On Beyond Ritalin...  
By Carol Watkins, MD, and Glenn Brynes, PhD, MD

Said Debra Ann Dilly O'Malley O'Clad  
Who had AD/HD and wow was it was bad,  
"I've tried Ritalin in the morning and night  
Doses low, doses high and it just isn't right.  
I've altered dose intervals; tried the SR.  
I've gone on-line lots; talked to friends near and far;  
I've learned all there is on this damned ADD.  
But my mind still can't focus, just how can this be?  
My children and husband are ready to bust  
I think I'll just give up and say I'm a klutz."

Then she almost fell out of the chair on the floor  
When I booted my laptop, showing symbols galore.  
The chemical structures appeared on the screen  
Next to pills red and yellow and capsules of green.  
And I said, "You can stop if you want, leave it be,  
Because some people stop and give up, but not me!"  
"Now your Ritalin's great with, say, 60 percent  
(Or 50 or 80) we get improvement.  
In people I meet there are things we achieve  
That we never could get if we just let things be.  
It may take some work, but you really can mend.  
A consultant's work starts where the first-line stuff ends."  
[etc.]

Learning Objectives

1. Summarize the evidence regarding the efficacy of atomoxetine for ADHD, and the efficacy of clonidine for both ADHD and tics

2. Identify adverse effects, risks, and necessary precautions associated with the use of atomoxetine and clonidine

3. Explain how to initiate, titrate, and monitor atomoxetine and clonidine

Outline

• Topics to be covered for both atomoxetine and clonidine:
  – Indications & clinical use
  – Pharmacodynamics & pharmacokinetics
  – Efficacy
  – Adverse effects
  – Contraindications & drug interactions
  – Dosing & monitoring

Atomoxetine
Indications and Clinical Use

- Atomoxetine is indicated by Health Canada and the FDA for the treatment of ADHD in children (down to age 6), adolescents, and adults
- Atomoxetine is not typically used for other psychiatric conditions
- Atomoxetine has been studied as a potential treatment for depression, but it was found to be ineffective

Advantages of Atomoxetine Compared to Stimulants

- More continuous coverage throughout the day
- No potential for drug abuse
- Less likely to be used for weight loss in an individual with an eating disorder
- Minimal effect on vertical growth in children treated for up to 5 years (Spencer et al., 2007)
- Likely lower risk of exacerbating tics, and may even improve tics (Allen et al., 2005)
- Less concern about sudden cardiac death, although 11 cases were reported from 2002 to 2005 (Stiefel & Besag, 2010)

Disadvantages of Atomoxetine Compared to Stimulants

- SMALLER EFFECT SIZE!
- Lower response rate (especially compared to the overall stimulant response rate of ~90% when both MPH and AMPH are tried [Arnold, 2000])
- Longer titration period and need to wait weeks to months for full response
- Less flexibility (e.g., can’t stop and start it as easily)
- Drug interactions with 2D6 inhibitors
- Risk of suicidality
- It’s still fairly new, so we have less information about its long-term effects (approved by the FDA in 2002 and Health Canada in 2005)

Pharmacodynamics

- Atomoxetine is a specific norepinephrine reuptake inhibitor (NRI):
  - Inhibition of the NE transporter prevents synaptic clearance of NE, resulting in ↑ synaptic NE
- In animal studies, atomoxetine has been shown to ↑ dopamine in the prefrontal cortex but not other brain regions (Bymaster et al., 2002)
- In vitro evidence suggests that atomoxetine blocks NMDA receptors (Ludolph et al., 2010)

Pharmacokinetics

- Absorption is rapid and not affected by food
- T_{max}=1-2 hours
- Metabolized primarily by CYP2D6, but does not inhibit or induce 2D6
- T_{1/2} is about 5 hours in extensive 2D6 metabolizers, and about 22 hours in poor 2D6 metabolizers (7-10% of whites)
- Administration of atomoxetine QD or BID is expected to result in the same systemic exposure over a 24-hour period

Efficacy

- >12 DBPC trials support the efficacy of ATX for ADHD in children, adolescents, and adults (Vaughan et al., 2009)
- Like antidepressants (and unlike stimulants), ATX must be taken every day to maintain a steady-state blood level, and the clinical response occurs gradually over weeks to months

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Efficacy (cont.)

