Anxiety serves a purpose
What’s “normal” anxiety?

• 70% School-aged children worry “every now and then”
  – n = 193, 8 – 13 years
• School, dying and health, social
• 2-3 days per week
• Modest interference
• Avoidance, difficult to control

Muris et al, 1998

Normative… what makes it go awry?
Anxiety as “Disorder”

- Intense
- Frequent
- Distressing
- Difficult to control
- Gets in the way
Anxiety Disorders Start EARLY

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Age 3 Assessment</th>
<th></th>
<th>Age 6 Assessment</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>95% CI</td>
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<tr>
<td>Any diagnosis(^a)</td>
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<td>27.5</td>
<td>23.5–31.9</td>
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<td>Any emotional disorder</td>
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<td>19.7</td>
<td>16.2–23.7</td>
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<tr>
<td>Any depression(^b)</td>
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<td>0.6–2.8</td>
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<tr>
<td>Major depression or dysthymia</td>
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<td>0.1–1.6</td>
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<td>Depression not otherwise specified</td>
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<td>0.9</td>
<td>0.3–2.2</td>
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<tr>
<td>Any anxiety disorder</td>
<td>89</td>
<td>19.3</td>
<td>15.9–23.1</td>
<td>72</td>
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<tr>
<td>Specific phobia</td>
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<td>9.5</td>
<td>7.2–12.5</td>
<td>38</td>
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<tr>
<td>Separation anxiety</td>
<td>26</td>
<td>5.6</td>
<td>3.9–8.1</td>
<td>22</td>
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<tr>
<td>Social phobia</td>
<td>17</td>
<td>3.7</td>
<td>2.3–5.8</td>
<td>10</td>
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<tr>
<td>Generalized anxiety disorder(^b)</td>
<td>18</td>
<td>3.9</td>
<td>2.5–6.1</td>
<td>7</td>
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<tr>
<td>Agoraphobia</td>
<td>15</td>
<td>3.2</td>
<td>2.0–5.3</td>
<td>8</td>
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<tr>
<td>Selective mutism</td>
<td>7</td>
<td>1.5</td>
<td>0.7–3.1</td>
<td>3</td>
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<tr>
<td>Any behavioral disorder</td>
<td>51</td>
<td>11.0</td>
<td>8.4–14.3</td>
<td>57</td>
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<tr>
<td>ADHD(^b)</td>
<td>11</td>
<td>2.4</td>
<td>1.3–4.2</td>
<td>25</td>
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<tr>
<td>Oppositional defiant disorder</td>
<td>47</td>
<td>10.2</td>
<td>7.7–13.3</td>
<td>41</td>
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<tr>
<td>Two or more diagnoses</td>
<td>42</td>
<td>9.1</td>
<td>6.8–12.1</td>
<td>41</td>
</tr>
</tbody>
</table>
Anxiety: normal to disorder

Developmental Continuum

<table>
<thead>
<tr>
<th>Age*</th>
<th>Normative Development</th>
<th>Anxiety Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-school</td>
<td>imaginary, objects/situations</td>
<td>specific phobias, separation anxiety</td>
</tr>
<tr>
<td>Grade School</td>
<td>health/harm, competence</td>
<td>GAD, OCD</td>
</tr>
<tr>
<td>Adolescence</td>
<td>social adequacy and performance</td>
<td>GAD, Social Phobia, Panic</td>
</tr>
</tbody>
</table>

*More common in girls than boys before and after puberty
Anxiety as disorder: COMMON

• Most common psychiatric illness of childhood
  – Community sample (n = 10,123; 13 – 17 years): 32%
    • 1 in 3! (Merikangas et al, 2010)

• Among anxiety disorders
  – SAD, GAD, and specific phobia most common: 5% to 10% each
  – Social phobia, agoraphobia, panic disorder, and OCD less common: 1% to 3% each

• More common than asthma, diabetes, cardiovascular, cancer, AIDS
Comorbidity is the Rule

• Other anxiety disorders
  – OCD: 50% with comorbid anxiety (Ivarsson et al, 2008)
  – SAD, Social Phobia, GAD: 36% all 3, 43% any 2
    • SAD (3%), SoPho (11%), GAD alone (7%) CAMS, n=488

• Mood Disorders: depression up to 69%

• Externalizing disorders: 7 to 39%
  – SAD/SoPho/GAD: 30% (CAMS)
  – OCD: 25-50% (POTS; Geller et al, 2002; ECA, Karno et al, 1988)

• ↑ Comorbidity → ↑ impairment, harder to treat

• Explanations for high comorbidity
  – Common etiology? Overlapping criteria? Correlated risk factors? (e.g., AD ↑ 3-4x if MDD)
Natural course?

