“Untangling Anxiety: Diagnostic Pearls and Evidence-Based Treatment for Children and Adolescents”

THE UNIVERSITY OF ARIZONA
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Psychiatry

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No Disclosures

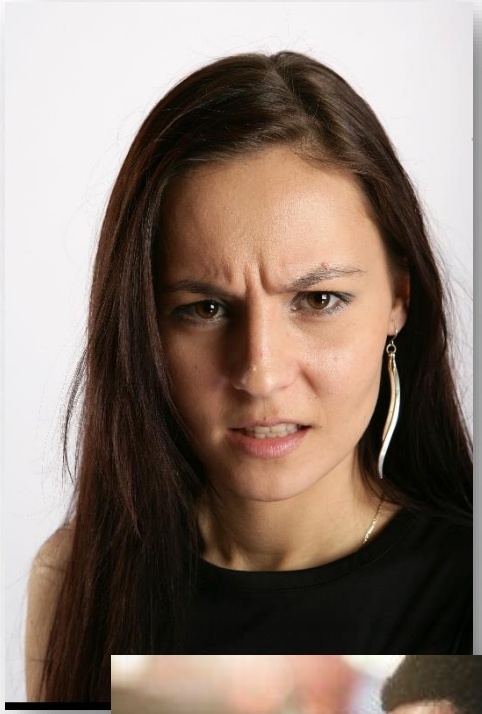
Learning Objectives

By the end of this session, participants will be able to:

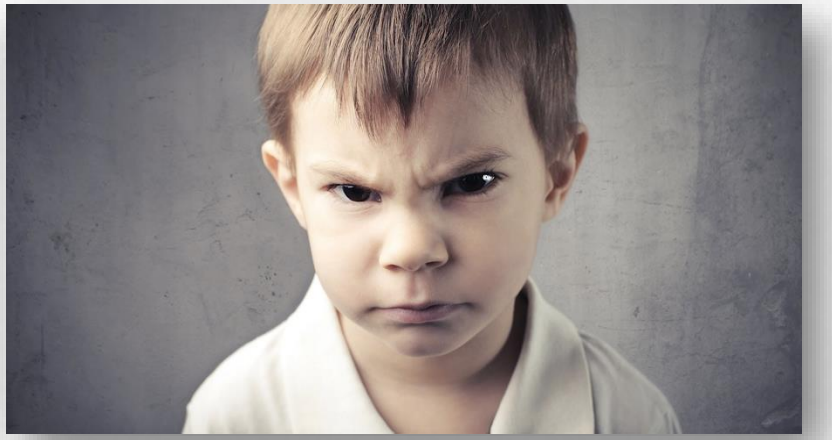
1. Describe the hallmark features of common anxiety disorders in children and adolescents.
2. Explain the current evidence-based psychopharmacological treatments of common anxiety disorders in children and adolescents.
3. Recognize complex presentations of anxiety disorders in children and adolescents to develop appropriate treatment interventions in children and adolescents.

What is "Anxiety?"

“They were really upset.”



An undifferentiated term



Anxiety Disorders

Fears: Emotional response to real/perceived imminent threat

- Fight/flight
- Hyperarousal - autonomic response and escape

Worries: Anticipation of future threat(s)

- Muscle tension
- Vigilance/cautious or avoidance

Excessive Fear/Worry (+) a Hallmark Feature

- **Generalized Anxiety Disorder:** Inability to control multiple worries; associated with physical symptoms
- **Separation Anxiety Disorder:** Fear that harm will come to caregivers or lead to separation
- **Social Anxiety Disorder:** Fear of scrutiny and negative judgment of others
- **"Other/Unspecified":** When there is insufficient information

Specific Phobia

Panic Disorder

Agoraphobia

Selective Mutism

Anxiety Disorders

- Severity
- Must persist for > 6 months
- Must have functional impairment
- It isn’t something else

Assess for Opportunities for Positive Stress Response

- Brief, mild/moderate in magnitude
- Requires caring/responsive adult to bring about return to baseline
- Growth promoting for development
- Provides important opportunities to learn, observe, and practice healthy responses to adversity

Help Caregivers Create Tolerable Stress

- Non-normative exposure to stress, greater magnitude
- With buffered protection from parents
- Facilitates adaptive coping and sense of control
- Lower risk of long-term negative outcomes for health and learning

Identify and Eliminate Toxic Stress

- Prolonged exposure of severe stress
- Develops without protective buffering from caregivers
- Disrupts normal development, changes in physiologic circuitry & regulation
- Negative long-term outcomes in health, learning, behavior

To Begin - What We Need to Know

- Primary Diagnosis or Target Symptoms
- Must persist for > 6 months (separate from transient stress)
- Assess level of functional impairment
- Severity
- It isn't something else
- Comorbidities
- Stressors
- Family Hx
- Family Functioning

TREATMENT

Am I going to use a medication?

CBT only:

- For mild severity
- Minimal functional impairment
- Supportive family interactions
- Minimal comorbidities
- 10-16 weeks

Add Medications:

- When psychotherapy fails
- For moderate-severe impairment
- Poor school performance
- School refusal
- Sleep impairment
- Comorbid depression

Walter HJ et al, Clinical Practice Guideline; AACAP, 2020.

Which Medication Should I Choose?

Which drugs have FDA approval for specific anxiety disorders?

