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Pediatric Anxiety Disorders

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Disclosures

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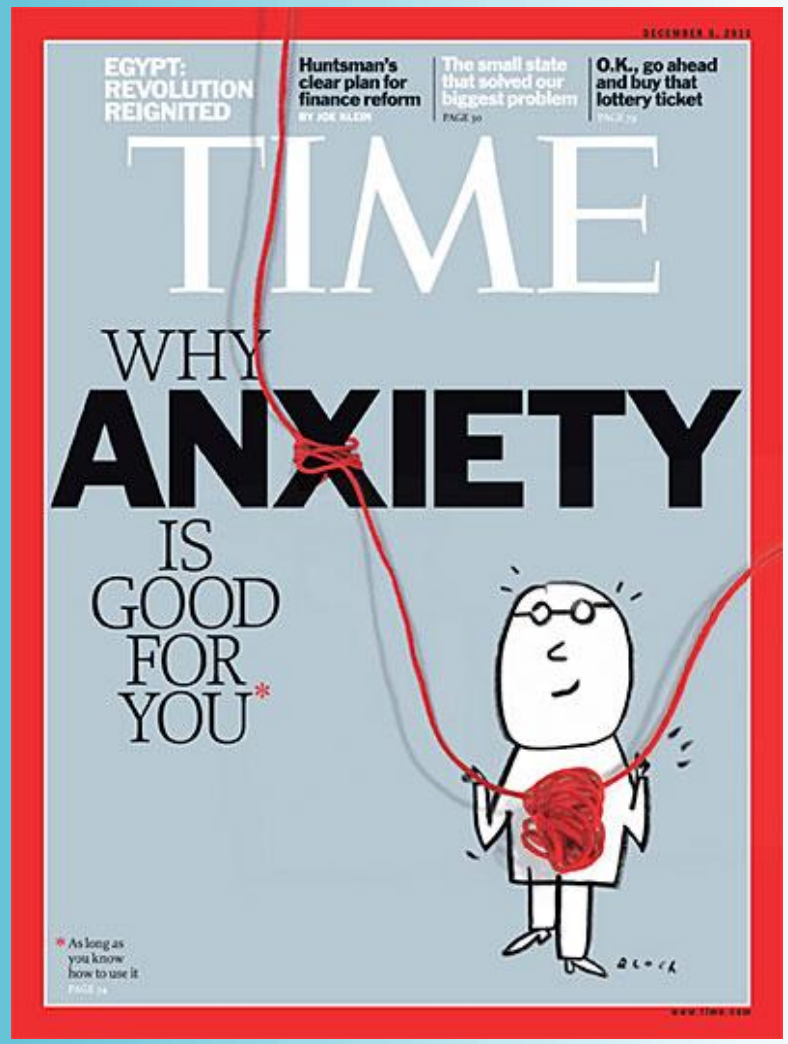
Emalex: Consultant and Medical Advisory Board



Anxiety Disorder

- Involve "**excessive fear**, **avoidance** of whatever is feared, and **anticipation** and **worry** when expected to encounter what is feared"
  p.2 Siegel and Dickstein 2012.
- **Persistent**, **unrealistic, disproportionate** worries that are **inappropriate** for age / stage
- **Distress** when engaging and participating in **age-appropriate**, **normal** developmental activities
- **Disorder** when "clinically significant" impairment/distress

Siegel and Dickstein (2012) *Adolesc Health, Med and Ther*

DSM-5 Diagnoses

- **Generalized anxiety disorder**
- **Separation anxiety disorder**
- **Social anxiety disorder**

Specific phobia

Panic disorder

*OCD

*No longer in anxiety disorder category

When Is Treatment Warranted

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When Do We Treat It?

- Impairment / Dysfunction / Distress
  - Moderate/severe symptoms
  - Interfering with school, social, family settings
  - Missing milestones, (i.e. secondary to **avoidance**)
  - Time-consuming

Why Do We Treat It?

