

# Pediatric Anxiety Disorders

John T. Walkup, MD  
Pritzker Department of Psychiatry  
& Behavioral Health



# Disclosures

Source	Advisory Board	Research Support	Honoraria	Royalties
Anxiety Disorders Association of America	<b>X</b>			
Guilford Press				<b>X</b>
Oxford University Press				<b>X</b>
Wolters Kluwer				<b>X</b>
Tourette Association		<b>X</b>	<b>X</b>	
Trichotillomania Learning Center	<b>X</b>			

# Objectives

At the conclusion of this presentation the participant will:

1. define the barriers to identify and treat the childhood onset anxiety disorders.
2. discuss the suicidal behavior and mania risk of antidepressants in children and adolescents
3. discuss the role of family factors in the successful treatment of children with anxiety disorders.
4. discuss the relative ages of onset for the major psychiatric problems in children and adolescents

# Overview

- We have very good treatments for the childhood anxiety disorders
- Medications (antidepressants) and CBT are effective,
- The evidence base is deep, yet.. anxiety disorders are under diagnosed and under treated
  
- Thus, the identification of anxiety and effective treatment requires special knowledge and attitudes which is the focus of today presentation
  
- So what is going on?
  - The Fundamentals
  - Suicide and mania hot topics

# Introduction -

- The Fundamentals
  - The Anxiety Disorders
  - Effective medications
  - Adverse effects
  - Integration with evidenced based psychotherapy
- Hot topics

# The Anxiety Disorders



# ‘Anxiety disorders aren’t just bad normal anxiety’

- Dimensional vs categorical view of anxiety
- Normal anxiety
  - Predictable triggers (they make everyone anxious)
  - Proportionate reaction
  - Can happen anytime in development
  - Can be severe and chronic
- Pathological
  - Triggers are normative experiences
  - Excessive, disproportionate reaction
  - Predictable age of onset – SAD, SoAD, GAD ages 6-12;
    - Panic – late adolescence
  - Highly stereotyped across anxious individuals

# Specific Phobia

- Animals, insects etc.
- Environmental - thunder, water, heights
- Blood, injection or other suspected painful event
- Situational - tunnels, bridges, elevators
- 70% have another anxiety disorder



# Separation Anxiety Disorder

- Excessive concern regarding separation from home or from attachment figures
  - Bad things happening to parent and or child
  - Cannot be alone
  - Avoidance S, M, L, XL, XXL
  - Difficulty falling asleep or sleeping with loved ones
  - Physical aches and pains
  - Accommodation by adults S, M, L, XL, XXL
- Impairment or distress
- Can diagnose over age 18 years
- Duration of 6 months

# Generalized Anxiety Disorder

- Excessive worry and apprehensiveness
  - Restless, keyed-up or on edge.
  - Fatigued at end of school day
  - Concentration problems “choking on tests”
  - Sleep problems (falling asleep)
  - Tense and irritable
- Unable to control the worry
- Impairment or distress

# Social Anxiety Disorder

- Fear of social or performance situations
  - Specific
  - Generalized
    - “slow to warm up” socially
    - anxious about being with other people
    - reticent to talk in social settings (short answers, soft spoken)
    - self-conscious and anticipate being embarrassed
    - anticipate that others will judge them
    - worry before an event where other people will be
    - avoid places where there are other people
    - blush, sweat, or tremble around other people
    - feel nauseous or sick to their stomach when with other people
    - depersonalize or derealize when with other people

# Selective Mutism

- Young children
  - Ability to speak
  - Not speaking in social situations
  - Not part of another disorder
- 
- Mild variant (single words, soft spoken)

# Acute Stress Disorder

- True stressful event – life threatening
- Re-experiencing the event
- Avoidance and numbing
- Increased arousal
- **Negative thoughts, feelings and moods**
- Time limited

# Post-traumatic Stress Disorder

- True stressful event – life threatening
- Re-experiencing the event
- Avoidance and numbing
- Increased arousal
- **Negative thoughts, feelings and moods**
- Risks for enduring symptoms
  - Pre-existing or genetic risk for mental disorder
  - Proximity
  - Post-traumatic environment
  - Stuck in unhelpful narrative about trauma

# Panic Disorder

- Attacks of anxiety (Physical Symptoms)
  - ↑ Heart rate, pounding heart, palpitations
  - Hyperventilation, shortness of breath
  - Choking sensation
  - Chest discomfort or pain
  - Abdominal pain
  - Some psychological symptoms
- Worry about the next one
- Avoidance behavior related to the attacks
- Agoraphobia....