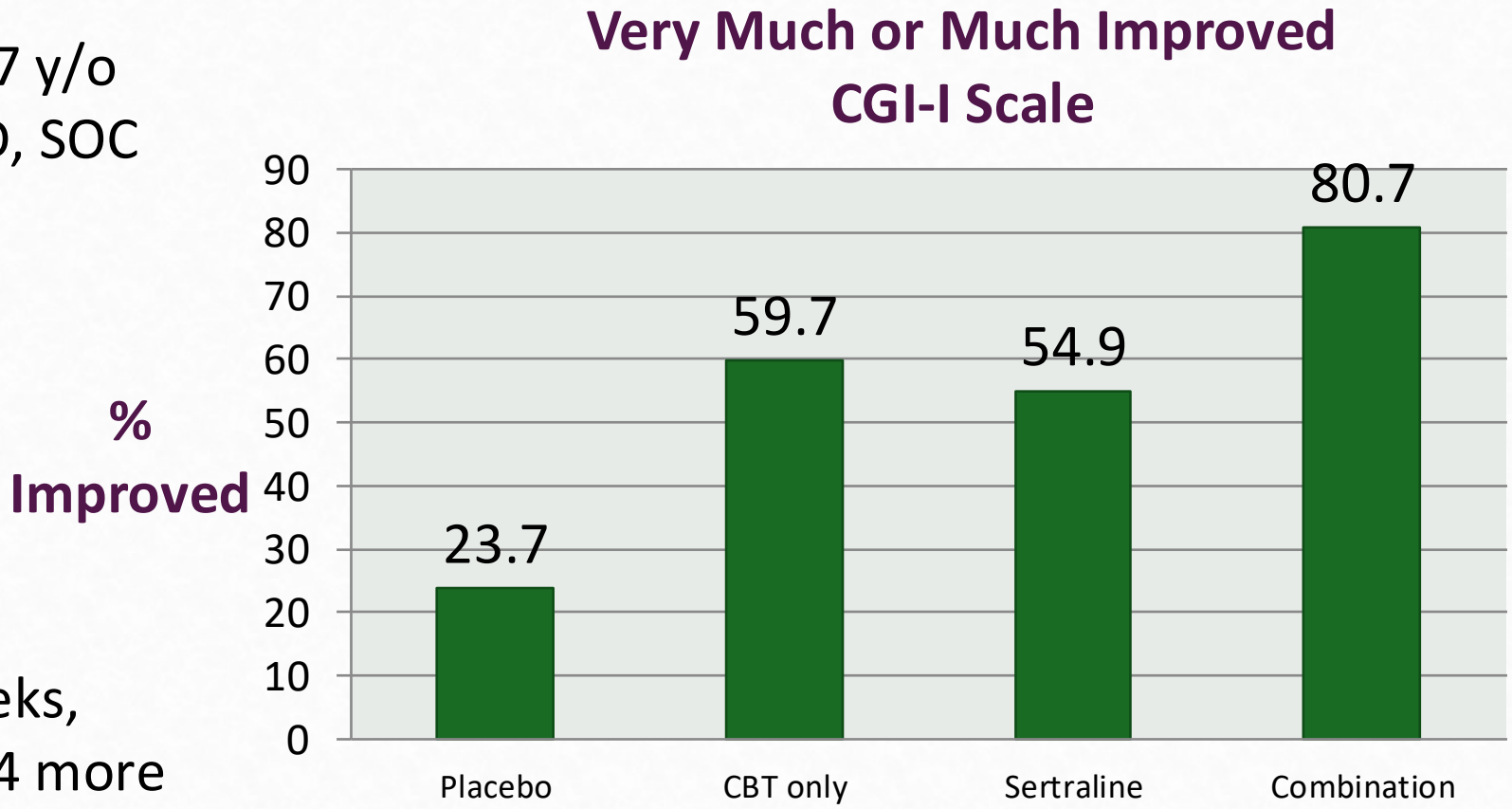
Which drugs have the most evidence for the treatment of anxiety disorders in youth?

Child/Adolescent Multimodal Anxiety Study (CAMS)

12-week study; N=488, 7-17 y/o
Moderate-Severe SAD, GAD, SOC

In SSRI group:

- NNT: 3
- *If no response by 8 weeks, unlikely to benefit after 4 more weeks (data not shown)



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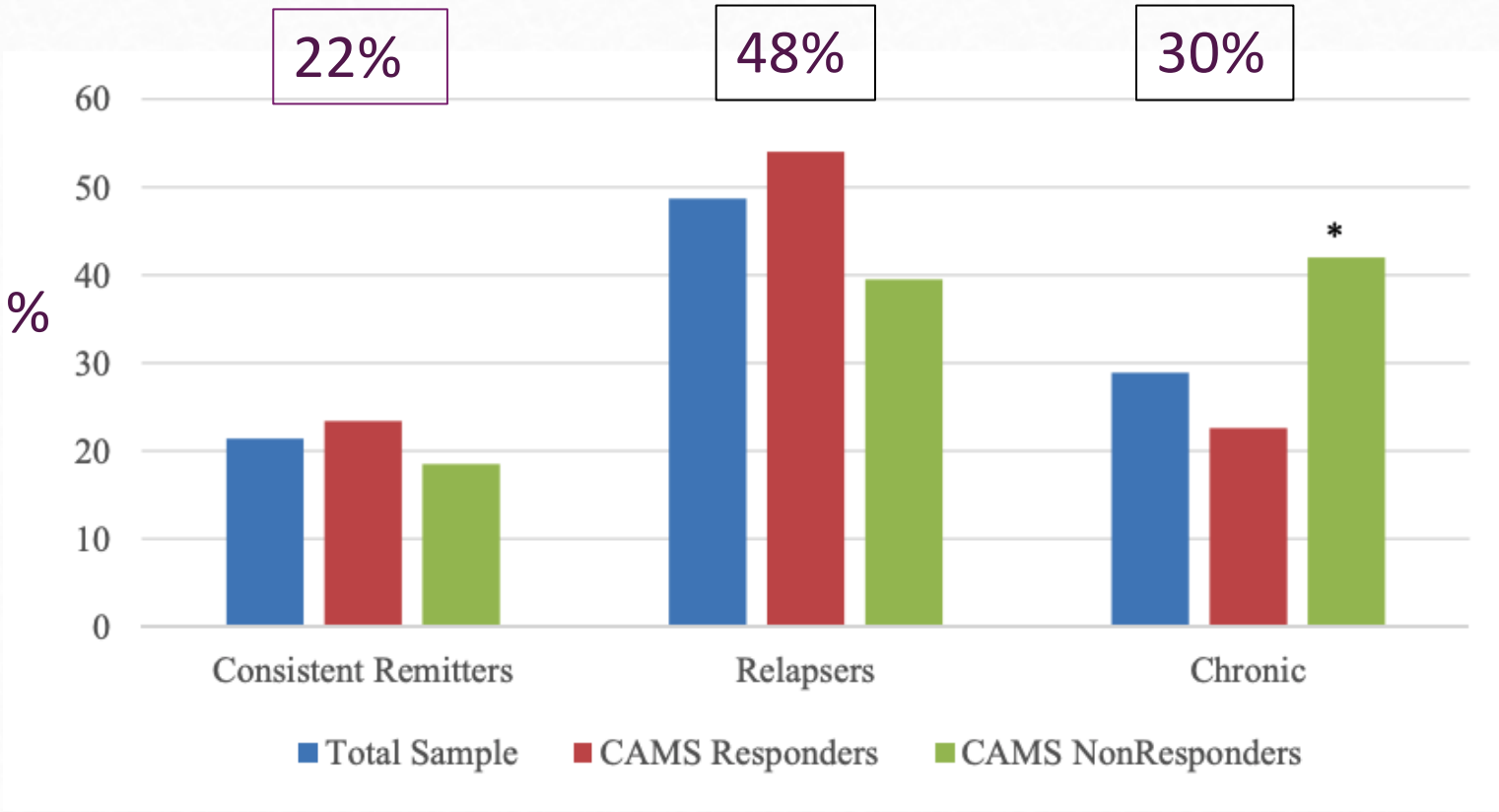
Walkup J et al.*N Engl J Med* 2008; 359:2753-2766.
*Strawn JR, Vaughn S, Ramsey LB; Focus, 2022.

