# Medication Management of ADHD, Depression and Anxiety Disorders

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# Disclosures

- Research Support-None to disclose

# Learning Objectives

- To incorporate a non-pharmacologic modality to address ADHD, Depression and Anxiety Disorders
- Differentiate between various psychostimulants when targeting clinical symptoms
- Establish criteria for psychiatric referrals
- Discuss Black box warnings associated with the use of psychotropics

# Why Care about ADHD?

- **Males** have 1.47 Hazard Ratio (HR) and **females** 1.45 HR risk of serious transport accidents
- **Children** and **adolescents** are at a higher risk for any type of accident
- In males there can be a 58% risk reduction with stimulant treatment
- The earlier treatment is started the lower the risk of developing a substance use disorder

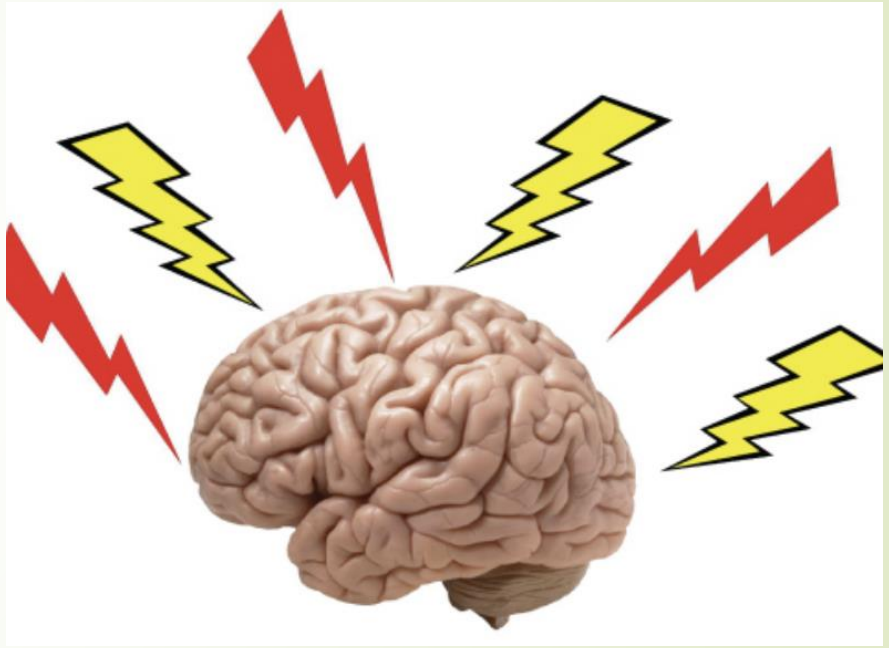
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3949159/
https://www.ncbi.nlm.nih.gov/pubmed/24470540
*J Am Acad Child Adolesc Psychiatry* 2016;55(6):479-486
*J Child Psychol Psychiatry*. 2014;55(8):878-885

# Duration of Management

- Early in ADHD, kids present mostly with **hyperactive/behavioral issues**
- **May "grow out" of symptoms** as they become adolescents
- **Sometimes symptoms internalize** and they can either develop or continue to have inattentive symptoms
- **May continue into adulthood** until brain is done developing (25?)
- **Some adults continue to need meds**
  - 4.4% have it but only 20% receive treatment

# Psychostimulants

- "Stimulate" the brain to focus
- Used since late 1800's
- Many studies document **safety and efficacy**
  - 230+ randomized controlled trials
- 70-85% **Response Rate**
  - do not use to confirm/refute diagnosis of ADHD !
- **Mechanism of Action**
  - Dopamine (DA) and Norepinephrine (NE) reuptake inhibition, and presynaptic release



# Match the Formulation with Needs of Patient & Family

- Know when the **patient "needs"** the psychostimulant most:
  - early in AM for school only, or including homework, peer activities, weekends
- Learn parent, teen, and HMO **preferences** for specific formulations
- Train parents to **observe efficacy and side effects** through the day and into the evening

# Serious Side Effects of Psychostimulants

- **Sudden Cardiac Death**
  - Anecdotal, but not irrelevant
  - Cases thus far have been primarily in patients with pre-existing cardiac conduction defects
  - Ask about history of sudden tachycardia, fainting, and family history of sudden cardiac death prior to initiating
- **Psychosis** or **Formal Hallucinations** (30+ cases): discontinue the medication
- **Growth Suppression** (Multi Modal Treatment of ADHD 2004, 2009) effects are likely to be made up in late teens or by drug holidays; especially at risk, those with nausea and vomiting
  - Plot heights every 3 months to ensure proper growth velocity

