Treatment Advances in Pediatric Anxiety Disorders

Moira A. Rynn, MD
Chair and Consulting Psychiatrist
Department of Psychiatry and Behavioral Sciences
<table>
<thead>
<tr>
<th>Source</th>
<th>Research Funding</th>
<th>Advisor/Consultant</th>
<th>Employee</th>
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Disclosure

- Most of the medications discussed in this presentation do not have FDA approval in the pediatric population.
- This will be highlighted throughout the presentation.
me mom
At School
“Mom, I need you to be there for me. I am getting pressure in the classroom. The work is making me nervous. Even with the easy pluses - 1 + 1 = what? I say, “I can’t do this.” I want to run out of the classroom. The work makes me nervous. My teacher has to slow down. She’s saying stuff too fast and I can’t catch up.”

- 8 year old girl
Outline

• Clinical Characteristics

• Acute and Long-term Treatment
  • Triad Anxiety Disorders
  • Obsessive Compulsive Disorder

• Treatment Development
Main Milestones of Childhood

• Language: speaking, communicating, understanding and reading non-verbal cues

• Cognitive: ability to reason, think, learn, problem-solve

• Social: develop and keep meaningful relationships; and respond to others’ feelings
Anxiety: Developmental Progression

Common Fears
- **Preschool:** Imaginary Objects/situations
- **Grade School:** Health/harm, Scrutiny/Competence
- **Adolescence:** Social adequacy, Performance

Anxiety Disorders
- **Preschool:** Phobic objects/situations, SAD
- **Grade School:** OCD, GAD
- **Adolescence:** Social anxiety, Panic Disorder
When Does Anxiety Become Problematic?

- Avoidance/Disruption
- Interferes with functioning (not facing developmental challenges)
- Distress
- Duration
Cumulative Lifetime Prevalence of Major Classes of DSM-IV Diagnoses

NCS-A, N=10,123

Merikangas et al., 2010
# Prevalence Estimates for Anxiety Disorders among US Adolescents

<table>
<thead>
<tr>
<th>DMS-IV Disorder</th>
<th>Lifetime Prevalence by Sex %</th>
<th>Lifetime Prevalence by Age %</th>
<th>Lifetime Prevalence Total %</th>
<th>Lifetime Prevalence-Severe Impairment %</th>
<th>12-Month Prevalence %</th>
<th>1-Month Prevalence %</th>
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<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>13-14 y</td>
<td>15-16 y</td>
<td>17-18 y</td>
<td></td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>3.4</td>
<td>1.4</td>
<td>2.5</td>
<td>2.5</td>
<td>2.0</td>
<td>2.4</td>
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<tr>
<td>Generalized Anxiety Disorder</td>
<td>3.0</td>
<td>1.5</td>
<td>1.0</td>
<td>2.8</td>
<td>3.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>11.2</td>
<td>7.0</td>
<td>7.7</td>
<td>9.7</td>
<td>10.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td>22.1</td>
<td>16.7</td>
<td>21.6</td>
<td>18.3</td>
<td>17.7</td>
<td>19.3</td>
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<tr>
<td>Panic Disorder</td>
<td>2.6</td>
<td>2.0</td>
<td>1.8</td>
<td>2.3</td>
<td>3.3</td>
<td>2.3</td>
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<tr>
<td>Posttraumatic Stress Disorder</td>
<td>8.0</td>
<td>2.3</td>
<td>3.7</td>
<td>5.1</td>
<td>7.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Separation Anxiety Disorder</td>
<td>9.0</td>
<td>6.3</td>
<td>7.8</td>
<td>8.0</td>
<td>6.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>38.0</td>
<td>26.1</td>
<td>31.4</td>
<td>32.1</td>
<td>32.3</td>
<td>31.9</td>
</tr>
</tbody>
</table>

Beedso-Baum & Knappe, 2012; Merikangas et al., 2011; Kessler et al., 2012
Childhood Anxiety Disorders

Greater risk for:

- Adult depression and anxiety\textsuperscript{1}
- Substance abuse/dependence\textsuperscript{2}
- Suicidal behaviors\textsuperscript{3}

\textsuperscript{1} Pine et al., 1998
\textsuperscript{2} Compton et al., 2007
\textsuperscript{3} Woodward et al., 2001
Genetics of Anxiety Disorders

- Moderate level of familial aggregation (OR=4-6)

- Proportion of the phenotypic variability explained by genetic factors ranged from 30 to 50%

- Similar to depression but less than disruptive behaviors & bipolar disorder

Hettema et al., 2001
Environment

• Parenting style (i.e. overprotective/ over controlling style)
• Stressful life events both acute and chronic
• Modeling observed behaviors
• May be partially mediated by genetic influences
Pediatric Anxiety Disorders

- **Generalized Anxiety Disorder (GAD):** excessive anxiety and worry about multiple areas including school, social activities, and health.

