## Disclosure: J Newcorn (Past 12 Months)

<table>
<thead>
<tr>
<th>Source</th>
<th>Consultant</th>
<th>Advisory Board</th>
<th>Speaker (Disease State)</th>
<th>Research Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippo T&amp;C</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ironshore</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumos</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medice</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MindTension</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NFL</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OnDosis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otsuka</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Supernus</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional research support provided by NIDA and NICHD
In the past 24 months, relationships with Adlon, Rhodes, Shire/Takeda, Corium, and Myriad have ended.
Educational Objective

Examine the efficacy, safety, formulation, and pharmacokinetics of new and novel drug delivery systems for ADHD management
# ADHD Medications Worldwide

(approved and investigational)

## Stimulants

### Methylphenidate

<table>
<thead>
<tr>
<th>Short Acting</th>
<th>Intermediate</th>
<th>Long Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin ‡</td>
<td>Ritalin SR ‡</td>
<td>Concerta ‡</td>
</tr>
<tr>
<td>Focalin *</td>
<td>Metadate ER ‡</td>
<td>Metadate CD ‡</td>
</tr>
<tr>
<td></td>
<td>Ritalin LA ‡; Focalin XR ‡</td>
<td>Daytrana (patch) ‡;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aptensio XR ‡; Adhansia XR ‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jornay PM ‡, Azstarys ‡</td>
</tr>
</tbody>
</table>

### Amphetamine

<table>
<thead>
<tr>
<th>Short Acting</th>
<th>Intermediate</th>
<th>Long Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrostat †</td>
<td>Dextedrine</td>
<td>Adderall XR ‡</td>
</tr>
<tr>
<td>Spansule †</td>
<td>Adderall ‡</td>
<td>Vyvanse ‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(tablets/chewable)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adzenys (ODT) ‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyanavel (liquid and tablet formulations) ‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mydayis ‡, Xelstrym ‡</td>
</tr>
</tbody>
</table>

## Non-Stimulant

### Approved

- Strattera †
- Qelbree ‡
- Intuniv ‡
- Kapvay *

### Not Approved

- TCAs §
- Provigil **
- Wellbutrin, Zyban ††
- Tenex ‡
- Catapres ‡
- Effexor/Pristiq ‡
- Duloxetine/Rexebetine

## Investigational Drugs

- Novel stimulant formulations (including tamper resistant)
- Centanafadine (Dasotraline)
- (Fasoracetam)
- (Mazindol)
- Misc. early phase

---

*N: Not all drugs and/or formulations available in all countries

**FDA approved in children/adolescents only

---

Emerging or relatively new to market:
- d,l-methylphenidate
- dextroamphetamine
- dextroamphetamine sulfate
- racemic amphetamine
- atomoxetine
- viloxazine ER
- tricyclic antidepressants (many brands)
- modafinil
- bupropion
- guanfacine
- clonidine
- venlafaxine

---

*Not all drugs and/or formulations available in all countries

**FDA approved in children/adolescents only
Rationale for New Medication Development in ADHD: Stimulants*

Stimulants are extremely effective, but:

○ Poor response or tolerability in some patients
  ■ Sub-optimal response is not uncommon, especially if AEs limit dose
  ■ Tolerability issues can limit higher dose treatment
  ■ Approval issues (insurance; pharmacy) can limit ability to prescribe higher doses

○ Time-action characteristics are problematic, even in responders

○ Relative or labeled contraindications for some comorbid conditions (e.g., tics, anxiety, substance abuse, ASD)

○ Some patients will not take stimulants; some doctors won’t prescribe them

○ Misuse, diversion and/or abuse of stimulants are more common and problematic than we would like to think (DEA schedule II drugs)

* Items in red text are addressed by investigational stimulant formulations
Ironshore Pharmaceuticals

Uniform, dual-layered microbeads with an inner drug-loaded core

Colonic absorption delays the initial release of drug by 8-10 hours

Onset of effect upon awakening that lasts into the evening

Dose: 20 – 100 mg

Side effects: Similar to other stimulants; no additional sleep or appetite problems
Delayed-release/extended-release MPH (Jornay PM): Pharmacokinetic (pK) Characteristics