# Growth Suppression

- Studies show height and weight loss
- Loss may be dose and drug holiday-dependent
- No difference between dexAMP, MTP, or atomoxetine
- It's possible this is an ADHD issue

# How to Initiate Dosing

- **Generally, not by weight**, unless patients are less than 25 kg
  (0.3- 1mg/kg/d for MPH)
  - (0.15 - 0.5 mg/kg/d for AMPH)
- **Titrate to efficacy or intolerable side effects**: start at 5 mg MPH or 2.5 mg AMP
  - Increase by 5 mg MPH, or 2.5 mg AMP every 3-5 days to first target dose, decided upon by doctor and family
  - Get **weekly reports** and adjust upward, checking for side effects and efficacy

# Errors in Dosing Psychostimulants

- Failure to increase dose slowly to maximum if no side effects
  (MTA study showed lower dosing in community sample)
- Beginning with a dose that is too high
  - ***"Start low and go especially slow" with patients who are developmentally delayed***
- Not assessing the duration of action (may need to "bunch up " dosing with IR formulations)
- Failure to use another psychostimulant if the first or second trial fails
- Failure to use input from school

# ADHD Treatment - Methylphenidate

## Short acting (lasts 3-5 hrs.)

- Ritalin
- Methylin (Chewable and Liquid. 2.5mg, 5mg, and 10mg, 5 or 10mg/tsp)
- Focalin

## Intermediate (lasts 4-8 hrs.)

- Ritalin SR
- Metadate ER
- Methylin ER

## Long Acting (lasts 8-12 hrs.)

- Metadate CD
- Ritalin LA
- Concerta (oros)
- Focalin XR
- Quillivant XR liquid/Quillachew
- Daytrana patch
- Aptensio XR (40/60 IR/pulse)
- Cotempla XR-ODT (25/75)
- Jornay
- Azstarys

# ADHD Treatment - Mixed Amphetamine Salts

## Short acting

- Dextroamphetamine sulfate (Dexedrine)
- DextroStat
- Adderall
- Procentra liquid 5mg/5ml
- Zenzedi tabs
- Evekeo tabs

## Intermediate

- Dextrostat SR: 5, 10, 15mg
- Adderall XR: 5, 10, 15, 20, 25, 30mg

## Long acting

- Vyvanse: 10, 20, 30, 40, 50, 60, 70mg
- Adzenys XR-ODT: 3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg
- Dyanavel XR 2.5mg/ml: up to 8ml qd
- Mydayis: 12.5mg, 25mg, 37.5mg, 50mg
- Xelstrym: 4.5mg, 9mg, 13.5mg, 18mg patch

# ADHD Treatments (**Non-Stimulant**)

- **Atomoxetine (*Strattera*)**
- **Viloxazine (Qelbree)**
- **Guanfacine (Tenex, Intuniv ER)**
- **Clonidine (Clonidine, Kapvay ER, Onyda XR 0.1mg/ml)**

# ADHD Treatments (**medication options**)

- **Atomoxetine**
  - Potent NE reuptake inhibitor
    - *highly selective*
    - *inhibits presynaptic NE transporter*

# ADHD Treatments (**medication options**)

- **Atomoxetine**
- Michelson, et al (2001) : n=297, ages 8-18, 71 % male; 67% ADHD-CT; 8-week randomized prospective controlled study
  - **Participants were moderately-to-severely impaired** prior to tx.
  - Results showed **superior response to placebo** (65% response rate)
    - ADHD symptoms
    - Measures of social and family functioning

# ADHD Treatments (**medication options**)**

## Atomoxetine

- Total database of several thousand pediatric and adult patients
- **Common side effects**: **Dizziness, drowsiness, dyspepsia, decreased appetite**

## CYP2D6 substrate

- Use cautiously when other medicines are used (e.g. paroxetine, fluoxetine, quinidine)
- Dose: 0.5 mg/kg/day—1.2 mg/kg/day; Max dose 1.4 mg/kg/day or 100mg (whichever is less)
- **Assess liver function** prior to start; **monitor for hepatotoxicity**
- ****Black Box warning** re: teen patients with suicidal thinking
  - 5/1357 with suicidal thinking during initial trials
    - 1 of these 5 attempted suicide

# Atomoxetine, cont'd**

- **Monitor height, weight, pulse and BP**
  - Potential exists for decreases in growth (up to 0.5 cm / year) and small increases in HR and BP)
- **May be used QD or BID**
  - Time to Cmax is 1-2 hours
  - Duration of action is 6-10 hours (may be up to 24 hours)
  - Allow 6-8 weeks for full effect!

