

Treatment Advances in Pediatric Anxiety Disorders

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Disclosure

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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.



In Her Own Words...

“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

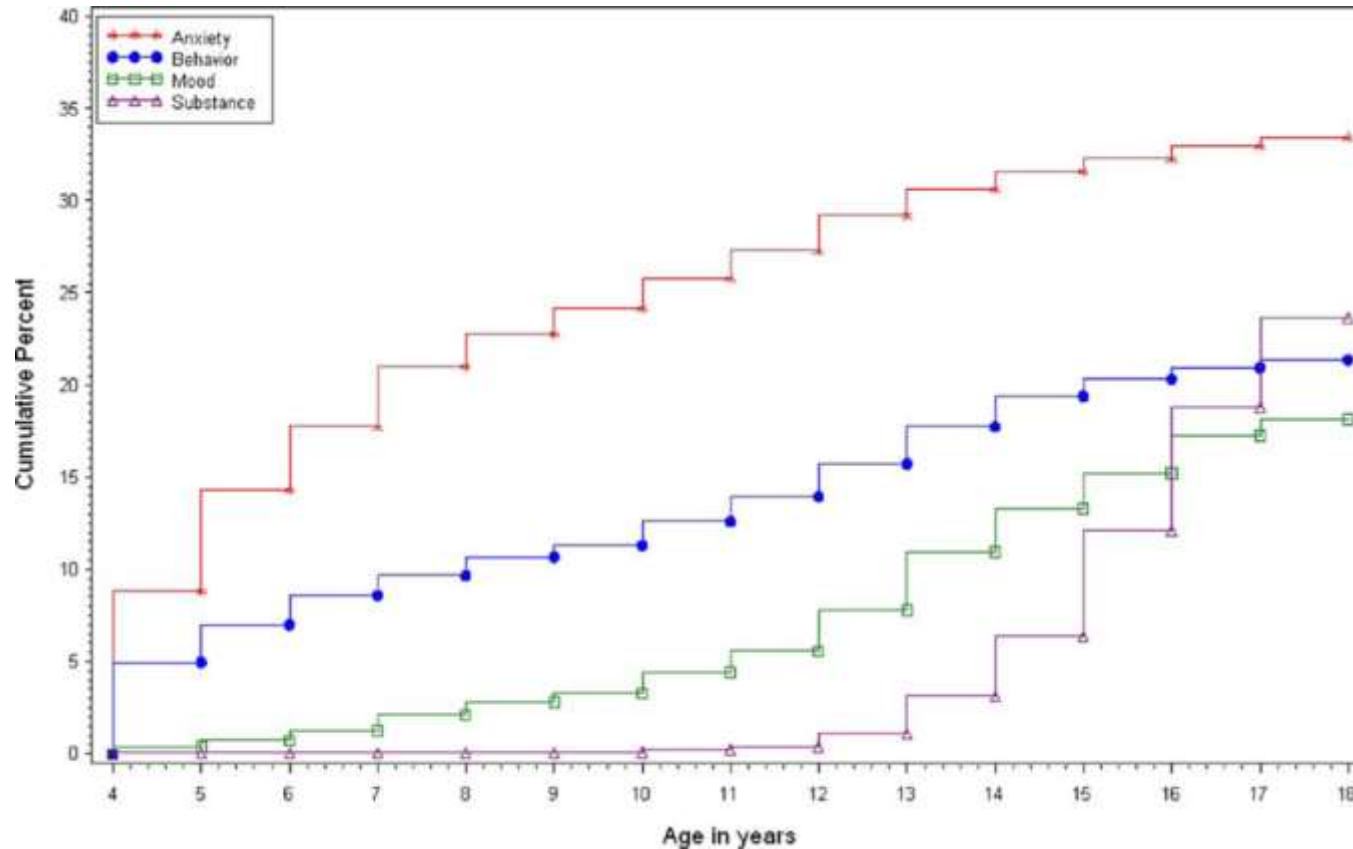
- **Preschool:** Phobic objects/situations, SAD
- **Grade School:** OCD, GAD
- **Adolescence:** Social anxiety, Panic Disorder

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

DMS-IV Disorder	Lifetime Prevalence by Sex %		Lifetime Prevalence by Age %			Lifetime Prevalence Total %	Lifetime Prevalence-Severe Impairment %	12-Month Prevalence %	1-Month Prevalence %
	Female	Male	13-14 y	15-16 y	17-18 y				
Agoraphobia	3.4	1.4	2.5	2.5	2.0	2.4	2.4	1.8	0.8
Generalized Anxiety Disorder	3.0	1.5	1.0	2.8	3.0	2.2	0.9	1.1	0.4
Social Phobia	11.2	7.0	7.7	9.7	10.1	9.1	1.3	8.2	4.6
Specific Phobia	22.1	16.7	21.6	18.3	17.7	19.3	0.6	15.8	9.5
Panic Disorder	2.6	2.0	1.8	2.3	3.3	2.3	2.3	1.9	0.8
Posttraumatic Stress Disorder	8.0	2.3	3.7	5.1	7.0	5.0	1.5	3.9	1.6
Separation Anxiety Disorder	9.0	6.3	7.8	8.0	6.7	7.6	0.6	1.6	0.6
Any Anxiety Disorder	38.0	26.1	31.4	32.1	32.3	31.9	8.3	24.9	14.9

*Beedso-Baum & Knappe, 2012;
Merikangas et al., 2011; Kessler et al., 2012*

Childhood Anxiety Disorders

Greater risk for:

- Adult depression and anxiety¹
- Substance abuse/dependence²
- Suicidal behaviors³

¹ *Pine et al., 1998*

² *Compton et al., 2007*

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 school, social activities, health
- **Separation Anxiety Disorder (SAD):** developmentally inappropriate and excessive anxiety concerning separation from primary care givers
- **Social Anxiety Disorder (SoP):** persistent fear of social performance situations or to scrutiny by others
- **Obsessive Compulsive Disorder (OCD):** repetitive behavior or thoughts that neutralize anxiety

Clinical Characteristics of Anxious Youth

Table 3

Anxiety disorders diagnostic summary.

Diagnosis	Current diagnosis, n (%)	ADIS CSR rating, M (SD)	
SAD	16 (3.29)	SAD	5.47 (1.41)
SP	56 (11.50)	SP	5.42 (0.92)
GAD	33 (6.78)	GAD	5.30 (0.77)
SAD & SP	33 (6.78)	SAD	5.27 (1.07)
		SP	5.15 (1.00)
SAD & GAD	39 (8.01)	SAD	5.18 (0.72)
		GAD	5.56 (0.91)
SP & GAD	135 (27.72)	SP	5.57 (1.05)
		GAD	5.50 (0.91)
SAD & SP & GAD	175 (35.93)	SAD	5.35 (0.99)
		SP	5.29 (1.02)
		GAD	5.43 (0.98)

Note: SP, social phobia; GAD, generalized anxiety disorder; SAD, separation anxiety disorder; ADIS CSR, Anxiety Disorders Interview Schedule Clinician Severity Rating.

