Recent Advances in the Psychopharmacologic Treatment of Pediatric Anxiety: Tailoring Treatments and Enhancing Outcomes
Jeffrey R. Strawn, MD, FAACAP
Associate Professor of Psychiatry and Pediatrics
University of Cincinnati
Cincinnati Children’s Hospital Medical Center

Disclosures of Potential Conflicts

Anxiety

Disclosure: Off Label Medication Use will be Discussed
The following are FDA-approved antidepressants in children and adolescents

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Age (years)</th>
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<tr>
<td>SSRI</td>
<td>Citalopram</td>
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<td></td>
<td>Escitalopram</td>
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<td></td>
<td>Fluoxetine</td>
<td>MDD</td>
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<td>Mirtazapine</td>
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<td>Trazodone</td>
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Source | Research Funding | Advisor/Consultant | Speaker’s Bureau | Books, Intellectual Property | Linked Services | Stock or Equity
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Precision Medicine

Psychopharmacologic Treatment of Anxiety in Pediatric Patients

General Principles

In most pediatric anxiety studies, SSRI/SNRI separates from placebo between week 2 and week 4
• Age
  – 6 to 17 years

• Randomization
  – Venlafaxine (N=157) or placebo (N=163) for 8 weeks.

• Primary outcome measure
  – Composite score for GAD section of a modified version of the K-SADS for School-Age Children

• Results
  – Pooled analysis, venlafaxine
    • Venlafaxine > placebo for decrease in K-SADS GAD score (−17.4 vs −12.7).
  – CGI Response
    • venlafaxine > placebo (69% vs 48%).

Pediatric GAD: Venlafaxine XR

Pediatric GAD: Duloxetine

• Patients
  – 7-17 years of age
    • Duloxetine, 12.6 ± 3 years
    • Placebo, 12.2 ± 3 years

• Inclusion
  – Moderate severity GAD

• Outcome
  – Change in PARS Severity for GAD
  – Change in PARS (total)


Adolescent GAD: Escitalopram vs. Placebo

• Patients
  – 12-17 years of age

• Dosing
  – Forced-Flexible
    – 5 mg qAM x 2 days then 10 mg qAM x 7 days then 15 mg qAM until week 4 at which time escitalopram could be increased to 20 mg qAM.

• Inclusion
  – Moderate severity GAD, no MDD
  – Stable psychotherapy

• Outcome
  – Change in PARS from baseline to endpoint
  – CGI-I and CGI-S

Strawn et al, 2019 (unpublished)

Adolescent GAD: Escitalopram vs. Placebo

Guanfacine ER in Pediatric Anxiety

- Dx: GAD, separation anxiety disorder, social anxiety disorder.
- No ADHD, no MDD, no BP
- N = 83
- Age 6-17 (mean: 12±3)

1-6 mg/day, 3:1 randomization


Predicting Treatment Response in Pediatric Anxiety

The Impact of Comorbidity

CAMS: Predictors of Remission

Social Anxiety/Social Phobia & Age

Predicting Treatment Response in Pediatric Anxiety

The Impact of Metabolism

Citalopram & Escitalopram

Metabolism and Outcome Relevance

Adolescent Escitalopram Response

Pharmacogenomic Predictors

Adolescent Escitalopram Response

Levels in Adolescent GAD

Strawn et al. Unpublished data.

Strawn et al. Unpublished data.
Adolescent Escitalopram Response
Pharmacogenomic Predictors

Strawn et al. Unpublished data.

Normal metabolizers, n=10
Intermediate metabolizers, n=10

5-HT Transporter Gene
SLC6A4 or 5HTT or SERT

• Encoded by the SLC6A4 gene
• Responsible for the reuptake of 5-HT into the presynaptic neuron
• SSRIs inhibit this process, resulting in increased 5-HT being present at the synaptic junction

5-HT Transporter Gene
SLC6A4 or 5HTT or SERT

• Meta-analyses of the association between 5-HTTTR polymorphism and SSRI efficacy for adult MDD (15 studies, N=1435) (Horstmann et al, 2009)
  – s/s variant → lower remission rates (p<0.0001)
  – s/s and s/l variants had lower response rates

Predicting weekly improvement:
- 2C19 phenotype, p<0.001
- Age, p=0.02 (older → better)
- SLC6A4 l/l, p=0.06
- SLC6A4 s/s, p=0.039

5-HT Transporter Gene
SLC6A4 or 5HTT or SERT

Precision Tx
Gen Psychopharm PGx
Biomarkers
Psychotherapy
Dosing
Placebo
Comparing meds
Time course
Side Effects
Placebo
Predicting Time to Response in Pediatric Anxiety

*How long should an SSRI trial last?*

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**CAMS: Probability of Response in Pediatric Anxiety Disorders**

If no improvement by wk 8 with sertraline, 3:1 odds against additional improvement

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**Predicting Response in Pediatric Anxiety**

*Not all antidepressants are the same*
**Meta-Analysis: Antidepressant Efficacy**

- **Effect Size**: 0.62, **p** = 0.002
- Weighted proportional 5-HT selectivity, **p** = 0.02


**SSRI Effect Size**: 0.65
**SNRI Effect Size**: 0.45

**Serotonergic Selectivity**

- R² = 0.7621
- Kᵣ/Kᵣ₅-HT (Serotonergic Specificity)

**Network Meta-Analysis: Medication Efficacy**

- SSRIs, SNRIs and alpha-2 agonists are more effective than placebo in producing 'treatment response'

Antidepressant Response in Pediatric Anxiety Disorders

SSRIs produce faster and greater improvement in anxiety symptoms

Antidepressant Dose and Response

CAMS: Placebo Response and its Relevance for Clinicians

- Change in PARS score over the course of 12 weeks of treatment was best predicted by:
  - Separation anxiety disorder (strongest predictor)
  - Parent expectations for treatment success
  - Child expectations for treatment success

Predicting Placebo Response in Pediatric Anxiety

Expectation is Critical
Meta-Analysis: SSRI and SNRI Adverse Events in Pediatric Patients

Mills and Strawn, 2019, under review.

