“We have all a better guide in ourselves, if we would attend to it, than any other person can be.”

Jane Austen, novelist (1775-1817)
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 darned 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 $\alpha_2$ agonists for both ADHD and tics
2. Identify adverse effects, risks, and necessary precautions associated with the use of atomoxetine and $\alpha_2$ agonists
3. Explain how to initiate, titrate, and monitor atomoxetine and $\alpha_2$ agonists

Outline
• Topics to be covered for both atomoxetine and $\alpha_2$ agonists:
  – Indications & clinical use
  – Pharmacodynamics & pharmacokinetics
  – Efficacy
  – Adverse effects
  – Contraindications & drug interactions
  – Dosing & monitoring

Atomoxetine
Indications and Clinical Use

- Atomoxetine (ATX) is indicated by Health Canada and the FDA for the treatment of ADHD in children (down to age 6 years), adolescents, and adults
- ATX is not typically used for other psychiatric conditions
- ATX 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
- Less concern about vertical growth suppression (Reed et al., 2016)
- 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 relatively new, so we have less information about its long-term effects (approved by the FDA in 2002 and Health Canada in 2005)

Pharmacodynamics

- ATX is considered a specific norepinephrine reuptake inhibitor (NRI):
  - Inhibition of the norepinephrine (NE) transporter prevents synaptic clearance of NE, resulting in ↑ synaptic NE
- Nonetheless...
  - In vitro and animal studies have found that ATX blocks serotonin as well as NE transporters (Ding et al., 2014)
  - In animal studies, ATX has been shown to ↑ dopamine in the prefrontal cortex but not other brain regions (Bymaster et al., 2002)
  - In vitro evidence suggests that ATX blocks NMDA receptors (Ludolph et al., 2010)

Pharmacokinetics

- Absorption of ATX is rapid and is not affected by food (T_{max}=1-2 hrs)
- ATX is metabolized primarily by CYP2D6, but does not inhibit or induce 2D6
- A minor metabolic pathway (<10%) involves CYP2C19 (ter Laak et al., 2010; Choi et al., 2014)

Pharmacokinetics (cont.)

- T_{1/2} is ~5 hours in extensive 2D6 metabolizers, and ~22 hours in poor 2D6 metabolizers
  - Note: Poor 2D6 metabolism is present in up to 10% of whites, up to 8% of blacks, 2-7% of Hispanics, 2-5% of South Asians, 1-2% of Saudi Arabsians, and 0-1% of East/Southeast Asians (Bernard et al., 2006)
- Administration of atomoxetine QD or BID is expected to result in the same systemic exposure over a 24-hour period
Efficacy

• A meta-analysis of 25 placebo-controlled trials supports the efficacy of ATX for ADHD in children and adolescents (Schwartz & Correll, 2014)

• 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

Efficacy (cont.)

• Schwartz & Correll, 2014 (meta-analysis):
  – Response rate: 45% (≥40% improvement) to 60% (≥25% improvement)
  – Effect size (ES) for core ADHD symptoms: 0.6
  – ES for ODD symptoms associated with ADHD: 0.3

• Note that ATX appears to be less efficacious in adults:
  – ES for core ADHD symptoms: 0.3-0.4 (Cunill et al., 2013 [meta-analysis])

Does ATX Improve Comorbid Anxiety?

• 2 DBPC trials (sponsored by Eli Lilly) 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…
ATX for ADHD+MDD

- Bangs et al., 2007:
  - Adolescents (12-18 years) with ADHD+MDD (n=142)
  - ATX > PBO for ADHD symptoms (ES=0.8)
  - ATX = PBO for depressive symptoms
  - No suicide-related events with ATX or PBO
  - 1 case of mania with PBO, but none with ATX

Adverse Effects

- Sedation
- Stomach upset
- ↓ Appetite, weight loss
- Insomnia
- Mood symptoms:
  - Irritable
  - Dysphoric
- ↑ HR (mean <10 bpm)
- ↑ BP (mean <4 mmHg)
- Dizziness
- Dry mouth
- Constipation
- Urinary hesitration/retention
- Dysmenorrhea
- Sexual dysfunction
- Case reports of life-threatening QT prolongation (Stuhec & Svab, 2013; Yamaguchi et al., 2014)

Risk of Suicidality: Clinical Trials

- 3 meta-analyses have found a numerically ↑ risk of suicide-related events (SREs) with ATX vs. PBO in youth
- All 3 meta-analyses found this ↑ risk to be 0.3-0.4%, but it was statistically significant in only the first of these:
  1. Bangs et al., 2008a (12 pediatric trials): 0.4% for ATX vs. 0.0% for PBO, p=0.01
  2. Schwartz & Correll, 2014 (25 pediatric trials): 1.3% vs. 0.9%, p=0.3
  3. Bangs et al., 2014 (23 pediatric trials, 9 adult trials): 0.4% vs. 0.1% in youth, p=0.42; 0.1% vs. 0.1% in adults, p=0.96
- No completed suicides in any of the trials