Delayed-release/extended-release MPH (Jornay PM): Parent Rating of Evening and Morning Behavior (PREMB-R)* AM and PM

**PREMB-R**: 11-item clinician-rated scale based on a parent interview that assesses at-home functioning (i.e., behaviors that impact activities of daily living, such as getting up and out of bed, doing or completing homework, and falling asleep) during the early morning (PREMB-R AM – 3 items) and late afternoon/evening (PREMB-R PM – 8 items)

Dexmethylphenidate - Ser-dexmethylphenidate (Azstarys)

- Corium (developed by KemPharm)
- Ser-dexmethylphenidate is a prodrug of dexmethylphenidate
- 30% d-MPH and 70% S-d-MPH
- Rapid onset (30 minutes); extended duration
- Little to no likability for S-d-MPH
- **Dose:** 26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg (equivalent to 20, 30 and 40 mg d-MPH-XR)
- Clinical trials began with the middle dose
- **Side effects:** Similar to other stimulants
Dexmethylphenidate - Ser-dexmethylphenidate (Azstarys): Drug Liking Following Oral Administration*

SDX Cl: serdexmethylphenidate chloride
d-MPH HCl: d-methylphenidate hydrochloride

Subjects responded to the question: “At this moment, my liking for the drug is?”: 0 = strong disliking, 50 = neither like nor dislike, and 100 = strong liking

† significantly higher vs placebo by >15 points (p<0.0001)
‡ significantly higher vs. SDX, 120 mg by >10 points (p<0.05)
§ significantly higher vs. SDX, 240 mg by >10 points (p=0.006)

*Human abuse potential studies were conducted with single-entity SDX only

Dexmethylphenidate - Ser-dexmethylphenidate (Azstarys): Drug Liking Following Intranasal and Intravenous Administration

Subjects responded to the question: “At this moment, my liking for the drug is?”: 0=strong disliking, 50=neither like nor dislike, and 100=strong liking

SDX Cl: serdexmethylphenidate chloride
d-MPH HCl: d-methylphenidate hydrochloride

Ser-d-MPH received a Schedule IV designation from the DEA

D-AMP Transdermal System (d-ATS) (d-AMP patch)

- **Noven Pharmaceuticals**
- **Absorption through the skin** – bypasses GI system
- **Dose**: 4.5 – 18 mg
- **Four patch strengths**: 4.5 (child starting dose), 9 (adult starting dose), 13.5, 18 mg
- **Onset of effects**: ~2 hours; offset: ~3+
- **Patch wear time**: 9 hours; duration 12+ in trial (variable wear time is possible)
- **Side effects**: Similar to other stimulants; also - rash at application site (alternate hips when placing the patch)
D-ATS Child and Adolescent Phase 2 Study: SKAMP Scores Over Time (Primary Outcome)

See source Figure 3 for original image: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8972004/
D-ATS Child and Adolescent Phase 2 Study: PERMP Scores Over Time (Secondary Outcome)

- Children 6-17 years (n=110; 106 completers)
- 2 week randomized, cross-over double blind treatment (1 week per condition)
- Outcome measures: SKAMP vs Placebo (primary); SKAMP duration; PERMP.
- SKAMP and PERMP significantly different than placebo
- SKAMP duration ~12 hours (back to 90% of baseline)

See source Figure 4 for original image: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8972004/
AMP- ER Tablets (Dyanavel-ER)

- **Tris Pharmaceuticals**
- **Racemic amphetamine, formulated to mimic Adderall XR**
- **Ratio: 3.2/1 (d-AMP/l-AMP)**
- **Tablet formulation based on and bioequivalent to Dyanavel suspension**
- **30 minute onset of action; extended duration of effects**
- **Dose: 2.5 – 20 mg daily (scored 5 mg tablets)**
- **Side effects: Similar to other stimulants**
Bioequivalence of AMPH – EROS and ER-MAS

