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Alpha-2a Receptor Agonists

General

- FDA-approved for ADHD in folks aged 6 and up
- Mechanism
  - Stimulates pre-synaptic alpha2-adrenergic receptors in the brain stem
  - -->reduce firing of noradrenergic sympathetic outflow of the locus coerulus
  - Reduce release of norepinephrine and dopamine from noradrenergic neurons
  - Reduce sympathetic nervous system outflow
  - Stimulates post-synaptic alpha2-adrenergic receptors in the prefrontal cortex
    - Post-synaptic alpha-2a receptor activation provides the most benefit in ADHD (vs. pre-synaptic alpha-2a or alpha-2b or alpha-2c)
    - Post-synaptic alpha-2a receptors may mediate norepinephrine neurotransmission in the PFC to enhance inhibition over lower central nervous system structures and to enhance working memory under distracting conditions
    - Stimulant of pre-synaptic alpha-2a or alpha-2b receptors causes more significant sedation than stimulation of other alpha-2 receptor subtypes
  - Onset of therapeutic effect (for clonidine with respect to ADHD symptoms) is delayed at least 4-6 weeks after therapeutic dose
  - May have antiepileptic affect (via action in the amygdala)
  - Stimulate release of growth hormone

Clonidine (must monitor blood pressure, may need EKG)

- Evidence
  - Clonidine Extended-Release
    - Jain et al, 2011
      - 8-wk, double blind, 236 children 6-17, ADHD
      - Received either placebo or clonidine ER 0.2 mg/day or clonidine ER 0.4 mg/day
      - Positive efficacy and safety at 5 weeks
    - Kollins et al, 2011
      - 8-wk, double-blind, 198 children 6-17, ADHD and previous inadequate response to a stimulant
      - Randomized to placebo vs. clonidine ER added to stimulant
      - Positive efficacy and safety at 5 weeks
      - 0.2 mg twice-a-day
  - Clonidine immediate release
    - Hazell et al, 2003: confirmed safety and efficacy of clonidine when added to stimulant medication in pediatric ADHD.
    - As effective as Risperdal in the treatment of Tourette syndrome (Gaffney et al, 2002)
    - Connor et al, 1999: meta-analysis of 11 studies of clonidine in the treatment of ADHD; small to moderate effect size
    - 6-week trial; 31 youth with clonidine alone; 29 with methylphenidate alone; 30 with place; somnolence and fatigue worse with clonidine.
    - NINDS: 16 week, multi-site study, 31 youth on clonidine, 29 on methylphenidate, 32 on both, 30 on placebo; safe and effective
    - 4 studies (2 controlled) of 122 children support the safety and efficacy of clonidine in the treatment of pediatric ADHD
    - Less effective in the treatment of tics than first generation antipsychotics
    - 2 controlled studies in autistic children with symptoms of ADHD
    - Leckman et al, 1991: clonidine 3-5 mcg/kg more effective than placebo in treating tics and ADHD symptoms
    - Negative RCTs: Dysken et al, 1981; Goetz et al, 1987
    - Positive RCTs: McKeith et al, 1981; Borison et al, 1983; Leckman et al, 1991
    - Less effective in the treatment of ADHD than TCA's (Shapiro et al, 1983)

