The Society for Clinical Child and Adolescent Psychology (SCCAP): Initiative for Dissemination of Evidence-based Treatments for Childhood and Adolescent Mental Health Problems

With additional support from Florida International University and The Children’s Trust.
Workshop
Multimodal Treatment for Internalizing Disorders

Anne Marie Albano, PhD, ABPP
Associate Professor of Clinical Psychology in Psychiatry
Director, Columbia University Clinic for Anxiety and Related Disorders
Columbia University School of Medicine

James Waxmonsky, M.D.
Medical Director: Center for Children and Families
Associate Professor of Psychiatry
Florida International University
Herbert Wertheim College of Medicine
Dr. Albano Disclosures

<table>
<thead>
<tr>
<th>Royalties</th>
<th>Paid Editorial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oxford University</td>
<td>Journal of Consulting and Clinical Psychology, Associate Editor</td>
</tr>
<tr>
<td>Press</td>
<td></td>
</tr>
<tr>
<td>2. Lynn Sonberg Books</td>
<td>Consulting Relationship</td>
</tr>
<tr>
<td></td>
<td>Brackett Global</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sources of Research Support</th>
<th>Stock Equity (&gt; $10,000)</th>
<th>Speaker’s Bureau</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. National Institute of Mental Health, NIH</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2. Duke Clinical Research Institute/Pfizer</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Description of the Disorders

DSM-IV Diagnostic Criteria
Separation Anxiety Disorder: “A” Criterion

• distress when separation is anticipated or occurs
• worry about harm befalling others
• worry that an untoward event will result in separation
• refusal to go to school or elsewhere

• fear or reluctance to be alone at home or in other settings
• refusal to sleep away from attachment figures
• nightmares
• physical complaints at separation
SAD: Symptom Age Trends

- Ages 5-8: fears of harm befalling attachment figures; nightmares, school refusal
- Ages 9-12: excessive distress at separation
- Ages 13-16: somatic complaints and school refusal
Social Phobia

• Marked and persistent fear of social situations in which the person is exposed to unfamiliar people or possible evaluation; fears embarrassment or humiliation

• The situation provokes anxiety

• The situation is avoided or endured with distress

• Interference in functioning

• Duration of at least 6 months
Age Trends in Social Phobia

• May begin as inhibited temperament in preschoolers
• Associated with selective mutism in young school-age children
• Higher prevalence in postpubertal adolescents
• Retrospective reports of adults place age of onset in adolescence
Generalized Anxiety Disorder

- Excessive anxiety and worry occurring more days than not for at least 6 months, about a number of activities or events
- The worry is difficult to control
- At least 1 physiologic symptom: restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbance
Worry in Children and Adolescents

• Unrealistic and excessive worry about future events occurs in over 95% of GAD children (Strauss, Lease et al., 1988)

• Future oriented worry: upcoming vacations, social and school events, family members’ health, doctors appointments, family finances, competence in sports or school
Age Trends: GAD

• Onset as early as age 4 (Beitchman et al., 1987)
• Mean age 10.8 years to 13.4 years (Last, Strauss et al., 1987; Last, Hersen et al., 1987)
• Occurs in 3% of younger children
• Estimates for adolescents 6% to 7%
What is the principal motivating condition for the school refusal behavior?

Diagnosis of specific phobia of school is appropriate only if the fear is circumscribed to a particular school-related situation (e.g., fire drills)

Must be distinguished from social phobia, separation anxiety, and panic
FOUR FUNCTIONS OF SCHOOL REFUSAL BEHAVIOR

1. To escape/avoid negative affect (dread, anxiety, depression, physiological symptoms).
2. To escape/avoid aversive social and/or evaluative situations at school.
3. To receive attention from significant others outside of school.
4. To obtain positive tangible reinforcement outside of school.
Scope of School Refusal

• **Rates**: About 5-10% of the school-aged population, although the problem is considerably more prevalent in some urban areas.

• **Gender/SES distribution**: Equal boys and girls and among families of various socioeconomic levels.

• **Age trends**: Mostly 10-13 years old.

• **Time issues**: The problem also peaks at times of school transition, such as 5-6 and 14-15 years as children enter new schools.
Prevalence of Anxiety Disorders

Among the most common disorders

Range = 12% - 20% of community youngsters

More Common (≈ 5%):

GAD, Sep Anx, Spec Phobia

Less Common (≈ 1-2 %):

Soc Phob, Ag/Panic, OCD, SM

Need to Differentiate Disorder from Developmentally Normal Fears

IMPAIRMENT
Developmental Aspects of Anxiety

Developmental Progression of Normative Fears

**Preschool**: Imaginary, Objects/situations

**Grade School**: Health/harm, Scrutiny/Competence

**Adolescence**: Social Adequacy & Performance

Developmental Progression of Anxiety Disorders

Spec Phob, SAD, OAD/GAD, OCD, Soc Phob, Ag/Pan

Age Trends Unclear: Panic ↑ with age; SAD ↓ with age
Comorbidity of Anxiety Disorders in Children and Adolescents

Comorbidity Rates Quite High

Anxiety > Depression > Externalizing Disorders

**Internalizing Disorders**: 13% - 72%
17% - 50% Anxious Ss → Comorbid Depression
33% - 75% Depressed Ss → Comorbid Anxiety

