Pharmacotherapy for Anxiety in Children & Adolescents

Daniel S. Pine, MD
Disclosures: Conflicts

Sources of Research Support
National Institute of Mental Health

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Am J Psychiatry– Deputy Editor

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None

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None

Speaker’s Bureau
None

Role in pharmacology, DSM-5

FDA Committee & Black Box Vote

“Off-Label” use

My perspective
Outline & Objectives

- **Classifying Pediatric Mood & Anxiety**
  - *Broad categorization schemes*
  - *Outcome & treatment implications*

- **Current Treatments**

- **Finding Novel Treatments**
  - *Underlying neurobiology*
  - *Using neuroscience to guide discovery?*
Outline & Objectives

- Classifying Pediatric Mood & Anxiety
  - Broad categorization schemes
  - Outcome & treatment implications
Defining Mental Illness

- Long history of debate
  - *Harmful dysfunction*

- Similar or different from other illness?
  - *Signs, symptoms, & impairment*
  - *Impact on function*
  - *Complexity of the brain*
  - *Context specificity of signs & symptoms*
  - *Identify extremes of “normal” behavior*
The Diagnostic and Statistical Manual

DSM-III
DSM-5 Classification & Anxiety

- Mostly minor change, except for structure
  - revision process
  - placement of child disorders
  - broad disorder groupings
  - move toward dimensions

- Changes in anxiety minor (*e.g.*, vs. Autism)
DSM-5 & Anxiety

OCD
- Associations with tics, ADHD
- Basal ganglia dysfunction, PANDAS
  - Leckman, Leonard, Peterson, Rosenberg, Swedo, others

PTSD
- Longitudinal associations with wide array of disorders
- HPA axis dysfunction
  - DeBellis, Heim, Nemeroff, Pynoos, others

Social Anxiety, GAD, Separation Anxiety, [Phobias]
- Considered as a group in most major treatment studies
  - Biederman, Kendal, Kessler, Pine, Rosenbaum, Weissman, others
- Specific Association with MDD and “distress vs. fear”? 
  - Particularly GAD?
Mostly minor, except bipolar disorder

Controversy about bipolar disorder

- Classic presentation is rare
- How to classify chronically irritable child?

Disruptive Mood Dysregulation Disorder
RDoC: What is RDoC???

- Based in neuroscience
- Focuses on Narrow Behaviors
- Focuses on Dimensions
Avoidance

- What is avoidance & where do we see?
- Predicts many bad things
- How does environment respond?
- Cut the sutures too short or long?
Longitudinal Data

Clinic-based
Family-based
Community-based
Sub-clinical Precursors
Any Adolescent Anxiety Disorder & Any Adult Mood/Anxiety Disorder

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<tr>
<th>Disorder as Adolescents?</th>
<th>Disorder as Adults?</th>
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Total: 581, 98, 679

*Pine et al. 1998, 2001, 2002*
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*Pine et al. 1998, 2001, 2002*
Outline & Objectives

- Classifying Pediatric Mood & Anxiety
  - *Broad categorization schemes*
  - *Outcome & treatment implications*
Outline & Objectives

- **Classifying Pediatric Mood & Anxiety**
  - *Broad categorization schemes*
  - *Outcome & treatment implications*

- **Current Treatments**
Treatment

- Major Depression
  - SSRI Medications
  - Psychotherapy: CBT? & IPT?

- Anxiety Disorders
  - SSRI Medications
  - Psychotherapy: CBT
SSRIs, CBT, & Efficacy in Pediatric Anxiety
SSRIs, CBT & Pediatric Anxiety: Efficacy

- SSRI evidence for efficacy in GAD, social anxiety, separation anxiety disorder
- Particularly good evidence for fluvoxamine, fluoxetine, paroxetine, sertraline, (duloxetine, venlafaxine)
- Also good evidence for CBT
- Comparative efficacy of SSRIs & CBT?
FLUOXAMINE FOR THE TREATMENT OF ANXIETY DISORDERS IN CHILDREN AND ADOLESCENTS