- **Response rate:**
  - ~60% in children, adolescents, and adults (Kratochvil et al., 2008; Michelson et al., 2003)

- **Effect size:**
  - Children and adolescents: 0.6 ("medium") (Cheng et al., 2007)
  - Adults: 0.3-0.6 ("small" to "medium"), with the lower ES after 10-12 weeks of treatment and the higher ES after 24 weeks (Michelson et al., 2003; Young et al., 2011)

Does ATX Improve Comorbid Anxiety?

- **2 DBPC trials support the efficacy of ATX for both ADHD and comorbid anxiety:**
  - Geller et al., 2007:
    - Youth (8-17 yrs) with ADHD+GAD/SAD/SP (n=176)
    - ATX > PBO for both ADHD and anxiety symptoms
    - ES=0.8 for ADHD symptoms, 0.4 for anxiety
  - Adler et al., 2009:
    - Adults with ADHD+SP (n= 442)
    - ATX > PBO for both ADHD and anxiety symptoms
    - ES=0.5 for ADHD symptoms, 0.3-0.4 for anxiety

A Closer Look at Geller et al., 2007...

- **Atomoxetine Treatment for Pediatric Patients with ADHD and Comorbid Anxiety**
  - Poster at the 2005 Joint Annual Meeting of the American and Canadian Academies of Child and Adolescent Psychiatry (Toronto)

Efficacy for ADHD+MDD

- **Bangs et al., 2007:**
  - Adolescents (12-18 years) with ADHD+MDD (n=142)
  - ATX > PBO for ADHD symptoms
  - ATX = PBO for depressive symptoms
  - No suicide-related events with ATX or PBO
  - 1 case of mania with PBO, but none with ATX
Efficacy for ADHD+ODD

- Bangs et al., 2008:
  - Children (6-12 years) with ADHD+ODD (n=226)
  - ATX > PBO for ADHD symptoms
  - ATX = PBO for ODD symptoms
- Dell’Agnello et al., 2009 & Dittmann et al., 2011:
  - Both trials included children and adolescents with ADHD+ODD (n=137 [Dell’Agnello], n=180 [Dittmann])
  - ATX > PBO for ADHD symptoms
  - ATX > PBO for ODD symptoms

Adverse Effects

- Sedation
- Stomach upset
- ↓ Appetite, weight loss
- Insomnia
- Mood symptoms:
  - Irritable
  - Dysphoric
- Dizziness
- ↑ HR (mean <10 bpm)
- ↑ BP (mean <4 mmHg)
- Dry mouth
- Constipation
- Urinary hesitation or retention
- Dysmenorrhea
- Sexual dysfunction

Risk of Suicidality: Clinical Trials (Bangs et al., 2008)

- Meta-analysis of suicide-related events (SREs) in 12 pediatric DBPC trials:
  - ATX=6/1,357 (0.44%) vs. PBO=0/851 (0%)
    - Of the 6 SREs with ATX, 5 were suicidal ideation and 1 was a nonfatal suicide attempt
    - Difference was statistically significant (p=0.01)
  - NNT=5 (ADHD symptom remission)
  - NNH=227 (SRE)

Suicidality: Postmarketing Reports (Health Canada, 2008)

- From February 2005 to the end of 2007, Health Canada received 189 reports of adverse reactions suspected of being associated with ATX
  - Of these 189 reports, 55 (41 children, 12 adults, 2 age unknown) were classified as SREs
  - Per Eli Lilly Canada (letter 2008), ~5 million patients had received ATX through Nov 2007, and data from the Strattera spontaneous adverse event database showed that SREs were reported with a frequency of <0.1%

Health Canada Advisory for Atomoxetine (Sept. 2005)

- "[A small number of patients] may experience unusual feelings of aggression, hostility or anxiety, or have impulsive or disturbing thoughts that could involve self harm … Doctors are advised to carefully monitor patients of all ages for emotional or behavioural changes that may indicate potential for harm, including suicidal thoughts and the onset or worsening of agitation-type adverse events."

Risk of Severe Liver Injury

- RCTs:
  - No evidence of severe liver injury in clinical trials of ATX that included a total of almost 8000 patients
- Post-marketing reports:
  - Rare cases of severe liver injury that were considered probably or possibly related to ATX
  - Such reactions may occur several months after the initiation of ATX
  - It is impossible to provide an accurate estimate of the true incidence of these events

References: Strattera product monograph; Erdogan et al., 2011
Health Canada Warning on Severe Liver Injury

- "Post-marketing reports indicate that Strattera … can cause severe liver injury in rare cases … Strattera should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction."

