Disclosures

None
Learning Objectives

• Improving provider’s comfort in screening and diagnosing anxiety disorders.

• Improving provider’s understanding of contributing factors to the development and maintenance of anxiety disorders.

• Increase knowledge about the current evidence base for using medications and therapy to manage pediatric anxiety.

• Briefly review PTSD and OCD which were formerly classified under anxiety disorders to help maintain awareness and screening for these disorders.
Anxiety Disorders

• The most common group of psychiatric disorders in children with prevalence rate of 10-30%.
• 20% of youth presenting to primary care will screen positive for anxiety on a brief screen.
• Most Common:
  • Social Anxiety Disorder
  • Specific Phobia
  • GAD
  *Preschoolers—Separation Anxiety D/O
Arranged by typical age of onset on DSM 5:

- Separation Anxiety Disorder
- Selective Mutism
- Specific Phobia
- Social Anxiety Disorder
- Panic Disorder
- Agoraphobia
- GAD
- Substance/Medication-Induced —
- — due to another medical condition
- Other Specified—
- Unspecified—(used when clinician chooses not to specify the reason the criteria is not met/insufficient info.)
No longer under DSM 5 Anxiety Disorders

• Fear/Anxiety is still a core feature of OCD, PTSD, Somatic Symptom Disorders.

• “Obsessive Compulsive and Related Disorders” recognize a spectrum of OCD presentations:
  - OCD
  - BDD
  - Hoarding Disorder
  - Trichotillomania
  - Excoriation Disorder
Disorders to keep in mind when screening:

- PTSD “Trauma and Stress Related Disorder”
  Reactive Attachment D/O
  Adjustment Disorder
  Disinhibited Social Engagement D/O

- “Somatic Symptom and Related Disorders”
  Illness Anxiety Disorder
  Conversion d/O
  Somatic Symptom Disorder
Adolescent Anxiety a Risk Factor for Future Outcomes:

Swedish Twin Study:
• 14,106 pts, 15 year old twins
  • adjusted for ADHD, ASD, Dev. Coordination Disorder
  • Adolescent Anxiety predicted future outcomes:
    • Anxiety Disorders (HR=4.92)
    • Depressive Disorders (HR=4.79)
    • Any Psychiatric Outcome (HR 3.4)

Results replicated in Dutch data. The proportion of outcomes attributable to adolescent anxiety over time (age 15-21):
• 29% for any psychiatric outcome
• 43–40% for anxiety disorders
• 39–38% for depressive disorders.

Doering et al. BMC Psychiatry (2019) 19:363
https://doi.org/10.1186/s12888-019-2349-3
Onset

Separation Anxiety:
• 2.7% of preschool age children already meet criteria*
• Onset occurs at any point including adulthood with lifetime prevalence of 4 percent. **

Specific Phobia:
• Majority have onset in early childhood and prevalence increases into teens—sample of 10,148 U.S. adolescence, 12-month prevalence was 15%***

Onset

• Social Anxiety:
  • Preschool prevalence rate up to 4.4%*
  • 75% of onset occurs between ages 8-15.

• GAD:
  • 4.7% of preschool age children**
  • Broader median age of onset, age 30.


Fear vs Anxiety vs Disorder

• Fear is an emotional response to real/perceived imminent threat.

• Anxiety is the anticipation of a future threat.

