Diagnosing and Treating Pediatric Depression and Anxiety

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Objectives:

1. Describe the diagnosis of depression and anxiety according to DSM-5 criteria

2. Identify patients with signs and symptoms that may require antidepressants/anxiolytics

3. Discuss pharmacological management of depression and anxiety
But humans are so much more than their diagnostic labels....
DSM-5 Anxiety Disorders

- Generalized Anxiety Disorder (GAD)
- Panic Disorder
- Separation Anxiety Disorder (SAD)
- Social Anxiety disorder
- Specific Phobia
Characteristics Common to All Anxiety Disorders

- Hypervigilant
- Reactive to novel stimuli
- Threat bias
- Avoidance coping
- Catastrophic reactions
- Parental accommodation
- Midline physical symptoms
- Tension headache
- Dizziness
- Perioral tingling (hyperventilation)
- Lump in the throat
- Can’t swallow pills
- Worry about gagging, choking, swallowing, vomiting
- Can’t catch breath/SOB
- Hyperventilation
- Chest pain
- Abdominal pain
- Bowel and bladder urgency
- Tingling in finger tips (hyperventilation)
Generalized Anxiety Disorder

- Six months or more of
  - Excessive worry
  - Which is difficult to control
  - And at least three of
    - Edginess/restlessness
    - Fatigue
    - Poor focus
    - Irritability
    - Muscle aches/tension
    - Difficulty sleeping

Which cause impairment and aren’t attributable to something else
**Panic Disorder**

Recurrent unexpected panic attacks; abrupt surge of intense fear/discomfort peaking within minutes, including at least 4 of these symptoms:

<table>
<thead>
<tr>
<th>Physical Symptoms</th>
<th>Psychological Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Palpitations, increased HR</td>
<td>Dizzy, light-headed</td>
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<tr>
<td>Sweating</td>
<td>Chills or heat sensations</td>
</tr>
<tr>
<td>Trembling/shaking</td>
<td>Paresthesias</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Derealization or depersonalization</td>
</tr>
<tr>
<td>Feelings of choking</td>
<td>Fear of losing control or “going crazy”</td>
</tr>
<tr>
<td>Chest pain/discomfort</td>
<td>Fear of dying</td>
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<tr>
<td><strong>Nausea/abdominal distress</strong></td>
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After attack, at least 1 month of persistent concern or worry or avoidance behavior
Separation Anxiety Disorder (SAD)

- Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached, as evidenced by at least three of the following:

1. Recurrent **excessive distress** when anticipating or experiencing separation from home or from major attachment figures.
2. Persistent and **excessive worry about losing major attachment figures** or about possible harm to them, such as illness, injury, disasters, or death.
3. Persistent and **excessive worry about experiencing an untoward event** (e.g., getting lost, being kidnapped, having an accident, becoming ill) that causes separation from a major attachment figure.
4. Persistent **reluctance or refusal to go out, away from home, to school**, to work, or elsewhere because of fear of separation.
5. Persistent and **excessive fear of or reluctance about being alone** or without major attachment figures at home or in other settings.
6. Persistent **reluctance or refusal to sleep away from home** or to go to sleep without being near a major attachment figure.
7. **Repeated nightmares** involving the theme of separation
8. **Repeated complaints of physical symptoms**

- **Functional impairment**
- **At least 4 week duration**
Social Anxiety Disorder

A. Marked fear or anxiety about one or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions.

B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing; will lead to rejection or offend others).

C. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.

D. The social situations are avoided or endured with intense fear or anxiety.

E. Functional impairment

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 months or more.
Specific Phobia

- Marked fear or **anxiety about a specific object or situation** (e.g., flying, heights, animals, receiving an injection, seeing blood).
- The phobic object or situation almost always **provokes immediate fear** or anxiety.
- The fear or **anxiety is out of proportion to the actual danger** posed by the specific object or situation and to the sociocultural context.
- The phobic object or situation is **actively avoided or endured with intense fear or anxiety**.
- The fear, anxiety, or avoidance causes clinically **significant distress or impairment in social, occupational, or other important areas of functioning**.
- Lasts **6 months or more**
Major Depression

- **Mood** (irritable or depressed) or **Anhedonia**
- 5 of following symptoms:
  - Fatigue ..............self-pity, pessimism
  - Change in appetite......tearful
  - Change in sleep........social withdrawal
  - Reduced concentration....lack of reactivity to environmental events
  - Motor retardation

- Thoughts of death or suicide
- Guilt
- Worthlessness
- (Helplessness)

Over a two week period

DSM-V; Rapp 1989
Brief Behavioral Interventions first

- Brief collaborative discussions over multiple visits
- Have fun
- Practice key

**ANXIETY**
- Reciprocal inhibition - two incompatible states cannot co-occur - (retrain breathing)
- Conditioned fear/anxiety can be subjected to counter-conditioning - (graded exposure)
- Involves shifting somatic attention and mastery of self-regulation - (cognitive reframing and behavioral activation)
- Behavioral activation - (exercise, hobbies)

**DEPRESSION**
- Cognitive behavioral therapy has most evidence.
- Behavioral activation
- Problem-focused, goal-setting
- Thought reframing
When Should I Use an Antidepressant?

