MEDICATIONS SAFETY ATTENTION DEFICIT HYPERACTIVITY DISORDER

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INTRODUCTION

- ADHD is one of the most common neuropsychiatric disorders of childhood and adolescence, that often persists into adulthood.
- ADHD in adulthood is associated with significant impairment in occupational, academic, and social functioning.

STIMULANTS

- Stimulants are considered first-line therapy in most cases of ADHD; however, comorbid conditions impact the drug selection process.
- They are the most effective drug treatment options.

FDA-APPROVED STIMULANTS

- Methylphenidate
- Dexmethylphenidate
- Mixed amphetamine salts
- Dextroamphetamine

STIMULANTS

- Methylphenidate is effective in adolescents and adults in doses up to 1.5 mg/kg daily.
- Administration of stimulant medications with food can delay the absorption and subsequently delay the onset of therapeutic effect.
- Total bioavailability of stimulant can be decreased by 10% to 30% with co-administration of food.

SAFETY

- **Stimulants have been used to treat ADHD since the 1930s and generally are considered to be safe.**
- **Rare, serious adverse events have been reported in children being treated with stimulants, but a causal association has not been established**
- **The potential risks of stimulants should be discussed with patients and families when choosing a management strategy.**

GENERAL ADVERSE EFFECTS

- **Many of the side effects of stimulants are mild, of short duration, and reversible with adjustments to the dose or dosing interval.**
- **Side effects may occur more frequently in preschool children than in older children.**
- **Relatively common side effects include anorexia, poor growth or weight loss, sleep disturbance, jitteriness, and emotional lability (eg, social withdrawal).**
- **Deceleration of linear growth may occur but appears to attenuate over time; cessation of treatment may result in normalization of growth, and adult height does not appear to be affected.**
- **Growth should be regularly monitored during treatment with stimulants.**
- **Less common side effects include increased heart rate and blood pressure, headache, dizziness, gastrointestinal symptoms, priapism, and peripheral vasculopathy, including Raynaud phenomenon.**

BOXED WARNINGS

- **Psychiatric** (psychosis/mania – aggression/violent behavior – severe anxiety/panic attacks); MUST be avoided in patients with primary psychotic illnesses.
- **Cardiac** (sudden unexplained death – increased heart rate and blood pressure); use with CAUTION in patients with structural cardiac abnormalities. [careful *screening* and baseline *ECG*)

PSYCHIATRIC EFFECTS

- **Psychosis** – Children and adolescents treated with stimulant medications **rarely** may develop psychotic symptoms (eg, hallucinations, delusional thinking, or mania), but causality has not been established.
- In pooled analysis of data from 49 randomized trials of medications used to treat ADHD (35 of which evaluated stimulants), psychotic symptoms developed in 11 children during 743 person-years of follow-up (incidence rate of 1.48 episodes per 100 person-years).
- In subsequent analysis of two commercial insurance claims databases that evaluated psychosis requiring treatment with antipsychotic medication after initiation of stimulant therapy in 221,846 adolescents and young adults (age 13 to 25 years), 343 episodes occurred in 143,286 person-years of follow-up (incidence rate of 2.4 episodes per 1000 person-years) . The median time between initiation of stimulant and the psychotic episode was 128 days. The absolute risk was higher with amphetamines than with methylphenidate (2.83 versus 1.78 episodes per 1000 person-years, hazard ratio 1.7, 95% CI 1.3-2.1).

PSYCHIATRIC EFFECTS

- Although it is not possible to predict which patients will develop psychotic symptoms after initiation of stimulants, the risk may be increased in children with a family history of mental illness (eg, major depressive disorder, bipolar disorder)
- **Suicidal thinking** – Rare cases of suicidal thinking have been reported among individuals taking stimulants for ADHD, but causality has not been established.

CARDIAC EFFECTS

- Reports of sudden unexpected deaths (SUDs) among patients taking stimulant drugs for ADHD have led to concerns regarding the safety of psychotropic medications.
- In particular, the question of whether or not stimulant drugs increase the risk of adverse cardiovascular (CV) events has led to a debate on the appropriate evaluation to identify patients with **undiagnosed at-risk congenital heart disease** (CHD) and/or **arrhythmias** prior to starting a patient on medications for the treatment of ADHD.