CAMELS Study Anxiety Outcomes

Predictors of Remission:

-CAMS responder to ANY treatment arm
-Male
-Younger
-No social phobia
-Better global function
-Better family functioning
-Fewer interim (-) life events



Naturalistic study, 6 sites; 4-yrs
N=319 (65.3% CAMS sample)

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Ginsburg GS, et al.. JAACAP, 2018.

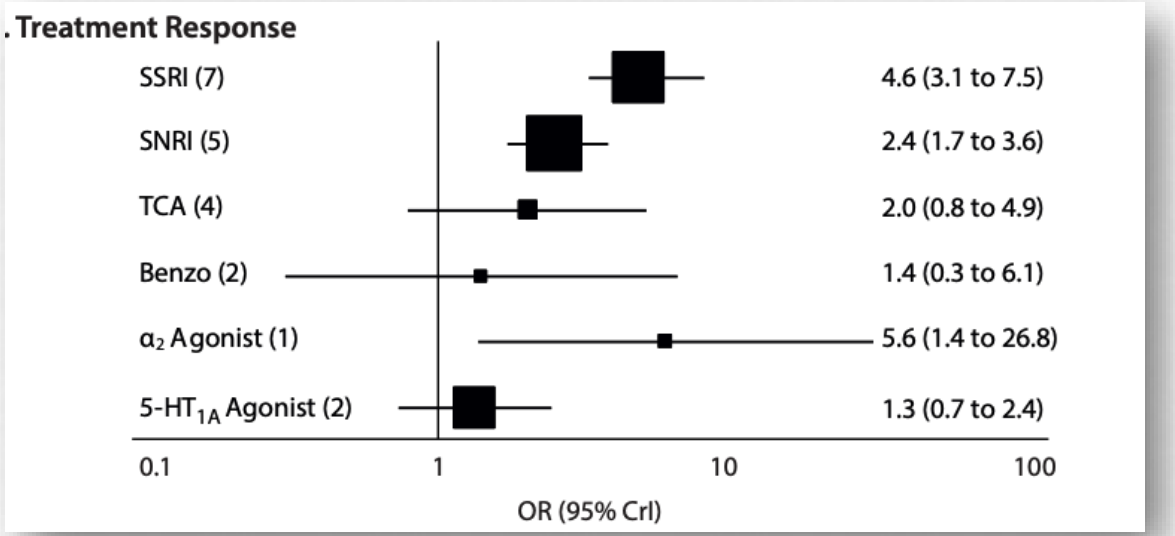
Network Meta-Analysis of Medications for Pediatric Anxiety Disorders

For treatment response and reduced anxiety symptoms:

- SSRIs were superior to SNRIs
- Sertraline most tolerated and efficacious

For treatment response:

- SNRIs and alpha-2 agonists also superior to placebo
- SSRIs had more discontinuation due to AEs than SNRIs



Dobson et al, J Clinical Psychiatry, 2019.

Other Medications

Not enough data:

- TCAs
- Benzodiazepines
- Buspirone - 1 (+) open label
- Mirtazapine
- Alpha-2 agonists - 1 (+) open label PTSD
- Atomoxetine - 1 (+) with comorbid ADHD
- 5-HT agonists

Stahl and Strawn; Prescriber's Guide – Children and Adolescents; 2nd Ed, 2024.

Which Medication to Choose?

Which drugs have FDA approval for specific anxiety disorders in youth?

General Anxiety Disorder

- Duloxetine, 7 – 17 y/o
- Escitalopram, 7 -17 y/o

Which drugs have the most evidence for the treatment of anxiety disorders in youth?

- SSRIs

Starting Medication

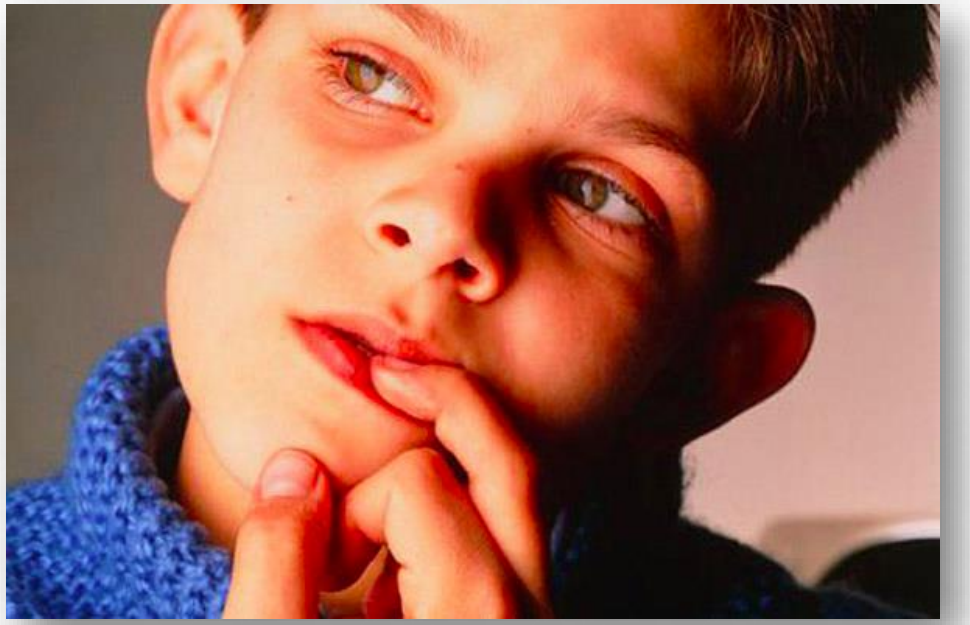
1. CONSIDER:

Drugs:

- FDA indications for specific diagnoses
- Clinical guidelines
- Best data
- Drug SE profile, interactions

Patient:

- Pharmacokinetics/Pharmacodynamics
- What worked for patient before
- What worked for family member
- Assess for baseline somatic symptoms
- Screen for bipolar disorder