• Prevalence in youth similar to prevalence in adults
  – Suggests most anxiety and depression emerges before adulthood
  – Justifies early intervention
  – However, prospective studies show that most childhood anxiety disorders remit by follow-up

• In retrospective studies, 50% of adults with anxiety or depressive disorders have a history of childhood anxiety disorder
Presentation predicts prognosis

- Comorbid anxiety at 14-16 years increases risk for persistent anxiety in young adulthood
  - No AD $\rightarrow$ 17.4%, 1AD $\rightarrow$ 28.8%, 2AD $\rightarrow$ 43.7, 3AD $\rightarrow$ 60.0%
- Recurrent internalizing sxs in childhood predict adult mental disorder
  - Two episodes $\rightarrow$ 70%
  - Single episode $\rightarrow$25%
- Childhood anxiety disorders may be more stable in girls
Predictor: Family Interactions

- Parents of anxious children are more likely than parents of nonanxious youth to reciprocate child avoidance responses, provide negative feedback, and be more restrictive towards their children.
- The interaction styles of the parents are likely to exacerbate anxious and avoidant behaviors in their children.
Younger Age at Intervention (CBT) $\rightarrow$ Better Response

Better response in younger patients INDEPENDENT from:
- comorbidity
- duration of illness

Olatunji et al, 2013
Which anxiety disorder is it?

• May impact prognosis/treatment
  – Social phobia: more pernicious course
  – GAD: waxes and wanes with MDD
  – CBT
  – Secondary medication interventions
• DSM distinctions define our literature to date
• BUT…….Research Domain Criteria
  – NIMH questions whether DSM tradition matters after all
RDoC Approach: Anxiety Symptoms and Anxiety–Related Diagnoses

• Specific Fear: Separation Anxiety Disorder, Selective Mutism, Social Phobia, Specific Phobia, Agoraphobia, Panic Disorder, Hypochondriasis

• Repetitive worries, thoughts, & behaviors: Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, (Distress) Generalized Anxiety Disorder

• Response to stress: Adjustment Disorder, Acute Stress Disorder, PTSD
DSM-5 Anxiety Disorders

- Separation Anxiety Disorder
- *Selective Mutism*
- Specific Phobia
- Agoraphobia
- Social Anxiety Disorder (Social Phobia)
- Panic Disorder
- Generalized Anxiety Disorder
- Substance/Medication-Induced Anxiety Disorder
- Anxiety Disorder Due to Another Medical Condition
- Other Specified Anxiety Disorder
- Unspecified Anxiety Disorder
DSM-5 Obsessive-Compulsive & Related Disorders

- Obsessive-Compulsive Disorder
- Body Dysmorphic Disorder
- Hoarding Disorder
- Trichotillomania (Hair-Pulling) Disorder
- Excoriation (Skin-Picking) Disorder
- Substance/Medication-Induced Obsessive-Compulsive & Related Disorder
- Obsessive-Compulsive & Related Disorder due to Another Medical Condition
- Other Specified Obsessive-Compulsive & Related Disorder
- Unspecified Obsessive-Compulsive & Related Disorder
DSM-5 Trauma- & Stressor-Related Disorders

- Reactive Attachment Disorder
- Disinhibited Social Engagement Disorder
- Posttraumatic Stress Disorder
- Acute Stress Disorder
- Adjustment Disorders
- Other Specified Trauma- and Stressor-Related Disorder
- Unspecified Trauma- and Stressor-Related Disorder
Anxiety Disorders

GAD, Separation, Social Phobia, Specific Phobia, Selective Mutism, Panic, Agoraphobia
Generalized Anxiety