Anxiety Triad

Kendall et al., 2010

School Refusal, Over Anxious, and Separation Anxiety Disorder

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

Triad Anxiety Disorders & Social Phobia

Reference	Diagnosis (Age Range)	Duration	Treatment	N	Dose Range (mg/day)	Outcome	% Meeting Remission or Response
RUPP Anxiety Study Group: Walkup, et al., 2001	GAD; SoP; SAD (6-17 yrs)	8 wks	Fluvoxamine	128	50-300	Fluvoxamine > PBO	CGI/I <4: 76%
Birmaher et al., 2003	GAD; SoP; SAD (7-17 yrs)	12 wks	Fluoxetine	74	20	Fluoxetine > PBO	CGI/I ≤ 2: 61%
Wagner et al., 2004	SoP (8-17 yrs)	16 wks	Paroxetine	322	10-50	Paroxetine > PBO	CGI/I = 1 : 47.8% or ≥70% reduction on SAS: 47.2%
March et al., 2007	SoP (8-17 yrs)	16 wks	Venlafaxine ER	293	37.5-225	Venlafaxine ER > PBO	CGI/I = 1 / 2: 56%

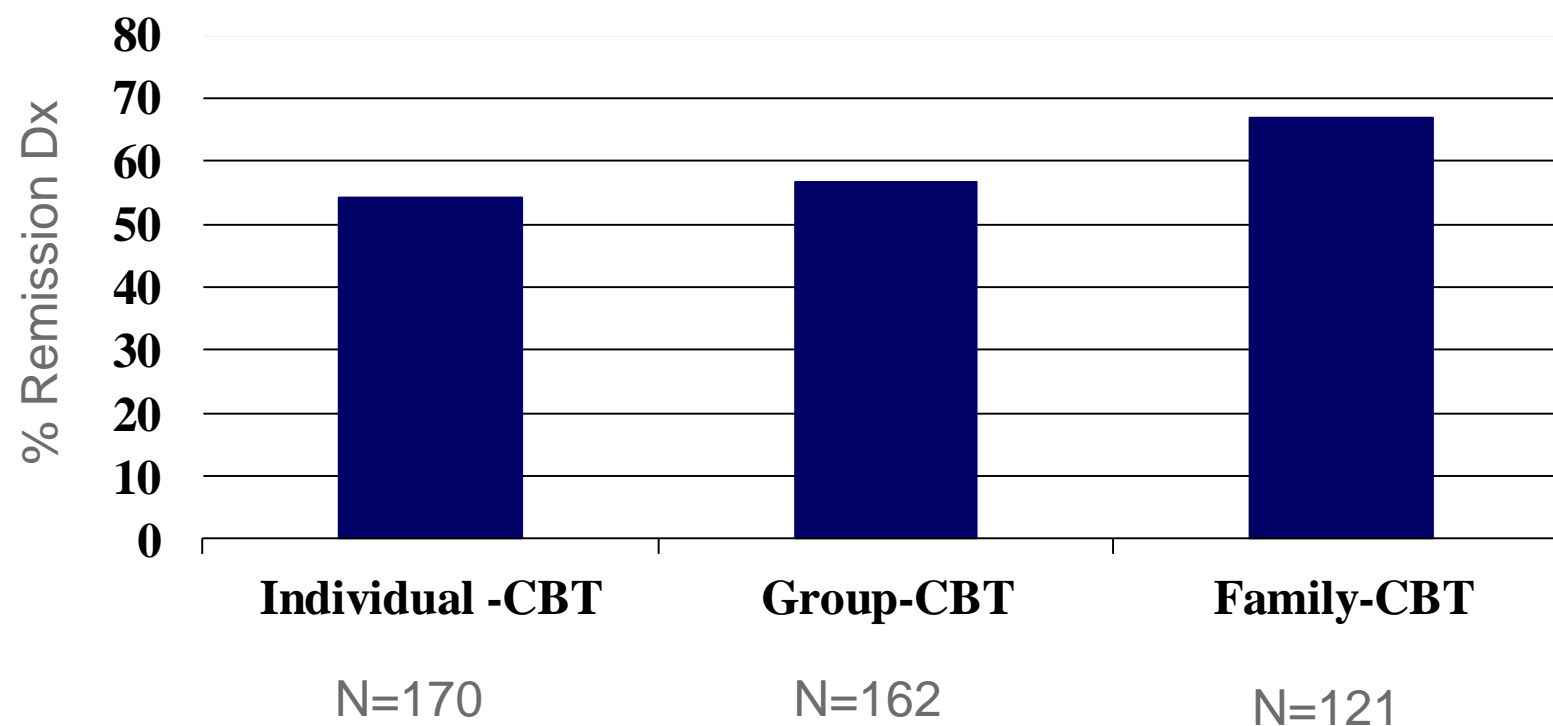
Generalized Anxiety Disorder

Reference	Diagnosis (Age Range)	Duration	Treatment	N	Dose Range (mg/day)	Outcome	% Meeting Remission or Response
Rynn et al., 2001	GAD (5-17 yrs)	9 wks	Sertraline	21	50	Sertraline > PBO	CGI/I = 1: 18%
Rynn, et al. (in prep)	GAD (5-17 yrs)	16 wks	Sertraline	51	50 -200	Sertraline > PBO	HAMA≤7: 4% 6 months later: 64%
Rynn et al., 2007	GAD (6-17 yrs)	8 wks	Venlafaxine ER	313	37.5 -225	Venlafaxine ER > PBO	CGI/I <3: 69% and 48%

Obsessive Compulsive Disorder

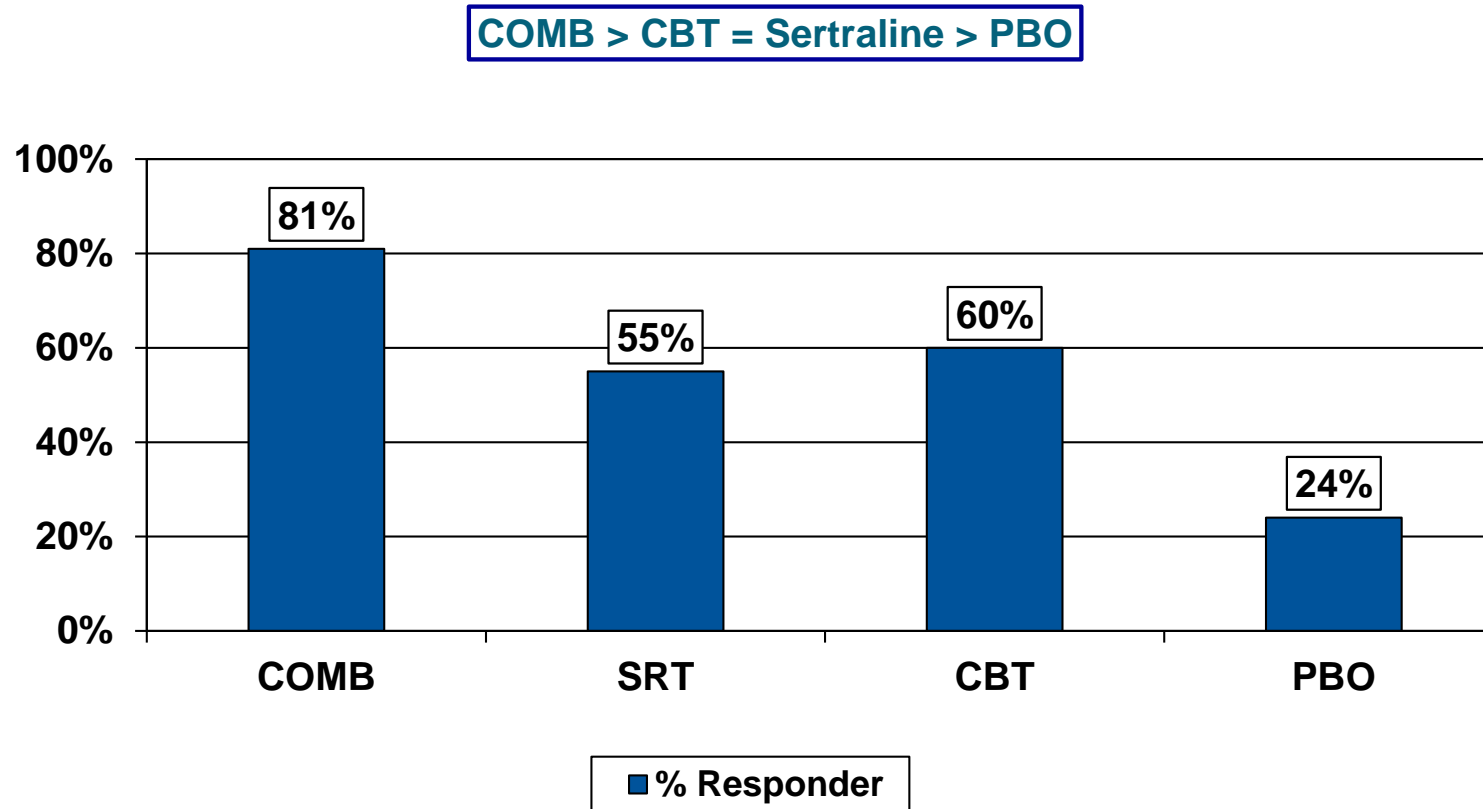
Reference	Duration Weeks (Age Range)	Treatment	N	Dose Range (mg/day)	Outcome	% Remission or Response
DeVeough-Geiss et al., 1992	8 (10-17 yrs)	Clomipramine	126	75-200	Clomipramine > PBO	CGI-I \leq 2: 60%
March et al., 1998	12 (6-17 yrs)	Sertraline	187	25-200	Sertraline > PBO	25% \geq in CY-BOCS: 53% or CGI-I score of \leq 2 : 42%
Riddle et al., 2001	10 (8-17 yrs)	Fluvoxamine	120	50-200	Fluvoxamine > PBO	25% \geq CYBOCS : 42.1%
Geller et al., 2001	13 (7-17 yrs)	Fluoxetine	103	20-60	Fluoxetine > PBO	40% \geq CYBOCS: 49%