CARDIAC EFFECTS

- Although there had been concerns of serious adverse cardiac e?ects, stimulant therapy does not appear to increase the risk of sudden unexpected cardiac death or other serious cardiac complications (eg, myocardial infarction or stroke) in patients without underlying cardiac disease.
- Stimulant medications are known to have modest cardiovascular effects including **small elevations in heart rate (3 to 10 beats per minute)**, **systolic blood pressure (3 to 8 mmHg),** and **diastolic blood pressure (2 to 14 mmHg)**.

EVALUATIONS

- Based upon the available evidence, we agree with the approach outlined by the American Academy of Pediatrics and the American Heart Association for a careful pretreatment evaluation including a **comprehensive CV-focused patient history, family history, and physical examination**.
- If the history and examination are not suggestive of cardiac disease, pharmacotherapy can be initiated or continued without additional evaluation.
- An electrocardiogram (ECG) is **not** required before initiating stimulant therapy for patients with ADHD. However, if the patient is known to have cardiac disease, or if the history or physical examination is suggestive of cardiac disease, further evaluation including ECG and/or consultation with a pediatric or adult cardiologist is needed.

MONITORING

- During treatment with ADHD stimulant therapy, the patient should be assessed for any changes in CV symptoms (eg, **fainting or dizziness, seizures, chest pain or shortness of breath with exercise, unexplained change in exercise tolerance, or palpitations**).

- Evaluation should include **measurement of heart rate** and **blood pressure** to ascertain whether there have been any significant changes in these signs, especially if the blood pressure reaches either prehypertension or hypertension levels.

- In patients with concerning symptoms, consultation with a pediatric cardiologist should be considered.

PRIAPISM

- Priapism is a rare complication of methylphenidate stimulants.
- Review of data submitted to the FDA Adverse Event Reporting System noted 15 cases of priapism in methylphenidate recipients between 1997 and 2012.
- Most of the cases occurred in boys <18 years (median age 12.5 years, range 8 to 33 years); two cases required surgical treatment.
- Priapism occurred in a variety of settings including increased dose, longer than typical dosing interval, and temporary or permanent discontinuation of methylphenidate stimulants.
- Priapism has also been reported among four patients taking amphetamine stimulants for ADHD. However, the correlation between amphetamine stimulants and priapism is uncertain because these patients were also taking other medications associated with priapism.

TICS

- Stimulant medications have been reported to cause new onset of tics or worsening of tics in children with tic disorders.
- Tics or a family history of tics are included as a contraindication to some forms of methylphenidate and a significant adverse effect of both methylphenidate and amphetamines. Nonetheless, stimulant medications often improve attention and behavior without worsening tics in children who have chronic tics or Tourette syndrome.
- Taken together: children with tics and ADHD can benefit from stimulant medications without worsening of tics, but higher-than-usual doses of dextroamphetamine should be avoided. For children in whom stimulant medications were discontinued because of new or worsening tics, rechallenge with stimulants may be warranted, particularly if the behavioral response to nonstimulant medications was inferior to that with stimulants.

SEIZURE

- **Although ADHD is common among children with epilepsy, methylphenidate does not appear to increase the frequency or severity of seizures in children who are receiving appropriate anticonvulsant medications.**

- Diversion and misuse

CONTRAINDICATIONS TO STIMULANT MEDICATIONS MAY INCLUDE

- Symptomatic cardiovascular disease
- Moderate to severe hypertension
- Hyperthyroidism
- Known hypersensitivity or idiosyncrasy to sympathomimetic amines
- Motor tics or Tourette syndrome
- Glaucoma
- Agitated states
- Anxiety
- History of drug abuse
- Concurrent use or use within 14 days of the administration of MAOI.

