New(er) Medication Treatments for ADHD

Timothy E. Wilens, MD
Chief, Division of Child and Adolescent Psychiatry
Co-Director, Center for Addiction Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

ADHD Overview

• ADHD prevalence among 8- to 15-year-olds: 8.7%
  • Percentage of children with ADHD who have been treated consistently during the past year: 32%
• ADHD prevalence among 18- to 44-year-olds: 4.4%
  • Percentage of adults with ADHD who received treatment within the previous 12 months: 11%
• Associated with high degrees of psychiatric comorbidity
• Associated with impairment in multiple domains
• Associated with chronic course
  • Circa 75% persistence from childhood into adolescence
  • Circa 50% persistence from childhood into adulthood

ADHD Overview

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
  • 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

Medications: ADHD

Pharmacologic Treatment

- Stimulants
  - FDA Approved
- Methylphenidate
- Amphetamines
- Atomoxetine
  - FDA Approved
- Alpha agonists
- Guanfacine (XR)
- Clonidine (XR)
- Guan XR or Clon XR + stimulants
  - FDA Approved
- Antidepressants
- Bupropion
- Tricyclics
- Modafinil
- Misc

Unmet Needs in Pharmacotherapy of ADHD

- Effect size of nonstimulants
  - Stimulants > Nonstimulants for efficacy
- Often need combination of nonstimulants + stimulants
- Effectiveness throughout the day
  - Early morning symptoms
  - After school, evening functioning
- Improved executive functioning
- Behavioral self regulation (eg, moodiness, frustration)
- Cognitive tasks (organization, planning, shifting, executing)
- Effectiveness for frequent Sx, traits, or comorbidity(ies)
- Anxiety, mood, tics, oppositionality
- Safety in substance use disorders, low misuse/diversion
- Tolerability
  - Ease of use
- Low side-effect burden

Developmental Impact and Targets of Treatment for ADHD

Behavioral disturbance

Preschool
Behavioral difficulties
Academic difficulties
Self-esteem issues
Legal issues
Smoking
Injuries

School-age
Behavioral disturbance
Academic difficulties
Self-esteem issues
Peer relationships

Occupational failure
Self-esteem
Substance abuse
Injuries/accidents

Adolescent
Behavioral disturbance
Academic difficulties
Self-esteem issues

College-age
Behavioral disturbance
Academic difficulties
Self-esteem issues

Adult
Behavioral disturbance
Academic difficulties
Self-esteem issues

Unmet Needs in Pharmacotherapy of ADHD

Medications: ADHD

Pharmacologic Treatment

- Stimulants
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- Tricyclics
- Modafinil
- Misc

### Methylphenidate (MPH) in ADHD: Optimizing Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose*</th>
<th>Usual Dosing</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>
<td></td>
</tr>
<tr>
<td>Focalin®</td>
<td>2.5 mg QD/BID</td>
<td>1 mg/kg/day</td>
<td>4–6 hr / BID-TID</td>
<td></td>
</tr>
<tr>
<td>Focalin XR®</td>
<td>5 mg QD</td>
<td>1 mg/kg/day</td>
<td>10–12 hr QD</td>
<td></td>
</tr>
<tr>
<td>Daytrana®</td>
<td>10 mg</td>
<td></td>
<td>6–16 hr</td>
<td></td>
</tr>
<tr>
<td>Concerta®</td>
<td>18 mg QD</td>
<td>2 mg/kg/day</td>
<td>12 hr / once</td>
<td></td>
</tr>
<tr>
<td>Metadate CD®</td>
<td>20 mg QD</td>
<td></td>
<td>8 hr / once</td>
<td></td>
</tr>
<tr>
<td>Ritalin LA®</td>
<td>20 mg QD</td>
<td></td>
<td>8 hr / once</td>
<td></td>
</tr>
<tr>
<td>Quillivant®</td>
<td>&lt;10 mg QD</td>
<td></td>
<td>12 hr /once</td>
<td></td>
</tr>
<tr>
<td>Quillichew™</td>
<td>&lt;10 mg QD</td>
<td></td>
<td>8 hr / once</td>
<td></td>
</tr>
</tbody>
</table>

*May exceed FDA approved dose.