17-year-old Andy is a high achiever. He gets straight As and captains the track team, but worries about grades, if he will get into college, and if he treats his team mates fairly. He finds these worries exhausting, and often experiences muscle tension and fatigue. He feels guilty that he often "snaps" at family members when he is trying to concentrate on his homework.
Generalized Anxiety Disorder
(formerly Overanxious Disorder)

- Characterized by excessive anxiety and worry along with other symptoms that occur more days than not for at least 6 months
- Person finds it difficult to control the worry
- Note: only 1 associated symptom is required in children (restlessness, easily fatigued, difficulty concentrating, irritability, muscle tension, sleep disturbance)
Differentiating GAD vs. OCD

- How far-fetched, unrealistic
- Is there a trigger?
- Associated compulsions

Comer et al, 2004
Separation Anxiety

9-year-old Sally refused to go to school after Thanksgiving break. She stays awake almost all night worrying about going to school. Before school, she cries and screams that she cannot go. She complains of headaches, stomachaches, and vomiting. If she attends school, she is less anxious until bedtime.
Separation Anxiety Disorder

- Developmentally inappropriate*, excessive*, recurrent fear of separation from parent
  - Worry that harm may befall loved one, or that untoward event will lead to separation
  - Reluctance to leave parent for school, elsewhere, sleeping alone, or home alone
  - Nightmares of separation
  - Somatic complaints at separation
- 4 weeks duration
- Impaired academic, social, emotional functioning
SAD Epidemiology

- Prevalence: 3 - 4%
- Early onset: 7 years, down to preschool
- Manifestation varies with age
- Course
  - Waxing and waning
  - School refusal following a period at home
- Comorbidities (50% anxiety, 30% depression)
- Differential
  - Pure anxious school refusal – SAD & depression
  - Pure truancy – ODD, CD & depression
Social Anxiety

16 year-old Julie worries what others think of her. She spends hours before school getting ready. With new peers, she blushing and feels that her mind “goes blank”. She is an excellent tennis player, but did not try out for the high school team.

She has begun to skip speech class, preferring to sit alone in her car in the school parking lot.
Social Anxiety Disorder

- Marked, persistent fear of social or performance situations with exposure to unfamiliar people or to possible scrutiny
- Fears of embarrassing self
- Exposure to feared social situation provokes anxiety, sometimes a “situationally-bound” panic attack
- Social situations are avoided or endured with intense anxiety or distress
- Specify if Generalized: the fears include most social situations
Social Phobia in Children

- Evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings.
- Anxiety may be expressed as crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.
- Children may not recognize that the fear is excessive or unreasonable.
- Unlike adults, children usually do not have the option of avoiding feared situations altogether and may be unable to identify the nature of their anxiety.
Feared Situations

**Children**
- Reading aloud in class
- Athletic or musical performance
- Joining/starting a conversation
- Speaking to adults
- Writing on a blackboard

**Adolescents**
- Informal speaking / interactions
- Formal speaking / interactions
- Assertion/conflict
- Being observed
- Offending others
- Physical appearance
Social Phobia Epidemiology

- Older age of onset: 13 years
- Prevalence: 1-7%
- Chronic course
- Increased risk for other anxiety disorders, depression and substance abuse
- Continuity into adulthood
Specific Phobia

Bobby is a 6 year old boy who stays inside most every day to avoid bugs and, when he has to go outside, he will cover his head with his blankie. The fear of bugs is “ruining Bobby’s summer” because he will not go out to play with his siblings or neighborhood friends.
Specific Phobia
(formerly Simple Phobia)

- Characterized by marked fear or anxiety about a specific object or situation
- Note: in children the fear may be expressed by crying, tantrums, freezing, or clinging
- Exposure to the phobic stimulus almost invariably provokes an immediate anxiety response, which may take the form of a situationally predisposed panic attack
- The phobic object or situation is avoided or else endured with intense anxiety or distress
Types of Specific Phobias

- Animal Type: insects and other animals
- Natural Environment Type: storms, water, heights generally has a childhood onset
- Blood-injection-injury: highly familial and is often characterized by a strong vasovagal response
Types of Specific Phobias

