Pediatric Anxiety Disorders

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Syneos Health	Research support: On IRB for ecopipam trial for individuals with TS at MGH
Tourette Association of America (TAA)	Medical Advisory Board

Anxiety Disorder

- **Distress** when engaging and participating in **age-appropriate**, **normal** developmental activities
  - Disorder when "clinically significant" impairment/distress
- DSM-5 diagnoses:
  - Generalized anxiety disorder
  - Separation anxiety disorder
  - Social anxiety disorder
  - Specific phobia
  - Panic disorder
  - "OCD"

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

When Is Treatment Warranted

When Do We Treat It?

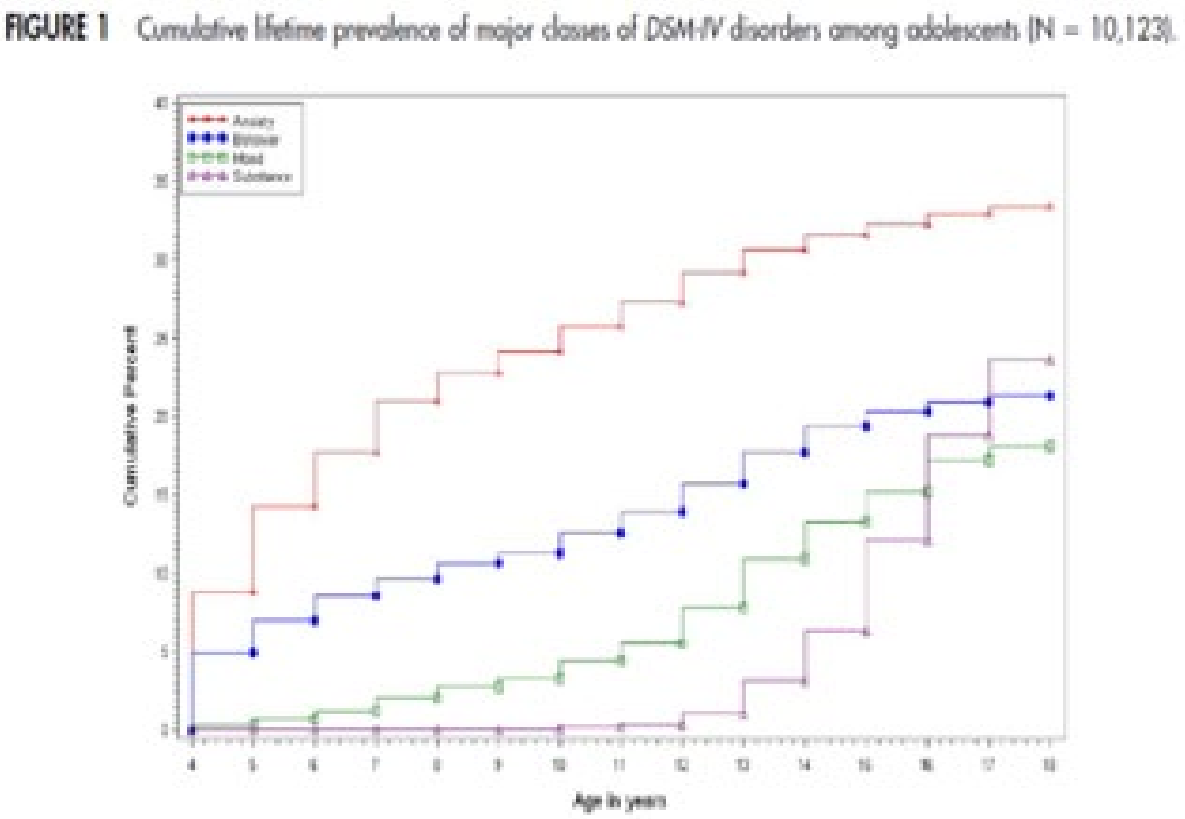
- Impairment
  - In school, social, family
  - In progress in therapy
- Disfunction
  - Missed developmental milestones, (i.e. secondary to avoidance)
  - Time consuming
- Distress
  - Associated anxiety is moderate/severe
  - Persistent (unrealistic) fears/worry inappropriate for stage/age

Why Do We Treat It?