• Becomes a ‘Disorder’ when there is:
  • high levels of distress & functional impairment.
  • when fear response persists beyond developmental expectations.
    • Stranger Anxiety at 9 months
    • Separation Anxiety (1-2 years)
Pathogenesis of Anxiety Disorders:

1. Heritability estimate of 40-65%.

2. Environment:
   - Parenting Styles: permissive, over-protective, over-critical.
   - Modeling: reactivity and coping strategies.
   - Family based factors linked with preschool onset anxiety:
     - Parent characteristics-internalizing disorder, younger, poorer, less educated.
     - Families where children don’t live with both biological parents.
     - More siblings in the home.
Pathogenesis:

3. Temperament*:
   - Behavioral Inhibition (BI): High reactivity and negative emotional response to any stimuli.*
   - Low Positive Affectivity
   - Low Sociability
   - High Negative Affect
   - Low Exuberance
   - Low effortful control

Pathogenesis Cont’d:

4. Neurobiological Factors

• Neurotransmitters:
  Serotonergic
  Noradrenergic
  GABA
4. Neurobiological Factors:

- Cortico-amygdala circuitry in role in fear learning.
  - Amygdala Signal: overactive “Bottom-up activity.”
  - Ventral Medial Prefrontal Cortex Signal: hypoactive “top-down control.”
  - The overactive amygdala signal & hypoactive vmPFC top-down control is correlated with hyperarousal to cues and impairment in extinction learning.
Pathogenesis Cont’d:

5. Learning—Classical Conditioning

• Pavlov’s Dog

• Little Albert & Rat
  • Pairing neutral cue + aversive cue (source of fear/anxiety) causes a patient to have the same fear response to what seems innocuous.

• Extinction of a conditioned response is difficult, especially if it guards against threat of injury.
### Pathogenesis:

5. Learning: Operant Conditioning & Negative Reinforcement

<table>
<thead>
<tr>
<th></th>
<th>Punishment (to decrease behavior)</th>
<th>Reinforcement (to increase behavior)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Add something to Decrease behavior (pain as consequence)</td>
<td>Adding something to Increase behavior (reward for wanted behaviors)</td>
</tr>
<tr>
<td>(to add something)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Taking something away to decrease behavior (removal of reward as consequence)</td>
<td>Taking something away that was already there, to increase behavior</td>
</tr>
<tr>
<td>(to subtract something)</td>
<td></td>
<td>AVOIDANCE CYCLE</td>
</tr>
</tbody>
</table>
Chief Complaint:

• Behaviors:
  • Avoiding
  • Excessive Need for Reassurance/Clingy
  • School Performance Declined
  • Oppositional, Explosiveness, Tantrums
  • Suicidal behaviors
  • Compulsions

• Somatic Complaints
  • Tension, aches/pains, fatigue, GI, Cardiac, Pulm.

• Sleep Problems
• Irritability/moody
Assessing focus of anxiety:

- Anxiety about:
  - being away from home or person
  - specific situations, places, animals/insect
  - many daily issues often
  - Embarrassment/scrutiny
- Intrusive Thoughts
- Compulsions
- Need to touch items
- Stress/Trauma Response
Assessment:

Safety Check:
- Abuse/Neglect
- Bullying*
- Psychosis
- Parental Impairment

Assessment:

- Family History
- Temperament
- Parenting style and parent-child fit
- Social History
- School History
- Neurodevelopmental Issues
- Medical History
- Substance Use History
Assessment:

Multimodal Approach

• Interview
  • Child
  • Parent
  • Child and Parent

• Corroborating data: teachers, etc.

• Screening Tools (SCARED, GAD-7, SPENCE)
  • Child
  • Parent

• Use of DSM 5.
SCARED

• Free, ages 9-17
• Parent and self-report
• Subscales for specific anxiety diagnoses
  • panic/somatic, GAD, Separation, Social, school attendance.
• Helpful for diagnosing and monitoring for effect of treatment.
• Several languages.

SCARED Traumatic Stress Disorder Scale

• Free, ages 7-19
• Sensitivity of 100%, specificity of 52%
SPENCE

- Free, ages 3-17
- Teacher, Parent, and self-report
- Subscales for somatization, panic, GAD, Separation Anxiety, and Social Phobia
- 28+ languages.
Screening Tools

GAD7

• Free, Age 14+
• Only 7 questions
• Classifies mild, moderate, severe
• Total score of 10 or above should trigger evaluation.
Consider comorbid conditions:

Anxiety Disorders are highly comorbid with other anxiety disorders.