Pooled Analysis CBT Modality for Childhood Anxiety



Child Anxiety Multimodal Study CAMS: N=488, 7-17 Years Old for 12 Weeks

CGI-I 1 and 2
(ITT, LOCF)



Walkup et al., 2008

CAMS Remission

Response and Remission Rates of CAMS Study Subjects at Week 12

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

^b No variability in this estimate across imputations, thus confidence interval not applicable

Ginsburg et al., 2001

CAMS Remission

Remission Rates and Social Phobia

Treatment	% no AD		CGI-I remission	
	No SOP	SOP	No SOP	SOP
COMB	88.0	64.0	52.0	44.2
SRT	52.0	44.4	40.6	32.3
CBT	72.0	40.6	28.0	18.7
PBO	46.1	19.1	17.3	14.5

Ginsburg et al., 2001

Predictors for Best Response

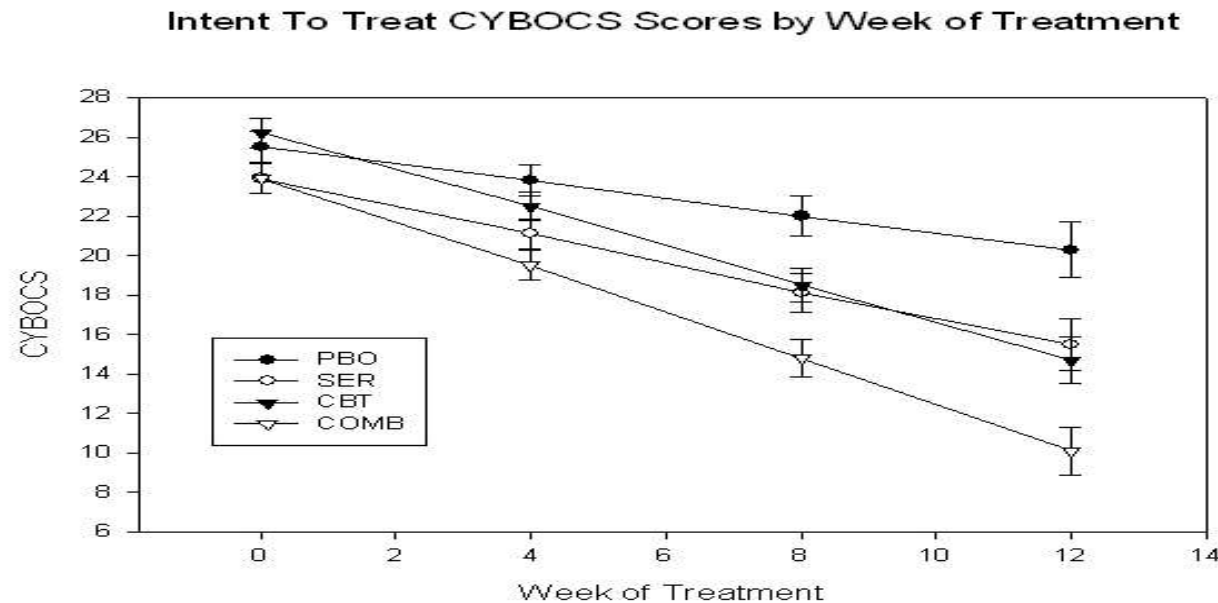
Baseline Variables that Predict Remission ($p < 0.05$):

- 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*

Pediatric OCD Study (POTS)

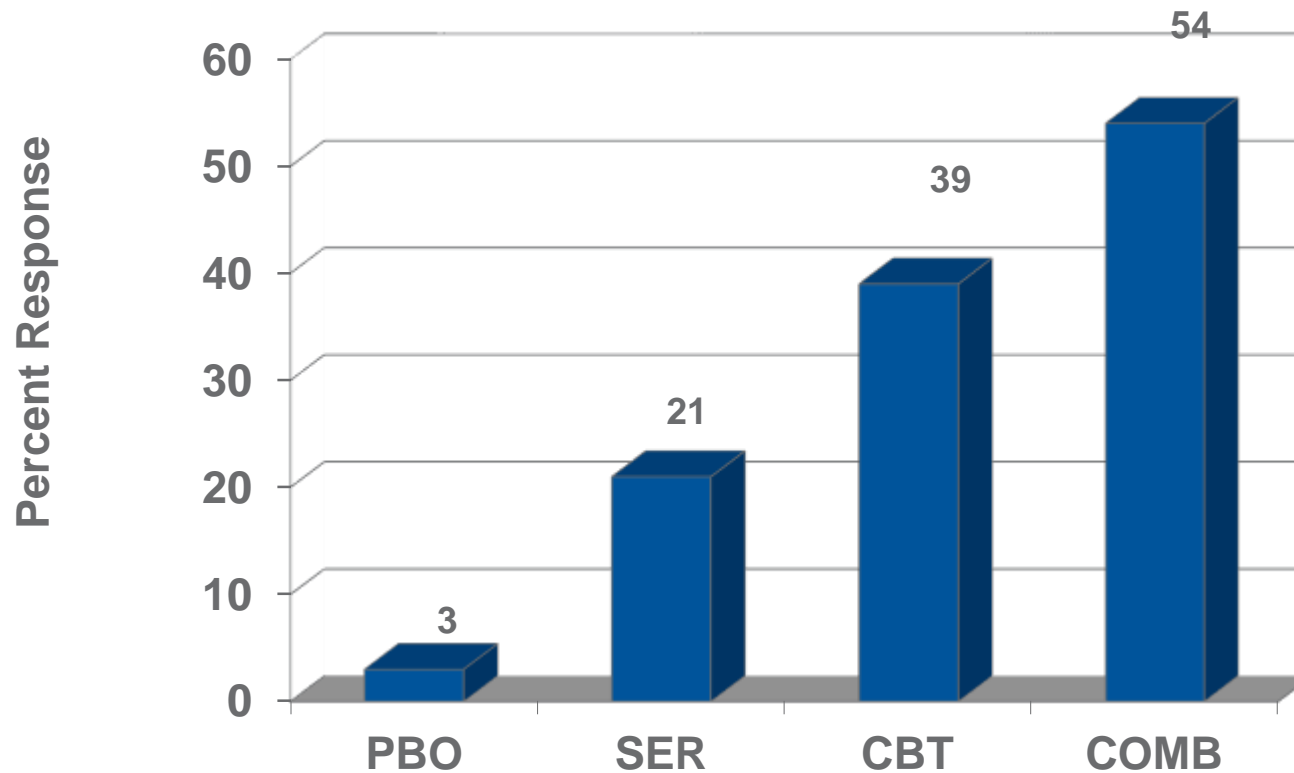
COMB > CBT = Sertraline > PBO



POTS Team: March, Foa, Gammon, Chrisman, Curry, Fitzgerald, Sullivan, Franklin, Huppert, Rynn, Zhao, Zellner, Leonard, Garcia, Freeman & Tu (2004)