### Amphetamine (AMPH) in ADHD: Optimizing Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose*</th>
<th>Usual Dosing</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>
<td></td>
</tr>
<tr>
<td>Adderall XR®</td>
<td>2.5–5 mg QD</td>
<td>12 hr /QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vyvanse®</td>
<td>30 mg QD</td>
<td></td>
<td>12–14 hr /QD</td>
<td></td>
</tr>
<tr>
<td>Dexedrine Tablets®</td>
<td>2.5–5 mg QD</td>
<td>1.5 mg/kg/day</td>
<td>3–5 hr /BID–QID</td>
<td></td>
</tr>
<tr>
<td>Evekeo®</td>
<td>2.5–5 mg QD</td>
<td></td>
<td>3–5 hr /BID–QID</td>
<td></td>
</tr>
<tr>
<td>Dexedrine Spansule®</td>
<td>5 mg QD</td>
<td></td>
<td>6 hr /QD–QID</td>
<td></td>
</tr>
<tr>
<td>Dyanavel XR™</td>
<td>2.5–5 mg QD</td>
<td>1.5 mg/kg/day</td>
<td>12 hr /QD</td>
<td></td>
</tr>
<tr>
<td>Adzenys XR™</td>
<td>6.3–12.5 mg QD</td>
<td></td>
<td>Not established</td>
<td>12 hr /QD</td>
</tr>
</tbody>
</table>

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


### Extended-Release MPH Solution and Chewable Preparations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose*</th>
<th>Usual Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quillivant XR® Suspension</td>
<td>12 hour duration</td>
<td>25 mg/5 cc (tsp)</td>
<td>Dosing to 60 mg daily</td>
<td>8 hour duration</td>
</tr>
<tr>
<td>QuillChew ER™</td>
<td>8 hour duration</td>
<td>20 mg scored, 30 mg scored, 45 mg tablets</td>
<td>Dosing to 60 mg daily</td>
<td>Approved in pediatrics</td>
</tr>
</tbody>
</table>


### AMPH Oral Disintegrating Tablets (Adzenys XR™) for Pediatric ADHD

Newly approved mixed AMPH (3 to 1 ratio of d- to l-amphetamine)

Duration of action to 12 hours

<table>
<thead>
<tr>
<th>Equivalent Dosing</th>
<th>Dosing to 60 mg daily</th>
<th>Not established</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPH ER disintegrating (Adzenys XR™)</td>
<td>3.1 mg</td>
<td>12.5 mg</td>
</tr>
<tr>
<td>Mixed AMPH salts ER (Adderall XR®)</td>
<td>5 mg</td>
<td>20 mg</td>
</tr>
</tbody>
</table>


### AMPH Suspension (Dyanavel XR™) for Pediatric ADHD

Newly approved AMPH suspension

Composition: 3.2 to 1 ratio of d- to l-amphetamine

Dosing: 2.5 to 5 mg QD

Duration of action: 12 hours


### D,L AMPH (Evekeo®) for Pediatric ADHD

Newly approved mixed AMPH

Composition: 50% d- and l-amphetamine

Duration of action to 10 hours

Dosing: 5 and 10 mg tablets

Laboratory classroom SKAMP-Combined scores. Lower scores denote more change. SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham.

The Ventromedial PFC: Emotional Regulation

Ventromedial PFC is thought to regulate emotion. Impairment may lead to aggressive and oppositional behavior.

PFC = prefrontal cortex.


Guanfacine XR in ADHD

Effect Size: 0.41–0.89

N = 228 (21 sites); 6 weeks active*. Mean Age = 11 ± 3 years.


Guanfacine XR Has Similar Efficacy with AM or PM Administration

Guanfacine XR in Adolescent ADHD

Objective: Despite the continuity of attention-deficit/hyperactivity disorder (ADHD) into adolescence, little is known regarding use of nonstimulants to treat ADHD in adolescents. This phase 3 trial evaluated the safety and efficacy of guanfacine extended release (GXR) in adolescents with ADHD.