- Study of 488 anxious children age 7 to 17. Social anxiety disorder, GAD, and Separation Anxiety Disorder co-occurred in nearly 60 percent of patients.*

- In CAMS, 78.6% of the sample had 2 or more of the anxiety disorders and 35.9% had all 3.

Anxiety Disorders are highly comorbid with other non-anxiety disorders:

- Preschool Anxiety—ADHD, ODD.
- Adolescent Anxiety—ADHD, ODD, LD, Depression.
- GAD and social phobia are the most strongly linked to Depression.
Treatment:

Mild Anxiety:
• Psychoeducation/CBT

Moderate Anxiety:
• CBT
• Consider Medication (SSRI)

Severe Anxiety:
• CBT and SSRI
Child & Adolescent Anxiety Multimodal Study (CAMS)

Design
• 488 7-17 year olds with GAD, Separation Anxiety, Social Anxiety Disorder
• Randomized to 14 sessions of CBT, Sertraline, Combination, Placebo
• 12 weeks

Results
• Response rate defined as Very Much of Much Improved on Clinical Global Impression Improvement Scale:
  • Combination Arm: 80.7%
  • CBT Alone: 59.7%
  • Sertraline alone: 54.9%
  • Placebo: 23.7%

Did not have anymore SI in Sertraline arm than placebo arm. No suicide attempt.

CAMS:

- Phase 2: Continuation of 12 week treatment with monthly CBT booster session, SSRI + CBT booster sessions, vs medication management sessions.

- >80% of responders from the 12 week trial that were receiving Combination, CBT alone, SSRI alone, maintained positive response at both weeks 24 and 36 in a later study.

- Consistent with acute outcomes, combination treatment maintained advantage over CBT and Sertraline outcomes for CAMS.

Cognitive Behavioral Therapy:

• CAMS: Coping CAT
• Relaxation Techniques
  • Deep breathing, Progressive Muscle Relaxation, mindfulness
• Cognitive Restructuring
  • Catastrophizing, all or none thinking, etc.
• Externalize symptoms
• Exposure Response Prevention
  • Tackle Avoidance: create a hierarchy of symptoms
  • Exposure in office and outside of office.

The Vicious Cycle of Escape & Avoidance

Begin Exposure → "TIME" → Mastery of Anxiety

- Begin Exposure
- Return of trigger
- Exposure Anxiety Climbing
- Anxiety quickly drops
- Avoidance/Escape
- PANIC PEAK
- Habituation Anxiety Climbing
- Relief
Common SSRI side effects:

- Anticholinergic (Paxil)
- Drowsiness (Paxil, Luvox)
- Weight gain (Paxil)
- Orthostatic Hypotension (Paxil)
- Insomnia/Agitation (Prozac, Sertraline. Try taking in AM)
- QTc prolongation (Celexa at dose above 40 mg in adults)
- Sexual dysfunction
- Gastrointestinal Problems, headaches (tend to be transient and care is supportive. Sertraline associated more with diarrhea)
- Platelet dysfunction (rare)
More Serious Side Effects:

- Serotonin Syndrome
  - Explain Symptoms (Tremor, diaphoresis, palpitations, etc.)
  - Explain what to do in case symptoms occur
  - Educate on not combining with OTC and other medications without talking to physician/pharmacist first.
- Activation (agitation, insomnia, hyperactivity)
- Panic Attacks—those with anxiety sometimes need to start at lower doses.
- Inducing Hypomania (look at family history)
- Black Box Warning for Suicide
Black Box Warning for Suicide 2004

Series of meta-analyses:
- 372 randomized clinical trials of antidepressants, 100,000 participants.
- 24 placebo controlled trials in >4400 children/adolescents, rate of suicidal thinking/behavior was 4% antidepressant vs 2% placebo. No suicides reported.
- Increased risk was significant only in those <18 years.