# ADHD Treatments (**medication options**)

- **Viloxazine (Qelbree)**
  - Selective Norepinephrine Reuptake Inhibitor
- **Dosing:** Initial: age 6-11:  100 mg once daily; may titrate in 100 mg increments at weekly intervals based on response and tolerability; maximum daily dose: 400 mg/**day**.
- Children ≥12 years and Adolescents ≤17 years: Oral: Initial: 200 mg once daily; may increase to 400 mg after 1 week based on response and tolerability; maximum daily dose: 400 mg/**day**.
- Adolescents ≥18 years: Oral: Initial: 200 mg once daily; may titrate in 200 mg increments at weekly intervals based on response and tolerability; maximum daily dose: 600 mg/**day**.
- **Side Effects:** increased heart rate and diastolic BP
  - **Black Box Warning:** higher rates of suicidal thoughts and behavior in patients with ADHD versus placebo

# ADHD Treatments (**medication options**)**

## Guanfacine extended release (Intuniv)

- Released in U.S. Nov 2009
- Alpha-2a agonist, non-stimulant; non-schedule II
- T ½ = 17 hours (5 hours to Cmax)
- Dose range 1-4 mg total daily dose
  - Consider 0.05-0.08 mg/kg/day (max 0.12 mg/kg/day)
  - 1mg QD to start, then increase by 1mg weekly, if needed, to 4mg QD
- Common side effects: **drowsiness, dyspepsia, fatigue
  - Monitor BP and HR for hypotension and bradycardia

## CYP3A4/5 substrate

- Use cautiously when other medicines are used (potential additive CNS effects, drug interactions)
- Assess cardiac function with good history

# ADHD Treatments (**medication options**)**

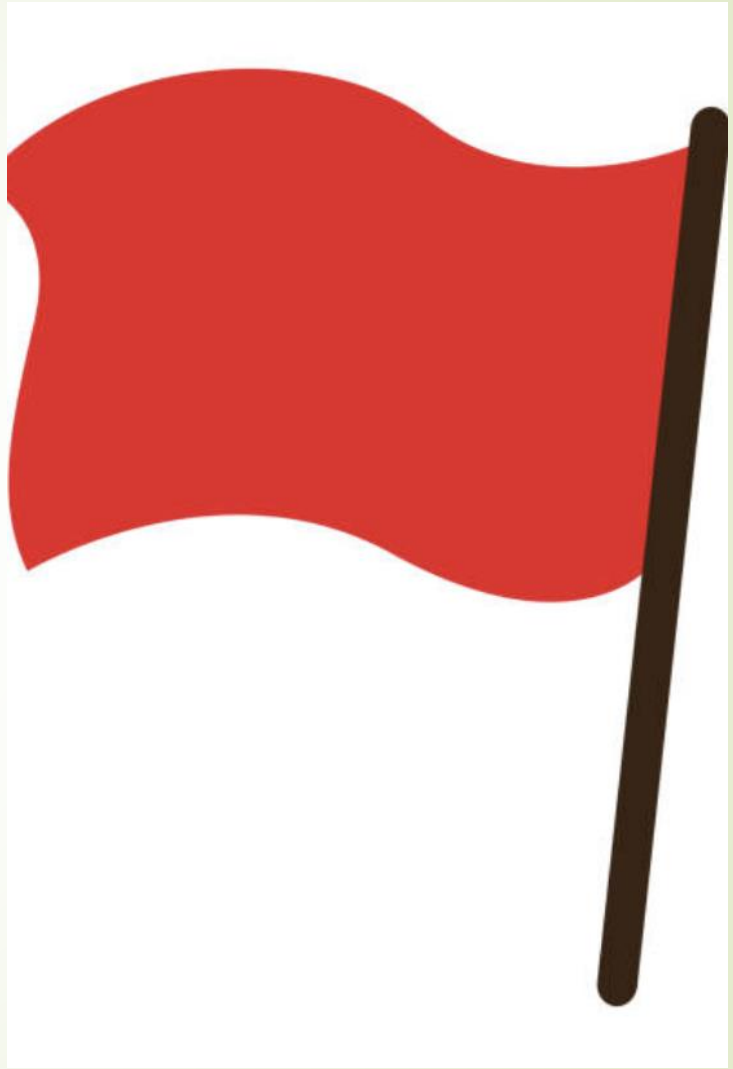
- **Clonidine extended release (Kapvay, Onyda XR 0.1mg/ml)**
  - Alpha-2a agonist, non-stimulant; non-schedule II
  - T ½ = 12 hours (6 hours to Cmax)
  - Dose range 0.1-0.4mg total daily dose
    - 0.1mg QHS to start, then increase by 0.1mg weekly, if needed, to 0.4mg total daily dose, divided BID; Not to be scored
  - **Common side effects**: **drowsiness, dyspepsia, fatigue, headache
    - Monitor BP and HR for hypotension and bradycardia
  - Use cautiously when other medicines are used (potential additive CNS effects, drug interactions)
  - **Assess cardiac function with good history**
- Also approved for adjunctive use with Methylphenidate