Method: This 13-week, multicenter, randomized, double-blind, placebo-controlled trial evaluated once-daily GXR (1–7 mg per day) in adolescents with ADHD aged 13 to 17 years. The primary endpoint was the change from baseline in the ADHD Rating Scale–IV (ADHD-RS-IV) total score; key secondary endpoints included scores from the Clinical Global Impressions–Severity of Illness (CGI-S), and Learning and School domain and Family domain scores from the Weiss Functional Impairment Rating Scale–Parent Report (WFRS-P) at week 13.

Results: A total of 314 participants were randomized (GXR, n = 157; placebo, n = 157). The majority of participants received optimal doses of 3, 4, 5, or 6 mg (30 [22.9%], 26 [19.8%], 27 [20.6%], or 24 [18.3%] participants, respectively), with 46.5% of participants receiving an optimal dose above the currently approved maximum dose limit of 4 mg. Participants receiving GXR showed improvement in ADHD-RS-IV total score compared with placebo (mean score change, –24.55 [GXR] versus –18.53 [placebo]; effect size, 0.52; P < .001). More participants on GXR also showed significant improvement in CGI-S scores compared with placebo (50.6% versus 36.1%; P = .010).

There was no statistically significant difference between treatments at week 13 in the 2 WFRS-P domains. Most treatment-emergent adverse events were mild to moderate, with sedation-related events reported most commonly.

Conclusion: GXR was associated with statistically significant improvements in ADHD symptoms in adolescents. GXR was well tolerated, with no new safety signals reported.

Clinical Trial Registration Information: Dose-Optimization in Adolescents Aged 13-17 Diagnosed With Attention-Deficit/Hyperactivity Disorder (ADHD) Using Extended-Release Guanfacine HCl; http://ClinicalTrials.gov/; NCT01081132.


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 CGI–Improvement of 1 or 2.

### Before School Functioning Questionnaire (BSFQ)

#### Investigator-Rated Component (6 AM to 9 AM)

**Past Week**

<table>
<thead>
<tr>
<th>Did your child have difficulty with:</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listening (to parents, other caregivers, siblings)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Following Directions (coming to breakfast, getting dressed, picking up necessary things)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Overall Organization (morning routines, getting things together, time awareness)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dressing (putting on shirts, blouses, pants, shoes, coats)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Attention (focusing on morning routines or activities)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Being Quiet (loud, cannot occupy self unless with TV/electronics)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Distraction (easily off task, distracted by objects, noise, others)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Preoccupation (putting and task)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Forgetfulness (memory of specific items; gym clothes, instrument, equipment)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Multitasking/Leaving Items (loose bag, lunch box, school work/paper)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

#### Investigator-Rated Component (continued)

<table>
<thead>
<tr>
<th>Did your child have difficulty with:</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity (excessive motor activity, running around in morning)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Talkativeness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Interrupt/Blurt Out (interrupting/intruding, blurting out before question is completed)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Stuttering (vocal step, stutters, speaking sound)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Waiting Time (at breakfast, in line for bus or ride, bathroom time)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Breakfast (not sitting down to eat, distracted while eating)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hygiene (washing, combing hair, brushing teeth)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Independence (ability to perform tasks by him/herself)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Time Awareness (not using time correctly, taking too long)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Getting to School (missing bus, disruptive car/bus ride, walking to school, tardy)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

### Summary: Reliability and Validity of the BSFQ

- **Reliability**
  - Self-rated BSFQ scores
    - Low internal homogeneity and test-retest reliability
  - Investigator-rated BSFQ scores
    - High internal homogeneity AND good test-retest reliability
- **Validity**
  - Self-rated BSFQ scores
    - Poor concurrent validity, no treatment effects
  - Investigator-rated BSFQ scores
    - Significant concurrent validity, strong treatment effects

**Faraone SV, et al. J Atten Disord. 2015 Jan 9;[Epub ahead of print].**

### Effect of MPH Transdermal Delivery System on Investigator-Rated BSFQ

**Effect of MPH Transdermal Delivery System on Investigator-Rated BSFQ**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>PTS Endpoint</th>
<th>MTS Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><strong>P &lt; .01</strong></td>
<td></td>
</tr>
</tbody>
</table>

