Treatment Advances in Pediatric Anxiety Disorders

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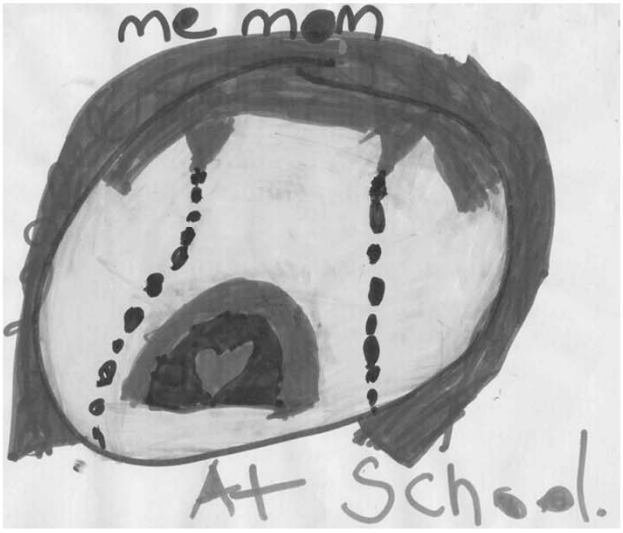
Disclosure

Source	Research Funding	Advisor/ Consultant	Employee	Speakers' Bureau	Books, Intellectual Property	In-kind Services (example: travel)	Stock or Equity	Honorarium or expenses for this presentation or meeting
NIH	X							
NICHD	X							
Eli Lilly	X							
Pfizer	X							
APPI					X			
Oxford Press					X			

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

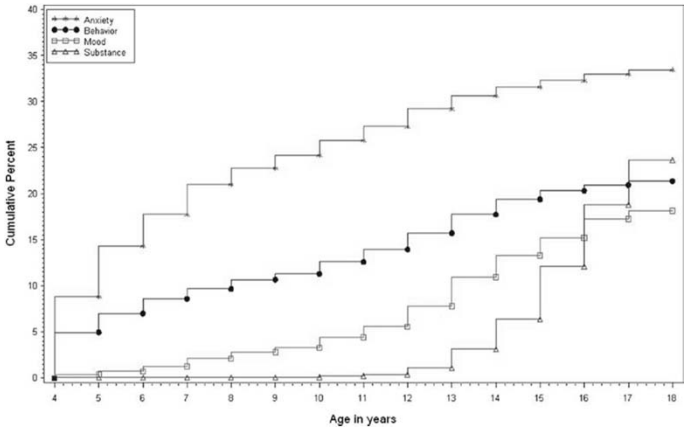
- Preschool: Phobic objects/situations, SAD
- Grade School: OCD, GAD
- Adolescence: Social anxiety, Panic Disorder

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

	Lifetime Prevalence by Sex %		Lifetime Prevalence by Age %			Lifetime Prevalence Total %	Lifetime Prevalence-Severe Impairment %	12-Month Prevalence %	1-Month Prevalence %
DMS-IV Disorder	**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 anxiety[1]
- Substance abuse/dependence[2]
- Suicidal behaviors[3]

[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

Anxiety Triad

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.

