Update on best practices and next steps in treatment of pediatric depression and anxiety

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1

Disclosures

- We do not have any financial interest, arrangement or affiliation with medical/pharmaceutical or equipment companies.
- We intend to reference off-label or investigation use of drugs or products in my presentation

2

Objectives

To be able to:

- Identify the role of screening tools as part of a comprehensive assessment process for youth depression and anxiety
- Understand best practice in first and second line treatment strategies for youth with depression
- Understand best practice in first and second line treatment strategies for youth with anxiety

3

Pediatricians, Child and Adolescent Psychiatrists and Children's Hospitals Declare National Emergency in Children's Mental Health

- **Washington, D.C., October 19, 2021** – the American Academy of Pediatrics (AAP), the American Academy of Child and Adolescent Psychiatry (AACAP) and the Children's Hospital Association (CHA) together representing more than 77,000 physician members and more than 200 children's hospitals, **declared** a national state of emergency in child and adolescent mental health and are calling on policymakers to join them.
- The COVID-19 pandemic has taken a serious toll on children's mental health as young people continue to face physical isolation, ongoing uncertainty, fear and grief. Even before the pandemic, mental health challenges facing children were of great concern, and COVID-19 has only exacerbated them

4

Facts

Anxiety and depression are amongst the most commonly diagnosed mental disorders in children. Estimates for ever having a diagnosis among children aged 3-17 years, in 2016- 2019:

- Anxiety 9.4% (approximately 5.8 million)
- Depression 4.4% (approximately 2.7 million)

1 in 6 children aged 2-8 years has a mental, behavioral, or developmental disorder.

5

Some of these conditions commonly occur together. For example, among children aged 3-17 years in 2016:

- Having another mental disorder was most common in children with depression: about 3 in 4 children with depression also had anxiety (73.8%) and almost 1 in 2 had behavior problems (47.2%).
- For children with anxiety, more than 1 in 3 also had behavior problems (37.9%) and about 1 in 3 also had depression (32.3%).
- For children with behavior problems, more than 1 in 3 also had anxiety (36.6%) and about 1 in 5 also had depression (20.3%).
- Depression and anxiety have increased over time, and they also increase with age.

6

Diagnosis

As with all mental health disorders, neither should not be diagnosed solely by a screening tool. Screening tools raise "red flags" that should be investigated further by sensitive clinical interviews. Your judgment trumps all.

- Consider:

Unspecified depression disorder/anxiety disorder (DSM-V)

7

Depression diagnosis screening tools

- The Patient Health Questionnaire-9 (PHQ-9) Modified for Teens
- The Center for Epidemiological Studies Depression Scale (CES-DC) for Children
- The Patient Health Questionnaire-2 (PHQ-2)
- Short Mood and Feelings Questionnaire – Child self-report (SMFQ-C)

8

Positive screening, what now? (also applicable to anxiety)

Consider potential causes/confounders:

- Medical conditions
- Medical treatments
- Psychosocial stressors

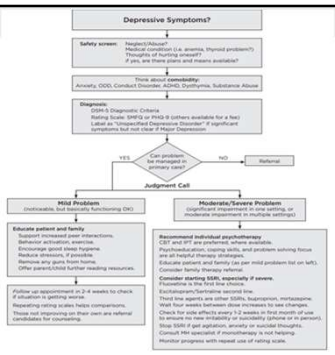
9

Suicide risk factors

- Past suicide attempts (greatest risk factor)
- Mental health or substance use disorder
- Recurrent self harm
- Family history of suicidal behavior
- Exposure to real or fictional accounts of suicide
- Parental mental health problems or substance abuse
- Gay or bisexual orientation
- History of child abuse
- Chronic medical illnesses (e.g., diabetes, epilepsy)
- Victim of bullying (e.g., cyberbullying) S

10

Treatment



11

Major Depression— Medication general tips

- Start low, go slow
- Change one medicine at a time
- Use the full dose range, wait 2-4 weeks before each increase
- Ask about previous antidepressant trials in family members
- Get baseline inventory of potential pre-medication somatic issues (e.g., frequency of headaches, sleep issues, etc.)
- Discuss potential side effects with caregivers and (when appropriate) with the patient
- Discuss importance of compliance

12

Medication	Usual Adolescent Starting Dose	Increase Increment (after 4 -6 weeks)	Max Dosage	Youth RCT benefits	Youth FDA Approval
Fluoxetine (Prozac)	10mg/day	10-20mg	60mg	Yes	Yes
Citalopram* (Celexa)	10mg/day	10-20mg	40mg	Yes	
Escitalopram (Lexapro)	5mg/day	5-10mg	20mg	Yes	Yes
Sertraline* (Zoloft)	25mg/day	25-50mg	200mg	Yes	

*Not FDA approved for depression
RCT=randomized controlled trial

Wagner et al 2003, 2004; March et al, 2004; Emslie et al 1997, 2002, 2008

13

Which SSRI to start with?