Strawn JR, Vaughn S, Ramsey LB; Pediatiric Psychopharmacology for Depressive and Anxiety Disorders; Focus, 2022.
Walter HJ et al. Clinical Practice Guideline, AACAP, 2020

Antidepressants - Pediatric Anxiety

Class	Medication	FDA Approval	Drug Attributes
SSRIs			**SSRIs more discontinuation syndrome and activation**
	Escitalopram	**≥ 7 y/o**	
	Fluoxetine		Long half-life, can dose QD
	Sertraline		Lower doses BID
	Fluvoxamine		Short half-life, higher risk discontinuation, dose BID, may have greater risk drug interactions
	Paroxetine		Short half-life, higher risk discontinuation, dose BID
	Citalopram		Concern for QTc prolongation above 40mg
SNRIs			**Less discontinuation, less activation than SSRIs**
	Duloxetine	**≥ 7 y/o**	GI SEs oropharyngeal pain, monitor HR/BP
	Venlafaxine		Some data, monitor HR/BP

Strawn et al; Focus, 2022. Rynn MA, Yanes-Lukin P, Goldberg P. Anxiety Disorders,; Clinical Manual of Child and Adolescent Psychopharmacology; 4th ed.; 2024

2. DOSING: Start Low

Developmental Differences in Psychopharmacology

Pharmacokinetics

Absorption: Faster

- Higher peak drug levels

Distribution: V_D smaller and less protein binding

- More bioactive drug in plasma

Metabolism: Faster

- Increased metabolite:parent blood levels
- Shorter half-life
- Larger dose/kg than adults

Excretion: Higher renal clearance

Pharmacodynamics

Differences in pathways and receptor densities

- More activation
- Different side effect profiles

Stahl and Strawn; Prescriber's Guide – Children and Adolescents; 2nd Ed, 2024.

Pharmacogenetics – A Supportive Role

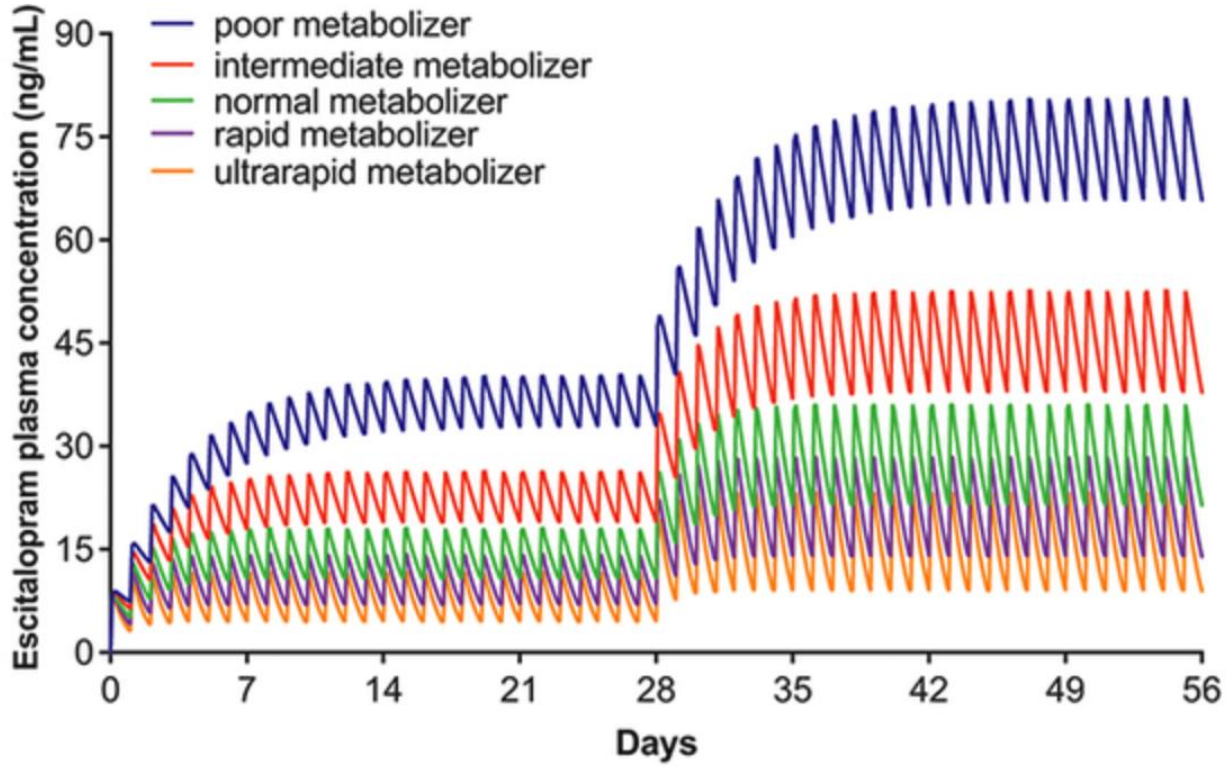


Figure 1 Escitalopram plasma concentrations in adolescents with different CYP2C19 phenotypes. Treatment was initiated at 10 mg daily and increased to 20 mg daily at week 4. There is considerable variation in blood concentrations of escitalopram among the CYP2C19 phenotypes, as demonstrated in this series of adolescent patients.

- Higher plasma concentration levels for poor or intermediate metabolizers
- Can consider dose adjustments for metabolizer phenotypes

Strawn JR & Stahl SM; Prescriber's Guide: Children and Adolescents, 2024.

Starting Medication

3. Informed Consent/Assent

- Target symptoms, prioritize
- Proposed medication plan
- Specific rationale and risks
- Alternatives to medication
- FDA-approved versus off-label
- Cost
- Monitoring plan
- Concurrent treatment/interventions

Stahl and Strawn; Prescriber's Guide – Children and Adolescents; 2nd Ed, 2024.

