Pharmacology of Anxiety Disorders and OCD in Childhood and Adolescence

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Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
DSM V Anxiety Disorders

Separation Anxiety Disorder  Selective Mutism  Specific Phobia  Social Anxiety Disorder (Social Phobia)  Panic Disorder  Panic Attack (Specifier)  Agoraphobia  Generalized Anxiety Disorder  Substance/Medication-Induced Anxiety Disorder  Anxiety Disorder Due to Another Medical Condition  Other Specified Anxiety Disorder  Unspecified Anxiety Disorder
Pediatric Anxiety Disorders

US National Comorbidity Survey; Anxiety disorders are the most prevalent class

- 12-Month Prevalence in Children: 3.7% - 8.9% (Costello, 1988, 1996; Ford, 2003)

- 6-Month Prevalence in Adolescents: 8.7% - 17% (Kashani & Orvaschel, 1988)

- Lifetime Prevalence in Adults: 15% - 25% (ECA & National Comorbidity Study)

Kessler et al, Arch Gen Psych, 2005; Pagura et al, J Ner Men Dis 2008; http://www.adaa.org
Family Genetic Risk Factors

Parental Anxiety Disorders

• Rates in *at-risk* offspring of parents with anxiety disorders ranged from 21-68% versus offspring of controls 0-26%

• Combining data from 14 studies, 37% of *at-risk* offspring of anxious parents had anxiety disorders compared with 15% of controls (OR 2.5)

Exposure to Maternal Anxiety Disorder Predicts Childhood Anxiety Disorders

Rates of Multiple Anxiety Disorders in Child

- No Disorder
- Disorder without Exposure
- Disorder with Exposure

OR=3.3, p=.082

OR=4.3, p=.042

OR’s with parental PD and MD covaried. Effect of exposure to GAD remains significant when presence of any maternal anxiety disorder is covaried as well.
ASSESSMENT OF CHILDHOOD ANXIETY DISORDERS

- STRUCTURED INTERVIEWS (K-SADS, ADIS-C)
- SELF REPORT INSTRUMENTS (e.g. R-CMAS, MASC, SCARED, STAI-C, FSSC-R, PARS)
- PARENT RATINGS (e.g. CBCL, PARS)
- TEACHER RATINGS (e.g. TRF)
- BEHAVIORAL OBSERVATIONS
- ANXIETY RATINGS (e.g. “Fear Thermometer”)
- FAMILY ASSESSMENT (e.g. FES)
Treatment of Pediatric Anxiety Disorders

- Psychotherapy Should Be Considered as Part of the Treatment of Childhood Anxiety Disorders
- Exposure-based CBT has the most empirical support

AACAP Guidelines: Connolly & Bernstein, 2007; Albano and Kendall, 2002
Treatment of Pediatric Anxiety Disorders

– 5 CBT components for childhood anxiety disorders:
  • psychoeducation,
  • somatic management skills training (relaxation),
  • cognitive restructuring (e.g., challenging negative expectations and modifying negative self-talk),
  • exposure methods (exposure w/desensitization)
  • relapse prevention plans (booster sessions)

AACAP Guidelines: Connolly & Bernstein, 2007; Albano and Kendall, 2002
Cognitive-Behavioral Interventions

- At least 20 controlled trials of CBT for childhood anxiety disorders (excluding studies of treatment of specific fears/phobias)
- All but two show efficacy for exposure-based protocols in reducing symptoms and diagnoses
- Limited by tendency to lump together different diagnoses, use of wait-list control groups in most (some of unequal duration), and omission of “intent to treat” analysis in some
Cognitive Behavioral Therapy (CBT)

Informed consent for pharmacotherapy is not “informed” without a discussion of CBT.