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; Bangs et al., 2008b; 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 Priapism

- Warnings from FDA (December 2013) & Health Canada (~October 2015):
  - Rare cases of priapism with MPH and atomoxetine
  - Risk not quantified, but appears to be greater with atomoxetine than with MPH
  - Cases of priapism associated with ADHD medications reported as of May 15, 2014 (Eiland et al., 2014):
    - 15 cases in youth taking MPH
    - 4 cases in youth taking AMPH; however, these individuals were taking illicit or unspecified amphetamines, as well as other agents known to cause priapism
    - 1 case in an 11-year-old boy taking atomoxetine, risperidone, and aripiprazole
  - Families should be counseled about the need for immediate medical attention if priapism occurs

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 medications, 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.”
*The advisory does not apply to guanfacine extended-release (Intuniv XR), which was approved by Health Canada in 2013
Effects on Vertical Growth

• Several studies evaluated vertical growth during the first 2-5 years of ATX treatment (Reed et al., 2016 [review]):
  – 1 study found a slight ↑ in vertical growth:
    • Wilens et al., 2006
  – 4 studies found a slight or small ↓ in vertical growth:
    • Spencer et al., 2005; Donnelly et al., 2009; Germinario et al., 2013; Kratochvil et al., 2006 (meta-analysis of 13 studies in children 6-7 years old)
  – 1 study found a small ↓ in vertical growth after 12-18 months, followed by catch-up at 24 months that was sustained until 5 years:
    • Spencer et al., 2007

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
• Significant cardiac problems
• Narrow angle glaucoma
• Concurrent MAOI

Drug Interactions

• No interaction with stimulants, but little evidence to support combining a stimulant with atomoxetine (Treuer et al., 2013)
• β2 agonist-induced ↑ in HR and BP can be potentiated by atomoxetine, so the combination should be used with caution
• ATX levels are ↑ by 2D6 inhibitors (e.g., fluoxetine, paroxetine) and, to a much lesser extent, 2C19 inhibitors
• MAOIs (possible serotonin syndrome)

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

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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
• BID dosing and slower titration may improve tolerability (especially ↓ appetite, GI side effects, and somnolence), and BID dosing may modestly improve efficacy:
  - Wietecha et al., 2013 [pooled analysis of 22 pediatric and 3 adult studies]; Waxmonsky et al., 2011; Adler et al., 2006 [adult study])
• Capsules should be swallowed whole

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

Alpha-2 Agonists: Clonidine & Guanfacine

Pediatric Indications

• Health Canada:
  – Clonidine is not approved for use in youth, but the immediate-release formulation (CLON-IR) is available as a treatment for hypertension in adults
  – Guanfacine extended-release (GFC-XR; trade name “Intuniv XR”) is approved as monotherapy and as an adjunct to a stimulant in the treatment of ADHD in children and adolescents (6-17 years)
  – Clonidine extended-release (CLON-XR) and guanfacine immediate-release (GFC-IR) are not available in Canada

Pediatric Indications (cont.)

• FDA:
  – CLON-XR (trade name “Kapvay”) is approved as monotherapy and as an adjunct to a stimulant in the treatment of ADHD in children and adolescents (6-17 years)
  – GFC-XR is approved as monotherapy and as an adjunct to a stimulant in the treatment of ADHD in children and adolescents (6-17 years)
  – GFC-IR (trade name “Tenex”) is approved (since 1986) for treating hypertension in adults and adolescents (≥13 years)
Clinical Use

- In child psychiatry, $\alpha_2$ agonists are used for:
  - ADHD:
    - Generally after stimulants, and arguably atomoxetine, have been tried
    - As an adjunct to a stimulant that has provided only partial response
  - Tics
  - Disruptive/aggressive behaviour
  - Insomnia (especially in children taking stimulants)

Pharmacodynamics

- CLON and GFC are centrally acting $\alpha_2$-adrenergic agonists
- Whereas CLON binds to all 3 $\alpha_2$-adrenergic receptor subtypes (2A, 2B, 2C) and other receptors (e.g., $\alpha_1$- and $\beta$-adrenergic, histamine, imidazoline), GFC binds more selectively to the $\alpha_{2A}$ receptor (Alamo et al., 2016)
- $\alpha_2$ agonists have agonist effects on presynaptic $\alpha_2$-adrenergic autoreceptors, resulting in decreased release of NE, especially in the locus ceruleus and prefrontal cortex

Pharmacodynamics (cont.)