        - ADHD and tics/Tourette syndrome: Cohen group: Cohen et al, 1979, 1980; Young et al, 1980—ADHD symptoms treated more than tics
    - Seems most effective in disinhibited and agitated youth, with less impact on attention.
- Pharmacokinetics/dynamics
    - Clonidine immediate release
        - Peak level in 1-3 hours in adults (elsewhere: peak level in 3-5 hours; ?in children)
        - Half-life of 8-12 hours in children and 12-16 hours in adults
        - Behavioral effects last 3-6 hours; usually needs to be given 3-4X/d
    - Clonidine Extended Release
        - Peak level in 3-5 hours
        - 50% lower plasma concentration than that of immediate release clonidine
- Functions by:
    - Activates pre-synaptic alpha-2a noradrenergic receptors as well as the alpha-2b and 2c receptors
    - Less selectively activates post-synaptic alpha-2a receptors
    - Has imidazoline I-1 receptor effects
- Side effects
    - Drowsiness/sedation (33-43%)
    - Dry mouth (~50%)
    - Faintness (~50% or less)Dizziness/exercise-related dizziness (16-50%)
    - Weakness (10%)
    - Sleep disturbance (10%)
    - Depression (5%)
    - Cardiac arrhythmia (5%)
    - Nausea/vomiting (5%)
    - Irritability (3-30%)
    - Cardiovascular
        - Decreases blood pressure and pulse; DO NOT USE IF have fainting spells, bradycardic arrhythmias, SA/AV node dysfunction, Raynaud's syndrome, cardiac conditions, diabetes mellitus
        - Low blood pressure on standing (3%)
    - Sudden death
        - Four cases of sudden death have been reported in children treated with clonidine plus methylphenidate (Silva, 1996)
            - There were extenuating circumstances
            - A review by the FDA determined that there was no evidence of causality.
        - Second series:
            - 10,000 exposures of clonidine in children less than 6 yo from 1993-1999—only one death
            - No evidence of causality
            - National Heart and Lung Institute Meeting in 1996 voiced that the association between clonidine and the cases of sudden death was not clear, and that the current guidelines for ECG monitoring were too conservative.
            - Non-adherence can result in adrenergic rebound: high blood pressure, sweating, fast heart rate, diarrhea, anxiety
- Dosing
    - Comes in tablets (0.1, 0.2, and 0.3 mg tabs) and transdermal therapeutic system (TTS; 0.1 mg, 0.2 mg, and 0.3 mg daily doses)
    - Immediate release tablets:
        - 3-5 mcg/kg/day (or 0.003-0.01 mg/kg/day)
        - usual range from 0.1-0.3 mg/d (occasionally up to 0.5 mg/d)
        - dose should not be increased by more than 0.05 mg every 3 days
        - Start at 0.025-0.05 mg/night; increase by 0.025-0.05 mg every 4-7 days to 0.15-0.3 mg/day in 3-4 divided doses
    - Patch:
        - can cut the patch to adjust the dose
        - put in area with least perspiration; may not adhere well in hot, humid environments; in kids
        - change every 5 days; in adults
        - change every 7 days

        - watch for rash
    - Clonidine Extended Release
        - Initial recommended dose 0.1 mg/pm
        - Titrate by 0.1 mg/week up to a maximum dose of 0.4 mg/day
        - With doses greater than 0.1 mg/day, divide dose with the higher dose given at bedtime

Guanfacine (Tenex)/Guanfacine Extended Release (Intuniv)

- Evidence
    - Intuniv
        - Same efficacy if whether given at night or AM.
        - Best efficacy (in Sallee et al, 2009) at 0.09-0.12 mg/kg/d
        - Wilens et al, 2015
            - Multicenter, randomized, placebo-controlled trial in adolescents with ADHD; 13-week
            - 1-7 mg/day
                - 23% received 3 mg/day
                - 20% received 4 mg/day
                - 20% received 5 mg/day
                - 18% received 6 mg/day
            - 314 participants (157 in Intuniv group and 157 in placebo group)
            - Safe and effective
                - Improvements began at week 1 and increase weekly through week 10
                - 75% response rate by week 10 vs. 60% with placebo
            - Side effects
                - **Somnolence OR fatigue OR sedation: 77.7% vs. 35.5% placebo**
                - **Somnolence 43.9% vs. 21.3% placebo**
                - Nausea OR vomiting OR upper abdominal pain OR abdominal pain 29.9% vs. 28.4% placebo
                - **Headache 26.8% vs. 18.1% placebo**
                - **Fatigue 22.3% vs. 12.3% placebo**
                - **Dizziness 15.9% vs. 10.3% placebo**
                - Decreased appetite 14.6% vs. 13.5% placebo
                - Nausea 12.1% vs. 13.5% placebo
                - **Nasopharyngitis 11.5% vs. 5.8% placebo**
                - **Sedation 11.5% vs. 1.9% placebo**
                - Increased appetite 8.9% vs. 8.4% placebo
                - **Insomnia 8.9% vs. 3.9% placebo**
                - URI 8.9% vs. 7.7% placebo
                - Diarrhea 7.6% vs. 8.4% placebo
                - **Dry mouth 7.6% vs. 0% placebo**
                - **Irritability 7% vs. 3.9% placebo**
                - Upper abdominal pain 6.4% vs. 4.5% placebo
                - Abdominal pain 5.7% vs. 3.9% placebo
                - Vomiting 5.7% vs. 6.5% placebo
                - **Dizziness on standing 5.1% vs. 1.9% placebo**
                - Cough 1.9% vs. 5.2% placebo
        - Scahill et al, 2015: kids with autism spectrum disorder and hyperactivity, 62 youth, 5-14 yo; 8 weeks
            - Modal dose 3 mg/day
            - Significant improvement in repetitive behaviors and communication; response rate
                - Intuniv: 50%
                - Placebo: 9.4%
            - Side effects
                - Drowsiness 87% vs. 9% placebo
                - Fatigue 63% vs. 9% placebo
                - Decreased appetite 43% vs. 6% placebo

