Anxiety Disorders in Children and Adolescents
Child and Adolescent Psychopharmacology

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Disclosures (Past 12 Months)

- Abide Therapeutics: Scientific Advisory Board
- American Academy of Child and Adolescent Psychiatry: Honoraria
- Bracket: Honoraria
- Cincinnati Children’s Hospital: Honorarium
- Harvard Medical School: Honoraria
- Neurocrine Biosciences: Research Support
- Nevada Psychiatric Association: Honorarium
- NIMH: Research Support
- Partners Healthcare: Honoraria
- Teva/Nuvelution: Research Support; Scientific Advisory Board
- Tourette Association of America: Co-Chair, Medical Advisory Board; TAA-CDC Partnership

- **Off label indications will be discussed**
Anxiety Disorders in Children and Adolescents

Learning Objectives:

- At the end of this session, the participant should be able to:
  - Review **elements of comprehensive evaluation** of anxiety disorders in children and adolescents
  - Understand the **presentation, differential diagnosis and evaluation** of anxiety disorders in children and adolescents
  - Understand **treatment options** for anxiety disorders in children and adolescents
Math anxiety

Latin convulsions

Chemistry connipitions

Physics floundering

Wood shop apathy

Basic stupidity

Classroom afflictions
Lifetime Prevalence of Mental Disorders in US Adolescents
(Merikangas, K. et al JAACAP; 2010; 49 (10); 980-989)

**Design:** National Comorbidity Survey-Adolescent Supplement

Face to face survey of 10,123 adolescents, age 13-18, in US

**Results:** Anxiety disorders (32%), Behavior Disorders (19%), Mood Disorders (14%) and Substance Use Disorders (11%).

Overall prevalence of disorders with severe impairment and/or distress was 22%.

Median age of onset was earliest for anxiety (6), behavior (11), mood (13), and SUD (15).

**Conclusion:** Common mental disorders in adults first emerge in youth.
FIGURE 1  Cumulative lifetime prevalence of major classes of DSM-IV disorders among adolescents (N = 10,123).
FIGURE 1. The age of onset distribution of (A) anxiety, depressive and substance use disorders and (B) specific anxiety disorders at age 33, and estimated cumulative incidence rates at age 33 (in parenthesis)

Data from the Early Developmental Stages of Psychopathology (EDSP) Study. Adapted from [8].

Wehry et al. (2015)
Anxiety and Fears: Normal Developmental Issues

- Specific fears are common in children
- 43% of 13-18 year olds have had at least one panic attack (Ollendick et al 1994)
- 22% experience frequent worry about school work (Perrin et al 1997)
- 23% are described with excessive reassurance seeking (Bell-Dolan et al 1990)
Pediatric Anxiety Disorders: When Does “Normal” Anxiety become a Symptom or Disorder?

Clinical Characteristics

- Persistent unrealistic fear or worry inappropriate for developmental stage/age
- Marked distress or avoidance
- Interference with school, social, or family functioning
- Time consuming symptoms
<table>
<thead>
<tr>
<th>Age range</th>
<th>Common fears</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy</td>
<td>Loud noises, being startled, strangers, large objects</td>
</tr>
<tr>
<td>Toddlers</td>
<td>Dark, separating from parents, imaginary creatures, sleeping alone, doctors</td>
</tr>
<tr>
<td>School-aged children</td>
<td>Injury, natural disasters or events (eg, storms)</td>
</tr>
<tr>
<td>Older children and adolescents</td>
<td>School performance, social competence, worries about their own and others health.</td>
</tr>
</tbody>
</table>
Classification: Pediatric Anxiety Disorders (DSM-5, 2013)

- Separation Anxiety Disorder
- Selective Mutism
- Specific Phobia
- Social Anxiety Disorder (Social Phobia)
- Panic Disorder
- Agoraphobia
- Generalized Anxiety Disorder
- Substance/Medication Induced Anxiety Disorder
- Anxiety Disorder due to Another Medical Condition
- Other Specified Anxiety Disorder
Pediatric Anxiety Disorders: Prevalence and Course

