Pharmacotherapy of ADHD with Non-Stimulants

Timothy E. Wilens, M.D.

Chief, Division of Child and Adolescent Psychiatry, (Co)Director of Center for Addiction Medicine, Massachusetts General Hospital
Massachusetts General Hospital for Children
Harvard Medical School
Disclosures

- **Grant Support & Consultant:** NIH, NIDA
- **Consultant:** Euthymics/Neurovance, Ironshore, Sunovion, TRIS, US National Football League ERM Associates,
- U.S. Minor/Major League Baseball, Bay Cove Human Services Clinical Services and Phoenix House
- **Co-Editing Books:** Guilford Press, Cambridge Press, Elsevier: Straight Talk About Psychiatric Medications for
- Kids (Guilford Press), ADHD in Children and Adults (Cambridge Press), and Massachusetts General Hospital
- Comprehensive Clinical Psychiatry (Elsevier)/ Psychopharmacology & Neurotherapeutics (Elsevier).
- **Licensing Agreement:** Dr. Wilens is co/owner of a copyrighted diagnostic questionnaire Before School
- Functioning Questionnaire (BFSQ). Dr. Wilens has a licensing agreement with Ironshore BSFQ Questionnaire.
Heterogeneity of ADHD

- DSM-IV subtypes
  - Inattentive
  - Hyperactive/impulsive
  - Combined

- Cognitive subtypes
  - LD
  - Executive function deficits subtypes
  - Various attentional defects (e.g. arousal; motivation, EF)

- Genetic subtypes
  » D4
  » DAT
  » 5HT
  » Nepi

- Comorbid subtypes
  » Disruptive Behavior disorders (CD/ODD)
  » Mood and anxiety disorders
  » Substance abuse

Courtesy T. Spencer
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**

(Wilens & Spencer, Postgraduate Medicine, 2010)
Representative Controlled Studies of Medications in Adults with ADHD (N=56 Studies; 7,169 Subjects)

Norepinephrine Frontal

Alpha 2 receptor

• Attention
• Concentration
• Other cognitive functions

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

DONNELLY, 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 for Youth with ADHD & Anxiety

<table>
<thead>
<tr>
<th></th>
<th>ADHD RS</th>
<th>Anxiety (PARS)</th>
</tr>
</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>** effect size = 0.5</td>
<td>* p&lt;.001</td>
</tr>
<tr>
<td></td>
<td>-10.5</td>
<td>-5.5</td>
</tr>
<tr>
<td></td>
<td>-1.4</td>
<td>** p=.011</td>
</tr>
</tbody>
</table>

Dose of ATMX = 1.26 mg/kg/day

(Geller et al. JAACAP 2007)
Atomoxetine: Long-Term Efficacy in Adults (34 Weeks)

Atomoxetine

• **Dosing (Wilens’ method):**
  – Start at 0.5 mg/kg/day for two weeks, then increase to 1.2 mg/kg/day. After six weeks if partial response, increase to 1.8-2 mg/kg/day

• **Adverse effects:**
  – Rare hepatic injury (2 cases): advise, LFTs NOT required
  – Suicidality (0.37% vs 0%): black box (pediatrics)
  – Somnolence, appetite suppression, GI upset/dyspepsia, blood pressure/pulse (adults), sexual dysfunction (adults), irritability
  – Potential drug interactions (lower dose if using with p448 inhibitor)
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
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\(^1\)–\(^3\)

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)

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
### TABLE 3  TEAEs That Occurred in ≥5% of Treatment Groups and Had at Least Twice the Incidence of Placebo (Safety Population)

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Placebo, n (%)</th>
<th>CLON-XR 0.2 mg/day, n (%)</th>
<th>CLON-XR 0.4 mg/day, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>5 (6.6)</td>
<td>30 (39.5)</td>
<td>24 (30.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1.3)</td>
<td>12 (15.8)</td>
<td>10 (12.8)</td>
</tr>
<tr>
<td>Irritability</td>
<td>3 (3.9)</td>
<td>7 (9.2)</td>
<td>6 (7.7)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>3 (3.9)</td>
<td>6 (7.9)</td>
<td>6 (7.7)</td>
</tr>
<tr>
<td>Increase in body temperature</td>
<td>2 (2.6)</td>
<td>4 (5.3)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (1.3)</td>
<td>4 (5.3)</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>Ear pain</td>
<td>1 (1.3)</td>
<td>4 (5.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Emotional disorder</td>
<td>1 (1.3)</td>
<td>3 (3.9)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Nightmare</td>
<td>0 (0)</td>
<td>3 (3.9)</td>
<td>7 (9.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (1.3)</td>
<td>0 (0)</td>
<td>4 (5.1)</td>
</tr>
</tbody>
</table>

Note: CLON-XR = clonidine hydrochloride extended-release tablets; TEAE = treatment-emergent adverse event.
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).

**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; LS = least squares; SEM = 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).

Newcorn et al. JAACAP 2013; 52; 921-930.
Guanfacine Extended-Release in ADHD
(N=324 (51 sites); 6 weeks, mean age 11±3 yrs)

• Cardiovascular changes (dose related)
  – Heart rate (-9.5 bpm at 4 mg [average change vs baseline])
    • 6-7% of subjects at 3-4 mg with HR<50
    • 1 subject with dizziness with standing (HR =64)
  – Systolic BP (-7.4 mmHg at 4 mg)
  – Diastolic BP (-5.4 mmHg at 4 mg)

• No apparent attenuation of CV effects with adjunct stimulants (Spencer et al. JCAP 2009)
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.