- Disruption of normal psychosocial development of children
- Increased rates of other anxiety disorders, depression, substance dependence, suicidality

Epidemiology

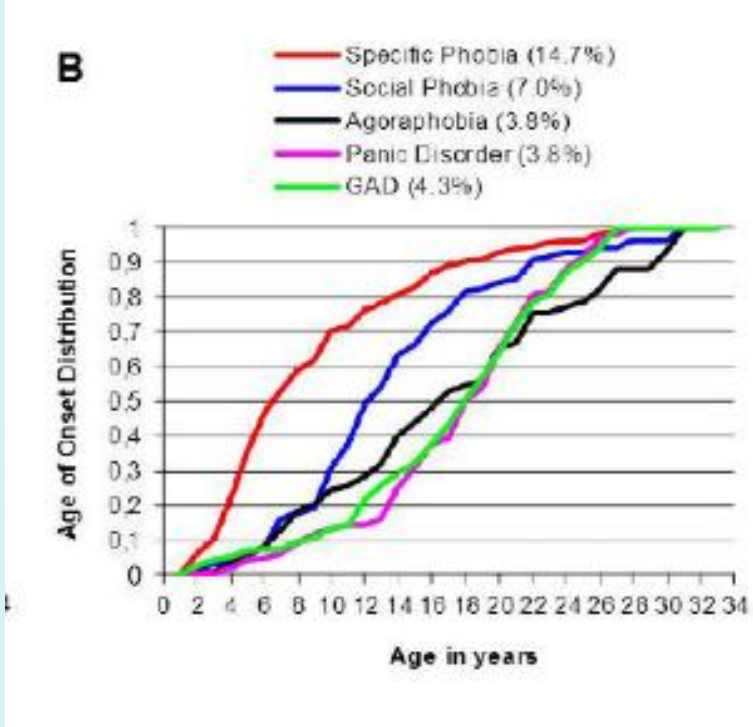
- Anxiety most prevalent psychiatric condition in youth
  - Median age onset < 15
- 6-20% of youth have at least one childhood anxiety disorder
- More females than males
- Increasing rates as one ages
- Longitudinal studies show that in those who are treated:
  - 1/3 to ½ are free of psychopathology over 10 years (long-term studies)
  - Most adults with persistent mood or anxiety had pediatric anxiety disorder

JAACAP Practice Parameters, 2007.
Zugman et al 2024

Pattern of Development

- Typical ages of onset
  - Overlapping
- Specific phobia symptoms and some GAD (ages 5-6)
- Social anxiety and separation anxiety 1-2 years later
  - (OCD ~ age 10)
- Panic symptoms/disorder in early teens
- Common early sign is behavioral inhibition

Costello et al (2005) Child Adolesc Psychiatric Clin N Am



Age of onset distribution of specific anxiety disorders, and estimated cumulative incidence rates (in parentheses), at age 33

Wehry et al (2015) *Curr Psychiatry Rep*
Data adapted from Early Developmental Stages of Psychopathology (EDSP) Study

Pediatric Presentation

- Somatic symptoms (mid-line)
  - Headaches, stomachaches, body pains, swallowing difficulty
- Inability to recognize excessive nature
- Oppositionality/defiance (when exposed to fearful stimuli)
  - Irritability, anger outburst
- Avoidance, excessive reassurance seeking
- Sleep disturbances (inability to sleep alone)
- Concentration and attention difficulty

Anxiety Disorder: Comorbidities and Sequelae

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- Co-morbidities
  - Other anxiety disorders, depression, ADHD, oppositional defiant disorder (ODD)
  - Learning and language disorders
- Sequelae:
  - Worsened school adjustment, social skills, relationships financial outcome, long-term health functioning
  - Increased risk of additional anxiety disorders, depression and substance abuse (esp. alcohol)
  - Increased risk of self-injurious behavior, suicidality

Wehry et al (2015) *Curr Psychiatry Rep*
Wood et al (2019) *JAMA Psych*

Neurobiology

- Overactive threat circuitry (amygdala)
- Underactive regulatory systems (frontal cortex)

- **Prefrontal-amygdala (limbic) circuits** dysfunction
  - "Over-activated" **amygdala** (initiates fear response) in fMRI studies of youth with anxiety.
- **Ventrolateral prefrontal cortex (VLPC)**
  - Regulates amygdala activity and plays big role in extinction in fear conditioning.
  - Escitalopram improved amygdala-ventrolateral prefrontal cortex (VLPFC) connectivity vs placebo (Lu et al 2021)
- **Cingulate cortex** also hyper-activated in youth with anxiety
  - Motivation and cognitive control