**L-methylfolate is not effective for attention deficit hyperactivity disorder (ADHD).** A recent double-blind, placebo-controlled trial in adults with ADHD found that adjunctive L-methylfolate (15 mg daily) did not improve ADHD symptoms when added to optimized methylphenidate therapy, and may have been associated with reduced efficacy of methylphenidate.[1]

Does L-Methylfolate Supplement Methylphenidate Pharmacotherapy in Attention-Deficit/Hyperactivity Disorder?: Evidence of Lack of Benefit From a Double-Blind, Placebo-Controlled, Randomized Clinical Trial.Surman C, Ceranoglu A, Vaudreuil C, et al.
Journal of Clinical Psychopharmacology. 2019 Jan/Feb;39(1):28-38.
doi:10.1097/JCP.0000000000000990.

# What if they are Abusing/Diverting?

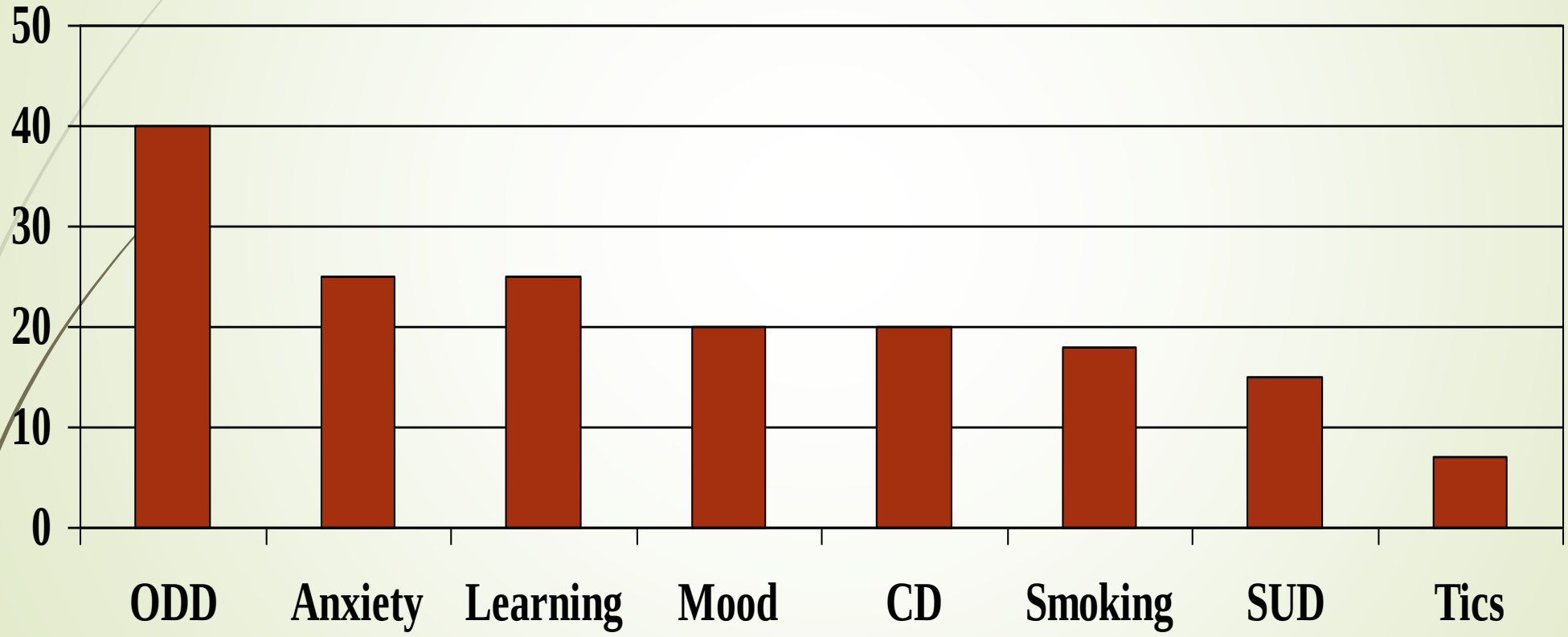
- **Red flags** should be …
  - Frequently lost prescriptions
  - Running out prior to schedule
  - Requesting IR formulations or specific medications
  - No improvement in performance despite saying they are adherent
- **Run an EPCS report**
- **Can switch to Atomoxetine, Qelbree, Alpha 2-agonist**