Risk of Psychosis & Mania

- Recall Mosholder et al., 2009 (see the "Stimulants" handout):
  - In clinical trial data, rates of psychosis/mania events with stimulants, atomoxetine, and modafinil vs. placebo:
    - 11/5717 (0.2%) vs. 0/3990 (0%)
    - 1.48 per 100 person-years vs. 0 in 420 person-years
  - Postmarketing data:
    - 865 unique case reports describing evidence of psychosis/mania with stimulants and atomoxetine

Mosholder et al., 2009 (cont.)

- Representative clinical narrative:
  - "A spontaneous report … described a 7-year-old girl who received 18 mg daily of atomoxetine for the treatment of ADHD. Within hours of taking the first dose, the patient started talking nonstop and stated that she was happy. The next morning the child was still elated. Two hours after taking her second dose of atomoxetine, the patient started running very fast, stopped suddenly, and fell to the ground. The patient said she had "run into a wall" (there was no wall there). The reporting physician considered that the child was hallucinating. Atomoxetine was discontinued. No additional information was provided."

Risk of Sudden Death?

- Although the controversy around ADHD medication and sudden death has been focused mainly on stimulants, ATX is not necessarily safer
  - Recall that like stimulants, ATX causes generally small ↑ in HR & BP
  - From 2002 to 2005, there were 11 case reports of sudden cardiac death associated with ATX (Stiefel & Besag, 2010):
    - 5 of the cases were in youth, and in 2 of these 5 there were no obvious confounding factors

Sudden Death (cont.)

- Recall that the Health Canada Advisory (May 2006) covers all ADHD drugs, not just stimulants (see the "Stimulants" handout)
- Therefore, the same CV considerations and precautions for stimulants also apply to ATX
- From the CPS:
  - "ATX generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the noradrenergic effects of ATX."

Effects on Growth

- Reference: Spencer et al., 2007

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Long-term Safety & Tolerability

- Donnelly et al., 2009:
  - Adverse event data from 16 trials were pooled
  - The analysis included 714 youth treated with ATX for ≥3 years (mean 4.8 years)
  - Results:
    • SREs: <1.6% (no completed suicides)
    • Potentially clinically significant hepatic changes: ≤2%
    • Aggressive/hostile behaviours: ≤6%
    • No clinically significant effects on growth, vital signs, or ECG

Contraindications

- Hypersensitivity to atomoxetine
- Narrow angle glaucoma
- Concurrent MAOI

Drug Interactions

- $\beta_2$ agonist-induced ↑ in HR and BP can be potentiated by atomoxetine, so the combination should be used with caution
- 2D6 inhibitors (e.g., fluoxetine, paroxetine) increase atomoxetine levels
- MAOIs (possible serotonin syndrome)
- No interaction with stimulants

Dosing

- Start at 0.5 mg/kg/day (max 40 mg) for 7-14 days
- Then ↑ to 0.8 mg/kg/day (max 60 mg) for 7-14 days
- Then ↑ to “target dose” of 1.2 mg/kg/day (max 80 mg)
- If inadequate response after at least 1 month, consider ↑ to between 1.4 mg/kg/day (Health Canada and FDA max) and 1.8 mg/kg/day (Pliszka et al., 2007 [AACAP Practice Parameter for ADHD])
- >1.8 mg/kg/day has been shown not to provide additional benefit (Kratochvil et al., 2007)
- Maximum absolute dose is 100 mg/day

Dosing (cont.)

- If the patient is a poor 2D6 metabolizer or is taking a drug that’s a 2D6 inhibitor, then continue 0.5 mg/kg/day (max 40 mg) for 2-4 weeks before considering ↑ in dose
- QD dosing (usually in the AM) is most common, but BID dosing may modestly improve tolerability and efficacy (Waxmonsky et al., 2011; Adler et al., 2006 [adult study])
- Capsules should be swallowed whole

Dosing (cont.)