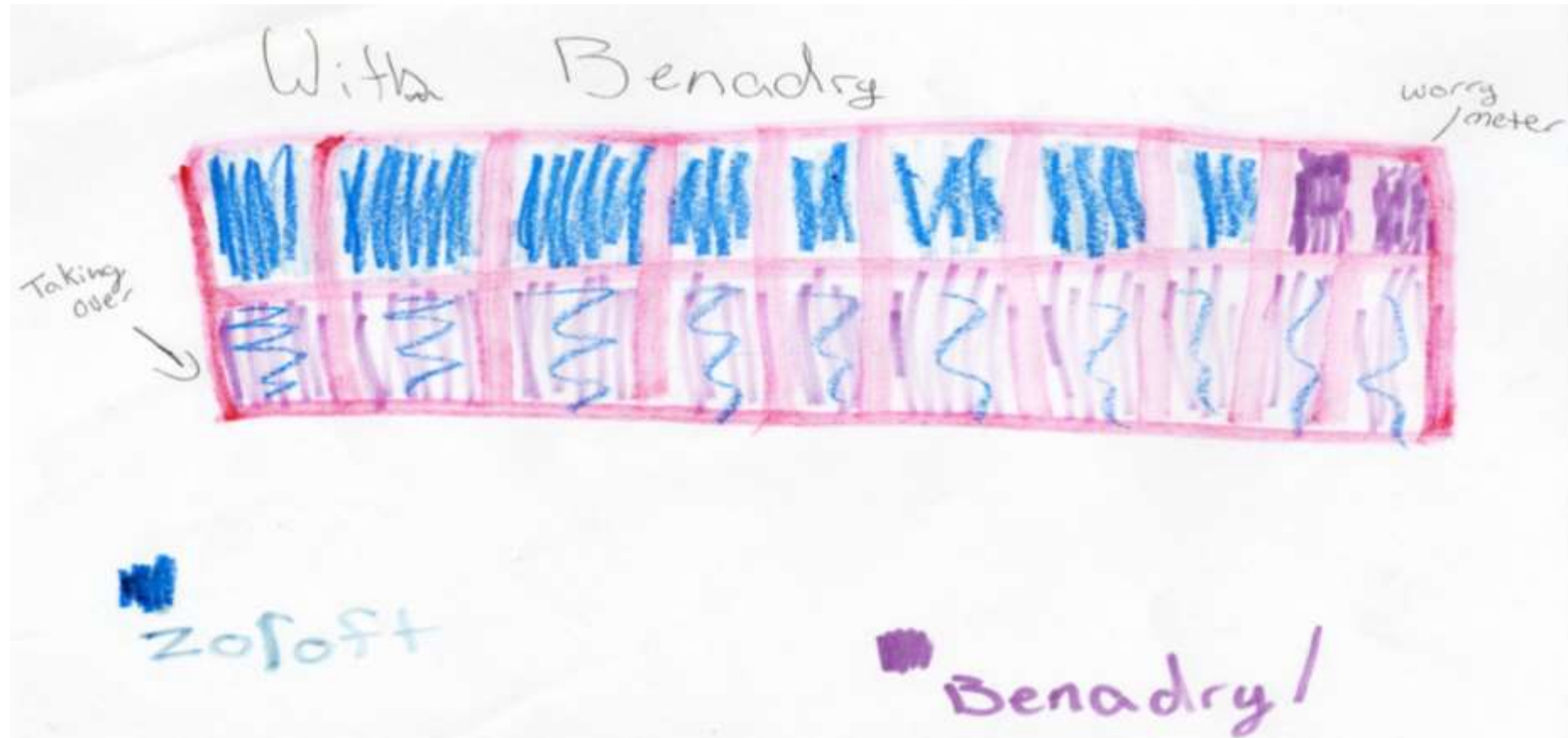
Excellent Responder (YBOCS ≤ 10)