- $\alpha_2$ agonists also have direct agonist effects at postsynaptic $\alpha_2$-adrenergic receptors, especially in the prefrontal cortex (Arnsten et al., 1996; Arnsten & Jin, 2012)
- GFC has especially high affinity for postsynaptic $\alpha_{2A}$ receptors (Arnsten et al., 2011); in fact, binding to presynaptic $\alpha_{2A}$ receptors is ~10 times greater with CLON than with GFC (Engberg et al., 1991; Arnsten & Jin, 2012)
- Compared to CLON, the greater selectivity of GFC for postsynaptic $\alpha_{2A}$ receptors is thought to contribute to a milder side effect profile

Pharmacokinetics: CLON-IR

- $T_{\text{max}}$ = 3-5 hours
- $T_{1/2}$ = ???
  - 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 CLON does not seem to interact with other drugs through the CYP450 system
- 50% is excreted unchanged by the kidneys

Pharmacokinetics: GFC-XR

(e-CPS; PDR.net; Swearingen et al., 2007)

- GFC-XR is readily absorbed, with a $T_{\text{max}}$ of 5 hrs in children/adolescents and 6 hrs in adults
  - Note: GFC-IR has a $T_{\text{max}}$ of 1-4 hrs in adults
- In adults, taking GFC-XR with a high-fat meal was found to increase absorption considerably
- GFC is metabolized through oxidation (phase I) and glucuronidation (phase II)

Pharmacokinetics: GFC-XR (cont.)

(e-CPS; Swearingen et al., 2007; Strange, 2008)

- CYP450 activity:
  - GFC is primarily metabolized by 3A4
  - GFC is also a substrate of 3A5, 2C9, and 2C19
  - GFC does not inhibit or induce any of the major CYP450 enzymes
- GFC is excreted by both the liver and the kidney
- $T_{1/2}$ of GFC (same for IR & XR formulations):
  - 13-14 hrs in children/adolescents
  - 17-18 hours in adults

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Efficacy: ADHD

• Hirota et al., 2014 (meta-analysis of α2 agonists):
  – Effect size for monotherapy (4 CLON studies, 5 GFC studies): 0.6
  – Effect size as adjunct to a stimulant (2 CLON studies, 1 GFC study): 0.3-0.4
  – No significant difference in response rate between CLON and GFC

• Ruggiero et al., 2014 (meta-analysis of GFC):
  – Response rate for GFC monotherapy: 59% (vs. 33% with placebo)
  – GFC-XR has not been studied in children <25 kg

Efficacy: Disruptive & Aggressive Behaviour Associated with ADHD

• Pringsheim et al., 2015 (meta-analysis):
  – Effect size of CLON for oppositional behaviour & conduct problems (6 studies): 0.3 (CI=0.0-0.5)
  – Effect size of GFC for oppositional behaviour (2 studies): 0.4 (CI=0.2-0.7)
  – Regarding the effect of α2 agonists on aggression specifically, no placebo-controlled studies are available

Efficacy: Tics

• Weisman et al., 2013 (meta-analysis):
  – Overall effect size (4 CLON studies, 2 GFC studies): 0.3
  – No significant difference between CLON and GFC
  – Effect size if comorbid ADHD is present: 0.7
  – Effect size if comorbid ADHD is absent: 0.15 (non-significant)

• Tourette’s Syndrome Study Group (TSSG), 2002:
  – Landmark RCT of MPH-IR vs. CLON-IR vs. MPH-IR + CLON-IR vs. PBO in 135 youth (7-14 years) with ADHD and a chronic tic disorder (federally funded)

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-IR: 56-61%
    – MPH-IR: 67-81%
    – MPH-IR + CLON-IR: 84-88%

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-IR: 63-70%
    – MPH-IR: 44-66% (!)
    – MPH-IR + CLON-IR: 72-78%

TSSG, 2002: Tic Results (cont.)

• Frequency of tic worsening:
  – PBO: 22%
  – CLON-IR: 26%
  – Methylphenidate (with or without clonidine): 20% (!)
• Dose increases limited because of tics:
  – PBO: 19%
  – CLON-IR: 18%
  – MPH-IR: 35%
  – MPH-IR + CLON-IR: 15%
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-IR group
- Overall, no evidence of cardiac toxicity based on ECG monitoring

Adverse Effects

- Sedation
- Bradycardia
- Hypotension
- Dizziness
- Headache
- Dry mouth
- Irritability & other emotional changes
- Gastrointestinal symptoms
- Modest ↑ in QT with guanfacine (~5 msec)
- ECG abnormalities (rare)
- Rebound tachycardia & hypertension:
  - GFC-XR has a Health Canada Warning about the risk of hypertensive encephalopathy upon abrupt discontinuation (October 2016)

Risk of Suicide-Related Events

- Health Canada Warning for "all" ADHD medications (March 2015):
  - "There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known."
  - "There is little evidence to establish that these drugs cause suicidal thoughts and behaviours, but it is possible that they may contribute to the risk."