- **Separation Anxiety Disorder (SAD):** developmentally inappropriate and excessive anxiety concerning separation from primary caregivers.

- **Social Anxiety Disorder (SoP):** persistent fear of social performance situations or scrutiny by others.

- **Obsessive Compulsive Disorder (OCD):** repetitive behavior or thoughts that neutralize anxiety.
### Table 3
Anxiety disorders diagnostic summary.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Current diagnosis, n (%)</th>
<th>ADIS CSR rating, M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAD</td>
<td>16 (3.29)</td>
<td>SAD</td>
</tr>
<tr>
<td>SP</td>
<td>56 (11.50)</td>
<td>SP</td>
</tr>
<tr>
<td>GAD</td>
<td>33 (6.78)</td>
<td>GAD</td>
</tr>
<tr>
<td>SAD &amp; SP</td>
<td>33 (6.78)</td>
<td>SAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP</td>
</tr>
<tr>
<td>SAD &amp; GAD</td>
<td>39 (8.01)</td>
<td>SAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD</td>
</tr>
<tr>
<td>SP &amp; GAD</td>
<td>135 (27.72)</td>
<td>SP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD</td>
</tr>
<tr>
<td>SAD &amp; SP &amp; GAD</td>
<td>175 (35.93)</td>
<td>SAD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD</td>
</tr>
</tbody>
</table>