CBT is also the first line treatment for mild to moderate cases of OCD in children (AACAP Practice Parameter for OCD, 2012)
Meta-analysis of (non-OCD) Anxiety RCTs

• Randomized Placebo Controlled Trials of antidepressants in youth; 6 trials; N=1136
  • Generalized Anxiety Disorder
    – Rynn et al 2001 (Sertraline to 50mg)
    – Rynn et al 2007 (Venlafaxine to 225mg)
  • Social Anxiety Disorder/Social Phobia
    – Wagner et al 2004 (Paroxetine to 50mg)
    – March et al (Venlafaxine to 225mg)
  • Social Phobia/Separation/Generalized Anxiety
    – RUPP 2001 (Fluvoxamine to 300mg)
    – Birmaher et al 2003 (Fluoxetine to 20mg)

Bridge et al, 2007
Clinical response and serious AEs to SSRIs

6 trials, 1136 participants, CGI-I, 2-4 months, all favored SSRI but widely variable

**Pooled response rates**
- SSRIs 69% (95% CI 65%-73%)
- Placebo 39% (95% CI 35%-43%)
- Pooled difference 37% (23%-52%)
- NNT 3

**Pooled SI rates**
- SSRIs 1% (0.2%-2%)
- Placebo 0.2% (-0.2% - 0.5%)
- Difference 0.7% (-0.4%-2%) p=0.21
- NNH 143

Bridge et al 2007
Child/Adolescent Anxiety Multimodal Study (CAMS)

• Randomized, controlled trial of 488 children (7-17 yrs)
• SAD, GAD or social phobia
  – 14 sessions of CBT
  – sertraline (to 200mg/day)
  – combined CBT and sertraline
  – placebo for 12 weeks
• Categorical and dimensional ratings of anxiety severity and impairment

Walkup et al, NEJM 2008
CAMS: % CGI-I response

Sertraline* (N=133)  
4 wk = 19%; 8 wk = 47%; 12 wk = 55%

CBT (N=139)  
4 wk = 9%; 8 wk = 30%; 12 wk = 60%

Combination (N=140)  
4 wk = 21%; 8 wk = 54%; 12 wk = 81%

Placebo (N=76)  
4 wk = 7%; 8 wk = 22%; 12 wk = 24%

\(a P<0.001\) vs placebo  
\(b P<0.001\) vs Sertraline + vs CBT

Walkup et al, NEJM 2008

* Denotes off label use
CAMS: Pediatric Anxiety Rating Scale

Walkup et al, NEJM 2008
Guide for Pediatric Anxiety Disorders

First Line - SSRIs*, venlafaxine*, duloxetine*

Second Line – buspirone*, benzodiazepines* and TCA’s*

Third Line – mirtazepine*, gaba-ergic anticonvulsants*, propranolol, alpha agonists

Fourth Line – low dose atypicals*, quetiapine*

ALL ARE OFF LABEL AS THERE ARE NO FDA-APPROVED MEDICINES FOR ANXIETY IN CHILDREN!!

* Denotes off label use
Retrospective studies suggest that untreated anxiety disorders are persistent
   (Keller, 1992; Biederman, 1997)

12 prospective studies found that having a childhood anxiety disorder increased risk of developing anxiety disorders in later childhood, adolescence, or adulthood
   (Last, 1996; Costello, 2003; Kim-Cohen, 2003; Gregory, 2007)

Homotypic as well as heterotypic continuity

Fluvoxamine (RUPP) and Fluoxetine (Clark et al 2005) have shown long term efficacy
DSM V Obsessive-Compulsive and Related Disorders

Obsessive-Compulsive Disorder  Body Dysmorphic Disorder  Hoarding Disorder  Trichotillomania (Hair-Pulling Disorder)  Excoriation (Skin-Picking) Disorder  Substance/Medication-Induced OC & Related Disorder  Obsessive-Compulsive & Related Disorder Due to Another Medical Condition  Other Specified Obsessive-Compulsive and Related Disorder  Unspecified Obsessive-Compulsive and Related Disorder
Specifiers

a spectrum of insight:

Good or fair insight
Poor insight
Absent insight/delusional obsessive-compulsive disorder beliefs (i.e., complete conviction that obsessive-compulsive disorder beliefs are true)