- Situational Type:
  public transportation, tunnels, bridges, elevators, flying, driving, or enclosed space
  bimodal distribution in age at onset

- Other Type:
  situations associated with choking or vomiting; children’s fears of loud sounds or costumed characters
Panic Disorder

13 year old George was playing hockey when he experienced a sudden episode of dizziness, heart racing, and numbness. His parents took him to the ER, but no medical problems were found. George is terrified that he will have another attack. He now leaves the ice during games due to fear that his heart is beating too fast and he might “lose control”.
Panic Attack

A discrete period of intense fear or discomfort, in which 4 or more of the following symptoms developed abruptly and reached a peak within 10 minutes:

1. palpitations or accelerated heart rate
2. sweating
3. trembling or shaking
4. sensations of shortness of breath
5. feeling of choking
Panic Attack

(6) chest pain or discomfort
(7) nausea or abdominal distress
(8) feeling dizzy, unsteady, lightheaded, or faint
(9) derealization or depersonalization
(10) fear of losing control or going crazy
(11) fear of dying
(12) paresthesias
(13) chills or hot flushes
Panic Disorder

- Recurrent unexpected panic attacks associated with
  (1) Persistent concern about having additional attacks
  (2) Worry about the implications of the attack
  (3) A significant change in behavior related to the attacks
- Median onset: 24 years, 5% prevalence
- Often preceded by childhood SAD
- Physiologic symptoms occur in context of other disorder (but not focus of anxiety)
Agoraphobia

- Marked fear or anxiety about 2 or more of the following 5 situations: public transportation, open spaces, enclosed places, standing in line or being in a crowd, being outside of the home alone
- Agoraphobia situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety
Selective Mutism
(formerly Elective Mutism)

- Consistent failure to speak in specific social situations in which there is an expectation for speaking despite speaking in other settings.

- Disturbance interferes with educational or occupational achievement or with social communication.

- Duration of disturbance is at least 1 month and is not limited to the first month of school.
Selective Mutism

- Failure to speak is not better accounted for by a lack of knowledge of, or comfort with, the spoken language required in the social situation
- Disturbance is not better accounted for by a communication disorder and does not occur exclusively during the course of autism spectrum disorder, schizophrenia, or another psychotic disorder
- Now classified as an anxiety disorder in DSM-5
Selective Mutism
(Muris & Ollendick, *Clin Child Fam Psychol Rev* 2015; 18:151-169)

- Aphasia voluntaria (Kaussmaul, 1877)
- SM is rare, accounting for <1% of all patients seen in psychiatric settings (Carlson et al., 1994)
- Incidence of SM ranges from 0.18% to 2.0%
- SM is 1.5 to 2.5 times more common in girls
Selective Mutism
(Muris & Ollendick, *Clin Child Fam Psychol Rev* 2015; 18:151-169)