Starting Medication

4. Titrate:
   - Increase slowly q1-2 weeks with short half-life
   - Increase q3-4 weeks with longer half-life
   - Faster if severe impairment

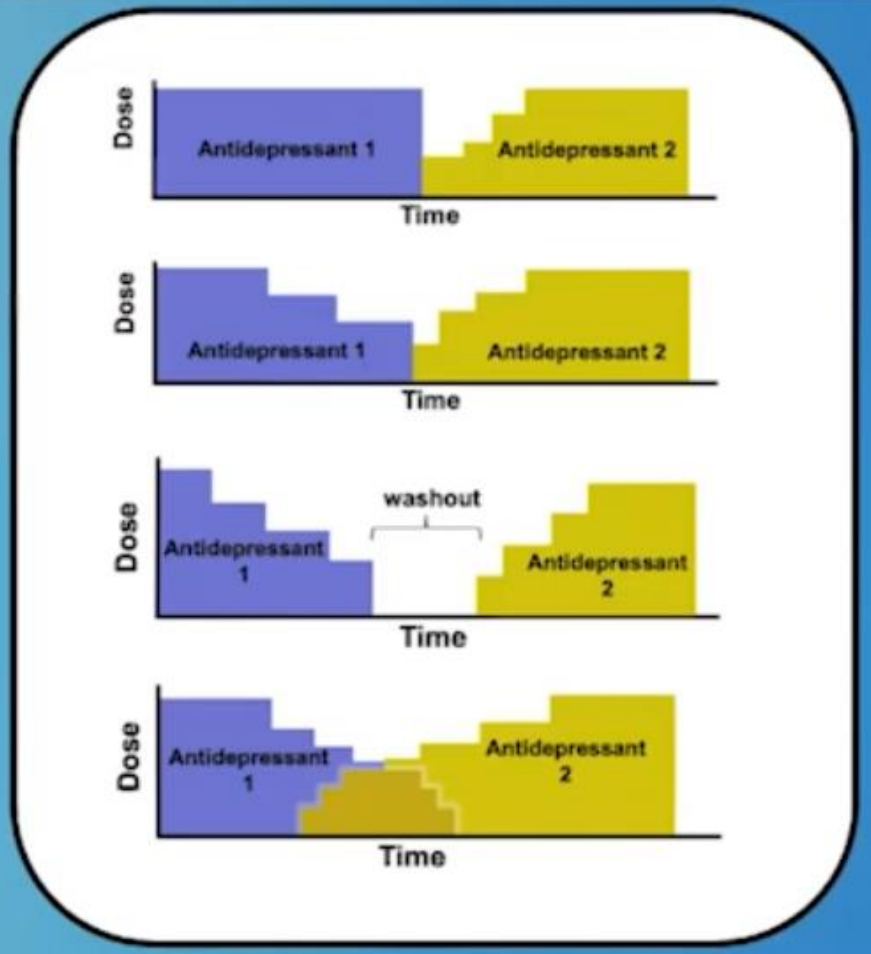
5. Optimize for at least 8 weeks
   - Until remission or intolerable side effects
   - May need higher doses, may take longer

6. If no response after 8 weeks: SWITCH
   - Another SSRI or SNRI

Strawn JR, Vaughn S, Ramsey LB; Pediatric Psychopharmacology for Depressive and Anxiety Disorders; Focus, 2022.
Walter HJ et al. Clinical Practice Guideline, AACAP, 2020

Switching Medications

- **Direct switch:** stop first antidepressant and start new antidepressant
- **Taper and switch immediately:** gradually taper the first antidepressant and start the new antidepressant immediately after discontinuation
- **Taper and switch after a washout:** gradually withdraw the first antidepressant then start the new antidepressant after a wash out period
- **Cross-tapering:** taper or maintain the first antidepressant while beginning the new antidepressant



Keks N et al. Aust Prescr 2016;39(3):76-83;
Stahl. Stahl's Essential Psychopharmacology: The Prescriber's Guide. 4th Edition.

Strawn S; AACAP Pediatric Psychopharmacology Update Institute, 2024.

Continuation Phase:

- Monitor for SEs to improve adherence
- Optimized treatment for 9-12 months
- What if there is a relapse?

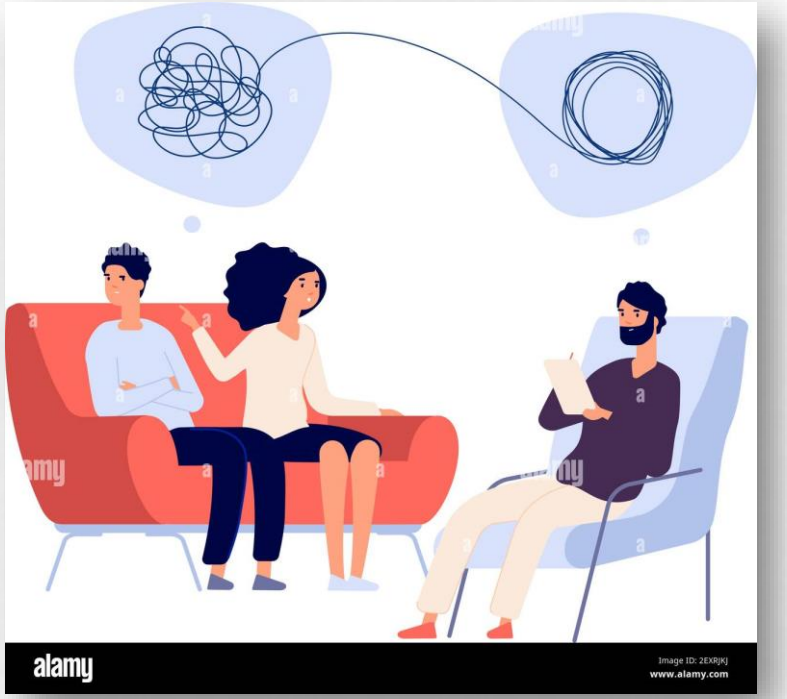
  ….Start Over…

Goal is remission,

not a shorter duration of treatment

Maintenance Phase:

- Monitor for risk factors recurrence
- What is there is a recurrence?
  - …Start Over…



Monitoring

Common:

SSRIs

- Nausea, diarrhea, GI distress
- Dry mouth
- Restlessness
- Bruxism, tremor
- Diaphoresis
- Headache, dizziness, vivid dreams
- Sleep changes
- Weight loss/gain

SNRIs - HR and BP changes

Side Effects

Serious:

- Behavioral activation
- Suicidal Ideation
- Serotonin syndrome
- Discontinuation syndrome
- Seizures
- Abnormal bleeding
- **Duloxetine** – liver failure

Walter HJ et al; Ciinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders; JAACAP, 2020.

Behavioral Activation

Activation

- 10-15% clinical trials
- Increased impulsivity, agitation, silliness, motor activity or irritability
- No mood changes
- Pharmacokinetics
  - Occurs early with initiation or increase in dose
  - gets worse with higher dose
- Remits with decreased dose or discontinuation
- “More of the same”
- Does not lead to suicidality

Hypomania/Mania

- <1.0%
- Increased motor activity or irritability
- Euphoria, grandiosity, hypersexuality, decreased need for sleep
- Pharmacodynamics
  - Occurs later (4-6 weeks)
- May not remit with decreasing dose
- Family Hx bipolar disorder
- “He has never been like this before” or “…and then one day…”

Luftt et al; Curr Probl Pediatr Adolesc Health Care, 2018.
Walter HJ et al; Practice Guideline; JAACAP, 2020.