- Disruption of normal psychosocial development of children
- Increased rates of other anxiety disorders, depression, substance dependence, suicidality
- With treatment, positive benefit on the family unit and long-term

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



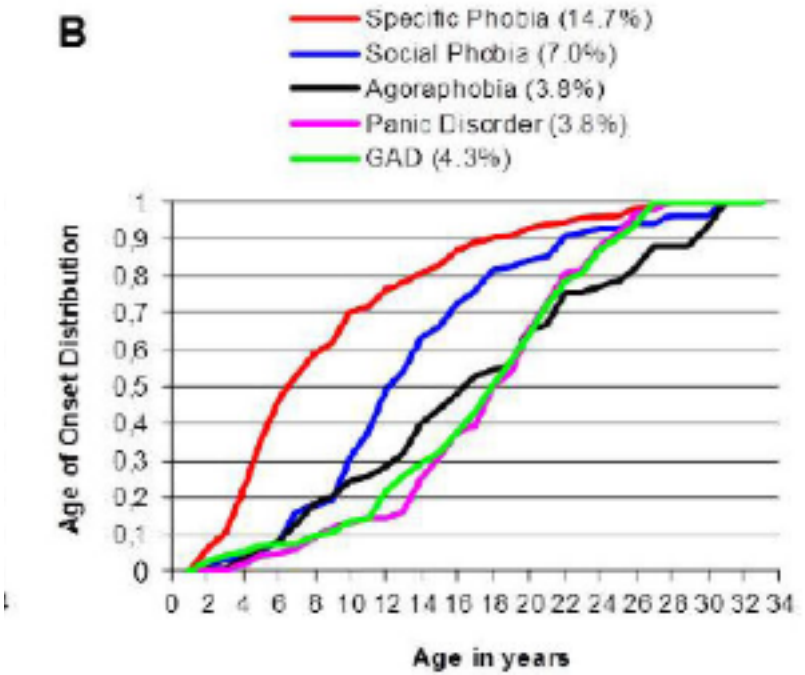
JAACAP Practice Parameters, 2007.

(Merikangas, K. et al JAACAP; 2010; 49 (10); 980-989)

Pattern of Development

Mean ages of onset

- Overlapping
- Specific phobia symptoms and some GAD (ages 5-6)
- Social anxiety and separation anxiety 1-2 years later
  - (Then OCD ~ age 10)
- Panic symptoms/disorder in early teens



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

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

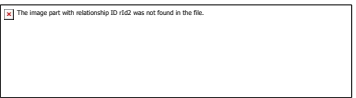
Wehry et al (2015) *Curr Psychiatry Rep*
Data adapted from Early Developmental Stages of Psychopathology (EDSP) Study

Anxiety Disorder: Comorbidities and Sequelae

- 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 *developing* other 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*



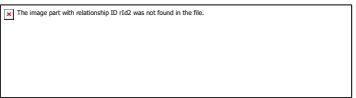
Pediatric Presentation

- Somatic symptoms – headaches, stomachaches, body pains
- 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 Differential

- **Psychiatric:**
  - ADHD (restlessness, inattention)
  - Learning disabilities
  - Autism spectrum symptoms
  - Depression (poor concentration, sleep difficulty, somatic complaints)

- **Medical / Medication / Substance-related**
  - Hyperthyroid conditions
  - Migraine
  - Asthma (+/- bronchodilators)
  - Steroids



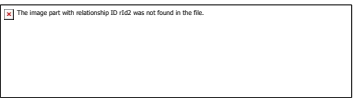
Diagnosis: Pediatric Anxiety Disorders: Diagnostic Instruments/Rating Scales