**MTS = methylphenidate transdermal system; PTS = placebo transdermal system.**


### Effect of Guanfacine XR on Parent-Rated BSFQ

**Effect of Guanfacine XR on Parent-Rated BSFQ**

**Effect of Guanfacine XR on Parent-Rated BSFQ**

<table>
<thead>
<tr>
<th>GuXr 100 +</th>
<th>Psychostimulant</th>
<th>GuXr 20 +</th>
<th>Psychostimulant</th>
<th>Placebo +</th>
<th>Psychostimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SEM) Parent-Rated BSFQ Score</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

**P < .01 = psychostimulant.**

**Wilens TE, et al. J Atten Disord. 2013 Sep 26;[Epub ahead of print].**

### Combination of Atomoxetine Plus Stimulants in the Treatment of ADHD

- Qualitative analysis of existing studies
- N = 3 prospective (1 RCT) + 7 retrospective reports
- Predominately children/adolescent with inadequate response to stimulants
- Most often used stimulant = MPH
- 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

- Multisite, controlled 9-week trial
- Dosing: 1 to 4 mg daily; mean = 3.2 mg (0.1 mg/kg)
- Inclusion: Stimulant partial responders (> 4 week use with improvement; ADHD-RS-IV > 24 and CIG > 3) ages 6–17 years
- Exclusion: Other psych, CV abnormal, weight < 55 lb or > 176 lb
- Design: 5-week optimization and 3-week dose maintenance period (visits 7–10)
- Primary outcome: ADHD-RS-IV (Investigator)


Combination of Guanfacine XR Plus Stimulants in the Treatment of ADHD

Adverse effects
- Most common adverse effect ≥ sedation/somnolence
- Serious adverse effects—all unrelated to medication: 1) syncope, 2) poison ivy, 3) emotional outbursts
- Cardiovascular indices at endpoint
  - Heart rate: -5.6 bpm
  - Systolic blood pressure: -2.2 mm Hg
  - Diastolic BP: -1.2 mm Hg
  - No ECG abnormal, no QT prolongation


Memantine for ADHD: MGH Open Trial

N = 34 adults (LOCF)
12-week trial
Titrate to 10 mg BID

Memantine is not FDA approved for the treatment of ADHD.
MGH = Massachusetts General Hospital
**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)
  - May be useful for mood symptoms in ADHD (under study)
- Dosing
  - High EPA to DHA or g-linoleic acid (omega-6)
  - Preparations, brands vary dramatically

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

**Adjunct Fish Oils in ADHD: MGH Preliminary Results**

- Meta-analysis of 10 studies; N = 699 children
- Examined EPA, DHA (omega-3), and g-linoleic acid (omega-6)
- < 1000 mg/day
- Preparations, brands vary dramatically

**New Medication Development in ADHD**

**Nighttime Administered MPH for ADHD**

**New ADHD Medications in Development**

Oradur®-Methylphenidate SR
- Mechanism: DAT/NET reuptake inhibitor
- Status: Phase 3 [Orient Pharma, Taiwan]
- Company: Durect
- Description: New technology release converts short-acting oral capsule dosages into sustained-release products
- Oradur® appears to facilitate delivery of MPH while reducing the potential for abuse via non-medically approved modalities of administration (eg, insufflation). [This technology has already been employed for oxycodone into what is known as Remoxy®.]

DAT = dopamine transporter; NET = norepinephrine transporter.
ClinicalTrials.gov Identifier: NCT02450890; NCT02704390.

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New ADHD Medications in Development

**Dasotraline (SEP-225289)**
- **Company:** Sunovion
- **Mechanism:** Triple reuptake inhibitor (Serotonin, DAT/NE)
- **Status:** Phase 2/3
- **Comments:** It appears as though the drug has a significantly greater affinity for the DAT than the SERT. For this reason, researchers suspected that it would likely be better suited for the treatment of attentional deficits than depressive symptoms. It is also suggested that the drug is a potent inhibitor of NET and affects levels of norepinephrine to a greater extent than serotonin.