Suicide Risk:

- FDA sponsored meta-analysis of 24 RCTs (2004)
  - Reported an increase in *spontaneous* reporting of suicidal thinking/behavior in treatment group (4%) compared to placebo (2%)
- Has never been replicated
- Monitor for disinhibition, interpersonal conflicts, substance abuse or activation

Discontinuation (Withdrawal) Syndrome:

- Can mimic relapse or recurrence or worsening of anxiety
- More likely with shorter acting drugs, and QD dosing
- Change to BID if needed
- Taper slowly

Birmaher B & Re M; Major Depressive Disorder; Clinical Manual of Child and Adolescent Psychiatry; 4th Ed.; 2024
Strawn JR, Vaughn S, Ramsey LB; Pediatiric Psychopharmacology for Depressive and Anxiety Disorders; Focus, 2022..

Continuation Phase:

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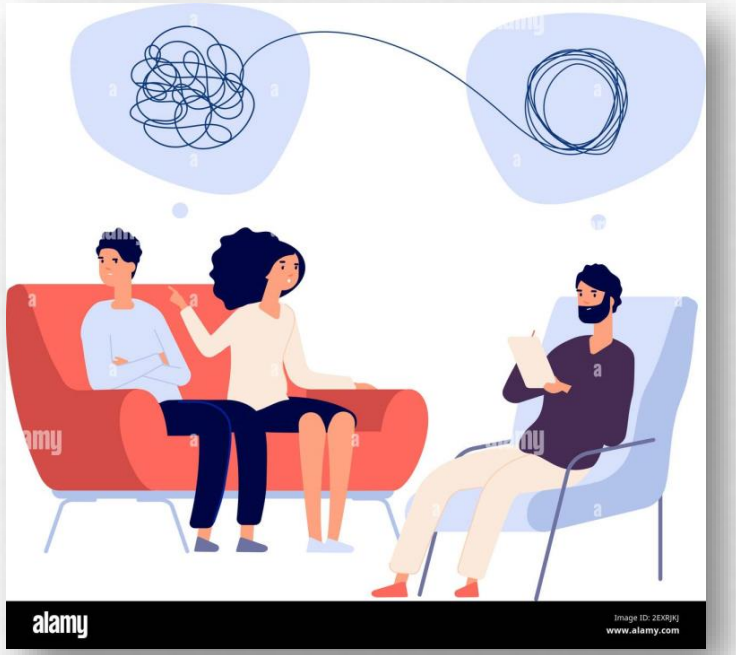


Treatment Resistance… Remember the NNT

Reassess for:

- Correct diagnosis
- Psychiatric/medical comorbidities complicating clinical picture or contributing factor to anxiety
- Adherence issues/Intolerable SEs
- Contributing stressors that need to be addressed
  - Family stressors, sleep, trauma
- Cytochrome P450 polymorphisms
- Appropriate length of drug trial/early discontinuation
- Evidence-based practices

Strawn, J. AACAP Psychopharm Update, 2024.

IF no response with evidence-based strategies
STOP and START OVER

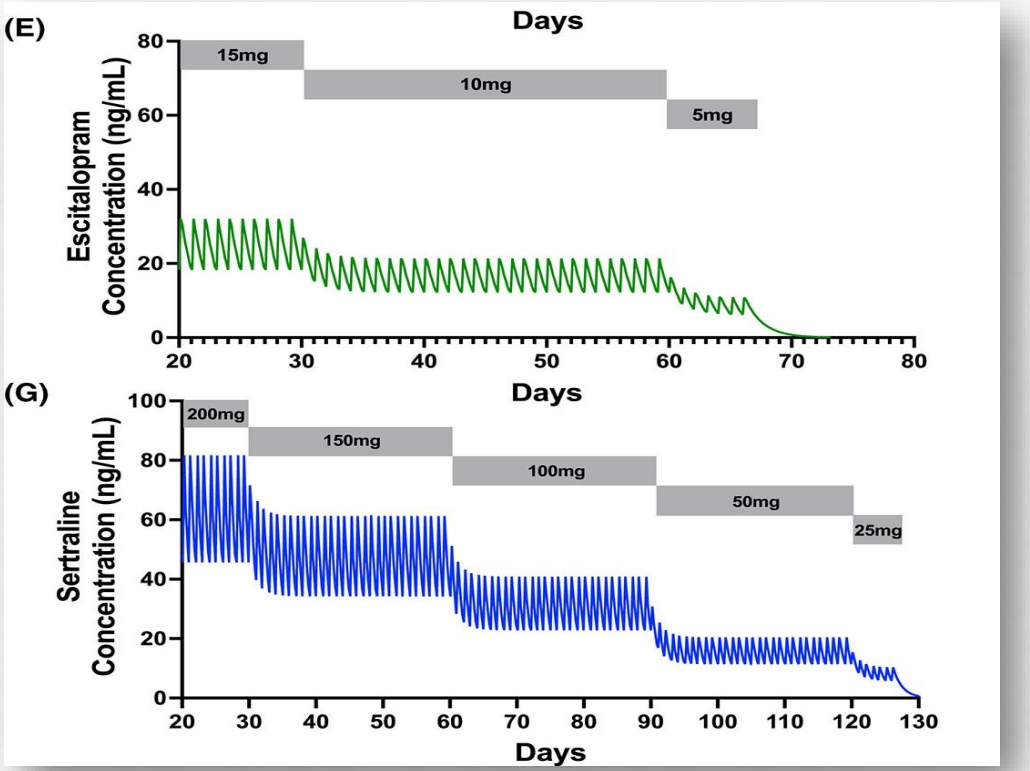
- If diagnosis correct, retrial of SSRI at higher dose
- Address specific comorbidities and stressors with evidence-based interventions
- There is no data for polypharmacy

If you are feeling the need for polypharmacy, refer or seek consultation for diagnostic clarification

Strawn JR, Vaughn S, Ramsey LB; Pediatric Psychopharmacology for Depressive and Anxiety Disorders; Focus, 2022.
Walter HJ et al. Clinical Practice Guideline, AACAP, 2020
Stahl & Strawn. The Prescriber's Guide: Children and Adolescents, 2024.