Predicting Antidepressant Side Effects in Anxiety

Activation

Activation and Drug Level

- Antidepressant-related activation emerges early in treatment or following an increase in dose (Reinblatt et al. 2009).
- Symptoms resolve when the dose is decreased or medication is discontinued (Riddle et al. 1990; Wilens et al. 2003).
  - Consistent with one prospective study of fluvoxamine in which higher plasma fluvoxamine concentrations were associated with a greater likelihood of activation in anxious youth (Reinblatt et al. 2009, right).
- The rate of symptom resolution is related to the rate of activation symptom onset (Wilens et al. 2003).

Activation and Antidepressant Class in Anxious Children & Adolescents

- SSRIs are more likely to produce activation compared to placebo.
- SNRIs do not differ from placebo in terms of the likelihood of producing activation.

Antidepressants and Activation in Youth with Anxiety Disorders

- SSRIs are more likely to produce activation than SNRIs (p<0.0001)
  - Odds against H0: 17:1

Mills and Strawn, in preparation.
Escitalopram-Related Activation

ANOVA for trend p=0.029

Clinical Recommendations for Managing Activation

- Rule out general medical condition
- Evaluate potential contributors
  - Diagnosis/Comorbidity
  - ADHD, manic symptoms?
  - Family factors that perpetuate anxiety (e.g., accommodation)
  - Occult substance use,
  - Medication adherence,
- Decrease in dose of SSRI
- Consider change to another SSRI or SNRI
- Consider individual or family psychotherapy
- May consider short-term adjunctive benzodiazepines for activation


Predicting Antidepressant Side Effects

Weight Gain

Antidepressant-Related Side Effects

Weight Gain and SSRIs

Escitalopram-Related Weight Gain


Escitalopram-Related Weight Gain


Predicting Treatment-Emergent Suicidality and Self Harm in Antidepressant-Treated Youth

Dosage and Medication

Antidepressants & Self-Harm

Treatment-emergent suicidality was significantly greater in paroxetine-treated patients compared to those receiving sertraline (logOR: 43.5, 95% CrI: [10.1 to 96.0]), placebo (logOR: 19.5, 95% CrI: [1.7 to 60.4]), and duloxetine (logOR: 20.3, 95% CrI: [1.5 to 67.7]).

Significant linear discontinuity in slope following onset of exposure in CBT

Trajectory varies by treatment and age

Onset of cognitive restructuring component of CBT
Onset of exposure exercises


ADHD Co-morbidity and Treatment Outcome in CAMS

- ADHD diagnosis moderated acute tx response and remission rates.
- Youth with co-occurring ADHD fared worse in the CBT condition:
  - When was CBT administered?
    - After school
  - When were stimulants more likely to have been administered?
    - Morning
- No differences in other tx conditions.
- ODD diagnosis did not moderate or predict any treatment outcomes

Ollendick T. Treatment outcomes in anxious youth with and without comorbid ADHD in the CAMS. Anxiety & Depressive Disorders Association of America, Chicago, IL, March, 2014.
Predicting Psychotherapy or Pharmacotherapy Response in Pediatric Anxiety

The Impact of Severity

Conclusions

• SSRIs/SNRIs are effective treatments for anxiety disorders
  - SSRIs associated with greater and faster improvement.
  - Adequate trial = 6 weeks.

• Psychotherapy is effective for pediatric anxiety disorders
  - Comorbid conditions affect engagement and likelihood of success and require optimizing of comorbidity-specific treatment.
  - Antidepressant side effects in adolescents
    - Activation may be related to drug level and metabolism.
    - SSRIs are associated with more activation compared to SNRIs.
    - Citalopram is associated with weight gain in youth with anxiety/depressive disorders.

• Pharmacogenetic markers of medication metabolism suggest:
  - Slower metabolism may be associated with greater weight gain and activation
  - Extreme metabolizers (e.g., very slow and very fast) are more likely to discontinue medication
  - SSRI dose requires adjustment in extreme metabolizers to produce similar exposure to normal metabolizers.

Anxiety Severity and Remission

• Child & Adolescent Multimodal Study
  - Sertraline
  - Sertraline + CBT
  - CBT
  - Placebo

• The most severely anxious youth probably require combined treatment (CBT+SSRI) to achieve the best outcomes.


Acknowledgments

University of Cincinnati
  - Heidi Schroeder, BS
  - Melissa P. DelBello, MD, MS
  - Sara Varney, BS
  - Sarah Mosiman, MA
  - Jeffrey Mills, PhD
  - Marissa Luft, BS
  - Eric Dobson, MD*

Duke University
  - Mora Flynn, MD
  - Scot Compton, MD

Cincinnati Children’s
  - Sergio Delgado, MD
  - Kim Cecil, PhD
  - Laura Ramsey, PhD
  - Ethan Poweleit, BS

Ann & Robert H. Lurie Children’s Hospital
  - John Walkup, MD

Columbia University
  - Amir Levine, MD

*Now MUSC