# Obsessive Compulsive Disorder

- Prominent obsessions or compulsions
  - Dirt, germs, or other contamination
  - Ordering and arranging
  - Checking
  - Repetitive acts
- Impairing or time consuming



# Infection-triggered Childhood Onset Conditions

- Neuropsychiatric disorders associated\* with infections
  - PANDAS (Strep)
  - PANS (acute onset with other infectious agents)

# Characteristics Common to All Anxiety Disorders

- Hypervigilance
- Reactivity to novel situations
- Biased interpretation of experiences as threatening
  
- Avoidance coping
- Catastrophic reactions
- Parental accommodation
- Midline physical symptoms

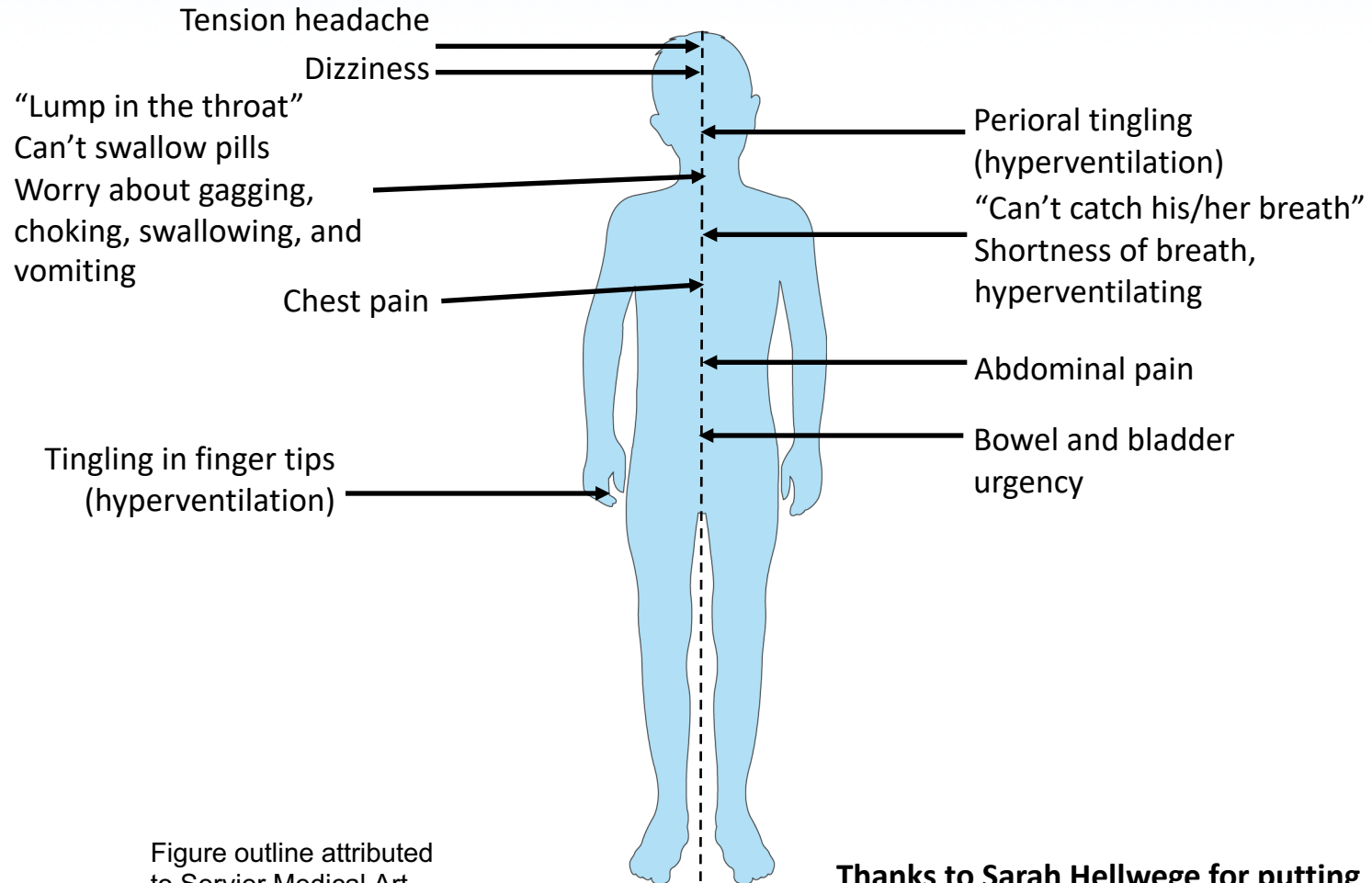


Figure outline attributed to Servier Medical Art, modified by addition of anxiety symptoms and midline.