# When to refer….

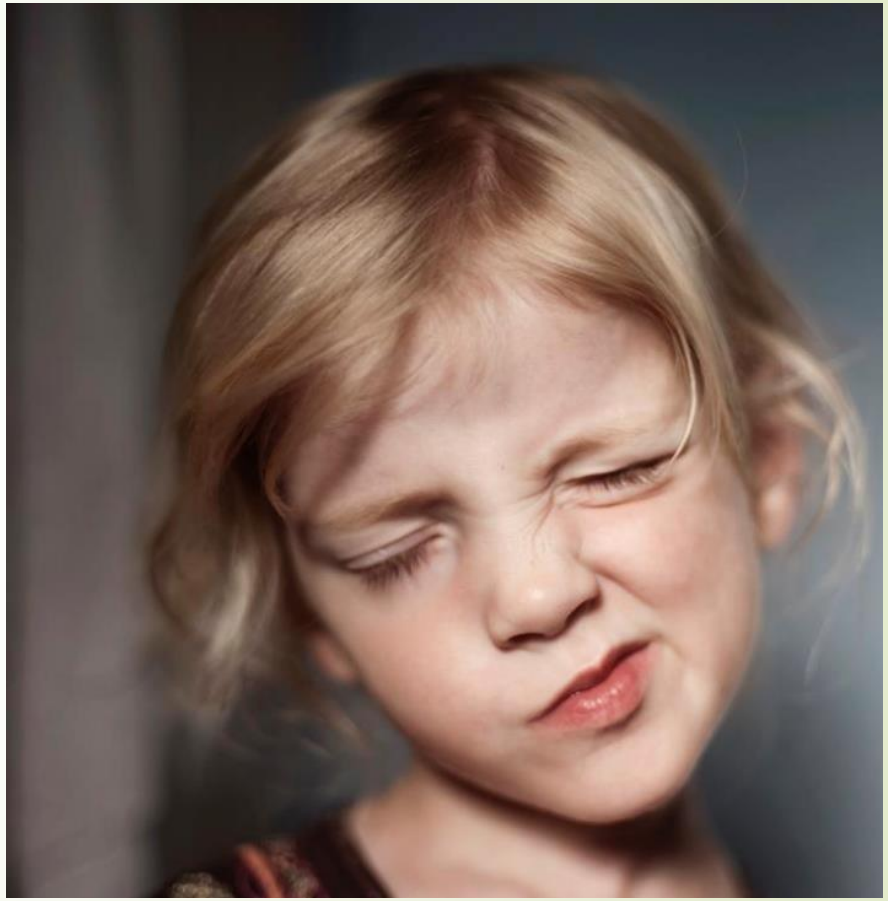
- Have tried 2 stimulants, one non-stimulant
- Increase in aggression with medication trials
- Development of tics
- Comorbid diagnoses that make treatment difficult

# Comorbidities with ADHD



# Tics and ADHD

- Mild or moderate tics occur in a significant number of patients with or without ADHD pharmacotherapy
- **5-20% of schoolchildren will experience a simple or complex tic in their lifetime
- Lipkin et al, in a review of 122 children treated with stimulant medication, found 9% developed transient tics and <1% developed chronic tics