- **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)

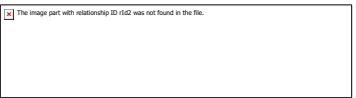
Adapted from Coffey BJ 2019 Anxiety Disorders in Children and Adolescents; Child and Adolescent Psychopharmacology Slides



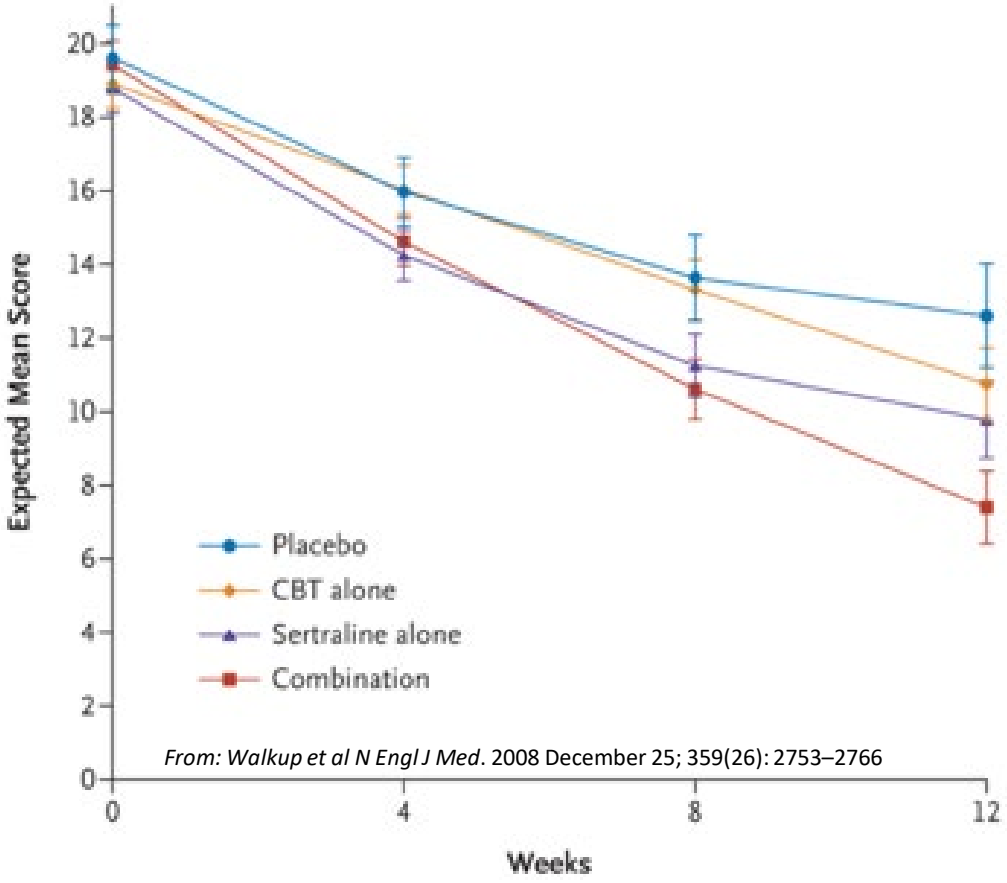
Anxiety Disorder Treatment

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

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



Child/Adolescent Anxiety Multimodal Study (**CAMS**)



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

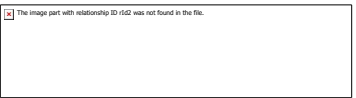
- Combined branch (sertraline and CBT) **most effective**
  - 81% responded - (CGI-I of 1 or 2)
    - (Vs ~60% CBT/SSRI; ~25% placebo)
  - 68% remitted
- Phase II: Combined treatment still most effective at 24 + 36w

Walkup et al (2008)
Compton et al (2010)