Wehry A et al (2015). *Curr Psychiatry Rep*

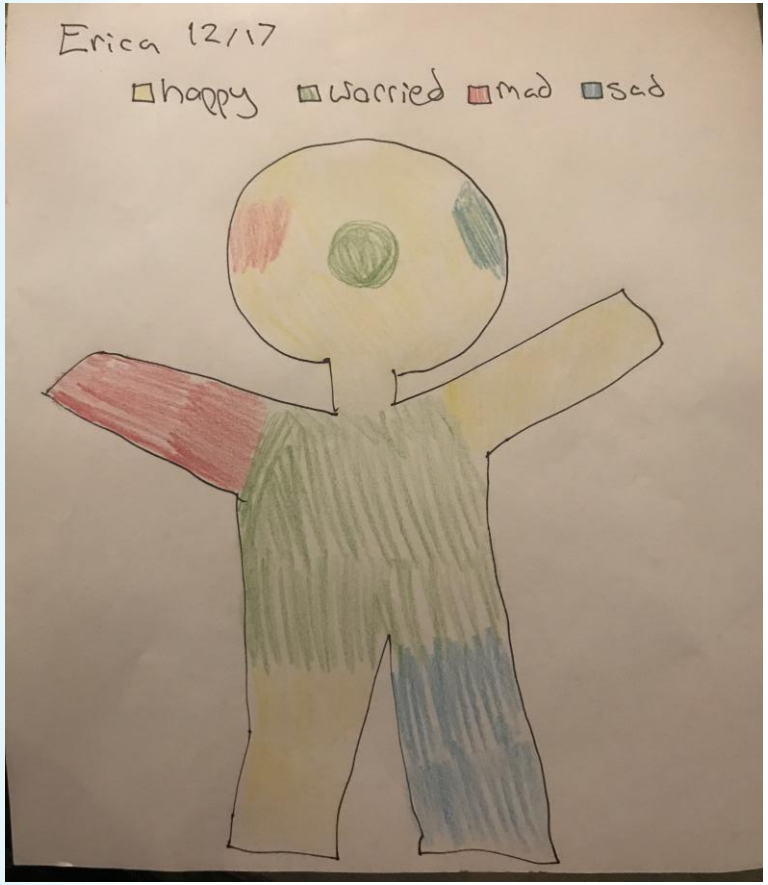
Adapted from Coffey BJ 2019 Anxiety Disorders in Children and Adolescents; Child and Adolescent Psychopharmacology Slides

Assessing Anxiety

- What are the situations that produce the anxiety?
- What is the frequency and the severity of the symptoms?
- Is there impairment or distress secondary to the anxiety?
- Reports from parent / child / teacher
- Assess for:
  - (Family) accommodation and avoidance!

Diagnosis: Pediatric Anxiety Disorders: Diagnostic Instruments/Rating Scales

- Self Report Instruments:
  - Multidimensional Anxiety Scale for Children (MASC)
  - *SCARED: Self Report for Childhood Anxiety Related Disorders
  - GAD-7: Self Report
- Parent/Teacher Ratings:
  - Child Behavior Checklist (CBCL)
- Clinician Ratings:
  - Pediatric Anxiety Rating Scale (PARS)
- Important to monitor functional impairment!



Adapted from Coffey BJ 2019 Anxiety Disorders in Children and Adolescents; Child and Adolescent Psychopharmacology Slides

Anxiety Differential

- Psychiatric (Not mutually exclusive!)
  - ADHD (restlessness, inattention)
  - Learning disabilities
  - Autism spectrum symptoms
  - Depression (poor concentration, sleep difficulty, somatic complaints)

- Medical / Medication / Substance-related

Consider Executive Functioning…

- 51 adolescents with GAD in escitalopram treatment study received BRIEF-SR (Behavior Rating Inventory of Executive Function – self-report)
  - Sub-scores all significantly elevated in adolescents with GAD
    - Inhibition, Shifting, Emotional Control, Initiation, Working Memory, Planning/Organization, Self-monitoring, Task Completion
  - Baseline Emotional Control, Working Memory, Planning/Organizing, Task Completion *predicted trajectory of PARS score* in escitalopram group
    - If clinically impaired **Working Memory** and **Emotional Control** baseline – less improvement
    - If clinically impaired **Task Completion** and **Planning/Organization** baseline – more improvement