Discontinuation

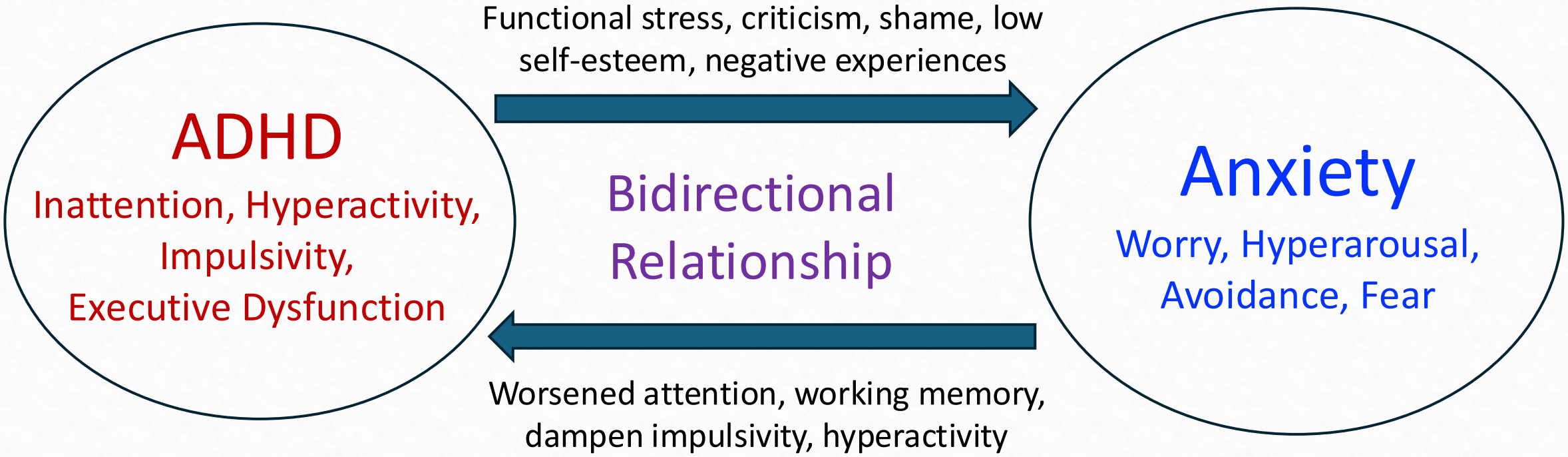
- After remission
- Timing: low stress
- “Hyperbolic” discontinuation
- Slow taper at least 6 weeks
- Avoids withdrawal symptoms which confuses clinical picture
- Rapid discontinuation can precipitate relapse



Strawn et al, Pharmacotherapy, Volume: 43, Issue: 7, January 2023.

CASEY *is a 16-year-old with a history of ADHD treated with a long-acting stimulant for the last 6 years, presents for evaluation of worsening anxiety and "always feeling stressed" for the last five months. The patient lives at home with two younger siblings and their parents who are both professionals and work outside the home.*

- *Constant worry about grades and recently received a "lower than expected" score on the PSAT.*
- *Increased muscle tension, more trouble concentrating, poor appetite with a 5 lb wt loss, and poor sleep secondary to ruminations at night (though parents report poor sleep related to excessive phone use in the evenings.)*
- *Denies depression, suicidal thoughts or illicit substance use.*
- *Sophomore in an academically accelerated high school, with increasing difficulties keeping up with schoolwork and spends several hours on homework most school nights, and on weekends.*
- *Has done well academically in the past, has a 504 plan for extra time for examinations but is worrying will no longer be competitive for a top tier university.*
- *Plays the trombone in a community orchestra with practice two afternoons/wk and performances 2x/yr and participates in an extramural lacrosse team which practices 3x/wk.*
- *Has good friends but is avoiding social events feeling too overwhelmed to attend, and embarrassed by the PSAT score stating, "EVERYONE did better than me."*



Recommend:

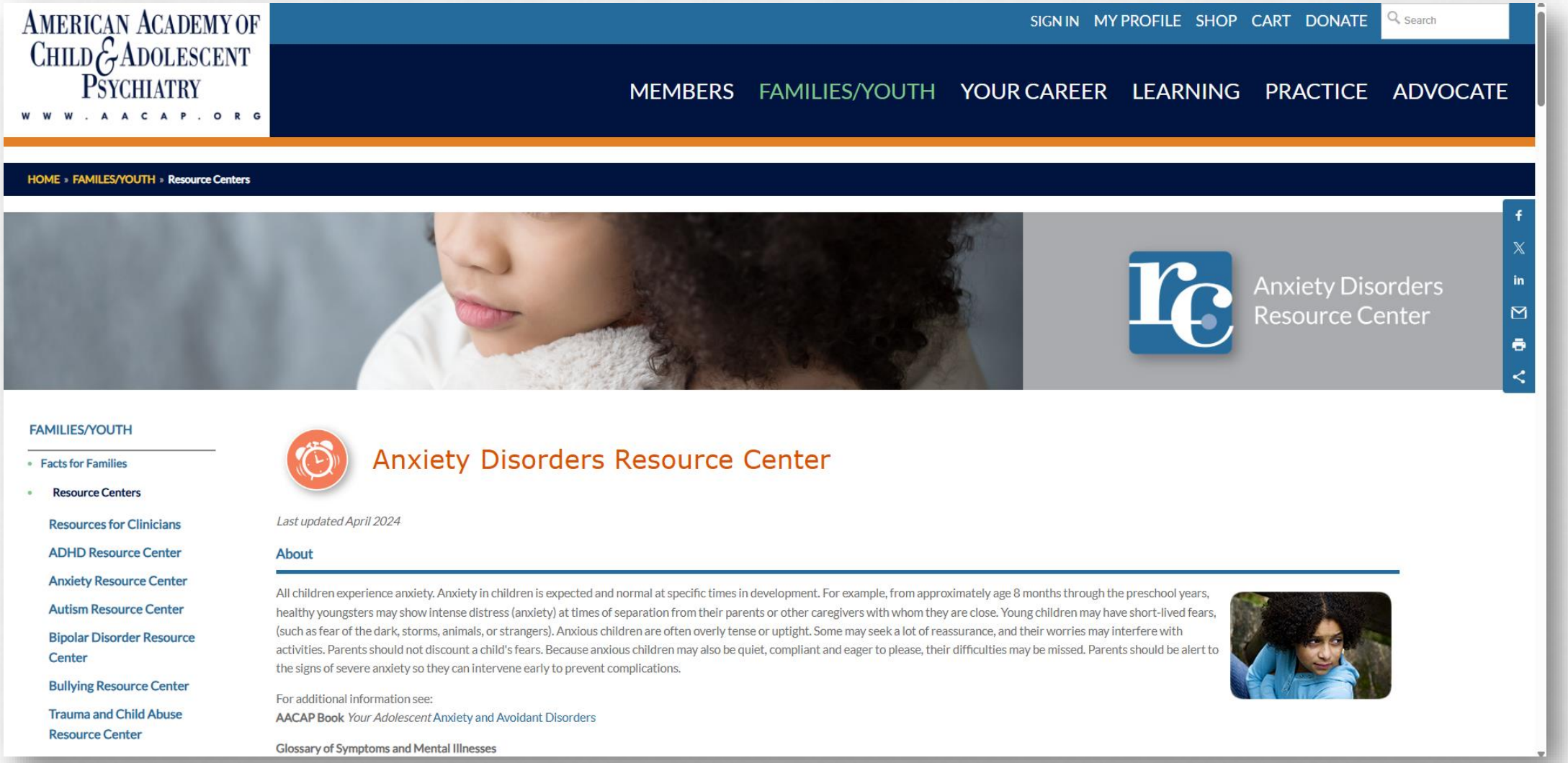
- Evaluate and treat separately
- Treat most impairing first
- If equal, treat ADHD first
- Add CBT/SSRIs when ADHD optimized