Predictors of Response in Anxiety Treatment

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

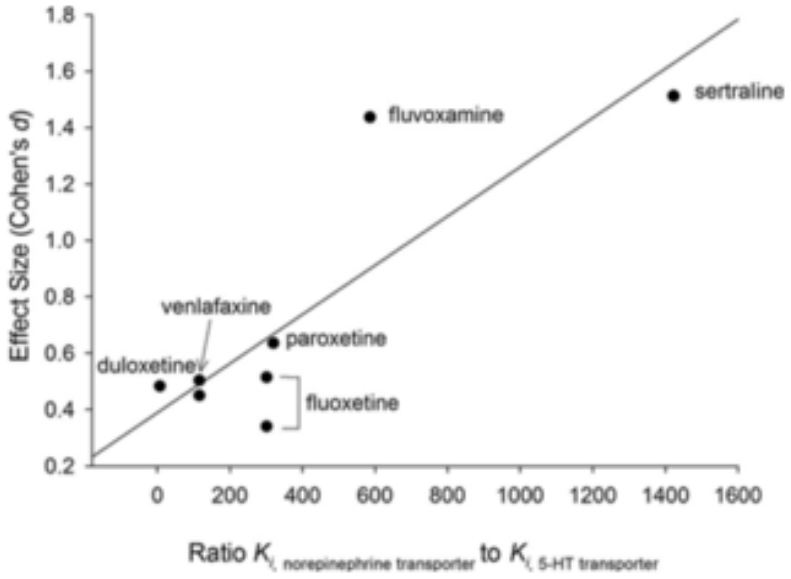
Ginsburg et al (2011) J Consult Clin Psychol



Recent Meta-analyses

Strawn et al (2015) Depress Anxiety

- 9 trials, 1,673 patients (6-17)
- 6 medications
  - Fluoxetine, duloxetine, sertraline, paroxetine, venlafaxine, fluvoxamine
- SSRI/SNRIs all showed superiority
  - "Moderate magnitude" of effect
  - Cohen's d = 0.62, p<.01
- Effect size correlated with serotonergic specificity
- Well tolerated
  - No increased risk for nausea/abdominal symptoms
- Activation trend (med vs placebo)
  - (OR: 1.86, CI: 0.98-3.53, P = .054)



Recent Meta-analyses Cont.

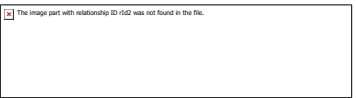
Wang et al (2017) JAMA Peds

- 115 studies, (7,719 patients); Medications, therapy, combination treatment
- Medications more effective compared to pill placebo:
  - Atomoxetine, duloxetine, venlafaxine, fluoxetine, fluvoxamine, paroxetine, sertraline
- TCAs - “marginally increased likelihood of treatment response”
- Benzos – no significant improvement
- CBT significantly improved symptoms, remission, response
- Combination of medication and therapy more effective than either alone

Pharmacotherapy in Pediatric Anxiety

- Typically developing children/adolescents, **SSRIs** and SNRIs are effective in treating pediatric anxiety disorders (and OCD) compared to placebo
  - SSRIs are associated with greater and faster improvement compared to SNRIs
  - "Sertraline has the greatest evidence of efficacy [in pediatric anxiety]" (p. 6, Strawn et al, 2017)

