Pharmacotherapy of ADHD with Non-Stimulants

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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
  (Adler, Spencer, Wilens; ADHD in Adults and Children, Cambridge Press 2016)
Previous MPH Exposure Influences Outcomes
(Huss et al., Neuropsychiatric Disease Tx, 2016: 12; 1085-1101)

Mean change from baseline in ADHD-RS-IV total score by treatment for prior MPH or stimulant-naïve 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.
Norepinephrine Frontal

- Alpha 2 receptor

- Attention
- Concentration
- Other cognitive functions

Arnsten et al. Arch Gen Psychiatry 1996:53:448
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
Atomoxetine in Adults with ADHD and Social Anxiety Disorder

Design
• Double blind, placebo controlled study
• Adults with DSM IV ADHD and Social Anxiety Disorder (SAD)
• Dosing of atomoxetine of up to 100 mg/day
• 2 week placebo washout followed by 14 week trial

Results (versus placebo)
• Significant effect on ADHD (2 scales)
• Significant effect on Anxiety (3 scales)
• Week to week improvement
• Side effects: predictable ATX effects

Conclusions: Atomoxetine effective for ADHD and Social Anxiety Disorder in adults

(Adler et al, Depress Anxiety. 2009;26(3):212-21)
Comparative Efficacy: Nonstimulants

Matching-adjusted indirect change from baseline in ADHD RS IV at LOCF: six-trial sensitivity analysis. *p < 0.05 compared with ATX. **p < 0.01 compared with ATX

FIGURE 3 Mean Attention-Deficit/Hyperactivity Disorder Rating Scale—IV (ADHD-RS-IV) total score from baseline to week 5 using a last observation carried forward (LOCF) method. Note: ADHD-RS-IV total score was significantly improved at week 1 for the CLON-XR 0.2-mg/day group. Significant improvement was achieved in both CLON-XR groups beginning at week 2 and continued through study termination. Error bars represent standard deviations. CLON-XR= clonidine hydrochloride extended-release tablets; a \( p = .0219 \) for CLON-XR 0.2 mg/day. b \( p < .0001 \) for both groups. c \( p < .0003 \) for both groups. d \( p = .0005 \) for both groups. e \( p < .0054 \) for both groups. f \( p < .0074 \) for both groups. g \( p \leq .0288 \) for both groups.
Guanfacine Extended-Release in ADHD
(N=324 [51 sites]; 6 weeks active*, Mean Age 11±3 yrs)

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

Effect size: 0.41-0.89

Extended-release Guanfacine Efficacy with AM or PM Administration
(6-12 years, dosing 1-4 mg/day; Samples size of GXR AM (107), GXR PM (114), or placebo (112))
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.

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

Results: A total of 314 subjects were randomized (GXR, n = 157; placebo, n = 157).

Subjects receiving GXR showed improvement in ADHD-RS-IV total score compared with placebo ($P < 0.001$; least squares mean score change, $-24.55$ [GXR] vs $-18.53$ [placebo]; effect size, 0.52). More subjects on GXR also showed significant improvement in CGI-S scores compared with placebo. There was no statistically significant difference between treatments at Week 13 on the 2 WFIRS-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.

Figure 2.

Guanfacine XR in Adolescent ADHD

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>GXR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>147 (93.6)</td>
<td>120 (77.4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>69 (43.9)</td>
<td>33 (21.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>42 (26.8)</td>
<td>28 (18.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35 (22.3)</td>
<td>19 (12.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25 (15.9)</td>
<td>16 (10.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>23 (14.6)</td>
<td>21 (13.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (12.1)</td>
<td>21 (13.5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18 (11.5)</td>
<td>9 (5.8)</td>
</tr>
<tr>
<td>Sedation</td>
<td>18 (11.5)</td>
<td>3 (1.9)</td>
</tr>
</tbody>
</table>

Includes biracial, more than 1 race, Ethiopian and unknown.

Table 2. Summary of TEAEs (≥10% of Subjects; Safety Population)

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

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)
Combination of Clonidine XR plus Stimulants in the Treatment Of ADHD

- Study of clonidine XR coadministration to partial responders on stimulants (≥ADHD RS 26 score)
- N= 197
- Dosing to 0.4 mg daily (in 0.2 mg BID dosing)
- Duration: 5 weeks (then taper)

Figure 4. Change Scores for ADHDRS-IV – Study 2

Statistically significant differences favoring the CLON groups also were observed for the following secondary endpoints: ADHD-RS-IV Inattention subscale, ADHD-RS-IV Hyperactivity/Impulsivity subscale, CPRS-L, CGI, and PGA. No statistically significant differences were observed for the HADS or SSR-CF scale.

(N=197)

(Kollins et al. Pediatrics epub 2011)
Combined (COMB) stimulant and guanfacine for ADHD: Comparative Study
(McCracken et al, JAACAP, 2016 doi 10.1016/j.jaac.2016.06.015)

8 week, RCT, 3-arm trial in 207 participants of 7-14 year olds treated with IR guanfacine (1-3 mg/day), IR d-MPH 5-20 mg/day, or the combination (COMB) with fixed flexible dosing (e.g. using CGI to guide dosing).