Guanfacine XR in Adolescent ADHD

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

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

<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>

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)
Clonidine plus Methyphenidate: ADHD plus Tic Disorders

- Prospective data indicating improved outcome for ADHD (Kurlan et al. Neurology 2002; Hazel et al. JAACAP 2003; Palumbo et al JAACAP 2007)
  - MPH + Clon > MPH > Clon > PBO

- Prospective data indicating improved outcome for tics (Kurlan et al. Neurology 2002; Hazel et al. JAACAP 2003; Palumbo et al JAACAP 2007)
  - No worsening systematically of tics vs PBO

- No cardiovascular issues in prospective data
  - No recent “events” reported
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)
Combination of Guanfacine XR plus Stimulants in the Treatment Of ADHD

-Multisite, controlled 9 week trial in 455 subjects
-Dosing: 1 - 4 mg daily; mean of 3.2 mg (0.1 mg/kg)
-Inclusion: Stimulant partial responders (> 4 wk use with improvement; ADHD RS ≥24 and CIG ≥3) age 6-17 yrs
-Exclusion: Other psych, CV abnl, Weight <55 or > 176 lb
-Design: 5 week optimization and 3 week dose maintenance period (visits 7-10)
-Primary outcome: ADHD RS IV (Investigator)

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).

Figure 2. GXR PM dosing plus psychostimulant group: change in ADHD-RS-IV total score from baseline by visit (FAS).
Combination of Guanfacine XR plus Stimulants in the Treatment Of ADHD: Adverse Events

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 abnl, no QT prolongation

Bupropion

- Combined Dopaminergic/Noradrenergic mechanism of action
- Effective anti-ADHD agent
- Effective antidepressant (adults)
- Anti-smoking (Zyban)
Bupropion

• Superior to placebo in children
  – N= 3 studies (104 subjects)

• Effective in ADHD adults
  – N= 5 controlled studies (including multisite)
Bupropion XL in Adults with ADHD: Percent Responders*

- Bupropion XL (N=81)
- Placebo (N=81)

*≥30% reduction from baseline; **p≤0.01, †p<0.05

(Wilens et al. Biol Psych 2005)
There was also a 6.9 drop in the YMRS (from 9.4 to 2.5; p=0.016)

(Wilens et al., Biological Psych:2003)
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)
Studies Show Symptom Reduction Can Improve Functional Impairment

Normalization of ADHD Symptoms Requires Significant Reductions in the ADHD RS-IV

ADHD Diagnosis
At diagnosis patients score up to 54 on the ADHD RS-IV

Standard Reduction
A score reduction of 16-18 points was accompanied by a detectable functional improvement

Achieving Normalization
A score reduction of 20-27 points was accompanied by pronounced functional improvement

OROS MPH plus ATMX: Improvement in Executive Functioning (BRIEF)

Initiation

SD ± 10
SD ± 11
SD ± 11
SD ± 13

More Disturbed

n=38

vs w4: p<0.001

T Score

Baseline
ATMX
ATMX+OROS MPH
MPH Alone (Historical)

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 (under study)

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

Bloch MH, Qawasmi A, J Am Acad Child Adolesc Psych 2011
Wozniak et al. Eur Neuropsychopharmacol. 2007 Jan 25 (epub)
Melatonin for Sleep Disturbances

- Controlled study of melatonin (5 mg) vs placebo
- N= 4 Week RCT Cross over of 62 youth (aged 6-12); 40% with ADHD receiving stimulants
  Findings:
  - Improvement in sleep questionnaire (RAND-GHRi)
  - Improvement in time of sleep onset (57 minutes earlier), and decreased sleep latency by 17 minutes
  - Well tolerated
- Long term open follow-up of 44 developmentally disabled youth for up to 3.8 years
  - Entered from cross-over study
  - Age 9.9 yrs at followup
  - Continued effectiveness for sleep, behavior & cognition
  - No apparent adverse effects, or deleterious effects on puberty noted
Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments

Edmund J.S. Sonuga-Barke, Ph.D.
Daniel Brandeis, Ph.D.
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 2,904 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.
Experimental pharmaceuticals

- Not Generally Demonstrated Efficacious for ADHD
  - Prohistaminergic agents (Herring et al. 2012)
  - Cholinesterase inhibitors (Wilens 2005, Biederman et al 2006)
  - Nicotinic partial agonist (Wilens et al. JAACAP 2011, Bain et al 2012)
  - Mixed catecholamine inhibitor (Wilens et al. Behav Brain Funct. 2008)
    - Nepi/DA uptake inhibitor (Theravance PR, Oct 2013)
    - Ampakines-mixed (Adler et al. APSARD, 2011)
    - Amino acids (Wender, Reimherr, Wood et al. 1980, 84)
- Effectiveness/efficacy demonstrated*
  - Evidoxetine (Lin et al. J Child Adolesc Psy 2014)
  - Dasatroline (2 adult RCT positive; press release)
  - Centanafadine (Wilens et al. ASCP, 2014)
  - New stimulant preparations (multiple)

*Not FDA approved for ADHD
Pharmacotherapy of ADHD Comorbidity

• Evidence of improved ADHD outcome with *treated comorbidity*
  – Anxiety
  – Depression
  – Bipolar disorder
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
• Emerging data and FDA approval on co-administration with stimulants