STIMULANTS ADVERSE EFFECTS & THEIR MANAGEMENT

Adverse Effect	Recommendation/Management Strategy
Common	
Reduced appetite, weight loss	Give high-calorie meal when stimulant effects are low (at breakfast or at bedtime), or consider cyproheptadine at bedtime
Stomachache	Administer stimulant on a full stomach; lower dose if possible
Insomnia	Give dose earlier in the day; lower the last dose of the day or give it earlier; consider a sedating medication at bedtime (guanfacine, clonidine, melatonin, or cyproheptadine)
Headache	Divide dose, give with food, or give an analgesic (e.g., acetaminophen or ibuprofen)
Rebound symptoms	Consider longer-acting stimulant trial, atomoxetine, or antidepressant
Irritability/jitteriness	Assess for comorbid condition (e.g., bipolar disorder); reduce dosage; consider mood stabilizer or atypical antipsychotic
Uncommon to Rare	
Dysphoria	Reduce dosage; reassess diagnosis; consider alternative therapy
Zombie-like state	Reduce dosage or change stimulant medication
Tics or abnormal movements	Reduce dosage; consider alternative medication
Hypertension, pulse fluctuations	Reduce dosage; change medication
Hallucinations	Discontinue stimulant; reassess diagnosis; mood stabilizer and/or antipsychotic may be needed

METHYLPHENIDATE (RITALIN ®)

- **Contraindications:** Concomitant treatment with MAOIs, or within 14 days following discontinuation of treatment with an MAOI, because of the risk of hypertensive crises.
- Usually prescribed in 2-3 divided doses.
- Better taken 3—45 minutes before meals.

NON-STIMULANTS

- Extended-release guanfacine, extended-release clonidine, and atomoxetine are less effective alternatives to the stimulants for treatment of ADHD in children and adolescents.
- Atomoxetine is also approved in adults.

- **Benefits relevant to stimulants:**
  - No abuse potential
  - Less potential for growth effects
  - Less sleep disturbance

NON-STIMULANTS

- Atomoxetine has a significantly slower onset of therapeutic effect than stimulants. (2 to 4 weeks vs. 1 to 2 hours with an effective stimulant dose) & full benefit may not be seen for 6 to 8 weeks.
- Atomoxetine is sometimes combined with a stimulant.

NON-STIMULANTS

- Atomoxetine's adverse effects;
  - Upset stomach
  - Psychiatric ADRs
  - Cardiac ADRs
- Atomoxetine has less growth suppression risk compared with stimulants, but it has a greater risk of fatigue, sedation, and dizziness compared with stimulants or bupropion.
- *Unlike stimulants, atomoxetine labeling includes a bolded warning of potential for severe liver injury.*

ATOMOXETINE ADRS

- Common General ADEs : weight loss, abdominal pain, decreased appetite, vomiting, nausea, dyspepsia, headache, dizziness, somnolence/fatigue, and irritability
- The risk of adverse effects may be affected by genetic variations in the cytochrome P450 (CYP2D6) enzyme pathway.
- Cardiovascular effects
- Priapism
- Suicidal thinking
- Psychiatric effects
- Tics
- Liver injury