COMB = CBT > Sertraline = PBO



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

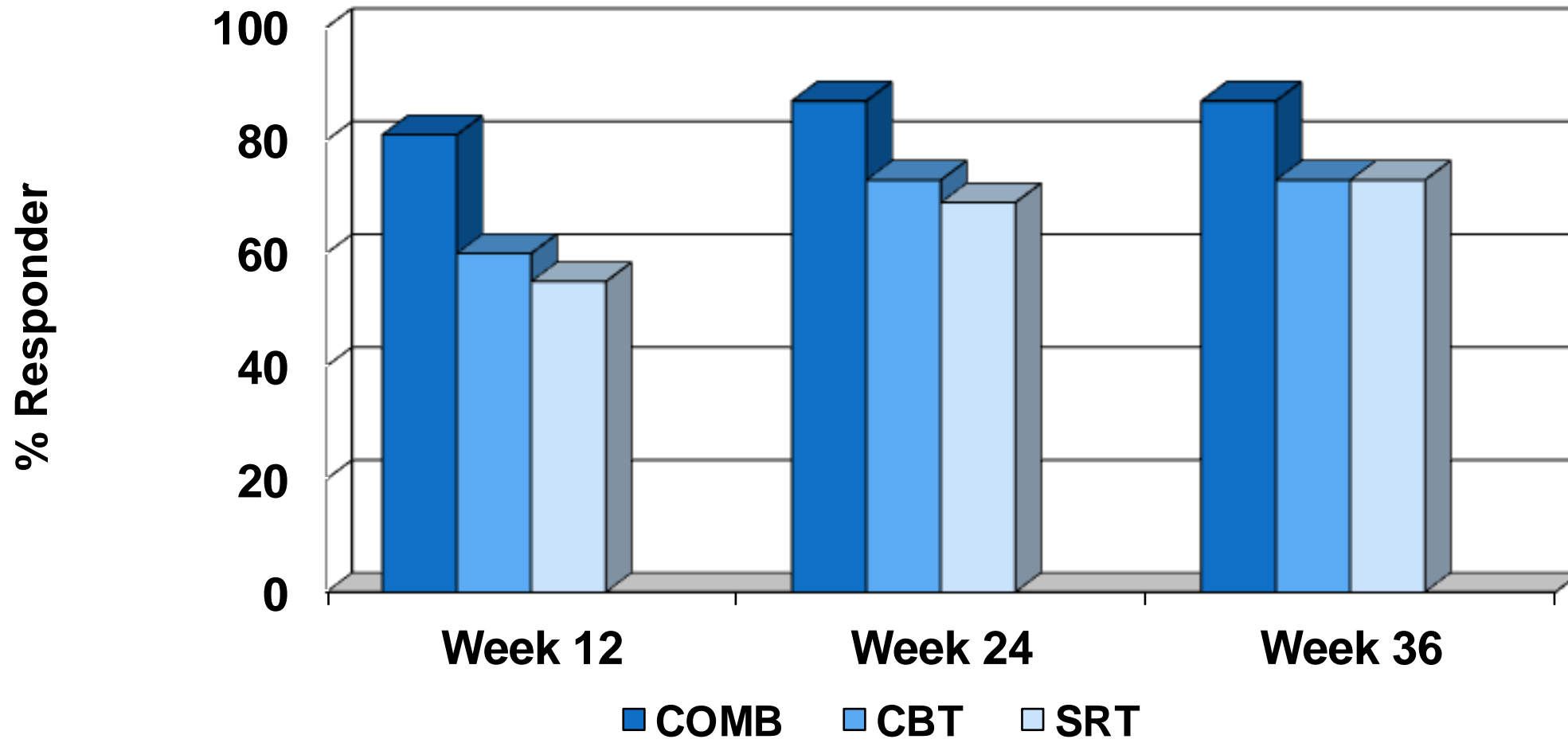
Clark et al., 2005

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

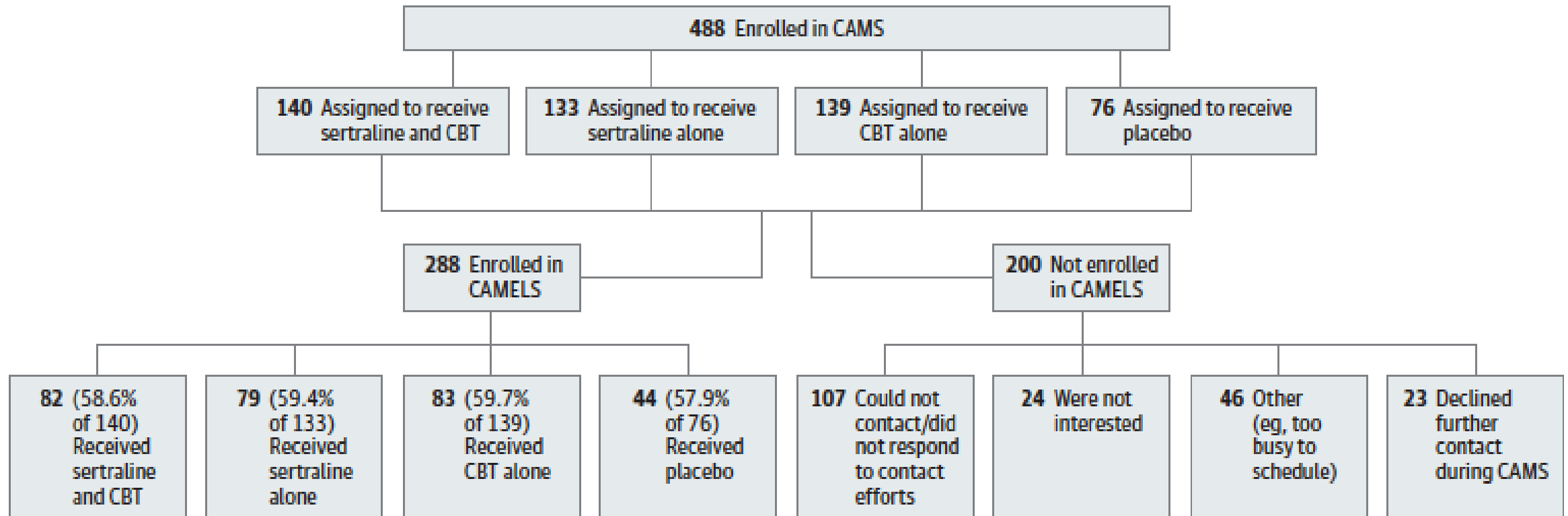
Walkup, J. et al. (2002)

CAMS Response: 12 to 36 weeks



ABCT 2009

CAM Extended Long-term Study (CAMELS)

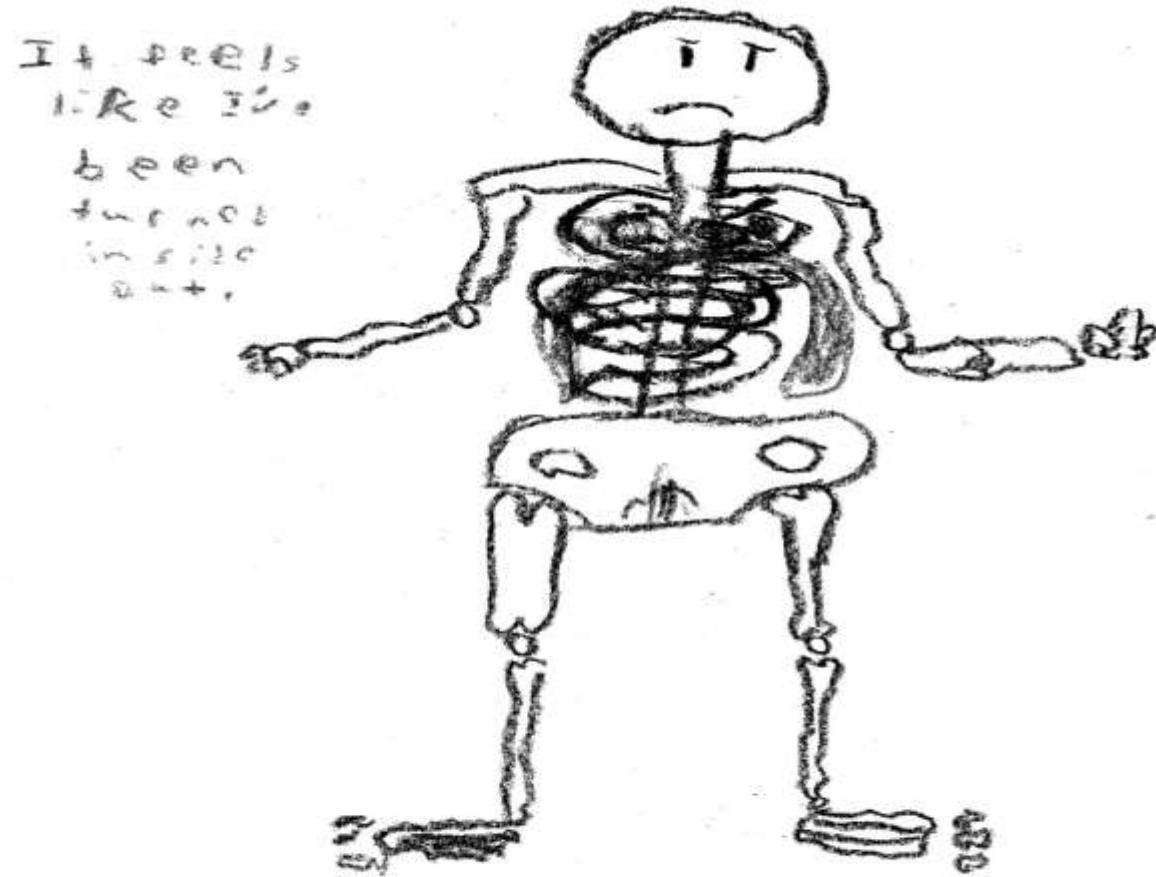


Ginsburg et al., 2014

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 predicated remission:
 - Male, family functioning and Higher SES