- Anxiety disorders are common in children and adolescence (6-20%) of youth.
- 12 month prevalence in children: 5.3-8.9% (Costello, 1998)
- 12 month prevalence in adolescents: 8.7-17% (Kashani and Orvaschel, 1988)
- Anxiety disorders are frequently comorbid with one another and with mood disorders in children and adolescents.
- Recurrences are common.
- Median odds ratios in meta-analysis of 15 population studies for association between anxiety disorder and ADHD 3.0, CD 3.1 and MDD 8.2. (Angold et al 1999)
Pediatric Anxiety Disorders: Neurobiology  

- Dysfunction in **prefrontal-amygdalect circuits**
- Dysfunction in default mode network and posterior structures (posterior cingulate, precuneus and cuneus)
- “Overactivated” **amygdala** (initiates fear response) in fMRI studies of youth with fear-based anxiety.
- **Ventrolateral prefrontal cortex (VLPC)** also plays important role as it regulates amygdala activity and plays pivotal role in extinction in fear conditioning.
- Plays compensatory role; i.e degree of activation inversely proportional to anxiety severity.
- **Cingulate cortex** also hyperactivated in youth with anxiety and subserves motivation and cognitive control.
Diagnosis: Pediatric Anxiety Disorders: Common Symptoms

- Excessive need for **reassurance**
- **Avoidance of or significant distress** with age appropriate interests/activities
- **Physical complaints**: headaches, stomach aches, body pains, change in appetite
- **Sleep disturbance**: initial, middle or late insomnia; inability to sleep alone or repeated visits to parents’ bedroom
- Difficulty with **concentration and attention**
Key Things a Child Psychiatrist Needs to Know About Evaluation of Pediatric Anxiety Disorders

(Practice Parameter: Assessment and Treatment of Children and Adolescents with Anxiety Disorders; JAACAP, 2007; 46; 2; 267-283)

- **Recommendations:**
  - **Minimal standards (MS):** based on rigorous empirical evidence such as randomized, controlled trials and/or overwhelming clinical consensus. Apply more than 95% of the time.
  - **Clinical guidelines (CG):** based on empirical evidence and/or strong clinical consensus. Apply more than 75% of the time.
  - **Options (OP):** practices that are acceptable but lack empirical evidence and/or clinical consensus.
  - **Not Endorsed (NE):** practices known to be ineffective or contraindicated
Behind the Scene.. Evidence Based Treatment Scholars

“Eraser fight!!”
Okay, now listen up. Nobody gets in here without answering the following question: A train leaves Philadelphia at 1:00 p.m. It’s traveling at 65 miles per hour. Another train leaves Denver at 4:00... Say, you need some paper?

Math phobic’s nightmare
Diagnosis: Pediatric Anxiety Disorders: Diagnostic Instruments/Rating Scales

- **Structured/Semi-Structured Diagnostic Interviews:**
  - Schedule for Affective Disorders and Schizophrenia (KSADS-PL; Kaufman et al, 1997))
  - Anxiety Disorders Interview Schedule (ADIS, Silverman and Albano)
  - Diagnostic Interview Schedule for Children (DISC)
Key Things a Child Psychiatrist Needs to Know About Evaluation of Pediatric Anxiety Disorders

(Practice Parameter: Assessment and Treatment of Children and Adolescents with Anxiety Disorders; JAACAP, 2007; 46; 2; 267-283)

2) **Evaluation:**

- If screening indicates significant anxiety, the clinician should conduct a formal evaluation to determine which anxiety disorder may be present,
- the severity of anxiety symptoms, and functional impairment. (MS)
Diagnosis: Pediatric Anxiety Disorders: Diagnostic Instruments/Rating Scales

- **Self Report Instruments:**
  - Multidimensional Anxiety Scale for Children (MASC) (DSM based; John March, 1997)
  - SCARED: Self Report for Childhood Anxiety Related Disorders

- **Parent/Teacher Ratings:**
  - Achenbach Child Behavior Checklist (CBCL)

- **Clinician Ratings:**
  - Pediatric Anxiety Rating Scale (PARS)
Self-Report for Childhood Anxiety Related Disorders (SCARED)

Below is a list of items that describe how people feel. For each item that describes you, please circle the 2 if the item is very true or often true of you. Circle the 1 if the item is somewhat true or sometimes true of you. If the item is not true of you, please circle the 0. Please answer all items as well as you can, even if some do not seem to concern you.