THE RESEARCH UNIT ON PEDIATRIC PSYCHOPHARMACOLOGY ANXIETY STUDY GROUP*

## Meta-Analysis: *Rates of Improvement*

<table>
<thead>
<tr>
<th>Study</th>
<th>Difference</th>
<th>PBO</th>
<th>SSRI</th>
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<tr>
<td>RUPP Anxiety Study (2001)</td>
<td>47%</td>
<td>29%</td>
<td>76%</td>
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<tr>
<td>Birmaher et al. (2003)</td>
<td>25%</td>
<td>36%</td>
<td>61%</td>
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<tr>
<td>Rynn et al. (2001)</td>
<td>80%</td>
<td>10%</td>
<td>90%</td>
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<tr>
<td>Wagner et al. (2004)</td>
<td>40%</td>
<td>38%</td>
<td>78%</td>
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<tr>
<td>Walkup et al. (2008)</td>
<td>31%</td>
<td>24%</td>
<td>55%</td>
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<tr>
<td>Rynn et al. (2007)</td>
<td>12%</td>
<td>24%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>30%</strong></td>
<td><strong>31%</strong></td>
<td><strong>61%</strong></td>
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NNT=3.3
Cognitive Behavioral Therapy

- Evidence of Efficacy
  - Quite strong
  - Specificity in therapy procedures

- How does CBT work?
  - Make “fear hierarchy”
  - Learn new techniques
  - Graded exposure
  - Importance of patient’s control and success
  - Role of the therapist?
Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety

John T. Walkup, M.D., Anne Marie Albus, Ph.D., John Piacentini, Ph.D., Scott Birmaher, M.D., Scott R. Compton, Ph.D., Joel T. Sherrill, Ph.D., Golda G. Gershberg, Ph.D., Moira A. Smyt, M.D., James McCracken, M.D., Bruce W. Wozniak, M.D., Batish Byengir, Ph.D., John S. March, M.D., M.P.H., and Philip C. Kendall, Ph.D.*

This article (10.1056/NEJMoa0804633) was published at www.nejm.org on October 30, 2008.

A Randomized, Placebo-Controlled Study of Duloxetine for the Treatment of Children and Adolescents With Generalized Anxiety Disorder

Jeffrey R. Strawn, MD, Apurva Prakash, BA, Qi Zhang, PhD, Beth A. Pangallo, RN, Chad E. Stroud, RN, Na Cai, PhD, Robert L. Findling, MD, MBA

Child/Adolescent Anxiety Multimodal Study: Evaluating Safety

Moira A. Rynn, MD, John T. Walkup, MD, Scott N. Compton, PhD, Dara J. Sakolsky, MD, PhD, Joel T. Sherrill, PhD, Sa Shen, PhD, Philip C. Kendall, PhD, James McCracken, MD, Anne Marie Albano, PhD, John Piacentini, PhD, Mark A. Riddle, MD, Courtney Keeton, PhD, Bruce W. Waslick, MD, Allan Chrisman, MD, Satish Iyengar, PhD, John S. March, MD, MPH, Boris Birmaher, MD

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 20, Number 8, 2010
© Mary Ann Liebert, Inc.
PP. 463–471
DOI: 10.1089/cap.2009.0115

Sertraline Treatment of Children and Adolescents With Posttraumatic Stress Disorder: A Double-Blind, Placebo-Controlled Trial

Adelaide S. Robb, M.D.; Jeanette E. Cueva, M.D.; Jonathan Sporn, M.D.; Ruoyong Yang, Ph.D., and Douglas G. Vanderburg, M.D., M.P.H.

Naturalistic Follow-up of Youths Treated for Pediatric Anxiety Disorders

Golda S. Ginsburg, PhD; Emily M. Becker, MS; Courtney P. Keeton, PhD; Dara Sakolsky, MD, PhD; John Piacentini, PhD; Anne Marie Albano, PhD; Scott N. Compton, PhD; Satish Iyengar, PhD; Kevin Sullivan, BS; Nicole Caporino, PhD; Tara Peris, PhD; Boris Birmaher, MD; Moira Rynn, MD; John March, MD, MPH; Philip C. Kendall, PhD

2015
SSRIs, CBT, & Efficacy in Pediatric Major Depressive Disorder (MDD)
SSRIs and Pediatric MDD: Efficacy

- fluoxetine works (3 of 3½ studies)
- Weak evidence for sertraline (not really), citalopram (2 of 4 studies)
- FDA Approval: fluoxetine/prozac; escitalopram/lexapro
- Some (very weak) evidence for paroxetine
- Virtually no evidence for other agents
- What gives?
  - Data in adults that strong?
  - Differences among the SSRIs?
  - Differences in placebo response, sample, assessment
Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression

Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial

Results
- Fluoxetine vs. placebo
- CBT vs. placebo

What does this mean?
- Strong role of expectancy
- What do we recommend to patients?