**Thanks to Sarah Hellwege for putting the slide together**

# Anxiety is not a great term

- Home sickness (separation)
- “Worry worts” (generalized)
- Self-conscious or shyness (social anx)
- Excessive interpersonal sensitivity (all)
- Fear (all)
- Apprehension (all)
- Dread (generalized)
- Worry (all)
- “Stressed out “

# Ages of Onset Risk

- ASDs – 0-3 years or later for mild
- ADHD - 4-7 or later for mild, but differential is broader
- **Anxiety – 6-12 years**
- Depression – 13-16 years
- Bipolar and psychosis - > 16 years
- **Panic Disorder 16-25 years**
- Disruptive behavior – almost anytime

# Assessment Strategies

- Global scales with anxiety subscales
  - Child Behavior Checklist
  - Behavioral Assessment System for Children
- MASC
- SCARED
  - Child version
    - Search on "U Pitt SCARED"
  - Parent on child version
    - Search on U Pitt SCARED
  - Adult SCAARED

# Epidemiology

- Very common up to 8-10% of kids
- Up to 25% of adults
- Under diagnosed
- Under treated
- Probably the most common childhood disorder and **the** prepubertal disorder associated with changes in mood and emotion regulation

# Environment and Genetics

- Genetic vulnerability (twin studies)
- Anxiety is self-perpetuating
  - Avoidance results in temporary relief
  - Perfectionism is highly valued
- Anxiety is “contagious”
  - Parental attention to the anxious child
  - Parental support for avoidance
  - Catastrophic reactions shape relationships



Everyone has anxiety  
but no one recognizes  
it as a meaningful  
condition and clinicians  
are unlikely to take it  
seriously and treat it.

Why?



# Under-recognized and Under-treated

- Extremely common, so considered “normal”
- Very early onset, so considered a temperamental or personality trait
- Triggered affective illness, if not triggered can appear “well”
- Not considered a serious condition
- Lack of knowledge re: course of illness/impairment
- Evidence base established in 2009
- Only FDA approved med in 2015
- Advocacy/awareness efforts are a recent phenomena
- Treatment barriers
- Overlapping syndromes

# It is just a phase.....

- Anxiety Disorders begin very early
- When untreated they can evolve and impair across the lifespan
  - Childhood anxiety to Panic Disorder
  - Childhood anxiety to Depression and Bipolar Disorder
  - Childhood anxiety to complex impairment
    - Accumulated disability
    - Maladaptive behaviors
- Some symptoms meet the 'just a phase' definition

# Course of Anxiety

- Onset in childhood -“Prepubertal affective illness”
- Adolescence - symptoms + accumulated disability
  - Intense symptoms “burn out” ..... sometimes
  - Generalized anxiety
  - Poor adaptation and coping – easily flooded and overwhelmed by typical life and developmental expectations
  - **Some morph to depression**
  - School drop out (fade away)
- Young adulthood – symptoms + failure in major roles
  - Work inhibition
  - Fail to leave home or stay in college
  - Evolution into panic disorder
  - Evolution to recurrent depression and risk for bipolar disorder
  - Substance abuse

# Anxiety and Personality Disorders

- 1) Distorted thinking patterns
  - 2) Problematic emotional responses
  - 3) Over- or under-regulated impulse control [L  
SEP]
  - 4) Interpersonal difficulties
- 
- Borderline Personality Disorder
  - Avoidant Personality Disorder
  - Dependent Personality Disorder
  - Obsessive Compulsive Personality Disorder
  - Schizoid Personality Disorder

# Implications of Anxiety Course on Treatment

- Three potential treatment targets
  - Anxiety symptoms – anxiety, distress tolerance
    - CBT and Medication
  - Accumulated disability – poor adaptation and coping
    - Life skills training
  - Maladaptive behaviors – suicidal and self injurious behavior and substance misuse
    - Behavioral treatments