*tic-related* specifier for obsessive-compulsive disorder reflects research validity (and clinical validity) of “identifying individuals with a current or past comorbid tic disorder, because this comorbidity may have important clinical implications.”
Obsessive Compulsive Disorder

Fourth most common mental illness\(^1\)
Under-recognized and under-reported\(^2\)
Among the ten leading global causes of disability (WHO)\(^3\)
Affecting children, adolescents and adults

\(^1\) DSM-IV-TR, \(^2\) Flament 1988, \(^3\) WHO
Epidemiology of OCD

In the British Child Mental Heath Survey
over 10,000 5-15 year olds
point prevalence 0.25%
almost 90% had been undetected and untreated. (Heyman et al., 2003)

Lifetime prevalence 1-2% (National Comorbidity Survey, Kessler et al 1994)

There appears to be two peaks of incidence for OCD, one occurring in pre-adolescent children and a later peak in early adult life (Geller et al., 1998)
The cortico-striato-thalamo-cortical model

Hypothesized neuro-circuit dysfunction in individuals with OCD

Two points in the circuit can lead to increased Glu signal from the thalamus to the frontal cortex:
• the GPi/SNr interaction with the thalamus and
• the interactions between the striatum and GPe

Heritability of Early Onset OCD = 45% - 65%
Heritability of Adult Onset OCD = 27% - 47%
Heritability for Obsessions = 33%
Heritability for Compulsions = 26%
Family studies find 24-28% risk for OCD in relatives of pediatric OCD probands (Nestadt et al., 2000; Hanna et al., 2005; Do Rosario-Campos et al., 2005)
Genome Regions Implicated in OCD
Age-Corrected Risk of OCD, TS, tics & ADHD in Relatives of Youth with OCD

<table>
<thead>
<tr>
<th>Subthreshold or Full OCD: Lifetime</th>
<th>Age-corrected rate (SE) in relatives of cases</th>
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<tbody>
<tr>
<td>OCD</td>
<td>26.3% (2.7%)</td>
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<tr>
<td>Tourette’s Syndrome</td>
<td>1.7% (0.8%)</td>
</tr>
<tr>
<td>Chronic Tics</td>
<td>7.5% (1.5%)</td>
</tr>
<tr>
<td>Tourette’s OR Chronic Tics</td>
<td>8.9% (1.6%)</td>
</tr>
<tr>
<td>ADHD</td>
<td>17.5% (2.1)</td>
</tr>
</tbody>
</table>

(Geller et al 2004)
Non-Genetic factors

Non-heritable etiological factors are as great or greater than genetic factors for risk of developing OCD.

Many if not most cases of OCD arise without a positive family history of the disorder, called “sporadic cases.”

Studies have focused on:
- perinatal (intrauterine, birth and postnatal)
- adverse psychosocial experiences
- immune mediated neuropsychiatric models of illness
Highly selective drug response to SSRIs led to “serotonergic hypothesis”

– Metabolic changes in 5HIAA with Rx
– Reduced responsiveness of post-synaptic receptors to endogenous serotonin

*Serotonergic hypothesis* remains unproven

SRI effect probably mediated by down-regulating auto-receptors $5HT_{1D}$
Quantitative Evaluation at baseline and post Rx

Scores of 8-15 represent mild illness, 16-23 moderate illness and scores ≥ 24 severe illness

The CY-BOCS is a \textit{clinician-administered} instrument that is most informative when given to both children \textit{and} their parents, where a “worst report” algorithm is likely to be most accurate

The Yale Brown OCD scale (Y-BOCS) is a copyrighted scale
Psychiatric comorbidity is the rule

Response rates in patients with comorbid disorders are significantly lower

Comorbidity is also associated with a greater rate of relapse following treatment (Geller et al., 2003)
Comorbid Disorders in Pediatric OCD
Review of Clinical Studies

- PDD: 5% (3%-7%)
- Enuresis: 17% (7%-37%)
- Speech/Developmental Disorder: 18% (13%-27%)
- Tic Disorders and TS: 21% (13%-26%)
- Disruptive Behavioral Disorders: 25% (3%-57%)
- Anxiety Disorder: 31% (13%-70%)
- Mood Disorder: 31% (8%-73%)
- Any Psychiatric Disorder: 80% (63%-97%)
Assess Family Accommodation

Parental efforts to relieve a child’s anxiety may inadvertently lead to accommodation and reinforcement of OC behaviors.