*Note: SP, social phobia; GAD, generalized anxiety disorder; SAD, separation anxiety disorder; ADIS CSR, Anxiety Disorders Interview Schedule Clinician Severity Rating.*
# School Refusal, Over Anxious, and Separation Anxiety Disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis (Age Range)</th>
<th>Duration</th>
<th>Treatment</th>
<th>N</th>
<th>Dose Range (mg/day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gittelman-Klein &amp; Klein (1971)</td>
<td>School Phobia (6-14 yrs)</td>
<td>6 wks</td>
<td>Imipramine</td>
<td>35</td>
<td>100-200</td>
<td>Imipramine &gt; PBO</td>
</tr>
<tr>
<td>Berney et al., 1981</td>
<td>School refusal (9-14 yrs)</td>
<td>12 wks</td>
<td>Clomipramine</td>
<td>51</td>
<td>40-75</td>
<td>Clomipramine = PBO</td>
</tr>
<tr>
<td>Klein et al., 1992</td>
<td>SAD (6-15 yrs)</td>
<td>6 wks</td>
<td>Imipramine</td>
<td>21</td>
<td>75-275</td>
<td>Imipramine = PBO</td>
</tr>
<tr>
<td>Bernstein, et al., 1990</td>
<td>School refusal (7-18 yrs)</td>
<td>8 wks</td>
<td>Alprazolam</td>
<td>24</td>
<td>0.75-275</td>
<td>Alprazolam = Imipramine</td>
</tr>
<tr>
<td>Simeon et al., 1992</td>
<td>Overanxious or avoidant (8-17 yrs)</td>
<td>4 wks</td>
<td>Alprazolam</td>
<td>30</td>
<td>0.5-3.5</td>
<td>Alprazolam = PBO</td>
</tr>
<tr>
<td>Graae et al., 1994</td>
<td>SAD (7-13 yrs)</td>
<td>8 wks</td>
<td>Clonazepam</td>
<td>15</td>
<td>0.5-2.0</td>
<td>Clonazepam = PBO</td>
</tr>
</tbody>
</table>
# Triad Anxiety Disorders & Social Phobia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis (Age Range)</th>
<th>Duration</th>
<th>Treatment</th>
<th>N</th>
<th>Dose Range (mg/day)</th>
<th>Outcome</th>
<th>% Meeting Remission or Response</th>
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</thead>
<tbody>
<tr>
<td>RUPP Anxiety Study Group: Walkup, et al., 2001</td>
<td>GAD; SoP; SAD (6-17 yrs)</td>
<td>8 wks</td>
<td>Fluvoxamine</td>
<td>128</td>
<td>50-300</td>
<td>Fluvoxamine &gt; PBO</td>
<td>CGI/I &lt;4: 76%</td>
</tr>
<tr>
<td>Birmaher et al., 2003</td>
<td>GAD; SoP; SAD (7-17 yrs)</td>
<td>12 wks</td>
<td>Fluoxetine</td>
<td>74</td>
<td>20</td>
<td>Fluoxetine &gt; PBO</td>
<td>CGI/I≤2: 61%</td>
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<tr>
<td>Wagner et al., 2004</td>
<td>SoP (8-17 yrs)</td>
<td>16 wks</td>
<td>Paroxetine</td>
<td>322</td>
<td>10-50</td>
<td>Paroxetine &gt; PBO</td>
<td>CGI/I= 1: 47.8% or ≥70% reduction on SAS: 47.2%</td>
</tr>
<tr>
<td>March et al., 2007</td>
<td>SoP (8-17 yrs)</td>
<td>16 wks</td>
<td>Venlafaxine ER</td>
<td>293</td>
<td>37.5-225</td>
<td>Venlafaxine ER &gt; PBO</td>
<td>CGI/I= 1/ 2: 56%</td>
</tr>
<tr>
<td>Reference</td>
<td>Diagnosis (Age Range)</td>
<td>Duration</td>
<td>Treatment</td>
<td>N</td>
<td>Dose Range (mg/day)</td>
<td>Outcome</td>
<td>% Meeting Remission or Response</td>
</tr>
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</tr>
<tr>
<td>Rynn et al., 2001</td>
<td>GAD (5-17 yrs)</td>
<td>9 wks</td>
<td>Sertraline</td>
<td>21</td>
<td>50</td>
<td>Sertraline &gt; PBO</td>
<td>CGI/I = 1: 18%</td>
</tr>
<tr>
<td>Rynn, et al. (in prep)</td>
<td>GAD (5-17 yrs)</td>
<td>16 wks</td>
<td>Sertraline</td>
<td>51</td>
<td>50 -200</td>
<td>Sertraline &gt; PBO</td>
<td>HAMA≤7: 4%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months later: 64%</td>
</tr>
<tr>
<td>Rynn et al., 2007</td>
<td>GAD (6-17 yrs)</td>
<td>8 wks</td>
<td>Venlafaxine ER</td>
<td>313</td>
<td>37.5 -225</td>
<td>Venlafaxine ER &gt; PBO</td>
<td>CGI/I &lt;3: 69% and 48%</td>
</tr>
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</table>

Generalized Anxiety Disorder
# Obsessive Compulsive Disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration Weeks (Age Range)</th>
<th>Treatment</th>
<th>N</th>
<th>Dose Range (mg/day)</th>
<th>Outcome</th>
<th>% Remission or Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeVeaugh-Geiss et al., 1992</td>
<td>8 (10-17 yrs)</td>
<td>Clomipramine</td>
<td>126</td>
<td>75-200</td>
<td>Clomipramine &gt; PBO</td>
<td>CGI-I ≤ 2: 60%</td>
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<tr>
<td>March et al., 1998</td>
<td>12 (6-17 yrs)</td>
<td>Sertraline</td>
<td>187</td>
<td>25-200</td>
<td>Sertraline &gt; PBO</td>
<td>25% ≥ CY-BOCS: 53% or CGI-I score of ≤ 2: 42%</td>
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<tr>
<td>Riddle et al., 2001</td>
<td>10 (8-17 yrs)</td>
<td>Fluvoxamine</td>
<td>120</td>
<td>50-200</td>
<td>Fluvoxamine &gt; PBO</td>
<td>25% ≥ CYBOCS: 42.1%</td>
</tr>
<tr>
<td>Geller et al., 2001</td>
<td>13 (7-17 yrs)</td>
<td>Fluoxetine</td>
<td>103</td>
<td>20-60</td>
<td>Fluoxetine &gt; PBO</td>
<td>40% ≥ CYBOCS: 49%</td>
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</table>
Pooled Analysis CBT Modality for Childhood Anxiety

![Bar chart showing remission rates for different CBT modalities.]