# Treatment Barriers

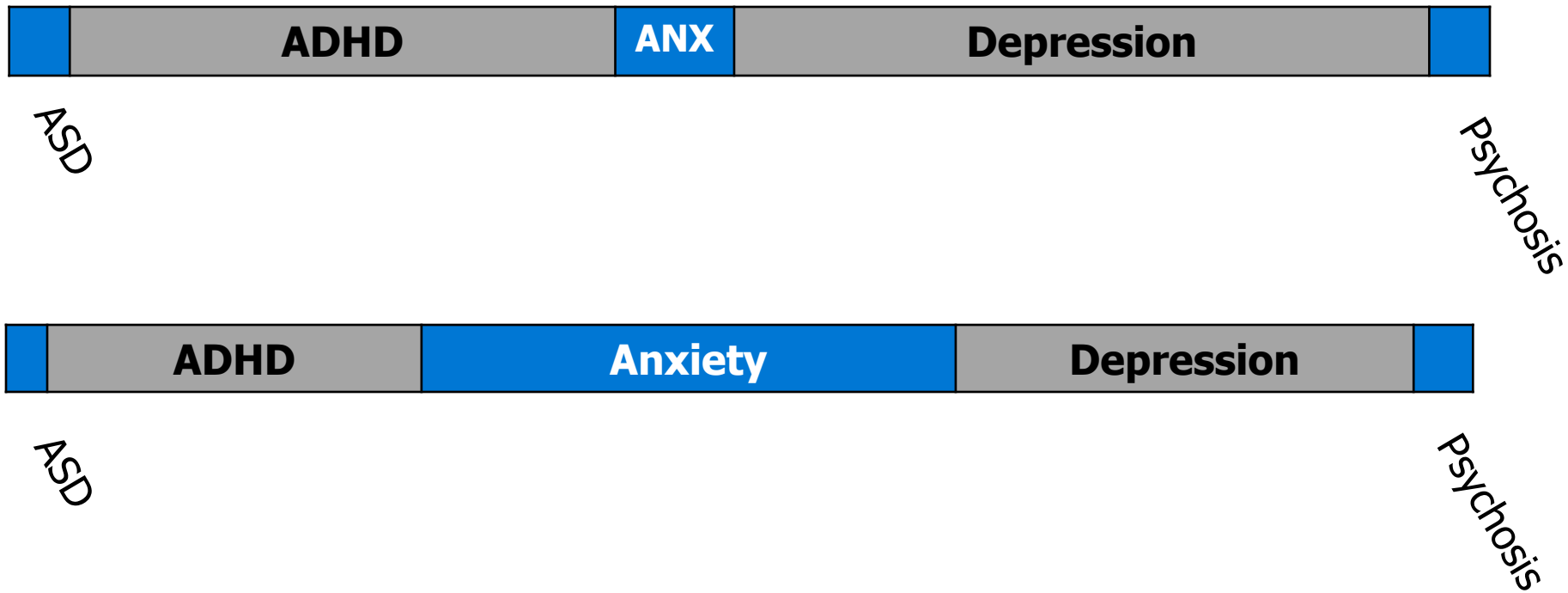
- Anxiety starts early and easily missed
- Overlapping syndromes
- Symptom patterns evolve and thus, confuse
- Fear – patients, parents, providers
- Misinformation
  - Scientific – not a serious mental health condition
  - Mass Media – trivializing by generalizing
- Stigma
  - Disorders
  - Treaters
  - Treatments

# Overlapping Syndromes

- **ASD**
- **ADHD**
- **Depression**
- **Somatic symptom disorders**
- **Personality disorders**
- **Bipolar disorder**
- **Psychosis**
  
- Medical problems



# The implication of identifying and treating the childhood anxiety disorders



# Overlapping Syndromes

- ASD
- ADHD
- Depression
- Somatic symptom disorders
- Personality disorders
- Bipolar disorder
- Psychosis
  