The role of individual family members in maintenance and management of OCD symptoms is important to assess.

Family Accommodation Scale for OCD - Interviewer-Rated (FAS-IR), (Calvocoressi et al 2011)
Pharmacotherapy of OCD

For moderate to severe OCD (CY-BOCS >16), medication is indicated

Indications for earlier drug intervention include:
- situations that impede CBT delivery
- concurrent psychopathology
- individual and family factors eg family accommodation
- poor insight
- shortage of skilled CBT practitioners

SSRIs are the first line medications recommended for OCD in children and should be used following AACAP guidelines to monitor response, tolerability, and safety
Pharmacotherapy of OCD

Serotonergic medications are effective in short, medium and long term treatment*

NNT ~ 3. Mean improvement on CY-BOCS is 6 points over placebo

Multimodal treatment (CBT plus medication) is recommended if CBT fails to achieve clinical response after several months and for more severe cases should be considered the “default” treatment

Meta-analysis of Pediatric OCD Trials

(Geller et al 2003)
Long-Term Sertraline OCD Trial

Mean CY-BOCS scores by age group for patients treated for 52 weeks with open-label sertraline who had received sertraline during initial 12 weeks of double-blind treatment.
The Pediatric OCD Treatment Study (POTS)

Intent To Treat CYBOCS Scores by Week of Treatment

Random Regression: CYBOCS = C + Site + Time + Tx + All 2 and 3 way interactions + Error

March et al J Am Med Assoc 2004
Meta-analysis of 18 studies
24 independent treatment comparisons
   10 pharmacological
   11 CBT
   3 combined interventions
control group
All were efficacious in reducing obsessive–compulsive symptoms with effect sizes
   $d = 1.203$ for CBT
   $d = 0.745$ for pharmacological treatments
   $d = 1.704$ for mixed treatments

Sanchez-Meca et al, J Anx Disorders 2014
124 pediatric OCD patients randomized to medication management with SSRI only 
med management with CBT (+CBT) 
med management with CBT “instruction” provided by psychiatrist (“CBT lite”) 

Primary outcome measure = 30% improvement on CY-BOCS 
Meds + CBT showed significantly greater improvement than meds alone or meds plus CBT instruction (“CBT lite”) 
The “plus CBT instruction” group was not significantly different from med management alone 

Franklin, ME, et al, 2011
POTS II Outcomes CY-BOCS Scores

Franklin, ME et al, 2011
Dosing Guidelines

Table 1: Dosing Guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose (mg)</th>
<th>Typical Dose Range (mg) (Mean Dose)*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Adolescent</td>
<td>Adolescent</td>
</tr>
<tr>
<td>Clomipramine †**</td>
<td>6.25-25</td>
<td>25</td>
</tr>
<tr>
<td>Fluoxetine †***</td>
<td>2.5-10</td>
<td>10-20</td>
</tr>
<tr>
<td>Sertraline †***</td>
<td>12.5-25</td>
<td>25-50</td>
</tr>
<tr>
<td>Fluvoxamine †**</td>
<td>12.5-25</td>
<td>25-50</td>
</tr>
<tr>
<td>Paroxetine ****</td>
<td>2.5-10</td>
<td>10</td>
</tr>
<tr>
<td>Citalopram ***</td>
<td>2.5-10</td>
<td>10-20</td>
</tr>
</tbody>
</table>

*Mean daily doses used in randomized controlled trials.
† FDA approved for OCD in children and adolescents.
**Doses < 25 mg/day may be administered by compounding 25mg into 5ml suspension.
***Oral concentrate commercially available.
****Oral suspension commercially available.