- Fluoxetine – multiple positive RCTs, FDA approved ages 8 and up
- Very little SI signal in controlled studies
- Long half-life means no withdrawal symptoms from missed doses
- Covered by all plans, and available generic
- Caution: Medication interactions

14

Depression - What Other Meds Can Be Tried?

- If first SSRI fails, a second SSRI will work approximately 1/3 of the time

Choose 2nd agent from the prior list (sertraline, escitalopram)

- How to switch?

If a major side effect—stop, wait until it resolves, then start new medication

The "side effect" may not be medication related

Consider a ~1-month cross taper (low dose of new med, at same time as starting lowered dose of old med)

If was on fluoxetine, long half life means it auto-tapers after stopping over 2 weeks.

15

Depression - After two SSRIs don't work

- Venlafaxine*

Combo of 2 RCTs (2ndary analysis) showed positive effect for adolescents

- Cymbalta*

1 open label safety study

- Bupropion*

Open label positive studies in adolescents

*Not FDA approved for depression treatment <18

16

Other meds for depression

- Tricyclic antidepressants*

Serious side effects, fatal in overdose

Meta-analysis – not superior over placebo in kids, therefore, NOT recommended

- Trazodone (Desyrel®)*

Occasionally useful as sleep aid, usually up to 100 mg (interacts with fluoxetine through hepatic metabolism pathways, so caution advised)

Full adult antidepressant doses are typically not tolerated

17

Other meds for depression (continued)

After two SSRI failures, there are other options:

- Bupropion (Wellbutrin®)* : More agitation side effects. A reasonable third choice if two SSRIs failed, or an older adolescent or young adult. Reasonable if adolescent has ADHD too.

- Mirtazapine (Remeron®)* : Sedating, increases appetite. Open label positive study in adolescents; older adolescents may respond like adults do for depression. Two negative child RCT's.

18

Patient is finally stable

Treatment should be continued for 6 to 12 months during the continuation phase

Patients typically should be seen at least monthly (or if doing well, every 3 months), depending on clinical status, functioning, support systems, environmental stressors, motivation for treatment, and the presence of comorbid psychiatric or medical disorders.

General rule of thumb: the longer it takes to recover or the higher the # of recurrences, the longer the period of maintenance.

≥ 2 episodes of depression, 1 severe episode, or chronic episodes should have maintenance treatment for > 1 yr.

19

Anxiety

- Median age 11 y/o.
- Tends to onset during specific developmental phases.
- Anxiety Disorders commonly co-occur. Other Common Comorbid diagnoses:
  - For preschoolers-ADHD and ODD.
  - For adolescents-ADHD, ODD, LD, Depression.
  - GAD and social phobia are the most strongly linked to Depression.

DSM 5 organized per age of onset:

- Separation Anxiety Disorder – preschool
- Selective Mutism
- Specific Phobia – school age
- Social Anxiety – later school age/early teens
- Panic Disorder – later teens/young adulthood
- Agoraphobia
- GAD – later onset, median age 30 y/o

20

Chief complaints

- Physical Complaints (more common in younger children)
- Sleep Problems (sleep onset, maintenance, nightmares)
- Hallucinations - Assess quality: organized, elaborate details, situation/time specific?
- Behaviors:
  - Avoidance
  - Excessive reassurance-seeking/clinginess
  - Restless, agitated
  - Distracted, declining school performance
  - Oppositional (misdiagnosis with ODD) Suicidality (teens 9% SI and 6% SA)
  - Panic D/O or GAD with comorbid depression conveys greatest risk.
  - Compulsive, touching, picking

21

Anxiety diagnosis screening tools

- Screen for Child Anxiety Related Emotional Disorders (SCARED), parent and child
- Spence Children's Anxiety Scale (SCAS), parent and child
- Generalized Anxiety Disorder 7 (GAD-7), teen/adult