- **Physical symptoms**

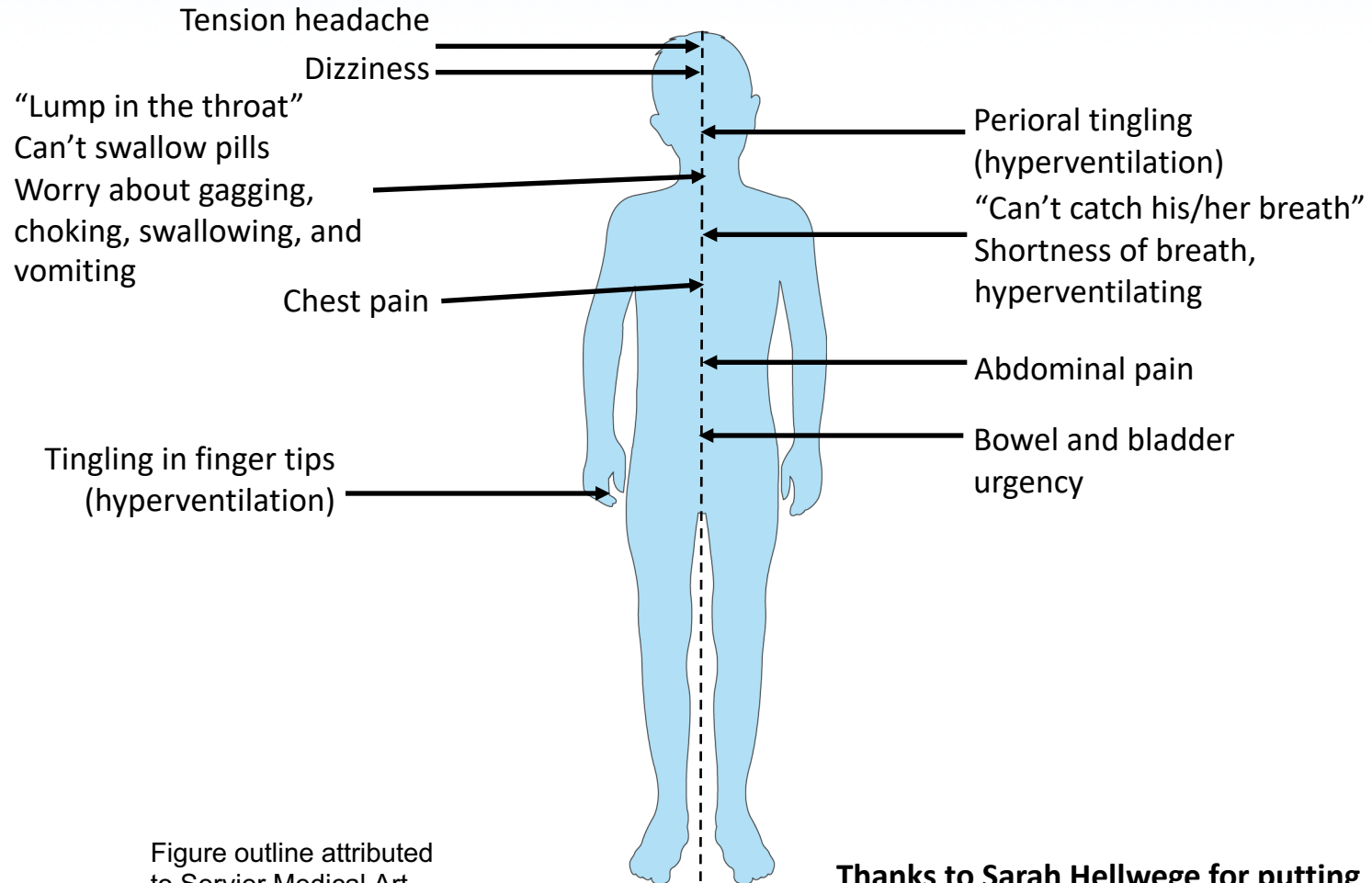


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# The Fundamentals of Anxiety Treatment

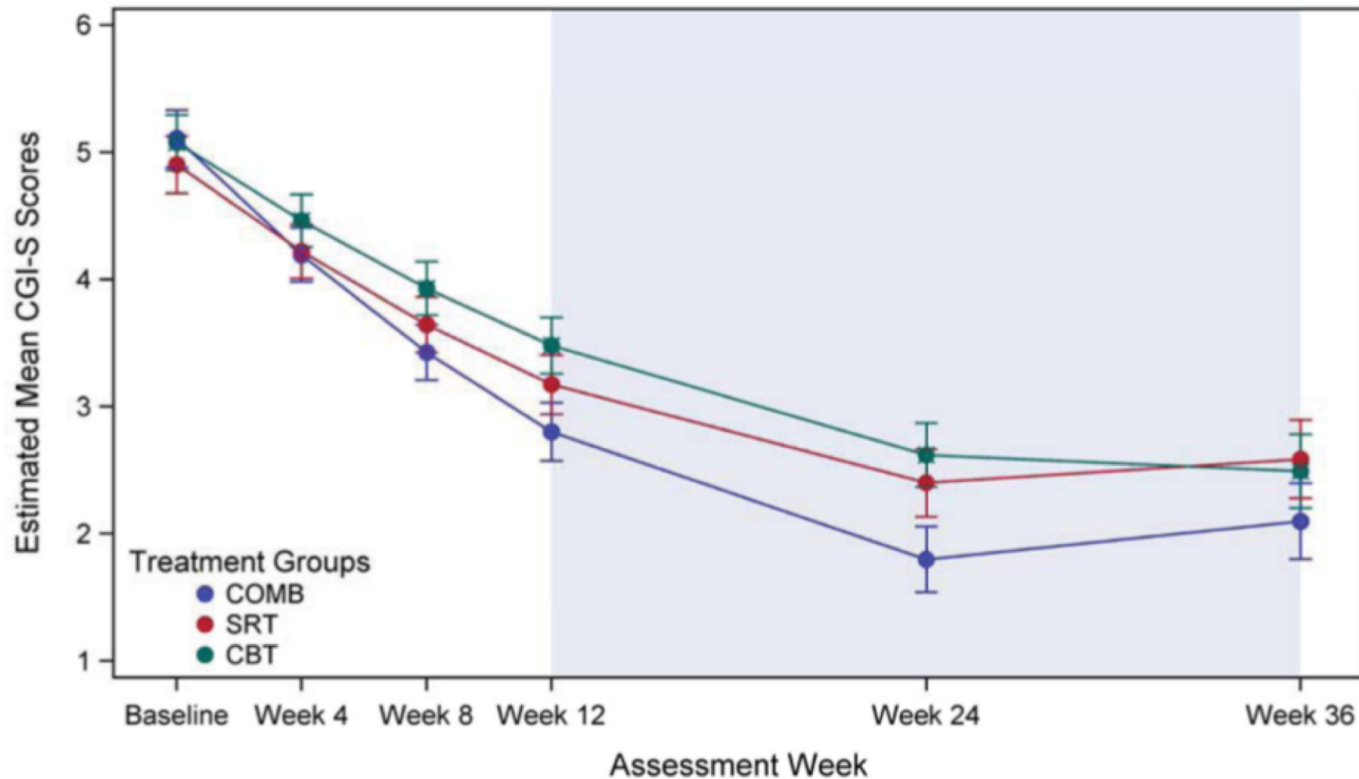
- Evidence base for children established in 2008 (Walkup et al., 2008)
  - Combination treatment most effective - 80% response rate
  - SSRIs and CBT are both effective – 55-60%
  - Placebo response rate is less than 25%
- Outcomes more clearly positive than for teen depression
- Only 1 med with FDA indication for non-OCD anxiety disorders – duloxetine (Strawn 2015)