- Among responders, initial improvement is generally observed by 4 weeks of treatment (Newcorn et al., 2009)
- However, full response may take longer, even up to 6-10 months (Kratochvil et al., 2007; Young et al., 2011 [adult study])
Monitoring

- Response and adverse effects (preferably using child/parent and teacher rating scales)
- HR & BP at baseline and regularly thereafter, especially with dose increases
- Height and weight plotted on a growth chart
- Suicidal ideation
- Baseline LFTs are not necessary, but LFTs should be done at the first sign or symptom of liver dysfunction

Pediatric Indications

- Health Canada:
  - Clonidine is not approved for use in youth
- FDA:
  - In 2010, clonidine XR (Kapvay) was approved as monotherapy and as an adjunct to stimulants for ADHD in youth (6-17 years)
  - In 2009, another α₂ agonist, guanfacine XR (Intuniv), was approved as monotherapy for ADHD in youth (6-17 years), and in 2011 it was also approved as an adjunct to stimulants
- Clonidine XR, guanfacine, and guanfacine XR are not available in Canada

Clinical Use

- In child psychiatry, clonidine is used for:
  - ADHD
    - Generally after stimulants and atomoxetine have been tried, or as an adjunct to a stimulant
  - Tics
  - Aggression/agitation
  - Insomnia (especially in children taking stimulants)

Pharmacodynamics

- Clonidine is a centrally acting α₂-adrenergic agonist
- Agonist effects on presynaptic α₂-adrenergic autoreceptors result in decreased release of NE (through negative feedback), especially in the locus ceruleus and prefrontal cortex
- Also found to have a direct agonist effect at postsynaptic α₂-adrenergic receptors, especially in the prefrontal cortex (Arnsten et al., 1996)

Pharmacodynamics (cont.)

- Clonidine binds to all 3 α₂-adrenergic receptor subtypes (2A, 2B, 2C), as well as other α receptors
- Note that guanfacine is more specific for the α₂A receptor, and this is thought to result in milder adverse effects
Pharmacokinetics

- $T_{\text{max}} = 3-5$ hours
- $T_{1/2} = \text{???}$
  - CPS: 12-16 hours
  - Leckman et al., 1985: 4-6 hours in children, 8-12 hours in adolescents and adults
- 50% is metabolized by the liver, but clonidine does not seem to interact with other drugs through the CYP450 system
- 50% is excreted unchanged by the kidneys

Efficacy: ADHD

- Until 2002, placebo-controlled evidence supporting the use of clonidine for ADHD symptoms was limited to a handful of small trials of the immediate-release formulation (clonidine XR did not become available in the U.S. until 2010)
- In a number of these trials, patients also had a tic disorder, autism, or conduct disorder

Efficacy: ADHD (cont.)

- Connor et al., 1999:
  - Meta-analysis of clonidine for ADHD symptoms
  - Overall effect size: 0.58 (“medium”)  
  - Adverse effects were common, especially sedation, irritability, and ↓BP
- Despite the limited evidence…
  - U.S. prescriptions of clonidine for children with ADHD increased from 20,000/year in 1990 to >150,000/year in 1995 (Swanson et al., 1999)

Tourette’s Syndrome Study Group, 2002

- Multisite RCT of 136 youth (7-14 years) with ADHD and a chronic tic disorder (federally funded)
- Randomized to 4 groups:
  - Immediate-release clonidine (CLON)
  - Immediate-release methylphenidate (MPH)
  - Combination of clonidine & methylphenidate (COMB)
  - Placebo (PBO)
- Outcomes:
  - ADHD severity
  - Tic severity

TSSG, 2002: ADHD Results

- ADHD severity improved significantly in all 3 active treatment groups compared to placebo
- Methylphenidate was better for inattention
- Clonidine was better for hyperactivity/impulsivity
- Percentages of subjects that improved with respect to ADHD symptoms (based on the CGI):
  - PBO: 31-37%
  - CLON: 56-61%
  - MPH: 67-81%
  - COMB: 84-88%

TSSG, 2002: Adverse Effects

- Medications were well tolerated except for sedation with clonidine
- 48% of subjects treated with clonidine reported sedation, including 28% who rated sedation as moderate or severe
- Lowest rate of reported side effects occurred in the MPH group
- Overall, no evidence of cardiac toxicity by ECG monitoring
Hazell & Stuart, 2003

- Placebo-controlled trial of clonidine augmentation of a stimulant in children with ADHD and comorbid ODD/CD (n=67)

<table>
<thead>
<tr>
<th>Hyperactivity Score (0-3 scale)</th>
<th>Conduct Score (0-3 scale)</th>
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<tbody>
<tr>
<td>Clonidine</td>
<td>Placebo</td>
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*Statistically significant

Palumbo et al., 2008 (Efficacy) & Daviss et al., 2008 (Adverse Events)