Bioequivalence of AMPH – EROS and AMP-ER tablets

## New Stimulants in Development: Alternative Delivery Options

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Structure / Formulation</th>
<th>Indication</th>
<th>Stage of development</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>KP484</td>
<td>KemPharm</td>
<td>d-MPH&lt;sup&gt;1&lt;/sup&gt; ER&lt;sup&gt;2&lt;/sup&gt; prodrug capsule serdexamethylphenidate</td>
<td>Adult ADHD&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Phase I</td>
<td>NE&lt;sup&gt;4&lt;/sup&gt;-DA&lt;sup&gt;5&lt;/sup&gt; reuptake inhibitor</td>
</tr>
<tr>
<td>CTx-1301</td>
<td>Cingulate</td>
<td>Triple-release (IR &amp; ER) formulation of d-MPH tablet</td>
<td>ADHD</td>
<td>Phase II (end)</td>
<td>NE-DA reuptake inhibitor</td>
</tr>
<tr>
<td>HLD-100</td>
<td>Ironshore Pharmaceuticals</td>
<td>Delayed release and ER capsule formulation of d-AMPH</td>
<td>ADHD</td>
<td>Phase II</td>
<td>NE-DA reuptake inhibitor, causes monoamine release from synaptosomes</td>
</tr>
<tr>
<td>CTx-1302</td>
<td>Cingulate</td>
<td>Triple-release IR &amp; ER formulation of d-AMPH tablet</td>
<td>ADHD</td>
<td>Phase I</td>
<td>NE-DA reuptake inhibitor, causes monoamine release from synaptosomes</td>
</tr>
<tr>
<td>KP922</td>
<td>KemPharm</td>
<td>IR &amp; ER AMPH prodrug</td>
<td>ADHD</td>
<td>Preclinical</td>
<td>NE-DA reuptake inhibitor, causes monoamine release from synaptosomes</td>
</tr>
<tr>
<td>TAH9901</td>
<td>TAHO</td>
<td>MPH transdermal patch</td>
<td>ADHD</td>
<td>Phase I</td>
<td>NE-DA reuptake inhibitor</td>
</tr>
</tbody>
</table>
## New Stimulants in Development: Abuse Deterrent or Tamper Resistant Formulations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Structure / Formulation</th>
<th>Indication</th>
<th>Stage of development</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORADUR - MPH ER</strong></td>
<td>Durect</td>
<td>Abuse deterrent MPH ER capsule</td>
<td>ADHD</td>
<td>Approved in Taiwan only</td>
<td>NE-DA reuptake inhibitor</td>
</tr>
<tr>
<td><strong>AR19</strong></td>
<td>Arbor Pharmaceuticals</td>
<td>AMPH IR abuse-deterrent capsule</td>
<td>ADHD</td>
<td>Phase III (recently withdrawn)</td>
<td>NE-DA reuptake inhibitor, causes monoamine release from synaptosomes</td>
</tr>
<tr>
<td><strong>ADAIR</strong></td>
<td>Vallon Pharmaceuticals</td>
<td>APMH IR abuse deterrent capsule</td>
<td>ADHD</td>
<td>Phase I</td>
<td>NE-DA reuptake inhibitor, causes monoamine release from synaptosomes</td>
</tr>
<tr>
<td><strong>PF8001 / PF8026</strong></td>
<td>Ensysce Biosciences</td>
<td>IR and ER abuse resistant AMPH prodrugs</td>
<td>ADHD</td>
<td>Preclinical</td>
<td>NE-DA reuptake inhibitor, causes monoamine release from synaptosomes</td>
</tr>
<tr>
<td><strong>AFI-0002</strong></td>
<td>Altus Formulations</td>
<td>ER abuse deterrent stimulant--drug unknown</td>
<td>ADHD</td>
<td>Unknown</td>
<td>Drug not known</td>
</tr>
</tbody>
</table>
## New Stimulants in Development: Combination Products