0 = Not true or hardly ever true
1 = Somewhat true or sometimes true
2 = Very true or often true

1. When I feel frightened, it is hard to breathe
2. I get headaches when I am at school
3. I don’t like to be with people I don’t know well
4. I get scared if I sleep away from home
5. I worry about other people liking me
6. When I get frightened, I feel like passing out
7. I am nervous
8. I follow my mother and father wherever they go
9. People tell me that I look nervous
10. I feel nervous with people I don’t know well
11. I get stomach aches at school
12. When I get frightened, I feel like I am going crazy.
13. I worry about sleeping alone
14. I worry about being as good as other kids
15. When I get frightened, I feel like things are not real
16. I have nightmares about something bad happening to my parents
17. I worry about going to school
18. When I get frightened, my heart beats fast
19. I get shaky
20. I have nightmares about something bad happening to me
21. I worry about things working out for me
22. When I get frightened, I sweat a lot
23. I am a worrier
24. I get really frightened for no reason at all
25. I am afraid to be alone in the house
26. It is hard for me to talk with people I don’t know well
27. When I get frightened, I feel like I am choking
28. People tell me that I worry too much
29. I do not like to be away from my family
30. I am afraid of having anxiety (or panic) attacks
31. I worry that something bad might happen to my parents
32. I feel shy with people I don’t know well
33. I worry about what is going to happen in the future
34. When I get frightened, I feel like throwing up
35. I worry about how well I do things
36. I am scared to go to school
37. I worry about things that have already happened
38. When I get frightened, I feel dizzy
39. I feel nervous when I am with other children or adults and I have to do something while they watch me (for example: read aloud, speak, play a game, play a sport)
40. I feel nervous about going to parties, dances, or any place where there will be people that I don’t know well
41. I am shy
# Multidimensional Anxiety Scale for Children (MASC)

**Client ID:**

**Age:**

**Gender:** Male Female

**Date:**

**School Grade:**

This questionnaire asks how you have been thinking, feeling, or acting recently. For each item, please circle the number that shows how often the statement is true for you. If a sentence is true about you a lot of the time, circle 3. If it is true about you sometimes, circle 2. If it is true about you once in a while, circle 1. If a sentence is not true about you, circle 0. Remember, there are no right or wrong answers, just answer how you have been feeling recently.

Here are two examples to show you how to complete the questionnaire. In Example A, if you were hardly ever scared of dogs, you would circle 1, meaning that the statement is rarely true about you. In Example B, if thunderstorms sometimes upset you, you would circle 2, meaning that the statement is sometimes true about you.

<table>
<thead>
<tr>
<th>Example A</th>
<th>Example B</th>
</tr>
</thead>
<tbody>
<tr>
<td>I'm scared of dogs</td>
<td>Thunderstorms upset me</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Now try these items yourself. Don't forget to do the items on the back of the questionnaire as well.

1. I feel tense or uptight
   - 0 1 2 3
2. I usually ask permission
   - 0 1 2 3
3. I worry about other people laughing at me
   - 0 1 2 3
4. I get scared when my parents go away
   - 0 1 2 3
5. I keep my eyes open for danger
   - 0 1 2 3
6. I have trouble getting my breath
   - 0 1 2 3
7. The idea of going away to camp scares me
   - 0 1 2 3
8. I get shaky or jittery
   - 0 1 2 3
9. I try to stay near my mom or dad
   - 0 1 2 3
10. I'm afraid that other kids will make fun of me
    - 0 1 2 3
11. I try hard to obey my parents and teachers
    - 0 1 2 3
12. I get dizzy or faint feelings
    - 0 1 2 3
13. I check things out first
    - 0 1 2 3
14. I worry about getting called on in class
    - 0 1 2 3
15. I'm jumpy
    - 0 1 2 3

*Please flip the questionnaire over; the items are continued on the back page...*
“Wait! Wait! Listen to me! ... We don’t have to be just sheep!”
“Well, heaven knows what it is or where it came from—just get rid of it! But save that cheese first.”