Baumel et al 2022

Anxiety Disorder Treatment

- Multimodal treatment is ideal
  - Psycho-education
  - Collaboration with school and other treaters
  - Family interventions

- Behavioral therapy interventions (i.e. CBT)
- Pharmacotherapy (i.e. SSRIs)

When to Consider Using Medication…

- Moderate-severe symptoms
- Partial response to psychotherapy
- Symptoms affecting participation in psychotherapy

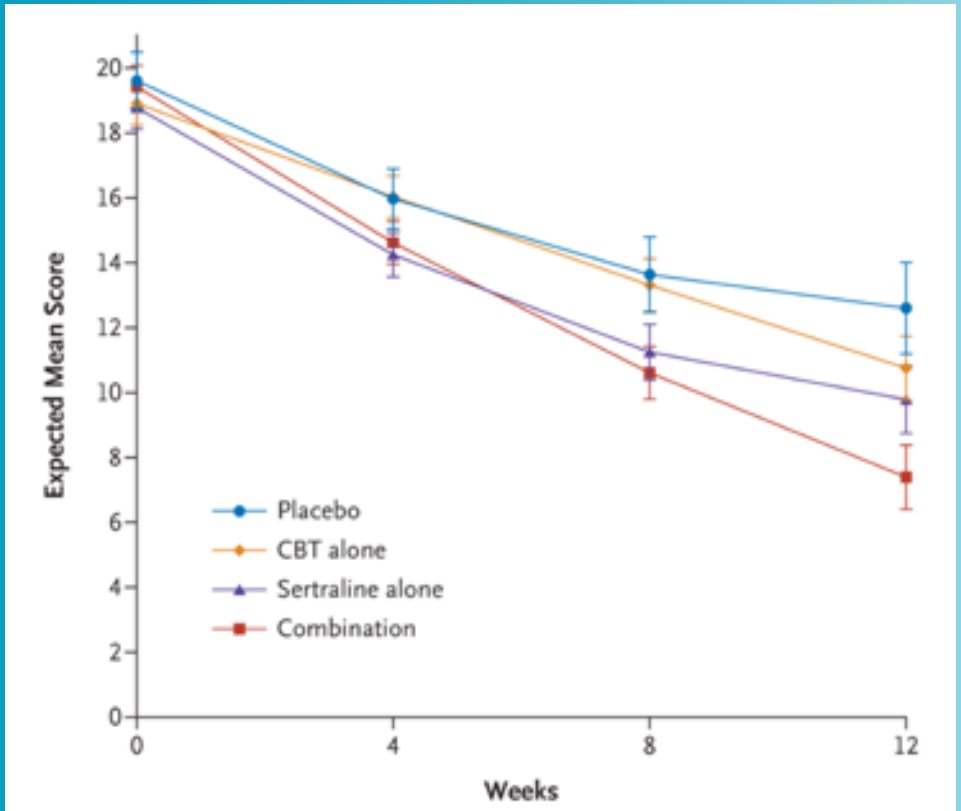
- **SSRIs should be considered first line medication treatment in youth with anxiety disorders**

FDA-approved SSRIs/SNRIs for Children/Adolescents

- Fluoxetine – MDD ages 8+; OCD ages 7+ (target 40mg)
- Fluvoxamine – OCD ages 8+ (target ≥ 150mg)
- Sertraline – OCD ages 6+ (target ≥ 150mg)
- **Escitalopram – GAD ages 7+**; MDD ages 12+ (target ≥ 10mg)
- **Duloxetine – GAD ages 7+ (target 60-90mg)**

Adapted from Strawn et al (2017) Curr Probl Pediatr Adolesc Health Care

Child/Adolescent Anxiety Multimodal Study (CAMS)



From: Walkup et al N Engl J Med. 2008 December 25; 359(26): 2753–2766

- Combined branch (sertraline and CBT) most effective at 12 weeks
  - 81% responded - (CGI-I of 1 or 2)
    - (Vs ~60% CBT or SSRI; ~25% placebo)
  - 68% remitted
- CAMS Phase II: Combined treatment still most effective at 24 + 36w
- CAMELS (extension study – 6 years later)
  - 50% in remission from anxiety 6 years later
  - Responders to initial treatment associated with remission (vs original CAMS group)