Ginsburg et al., 2014



Adverse Events

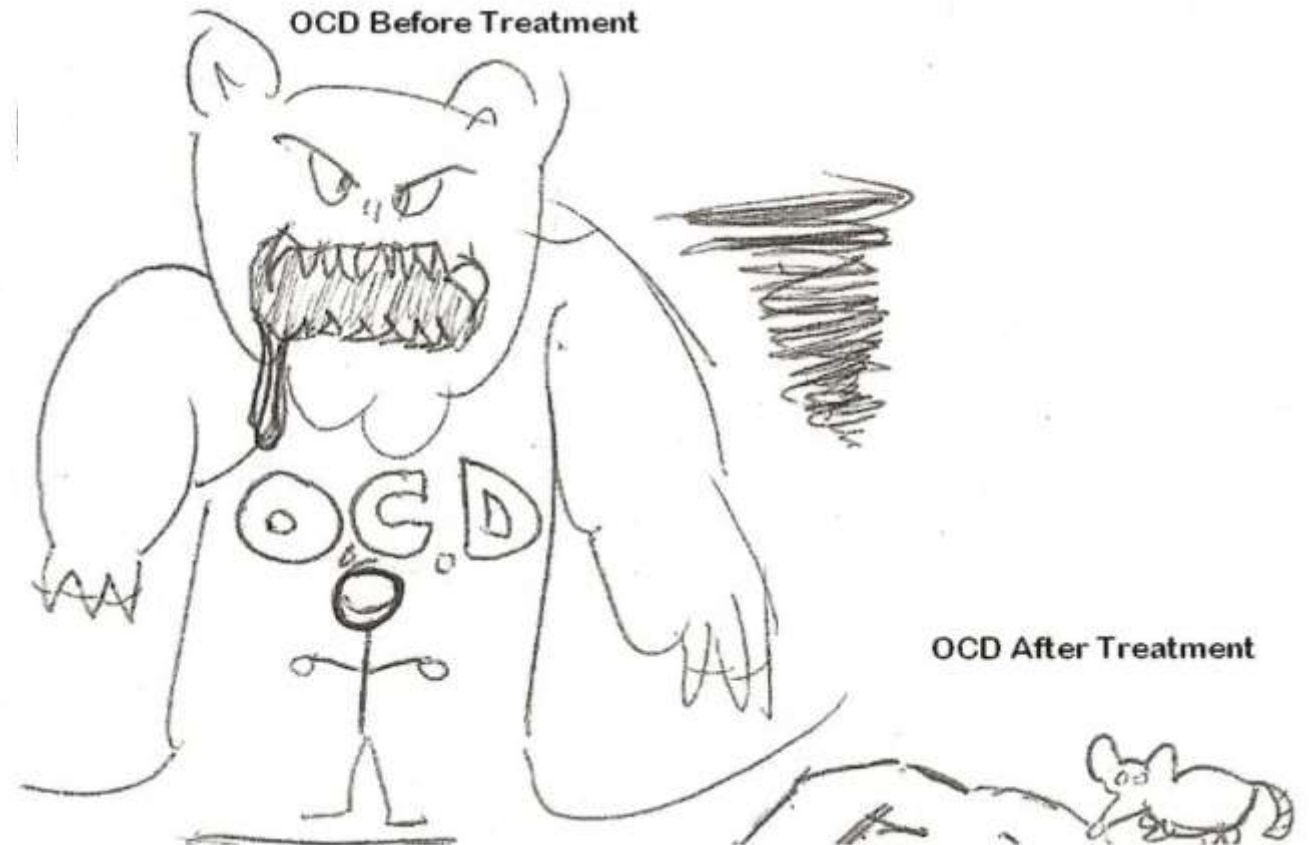
Safety Concerns

- 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

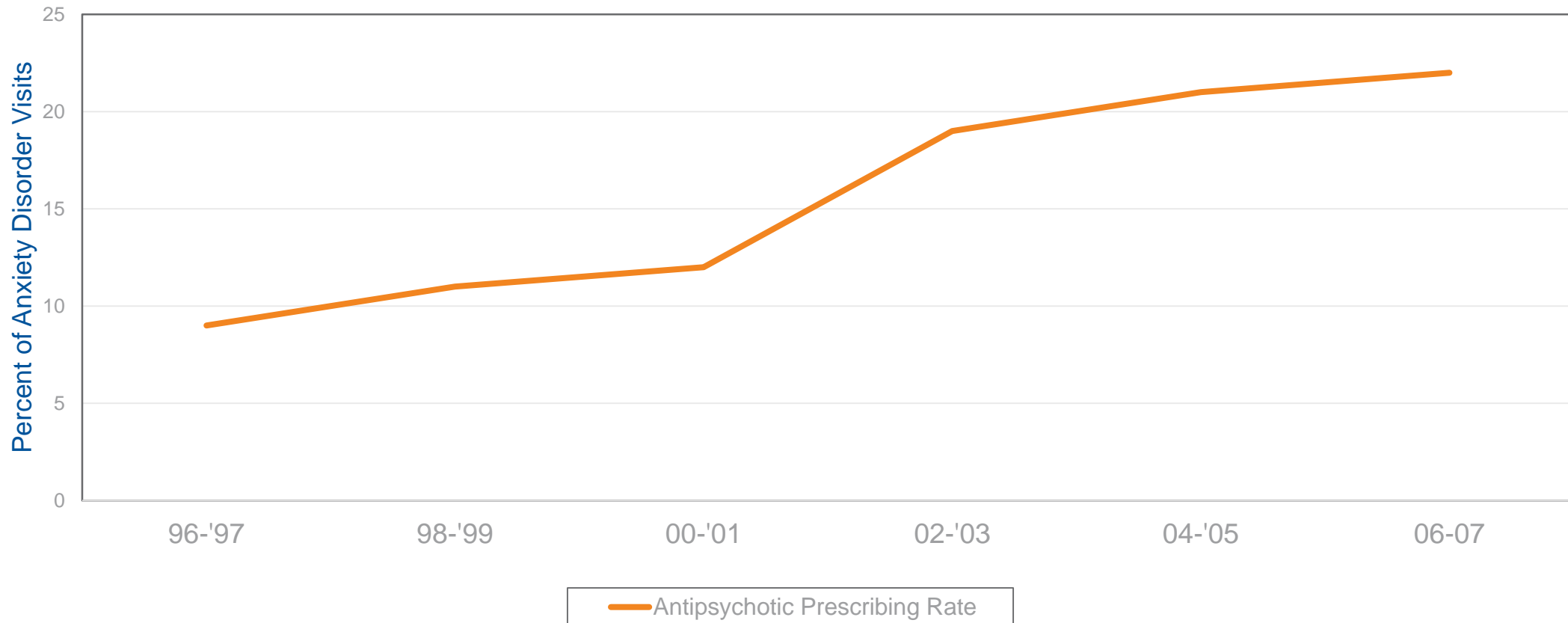
First Line Treatments

- Monotherapy:
 - CBT
 - SRI & SNRI
- Combination Treatment
- Family/Environment
- Maximize Treatment

But approximately 30 to 50 %
do not achieve this response:

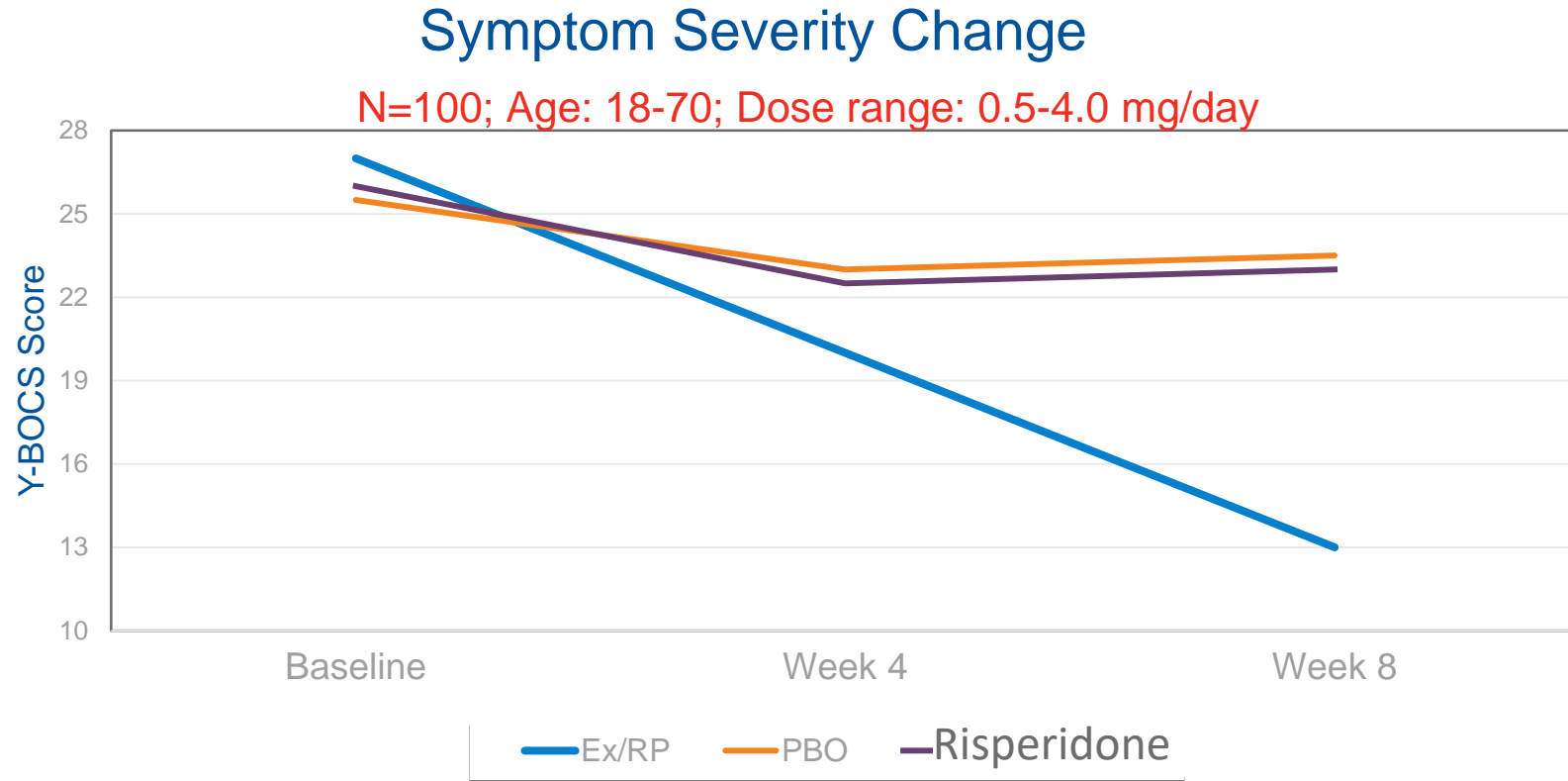


Antipsychotic Use for Sedative Properties



Comer et al., 2011

CBT vs Risperidone for Augmenting SSRIs in Adult OCD



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)



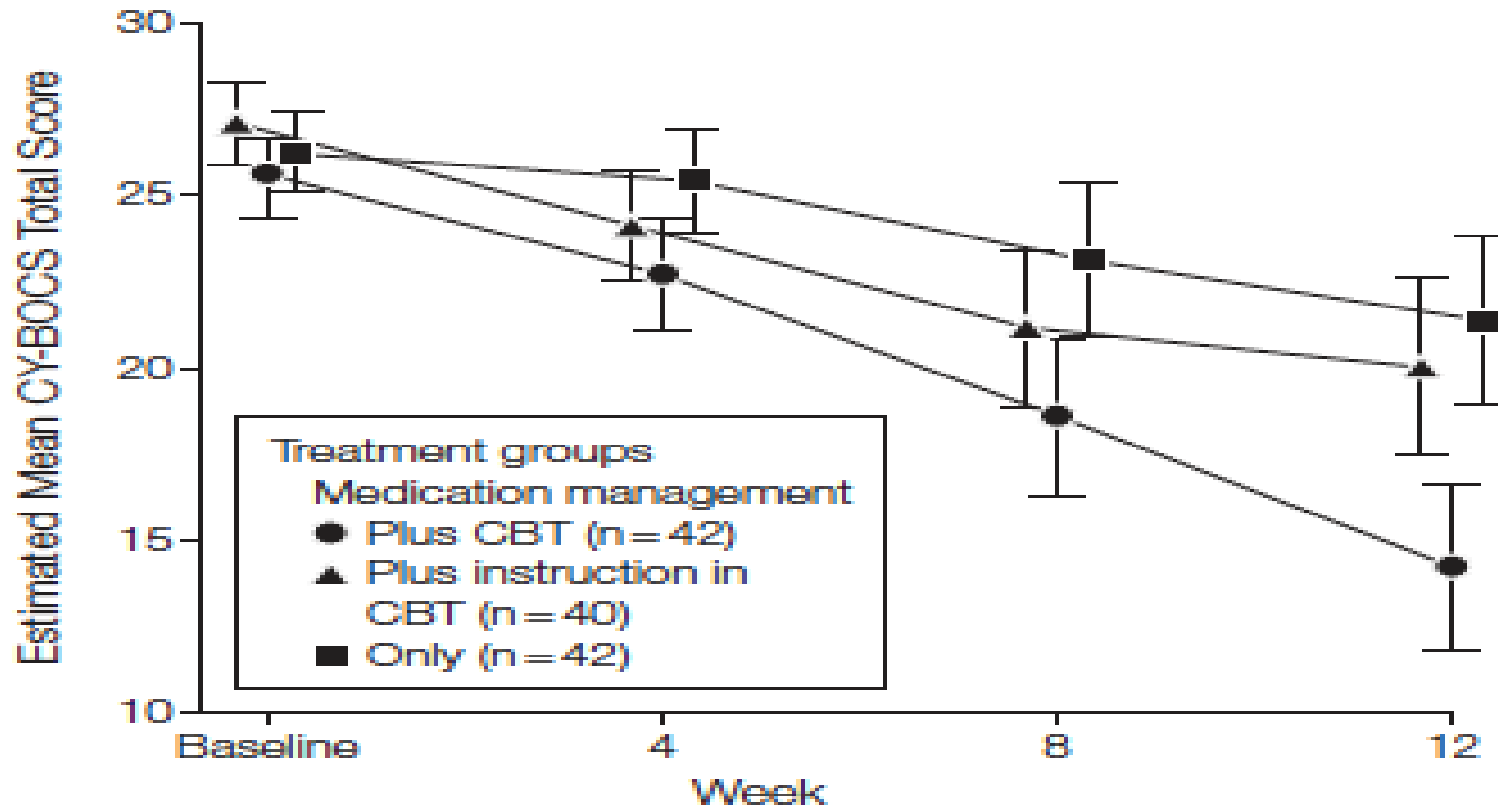
MM
+
CBT



MM
+
Instructions on CBT

Franklin et al., 2011

CY-BOCS Scores During 12 Weeks



Response Status:

MM + CBT = 68.6%

MM + instruction = 34.0%

MM only = 30.0%

Franklin et al., 2011

Anxiety Disorders Treatment Development

- 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 (RIL)

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;