- Children with SM speak significantly later than non-clinical controls (Kolvin & Fundudis, 1981)
- Between 11% and 50% also have a communication disorder (Kristensen, 2000)
- Some have a more general developmental delay, with coordination disorder, elimination disorder, mild MR, or ASD (Kristensen, 2000)
- Behavioral inhibition may be a key factor in the etiology of SM in most affected children
- Frequent family history of shyness, SM, or anxiety disorder
Treatment
## Placebo-Controlled Pharmacotherapy Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Demographics</th>
<th>Diagnoses</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black and Uhde, 1994 [rdb]</td>
<td>Fluoxetine (12–27 mg/d)</td>
<td>$N = 15$, 6–11 y.o.</td>
<td>SM plus SoP or AD</td>
<td>Fluoxetine &gt; PLC</td>
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<tr>
<td>RUPP, 2001 [rct]</td>
<td>Fluvoxamine (50–250 mg/d child, max 300 mg/d adolescent)</td>
<td>$N = 128$, 6–17 y.o.</td>
<td>SoP, SAD, GAD</td>
<td>Fluvoxamine &gt; PLC</td>
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<tr>
<td>Rynn et al., 2002 [rdb]</td>
<td>Sertraline (50 mg/d)</td>
<td>$N = 22$, 5–17 y.o.</td>
<td>GAD</td>
<td>Sertraline &gt; PLC</td>
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<tr>
<td>Birmaher et al., 2003 [rdb]</td>
<td>Fluoxetine (20 mg/d)</td>
<td>$N = 74$, 7–17 y.o.</td>
<td>GAD, SoP</td>
<td>Fluoxetine &gt; PLC</td>
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<tr>
<td>Wagner et al., 2004 [rdb]</td>
<td>Paroxetine (10–50 mg/d)</td>
<td>$N = 322$, 8–17 y.o.</td>
<td>SoP</td>
<td>Paroxetine &gt; PLC</td>
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<td><strong>Other antidepressants</strong></td>
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<tr>
<td>Gittleman-Klein and Klein, 1971 [rdb]</td>
<td>Imipramine (100–200 mg/d)</td>
<td>$N = 35$, 6–14 y.o.</td>
<td>School phobia with anxiety disorders</td>
<td>Imipramine &gt; PLC</td>
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<tr>
<td>Berney et al., 1981 [rdb]</td>
<td>Clomipramine (40–75 mg/d)</td>
<td>$N = 51$, 9–14 y.o.</td>
<td>School refusal</td>
<td>Clomipramine = PLC</td>
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<tr>
<td>Klein et al., 1992 [rdb]</td>
<td>Imipramine (75–275 mg/d)</td>
<td>$N = 21$, 6–15 y.o.</td>
<td>SAD with or without school phobia</td>
<td>Imipramine = PLC</td>
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<tr>
<td><strong>Benzodiazepines</strong></td>
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<tr>
<td>Bernstein et al., 1990 [rdb]</td>
<td>Alprazolam (0.75–4.0 mg/d) vs. Imipramine (50–175 mg/d)</td>
<td>$N = 24$, 7–18 y.o.</td>
<td>School refusal, SAD</td>
<td>Alprazolam = Imipramine = PLC</td>
</tr>
<tr>
<td>Simeon et al., 1992 [rdb]</td>
<td>Alprazolam (0.5–3.5 mg/d)</td>
<td>$N = 30$, 8–17 y.o.</td>
<td>OAD, AD</td>
<td>Alprazolam = PLC</td>
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<tr>
<td>Graae et al., 1994 [rdb]</td>
<td>Clonazepam (0.5–2.0 mg/d)</td>
<td>$N = 15$, 7–13 y.o.</td>
<td>SAD</td>
<td>Clonazepam = PLC</td>
</tr>
</tbody>
</table>

*Note: SSRIs = selective serotonin reuptake inhibitors; y.o. = years old; SM = selective mutism; SoP = social phobia; AD = avoidant disorder; PLC = placebo; SAD = separation anxiety disorder; GAD = generalized anxiety disorder; OAD = overanxious disorder.*
Fluvoxamine Treatment of Anxiety Disorders
(RUPP, *NEJM* 2001;344:1279-1285)

- 128 children (6-17 years old) with a diagnosis of SAD, GAD, or social phobia
- 63 assigned to fluvoxamine, 65 to placebo
- Dose ↑ by ~50 mg/wk to maximum of 300 mg/day in adolescents and 250 mg/day in those less than 12 years old
- 76% on fluvoxamine responded compared to 19% on placebo
- Abdominal distress & increased motor activity were more frequent in the fluvoxamine group
Child and Adolescent Anxiety Multimodal Study (CAMS)

COMB > CBT = SRT > PBO

Walkup et al, 2009
CAMS

- CBT = Coping Cat
  - 14-16 sessions
    - 1-6 psychoed, relaxation, cognitive restructuring
    - 7-14 exposure
CAMS

- Sertaline dosing 25-200 mg/day
- Mean dose: 150 mg/day
- Flexible titration schedule
  - Week 1 25 mg/day
  - Weeks 2-3 50 mg/day
  - Week 4 100 mg/day
  - Week 6 150 mg/day
  - Week 8 200 mg/day
CAMS: Safety Profile

No suicides in any group

Walkup et al, 2009
General Treatment Reccs (CAMS)

• CBT, CBT/SSRI, SSRI alone all may be recommended
• Consider:
  – Family treatment preferences
  – Treatment availability
  – Cost, and time burden

Walkup et al, 2009
SSRIs Effective

Even better effect of ADs for pediatric anxiety than for pediatric depression (JAMA, Bridge et al, 2007)

– Non-OCD Anxiety: 69% SSRI vs. 39% pbo (NNT = 3)
– OCD: 52% SSRI vs. 32 % pbo (NNT = 6)
– MDD: 61% SSRI vs. 50% pbo (NNT = 10)
SSRIs: Equal?