*Paroxetine and citalopram are off label for pediatric OCD.
What is an Adequate Drug Trial?

Adequate dosage and duration (10 to 12 weeks) needed to determine response to a given SSRI

Relatively high doses of SSRIs have been used in published studies

Systematic dose response data not available for children (mean dose in sertraline trial 178 mg/d)

Fluoxetine slow (at least 4 weeks), fluvoxamine faster (1-3 weeks)
Safety and Tolerability

• In general, SSRI medications are well-tolerated and safer than their predecessor TCAs

• Behavioral side effects are more likely in younger children and may be a late-onset effect. These are sensitive to dose adjustment

• Most commonly described adverse effects of SSRIs
  – CNS: headache, tremor, drowsiness, insomnia, sexual problems, disinhibition, agitation, or hypomania
  – GI: nausea, gastro-intestinal complaint,
SSRI’s and Suicidality

FDA black box warnings exist for all antidepressants but no suicides occurred in any of the pediatric OCD RCTs of SSRIs

Bridge et al. (2007) found no statistically increased risk of suicidal thinking or behavior in the pooled pediatric OCD trials

pooled absolute rate of suicidal ideation/attempt in OCD trials:

SSRI 1% (4/362) (95%CI 0-2%), Placebo 0.3% (1/339) (95%CI -0.3-1%), pooled risk difference 0.7% (95%CI -1%-2%, p=.57 NNH = 143-200) (Bridge et al 2007)

The risk of suicide from under treatment cannot be ignored in the risk:benefit assessment of prescribing medications
OCD with Tourette’s Disorder

SSRI alone (may be less effective)

Clomipramine alone

SSRI and clomipramine

SSRI or clomipramine & typical or atypical neuroleptic* (watch QTc)

SSRI or clomipramine & alpha 2 agonist*

* denotes off label use
OCD with Bipolar Disorder

The pharmacotherapist’s nightmare

Higher rates of comorbid BPD than expected (5-10%)

Drawbacks of using SRI’s to treat OCD: behavioral activation and organic mood changes with hypomania

Mood stabilizers or atypical neuroleptics* may be needed to counteract activating effects of SRI’s

Treat bipolar disorder first

* Denotes off label use for OCD but not Bipolar Disorder
OCD with ADHD

Comorbidity of OCD with ADHD requires further treatment

Stimulants are often needed for ADHD with OCD

Treat OCD first

Stimulants may increase primary obsessions and rituals or anxiety

Consider clomipramine
Consider atomoxetine
Consider bupropion*
Consider clonidine* or guanfacine*  

* Denotes off label use
OCD with Psychotic symptoms

Rate = 6% in MGH sample (N = 130)

Obsessions or overvalued ideas or delusions? Insight diminishes with younger age

Symptoms atypical/bizarre for OCD

Other positive and negative psychotic symptoms present Poor response or deteriorating course May be associated with mood disorder, especially bipolar

Atypical Antipsychotics useful*

* Denotes off label use for OCD but not Psychosis
Most children are partial responders, not non-responders

If no clinical response after 10 to 12 weeks of first SSRI, switch to another SSRI or to clomipramine

Increase intensity, frequency of CBT (ERP). You are not alone

For patients with only partial therapeutic response after several successive trials, *augmentation* strategies may be useful
Medication Augmentation Strategies

are reserved only for treatment resistant cases where impairments are deemed moderate in at least one important domain of function

SSRI + Anafranil (beware CYP interactions eg 2D6 and 3A4, monitor serum CMI levels and QTc)

SSRI + benzodiazepine* (clonazepam*) (Leonard et al, 1994)

SSRI + Atypical antipsychotic* (Bloch 2006)

Switch to venlafaxine* or duloxetine* (Dell’Osso 2006)

* Denotes off label use
Adjunctive Atypical Antipsychotics

Adult studies: typical* and atypical antipsychotics* are effective neuroleptics (Bloch et al., 2006; McDougall et al., 2000)

