Treating Mood and Anxiety Disorders in Children & Adolescents

Daniel S. Pine, MD
Section on Development & Affective Neuroscience

Outline & Objectives

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

- Current Treatments

- Finding Novel Treatments
  - Underlying neurobiology
  - Using neuroscience to guide discovery?

Disclosures: Conflicts

- Sources of Research Support
  - National Institute of Mental Health

- Role in pharmacology, DSM-5, RDoC
- FDA Committee & Black Box Vote
- "Off-Label" use
- My perspective

- Paid Editorial Relationship
  - Am J Psychiatry- Deputy Editor

- Consulting Relationships
  - None

- Stock Equity (>510,000)
  - None

- Speaker’s Bureau
  - None

My perspective
Outline & Objectives

- Classifying Pediatric Mood & Anxiety
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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”? [Pine, 2007]

- ** DSM-5 Classification & Mood Disorders **
  - Mostly minor, except bipolar disorder
    - Controversy about bipolar disorder
      - Classic presentation is rare
      - How to classify chronically irritable child?
  - Disruptive Mood Dysregulation Disorder

- **RDoC**
  - Based in neuroscience
  - Focuses on Narrow Behaviors
  - Focuses on Dimensions
Longitudinal Data

- Clinic-based
- Family-based
- Community-based
- Sub-clinical Precursors

### Any Adolescent Anxiety Disorder & Any Adult Mood/Anxiety Disorder

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  - Outcome & treatment implications
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- 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?

Rates of Improvement

<table>
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<tr>
<th>Study</th>
<th>Difference</th>
<th>PBO</th>
<th>SSRI</th>
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<tr>
<td>9 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>Birmaher et al. (2004)</td>
<td>40%</td>
<td>38%</td>
<td>78%</td>
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<tr>
<td>Sup et al. (2008)</td>
<td>31%</td>
<td>24%</td>
<td>55%</td>
</tr>
<tr>
<td>Rynn et al. (2007)</td>
<td>12%</td>
<td>24%</td>
<td>36%</td>
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<tr>
<td>Total</td>
<td>30%</td>
<td>31%</td>
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Meta-Analysis: Rates of Improvement

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?
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?
• **Bottom Line?**
  - Only significant benefit was for CBT

**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>
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<tr>
<th>Age Group</th>
<th>Odds Ratio (95% CI)</th>
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<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 (0.95−2.70)</td>
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<tr>
<td>25–30 yr</td>
<td>1.00 (0.60−1.69)</td>
</tr>
<tr>
<td>31–64 yr</td>
<td>0.77 (0.60−1.00)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>0.39 (0.18−0.78)</td>
</tr>
<tr>
<td>All adults</td>
<td>0.84 (0.69−1.02)</td>
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FDA Analysis from December, 2006
SSRIs and Controversy

- FDA & Black Box

Bottom Line of the SSRIs

- 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
DSM-5 Classification & Mood Disorders

- 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:
    - aripiprazole (Abilify) (age 10 to 17)
    - 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
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

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


5-HT1a receptor must be present pre-adolescence to "rescue" anxious phenotype.

Article:
Fluoxetine Administered to Juvenile Monkeys: Effects on the Serotonin Transporter and Behavior
Attention Retraining Therapy

Training of Attention

Meta-Analysis: Training Studies

Hakamata et al., 2010
Randomized Controlled Trial

Eldar et al. 2012

Four-Week Treatment Outcomes in Pediatric Anxiety Disorders

Anxiety Symptoms

- ABM
  - n=15
- Placebo
  - n=15
- NN
  - n=10

Pre-treatment vs. Post-treatment

Exposure to Stress

- Test at 0 hour
- Test at 24 hours

Testing Card

- Test at 1 hour
- Test at 24 hours

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Extinction:
Not forgetting but new learning
Anxiety disorders as problems in new learning

Ressler & Davis 2003
Acrophobia within the virtual environment is improved with D-cycloserine. Data on Social Phobia are equivocal. Positive findings in some... but not in other... studies.

Practical Points

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