Koyuncu et al, Current Psychiatry Reports, 2022.

Final Thoughts:

- Medications have an important role, but should be driven by accurate diagnosis with evidence-based treatment interventions
- Define a therapeutic goal and track to determine response
- SSRIs/SNRIs are effective for anxiety disorders
  - SSRIs have greater and faster improvement, but more activation and discontinuation symptoms
- CBT only for “mild” anxiety
- CBT/SSRIs is best
- Psychoeducation is key to maintain adherence and prevent early termination and misdiagnosis
- Watch for comorbidities and stressors, particularly if “treatment resistant” and manage

Resources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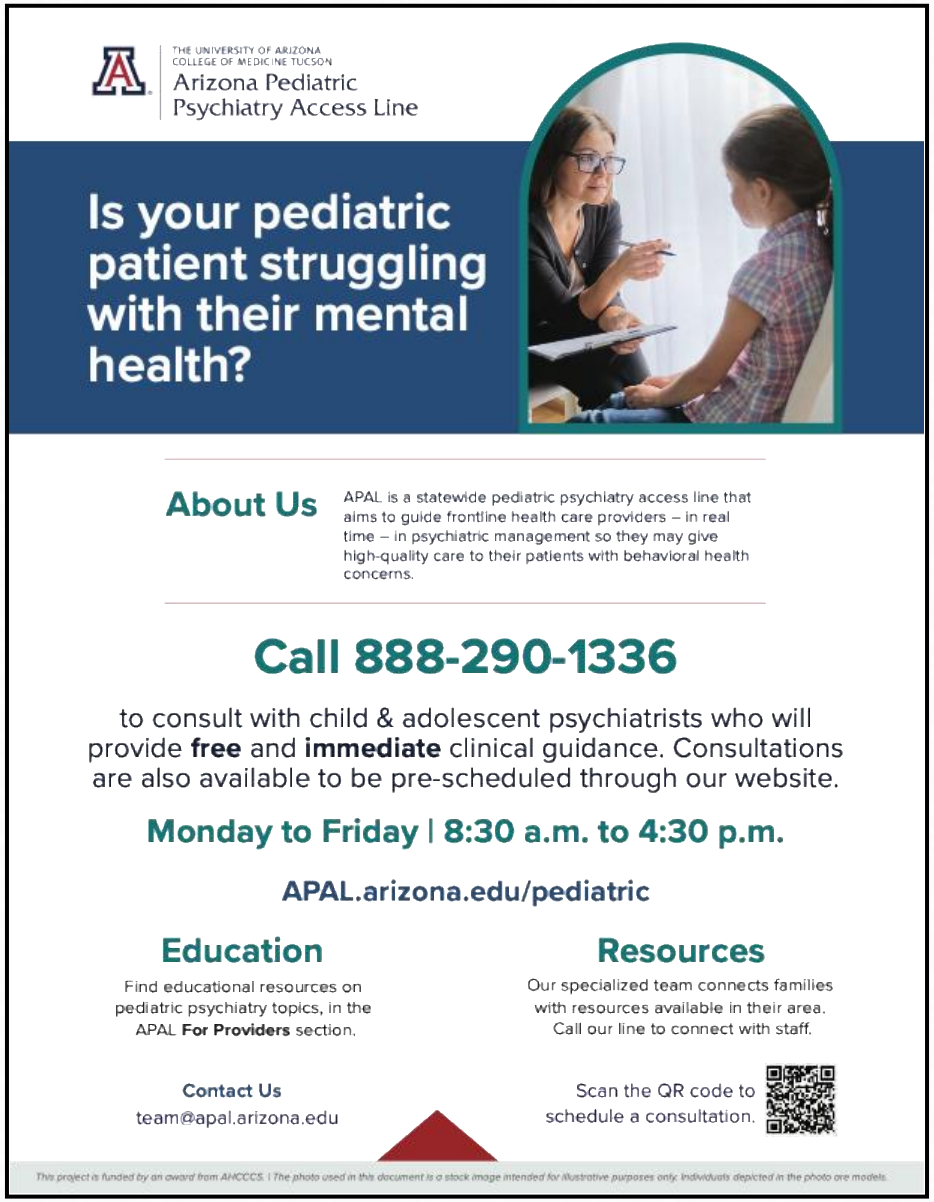
Last updated April 2024
About
All children experience anxiety. Anxiety in children is expected and normal at specific times in development. For example, from approximately age 8 months through the preschool years, healthy youngsters may show intense distress (anxiety) at times of separation from their parents or other caregivers with whom they are close. Young children may have short-lived fears, (such as fear of the dark, storms, animals, or strangers). Anxious children are often overly tense or uptight. Some may seek a lot of reassurance, and their worries may interfere with activities. Parents should not discount a child's fears. Because anxious children may also be quiet, compliant and eager to please, their difficulties may be missed. Parents should be alert to the signs of severe anxiety so they can intervene early to prevent complications.
For additional information see:
AACAP Book Your Adolescent Anxiety and Avoidant Disorders
Glossary of Symptoms and Mental Illnesses

Resources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Thank You!!

Kathy W Smith, MD

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