Walkup et al (2008)
Compton et al (2010)
Ginsburg et al (2018) J Consult Clin Psychol

Predictors of Response in Anxiety Treatment

- Positive predictors of response:
  - Younger age -- No other internalizing disorders
  - Lower baseline anxiety
- Negative predictors of response:
  - Increased caregiver strain -- Poor family functioning
  - Family history of anxiety --Social anxiety disorder

Ginsburg et al (2011) J Consult Clin Psychol

Anxiety Treatment Meta-analyses

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Strawn et al (2015) Depress Anxiety

- 9 trials, 1,673 patients (aged 6-17)
- Assessed 6 medications
  - Fluoxetine, duloxetine, sertraline, paroxetine, venlafaxine, fluvoxamine
- SSRI/SNRIs all showed superiority
  - "Moderate magnitude" of effect, Cohen's d = 0.62, p<.01
- Well-tolerated
  - Activation trend (med vs placebo)
    - (OR: 1.86, CI: 0.98-3.53, P = .054)

Wang et al (2017) JAMA Peds

- 115 studies with >7500 patients
- Those assessed in Strawn and atomoxetine all effective for anxiety
- No differences between CBT and any medication
  - CBT significantly improved symptoms, remission, response
- Combination of medication and therapy more effective than either alone
- TCAs - "marginally increased likelihood of treatment response"
- Benzodiazepines – no significant improvement

