthood.

Key words: stimulants, adolescent, prescription drug misuse, substance-related disorders, adult

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Sean Esteban McCabe

Objective: To assess the pro between the medical and non-stimulants during adolescence and subsequent symptoms in adulthood (age 35, 1993–2013).

Method: A survey was self-representative probability samples from the Monitoring the Individuates individuals were followed during adolescence (age 18, high school) and adulthood (age 35, 1993–2013).

Results: An estimated 8.1% of prescription stimulants, and 16% of nonmedical use by 43% of adolescent medical users had also engaged in nonmedical stimulants during adolescence. Among past-year nonmedical users of prescription stimulants, 97.3% had used at least one other substance during the past year. Medical users of prescription stimulants without any history of nonmedical use during adolescence had more population controls for activity disorder [ADHD] and SUD symptoms in their nonmedical users of prescription stimulants.

• About one in every six US high school seniors reported lifetime nonmedical use of prescription stimulants for ADHD. Especially noteworthy is that nonmedical use of prescription stimulants is highly prevalent (43%) among adolescent medical users of prescription stimulants.

• Nonmedical use of prescription stimulants (within or outside of stimulant medication therapy) during adolescence is associated with a higher risk of SUD symptoms and lower educational attainment almost two decades later at age 35 years, controlling for adolescent sociodemographic, other drug use, and behavioral controls.

• In contrast, adolescents who use prescription stimulant therapy appropriately have risks of adult SUD symptoms and educational attainment in adulthood similar to those of population controls.

Key words: stimulants, adolescent, prescription drug misuse, substance-related disorders, adult

Nonmedical Use of Prescription Stimulants at Age 18 Years Predicts Substance Use Disorder Sx at Age 35 years (N=8362)

Medical use only
Medical and nonmedical use
Nonmedical use only

≥ 2 SUD Symptoms at Age 35
Adjusted Odds Ratio (95% CI)

p NS
p < .01
p < .001

Educational Attainment at Age 35 Years as a Function of Medical and Nonmedical Use of Prescription Stimulants at Age 18 Years (N=7813)

Obtained Associate’s Degree or Higher

- No medical or nonmedical use
- Medical use only
  - AOR\(^a\) = 0.874
- Medical and nonmedical use
  - AOR\(^a\) = 0.672
- Nonmedical use only
  - AOR\(^a\) = 0.749

Note: AOR = adjusted odds ratio
All analyses control for race/ethnicity, sex, truancy, average grade during high school, parental education, geographical region, metropolitan statistical area, cohort year at baseline, annual alcohol use at baseline, annual cannabis use at baseline, and annual other drug use at baseline.
Attrition weights applied and sample sizes vary due to missing data on the dependent measures

Conclusions

• ADHD is considered a lifespan disorder

• Careful assessment of ADHD and associated psychiatric, psychosocial, and medical comorbidities is necessary prior to initiating treatment

• New diagnostic criteria (DSM-5) are similar to previous criteria

• Consider the implications of not treating ADHD

• Psychosocial interventions can be an important part of the treatment

• Treatment with both stimulants and nonstimulants demonstrated both effective and safe

• Management requires ongoing reassessment and intervention