- Individual-CBT: N=170
- Group-CBT: N=162
- Family-CBT: N=121
Child Anxiety Multimodal Study CAMS: N=488, 7-17 Years Old for 12 Weeks

CGI-I 1 and 2 (ITT, LOCF)

COMB > CBT = Sertraline > PBO

Walkup et al., 2008
### Response and Remission Rates of CAMS Study Subjects at Week 12

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No AD remission</th>
<th>CGI-I remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMB (n = 140)</td>
<td>68.3 [58.7, 76.5]</td>
<td>45.6 [36.2, 55.3]</td>
</tr>
<tr>
<td>SRT (n = 133)</td>
<td>45.9 (^b)</td>
<td>33.9 [25.9, 42.9]</td>
</tr>
<tr>
<td>CBT (n = 139)</td>
<td>46.2 [37.9, 54.8]</td>
<td>20.4 [14.4, 28.0]</td>
</tr>
<tr>
<td>PBO (n = 76)</td>
<td>23.7 [15.5, 34.6]</td>
<td>15.0 [3.4, 46.4]</td>
</tr>
</tbody>
</table>

\(^b\) No variability in this estimate across imputations, thus confidence interval not applicable
## Remission Rates and Social Phobia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% no AD</th>
<th>CGI-I remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No SOP</td>
<td>SOP</td>
</tr>
<tr>
<td>COMB</td>
<td>88.0</td>
<td>64.0</td>
</tr>
<tr>
<td>SRT</td>
<td>52.0</td>
<td>44.4</td>
</tr>
<tr>
<td>CBT</td>
<td>72.0</td>
<td>40.6</td>
</tr>
<tr>
<td>PBO</td>
<td>46.1</td>
<td>19.1</td>
</tr>
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</table>
Baseline Variables that Predict Remission (p<0.05):

- Lower baseline anxiety severity*
- Absence of social phobia*
- Nonminority race/ethnicity*
- Younger age
- Absence of a comorbid internalized disorder (e.g. depression, anxiety)

*Denotes variables that, when combined into a single model, still significantly predicted remission based on ADIS-C/P
COMB > CBT = Sertraline > PBO

Excellent Responder (YBOCS ≤ 10)

COMB = CBT > Sertraline = PBO

Percent Response

- PBO: 3
- SER: 21
- CBT: 39
- COMB: 54

POTS, 2004
Long-term Treatment
Triad Anxiety Follow-up Studies

Fluoxetine 1 Year Follow-up

- 56 of 74 subjects completed the 1 year F/U
- 42 received medications and 10 did not
- FLX/FLX continued significant improvement (CGI-S, p=0.047, CGI-I, p=.01)
- PBO/FLX = greatest improvement
- PBO/no medication = least improvement

Fluvoxamine 6 Month Follow-up

- 94% (33 of 35) subjects who initially responded and continued on fluvoxamine remained well
- 71% (10 of 14) of fluvoxamine non-responders responded to fluoxetine
- 56% (27 of 48) of placebo non-responders responded to fluvoxamine

Clark et al., 2005

Walkup, J. et al. (2002)
CAMS Response: 12 to 36 weeks

Week 12 | Week 24 | Week 36

% Responder

- COMB
- CBT
- SRT

ABCT 2009
CAM Extended Long-term Study (CAMELS)

488 Enrolled in CAMS

140 Assigned to receive sertraline and CBT
133 Assigned to receive sertraline alone
139 Assigned to receive CBT alone
76 Assigned to receive placebo

288 Enrolled in CAMELS

82 (58.6% of 140) Received sertraline and CBT
79 (59.4% of 133) Received sertraline alone
83 (59.7% of 139) Received CBT alone
44 (57.9% of 76) Received placebo

200 Not enrolled in CAMELS

107 Could not contact/did not respond to contact efforts
24 Were not interested
46 Other (eg, too busy to schedule)
23 Declined further contact during CAMS

Ginsburg et al., 2014
CAMELS Naturalistic Follow-up

- N= 288 ; 11-26 years; M=16.8
- Responders vs non-responders.
- Remission = absence of all study anxiety disorders
- 46.5% were in remission 6 years after randomization. Acute treatment responders were more likely to be in remission
- The following predicted remission:
  - Male, family functioning and Higher SES