- 16-week DBPC trial conducted in 122 children (7-12 years) with any subtype of ADHD (federally funded)
- Randomized to 4 groups:
  1. Immediate-release clonidine (CLON)
  2. Immediate-release methylphenidate (MPH)
  3. Combination of clonidine & methylphenidate (COMB)
  4. Placebo (PBO)

Palumbo et al., 2008: Results for Primary Outcome

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Treatment Effects on the Conners ASQ-Teacher</th>
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<tbody>
<tr>
<td>Comparison</td>
<td>Treatment Effect</td>
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<tr>
<td>MPH vs. PBO</td>
<td>-2.5</td>
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<tr>
<td>CLON vs. PBO</td>
<td>-1.0</td>
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<td>COMB vs. PBO</td>
<td>-4.4</td>
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<tr>
<td>MPH vs. CLON</td>
<td>-1.5</td>
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<tr>
<td>COMB vs. MPH</td>
<td>-1.9</td>
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<tr>
<td>COMB vs. CLON</td>
<td>-3.4</td>
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</tbody>
</table>

Palumbo et al., 2008: Results for Secondary Outcomes

- ASQ-Parent:
  - Clonidine > No clonidine
  - Methylphenidate = No methylphenidate
- CGAS:
  - Clonidine > No clonidine
  - Methylphenidate ≥ No methylphenidate (p=0.06)
- Iowa CTRS and classroom observations of on-task behaviour:
  - Methylphenidate > No methylphenidate
  - Clonidine = No clonidine

Daviss et al., 2008

- Specific adverse events associated with clonidine:
  - Bradycardia:
    - Clonidine > No clonidine (17.5% vs. 3.4%)
  - Minimal effects on BP:
    - On 5/6 measures of BP: Clonidine = No clonidine
  - Sedation:
    - "Somnolence": Clonidine > No clonidine (38.1% vs. 6.8%)
    - "Fatigue": Clonidine > No clonidine (19.0% vs. 5.1%)
    - However, drowsiness generally improved by 6 to 8 weeks
  - "Nervousness":
    - Clonidine > No clonidine (31.7% vs. 15.3%)
  - Dry mouth (parent-rated):
    - CLON=16.1%, COMB=6.3%, MPH=0%, PBO=0%
Daviss et al., 2008 (cont.)

- Overall rates of moderate/severe adverse events:
  - Clonidine (79.4%) > No clonidine (49.2%)
  - Note that the rate was 40.0% in the PBO group!
- No significant group differences on ECG except for ↑ bradycardia with clonidine
- No evidence of interactions between clonidine and methylphenidate with respect to cardiovascular outcomes

Palumbo/Daviss et al., 2008: Conclusions

- Methylphenidate offers the best combination of efficacy and tolerability for ADHD
- Clonidine offers some benefit for ADHD
- Clonidine, used alone or with methylphenidate, appears safe and well tolerated in the treatment of ADHD
- Physicians prescribing clonidine should monitor for bradycardia and advise patients about the high likelihood of initial drowsiness (likely to improve by 6-8 weeks of treatment)

Efficacy of Clonidine XR for ADHD

- Jain et al., 2011 (funded by Addrenex):
  - n=236, 6-17 years, ADHD-HI or ADHD-C
  - 8-week trial of CLON-XR 0.2 mg/d vs. CLON-XR 0.4 mg/d vs. PBO
  - Results:
    • CLON-XR > PBO (for both doses)
    • ES=0.7-0.8 (similar for both doses)
    • Adverse effects with CLON-XR included sedation/fatigue, irritability/emotional problems, constipation, dry mouth, sore throat, insomnia, nightmares, and small ↓ in HR & BP

Efficacy of Clonidine XR (cont.)

- Kollins et al., 2011 (funded by Addrenex):
  - n=198, 6-17 years, ADHD-HI or ADHD-C
  - 8-week trial of CLON-XR (0.1-0.4 mg/d dosed flexibly) vs. PBO as an adjunct to a stable stimulant regimen with inadequate response
  - Results:
    • CLON-XR+stimulant > PBO+stimulant
    • ES=0.3
    • Adverse effects with CLON-XR+stimulant included sedation/fatigue, headache, upper abdominal pain, nasal congestion, and small ↓ in HR & BP

Efficacy: Tics

- Several positive placebo-controlled studies:
  - 3 small (n<50), older studies:
    • Borison et al., 1983; Leckman et al., 1985; Leckman et al., 1991
  - Du et al., 2008 (n=437, clonidine patch)
    • Tourette’s Syndrome Study Group, 2002
- 2 negative placebo-controlled studies:
  - Goetz et al., 1987 (n=30)
  - Singer et al., 1995 (n=23)

TSSG, 2002: Tic Results

- Tic severity decreased significantly in all 3 active treatment groups compared to placebo
- Percentages of subjects that improved with respect to tics (based on the CGI):
  - PBO: 28-33%
  - CLON: 63-70%
  - MPH: 44-66% (!)
  - COMB: 72-78%
TSSG, 2002: Tic Results (cont.)