        - Dry mouth 40% vs. 3% placebo
        - Emotional/tearful 40% vs. 9% placebo
        - Irritability 37% vs. 9% placebo
        - Anxiety 30% vs. 3% placebo
        - Mid-sleep awakening 30% vs. 6% placebo
        - Blood pressure readings returned to baseline measures by week 8
        - Heart rate remained 10 bpm below baselines measures at week 8
        - No clinically significant changes in ECG
    - Hirota et al, 2013
        - Meta-analysis looking at immediate release and extended release forms of clonidine and guanfacine; 12 studies, 2276 youth, monotherapy and adjunctive studies included
        - Monotherapy>adjunctive therapy>placebo
        - Side effects
            - Fatigue
            - Sedation
            - Somnolence
            - When monotherapy studies pooled, no difference in blood pressure or heart rate
                - When looked at separately, only clonidine immediate release showed a drop in systolic blood pressure (by -5.2 mm Hg)
            - When augmentation therapy studies pooled, blood pressure was lower by -3.5 mm Hg and heart rate was lowered by -6.8 bpm.
    - Newcorn et al, 2013, 333 youth, 6-12 yo with ADHD, monotherapy, once daily dosing, 1-4 mg, either in AM or in PM; safe and effective regardless of time of dose
        - Side effects
            - Somnolence 44.3% vs. 12.5% placebo
            - Headache 16.7% vs. 10.7% placebo
            - Sedation 14.5% vs. 2.7% placebo
            - Abdominal pain 12.2% vs. 7.1% placebo
            - Fatigue 10.9% vs. 2.7% placebo
            - Irritability 7.2% vs. 2.7% placebo
            - Nausea 5.4% vs. 0.9% placebo
            - Vomiting 5% vs. 1.8% placebo
            - Wetting 3.2% vs. 0.9% placebo
    - Connor et al, 2013, youths with PTSD, open-label; effective
    - Wilens, et al, 2012, 461 youth, 6-17 yo with ADHD, adjunctive Intuniv vs. plac added to stimulant; positive
    - Connor et al, 2009; 217 youth with ADHD; positive
    - Sallee et al, 2009, 324 youth 6-17 with ADHD; monotherapy over 8-9 weeks with medicine tapered at weeks 5-6; double blind; positive; 2 year open-label follow-up demonstrated continued benefit
        - **Best efficacy at 0.09-0.12 mg/kg/day**
    - Biederman, 2008, 345 youth 6-17 with ADHD; monotherapy over 8-9 weeks with medicine tapered at weeks 5-6; double blind; positive
    - Melmed et al, 2006 (Intuniv)
        - Multicenter, double-blind, parallel group, RCT, 2 or 3 or 4 mg/day, vs. placebo, youth aged 6-17—safe and effective for symptoms of inattention, impulsivity, and hyperactivity; 345 youth
        - Children exhibit higher peak levels than adolescents
        - No discontinuation symptoms, cardiac/blood pressure or otherwise
        - Main side effects—sleepiness and fatigue
        - Over two years, no ECG, growth, or pulse rate abnormalities were reported
    - Posey, 2005: retrospective analysis of 80 cases of treatment of hyperactivity and inattention in children with pervasive developmental disorders; evidence of efficacy (with tics and insomnia as well) and safety with no significant changes in blood pressure or heart rate
- ADHD and Tourette syndrome
    - Not efficacious (Cummings et al, 2002)
- ADHD