• Yes…..across the population
• No……for individual patients
  – 71% of fluvoxamine non-responders, respond after switch to fluoxetine (RUPP)
  – Side effects
    • Nausea, diarrhea, sedation, headache
    • Activation in younger kids
      – Motor disinhibition
      – Responsive to lowering dose
      – Med side effect, NOT mania
SSRI Safety

• Meta-analysis
  – OCD: SI/SA 1% AD vs 5% pbo (NNH = 200)
  – Non-OCD Anxiety: 1 % AD vs vs 0.2 pbo (NNH = 143)
  – MDD: SI/SA 3% AD vs. 2% pbo (NNH = 112)

• CAMS, POTS
  – No suicide or homicide attempts
  – <20 instances of emergent SI, and no apparent pattern with meds vs. placebo
  – TADS study suggests CBT may be protective
Adverse Events (POTS)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Sertraline (n = 28)</th>
<th>Combined Treatment (n = 28)</th>
<th>Placebo (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased appetite</td>
<td>5 (18)</td>
<td>4 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (21)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Enuresis</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Motor overactivity</td>
<td>1 (4)</td>
<td>6 (21)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (25)</td>
<td>5 (18)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Stomachache</td>
<td>8 (29)</td>
<td>4 (14)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

*Data are for events occurring in at least 5% of sertraline-treated patients and with an incidence of at least 2 times that seen in placebo-treated patients in either the sertraline-alone or the combined-treatment group. Medication-related adverse events were not recorded for patients treated with cognitive-behavior therapy alone.*

Insomnia
Drowsiness
Leg spasms
Dry mouth

No treatment-emergent suicidal ideation
Motor activity versus Mania?

• Subsample of RUPP (fluvoxamine)
• Activation, typically 1 month from initiation
  – ↑ activity level, impulsivity, insomnia, or disinhibition without manic symptoms (NO euphoria, NO decreased need sleep
  – more animated, talkative, saying things wouldn’t normally say, hyper
  – 10/22 fluvoxamine vs 1/23 placebo
• Onset Younger children
• Responsive to lowering of dose

Reinblatt et al, 2009
Other Medications

- Venlafaxine (SoPho)
  - Suicidality “signal”, height, weight, BP, pulse, cholesterol
- Benzodiazepines (SAD, SoPho, SoPho)
- Buspirone (SAD, SoPho, SoPho)
- Lamictal
Tricyclic Antidepressant Treatment of SAD

- Four controlled trials of TCA treatment with equivocal results
- TCAs are less well tolerated than SSRIs
- Side-effects include mouth dryness, constipation, blurred vision, urinary retention, sedation, weight gain, dizziness, and cardiac conduction delay
- Clomipramine may be more effective than other TCAs for anxiety and mood disorders in youth
Part II.

Neuroscience-guided development of novel treatments
Attention Bias to Threat in Anxiety

Threat probe RT – neutral probe RT = attention bias
Study Design

• Pre-study clinical screen
• Pre-study attention bias assessment
• Primary outcome measures
  – total anxiety symptom counts as reported by parents and children
  – clinician severity ratings on the Anxiety Disorders Interview Schedule for DSM-IV–
• Secondary outcomes
  – clinical diagnostic status, SCARED, CDI
ABM vs Pbo Trainings

- Weekly training sessions x 4-weeks
  - 480 dot-probe trials for each session
- ABM: angry-neutral pairs w/ targets always at location of neutral face
- Pbo1: angry-neutral stimuli but w/ targets appearing equal probability in the angry and neutral locations.
- Pbo2: neutral-neutral condition, neutral-neutral face pairs w/ targets equal probability in each hemifield (non-affective attention control)
Anxiety Sx Counts, Severity from pre-to post-training for ABM vs control groups
3. Of remaining 71, 31 have NO attn bias to threat (i.e., ≤ 8 msec slower RT for targets on side of threatening face)

Training AWAY from threat
In those who don’t exhibit Attn bias to it my have risk?