- Frequency of tic worsening:
  - PBO: 22%
  - CLON: 26%
  - Methylphenidate (with or without clonidine): 20% (!)
- Dose increases limited because of tics:
  - PBO: 19%
  - CLON: 18%
  - MPH: 35% (!)
  - COMB: 15%

Meta-Analysis of $\alpha_2$ agonists for Tics (Weisman et al., 2012)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means and 95% CI</th>
<th>a measure of effect size</th>
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<tr>
<td>Scahill 2001</td>
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<td>TSSG 2002</td>
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<td>Leckman 1997</td>
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<td>Cummings 2002</td>
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<td>Singer 1995</td>
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Note: Scahill 2001 and Cummings 2002 used guanfacine, while the other studies used clonidine.

(enlarged slide appended)

Weisman et al., 2012 (cont.)

- Clonidine’s overall effect size for tics was **0.31** (significant)
- However, clonidine worked much better for tics in children with comorbid ADHD compared to those without ADHD:
  - In trials that enrolled subjects with comorbid ADHD, the effect size for tics was **0.68** (significant)
  - In trials that excluded subjects with comorbid ADHD, the effect size for tics was only **0.15** (non-significant)

Adverse Effects

- Sedation
- Bradycardia
- Hypotension
  (orthostatic)
- Rebound hypertension
- Irritability, dysphoria
- Anxiety
- Nausea/vomiting
- Abdominal pain
- Constipation
- Dry mouth
- Sleep disturbance
- Nightmares

Clonidine+Stimulant Controversy

- Risk of sudden death with combination of clonidine and methylphenidate?
  - 4 cases, each with extenuating circumstances
  - Causation not established, but not ruled out
- In the past, ECG monitoring has been recommended if the combination of clonidine and a stimulant is used
- See “Debate Forum” in the May 1999 issue of JAACAP (Wilen & Spencer vs. Swanson et al.)

Clonidine+Stimulant (cont.)

- More recently, 3 large studies that combined clonidine and a stimulant found no significant ECG changes except for sinus bradycardia (TSSG, 2002; Daviss et al., 2008; Kollins et al., 2011)
- Furthermore, the U.S. product monograph for clonidine XR (Kapvay) does not indicate a need for ECG monitoring when it is used alone or as an adjunct to a stimulant
Contraindications

- Hypersensitivity to clonidine
- Severe cardiac arrhythmias

Drug Interactions

- No significant CYP450 interactions
- Clonidine’s antihypertensive effect may be reduced and orthostatic regulation disturbances may be exacerbated with concomitant administration of TCAs or neuroleptics with α-receptor blocking properties
- Clonidine may enhance the CNS-depressive effects of alcohol, barbiturates, or other sedatives
- Clonidine’s antihypertensive effect can be potentiated by other antihypertensive agents (diuretics, vasodilators, β-blockers, calcium channel blockers, and ACE-inhibitors, but not α1-blocking agents)

Drug Interactions (cont.)

- Concomitant use of β-blockers and/or cardiac glycosides can further ↓ HR or cause dysrhythmia (AV-block) in isolated cases
- Sympathomimetic amines, indomethacin, and possibly other NSAIDs may reduce the antihypertensive effects of clonidine
- Substances with α2-receptor blocking properties, such as phentolamine or tolazoline, may abolish the α2-receptor mediated effects of clonidine (note that tolazoline can therefore be used as an antidote)

Suggested Dosing

- Start 0.025 mg BID or 0.05 mg QD
- ↑ every 3-7 days by 0.05 mg/day
- Multiple daily doses is recommended:
  - QID dosing is often ideal, but TID or even BID dosing may do (especially if compliance is a concern)
  - More frequent dosing is preferred because of clonidine’s short half-life and because a greater number of smaller doses may be less sedating than a smaller number of bigger doses

Dosing (cont.)