Ginsburg et al., 2014
Adverse Events
Safety Concerns

- Antidepressant treatment leads to more frequent adverse events as compared to placebo
- Physical development and growth
- Activation and psychiatry symptoms greater in children
- Medication withdrawal symptoms
- Monitoring of suicidal ideation and behaviors
Monotherapy:
- CBT
- SRI & SNRI

Combination Treatment
- Family/Environment
- Maximize Treatment

But approximately 30 to 50% do not achieve this response:
Antipsychotic Use for Sedative Properties

Comer et al., 2011
EX/RP arm had significantly greater reduction in Y-BOCS scores at wk 8 versus Risperidone or PBO arms.

Simpson et al., 2013
The Pediatric OCD Treatment Study II

Treatment Arms N=124; 7-17 years

- Medication Management (MM)
- MM + CBT
- MM + Instructions on CBT

Franklin et al., 2011
Response Status:
- MM + CBT = 68.6%
- MM + instruction = 34.0%
- MM only = 30.0%

Franklin et al., 2011
Children diagnosed with GAD and fMRI results studies

- Greater pretreatment amygdala activation associated with better response to both CBT and pharmacological treatments.\(^1\)

- Increased right VLPFC activation relative to controls in the medication \((t(15) = 3.01, p < 0.01)\) and CBT \((t(15) = 3.22, p < 0.01)\) groups following treatment. \(^2\)

\(^1\)McClure et al., 2007
\(^2\)Maslowsky et al., 2010
Anxiety Disorders Treatment Development

• Children and adolescents with GAD underwent fMRI scanning before and after treatment with either an SRI medication (Fluoxetine) or CBT.

• Found negative association between activation in the left amygdala in an afraid–fear vs afraid–happy contrast task and post-treatment CGI-I score ($\rho=-0.65$, $p<0.02$).

• Suggests that SRIs and CBT treatment are most effective for the youth with amplified amygdala reactivity.

McClure et al., 2007
OCD Treatment Development

• Associations between OCD and genes related to the glutamate system

• Disrupting glutamatergic transmission in corticostriatal circuits (i.e. deletion of the synaptic protein Sapap3 or the transmembrane protein Slitrk5) leads to OCD-like behaviors in mice.

• Medications that modulate glutamatergic transmission (e.g., riluzole in adults) show preliminary data effect of in some patients.

_Pittenger et al., 2011_
OCD & Glutamatergic System

- Human MRS studies have linked striatal glutamatergic abnormalities to OCD symptoms.

- Rosenberg et. al (2000) examined the caudate nucleus in 11 psychotropic drug-naïve youth with OCD.

- Compared to matched controls, patients had increased glutamatergic compounds that decreased with successful paroxetine treatment.

- Decrease correlated with a decrease in OCD severity measured by the CYBOCS (r=0.80, p=.006).
Riluzole is a potent antiglutamatergic agent.

- FDA approved for amyotrophic lateral sclerosis
- Increased extra-synaptic glutamate reuptake glial cells
- Stimulation of growth factor synthesis, BDNF
- Promotion of neurogenesis

Side effects: nausea and sedation
Rare: hepatotoxicity and in children reports of pancreatitis

Mathew et al., 2008; Coric et al., 2005
Placebo-Controlled Trial of Add-on RIL for the Treatment of OCD

- RIL vs PBO for 12 weeks
- N= 60 treatment-resistant children & adolescents with OCD (17 subjects also had concomitant ASD)
- Aged 7-17 years; M=14.5; Mean CY-BOCS at baseline 28.2
- Outcome measures: CY-BOCS, CGI-S and CGAS
- Dose range of 10 mg to the maximum of 100 mg/day

Grant et al., 2014
There was no effect of study group on change in the CY-BOCS total scores between baseline and week 12; average improvement in the RIL group (21± 18%, 5.52± 4.40 points) very similar to that observed in PBO (19± 15%; 5.83± 4.86 points; F. 0.04, p. 0.84).