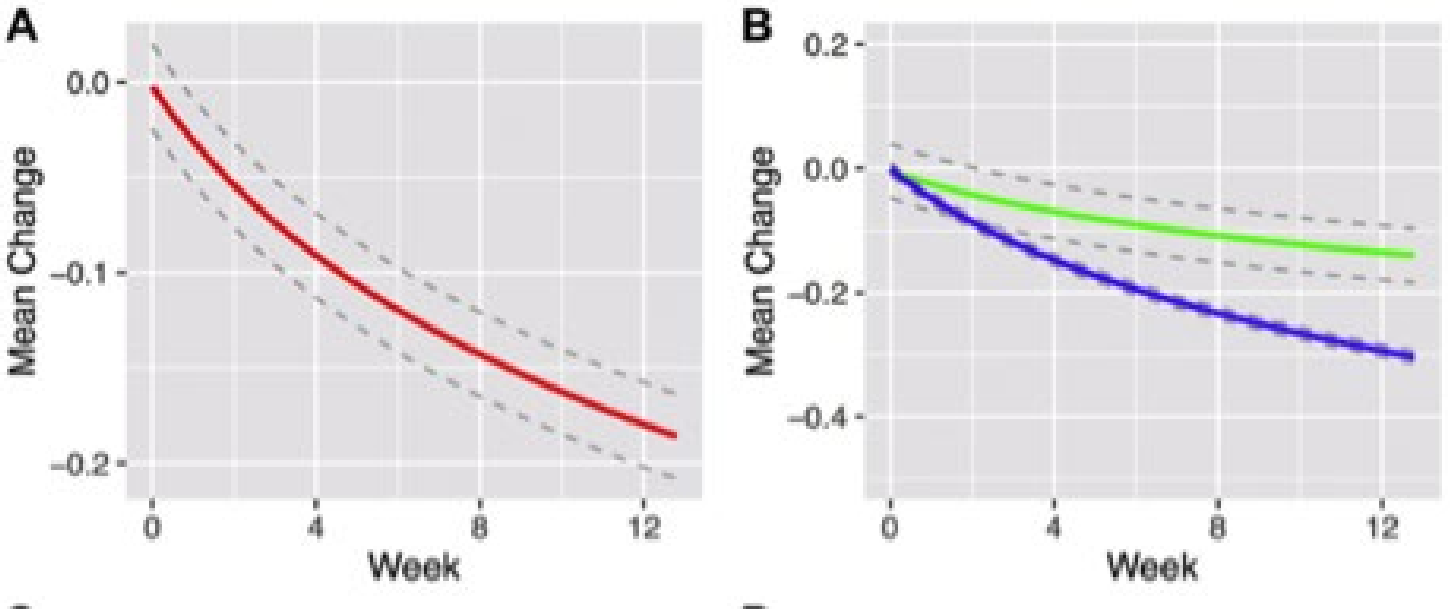
Strawn et al (2018) *JAACAP*
Strawn et al (2017) Curr Probl Pediatr Adolesc Health Care
Strawn et al (2015). Depression Anxiety.
Wang et al (2017). JAMA Peds



Strawn et al (2018) *JAACAP*

"Impact of Antidepressant Dose and Class on Treatment Response in Pediatric Anxiety Disorders: A Meta-Analysis"

IGURE 1 Response Trajectory in Antidepressant-Treated Youth With Generalized, Separation, and Social Anxiety Disorders



Green line represents SNRIs; Blue line represents SSRIs

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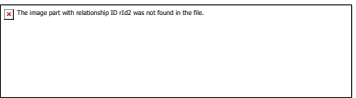
FDA-approved SSRIs/SNRIs for Children/Adolescents

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

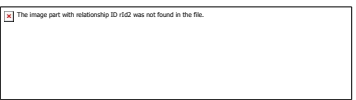
Strawn et al (2017) Curr Probl Pediatr Adolesc Health Care



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

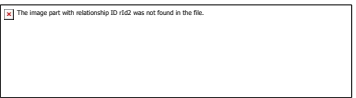


Adverse Effects

- SSRIs and SNRIs are generally well-tolerated
  - Adverse events in general decreased over time

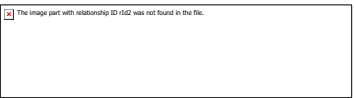
- "Activation" - separate from treatment-emergent mania
  - More common in children than in adolescents
    - 10.7% children compared to 2.1% adolescents (Luft et al 2017)
  - Less risk of activation in SNRI compared to SSRI