        - Hunt et al, 1995: 13 youths; average dose 3.2 mg/day
        - Horrigan and Barnhill, 1995: 15 youths; 0.5-3 mg/day; but in youth with risk factors for bipolar disorder, it can precipitate mania
    - ADHD and tics
        - Chappell et al, 1995: 10 youths with ADHD and Tourette syndrome
        - Walkup et al, 1995
            - More pro-cognitive effects than clonidine (more specific to prefrontal cortex)
            - Less effective than TCA's in ADHD
    - Mixed evidence of benefit in PTSD (no improvement seen in war veterans with PTSD; Neylan et al, 2006))
    - Prospective open trial in pervasive developmental disorders (Scahill et al, 2006); beneficial; irritability, sleep disturbance, sedation
    - Overall, improves
        - working memory
        - reduced distractibility
        - improved attention regulation
        - improved behavioral inhibition
        - enhance impulse control
- Pharmacokinetics/dynamics
    - Guanfacine immediate release
        - Peak level in 1-4 hours (average 2.6 hours in adults)
        - Half-life of 13-14 hours in children and 10-30 hours (average 17 hours) in adults
        - Behavioral effects last longer than clonidine; requires 2-3X/d dosing
    - Guanfacine Extended Release
        - Peak level in 5 hours
        - Maximum plasma concentration is 60% lower than immediate release guanfacine
- Works by
    - Selective activation of post-synaptic alpha-2A receptors (greater than 20 times greater affinity for alpha-2a than the other subtypes
- Side effects
    - Drowsiness/sedation 13-21%; Intuniv associated with 39-60% sedation or somnolence or fatigue (vs. 14% with placebo in Wilens); tends to decrease over 2-6 weeks
    - Headache; 28-32% with Intuniv (vs. 20% with placebo in Wilens)
    - Upper abdominal pain in 10%; 12-13% with Intuniv (vs. 3% with placebo in Wilens)
    - Decreased appetite; 9-11% with Intuniv (vs. 6% with placebo in Wilens)
    - Dizziness 8%; 8-15% with Intuniv (vs. 6% with placebo in Wilens)
    - Weakness 7%
    - Insomnia 5%; 8-18% with Intuniv (vs. 6% with placebo in Wilens)
    - Nausea/vomiting >1%; 4-11% with Intuniv (vs. 5% with placebo in Wilens)
    - Depression (<1%)
    - Cardiac arrhythmia (<1%)
    - Irritability (<1%)
    - Orthostatic hypotension (<1%)
    - Weight gain (<1%)
    - Hallucinations (<1%)
    - Fewer side effects, more tolerable, and less risky than clonidine
    - Case report of seizure when used with Wellbutrin
    - Dry mouth
    - Fatigue
    - Less frequent: nervousness, agitation, headache, nightmares, frequent waking, weight gain, nausea, vomiting. Low blood pressure, slower heart rate. Question of electrocardiographic abnormalities, depression, irritability, changes in blood counts, changes in liver/kidney function
- Dosing
    - Comes in immediate release tablets (1 mg and 2 mg) and XR tabs (1 mg, 2 mg, 3 mg, and 4 mg)

- 0.5-4 mg/day (up to 6 mg/day in adults); can be increased by 0.5 mg every 3-4 days
- Intuniv
  - Start at 0.05-0.08 mg/kg/day, usually 1 mg/AM
  - Increase to max 0.12 mg/kg/day; usually by 1 mg/week up to 4 mg/day