Effect: Significant post-warning reductions in the rate of new diagnoses of depression by PCPs.

FIGURE 1. SSRI Prescription Rates in the United States, 2002–2005, Stratified by Age Group and Expressed as a Percentage of the 2003 Rate

FIGURE 2. Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004

• **Bridge et al, JAMA. 2007;297:1683-1696**

  • Meta-analysis of 27 RCTs for antidepressants relative to placebo for pediatric MDD and anxiety (OCD and non-OCD)

  • **Results:**

    • Overall small but increased risk of treatment-emergent suicidal ideation/suicide attempt.
      
      • Pooled risk of suicidal ideation/suicide attempt for each indication were all less than 1%.

    • Depending on treatment indication, **NNT ranges from 3 to 10**, while **NNH via emergence of suicidal ideation/suicide attempt ranges from 112 to 200**
Black box warning for suicide

- Suicidality could be linked to SSRI activation (more impulsive, insomnia, lability, agitation/restlessness)
- Usually occurs when first starting or increasing SSRI.
- Consider starting at a very low dose and titrating more slowly to decrease risk of activation.
- Opportunity for reviewing risks/benefits/alternatives of treatment as well as:
  - encouraging open communication/therapeutic trust
  - going back over suicide risk assessment
  - reinforcing evidence based individual therapy
  - ensuring crisis prevention plan is in place if needed.
## Anxiety Medications

Starting at a very low dose of SSRI for the first week or two with anxiety disorders is especially essential to reduce the child’s experience of side effects (augmented by associated somatic anxieties).

<table>
<thead>
<tr>
<th>Name</th>
<th>Dosage Form</th>
<th>Usual starting dose for adolescents</th>
<th>Increase increment (after ~4 weeks)</th>
<th>RCT anxiety treatment benefit in kids</th>
<th>FDA anxiety approved for children?</th>
<th>Editorial Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>10, 20, 40mg 20mg/5ml</td>
<td>5-10 mg/day (60mg max)*</td>
<td>10-20mg**</td>
<td>Yes</td>
<td>Yes (For OCD ≥7yr) (For MDD ≥8yr)</td>
<td>Long 1/2 life, no SE from a missed dose</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>25, 50, 100mg 20mg/ml</td>
<td>25 mg/day (200mg max)*</td>
<td>25-50mg**</td>
<td>Yes</td>
<td>Yes (For OCD ≥6yr)</td>
<td>May be prone to SE from weaning off</td>
</tr>
</tbody>
</table>

Sertraline and Fluoxetine are both first line medications for child anxiety disorders, per the evidence base.

<table>
<thead>
<tr>
<th>Name</th>
<th>Dosage Form</th>
<th>Usual starting dose (300mg max)*</th>
<th>Increase increment (40mg max)*</th>
<th>Yes</th>
<th>Yes (For OCD ≥8yr)</th>
<th>Often more side effect than other SSRIs, has many drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>25, 50, 100mg</td>
<td>25 mg/day</td>
<td>50 mg**</td>
<td>Yes</td>
<td>Yes (For OCD ≥8yr)</td>
<td>Not preferred if child also has depression. Can have short 1/2 life</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>10, 20, 30, and 40 mg 10mg/5ml 12.5, 25, 37.5mg CR forms</td>
<td>5-10 mg/day (60mg max)*</td>
<td>10-20mg**</td>
<td>Yes</td>
<td>No</td>
<td>Very few drug interactions</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>10, 20, 40 mg 10mg/5ml</td>
<td>5-10 mg/day (40mg max)*</td>
<td>10-20mg**</td>
<td>Yes</td>
<td>No</td>
<td>Active isomer of citalopram</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>5, 10, 20mg 5mg/5ml</td>
<td>2.5 to 5 mg/day (20mg max)*</td>
<td>5-10mg**</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>20, 30, 40, 60mg</td>
<td>30 mg/day (120mg max)</td>
<td>30mg</td>
<td>Yes</td>
<td>Yes (For generalized anxiety ≥7yr)</td>
<td></td>
</tr>
</tbody>
</table>