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/1= 1/ 2: 56%**

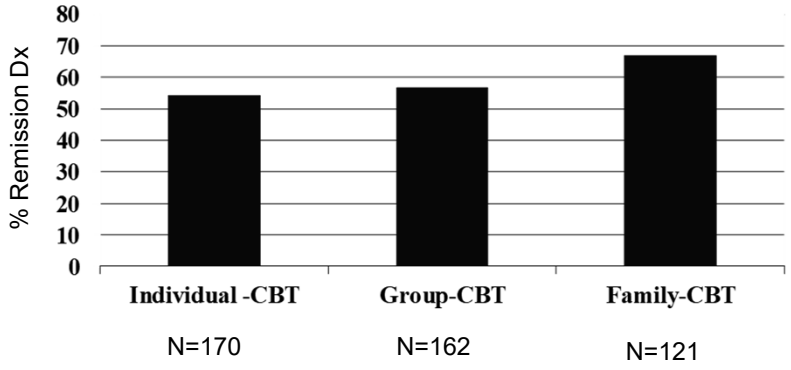
Generalized Anxiety Disorder

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

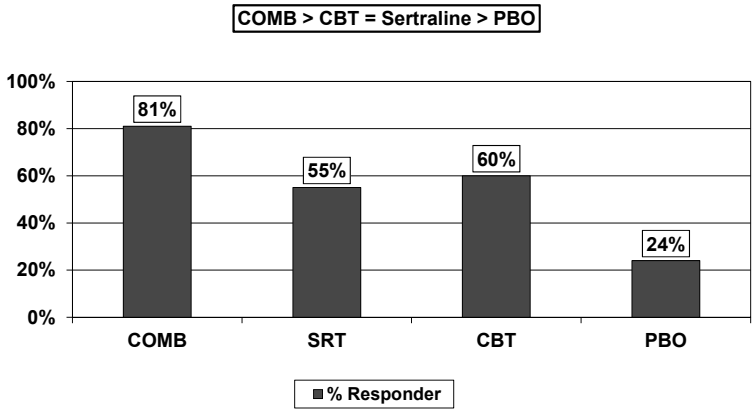
Reference	Duration Weeks (Age Range)	Treatment	N	Dose Range (mg/day)	Outcome	% Remission or Response
DeVeaugh-Geiss et al., 1992	8 (10-17 yrs)	**Clomipramine**	**126**	75-200	**Clomipramine > PBO**	CGI-I ≤ 2: 60%
March et al., 1998	12 (6-17 yrs)	**Sertraline**	**187**	25-200	**Sertraline > PBO**	25%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

[b] *No variabil*

Ginsburg et al., 2001

Predictors for Best Response

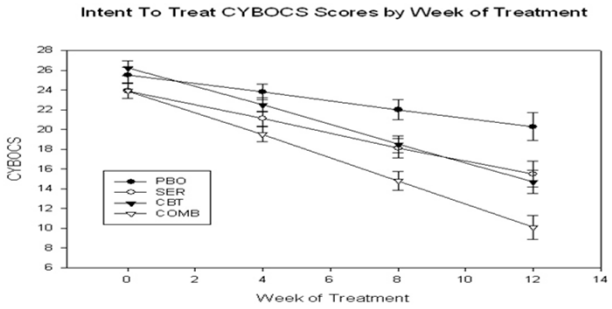
Baseline Variables that Predict Remission ($p<0.05$):

- 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)