Diagnosis: Hidden Traps......
3) **Evaluation:**
- The psychiatric assessment should consider
  - differential diagnosis of other physical conditions
  - and psychiatric disorders that may mimic anxiety symptoms. (MS)
Pediatric Anxiety Disorders: Differential Diagnosis

- **Medical disorders** (hyperthyroidism, migraine, caffeinism, asthma, hypoglycemia, cardiac arrhythmias, etc.)

- Other **psychiatric disorders** which can also be comorbid:
  - Mood disorders (non-bipolar or bipolar depression)
  - Disruptive behavior disorders (ADHD)

- **Adverse effects of medications** such as bronchodilators, sympathomimetics, steroids, SSRIs
<table>
<thead>
<tr>
<th>System</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Endocrine/Metabolic</td>
<td>Hyperthyroidism (Graves’s, initial presentation of subacute thyroiditis)</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Temporal lobe epilepsy</td>
</tr>
<tr>
<td></td>
<td>Vestibular dysfunctions</td>
</tr>
<tr>
<td></td>
<td>Intracranial mass lesions</td>
</tr>
<tr>
<td></td>
<td>Postconcussive states/traumatic brain injury</td>
</tr>
<tr>
<td></td>
<td>Encephalopathies</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>Medications</td>
<td>Akathisia (secondary to antipsychotic agents, SSRI)</td>
</tr>
<tr>
<td></td>
<td>Anticholinergic toxicity</td>
</tr>
<tr>
<td></td>
<td>Benadryl, tricyclics</td>
</tr>
<tr>
<td></td>
<td>Stimulants</td>
</tr>
<tr>
<td></td>
<td>Methylphenidate, dextroamphetamine</td>
</tr>
<tr>
<td></td>
<td>Bronchodilators</td>
</tr>
<tr>
<td></td>
<td>Sympathomimetics</td>
</tr>
<tr>
<td></td>
<td>OTC agents</td>
</tr>
<tr>
<td></td>
<td>Pseudoephedrine</td>
</tr>
<tr>
<td>Illicit substance use</td>
<td>Marijuana—toxic reaction</td>
</tr>
<tr>
<td></td>
<td>Hallucinogens</td>
</tr>
<tr>
<td></td>
<td>Stimulant</td>
</tr>
<tr>
<td></td>
<td>Cocaine, amphetamines</td>
</tr>
<tr>
<td></td>
<td>Withdrawal syndromes</td>
</tr>
<tr>
<td></td>
<td>Alcohol, sedative-hypnotics</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia</td>
</tr>
<tr>
<td>Immunologic/Rheumatologic</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>Excessive caffeine, use of energy drinks/aids</td>
</tr>
</tbody>
</table>
Impact of Stressful Environments...

The dam bursts.
Timing is Everything
Professor Gallagher and his controversial technique of simultaneously confronting the fear of heights, snakes, and the dark
<table>
<thead>
<tr>
<th>Available forms</th>
<th>Generic available</th>
<th>&lt;40 lbs</th>
<th>40-90 lbs</th>
<th>&gt;90 lbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetineb (Prozac)</td>
<td>Solution; 10, 20, 40 Pulvules; 90 mg Prozac weekly</td>
<td>Yes</td>
<td>2.6 mg</td>
<td>6.20 mg</td>
</tr>
<tr>
<td>Sertralineb (Zoloft)</td>
<td>25, 50, 100 mg tablets</td>
<td>Yes</td>
<td>12.5-25 mg</td>
<td>12.5-100 mg</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>10, 20, 30, 40 mg tablets CR 12.5, 25, 37.5 mg tablets; solution</td>
<td>Yes</td>
<td>2.5 mg</td>
<td>5-30 mg</td>
</tr>
<tr>
<td>Fluvoxamineb (Luvox)</td>
<td>25, 50, 100 mg tablets</td>
<td>Yes</td>
<td>12.5-25 mg</td>
<td>25-100 mg</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>Extended release (XR) 37.5, 50, 75, 100 mg tablets; 37.5, 75, 150 mg capsules</td>
<td>No</td>
<td>37.5 mg</td>
<td>37.5-112.5 mg</td>
</tr>
<tr>
<td>Yes</td>
<td>25-50 mg</td>
<td>25-150 mg</td>
<td>25-300 mg</td>
<td></td>
</tr>
<tr>
<td>Clomipramineb (Anafranil)</td>
<td>25, 50, 75 mg capsules</td>
<td>Yes</td>
<td>1-5 mg/kg/day</td>
<td>1-5 mg/kg/day</td>
</tr>
<tr>
<td>Imipramine (Tofranil)</td>
<td>10, 25, 50 mg tablets; 75, 100, 125, 150 mg capsules</td>
<td>Yes</td>
<td>1-5 mg/kg/day</td>
<td>1-5 mg/kg/day</td>
</tr>
</tbody>
</table>