• Depression
  • Persistent low mood
  • Fatigue
  • Low appetite
  • Poor sleep
  • Self-harm/suicidal thoughts

• Anxiety
  • Panic attacks
  • Low appetite
  • Poor sleep
  • Fatigue
  • Disruption to day-to-day activities

Failure of individual therapy
Thinking of Prescribing Medication?

<table>
<thead>
<tr>
<th>“Do no harm”</th>
<th>Coping Skills</th>
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<tbody>
<tr>
<td>Safety? Suicidal ideation, homicidal ideation, psychosis, D&amp;A</td>
<td>Non-medication strategies – therapy, improve medical comorbidities, sleep hygiene, healthy food choices, “less is more”: alcohol, caffeine</td>
</tr>
<tr>
<td>Severity of Symptoms/Appropriate level of care?</td>
<td>Past medication trials (with at least 6 weeks duration at max dose)</td>
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<tr>
<td>Comorbidities, psychiatric and medical</td>
<td>Drug Drug Interactions</td>
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<tr>
<td>Differential Diagnosis</td>
<td>Patient preference</td>
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<tr>
<td>Stressors</td>
<td>If medication necessary, choosing best side effect profile for patient</td>
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<tr>
<td>Support Network</td>
<td>How will you measure &amp; track success?</td>
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</table>
FDA approved doses for antidepressants

- Fluoxetine (20-80)
- Citalopram (20-40)
- Escitalopram (10-20)
- Sertraline (50-200)
  - Paroxetine (20-50)
- Venlafaxine XR (37.5-225)
- Duloxetine (30-120)
- Vortioxetine (5-20)
SSRI US FDA Approvals for Children and Adolescents

• Approved for depression
  • Fluoxetine ≥ 8 years
  • Escitalopram ≥ 12 years

• Approved for GAD
  • Duloxetine 7-17 years
Dosing of SSRIs based on clinical trials

- Fluoxetine up to 40 mg by week 12 (TADS, 2004)
- Fluvoxamine 100-150 mg by week 10 (RUPP, 2001)
- Sertraline 100-150 mg by week 8 (CAMS, 2009)
- Paroxetine 40-50 mg by week 10 (Geller, 2004)
- Duloxetine 30-120 mg daily (FDA guidelines)
SSRI for Anxiety Disorders

• **SAD, GAD, Specific Phobia**
  - Fluvoxamine – RUPP 2001
  - Fluoxetine- Birmaher 2003
  - Sertraline- Walkup 2008

• **Specific Phobia**
  - Paroxetine- Wagner 2004
  - Fluoxetine – Beidel 2007
  - Venlafaxine– March 2007

• **GAD**
  - Sertraline- Rynn 2001
  - Venlafaxine- Rynn 2007
  - Duloxetine- Strawn 2015
  - Buspirone – unpublished negative trial
Meta-analysis of antidepressants in pediatric anxiety (Strawn 2015)

- 9 studies (fluoxetine, duloxetine, sertraline, paroxetine, venlafaxine, fluvoxamine)
- Overall Cohen’s d effect size  $d=0.62$
- Activation OR  $1.86\ (p=.054)$
- Nausea/GI symptoms  $(p=.26)$
- Discontinuation due to adverse event  $(p=.13)$
Treatment of Depressed Teens

• Treatment for Adolescents with Depression Study (TADS)
• Treatment of Resistant Depression in Adolescents (TORDIA)
• ADAPT
• Treatment of Adolescent Suicide Attempters (TASA)

• NIMH funded studies
  • Demonstrated efficacy
  • Low placebo response rates
  • Many quality indicators

• Industry-funded studies
  • Multiple sites
  • High placebo rates
  • No quality indicators
SSRIs for Depression

- Higher response when combined with CBT (TADS) (weeks 12, 18 and 36)
- Higher response when combined with brief therapy (ADAPT) (week 12)
- Treatment resistant (failed > 8 weeks SSRI) randomized to alternate SSRI, SSRI + CBT; venlafaxine (SNRI), venlafaxine + CBT (TORDIA)
  - Antidepressants alone- 50% response
  - Combination- 60% response
  - Moderators- lower depression or anxiety at baseline; SI, anxiety and family problems at week 12
  - Week 24 < 50% adherent to taking medications
- Open trial for suicide attempters (Brent 2009)
  - 72% responded for depression
Summary of Depression Studies