- Medical issues:
  - Obtain initial physical exam, EKG, lab tests, vital signs
  - Heart rhythm problems and kidney disorders are relative contraindications to use of these medications
  - Repeat EKG once on stable dose
  - If sudden dizziness, fatigue, light-headedness, sleepiness, fainting—decrease dose, obtain EKG, further evaluation by internist
  - If sudden fast pulse, fast breathing, anxiety, panic, changes in mental status—check to see if dose was missed, re-start it and then taper medication

Acute and Long-Term Cardiovascular Effects of Stimulant, Guanfacine, and Combination Therapy for Attention-Deficit/Hyperactivity Disorder

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OBJECTIVES: This study examines cardiovascular (CV) effects of guanfacine immediate-release (GUAN-IR), dexmethylphenidate extended-release (DMPH), and their combination (COMB) during acute and long-term treatment of youth with attention-deficit/hyperactivity disorder.

METHODS: Two hundred seven participants aged 7-14 years enrolled in an 8-week double-blind randomized trial of GUAN-IR (1-3 milligrams (mg)/day), DMPH (5-20mg/day), or COMB with fixed-flexible dosing and titrated to optimal behavioral response. Heart rate, systolic blood pressure (BP), diastolic BP, and electrocardiograms were assessed at baseline, end of blinded optimization, and over a 1-year open-label maintenance phase.

RESULTS: During acute titration, GUAN-IR decreased heart rate, systolic BP, and diastolic BP; DMPH increased heart rate, systolic BP, diastolic BP, and corrected QT (QTc) interval; COMB increased diastolic BP, but had no effects on heart rate, systolic BP, or QTc. During maintenance, GUAN-IR-associated decreases in heart rate and DMPH-associated increases in systolic BP returned to baseline values. Other variables across the three groups remained unchanged from the end of blinded titration. There were no discontinuations due to CV adverse events.

CONCLUSION: GUAN-IR, DMPH, and COMB were well tolerated and safe. Expected changes in CV parameters during acute titration were seen in GUAN-IR and DMPH groups, with COMB values falling intermediately between the two other treatment groups. No serious CV events occurred in any participant. GUAN-IR- and DMPH-associated CV changes generally returned to baseline with sustained therapy. These data suggest that COMB treatment might attenuate long-term CV effects of GUAN-IR and stimulant monotherapy, possibly reducing risk of the small but statistically significant changes associated with either single treatment. Clinicaltrials.gov Identifier: NCT00429273.

Efficacy of guanfacine extended release assessed during the morning, afternoon, and evening using a modified conners' parent rating scale-revised: short form

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OBJECTIVE: The purpose of this study was to evaluate the efficacy of once-daily guanfacine extended release (GXR) monotherapy administered either in the morning or evening, using a modified Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) assessed three times/day in children with attention-deficit/hyperactivity disorder (ADHD).

METHODS: This multicenter, double-blind, placebo-controlled study randomized children 6-12 years of age with ADHD into three groups: GXR a.m. (GXR in the morning and placebo in the evening), GXR p.m. (placebo in the morning and GXR in the evening), or twice-daily placebo. The CPRS-R:S, administered in the morning, afternoon, and evening prior to each study visit, was a secondary measure of efficacy.

RESULTS: A total of 333 subjects were included in the analysis population (GXR a.m., n=107; GXR p.m., n=114; placebo, n=112). At visit 10, last observation carried forward (LOCF), subjects receiving GXR demonstrated significantly greater improvement from baseline in the daily mean CPRS-R:S total score, as well as in each of the morning, afternoon, and evening CPRS-R:S assessments, compared with placebo, regardless of the time of GXR administration ($p<0.001$ vs. placebo for GXR a.m. and GXR p.m.). In addition, subjects receiving GXR showed significantly greater improvements from baseline in each subscale score (oppositional, cognitive problems/inattention, hyperactivity, and ADHD index) compared with those receiving placebo, regardless of time of administration ($p<0.003$ vs. placebo across all subscales for GXR a.m. and GXR p.m.).

CONCLUSIONS: These results provide further support for the demonstrated efficacy of once-daily GXR in reducing ADHD symptoms, and demonstrate that response is consistent throughout the day regardless of the time of administration, with improvement seen in ratings of oppositional as well as of ADHD symptoms.