**Edivoxetine (LY-2216684)**
- **Company:** Eli Lilly
- **Mechanism:** NET inhibitor
- **Status:** Phase 3
- **Edivoxetine** is a drug under development for the treatment of ADHD. The drug had previously undergone clinical trials as an adjunct treatment for depression, ultimately failed to get FDA approval in 2012. The drug functions primarily as a selective NET reuptake inhibitor, increasing extracellular concentrations of norepinephrine. Some reported side effects associated with the drug include headaches, nausea, constipation, dry mouth, and insomnia—all of which are common with other norepinephrine reuptake inhibitors.

**Dasotraline for ADHD in Adults**

*ClinicalTrials.gov Identifier: NCT02428088; NCT02276209; NCT02457819; NCT02734693; NCT01982862. NCT01987082.*

**OBJECTIVE:**
The purpose of this study was to assess the efficacy and safety of dasotraline (SEP-225289), a selective norepinephrine reuptake inhibitor, in pediatric patients with attention-deficit/hyperactivity disorder (ADHD).

**METHOD:**
A fixed-dose, randomized, double-blind, 8-week study was conducted in children 6–11 years of age, who were randomized to one of two treatment groups: 1) Patients with prior stimulant use randomized to placebo, edivoxetine 0.1 mg/kg/day, 0.2 mg/kg/day, or 0.3 mg/kg/day (2:1:1 ratio); 2) Stimulant-naive patients randomized to placebo, edivoxetine 0.1 mg/kg/day, 0.2 mg/kg/day, or 0.3 mg/kg/day, or osmotic-release oral system methylphenidate (CIRP MPH) (18–54 mg/day based on body weight) arms in a 1:1:1:1 ratio. The primary efficacy measure was baseline-to-week 8 change of ADHD Rating Scale (ADHD-RS) total score for edivoxetine 0.2 mg/kg/day and 0.3 mg/kg/day.

**Edivoxetine in ADHD**

Edivoxetine in ADHD

RESULTS: A total of 340 patients were randomized to placebo (n = 78); edivoxetine 0.1 mg/kg/day (n = 78), 0.2 mg/kg/day (n = 77), or 0.3 mg/kg/day (n = 75), or OROS MPH (n = 36). In the stimulant-naïve stratum, the positive control, OROS MPH, was significantly superior to placebo in mean ADHD-RS total score change at endpoint (P = 0.015). The edivoxetine 0.2 mg/kg/day and 0.3 mg/kg/day arms had statistically significantly greater improvement than the placebo arm (P = 0.011). In the overall efficacy-analyses data set (n = 270), the effect size estimates for edivoxetine doses 0.1 mg/kg/day, 0.2 mg/kg/day and 0.3 mg/kg/day at the week 8 time point were 0.17, 0.51, and 0.54, respectively (for the stimulant-naïve stratum, the effect size estimate for OROS MPH was 0.69). Compared with placebo, edivoxetine treatment was associated with statistically significant increases in blood pressure and pulse (P < 0.005), and a smaller increase or slight decrease in weight.

CONCLUSIONS: Edivoxetine at doses of 0.2 mg/kg/day and 0.3 mg/kg/day demonstrated efficacy in ADHD treatment, despite the presence of a sizable placebo response. No unexpected adverse events were identified. Clinical Trial Registry identifier: NCT01243242.

New ADHD Medications in Development

Edivoxetine in ADHD

Mechanism: 5-HT2B selective agonist / GABA modulator
Company: Alcobra
Status: Phase 3
Metadoxine is a drug primarily used to treat alcohol intoxication in Europe, but has also demonstrated efficacy for the treatment of ADHD. The drug is unique to other ADHD medications in that it is comprised of an ion pair salt of GABA and L-prolylguatamate. The drug appears to function as a 5-HT2B selective agonist and has a high affinity for the GABA transporter, thereby preventing GABA degradation. Its mechanism of action is novel in that it doesn’t significantly alter monoamines (serotonin, norepinephrine, and dopamine). It solely acts on the 5-HT2B receptor as an agonist, and modulates GABA.