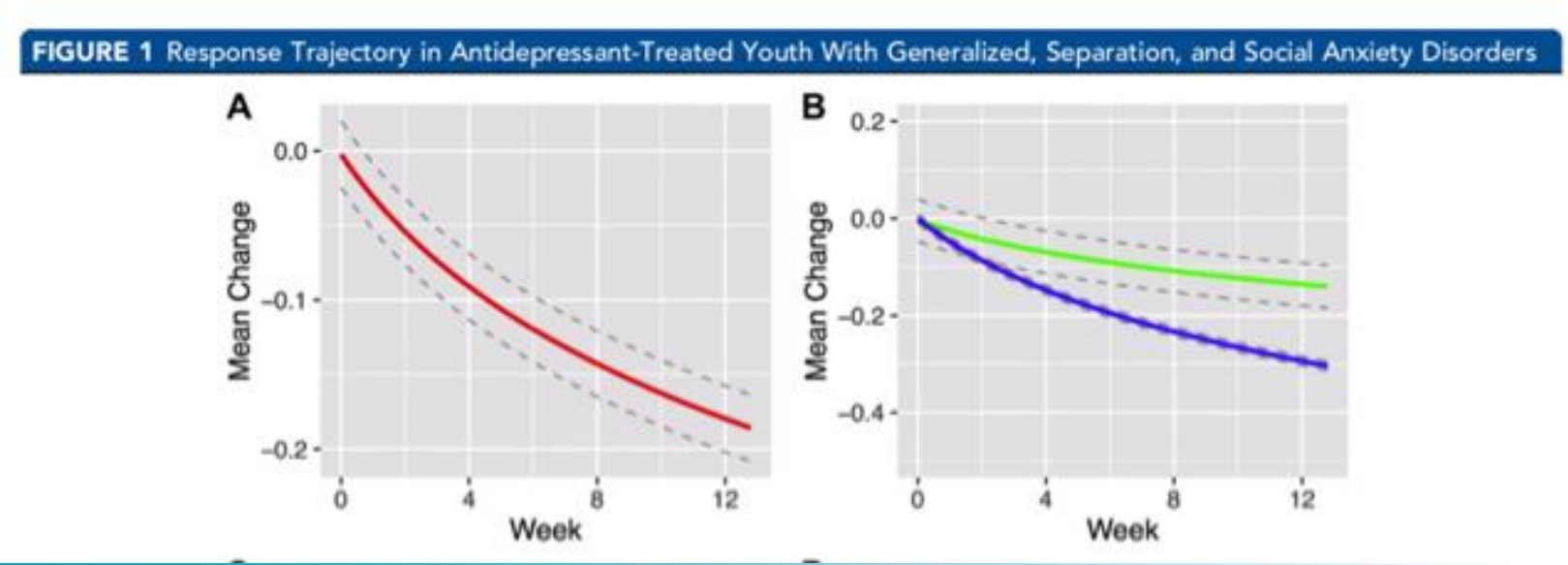
Adverse Effects

Mills and Strawn (2020) *JAACAP*

- Meta-analysis of adverse events, suicidality and AE-related discontinuation in youth with GAD and OCD
  - 18 trials, ~2500 patients, 7 medications
- SSRIs associated with greater likelihood of:
  - AE-related discontinuation, *activation, sedation, insomnia, abdominal pain, headache
    - Activation was more common in SSRIs compared to SNRIs (p=0.007)
  - **Neither SSRI nor SNRIs associated with treatment-emergent suicidality**
    - Paroxetine and venlafaxine
- That said… important to monitor: sleep changes, mood/irritability, akathisia, suicidal thoughts/behavior
  - "Vigilance, not fear"

Pharmacotherapy in Pediatric Anxiety

- Symptom change is observable within 2 weeks, and ~50% of change is observable within 4 weeks
- SSRIs are associated with greater and faster improvement compared to SNRIs
- Higher doses may associate with faster (though not greater) improvement



Green line represents SNRIs; Blue line represents SSRIs

Strawn et al (2018)
JAACAP
"Impact of Antidepressant Dose and Class on Treatment Response in Pediatric Anxiety Disorders: A Meta-Analysis"

Strawn et al (2017) Curr Probl Pediatr Adolesc Health Care
Strawn et al (2015). Depression Anxiety.
Wang et al (2017). JAMA Peds

Off-label Pharmacological Treatments

- **Tricyclic antidepressants (TCAs)** – slight positive, benefits often don't outweigh risks
- **Benzodiazepines** – typically okay for temporary/short-term use, clonazepam can be standing; watch for paradoxical response
- **Buspirone** – mixed data, some positive, anecdotally helpful (up to 40-60mg total daily split bid or tid)
- **Alpha-agonists** – guanfacine trial in 80 peds pts, no difference in PARS, difference in global severity; can consider especially when co-occurring ADHD, sleep-initiation trouble, tics

Zugman et al 2024

Off-label Pharmacological Treatments

- **Propranolol** – small trial in youth with ASD and anxiety, some CGI benefit in anxiety
- **Gabapentin** – no trials in youth, but small positive trials in adults
- **Pregabalin** – approved in Europe for GAD (in adults)
- **Hydroxyzine** – limited evidence, though anecdotally sometimes helpful for 'as needed'
- **Quetiapine** – quite anxiolytic, but more potent and higher side effect burden… reserve for more severe symptoms ~25-50mg

Zugman et al 2024

Guided SSRI-dosing?

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Strawn et al (2019) JCAP

- Modeled SSRI dosing across CYP2C19 phenotypes
  - Types: Poor, normal, rapid, ultrarapid metabolizers
- Cmax/AUC higher in slower metabolizers / lower in faster metabolizers
  - Escitalopram > sertraline
- **Escitalopram: 10mg poor metabolizer ≈ 30mg in ultrarapid ≈ 20mg in normal metabolizer**
  - In ultrarapid, bid escitalopram needed for ≈ troughs

Aldrich et al (2019) Front Pharma

- Slower metabolizers had significantly greater activation, weight gain and treatment discontinuation

Anxiety and ADHD (!)

- Anxiety and ADHD are often co-morbid
  - ~1/3 youth have co-occurring anxiety and ADHD
- When treating ADHD with stimulants:
  - Co-occurring anxiety does Not alter response of ADHD to treatment
  - Side effects to stimulants were Not higher in those with ADHD and anxiety (vs. ADHD alone)
- Could consider atomoxetine / viloxazine

March JS, Swanson JM, Arnold LE et al. (2000). JJ Abnorm Child Psychol.
Coughlin et al 2015 J Child Adolesc Psychopharmacol

Anxiety: Final Thoughts

- **Most common childhood psychiatric disorder**
- Behavioral and pharmacotherapy options both effective
  - Combined approach is best
  - SSRIs > SNRIs, which are both better than placebo
  - Recommendation to try two SSRIs prior to SNRI prior too alternative agents
- Evaluate for comorbidities
- Watch for 'specific to pediatric' presentation (e.g. somatic and oppositionality)
- Need more research for better treatment options:
  - Longer-term outcomes, head-to-head comparisons, other treatment options, neurobiology

Thank you!

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