# Tics and ADHD

- **Tics are usually transient**
  - Very rarely do patients develop a chronic tic disorder
- **When tics do occur or are worsened**
  - Decrease dose
  - Switch to another stimulant
  - Add adjunctive drug to treat tics
    - Clonidine / Guanfacine
  - Try nonstimulant medication
    - Atomoxetine (Strattera), Viloxazine (Qelbree), Guanfacine Extended Release (Intuniv), Clonidine ER (Kapvay)
    - Modafinil

# Mood and ADHD

- Increased dopamine can cause increased focus (hypervigilance)
- May make moody/depressed/anxious teenagers moodier
- Stimulants can affect sleep
- Kids will complain that they are “like a zombie” because they do not talk as much

| Methylphenidate- Short-Acting | Duration of Action | Unique Properties | Short/Long % | D:L | D Improves attention span<br>L improves hyperactivity/impulsivity |
|---|---|---|---|---|---|
| Ritalin | 3-5 hours | | | | |
| Methylin | 3-5 hours | Chewable/Liquid | | | |
| Focalin | 3-5 hours | | | D | |
| | | | | | |
| Methylphenidate-Intermediate | | | | | |
| | | | | | |
| Ritalin SR | 4-8 hours | | | | |
| Metadate ER | 4-8 hours | | | | |
| Methylin ER | 4-8 hours | | | | |
| | | | | | |
| Methylphenidate- Long Acting | | | | | |
| | | | | | |
| Metadate CD | 8-12 hours | | 30/70 | | |
| Ritalin LA | 8-12 hours | | 50/50 | | |
| Concerta (oros) | 8-12 hours | | 22/78 | | |
| Focalin XR | 8-12 hours | | | D | |
| Quillivant XR | 8-12 hours | | 20/80 | | |
| Daytrana Patch | 8-12 hours | Embedded in the glue | | | |
| Aptensio XR | 8-12 hours | | 40/60 | | |
| Jornay | 8-12 hours | Night time dose | | | |
| Cotempla XR | 8-12 hours | ODT | 25/75 | | |
| Azstarys | 8-12 hours | serdexmethylphidate (SDX) and d MPH | 70/30 | | 26.1 mg SDX/5.2mg D-mph<br>39.2/7.8 and 52.3/10.4 |
| Quillachew/Liquid | 8-12 hours | | 30/70 | | |

| | | | | | |
|---|---|---|---|---|---|
| Amphetamine Salts- Short | | | | | |
| | | | | | |
| Dexedrine | 3-5 hours | | | | |
| DextroStat | 3-5 hours | | | | |
| Adderall | 3-5 hours | | | 3:1 | |
| Procentra | 3-5 hours | Liquid | | | |
| Zenzedi | 3-5 hours | Age 3> | | | |
| Evekeo | 3-5 hours | Less Apetite Suppression | | 1:1 | |
| | | | | | |
| Amphetamine-Intermediate | | | | | |
| | | | | | |
| DextroStat SR | 8-10 hours | | | | |
| Adderall XR | 8-10 hours | | | 3:1 | |
| | | | | | |
| Amphetamine-Long Acting | | | | | |
| | | | | | |
| Vyvanse | 8-14 hours | Pro-Drug | | | |
| Adzenys XR | 8-14 hours | ODT | 50/50 | 3:1 | |
| Dyanavel XR | 8-14 hours | Liquid | | 3.2:1 | |
| Mydayis | 8-14 hours | Triple Beaded | | | |
| Xelstrym | 9 hours | Transdermal Patch | 4.5, 9, 13.5, 18mg | | |
| | | | | | |
| | | | | | |
| | | | | | |

# Anxiety Disorders

- An estimated **31.9% of adolescents** had any anxiety disorder.
- Of adolescents with any anxiety disorder, an **estimated 8.3% had severe impairment**.
- The prevalence of any anxiety disorder among adolescents was **higher for females** (38.0%) than for males (26.1%).
- The **prevalence** of any anxiety disorder was **similar across age groups**.