Edivoxetine in ADHD

Efficacy of Metadoxine Extended Release in Patients with Predominantly Inattentive Subtype Attention-deficit Hyperactivity Disorder.
Manor I, Newcorn JH, Faraone SV, Adler LA.
OBJECTIVES: To compare the effects of metadoxine extended release (ER) with those of placebo on inattentive (IA) versus hyperactive-impulsive (HI) symptoms and predominantly inattentive (PI) versus combined type (CT) subtypes in adults with attention-deficit/hyperactivity disorder (ADHD).
METHODS: This was a 1:1 randomized, double-blind, parallel-design study of metadoxine ER 1400 mg/d for 6 weeks in 120 adults with ADHD. Efficacy measures were baseline to end-of-treatment changes in Conners’ Adult ADHD Rating Scale-Investigator Rated (CAARS-INV) Total ADHD Symptoms scores for patients with ADHD-PI, but not those with ADHD-CT. Test of Variables of Attention ADHD scores, and response rates (≥ 25% or ≥ 45% improvement in CAARS-INV Total ADHD Symptoms scores).

RESULTS: A total of 340 patients were randomized to placebo (n = 78); edivoxetine 0.1 mg/kg/day (n = 78), 0.2 mg/kg/day (n = 77), or 0.3 mg/kg/day (n = 75), or OROS MPH (n = 36). In the stimulant-naïve stratum, the positive control, OROS MPH, was significantly superior to placebo in mean ADHD-RS total score change at endpoint (P = 0.015). The edivoxetine 0.2 mg/kg/day and 0.3 mg/kg/day arms had statistically significantly greater improvement than the placebo arm (P = 0.011). In the overall efficacy-analyses data set (n = 270), the effect size estimates for edivoxetine doses 0.1 mg/kg/day, 0.2 mg/kg/day and 0.3 mg/kg/day at the week 8 time point were 0.17, 0.51, and 0.54, respectively (for the stimulant-naïve stratum, the effect size estimate for OROS MPH was 0.69). Compared with placebo, edivoxetine treatment was associated with statistically significant increases in blood pressure and pulse (P < 0.005), and a smaller increase or slight decrease in weight.

CONCLUSIONS: Edivoxetine at doses of 0.2 mg/kg/day and 0.3 mg/kg/day demonstrated efficacy in ADHD treatment, despite the presence of a sizable placebo response. No unexpected adverse events were identified. Clinical Trial Registry identifier: NCT01243242.

New ADHD Medications in Development

Metadoxine in ADHD (Adults)

Figure 2. Efficacy of Metadoxine ER vs Placebo Change From Baseline in CAARS-INV Total ADHD Symptoms Scores

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Edivoxetine in ADHD

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SAN DIEGO -- October 27, 2014 --
Metadoxine extended release (ER) produced positive but not statistically significant effects on ADHD symptoms in adult patients, according to results of a phase 3, modified intention-to-treat (ITT) trial presented at the 61st Annual Meeting of the American Academy of Child and Adolescent Psychiatry (AACAP).

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**Open Trial of Centanafadine SR in Adults with ADHD**

<table>
<thead>
<tr>
<th>Week</th>
<th>Total Score Over Total Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45.1</td>
</tr>
<tr>
<td>2</td>
<td>41.2</td>
</tr>
<tr>
<td>3</td>
<td>37.3</td>
</tr>
<tr>
<td>4</td>
<td>33.4</td>
</tr>
<tr>
<td>5</td>
<td>29.5</td>
</tr>
<tr>
<td>6</td>
<td>25.6</td>
</tr>
<tr>
<td>7</td>
<td>21.7</td>
</tr>
</tbody>
</table>