# Antidepressant Efficacy for Non-OCD Anxiety Disorders

- SAD, GAD and SoP
  - Fluvoxamine – RUPP, 2001
  - Fluoxetine – Birmaher et al, 2003
  - CAMS – Walkup et al, 2008
- SoP
  - Paroxetine - Wagner et al, 2004
  - Fluoxetine - Beidel et al 2007
  - Venlafaxine - March et al, 2007
- GAD
  - Sertraline - Rynn et al., 2001
  - Venlafaxine, Rynn et al., 2007
  - Duloxetine, Strawn et al 2015
  - Buspirone in GAD, Strawn et al 2015 (huge placebo response)

# Long Term Treatment

- CAMS long term data
  - >80% maintained response at 24 and 36 week time points
  - Combined continue to be better than the monotherapies
  - Participants on medication pursued more concomitant psychosocial treatment than those in combined and CBT.
- CAMELS
  - 46% were in remission for a mean of 6 years
  - Those who achieved remission in the acute phase were more likely to be in remission at long term follow up
  - 48% of acute phase responders relapsed during the follow-up.
- The challenges of long term studies
- Remission rates



**FIGURE 3.**

Estimated mean scores for the Clinical Global Impressions-Severity Scale (CGI-S) by treatment group over 36 weeks. Note: Shaded area indicates follow-up period. CBT = cognitive behavior therapy; COMB = combined (CBT+sertraline) treatment; SRT = sertraline.

## Response/Remission Rates for Various Categorical Phase II Outcomes Among COMB, SRT, and CBT

Variable	COMB (N=140)	SRT (N=133)	CBT (N=139)	p-values for Pairwise Comparisons		
				COMB vs. SRT	COMB vs. CBT	SRT vs. CBT
<b>Responder (CGI-I = 1 or 2)</b>						
Week 12	80.71	54.89	59.71	<0.001	<0.001	0.419
Week 24	81.24 (71.51–90.98)	67.62 (52.78–82.45)	69.37 (57.08–81.66)	0.092	0.162	0.859
Week 36	82.69 (72.77–92.61)	70.49 (55.17–85.82)	71.54 (62.30–80.78)	0.176	0.144	0.931
<b>Excellent Response (CGI-I = 1)</b>						
Week 12	45.46 (35.50–55.41)	33.15 (24.41–41.88)	19.36 (12.69–26.04)	0.068	<0.001	0.013
Week 24	46.48 (37.94–55.03)	36.55 (25.28–47.83)	33.90 (24.55–43.25)	0.171	0.055	0.723
Week 36	47.42 (38.90–55.93)	42.57 (31.12–54.03)	41.27 (32.36–50.18)	0.506	0.331	0.864
<b>Remission - Severity (CGI-S = 1 or 2)</b>						
Week 12	65.50 (55.82–75.19)	46.14 (35.10–57.18)	35.35 (27.19–43.52)	0.011	<0.001	0.125
Week 24	64.56 (52.54–76.58)	48.78 (35.99–61.58)	44.59 (35.30–53.88)	0.010	0.012	0.609
Week 36	66.74 (54.91–78.57)	62.86 (48.39–77.34)	58.39 (48.33–68.45)	0.685	0.305	0.612
<b>Remission - Diagnosis (No ADIS SAD, SOP or GAD Diagnosis)</b>						
Week 12	69.23 (60.30–78.17)	45.71 (37.03–54.39)	46.10 (37.33–54.87)	<0.001	<0.001	0.950
Week 36	73.42 (62.49–84.36)	51.53 (42.56–60.50)	52.01 (43.51–60.50)	<0.005	<0.006	0.940