- Usual dose range is 0.1-0.4 mg/day, but clonidine has been studied and found to be generally safe up to 0.6 mg/day (TSSG, 2002; Daviss et al., 2008)
- Improvements may occur as early as 1-2 weeks of treatment (Jain et al., 2011), but it may be necessary to wait up to 6-8 weeks for response (Leckman et al., 2001)

Monitoring

- Response and adverse effects (preferably using child/parent and teacher rating scales)
- Sedation:
  - Often limits use of clonidine, but tends to improve by 6-8 weeks of treatment (Daviss et al., 2008)
- HR & BP at baseline, weekly during titration, and every 2 months during maintenance (Connor & Meltzer, 2006)
Discontinuing Clonidine

• Clonidine should be tapered gradually, as abrupt discontinuation can result in withdrawal effects such as rebound hypertension, tachycardia, and arrhythmias

• Suggested tapering schedule: ↓ by 0.05 mg/day every 3-4 days (Connor & Meltzer, 2006)
Atomoxetine Treatment for Pediatric Patients with ADHD and Comorbid Anxiety

→ Calvin Sumner, MD1; Lawrence Sher, MD2; Virginia Sutton, PhD1; Rosalie Bakken, PhD1; Martin Paczkowski, MPH1; Douglas Kelsey, MD, PhD1

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Atomoxetine Treatment for Pediatric Patients With Attention-Deficit/Hyperactivity Disorder With Comorbid Anxiety Disorder

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Effects on Growth

Weight (A) and height (B) percentiles in 61 youth (6-17 years) treated with atomoxetine for up to 5 years. Dashed lines represent baseline percentiles.

\(^{a}p<0.05, \text{relative to baseline percentile; } ^{b}p<0.001, \text{relative to baseline percentile}\)

Reference: Spencer et al., 2007
Hazell & Stuart, 2003

- Placebo-controlled trial of clonidine augmentation of a stimulant in children with ADHD and comorbid ODD/CD (n=67)

Hyperactivity Score (0-3 scale)

Conduct Score (0-3 scale)

*Statistically significant

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**Palumbo et al., 2008: Results for Primary Outcome**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Treatment Effect</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate vs. no methylphenidate</td>
<td>-2.9</td>
<td>-5.1 to -0.8</td>
<td>.008</td>
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<tr>
<td>Clonidine vs. no clonidine</td>
<td>-1.4</td>
<td>-3.6 to 0.7</td>
<td>.19</td>
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<td>Methylphenidate × clonidine interaction</td>
<td></td>
<td></td>
<td>.69</td>
</tr>
<tr>
<td>MPH vs. PBO</td>
<td>-2.5</td>
<td>-6.3 to 1.3</td>
<td>.12</td>
</tr>
<tr>
<td>CLON vs. PBO</td>
<td>-1.0</td>
<td>-4.7 to 2.7</td>
<td>.52</td>
</tr>
<tr>
<td>COMB vs. PBO</td>
<td>-4.4</td>
<td>-8.0 to -0.7</td>
<td>.005</td>
</tr>
<tr>
<td>MPH vs. CLON</td>
<td>-1.5</td>
<td>-4.6 to 1.6</td>
<td>.34</td>
</tr>
<tr>
<td>COMB vs. MPH</td>
<td>-1.9</td>
<td>-4.9 to 1.2</td>
<td>.23</td>
</tr>
<tr>
<td>COMB vs. CLON</td>
<td>-3.4</td>
<td>-6.4 to -0.4</td>
<td>.03</td>
</tr>
</tbody>
</table>
Fig. 2 Primary efficacy outcomes. Mean change from baseline on the Conners Abbreviated Symptom Questionnaire for Teachers (Conners ASQ-Teacher) at each evaluation visit for the four treatment groups. Error bars represent 1 SEM. MPH = methylphenidate.
Meta-Analysis of $\alpha_2$ agonists for Tics (Weisman et al., 2012)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Std diff in means and 95% CI</th>
</tr>
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<tbody>
<tr>
<td>Scahill 2001</td>
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<tr>
<td>TSSG 2002</td>
<td></td>
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<tr>
<td>Leckman 1991</td>
<td></td>
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<td>Cummings 2002</td>
<td></td>
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<td>Du 2008</td>
<td></td>
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<td>Singer 1995</td>
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Note: Scahill 2001 and Cummings 2002 used guanfacine, while the other studies used clonidine.