---

**Clinical Scales of Executive Functioning (BRIEF-A) with Centanafadine**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit Shift Emotional Control</td>
<td>60</td>
<td>50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Self-Monitoring</td>
<td>50</td>
<td>40</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Initiate Working Memory</td>
<td>60</td>
<td>50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Plan/Organize Task</td>
<td>60</td>
<td>50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Monitor Organization of Materials</td>
<td>60</td>
<td>50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Behavioral Regulation</td>
<td>60</td>
<td>50</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Metacognition</td>
<td>60</td>
<td>50</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

---

**Most Common Adverse Events Defined as ≥ 5% (≥ 2)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Patients (N = 41)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>12*</td>
<td>29%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>7</td>
<td>17%</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>17%</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>6</td>
<td>15%</td>
</tr>
<tr>
<td>Dryness</td>
<td>4</td>
<td>10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Middle Insomnia</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>7%</td>
</tr>
</tbody>
</table>

*2 on placebo; 7 mild; 3 moderate; no patients discontinued due to diarrhea.

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**New ADHD Medications in Development**

**Centanafadine**
- **Mechanism:** DAT > NET > 5-HT uptake inhibitor (triamine)
- **Company:** Neurovance Bioscience
- **Status:** Phase 2

- The drug functions primarily as a DAT/NB/5-HT reuptake inhibitor and is being examined for core ADHD, comorbid ADHD, and executive functioning issues.

**AR-08**
- **Mechanism:** Adrenergic receptor agonist
- **Company:** Arbor Pharmaceuticals
- **Status:** Phase 2

- AR-08 is a drug under development for the treatment of ADHD among children and adolescents (between ages 6 and 17 years). While its exact mechanism of action hasn’t been made publicly available, it is known that AR-08 functions as an adrenergic receptor agonist. In other words, it stimulates specific receptors of norepinephrine, leading to increased psychomotor activation.

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**New ADHD Medications in Development**

New ADHD Medications in Development

Eltoprazine
- **Mechanism:** 5-HT<sub>1A/1B</sub> partial agonist
- **Company:** Amarantus Bioscience
- **Status:** Phase 2

Eltoprazine is a drug that was originally developed as an anti-aggressive agent. It is classified as a phenylpiperazine drug and was intended to be used as a serenic agent, attenuating aggressive behaviors and impulses.

- The drug functions primarily as a 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> partial agonist, but acts as a 5-HT<sub>2C</sub> receptor antagonist. It is primarily under investigation for the treatment of levodopa-induced dyskinesia as a result of Parkinson's disease, but is also in Phase 2 clinical trials for the treatment of adult ADHD. Thus far, the drug is considered safe, well-tolerated, and has been tested in nearly 700 humans.

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New ADHD Medications in Development

SPN-810 (Molindone HCl)
- **Mechanism:** Indole-derivative; D<sub>2</sub> receptor selective antagonist
- **Company:** Supernus Pharmaceuticals
- **Status:** Phase 3

Supernus Pharmaceuticals has taken the typical antipsychotic molindone and repackaged it as chemical “SPN-810.” It is being tested (in Phase 3 clinical trials) for the specific treatment of “impulsive aggression” associated with ADHD. It is not anticipated that SPN-810 would be first-line; however, it would be used as an adjunct for impulsive aggression. This agent may be helpful for conduct +ADHD. It is thought to function primarily as a selective D<sub>2</sub> receptor antagonist to minimize aggression, hyperactivity, and psychotic symptoms. It also has a moderate affinity for cholinergic and adrenergic receptors, with a low affinity for D<sub>1</sub> receptors.

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Experimental Pharmaceuticals*

- **Not Generally Demonstrated Efficacious for ADHD**
  - NET/DAT uptake inhibitor (ClinicalTrials.gov Identifier: NCT01458340)
  - Ampakines-mixed (Adler L, et al. APSARD. 2011)

*Not FDA approved for ADHD.

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Summary

- Many existing medications and/or medication combinations that are FDA approved; and non-FDA approved for ADHD
- New stimulant preparations are now available and being developed for ADHD
- Nonstimulant medications continue to be developed with catecholamine and indoleamine reuptake inhibition as a general profile; though derivatives of older class agents are also being tested
- Stay tuned—newer treatments may assist in the management of non-responsive or partially responsive ADHD