* Recommend decrease maximum dosage by at least 1/3 for pre-pubertal children
** Recommend using the lower dose increase increments for younger children.
Successful medication trials should continue for 6-12 months.
SSRI trials

• At Adequate dose for adequate length of time.
• If failed one SSRI, trial another SSRI.
• If switching, monitor for:
  • Discontinuation syndrome
  • Potential side effect to new SSRI
  • Symptom relapse of partially treated symptoms
  • Serotonin Syndrome
  • P450 interactions
    • Prozac and Paxil - potent 2D6 inhibitors
    • Prozac and Luvox - moderate 2C19 inhibitors
### Approximate dose equivalents of antidepressants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>20 mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-75 mg</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20 mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10 mg</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100 mg</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75 mg</td>
</tr>
</tbody>
</table>
Maintenance:

- Once stabilized, continue SSRI for 6-12 months (except with OCD, continue for a year).

- The longer it takes to recover or the higher the number of recurrences, the longer the period of maintenance.
If 2 SSRIs don’t work:

- Duloxetine (Cymbalta) — FDA Approved for GAD age 7 and up
- Venlafaxine* (Effexor XR) — Side effect profile makes this a 2nd tier option
- Mirtazapine* (Remeron) — no controlled trials
  - Consider if need sedation and appetite stimulation
- Buspirone* (Buspar) — 2 negative RCTs in youth with GAD
- Beta-blockers* — no controlled trials
  - Used for performance anxiety
- Antihistamines — no controlled trials
  - Hydroxyzine used for as adjunctive, often for insomnia/anticipatory anxiety
  - Hydroxyzine can increase QTc
  - FDA approval for “symptomatic relief of anxiety and tension associated with psychoneurosis”
- Tricyclic antidepressants
  - Clomipramine shown to be efficacious in OCD, FDA approved ≥ 10yo
  - Anticholinergic side effects, cardiac monitoring, risk of fatality with overdose

*Not FDA approved for anxiety treatment <18

Sleep

• Ask About:
  • Snoring, restless legs, potential medical causes.
  • Adherence to bedtime routine.
  • Sleep environment.
  • What they’re thoughts are like before falling asleep.

• Treatment:
  • Sleep hygiene.
  • CBT-I (CBT for insomnia).
  • Medications:
    • Generally use is short term.
    • Targeting anxiety treatment can reduce medication burden for sleep.
Anxiety with ADHD

• Child presents as distracted, fidgety, impulsive:
  • What is distracting your patient (anxious thoughts?)
  • Is the anxiety solely over ADHD related sx and consequences?

• In general, anxiety is treated first when ADHD and Anxiety co-occur.

• Medication Considerations:
  • Stimulants—could worsen anxiety (Effect Size 10)
  • Clonidine/Guanfacine—may help hyperarousal (Effect Size 0.65)
  • Atomoxetine—may help anxiety (Effect Size 0.7)
Sleep

- Melatonin 1-6 mg, 1 hour before bedtime
- Hydroxyzine or Diphenhydramine 12.5-25 mg to 50 mg (short term).
- Trazodone 25-50 mg to maximum of 200 mg (Priapism, dizziness, more serotonergic at higher doses).
- Clonidine with comorbid ADHD.
PTSD

- Psychotherapy as first line for PTSD

- Most effective therapies in multiple clinical trials in adults include: exposure therapy OR combination of exposure & cognitive therapy (TF-CBT or Cognitive Processing Therapy).