Response rate (CGI-I + ADHD RS IV): 62% (guan), 63% (D-MPH), 75% (COMB)
Guanfacine XR plus Stimulants in the Treatment Of ADHD (N=455)


Figure 1. GXR AM 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 0.377.
Endpoint is the last valid assessment obtained after baseline and before dose taper.

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 0.647.
Endpoint is the last valid assessment obtained after baseline and before dose taper.
Bupropion

- Effective in children with ADHD
  - N= 3 studies (104 subjects)
- Effective in adults with ADHD
  - N= 5 controlled studies (including multisite)
- Effect size ca 0.5 (lower than stimulants)
- Use in ADHD plus mood, cigarette smoking, adjunct with stimulants
# Bupropion versus Methylphenidate: Analyses

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Sample size (years)</th>
<th>Study duration (weeks)</th>
<th>Drug/dose</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrickman et al. (1995)</td>
<td>Double-blind, crossover, randomized controlled trial</td>
<td>18</td>
<td>7 to 17</td>
<td>16</td>
<td>Bupropion IR 50–200mg/day, flexible dose titration, Methylphenidate 20–60mg/day, flexible dose titration</td>
</tr>
<tr>
<td>Connors et al. (1996)</td>
<td>Multisite, double-blind, placebo-controlled trial</td>
<td>109</td>
<td>6 to 12</td>
<td>6</td>
<td>Bupropion IR 150–250 mg/day, flexible dose titration, Placebo</td>
</tr>
<tr>
<td>Daviss et al. (2001)</td>
<td>Single-blind, placebo lead-in</td>
<td>24</td>
<td>11 to 16</td>
<td>8</td>
<td>Bupropion SR 100–150mg/day, flexible dose titration</td>
</tr>
<tr>
<td>Jafarinia et al. (2012)</td>
<td>Double-blind, parallel-group, randomized controlled trial</td>
<td>44</td>
<td>6 to 17</td>
<td>6</td>
<td>Bupropion NS 100–150mg/day, fixed dose titration, Methylphenidate 20–30mg/day, fixed dose titration</td>
</tr>
<tr>
<td>Kuperman et al. (2001)</td>
<td>Single-blind, 7-day placebo lead-in, randomized controlled trial</td>
<td>30</td>
<td>18 to 60</td>
<td>8</td>
<td>Bupropion SR 100–300mg/day, flexible dose titration, Methylphenidate 0.9mg/ (kg·day), flexible dose titration</td>
</tr>
<tr>
<td>Riggs et al. (1998)</td>
<td>Open-label trial</td>
<td>13</td>
<td>14 to 17</td>
<td>5</td>
<td>Bupropion NS 100–300mg/day, flexible dose titration</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder; CGI, clinical global impressions; IR, immediate release formulation; NS, formulation not specified; SR, sustained release formulation.
Tricyclic Antidepressants in ADHD

- Effective in children with ADHD
  - Use as monotherapy and adjunctly
  - Trials predominately of imipramine, desipramine, 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
• Effective in child but not adult studies (ADHD)
• Weak stimulant effects (Spencer et al)
• Stimulant or nonstimulant non or 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 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)

Combination of Atomoxetine plus Stimulants in the Treatment Of ADHD

- Qualitative analysis of existing studies
- N= 3 prospective (1RCT)+ 7 retrospective reports
- Predominately children/adolescent 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".

Memantine for ADHD: MGH Open Trial
AISRS Total

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

Omega-3/Omega-6 Fatty Acids for ADHD

- **Metanalysis 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 (adjunct with ADHD medications)

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

Wozniak et al. Eur Neuropsychopharmacol. 2007 Jan 25 (epub)
**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.
Experimental pharmaceuticals

- Effectiveness/efficacy demonstrated*
  - Evidoxetine (Lin et al. J Child Adolesc Psy 2014)
  - Dasatroline (2 adult RCT positive; Neuropsychopharm. 2015 Nov;40(12):2745-527.
  - Centanafadine (Wilens et al. ASCP, 2014)
  - Molindone (impul/ADHD; child and adults, Britain et al, Neurol 2016)
  - New stimulant preparations (multiple)

*Not FDA approved for ADHD
Summary: Non-Stimulant Pharmacotherapy of ADHD

- A number of non-stimulant medications for ADHD
- Often somewhat lower effect size than stimulants
- A variety of effective drugs
  - Noradrenergic agents (ATMX) -(FDA Approved)
  - Alpha agonists - FDA approved
  - Antidepressants /arousal agents -second line
- Often delayed onset-of action for ADHD
- Useful in comorbidity
- FDA approval on co-administration with stimulants
- Multiple ‘pipeline’ nonstimulants in development
QUESTIONS?