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# How many in CBT went onto meds

**TABLE 4**

Proportion of Subjects Receiving Concomitant Off-Protocol Treatment During Phase II

Type of Treatment	COMB N (%)	SRT N (%)	CBT N (%)
None	102 (72.9)	68 (51.1)	89 (64.0)
New Psychosocial Only	10 (7.1)	26 (19.6)	12 (8.6)
New Medication Only	7 (5.0)	4 (3.0)	12 (8.6)
Both New Psychosocial and New Medication	2 (1.4)	9 (6.8)	14 (10.1)
Information Missing	19 (13.6)	26 (19.6)	12 (8.6)
Total	140	133	139

49/139 Remitted

12/139 kids started Med

If your not better why wouldn't  
you explore more treatment?

# Antidepressant USA FDA Approvals

- Approved for OCD
  - Clomipramine  $\geq$  10 yrs
  - Fluvoxamine  $\geq$  8 yrs
  - Sertraline  $\geq$  6 yrs
  - Fluoxetine  $\geq$  7 yrs
- Approved for Depression
  - Fluoxetine  $\geq$  8 yrs
  - Escitalopram  $\geq$  12 yrs
- Approved for Non-OCD Anxiety
  - Duloxetine  $\geq$  7 yrs GAD

# Dosing of Antidepressants with Efficacy for Anxiety

- Use clinical trials for timing of dose changes for 'maximum safe doses'
  - Fluoxetine up to 40 mg by week 12 (TADS, 2004)
  - Fluvoxamine 100-150 mg by week 10 (RUPP, 2001)
  - Sertraline 100-150 mg by week 8 (CAMS, 2009)
  - Paroxetine 40-50 mg by week 10 (Geller, 2004)
  - Citalopram 40 mg\* (Uchida M, et al. J Clin Psychopharmacol. 2017 Jun;37(3):359-362.)
  - Escitalopram 20 mg (Wagner, 2006; Emslie, 2009)
  - Duloxetine 60-120 mg (Strawn, 2015)
- What about other meds?

# Refractory Anxiety

- Pharmacological augmentation
  - Serotonin agonists
  - Antipsychotics
  - Dopamine agonists
- Re-assess for more intensive behavioral interventions
  - Familial factors
  - Functional assessment

# Family Factors

Peris et al., 2009

- The Resistant Triad
  - High conflict
  - Low cohesion
  - High blame
- Watch for how behavior change will be accepted in the family.



# Function-Based Assessment

- Assess and address antecedents and consequences
  - Provoking experiences – triggers
  - Intrapsychic reward (+) and relief (-)
  - Interpersonal consequences
    - Positive reinforcement – active rewards
    - Negative reinforcement – escape consequences

# Types of Reinforcement and Related Treatment Options

	Positive Reinforcement	Negative Reinforcement
Internally Reinforcing	Provides gratification	Relieves distress
Interpersonally Reinforcing	Attention and support	Avoidance Accommodation

# Types of Reinforcement and Related Treatment Options

	Positive Reinforcement	Negative Reinforcement
Internally Reinforcing	Provides gratification <b>(Raise the cost)</b>	Relieves distress <b>(ERP)</b>
Interpersonally Reinforcing	Attention and support <b>(Redirect parents and others)</b>	Avoidance Accomodation <b>(Re-engage, not escape)</b>

# Antidepressants Cause Mania etc

- Activation is common **10-15%**
  - Early in course or after dose change – think diphenhydramine
  - Younger kids
  - “Minimal brain dysfunction”
- Bipolar switches uncommon **<1%** - later
- Frontal lobes symptoms at higher doses
- GI issues early
- Easy bruising and bloody noses
- Some case reports about growth

# Suicidality – Benefit/Risk

- % Difference for Efficacy
  - MDD - 11.0% = NNT of 10 (3 for NIH Studies)
  - OCD - 19.8% = NNT of 5
  - Non-OCD anxiety disorders - 37.1% = NNT of 3
- % Difference for Suicidality
  - 1-2% = NNH 50-100 (Hammad et al., 2006)
  - 0.7% = NNH 143 (Bridge et al., 2007)
    - But not for individual disorders
      - MDD - 0.9%; NNH ~100
      - OCD - 0.5%; NNH ~200
      - non-OCD anxiety disorders - 0.7% ; NNH ~140