9 trials N = 143 atypicals, 135 placebo
Haloperidol* 1/1, risperidone* 1/3, olanzepine* 1/2, quetiapine* 1/3

In meta-analysis: Effect size modest d=0.22 but p <.001
Antipsychotics for poor insight or comorbid tics d=0.43
One third responded well after 12 weeks

Pediatric open label augmentation with risperidone* or aripiprazole* in tic-related OCD not responsive to SSRI monotherapy highly effective

* denotes off label use

All are off label for pediatric OCD
Novel augmentation strategies*

stimulants, sumatriptan, pindolol, inositol, St. John’s wort, morphine, tramadol
propanolol, alpha agonists (especially for PTSD and reactive attachment disorder)
gaba-ergic: benzodiazepines, gabapentin, pregabalin
glutamatergic drugs & cognitive enhancers (Grados 2013)
   Riluzole
   Memantine
   D cycloserine
   N acetyl cysteine
   Glycine
   Ketamine
   Acamprosate

– none of these meet minimal standards that permit recommendation for their routine use. * All are off label.
Exposure and Response Prevention Enhancement using glutamate drugs*

Extinction of fear may be mediated by NMDA receptor-dependent LTP-like plasticity within the baso-lateral amygdala (BLA)

- Memantine: glutamate receptor antagonist, reduced OCD symptoms by 25% in 44 matched case study treatment-resistant adults, p=ns (Stewart et al, 2010, Ghaleiha et al 2013)

- Riluzole?
- N-acetyl cysteine (NAC)?
- D Cycloserine?
Riluzole Augmentation in Pediatric OCD

12-week, double-blind, placebo-controlled study, 60 treatment-resistant children and adolescents (14.5±2.4 years), with moderate to severe OCD [mean Children’s Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) = 28.2±3.7]

17 also had concomitant autism spectrum disorder

randomized to riluzole (final dose 100 mg/day) or placebo in addition to the existing treatment regimen

All improved, no group differences
D-Cycloserine Augmentation of CBT

D-Cycloserine (DCS) is a partial NMDA agonist
Enhances NMDA neurotransmission

Pilot Study:

- CGI-Severity: main effect for group ($p=.02$, $d=0.97$);
- CY-BOCS: main effect for group ($p=.09$) ES moderate ($d=0.67$)

Double blind placebo controlled trial (NIMH)

N=144

No group differences

(* = off label use (Storch and Geller 2010))
“Third Wave” Therapies

Acceptance and Commitment Therapy (ACT)
   Cognitive de-fusion and acceptance

Attention Bias Modification
   Retraining attention biases away from “threat”

BRAVE-Online
   Body, Relax, Activate, Victory, Enjoy

Trauma Focused CBT (TF-CBT)

Cognitive Behavioral Intervention for Trauma in Schools (CBITS)
Deep Brain Stimulation Y-BOCS Scale

Percent of Improvement with DBS Follow-up Study Results

* Within-subject change statistically significant (p ≤ .001, two-sided test).

Courtesy of D. Dougherty et al
Cymbalta

FDA approved Oct 16th 2014
Pediatric Advisory Committee Focused Safety Review, March 2015

- Strawn et al JAACAP 2015, 54:4:283-293
- Single 10 week study, N 272 (135 active) in age 7-17 years
- Start 30 mg/d and increase to 60 mg/d

<table>
<thead>
<tr>
<th></th>
<th>Cymbalta</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Response &gt;50%</td>
<td>59%</td>
<td>42%</td>
</tr>
<tr>
<td>Remission ≤8 PARS</td>
<td>50%</td>
<td>34%</td>
</tr>
<tr>
<td>Function Remission</td>
<td>37%</td>
<td>24%</td>
</tr>
</tbody>
</table>

- Sig effect above placebo using PARS -9.7 vs. -7.1 p=.001, Cohen’s D = 0.5
- AE’s GI, dizziness, palpitations, +6.5 pulse, -0.1Kg
- FDA Adverse Event Reporting System (FAERS) Worldwide SAE’s in decade to 2014 = 198/28 and 12/5 fatal

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