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 endpoint.

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.
Safety and Tolerability of Atomoxetine Over 3 to 4 Years in Children and Adolescents With ADHD.

DONELLEY, CRAIG, BANGS, MARK, TRZEPACZ, PAULA, JIN, LING, ZHANG, SHUYU, WITTE, MICHAEL, BALL, SUSAN, SPENCER, THOMAS

Objective: To assess the long-term safety and tolerability of atomoxetine hydrochloride in children and adolescents with attention-deficit/hyperactivity disorder treated for $\geq 3$ years. Method: Data from 13 double-blind, placebo-controlled trials and 3 open-label extension studies were pooled. Outcome measures were patient-reported treatment-emergent adverse events (AEs); discontinuations due to AEs, serious AEs, and changes in body weight, height, vital signs, electrocardiogram, and hepatic function tests. Results: In total, 714 patients were treated with atomoxetine for $\geq 3$ years (mean follow-up 4.8 years [SD 1.1 years]), including a subset of 508 treated for $\geq 4$ years (mean follow-up 5.3 years [SD 0.8 years]). Most subjects were younger than 12 years at entry (73.8%), male (78.4%), and white (88.9%). The mean final daily dose of atomoxetine was 1.35 mg/kg (SD 0.37 mg/kg). No new or unexpected AEs were observed compared with acute-phase treatment. Less than 6% of patients exhibited aggressive/hostile behaviors, and less than 1.6% reported suicidal ideation/behavior. No clinically significant effects were seen on growth rate, vital signs, or electrocardiographic parameters, and $\leq 2\%$ of patients showed potentially clinically significant hepatic changes. Conclusion: Atomoxetine was safe and well tolerated for children and adolescents with $\geq 3$ and/or $\geq 4$ years of treatment.
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 for Youth with ADHD & Anxiety

<table>
<thead>
<tr>
<th></th>
<th>ADHD RS</th>
<th>Anxiety (PARS)</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Baseline</td>
<td>33.9 (8.9)</td>
<td>17.5 (3.0)</td>
</tr>
<tr>
<td>Mean Change from Baseline</td>
<td><strong>effect size = 0.5</strong></td>
<td><strong>effect size = 0.5</strong></td>
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</tbody>
</table>

Atomoxetine for Youth with ADHD & Anxiety

- Dose of ATMX = 1.26 mg/kg/day (Geller et al. JAACAP 2007)

Effect sizes:
- ADHD RS: **effect size = 0.5**
- Anxiety (PARS): **effect size = 0.5**

Statistical significance:
- * p<.001
- ** p=.011

(Geller et al. JAACAP 2007)
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

The Ventromedial Prefrontal Cortex (PFC): Emotional Regulation

Ventromedial PFC is thought to regulate emotion\textsuperscript{1–3}

Impairment may lead to aggressive and oppositional behavior

Alpha Agonists: Clonidine & Guanfacine

- Alpha agonist agents
  - Mimics Norepinephrine at alpha and beta receptors
  - Presynaptic Alpha 2a (guanfacine more specific)
  - Post synaptic alpha 1, 2 a-c (alpha 2a in PFC)
- Effect on Prefrontal cortex (PFC)
  - May be dose dependent effects on pre/post 2a
  - Largely inhibitory
  - Modulated by “stress” dependent release of Nepi
  - Improves PFC blood flow and functioning in animal models
- Effect on Locus Coerulus
- Modulate of neurotransmission of other neuronal systems (glutamate, GABA, cholinergic, opioid)

Extended Release Clonidine for ADHD

**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.

*N=236; 61% completion rate*
Guanfacine Extended-Release in ADHD
(N=324 [51 sites]; 6 weeks active*, Mean Age 11 ± 3 yrs)

Effect size: 0.41-0.89

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

**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.


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**Figure 2.**

[Graph showing change in ADHD-RS-IV total score over time for Treatment, Placebo, and GXR.]
# Guanfacine XR in Adolescent ADHD