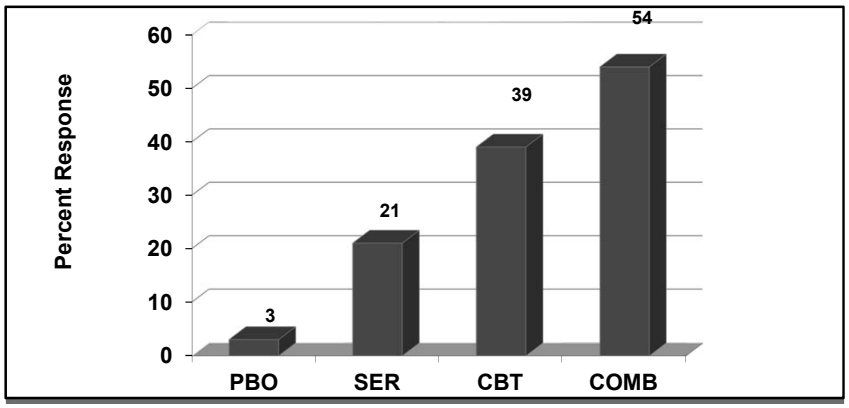
COMB > CBT = Sertraline > PBO



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

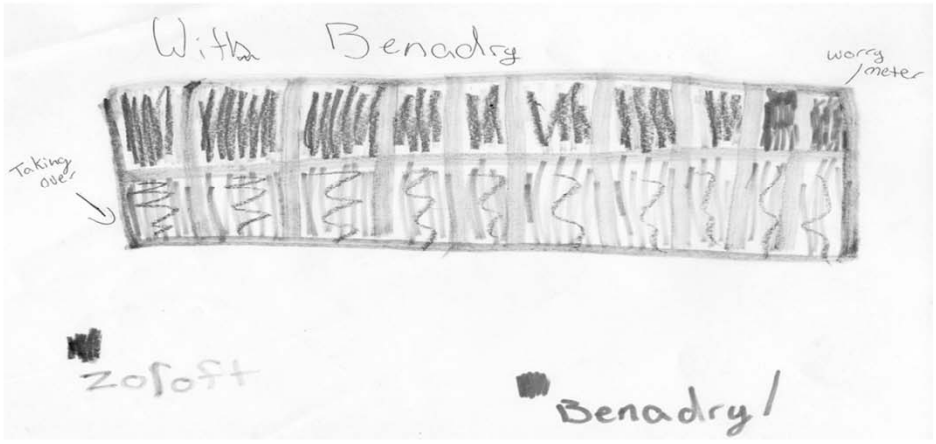
Excellent Responder (YBOCS ≤ 10)

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

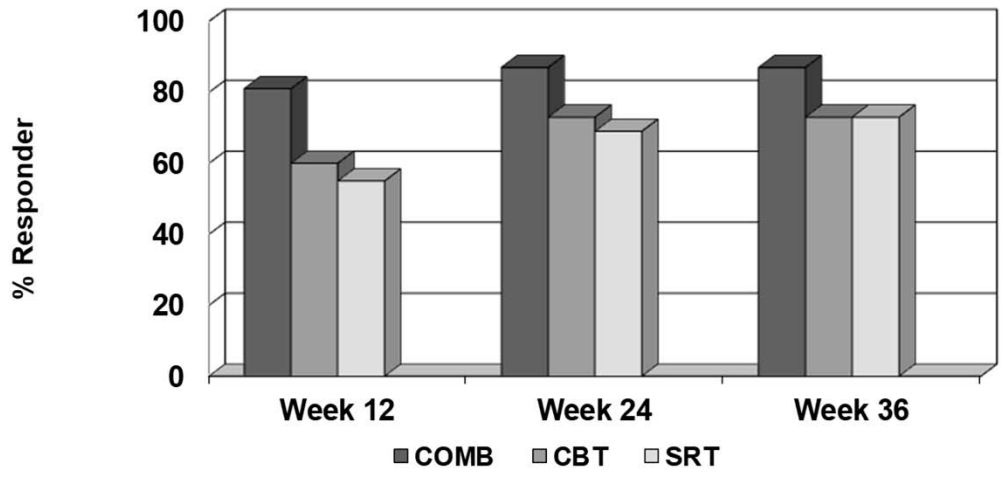
Clark et al., 2005

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

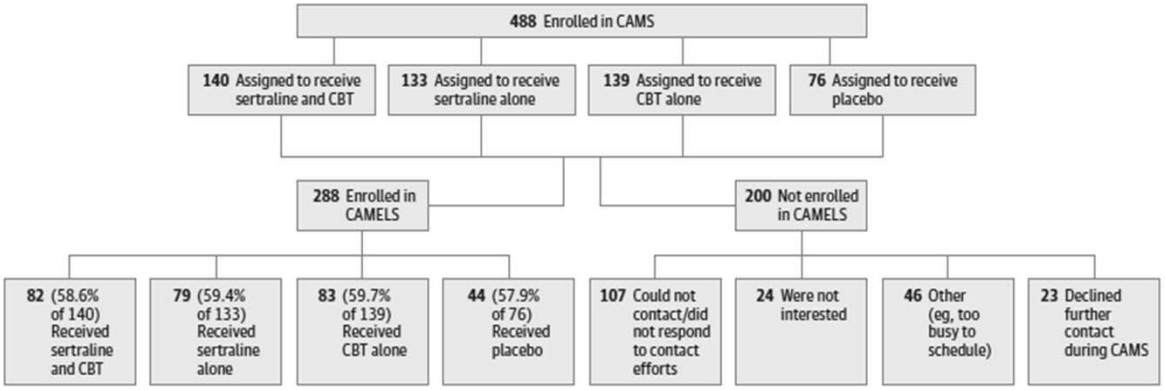
Walkup, J. et al. (2002)