- Therapies with evidence in PTSD in children include TF-CBT, ARC (Attachment, Regulation, and Competency), IY, PCIT, Parent Child Therapy.*

PTSD

• No medication is FDA approved for PTSD.
• Tend to trial SSRI first.
• Prazosin- alpha-1adrenergic receptor antagonist for nightmares. Mixed results in adults.*

PTSD

• Propranolol—Cross over pilot study in 11 children where most children improved in hyperarousal and intrusivity.*

• Clonidine—small open-label trial, decreased aggression in 7/7 3-6 y/o, and in 5/7, impulsivity/emotional outbursts and mood lability, hyperarousal, hypervigilance, GAD, oppositionality, insomnia, NM improved.

OCD

- POTS-1
  12 week RCT 112 children age 7-17 in 4 treatment arms. Remission rates:
  - 53.6% CBT+Sertraline
  - 39% CBT
  - 21% Sertraline
  - 4% Placebo

  - All three treatment arms did better than placebo
  - Combination Treatment was superior to either treatment alone
  - CBT and sertraline only groups did not statistically differ
  - Site difference as a cause to reinforce CBT

OCD—POTS II

- 124 SRI partial responders randomized to receive 12 weeks of:
  - 7 Medication Management (MM) sessions
  - 7 sessions of MM+I-CBT (Instructional CBT)
  - MM+CBT (7 sessions MM & 14 ERPT/CBT sessions).

- Response defined as CY-BOCS reduction of 30% or greater from baseline over 12 weeks.
  - MM+CBT 68.6% was statistically superior to MM (30%) and to MM+I-CBT (34%). MM and MM+I-CBT did not statistically separate.

Benzodiazepine

- NO RCT to support use of BZ in children.
- BZ Concerns: memory/learning, tolerance/dependence, activation. Takes away from effectively learning coping strategies and mastery over anxiety provoking situations.
- If BZ is used, reserved for short term use at low doses in severe anxiety.
Marijuana Plant

• Contains more than 100 different chemicals ‘cannabinoids’.
• Tetrahydrocannabinol (THC) and Cannabidiol (CBD)
• If Cannabis is used, it may alleviate anxiety in the short term but worsens anxiety long term.

“Anxious mood lability was significantly higher for adolescents reporting recent marijuana use compared to those reporting no recent marijuana use (past 30 days).”

Marijuana

Systematic Review and Meta-analysis of 83 eligible studies (40 RCT n=3067)

- 31 studies for anxiety (17 RCT, n=605)
- Pharmaceutical THC (with/without CBD) improved anxiety sx. among individuals with medical conditions (chronic non-cancer pain & MS) in 7 studies but evidence GRADE was very low.
- Did not significantly affect any other primary outcomes for the mental disorders examined.
- Increased adverse events and withdrawal from studies due to adverse events

Patient A

8 year old male with FH of father with Bipolar 1 Disorder and mother with anxiety disorder. He has been complaining of stomach aches. There is a two year old in the family that has had some medical issues demanding parents time. Child and toddler are in separate bedrooms. Patient A has history of trying to go to bed with parents versus sleeping on his own and has tried to do this a few times but parents have been steadfast with implementing your recommendations against cohabitation.

Differential Diagnosis/Questions to ponder—?
Patient A

8 year old male returns to your office as he has been throwing a tantrum before being driven to school. He refuses to get into, then out of the car at times so parents have to call the main office for someone to come out and help escort the child into the school, or parent will give up and take the child home occasionally. He says would rather die than have to go to school and thinks about suicide. He has no plan toward suicide and no firearms are in the home.

Differential Diagnosis/Questions to ponder—?
Patient A

You have done a multimodal assessment with interviews, use of screens, and work with the family on:

• crisis prevention plan
• referral to CBT therapist for patient and parent psychoeducation.
• education on school avoidance worsening if they allow child to stay home. Making certain home is not too comfortable when he does refuse to go to school.
• encourage the family to collaborate with school and work with them on school drop off.

• family requests SSRI for the child.

What are your concerns about SSRI, family, child, etc.?