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# Antidepressant Trials

- 2 NIMH-funded
  - Demonstrated efficacy
  - Low placebo response rates
  - Many quality indicators
- 17+ industry-funded (FDAMA)
  - Multiple sites
  - High placebo response rates
  - No quality indicators
  - FDAMA exclusivity
  - No investment in outcome

Data Source	Medication	Duration	Response Assessment	Children	Active%	Placebo %	Number of Sites & (Participants)	Exclusivity Granted Nov 2016 <sup>34</sup>
<b>NIMH Studies</b>								
<b>Emslie et al., 1997<sup>15</sup></b>	Fluoxetine	8 weeks	GGI-I	Yes	56%	<b>33%</b>	1(96)	Yes
<b>TADS, 2004<sup>9</sup></b>	Fluoxetine	12 weeks	CGI-I	No	61	<b>35</b>	13(439)*	
<b>IINDUSTRY Studies</b>								
<b>Emslie et al., 2002<sup>19</sup></b>	Fluoxetine	8 weeks	CGI-I	Yes	65	<b>53</b>	15(219)	Yes
<b>Keller et al., 2001<sup>20</sup></b>	Paroxetine	8 weeks	CGI-I	No	66	<b>48</b>	12(275)*	
<b>Berard et al., 2006<sup>21</sup></b>	Paroxetine	12 weeks	CGI-I	Yes	69	<b>57</b>	33(286)	
<b>Emslie et al., 2006<sup>22</sup></b>	Paroxetine	8 weeks	CGI-I	Yes	49	<b>46</b>	40(206)	Yes
<b>Wagner et al., 2003<sup>23</sup></b>	Sertraline	10 weeks	CDRS	Yes	69	<b>59</b>	53(376)	
<b>Wagner et al., 2004<sup>24</sup></b>	Citalopram	8 weeks	CGI-I	Yes	47	<b>45</b>	21(178)	
<b>von Knorring et al., 2006<sup>25</sup></b>	Citalopram	12 weeks	Kiddie-SADS-P	No	60	<b>61</b>	31(244)	Yes, single exclusivity for both medications
<b>Wagner et al., 2006<sup>26</sup></b>	Escitalopram	8 weeks	CGI-I	Yes	63	<b>62</b>	25(264)	
<b>Emslie et al., 2009<sup>27</sup></b>	Escitalopram	8 weeks	CGI-I	No	64	<b>53</b>	40(312)	
<b>Emslie et al., 2007<sup>28</sup></b>	Venlafaxine XR	8 weeks	CGI-I	Yes	61	<b>52</b>	50(367)	Yes
<b>Atkinson et al., 2014<sup>28</sup></b>	Duloxetine	10 weeks	CDRS	Yes	67	<b>63</b>	65 (337)*	Yes
<b>Emslie et al., 2014<sup>30</sup></b>	Duloxetine	10 weeks	ΔCDRS-R >50%	Yes	69	<b>60</b>	60 (463)*	
<b>Delbello et al., 2014<sup>31</sup></b>	Selegiline	12 weeks	CGI-I	No	59	<b>59</b>	26(308)	No
<b>CN104-141<sup>32</sup></b>	Nefazodone	8 weeks	CGI-I	No	63	<b>44</b>	15(206)	Yes
<b>CN104-187<sup>32</sup></b>	Nefazodone	8 weeks	ΔCDRS-R	Yes	>30%↓	<b>&gt;30%↓</b>	28(317)	
<b>003-045<sup>33</sup></b>	Mirtazapine	8 weeks	CDRS-R Raw Score	Yes	No between group difference		15/17 (126/153)* *	No



‘We don’t have long term safety data...’

- Long-term comparison of affected individuals on drug vs placebo. Or....

‘We don’t know what treatment is best for whom’

- Need very large samples to find moderators
- When treatments are good for a respectable sampling frame you wont find moderators

‘We don’t don’t know how best to start treatment’

- Need very large samples to do sequence studies, especially if the first step in treatment is good... rerandomize non-responders

# Summary

- Anxiety disorders start very early
  - Under-recognized and under-treated
  - Identifying anxiety is the place to start!
  - Understanding the Hot Topics is critical to understanding the literature and sophisticated treatment.
- 
- Complex treatments for refractory anxiety
  - For refractory anxiety think...
    - Medication augmentation strategies
    - Functional assessment and family involvement