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Structure / Formulation</th>
<th>Indication</th>
<th>Stage of development</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATT-377</td>
<td>Attentive Therapeutics</td>
<td>MPH + cyproheptadine</td>
<td>ADHD</td>
<td>Phase II</td>
<td>NE-DA reuptake inhibitor + antihistamine</td>
</tr>
<tr>
<td>AVK-001</td>
<td>Avekshan</td>
<td>MPH + naltrexone</td>
<td>ADHD &amp; substance use disorder</td>
<td>Unknown</td>
<td>NE-DA reuptake inhibitor + opioid antagonist</td>
</tr>
</tbody>
</table>
Rationale for New Medication Development in ADHD: Non-stimulants

- Current non-stimulants have substantial limitations
  - Smaller effect sizes than for
    - Large number of non-responders to atomoxetine (ATX)
    - Possibly true for alpha-2 agonists too, but no data
  - Alpha-2 ($\alpha_2$) agonists are somewhat better for H/I than IA
    - Often used in combination with stimulants in children
    - Often not ideal for monotherapy in adults
  - Both non-stimulant classes are less effective in adults, and have limitations on their use
    - Alpha-2 agonists are not FDA-approved in adults
  - Both classes can take a fairly long time to show full effects
Opportunities for Non-Stimulant Treatment of ADHD

- Preferential response or tolerability in selected individuals
  - Presumably linked to novel MOA

- Improve temporal characteristics
  - Need for sustained activity across the full day and into the evening, without adversely affecting sleep

- Treatment of ADHD + comorbidity
  - Stimulants have relative labeled contraindications for anxiety, tic and substance use disorders
  - Non-stimulants are known to be effective for anxiety and tics, and should not make SUD worse (not contraindicated)
  - Opportunity to also treat ADHD + depression

- Combination treatment with stimulants could potentially improve response and/or lower the required stimulant dose
Fate of Recent Investigational Non-stimulant Drugs for ADHD

- **Several novel non-stimulants have not separated from placebo in Phase III (or later) trials**
  - Nicotinic agonists
  - H₃ antagonists or inverse agonist
  - Metadoxine – Pyridoxine + L-PGA – 5-HT₂B agonist/GABA modulator
  - Edivoxatine – Selective NE Reuptake inhibitor
  - Trintellix – SNRI; 5-HT₁A/₁B agonist
  - Ampakines – AMPA receptor (glutamate) modulators
  - Fascoracetam – Metabotropic glutamate agonist; also increases ACh and GABA
  - Molindone – Potent D2 and 5-HT2B antagonist

- **Several others failed due to side effects**
  - Long-acting modafinil (Sparlon), an atypical C4 stimulant with orexin agonist activity, was effective - but failed due to skin rash
  - Dasotraline- DA + NE reuptake inhibitor; Submitted to FDA in 2018 but not approved

- **Why have novel non-stimulants all failed?**
  - Complexities of negotiating Phase III
    - Increasing placebo response in trials; lower ES for non-stimulants
  - (?) Inadequate impact on catecholamine neurotransmission
Viloxazine (SPN 812)

- **Supernus Pharmaceuticals**
- **Mechanism**: Norepinephrine reuptake inhibitor and post-synaptic 5-HT agonist
- **Status**: Approved by FDA in November, 2020
- Re-purposed antidepressant; previously approved in UK/EU
- Strong CYP1A2 inhibitor; weak CY2D6 and CYP3A4 inhibitor
- **Dose**: Youth 100-400 mg; Adults 200-600 mg
- **Side effects**: (13-35%): somnolence, fatigue, headaches, decreased appetite and nausea
Viloxazine: Proposed Mechanism of Action in ADHD

Viloxazine: Pediatric Phase 3 Study

Viloxazine: Adult Phase 3 Study

- Adults 18 – 65 years old (n = 374)
- Flexible dose 200 – 600 mg (Mean dose: 504 mg)
- Significant group differences on: AISRS total and subscales, CGI-S and CGI-I, BRIEF-A GEC and Metacognition Index.
- Profile of responders and non-responders consistent with other non-stimulants
- Adverse events > 5% and significantly different from placebo: insomnia, fatigue, nausea, decreased appetite, dry mouth, headache, and constipation

