NON-STIMULANT MEDICATION

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Learning Objectives

1. List non-stimulant medication options for treating ADHD
2. Compare and contrast the time to benefit and expected efficacy of non-stimulant medications used in treating ADHD
3. Compare and contrast the safety/tolerability profiles of non-stimulant medication classes used in treating ADHD
4. Formulate key counseling pearls for a patient newly starting on a non-stimulant medication for ADHD, including onset of action, administration principles, common and serious adverse effects, follow-up monitoring, and expected duration of use
5. Select a non-stimulant medication as adjunct therapy or monotherapy for treating ADHD in an individual patient

Treatment Options

- Pharmacotherapy
  - CNS stimulants
  - NE reuptake inhibitor
  - Alpha-2-adrenergic agonists
  - Antidepressants
- Behavioral/cognitive interventions
- Combination treatment

↑ executive function
↑ attentiveness
↓ distractibility
↓ hyperactivity and restlessness
↓ behavioral disruption
↓ impulsive decisions and risk taking

Atomoxetine (Strattera®)

- Norephinephrine re-uptake inhibitor (selectively inhibits presynaptic NE transporter)

- Demonstrated efficacy in treating core symptoms of ADHD, but less robust than that of stimulant medications
- Delayed onset of action: 4 to 6 weeks to see max therapeutic effect
- Metabolized via CYP2D6: requires dose adjustment with strong 2D6 inhibitors (i.e. fluoxetine, paroxetine)
- Low abuse potential

Atomoxetine (Strattera®)

- Black Box Warning:

  “There is an increased risk of suicidal ideation in children and adolescents. No suicides occurred in clinical trials. Monitor patients closely for suicidal thinking and behavior, clinical worsening, or unusual changes in behavior.”

Atomoxetine (Strattera®)

Possible SEs

- **N/V, GI upset**
- ↓ appetite
- Dyspepsia
- Dizziness
- Irritability
- Insomnia / **Somnolence**
- ↑ BP and HR
- Hepatitis (rare)

Alpha-2 Adrenergic Agonists

- Mechanism of action
  - Clonidine ER (Kapvay®): nonspecific alpha$_2$-receptor agonist
  - Guanfacine ER (Intuniv®): selective alpha$_{2A}$-receptor agonist
  - Reduces sympathetic outflow and mediates cognitive effects of NE in frontal cortex
- Possible SEs
  - **Sedation**, bradycardia, headache, **hypotension**, **dizziness**, constipation, dry mouth

Alpha-2 Adrenergic Agonists

- Quicker onset of action compared to atomoxetine and antidepressants
- Start at night due to potential sedation and dizziness when initiating
- **Titration required when starting (hypotension) and stopping (rebound hypertension)**
- Guanfacine metabolized via CYP3A4/5: requires dose adjustment with strong 3A4 inhibitors/inducers
- **More effective for hyperactive/impulsive symptoms**
- May be helpful in co-morbid aggression or to alleviate side effects of insomnia, tics
- Low abuse potential

Antidepressants

- Less supporting evidence compared to stimulants, atomoxetine and alpha-2 agonists
- Option if substance abuse concern or co-morbid depression diagnosis
- Limited to agents with noradrenergic activity:
  - **Bupropion**
  - TCAs
  - SNRIs

Role in Adjunct Therapy

- Adjunctive therapies may be considered if stimulant therapy is not fully effective or is limited by side effects
- Extended-release guanfacine and extended-release clonidine are FDA-approved as adjunctive therapy with stimulant medications for treating ADHD
- Limited evidence exists supporting the efficacy and safety of using atomoxetine in combination with stimulant medications to augment treatment of ADHD, although this would be an off-label use
- In practice antidepressant are also sometimes used off-label in combination with stimulants for treating ADHD

Medication	Onset of Action	Safety	Efficacy	Other Considerations
Stimulants	Immediate	Cardiovascular risk; abuse potential	Most effective (1st line therapy)	Controlled substances
Atomoxetine	4-6 wks	Black box suicidal ideation warning; low abuse potential	2nd line to stimulants given less robust response	Interaction potential (2D6)
Guanfacine	1-2 wks	Hypotension; low abuse potential	3rd line option behind stimulants and atomoxetine; Less effective for inattentive sxs; Comorbid tics, insomnia, aggression,	Requires titration and taper; Interaction potential (3A4)
Clonidine				Requires titration and taper; less interaction potential
Bupropion	2 wks	Black box suicidal ideation warning; seizure risk; low abuse potential	Non FDA-approved; Helpful for comorbid depression; May worsen anxiety and tics	Requires taper, interaction potential (2D6)
TCAs	2-4 wks	Black box suicidal ideation warning; seizure and cardiovascular and OD risk; low abuse potential	Non FDA-approved; Helpful for comorbid depression, anxiety, tics, insomnia	Requires taper, interaction potential (2D6)

Practice Assignments

- ADHD Practice Patient Cases in Canvas

Questions??

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