1. 91 screen out: PTSD, OCD, MDD psychotropic learning and/or conduct problems Concurrent psychotherapy;

2. 24 decline

8-14 yrs

Randomly Assigned (N=40)

Excluded (N=146)
- Met exclusion criteria 1-4 (N=91)
- Met exclusion criterion 5 (N=31)
- Declined participation (N=24)

Assessed for Eligibility (N=186)

Allocated to Attention Bias Modification Condition (N=15)
- Discontinued (N=0)
- Analyzed (N=15)

Allocated to Placebo Condition (N=15)
- Discontinued (N=0)
- Analyzed (N=15)

Allocated to Neutral-Neutral Condition (N=10)
- Discontinued (N=0)
- Analyzed (N=10)
Caveats

• Threat-related attention bias is reliably observed in as a group-mean effect in anxiety patients, approximately one-half of clinically anxious individuals do not show an attention bias toward threat!
  – Pretty unreliable, so how meaningful?
  – Subtypes of anxiety?
  – Developmental effect?
Other models of anxiety

Impoverished or Excessive Recruitment of Prefrontal Control?
Pediatric Anxiety: Reduced Prefrontal control?

Passive Viewing: Reduced

Angry: Anx > HC

Amygdala - VLPFC: Anx < HC

Reduced PFC: imbalance?
Imbalance of PFC-amygdala → amygdala-based responsivity to threat predominates

Monk et al, 2008
Pediatric Anxiety: Increased PFC?

*Increased PFC: ACT?*

“Attentional Control Theory”

Reduced efficiency → PFC hyperax reflects compensatory effort to maintain performance

*McClure et al, 2008*
Impoverished PFC Recruitment to COGNITIVE task

Cognitive Interference: Low – High perceptual load (i.e., Incong – Cong)

Impaired PFC recruitment when primary task does not fully occupy attentional resources.

Bishop et al, 2009
Peripubertal Imbalance: Threat reactivity/regulatory control

Critical period of vulnerability for anxiety

Ernst et al, 2007; Casey et al, 2011
Peripubertal increase in amygdala reactivity to threat
Gradual development of cortical engagement for regulatory control

Fitzgerald et al, 2009

Durston et al, 2006
Increasing rates clinically significant anxiety (i.e., disorder) at transition from late childhood to early adolescence
Decreasing levels of normative anxiety at transition from late childhood to early adolescence
Divergent trajectories of anxiety

Differential patterns of development in threat reactivity: regulatory control?
Threat reactivity: regulatory control $\rightarrow$ anxiety

- More anxiety
- Less anxiety

Limbic reactivity to threat

Cortical circuitry for regulatory control
Study Measures: Clinical assessment + fMRI

**EFAT**
Explicit (deliberative) emotion processing:
Limbic reactivity to threat and regulatory control

**EFSAT**
Implicit emotion processing:
Limbic reactivity to threat

**MSIT**
Cognitive control
Limbic reactivity to threat
Regulatory control
Preliminary Data
Greater limbic reactivity to threat, lesser cortical engagement for regulatory control in anxious vs. health youth

Explicit
Implicit

Emotion Processing

Differential development of threat reactivity (amygdala) and regulatory control (dACC) in anxious vs. healthy youth
Greater engagement of reg control circuitry drives anxiety down

- dACC and LPFC activation to performance monitoring inversely correlate with anxiety severity monitoring
Aim 1: cross-sectional

Non-Treatment seeking
Community controls
(n = 60)

Aim 2: longitudinal

Baseline
(n = 60)
4 mos
(n = 57)
12 mos
(n = 54)
24 mos
(n = 54)

Aim 3: translational

Baseline
(n = 60)
4 mos
(n = 57)
12 mos
(n = 54)
24 mos
(n = 54)
Thank you!