CAMS Response: 12 to 36 weeks



ABCT 2009

CAM Extended Long-term Study (CAMELS)

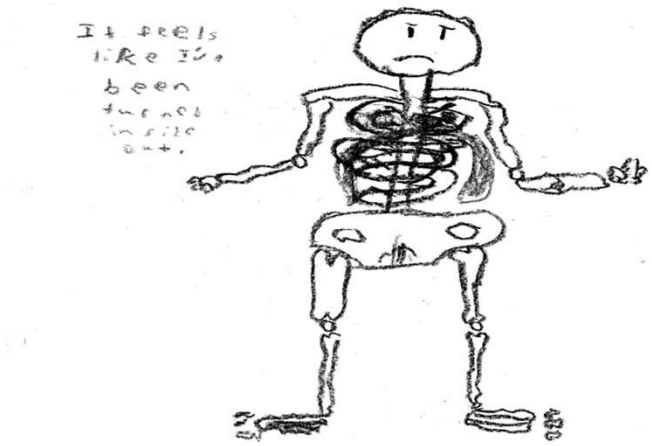


Ginsburg et al., 2014

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

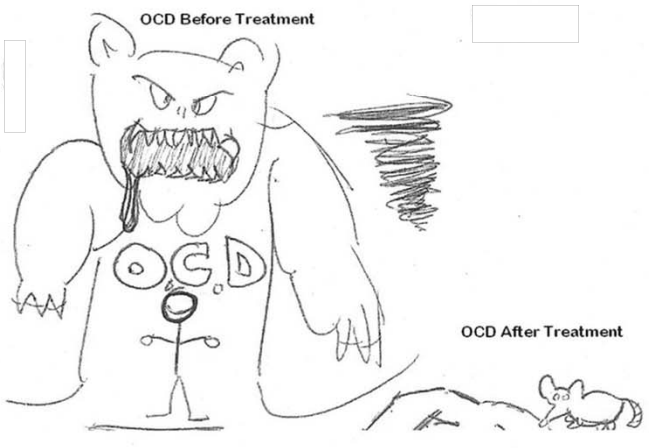
Safety Concerns

- 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

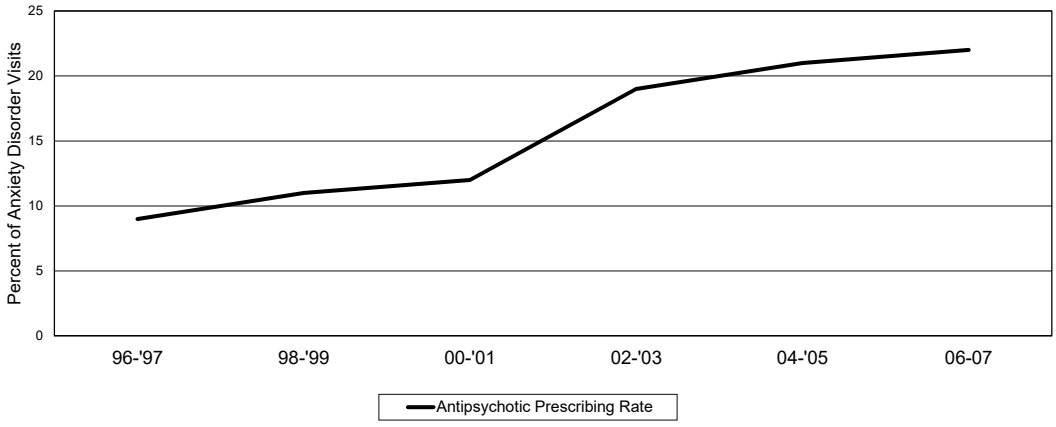
First Line Treatments

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

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