• Depression outcomes- very good
• Moderators- predictable
• Suicidal behavior- minimal risk
• Role of psychotherapy- complex
Long-term Outcomes

• TADS- all active treatments converge (80-85%)
• ADAPT- estimated 80% responded; 10% refractory
• TASA- 72% response rate
• TORDIA- 60% remitted

• The earlier the response the better

• Moderators- predictable
  • Complex presentations- worse
  • Simpler presentations- better
Suicide Summary

• Treatment reduces risk
• Lack of response increases risk
  • Slow depression response (too low, too slow)
  • Predictors of poor response
• Only TADS had a finding supporting a relationship of suicidal ideation to SSRI treatment
General tips For SSRI Prescribing

• Start low, go slow
  • For younger kids (non-adolescents), start at half the “regular” starting dose
    • For example, 12.5 mg of sertraline rather than 25 mg
    • Better tolerated in case of side effects
• Don’t need to worry about weight-based dosing
• Okay to titrate every two weeks
  • Or every month
What Should A Patient Expect With an SSRI?

• Timeframe for efficacy
  • Most of the time full results not seen for 4-6 weeks
  • Sometimes as soon as 2 weeks, as long as 8 weeks

• Difference won’t be drastic
  • Many times it’s parents/family/friends who notice the change

• Expect side effect before efficacy
Which SSRI Should I Pick?

• Prozac (fluoxetine)
  • Most evidence for kids/adolescents
  • Useful in many situations
    • Depression, anxiety, OCD, sometimes irritability/aggression
  • Can be activating
    • More likely to cause sleep disruption
  • Weekly formulation available
    • 90 mg delayed release weekly ≈ 20 mg daily
Which SSRI Should I Pick?

• Lexapro (escitalopram)
  • Isomer of Celexa (citalopram)
  • Somewhat fewer drug-drug interactions than fluoxetine or sertraline
    • But still some (NSAIDS, SNRI, buspirone)
  • Tends to be more calming
    • Higher likelihood of drowsiness
• Narrower dose range
  • Pills difficult to split
Which SSRI Should I Pick?

- Zoloft (sertraline)
  - Approval for OCD in kids, PTSD in adults
    - Thus, reasonable to use in trauma history
  - Also more calming
  - Wide dose range (25 mg to 200 mg)
  - Comes in liquid formulation
Basic Algorithm

- Child/teen presents with depression/anxiety
  - Try counseling first, if mild to moderate
    - Give that at least a month or two to see the reaction
    - And emphasize the importance of doing what the counselor asks them to do
  - If moderate to severe, best bet is counseling plus medication
    - Start an SSRI
      - Titrate based on response and adverse effects
      - If dose ceiling reached (or adverse effects intolerable), switch to another

- Treatment failure
  - Missed diagnosis
  - Too low too slow
  - Poor management of adverse evens
  - Unaddressed behavioral support for anxiety symptoms
Switching SSRIs

• General rule of thumb is to cross-taper
  • Cut down the dose of the current SSRI while starting the second
  • May need to adjust based on dose or on half-life
    • For example, if a kid is on 200 mg sertraline
    • Or if a kid is taking fluoxetine
• In lower doses, okay to stop and switch
Newer Antidepressants

• Desvenlafaxine not superior to placebo for depression in age 7-17
• Vortioxetine for anxiety disorder and depression- open label study 5-20 mg for 14 day showed pharmacokinetics concentration proportional to dose. No serious adverse effects
• Vortioxetine (age 7-17) improved CGI-S over 182 days (Findling et al., 2017) but high GI abdominal pain (21%)
• Vilazadone – pediatric depression
• Levomilnacipran- adolescent depression
• Ketamine- adolescent refractory depression
Augmentation to SSRI for treatment resistant depression

- Atypical antipsychotics
- Antidepressants- bupropion, mirtazapine
- Mood stabilizer- lithium
Algorithm for treatment-resistant depression

• SSRI + CBT
• Alternate SSRI.....if partial response-augment with aripiprazole, bupropion, lithium
• If no response...different class of antidepressant (bupropion, duloxetine, venlafaxine, desvenlafaxine.....if partial response-augment with aripiprazole or lithium
• If no response....newer antidepressants (vortioxetine, vilazodone, levominacipran)
Antidepressant Dose and Response (Wehry et al., 2018)

- Most of improvement in first 6 months
- Higher dose not necessarily better (Strawn 2017)
Adverse Effects of SSRIs