Luft et al (2017) Curr Probl Pediatr Adolesc Health Care
Mills and Strawn (2020) *JAACAP*



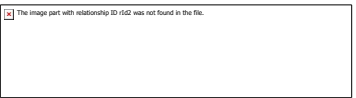
Antidepressants and Black-box Label

- Black-box warning on antidepressants (2004)
- “Did not observe an increased risk of treatment-emergent suicidality in youth with anxiety disorders” (Strawn et al 2015, p.154)
  - Venlafaxine and paroxetine



Off-label Pharmacological Treatments

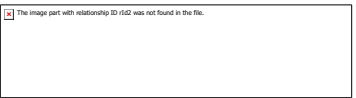
- Tricyclic antidepressants (TCAs)
- Benzodiazepines
- Buspirone
- Alpha-agonists
- Pregabalin
- Natural supplements / Cannabis



Additional Future Pharmacological Considerations

Sonmez et al (2020) *Depress Anxiety*

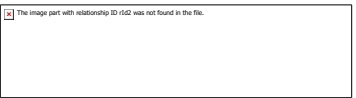
- Eszopiclone (GABAa receptor agonist)
  - Sleep in adults, schedule IV, not trialed in youth with GAD, generally safe, well-tolerated
- Riluzole (glutamate modulator)
  - Tested in youth with OCD, negative study, generally safe, well-tolerated
- Agomelatine (melatonin agonist/serotonin antagonist/GABA)
  - Superior to placebo in adults, well tolerated but reports of liver toxicity
- Pimavanserin (Serotonin inverse agonist/antagonist)
  - Good safety profile, used in Parkinson's psychosis



Strawn et al (2020) *J Clin Psychiatry*

- Do variants in the serotonin transporter (SLC6A4) genes, HTR2A, cytochrome p450 2C19 impact tolerability and efficacy of escitalopram in youth with GAD?
  - Followed: PARS, CGI, adverse events, vital signs
  - Analyzed: Plasma levels AUC and max concentration (Cmax)

- Escitalopram was superior to placebo (p=0.005)
  - Increased CYP2C19 metabolism ~ decreased escitalopram Cmax (p=0.07) and AUC (p<0.05)
  - Having CGI-I 1,2 associated with 1+ long SLC6A4 allele, G/G type HTR2A, intermediate Cyp metabolizer..
- Activation associated with higher AUC and Cmax



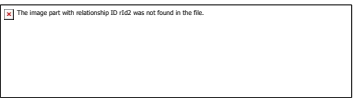
Guided SSRI-dosing?

Strawn et al (2019) *JCAP*

- Modeled SSRI dosing across CYP2C19 phenotypes
    - Poor, normal, rapid, ultrarapid metabolizers
  - AUC, Cmax, and dosing schedule in rapid/ultrarapid metabolizers
- Cmax/AUC higher in slower metabolizers; lower in faster metabolizers (escitalopram > sertraline)
- Escitalopram: 10mg poor metabolizer equivalent to 30mg in ultrarapid equivalent to 20mg in normal
- Sertraline: 100mg in poor, 200mg in rapid/ultrarapid, equivalent to 150mg in normal metabolizers
- In ultrarapid, bid escitalopram needed for comparable troughs

Aldrich et al (2019) *Front Pharma*

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



Impact of COVID-19?

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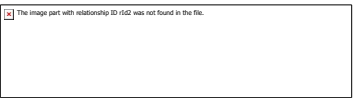
Anxiety: Final Thoughts

- **Most common childhood psychiatric disorder**
- Behavioral and pharmacotherapy options both effective
  - Combined approach is best
  - SSRIs > SNRIs
- Evaluate for comorbidities
- Watch for ‘specific to pediatric’ presentation (e.g. somatic and oppositionality)
- Need more research:
  - Longer-term outcomes, head-to-head comparisons, other treatment options, neurobiology



Thanks!

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