CONTRAINDICATIONS TO ATOMOXETINE

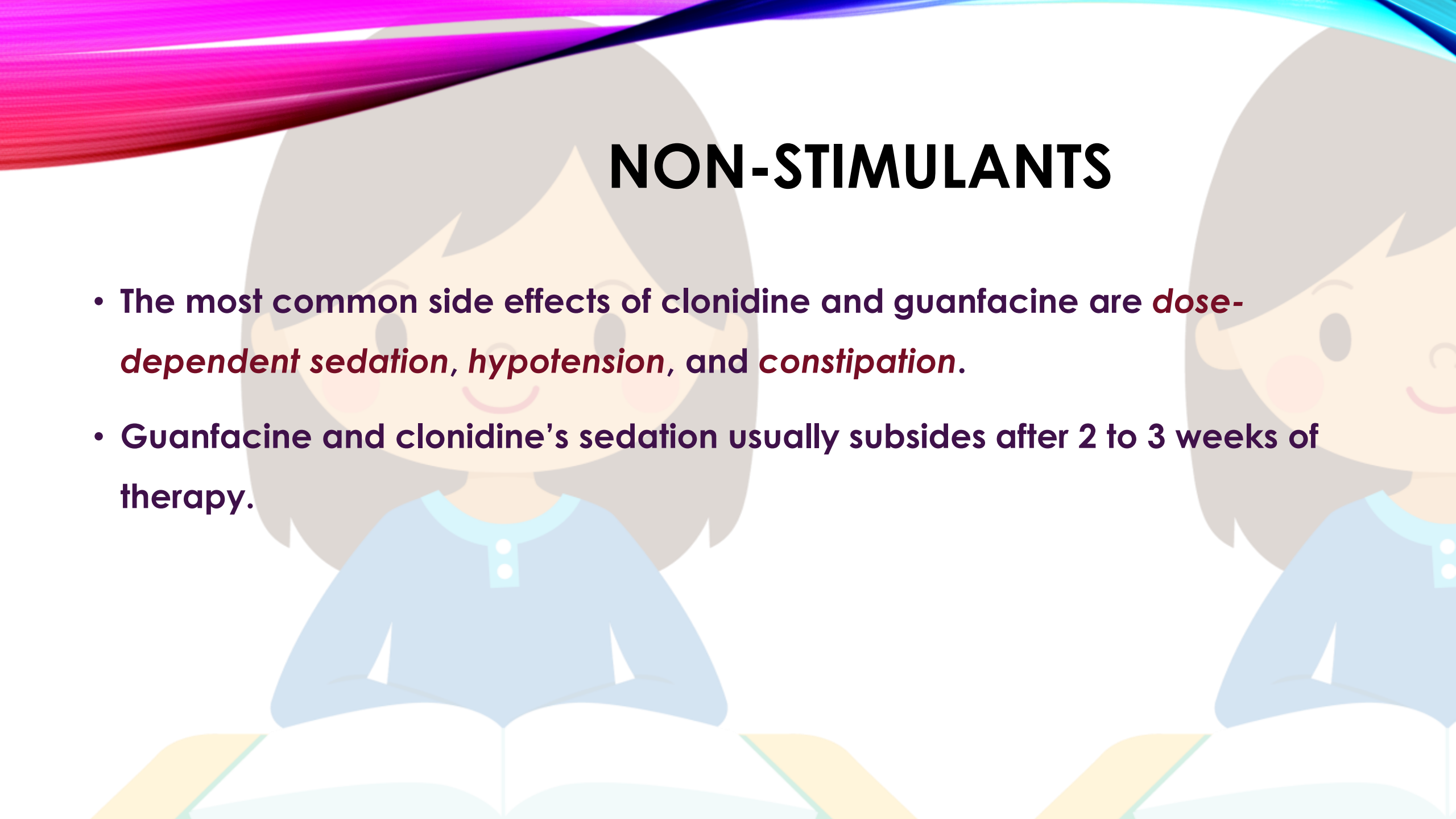
- Hypersensitivity to atomoxetine or any component
- Concurrent use or use within 14 days of the administration of MAOI
- Glaucoma
- Current or past history of pheochromocytoma
- Severe cardiovascular disorders in which increases in diastolic blood pressure >15 mmHg, systolic blood pressure >20 mmHg, or heart rate >20 beats/minute would be expected to cause clinical deterioration

NON-STIMULANTS

- Guanfacine and clonidine are central a2-adrenergic agonists.
- Clonidine and guanfacine are not as effective as stimulants for monotherapy treatment.
- Clonidine and guanfacine are FDA approved as adjuncts to stimulants.

NON-STIMULANTS

- The most common side effects of clonidine and guanfacine are *dose-dependent sedation*, *hypotension*, and *constipation*.
- Guanfacine and clonidine's sedation usually subsides after 2 to 3 weeks of therapy.



BUPROPION AND TRICYCLIC ANTIDEPRESSANTS

- Bupropion has been found beneficial for adolescents with depression and ADHD.
- Bupropion causes less appetite suppression and weight loss compared with stimulants.
- Bupropion has a greater risk of seizures.

BUPROPION AND TRICYCLIC ANTIDEPRESSANTS

- Bupropion's adverse effects include nausea, which can resolve over time or with slower dosage titration, and rash, which can require discontinuation of therapy if severe.
- Possible CNS adverse effects of TCAs include dizziness, aggressiveness, excitement, nightmares, insomnia, forgetfulness, and irritability.

Thank you