First Line Treatments?
Switching to Another SSRI or to Venlafaxine With or Without Cognitive Behavioral Therapy for Adolescents With SSRI-Resistant Depression
The TORDIA Randomized Controlled Trial

**Bottom Line?**

- Only significant benefit was for CBT
SSRIs and Controversy
SSRIs and Controversy

- Biased reporting of data for efficacy
Biased Reporting in Adult Antidepressant Trials

Turner et al. NEJM 2008

Bias in Publication

Bias in Magnitude of Clinical Effect
SSRIs and Controversy

- Concerns about suicidal ideation
Antidepressants and Thoughts About Suicide

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Children</td>
<td>2.22 (1.40–3.60)</td>
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<tr>
<td>18–24 yr</td>
<td>1.55 (0.91–2.70)</td>
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<tr>
<td>25–30 yr</td>
<td>1.00 (0.60–1.69)</td>
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<tr>
<td>31–64 yr</td>
<td>0.77 (0.60–1.00)</td>
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<tr>
<td>≥65 yr</td>
<td>0.39 (0.18–0.78)</td>
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<tr>
<td>All adults</td>
<td>0.84 (0.69–1.02)</td>
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SSRIs and Controversy

- FDA & Black Box
SSRIs are very effective in the treatment of pediatric anxiety (and OCD).

Of the SSRIs, only fluoxetine and citalopram have been shown to be effective in pediatric MDD, and the NNT is large.

Increased risk of suicidality with SSRIs is real, but the magnitude of the effect is small.
Pediatric Bipolar Disorder
Mostly minor, except bipolar disorder

- Controversy about bipolar disorder
  - Classic presentation is rare
  - How to classify chronically irritable child?

Disruptive Mood Dysregulation Disorder
Treatment of Bipolar Disorder

- Wide use of many medications

- FDA:
  - aripipazole (Abilify)
  - quetiapine (Seroquel)
  - risperidone (Risperdol)
  - olanzapine (Zyprexa) (ages 13 to 17)

- No evidence for anticonvulsants

- FDA Approval for lithium (13 to 17)

- Not much other strong data; concerns about safety
A Randomized Controlled Trial of Risperidone, Lithium, or Divalproex Sodium for Initial Treatment of Bipolar I Disorder, Manic or Mixed Phase, in Children and Adolescents

Trial Registration: clinicaltrials.gov identifier: NCT00057681

Barbara Geller, MD; Joan L. Luby, MD; Paramjit Joshi, MD; Karen Dineen Wagner, MD, PhD; Graham Emshlie, MD; John W. Walkup, MD; David A. Axelson, MD; Kristine Bolhofner, BS; Adelaide Robb, MD; Dwight V. Wolf, MD; Mark A. Riddle, MD; Boris Birmaher, MD; Nasima Nusrat, MD; Neal D. Ryan, MD; Benedetto Vitiello, MD; Rebecca Tillman, MS; Philip Lavori, PhD

Arch Gen Psychiatry.

Published online January 2, 2012.

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5671 Subjects screened for eligibility for baseline assessments

4599 Were not eligible and were given clinical referrals

335 Were given clinical referrals

300 Were ineligible

197 Did not meet entry criteria

33 Had PDD or schizotypal

22 Refused to participate in study

17 Excluded for medical reasons

17 Excluded for other reasons

8 Had substance abuse problems

6 Had substance abuse problems

3 Refrigerated study medications

2 Required intensive outpatient services

28 Refused baseline after being scheduled

249 Were maintenance medication-naive subjects at baseline who were randomly assigned to risperidone, lithium, or divalproex sodium

89 Were partial responders or nonresponders to 1 medication at baseline who were randomly assigned to add on or cross-taper to either of the 2 other medications