Separation Anxiety Disorder, Generalized Anxiety Disorder and Social Phobia

- Pharmacotherapy
  - RUPP trial, 2001
  - Birmaher et al., 2003
  - CAMS, 2008

- Psychotherapy
  - Kendall, 1994
  - Kendall et al., 1997
  - Many others
Fluvoxamine for the Treatment of Anxiety Disorders in Children and Adolescents

(Research Units in Pediatric Psychopharmacology Anxiety Study Group; N Engl J Med 2001;344:1279-85.)

- **Design:** Randomized double-blind, placebo-controlled
- Ages 6-17 years
- N=128
- Fluvoxamine up to 250-300 mg/day
- 8 weeks.

- **Results:**
  - FLV > placebo on CGI-I
    - 76% (48/63) vs. 29% (10/65)
  - Pediatric Anxiety Rating Scale
    - Fluvoxamine 18.7 to 9.0 > 50% change
    - Placebo 19.0 to 15.9 = No Change

**Conclusion:** Fluvoxamine is an effective treatment for children with anxiety disorders
Fluoxetine for Treatment of Childhood Anxiety Disorders

- **Design:** N=74; Ages 7-17 years; SAD, GAD and Social Phobia
- Fluoxetine 20 mg/day
- Randomized, double-blind, placebo controlled
- 12 weeks

**Results:**
- Fluoxetine was effective in reducing anxiety and improving functioning in all measures.
- Using ITT (intent-to-treat) analysis:
  - CGI 1 or 2:
  - Achieved by 61% of patients on fluoxetine
  - 35% on placebo.
- **Conclusion:** Fluoxetine is an effective treatment for childhood anxiety disorders.
Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety


- **Design:**
  - NIMH-funded randomized, controlled trial comparing sertraline, CBT, combination and placebo
  - SAD, GAD and Social Phobia
  - N=488
  - Mean age: 10-11
  - 12 weeks acute phase
  - 6 month follow-up
- **Results:**
  - Mean dose ~140 mg/day
  - Response: Combination 81%
    - CBT 60%
    - Sertraline 56%
    - PBO 24%
Figure 2. Scores on the Pediatric Anxiety Rating Scale during the 12-Week Study
Scores on the Pediatric Anxiety Rating Scale range from 0 to 30, with scores higher than 13 consistent with moderate levels of anxiety and a diagnosis of an anxiety disorder. The expected mean score is the mean of the sampling distribution of the mean. The I bars represent standard errors.
Summary: Pediatric Anxiety Disorders

- Anxiety disorders are highly prevalent, tend to be early in onset, and comorbid with other anxiety disorders and mood disorders in children and adolescents
- May be prodrome for later depressive illness in youth
- Systematic screening for anxiety disorders is recommended in all child and adolescent psychiatric patients
- Psychopharmacological treatment is with behavioral treatment and selective serotonin reuptake inhibitors
- CAMS, a classic NIMH funded study of treatment of pediatric anxiety disorders, results indicated most effective treatment was a combination of behavioral and psychopharmacological treatment