# DSM 5-TR – **Anxiety Disorders**

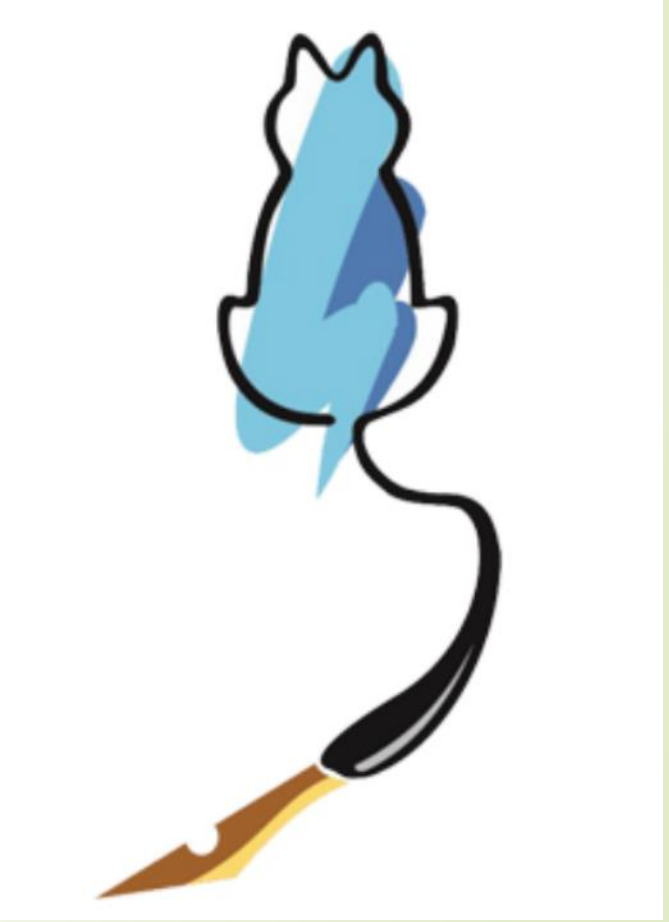
- *Generalized* Anxiety Disorder
- *Social* Anxiety Disorder
- *Panic* Disorder
- *Separation* Anxiety Disorder
- Selective Mutism
- Specific Phobia
- *Substance Induced* Anxiety Disorder
- *Other/Unspecified* Anxiety Disorder

# **First Line** Recommendations

- **Cognitive Behavioral Therapy**
  - Cognitive Triad
  - Thoughts → Behaviors → Mood
  - Coping Cat
  - Recommended by AACAP as first line treatment

# Coping Cat

- For children 7-13
- Also a different program for 14+ CAT project
- Has online modules and a workbook for purchase
- https://www.copingcatparents.com/



# Treatment of Depression

**RECOMMENDATION 1:**

***Consider using a collaborative model***

- Depression is best managed with a **multi-disciplinary team**
- Team should include **psychiatrists, case managers, in-house counselors**

**RECOMMENDATION 2:**

***In mild depression consider active support and monitoring***

- Psychosocial interventions
  - Discuss depression with child and family
    - Ask yourself if this is a normal reaction to a stressor. Kids often show regression or changes in behaviors after changes or stressful events. It is important to know that what is considered a stressor is dependent on the individuals experience. This can be anything from school beginning or ending, an argument with a friend to a major life event.
    - Encourage patience and consistency, along with implementation of basic behavioral principles, with parents. Remember kids and teens, like adults, are allowed to have periods of feeling grumpy, sad or mad.
    - Begin with lifestyle interventions. Nutrition, sleep, and mindfulness can have a big impact on mood and are good places to begin to intervene.

**RECOMMENDATION 3:**

***If an adolescent with mild to severe depression is identified, consider consulting a mental health professional***

- ***CBT, IPT***

**RECOMMENDATION 4:**

***Scientifically supported treatments should be part of treatment plan***

- ***Includes both medications and therapy***

# Pharmacologic Interventions – SSRI's

- Treatment of Choice
- Studies show efficacy in GAD, SAD (Separation Anxiety) ,and SoP (Social Phobia), SM (Selective Mutism)
- The three largest RCT's looked at Fluvoxamine, Fluoxetine, and Sertraline
- Many other trials supporting other SSRI's

# What **Other Agents** May be Useful?

- **SNRI's**
  - Venlafaxine ER was found to have positive results in 2/3 studies
  - Duloxetine – FDA approved for GAD (7-17)

- **Atypical Agents**
  - Mirtazapine, Bupropion, Trazodone – No evidence

# What Has **FDA Approval?**

- **Approved for OCD**
  - Clomipramine ≥ 10 yrs.
  - Fluvoxamine ≥ 8 yrs.
  - Sertraline ≥ 6 yrs.
  - Fluoxetine ≥ 7 yrs.
- **Approved for Depression**
  - Fluoxetine ≥ 12 yrs.
  - Escitalopram ≥ 12 yrs.
- **Approved for Non-OCD Anxiety**
  - Duloxetine for GAD 7-17 yrs.