95 Randomized to risperidone for 8 weeks

14 Discontinued treatment

28 Discontinued treatment

5 Changed their minds

1 Had adverse effects

0 Had worsening symptoms

2 Were hospitalized

2 Geographically relocated

1 Worst medical illness

1 Had 15% Weight gain and BMI >25th percentile

1 Discontinued for other reasons

15 Completed the study

10 Partial or nonresponders

12 Partial responders

3 Nonresponders

90 Analyzed

31 Randomized to lithium for 8 weeks

15 Changed their minds

0 Had adverse effects

3 Had worsening symptoms

2 Were hospitalized

2 Geographically relocated

3 Worst medical illness

1 Had 15% Weight gain and BMI >25th percentile

1 Discontinued for other reasons

4 Discontinued

28 Discontinued for other reasons

14 Completed the study

8 Partial or nonresponders

9 Partial responders

1 Nonresponder

90 Analyzed

104 Randomized to divalproex sodium for 8 weeks

26 Discontinued treatment

14 Changed their minds

27 Discontinued treatment

5 Had adverse effects

2 Had worsening symptoms

23 Were hospitalized

10 Geographically relocated

1 Worst medical illness

4 Had 15% Weight gain and BMI >25th percentile

2 Discontinued for other reasons

11 Discontinued for other reasons

41 Completed the study

57 Partial or nonresponders

28 Partial responders

10 Nonresponders

100 Analyzed

---

Subjects With CGI-BP-M Score ≤2 %

Risperidone (n=89) 68.5

Lithium (n=90) 35.6

Divalproex Sodium (n=100) 24.0

---

P < .001

P < .001

P = .20
Practical Points

- Anxiety easier to treat than mood
- Two good treatments available
- Importance of exposure in anxiety
- Mood disorders are very serious; handle with care and experts
Outline & Objectives

- **Classifying Pediatric Mood & Anxiety**
  - Broad categorization schemes
  - Outcome & treatment implications

- **Current Treatments**

- **Finding Novel Treatments**
  - Underlying neurobiology
  - Using neuroscience to guide discovery?
SEROTONIN ANATOMY
Development, Anxiety, & 5-HT1a R

Gross et al. Nature 2002

The effect of SSRIs on developing nervous system is not fully understood


5-HT1a receptor must be present pre-adolescence to “rescue” anxious phenotype.
Fluoxetine Administered to Juvenile Monkeys: Effects on the Serotonin Transporter and Behavior


Effects of Fluoxetine and Maternal Separation on Serotonin Transporter (SERT) in the Neocortex

FIGURE 1. Distribution of $^{11}$C-DASB Binding to Serotonin Transporters (SERT) and $^{11}$C[(R)-RWAY Binding to Serotonin 1A (5-HT$_{1A}$) Receptors in the Representative Brain of a Normally Reared Monkey That Received Placebo

FIGURE 3. Fluoxetine Increased Serotonin Transporter (SERT) Binding in the Lateral Temporal, Cingulate, and Orbitofrontal Cortices as Shown by Whole-Brain Voxel-Wise Analysis

Effects of Fluoxetine and Maternal Separation on Serotonin Transporter (SERT) in the Neocortex
Attention Retraining Therapy

Training of Attention

Changes in SPAI in n=36 patients with Social Phobia

Schmidt et al. 2008
Meta-Analysis: Training Studies

Hakamata et al. 2010
Randomized Controlled Trial

Four-Week Treatment Outcomes in Pediatric Anxiety Disorders

Eldar et al. 2012

Anxiety Symptoms

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Eldara, Ricona, & Bar-Haim 2008

Training of Attention Altered Response to Stress
TRAINING

Exposure to context (2 min)

Onset of sound (CS: 30 s)

Onset of shock (US: 2 s)

TESTING: Context
Test at 1 hour and 24 hours

Same context (5 min)

Onset of sound (CS: 3 min)

TESTING: Cued
Test at 1 hour and 24 hours
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Extinction:

Not forgetting but new learning

Anxiety disorders as problems in new learning

Ressler & Davis 2003
NMDA manipulations?

Ressler & Davis 2003
Acrophobia within the virtual environment is improved with D-cycloserine

Data on Social Phobia are equivocal


Panic Disorder is improved with D-cycloserine


Positive findings in some...

Guastella et al. 2008; Hofmann et al. 2006; Wilhelm et al. 2008;

but not in other...studies.

Guastella et al. 2007; Kushner et al. 2007; Rothbaum et al. 2014; Storch et al. 2007, 2010

Otto et al. Biol Psychiatry 2010
Practical Points

- We know much about anxiety
- Basic knowledge informs treatment
- Informs treatments we have
- May lead to new treatments
Outline & Objectives

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  - Broad categorization schemes
  - Outcome & treatment implications

- Current Treatments

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