Predicting Viloxazine ER Response at 6 Weeks from Response at Week 2 or 3

- Machine learning model conducted in pre-marketing studies of Viloxazine ER
- \( N = 1397 \) children/adolescents (ages 6-17)
- Variables used: ADHD-RS-5 Total score, age, body weight, and body mass index at baseline; CFB ADHD-RS-5 Total score at Week 1, cumulative change in ADHD-RS-5 Total score at Week 2, and cumulative change in ADHD-RS-5 Total score at Week 3; Clinical Global Impressions-Improvement (CGI-I) score at Week 1, 2, and 3; and target dose
- Best predictors: ADHD-RS-5 Total score and CGI-I
- PPP, sensitivity and specificity for ADHD-RS-5 Total score at 2 weeks were each ~75%

Selected Investigational Non-stimulant Drugs*

- **Centanafadine**
  - Repurposed anti-psychotic
  - Mechanism: triple reuptake inhibitor (SDN-RI) - ratio of 14:6:1 respectively
  - Status: Completed Phase III adult; Phase III child study nearly completed
  - Side Effects (18-24%): decreased appetite, headaches, nausea, diarrhea, rash (uncertain significance)

- **Sunosi**
  - Dopamine and norepinephrine reuptake inhibitor
  - Approved for treatment of excessive daytime sleepiness in association with narcolepsy and obstructive sleep apnea.
  - Mechanism through which it promotes alertness is not entirely known
  - Does not bind to dopamine, serotonin, norepinephrine, GABA, adenosine, histamine, orexin, benzodiazepines, or muscarinic and nicotinic receptors
  - Schedule IV designation from DEA
  - Positive results in Phase 2a; Phase 2b study is starting soon

- **Mazindol**
  - Atypical stimulant; triple reuptake inhibitor + orexin 2a partial agonist
  - Previously approved for appetite suppression; used off-label in narcolepsy
  - Large ES in Phase II (comparable to AMP), but with previous Schedule IV designation in US

*potential advantages indicated in italics
Emerging and Investigational Devices for ADHD

- **Monarch e-TNS (Trigeminal Nerve Stimulation) system**
  - Used in Europe/Canada for depression; cleared by FDA for ADHD (4/19)
    - Patch worn at night across the forehead delivers electrical signal to deep brain areas associated with concentration and impulse control

- **Video game technology** (1 product cleared by FDA; others being developed)
  - **AKL-T01 (Akili Interactive)**
    - Deploys interference-based cognitive control-targeting mechanics
    - Currently “cleared” by FDA – emergency approval; to distribute
  - **ATENTIVmynd (ATENTIV)**
    - Video game technology + QEEG measurement
    - Currently no published data

- **OYSTA Dosage Manager**
  - Holds and dispenses stimulant medication formulated as pellets
  - Pre-programmed to comply with medical prescription
  - Tamper resistant
  - Electronic dosing diary
Endeavor Rx (Akili): Video Game System for Pediatric ADHD

Monarch eTNS: Trigeminal Nerve Stimulation in Children with ADHD

See source Figure 1 for original image: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6481187/

ES of 0.5 at 4 weeks
Conclusions

- Currently approved medications for ADHD are highly effective, but there are still significant unmet needs
  - Time-action effects of stimulants remain problematic, and are a target for new formulations
  - Need for non-stimulant drugs with efficacy comparable to stimulants is a priority, but has been difficult to achieve
  - Safety/tolerability issues and poor adherence to existing treatments represent opportunities for new drug development

- New and emerging drugs and devices for ADHD address unmet needs and offer new therapeutic options
  - Stimulants: Jornay PM, Azstarys, Dyanavel tablet, Xelstrym
  - Non-stimulants: Viloxazine ER
  - Devices: Endeavor Rx; Monarch eTNS

- Several pipeline drugs/devices are in Phase III
  - Centanafadine
  - Several stimulant formulations
The Patient Perspective

Q&A with Keynote Dani Donovan
Audience Q&A
Posttest Survey