# Prozac (fluoxetine)

- Initial dose 5mg - 10mg daily
- Increase by 10mg weekly
- Maximum 60mg
- Some improvement in 2 weeks, maximum in 6
- Half-life 40 hours
- GI upset, headache, activation
- Do not need to taper due to long half life

# Zoloft (sertraline)

- selective inhibitory effects on presynaptic serotonin (5-HT) reuptake
- 12.5 mg -25 mg depending on age
  - Increase by doubling weekly up to 200mg depending on age/weight
- Some improvement in 2 weeks, maximum in 6
- Half-life 26 hours
- GI upset, headache, activation
- Taper to avoid withdrawal

# Lexapro (escitalopram)

- 5mg-10mg daily
- Increase in 5mg increments
- Maximum dose 20mg
- Initial effects may be observed within 1 to 2 weeks of treatment, with continued improvements through 4 to 6 weeks
- Half Life 19 hours
- GI upset, headache, activation

# Effexor (venlafaxine)

- 37.5mg-150mg daily
- Increase in 37.5mg increments
- Maximum dose 225mg
- Initial effects may be observed within 2 to 4 weeks of treatment, with continued improvements through 4 to 6 weeks
- Half Life 11-12.5 hours
- GI upset, headache, palpitations, agitation, hypertension, and blurred vision.

# Cymbalta (duloxetine)

- 20 mg-60 mg daily
- Increase in 10 mg increments
- Maximum dose 60 mg
- Initial effects may be observed within 2 to 4 weeks of treatment, with continued improvements through 4 to 6 weeks
- Half-life 12 hours
- GI upset, insomnia, sedation, dizziness, sweating, and urinary retention

# Pristiq (desvenlafaxine)

- 25mg-100mg daily
- Increase in 25mg increments
- Maximum dose 100mg
- Initial effects may be observed within 2 to 4 weeks of treatment, with continued improvements through 4 to 6 weeks
- Half-Life 9-13 hours
- GI upset, hypertension, tremor, abnormal dreams and blurred vision

# Black Box Warning

- All SSRI's
- Possible increase in suicidal ideation in patients under 24 years of age
- Meta-analysis of RCT 4000 kids, less than 5% but statistically significant.
- Monitor closely- get a good family history of suicide and mood disorders

# **Adverse Events** of SSRIs

- **Activation is common 10-15%**
  - Early in course or after dose change
  - Younger kids
- Bipolar switches uncommon <1% - later
- **Frontal lobe symptoms at higher doses**
- GI issues early
- Easy bruising and bloody noses

# What to do about **activation**?

- **Psychoeducation**
  - **Early in treatment** or right after dose change 24-72 hours
  - **Late activation?** Probably unrecognized early activation that crosses a severity threshold at higher doses
  - **Stop immediately**
    - Doesn't go away with time
    - Won't get to effective treatment dose

# What to do about **activation**?

- Switch to second SSRI
- Consider referral to psychiatry

# Serotonin Syndrome

**Discontinue all serotonergic agents**

Hyperthermia
Agitation
Slow, continuous, horizontal eye movements (referred to as ocular clonus)
Dilated pupils
Tremor
Akathisia
Deep tendon hyperreflexia (common)
Inducible or spontaneous muscle clonus (common)
Muscle rigidity
Bilateral Babinski signs
Dry mucus membranes
Flushed skin and diaphoresis
Increased bowel sounds

# Serotonin Withdrawal

## somatic symptoms

dizziness, chills, light-headedness, vertigo, ‘shock-like’ sensations, paresthesia, fatigue, headache, nausea, tremor, diarrhea, visual disturbances

## psychological symptoms

anxiety, agitation, confusion, insomnia, irritability

# When to refer

Continued or worsening behaviors that have not responded to routine interventions.

A change in behavior without an identifiable precipitant that causes significant distress leading to inability to participate in day-to-day activities

Initial pharmacological interventions have been ineffective, and you are thinking of adding a second medication or are uncomfortable changing a medicine.

The child or adolescent has complicated medical issues which may make adding a medication more difficult

# Crisis contacts

- **Central Arizona Crisis Line (Local)**
- 602-222-9444

- **Central Arizona Crisis Line (800)**
- 1-800-631-1314

- **Central Arizona Crisis Line (TTY)**
- 1-800-327-9254

- **Central Arizona Warm Line**
  602-347-1100

- **Northern Arizona Crisis Line**
  1-877-756-4090