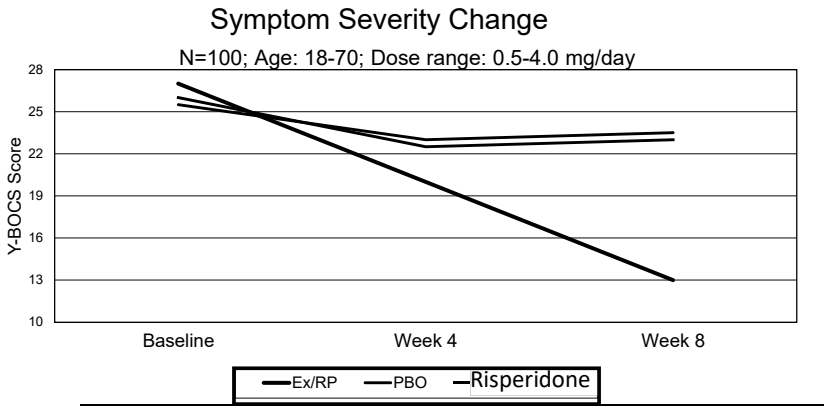


Antipsychotic Use for Sedative Properties



Comer et al.,2011

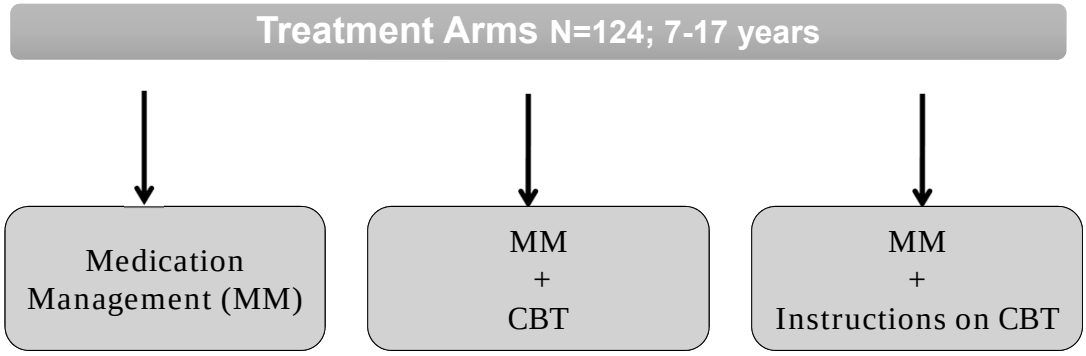
CBT vs Risperidone for Augmenting SSRIs in Adult OCD



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

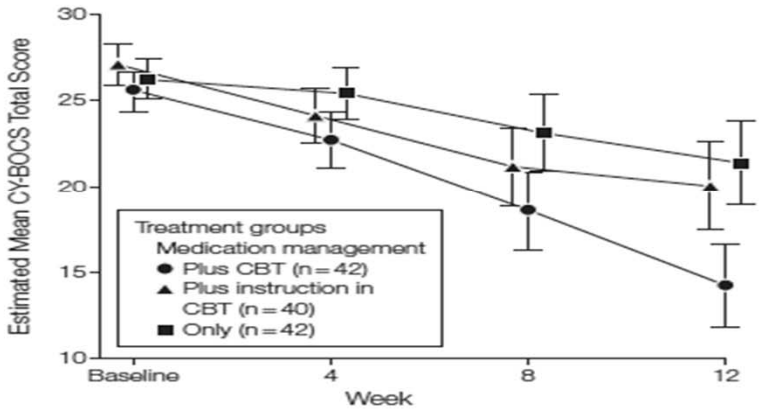
Simpson et al., 2013

The Pediatric OCD Treatment Study II



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: hepatoxicity and in children reports of pancreatitis