Contraindications

- Hypersensitivity to CLON or GFC
- Significant cardiac problems

Drug Interactions

- CYP450 interactions:
  - CLON: None of significance
  - GFC: Inhibitors and inducers of 3A4 (primary metabolic pathway), 3A5, 2C9, and 2C19
- Drugs that ↓ HR or BP:
  - Additive effects may cause clinically significant ↓ in HR or BP
- Drugs that prolong the QT interval (for GFC):
  - Recall that GFC has been found to cause a modest ↑ in QT

Drug Interactions (cont.)

- CNS depressants:
  - Additive effects may result in ↑ sedation
- Valproic acid (for GFC):
  - GFC can ↑ VPA levels (mechanism is unknown, but may involve competitive inhibition of glucuronidation)
- TCAs or neuroleptics with α-receptor blocking properties:
  - Antihypertensive effect of α2 agonists may be reduced and orthostatic regulation disturbances may be exacerbated
**GFC: Food Interactions**

- Patients taking GFC should **not** consume grapefruit, because grapefruit inhibits 3A4 and thereby **increases** guanfacine levels.
- GFC-XR should **not be taken with high-fat meals**, because high-fat meals increase drug absorption and thereby **increase** guanfacine levels.

**Dosing: CLON-IR**

- 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 adherence is a concern)
  - More frequent dosing is preferred because of CLON’s short half-life, and because a greater number of smaller doses may be less sedating than a smaller number of bigger doses

**Dosing: CLON-IR (cont.)**

- Usual dose range is **0.1-0.4 mg/day**, but CLON-IR has been studied and found to be generally safe up to **0.6 mg/day** (TSSG, 2002; Daviss et al., 2008)
- Improvement (for both ADHD and tics) occurs gradually over several weeks

**Dosing: GFC-XR**

- Start GFC-XR **1 mg/day for at least 1 week**
- Based on efficacy and tolerability, the dose may be ↑ by no more than **1 mg/week up to a maximum of**:
  - 4 mg/day in children (6-12 yrs), whether used as monotherapy or as an adjunct to a stimulant
  - 4 mg/day in adolescents (13-17 yrs) when used as an adjunct to a stimulant
  - 7 mg/day in adolescents (13-17 yrs) when used as monotherapy
- In both monotherapy and adjunctive trials, the optimal weight-based dose was generally in the range of **0.05-0.12 mg/kg/day**

**Dosing: GFC-XR (cont.)**

- GFC-XR is dosed once daily in the morning or evening:
  - QAM and QPM dosing were found to have similar efficacy and tolerability (Newcorn et al., 2013)
- Tablets should **not be cut, crushed, or chewed**
- If ≥2 consecutive doses are missed, re-titration is recommended
- Improvement (for both ADHD and tics) occurs gradually over several weeks

**Monitoring**

- Response and adverse effects (preferably using child/parent and teacher rating scales)
- Sedation (often improves over several weeks)
- HR & BP:
  - At baseline, after dose adjustments, and then periodically
- Routine ECG monitoring is not required
Discontinuing $\alpha_2$ Agonists

- $\alpha_2$ agonists should be tapered gradually, as abrupt discontinuation can result in rebound hypertension, tachycardia, and arrhythmias.

- Suggested tapering schedule:
  - CLON-IR: ↓ by 0.05 mg/day every 3-4 days (Connor & Meltzer, 2006)
  - GFC-XR: ↓ by no more than 1 mg every 3-7 days (eCPS)

- HR & BP should be monitored while $\alpha_2$ agonists are being tapered and shortly after they have been discontinued.
Atomoxetine Treatment for Pediatric Patients with ADHD and Comorbid Anxiety

DANIEL GELLER, M.B.B.S., CRAIG DONNELLY, M.D., FRANK LOPEZ, M.D., RICHARD RUBIN, M.D., JEFFREY NEWCORN, M.D., VIRGINIA SUTTON, PH.D., ROSALIE BAKKEN, PH.D., MARTIN PACZKOWSKI, M.P.H., DOUGLAS KELSEY, M.D., AND CALVIN SUMNER, M.D.
Spencer et al., 2007

A

Mean Percentile Weight

0 10 20 30 40 50 60 70 80 90 100

0 6 12 18 24 30 36 42 48 54 60

Months of Exposure

b b b b b a a

B

Mean Percentile Height

0 10 20 30 40 50 60

0 6 12 18 24 30 36 42 48 54 60

Months of Exposure

a b

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