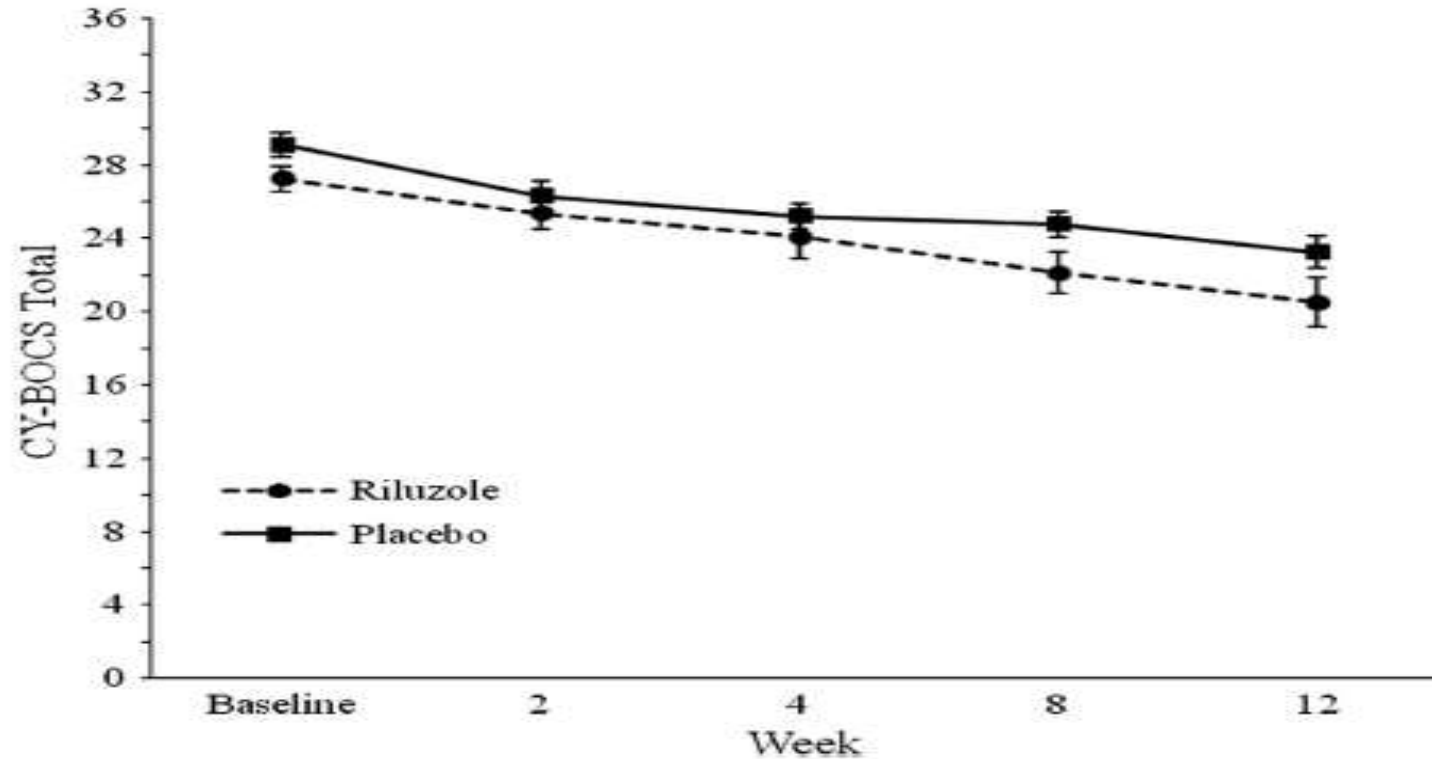
Coric et al., 2005

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

CY-BOCS Total Scores for RIL vs PBO



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 ($21 \pm 18\%$, 5.52 ± 4.40 points) very similar to that observed in PBO ($19 \pm 15\%$; 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”

- 2nd 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.

Open Pilot Data

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 $\geq 40\%$ YBOCS reduction & had OCD onset in childhood

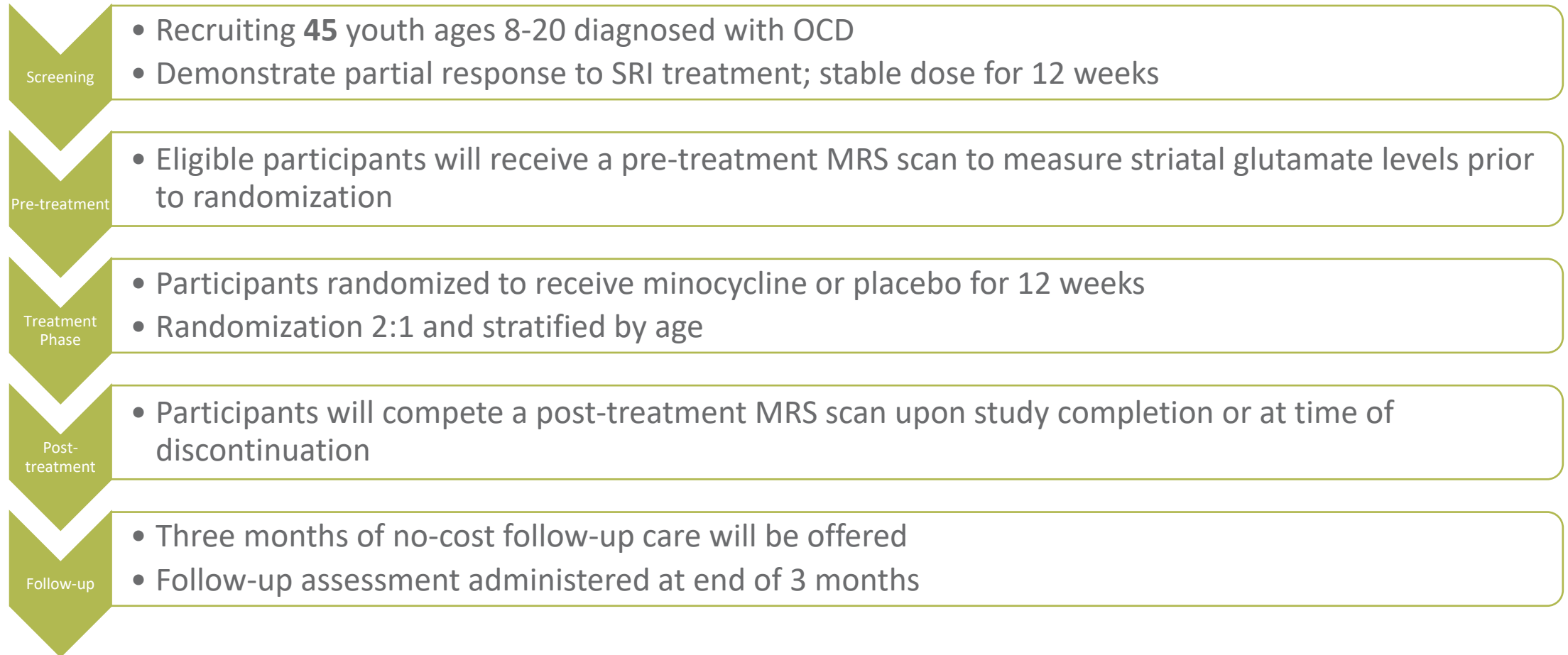
Rodriguez CI et al, 2011

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.

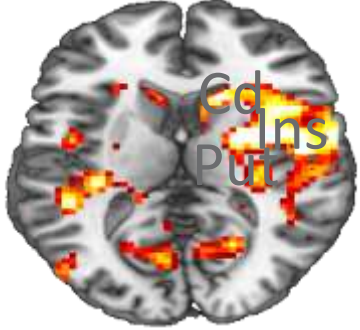
PIs: Moira Rynn, M.D., Helen Blair Simpson, M.D., Ph.D., Larry Kegeles, M.D., Dikoma Shungu, Ph.D. (Weill Cornell Medical Center) NIMH #1R34MH095502-01

Design



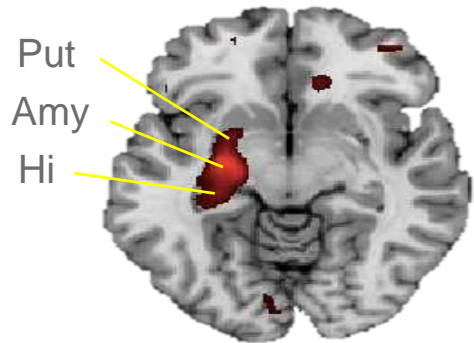
Abnormal Functioning of Control and Reward Circuits in Unmedicated Adults with OCD

OCD > HC



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.

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.