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

<table>
<thead>
<tr>
<th>Table 2. Summary of TEAEs (≥10% of Subjects; Safety Population)</th>
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<tbody>
<tr>
<td>Preferred term</td>
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<tr>
<td>----------------</td>
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<tr>
<td>Any TEAE</td>
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<tr>
<td>Somnolence</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Fatigue</td>
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<td>Dizziness</td>
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<td>Decreased appetite</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Nasopharyngitis</td>
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<tr>
<td>Sedation</td>
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</table>

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)

(Kollins et al. Pediatrics epub 2011)
RCT on Guanfacine (GUAN), D-Methylphenidate (D-MPH), or the Combination (COMB) on ADHD in Children

* Denotes LS mean end point changes versus baseline

**ADHD-RS IV Inattention Subscale LS Means for Current Treatment By Time**

**Med Group p<0.0001; Visit p=0.0002**

Baseline: 21.1 21.3 20.4

Baseline: 36.8 35.6 35.6

Age: 7 – 14 years

Sample Size:

Guan (N=68), D-MPH (N=69), COMB (N=70)

Dosing:

Guan (1-3 mg/days), D-MPH (5-20 mg/day)

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 0.447.
Endpoint is the last valid assessment obtained after baseline and before dose taper.
Bupropion

- Effective in children with ADHD
  - N= 3 studies (104 subjects)
- Effect size ca 0.5 (lower than stimulants)
- Use in ADHD plus mood, cigarette smoking, adjunct with stimulants
Nortriptyline in Pediatric ADHD

(Prince, et al., JCAP, 2000)
Modafinil: When to Use

- 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 (mean age 9yrs) 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)

Risperidone + Stimulants in ADHD + Aggression (TOSCA Study)

- Re-analyses of study
- >Moderate effect sizes when adding risperidone (ES 0.6-0.7)
- Those most benefiting did NOT benefit from parent training alone (e.g. continued to manifest aggressive behavior (by Nisonger disruptive sc))
- Given design; authors suggest that aggressive children should be tried with optimized stimulant AND parent training (at least commenced) for > 1 month. If continued disruptive behavior, then add 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”.

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

75% of Patients Improved

(Wilens et al., JCAP 2017)
Strategies for Common Nonstimulant-Induced Side Effects

• Alpha Agonists
  – Sedation
    • Monitor (improves with time), lower dose, change formulation, change to alternative alpha agonist, add stimulant or modafinil
  – Wear off
    • Administer multi doses daily, change formulation to XR
  – Early AM difficulties
    • Administer XR at night, administer med very early in AM
  – Depression/moodiness
    • Reassess for comorbidity, change formulation, change to other alpha agonist, discontinue
  – Insomnia
    • Change to shorter acting preparation, change to other alpha agonist, avoid nighttime administration
Strategies for Common Nonstimulant-induced Side Effects

- **Atomoxetine**
  - **Initial sedation**
    - Monitor as improves over time, administer initial 2 week dosing qHS (then move to qAM), consider qHS dosing
  - **Wearoff**
    - Administer BID, increase dose
  - **Low efficacy**
    - Add stimulant, alpha agonist

- **Bupropion**
  - **Agitation/activation**
    - Lower dose, change preparation (e.g. to IR form)
  - **Insomnia**
    - Administer earlier in day, change to QD dosing, add adjunct agent (e.g. melatonin, alpha agonist, mirtazpine)
  - **Lower efficacy**
    - Add stimulant, modafinil, atomoxetine
Strategies for Common Nonstimulant-induced Side Effects

- **Bupropion**
  - Agitation/activation
    - Lower dose, change preparation (e.g. to IR form)
  - Insomnia
    - Administer earlier in day, change to QD dosing, add adjunct agent (e.g. melatonin, alpha agonist, mirtazpine)
  - Lower efficacy
    - Add stimulant, modafinil, atomoxetine
Summary: Non-Stimulant Pharmacotherapy of ADHD

- A number of non-stimulant medications for ADHD
- Often somewhat lower effect size than stimulants
- Response may be related to previous stimulant exposure
- 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
- Emerging data and FDA approval on co-administration with stimulants