Grant et al., 2014
Enhancement of Psychotherapy with D-cycloserine (DCS)

- N-methyl-D-aspartate (NMDA) is a glutamate receptor complex involved with synaptic plasticity and memory
- DCS is a partial agonist of the glycine site of the NMDAR
- Enhancement of NMDA receptor activity may enhance extinction of previously conditioned fear

Kessler & Mayberg, 2007
D-Cycloserine – Pediatric OCD

• CBT+ D-Cycloserine (25-45kg=25 mg/day and 46-90 kg=50 mg/day) = CBT+PBO; (N=30) for 8 wks
  • Primary comparison was not statistically significantly different.
  • Treatment group showed small to moderate treatment effects (d = .31-.47) on primary outcome measures (C-YBOS & CGI measures).

Storch et al., 2010
Minocycline: “Repurposing Approach”

- 2\textsuperscript{nd} generation tetracycline; high CNS penetration; & FDA approved for children 8 & older
- Modulates glutamate, anti-oxidant & anti-inflammatory properties
- Human clinical trials of neurological diseases minocycline may have neuroprotective effects.
- Animal studies suggest minocycline inhibits glutamate-induced cell death, increases glial glutamate transport & inhibits microglial proliferation.
Pediatric Study

- N = 6 (ages 12 - 19) diagnosed with OCD with CYBOCS score ≥16 (mean=24) & 12 weeks of adequate SSRI dose.
- Stayed on SSRI with the addition of minocycline (dosing from 75 mg to 100 mg bid).
- 4 out of 6 met response defined as a CYBOCS reduction of at least 30%. (unpublished data)

Adult Study

- N= 9 treatment-resistant adults with OCD & adequate SSRI trial
- Continued SSRI with minocycline 200 mg a day for 12 weeks.
- 2 of 9 responded ≥ 40% YBOCS reduction & had OCD onset in childhood

Rodriguez CI et al, 2011
Medication Strategies Targeting Brain Mechanisms in Pediatric OCD

• Hypothesis 1: When added to SSRI medication, minocycline will be superior to PBO in reducing OCD symptoms.

• Hypothesis 2: Adding minocycline (versus placebo) to an SSRI will reduce glutamate levels in the head of caudate.

• Hypothesis 3: Reduction in glutamate levels will be associated with reduction in OCD severity.

PIs: Moira Rynn, M.D., Helen Blair Simpson, M.D., Ph.D., Larry Kegeles, M.D., Dikoma Shungu, Ph.D. (Weill Cornell Medical Center) NIMH #1R34MH095502-01
Recruiting 45 youth ages 8-20 diagnosed with OCD
Demonstrate partial response to SRI treatment; stable dose for 12 weeks

Eligible participants will receive a pre-treatment MRS scan to measure striatal glutamate levels prior to randomization

Participants randomized to receive minocycline or placebo for 12 weeks
Randomization 2:1 and stratified by age

Participants will compete a post-treatment MRS scan upon study completion or at time of discontinuation

Three months of no-cost follow-up care will be offered
Follow-up assessment administered at end of 3 months
Abnormal Functioning of Control and Reward Circuits in Unmedicated Adults with OCD

Hyperactivation of a right hemisphere frontostriatal circuit during the engagement of control on a conflict task.  
*Marsh et al, Biological Psychiatry, April 2013*

Abnormal recruitment of mesolimbic and ventral striatal circuitry during reward-based learning.  
*Marsh et al, American Journal of Psychiatry, 2015*
Untreated OCD Diagnosed with OCD: How does these overlapping circuits function earlier in development?

• **Aim 1**: To use multimodal imaging to assess the function, connectivity, and organization of control and reward circuits in untreated youth with OCD.

• **Aim 2**: To determine how these circuits change following significant reduction in symptoms.

• Unmedicated pediatric OCD (6 -17 years) and matched healthy control (HC) participants are scanned and assessed at baseline.

• OCD participants are scanned again following 16-20 weeks of CBT.

• Healthy participants are re-scanned within the same time frame.

• Circuit-based changes in the OCD group are compared to non-specific changes in HC group.

R21MH101441 (Marsh & Rynn)
Conclusions

• There are effective first line treatments & limited data to inform second line approaches.

• There is still a significant number of children and adolescents that do not respond.

• Treatment response differences most likely are due to differences in underlying anxiety pathophysiology & will require developmentally informed investigation.

• Longitudinal studies of pediatric anxiety samples with multilevel of analysis will be important to understand brain-behavior anxiety interface.