- Activation common- 10-15%
  - Early in course or after dose change- consider diphenhydramine
  - Younger kids

- Bipolar switches uncommon <1%
- Frontal lobe syndromes at higher doses
- GI symptoms early
- Easy bruising and bloody noses
- Some case reports about delayed growth
Activation

• Impulsivity
• Disinhibition
• Insomnia
• Restlessness
• Hyperactivity
• Irritability

• Luft et al. 2017
Safety of psychotropic medications in children and adolescent (Solmi et al 2020)(n=337,000)

• Among antidepressants- safety/coverage ratio (**best to worse**) = citalopram > fluoxetine> vilazodone > paroxetine > sertraline > venlafaxine
• Nausea/vomiting (duloxetine, paroxetine, sertraline, vilazodone)
• Discontinuation due to adverse event (duloxetine, imipramine, venlafaxine, vilazodone)
• Extrapyramidal side effects (clomipramine, imipramine, paroxetine)
• Sedation (imipramine)
• Diarrhea (duloxetine, sertraline)
• Headache (venlafaxine)
• Anorexia (amitriptyline, venlafaxine)
• Weight gain/ increased BMI (escitalopram, sertraline)
• Weight loss (fluoxetine)
• Suicidality (venlafaxine)
Activation and Drug Level

- When present, antidepressant related activation emerges early in treatment or following dose increase (Reinblatt et al., 2009)
- Symptoms resolve when dose decreased or medication stopped (Riddle 1990; Wilens 2003)
- The rate of symptom resolution related to rate of activation symptoms onset (Wilens 2003)
Clinical management of activation (Luft 2018)

- Psychoeducation- early in treatment (24-72 hours)
- Stop immediately- doesn’t go away with time or dose increase
- Rule out general medical condition
- Evaluate potential contributors
  - ADHD, manic symptoms
  - Family factors that perpetuate anxiety
  - Substance use
  - Medication adherence
  - Childhood trauma
- Decrease dose of SSRI
- Consider another SSRI
- Individual or family therapy
Non-activating antidepressants*

- Mirtazapine (Remeron)
- Duloxetine (Cymbalta)
- TCAs
  - Nortriptyline (Pamelor)
  - Clomipramine (Anafranil)
  - Desipramine (Norpramin)

* NE reuptake inhibitors may cause initial anxious reaction that goes away with time
When medications don’t work

• Function-based assessment
  • Assess and address antecedents and consequences
  • Provoking experience
  • Symptom Support and elaboration
    • Positive reinforcement- rewarding
    • Negative reinforcement- escape
## Types of Reinforcement and Related Treatment Options

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<thead>
<tr>
<th></th>
<th>POSITIVE REINFORCEMENT</th>
<th>NEGATIVE REINFORCEMENT</th>
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<tbody>
<tr>
<td>INTERNALLY REINFORCING</td>
<td>Provides gratification</td>
<td>Relieves distress</td>
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<td></td>
<td>Raise the cost</td>
<td>Exposure and response prevention</td>
</tr>
<tr>
<td>EXTERNALLY REINFORCING</td>
<td>Attention and support</td>
<td>Avoidance</td>
</tr>
<tr>
<td></td>
<td>Redirect parents and others</td>
<td>Re-engage, not escape</td>
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Summary: Anxiety Treatment

• Mild anxiety- psychotherapy alone
• Mod/severe anxiety- psychotherapy + SSRI
• SSRIs are relatively more potent “anti-anxiety” than “anti-depressant” agent in kids (per RCT effect sizes and real-world observations)
• Fluoxetine, sertraline, and fluvoxamine all have strong level of evidence support and FDA approvals.
• Benzodiazepines not an evidence-based treatment for child anxiety
Summary: Depression Treatment

• Mild depression- psychotherapy alone
• Mod/severe depression- SSRI (fluoxetine or escitalopram/citalopram or sertraline) + psychotherapy
  • Per level of randomized controlled trial evidence
  • Family history, preference, adherence
  • Fluoxetine and escitalopram have FDA approval
• 5 of 6 tricyclic antidepressant RCTs in youth don’t work
Managing prescriber anxiety with SSRIs

• Black box warning of suicidality
  • Population studies indicate SSSRIs reduce suicides
  • Some kids do get increased suicidal thoughts

• Check in with patients 2 and 4 weeks after starting SSRI

• SSRI related suicidality risk increases with triggers of interpersonal conflict and substance abuse
Adherence

• Factors to consider in prescribing and adherence:
  • Adverse effects
  • No medication can be guaranteed to be clinically effective and safe for every patient

• Assent:
  • “Agreement obtained from those who are unable to enter a legal contract”
  • Reflection of children’s participation in decisions
References