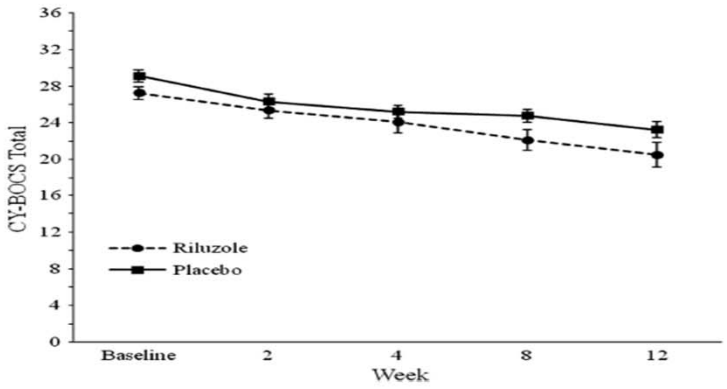
Mathew et al., 2008;
Coric et al., 2005

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± 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"

- 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 ≥ 40% YBOCS reduction & had OCD onset in childhood

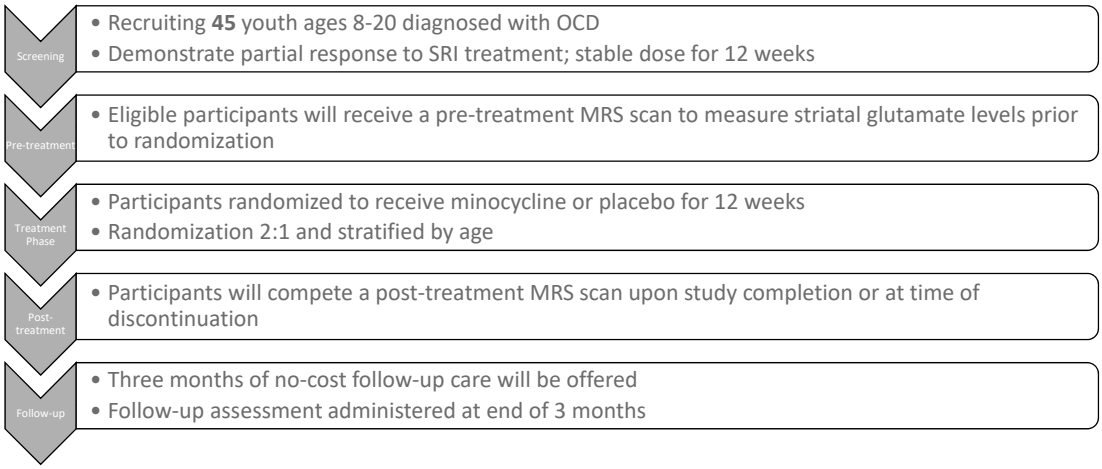
Rodriguez CI et al,2011

Medication Strategies Targeting Brain Mechanisms in Pediatric OCD

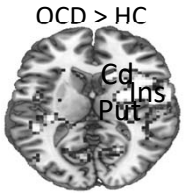
- Hypothesis 1**:** When added to SSRI medication, minocycline will be superior to PBO in reducing OCD symptoms.
- Hypothesis 2**:** Adding minocycline (versus placebo) to an SSRI will reduce glutamate levels in the head of caudate.
- Hypothesis 3**:** Reduction in glutamate levels will be associated 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

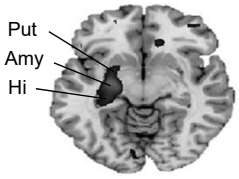


Abnormal Functioning of Control and Reward Circuits in Unmedicated Adults with OCD



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.