22

Anxiety treatment

Mild Anxiety:

- Psychoeducation
- CBT Referral

Moderate Anxiety:

- CBT
- Discuss and consider Medication (SSRI)

Severe Anxiety:

- CBT and SSRI

23

Anxiety treatment

- Fluoxetine, Sertraline, Fluvoxamine which are FDA approved for OCD.
- RCT support: Fluoxetine, Sertraline, Citalopram, Fluvoxamine, and Paroxetine.
- Activation: Fluoxetine>Sertraline>Escitalopram.
- P450 drug interactions.
- Half-life considerations. - Cross taper considerations: Most SSRI reach [peak plasma] in 1-8 hours. Fluoxetine peaks at 1-3 days, norfluoxetine (active metabolite) takes up to 16 days to reach peak plasma concentrations. - Paxil and Fluvoxamine have shortest half-life. Monitor for withdrawal symptoms.
- Not used as often: - Paxil (suicidality if also depressed). - Fluvoxamine (drug interactions).

24

Anxiety treatment

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

25

Anxiety treatment

SNRI is a good second choice in youth activated by SSRI

Venlafaxine - greater suicide risk

Duloxetine - split doses >60 mg due to potential liver inflammation

26

Anxiety treatment

Maintenance:

- Up to 12 months after remitting is appropriate.
- 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.

27

- 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

28

Black box warning for suicide 2004

Series of meta-analyses:

- 24 placebo controlled trials in >4400 children.

- Rate of suicidal thinking/behavior 4% antidepressant vs 2% placebo.

- No suicides reported.

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

29

Black box warning for suicide 2004

Overall risk is low.

Usually occurs when first starting or increasing so consider starting at a lower dose and titrating in smaller increments.

Opportunity for:

- reviewing risks/benefits/alternatives of treatment while encouraging open communication

- reinforcing tenacity to evidence based therapy and crisis prevention planning.

- When there's suicidality/higher risk, have a crisis prevention plan in place before starting an SSRI.

30

TABLE 7 SSRI Side Effects

Side Effect	Management
Gastrointestinal distress	Typically self-resolves Symptomatic care
Headache	Typically self-resolves Symptomatic care
Appetite change	Counsel on healthy nutrition
Sedation	Administration at bedtime
Sleep disturbance	Administration in morning Counsel on sleep hygiene Consider melatonin as needed
Diaphoresis	No action if mild
Sexual side effects	Consider medication change
Activation (disinhibition, agitation, irritability, silly)	If persistent and significant, discontinue medication
Platelet dysfunction (rare)	Discontinue medication

If any symptoms are severe, prescriber may decrease medication dose or switch to another.

31

Other medications:

Antipsychotics: No RCTs of combination of antipsychotics and antidepressants. Potential development of movement disorders and seizure should be carefully considered with the use of adjunctive antipsychotics for the treatment of depression in children and adolescents. Off-label use for anxiety and depression.

Esketamine: Case series. Significant decrease of depressive symptoms, and SI.

Electroconvulsive therapy: No RCTs. Systematic review, the investigators suggest that ECT is safe and effective for the treatment of mood disorders in child and adolescent populations and should be considered in severe and treatment-refractory cases.

32

Trendy: Marijuana use

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).

Cognitive changes.

Inhibitory Control: tenth graders who have concurrent use and past-year use of cannabis perform like seventh graders who have never used cannabis.

33

Psychiatric Intake Response Center (PIRC)

205.638.PIRC (7472)

PIRC

Children's of Alabama

HOPE Anne B. LaRussa Foundation of Hope

Navigating mental health resources for those who care for children and teens

34

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35

Questions?

36

Multiple choice questions:

1. FDA approved for pediatric depression:
   a. Escitalopram, Sertraline
   b. Fluoxetine, Escitalopram
   c. Fluoxetine, Venlafaxine
2. First line treatment for pediatric depression or anxiety:
   a. SSRI
   b. SNRI
   c. Antihistamine
3. Greater risk of suicidality if depressed:
   a. Fluoxetine
   b. Paroxetine
   c. Venlafaxine
4. Second line treatment for pediatric depression or anxiety:

   A. Antipsychotic adjuvant
   B. Another SSRI
   C. Buspar

5. SSRI most common to interact with other medications:

   A. Sertraline
   B. Escitalopram
   C. Fluoxetine

37