**Externalizing Disorders**: 7% to 39%

Comorbidity: ↑ severity and impairment
Course / Continuity of Anxiety

Prospective vs. Retrospective Studies

**Retrospective:**

\[ \approx 50\% \text{ Anx/Dep Adults} \rightarrow \text{History of Childhood Anxiety} \]

**Prospective:**

Some stability of Anxiety Symptoms in childhood

Most Anxiety Disorders (\(\approx 80\%)\) remit by follow-up

Child Anxiety predicts both later Anxiety and MDD

May be more stable in girls and adolescents
Family Genetics: Anxiety

Top-Down vs. Bottom-Up

Many studies show nonspecific findings:
Anx, Dep, Comorbid Parents $\rightarrow$ Anx Youths

Better specificity found for:
Child Social Phobia $\rightarrow$ Adult Social Phobia
Child Sep Anxiety $\rightarrow$ Adult Panic Disorder
Child GAD/OAD/MDD $\rightarrow$ Adult GAD/MDD
Family Environment

Parents of Anxious Children are more likely to:

- Reciprocate child avoidance behaviors
- Provide negative feedback
- Act in more restrictive manner to children

These parental behaviors have been shown to exacerbate anxious and avoidant behavior in children.

Anxious mothers are more critical, less warm towards their children, especially when the child is also anxious.
Other Risk Factors for Anxiety

Environmental Stressors:
- Traumatic Events
- Psychosocial Disadvantage

Constitutional Factors:
- Neurologic Soft Signs
- Psychophysiologic/Cardiac Hyperreactivity
- Anxious/Resistant Attachment
- Behavioral Inhibition
Significance of Child Anxiety

Most Common Class of Childhood Disorders

12% - 20% of community children

Associated with Significant Impairment

As much or more than CD

Often Unrecognized and Untreated

Due to perception as developmentally normal and innocuous

Public Health Significance is High
Depression in DSM-IV

- Depressed or irritable mood
- Lack of pleasure
- Weight or appetite change
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Worthlessness or guilt
- Problems with concentration, memory, or indecisiveness
- Recurrent thoughts of death or frank suicidality
• Five of nine symptoms
• Symptoms occur nearly every day
• Cause distress and dysfunction
• Not due to substance abuse or medical illness
• Not due to bereavement
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>2-7%</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>5-10%</td>
</tr>
<tr>
<td>Separation Anxiety Disorder</td>
<td>2-5%</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>3-4%</td>
</tr>
<tr>
<td>Simple Phobia</td>
<td>2-3%</td>
</tr>
<tr>
<td>ADHD</td>
<td>6-10%</td>
</tr>
<tr>
<td>Oppositional Disorder</td>
<td>6-10%</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>3-5%</td>
</tr>
</tbody>
</table>
Epidemiology (2)

- Prepubertal: males = females
- Adolescence: females rise, males decrease
- Dysthymia >> Major Depression
- Moderate stability
- High recurrence rates
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>MDD</th>
<th>DYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>ODD and CD</td>
<td>40%</td>
<td>15%</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>45%</td>
<td>15%</td>
</tr>
<tr>
<td>OCD</td>
<td>5%</td>
<td>30%</td>
</tr>
<tr>
<td>PTSD</td>
<td>?</td>
<td>60%</td>
</tr>
</tbody>
</table>
Depression Risk: Negative Life Events

- Parental loss
- Abuse or neglect
- Marital discord
- Peer problems
- School failure
- Chronic illness
- Low SES
Depression Risk: Family Characteristics

- Mood disorders
- Anxiety disorders
- Substance abuse
- Negative life events
Depression Risk: Medical Causes

- Chronic illness
- Medications
- Endocrinopathies
- Anemia
- Liver disease
- Heavy metal poisoning
Vulnerability for Depression

1. Biological (Genetic) Factors
2. Negative Life Events
3. Early Experience & Insecure Attachment
4. Affect Regulation
5. Social Behavior; Social Support
6. Cognitive Biases / Deficits
Cumulative lifetime prevalence of major classes of DSM-IV diagnoses

NCS-A, N=10,123; Merikangas et al., 2010, JAACAP
What do we know about teenage suicide?

- Suicide is 3rd leading cause of death in teenagers
- More boys than girls
- Depression, substance use, and suicide attempts increase risk
- Roughly 1 in every 10,000 teenagers complete suicide... It is rare
Thoughts about suicide...

- Sometimes occur in teenagers who are not depressed
- More common in girls than boys
- Can be brief and passing, or they can be long lasting
- Are common in teenage depression
Diagnostic Assessment and Treatment Planning
General Principles

• Multi-domain (e.g., symptoms, disorders, comorbidity, functional status)
• Multi-informant (child, parent, clinician, teacher)
• Repeated measures (to track symptoms over time and response to treatment)
• Independent evaluators (provide objective assessment of functioning separate from clinician)
Assessment Methods

• Diagnostic Interview Schedules
  – Provides reliable differential diagnoses

• Behavioral Assessment Techniques
  – Fear and Avoidance Hierarchies
  – Activity Schedules
  – Behavioral Avoidance Tasks

• Questionnaires
  – Self-Report; Parent-Report; Teacher Ratings
Depression-Specific Clinician Interview

- **Children’s Depression Rating Scale (CDRS)**
  - Semi-structured interview
  - Provides accurate information beyond a self-report measure (increased validity as a measure of depressive symptoms)
  - May be more time and cost effective for identifying affected youth than larger structured interviews
Distinguishing non-clinical from clinical levels of anxiety in youth

- Intensity of the fear: within expected limits or out of proportion to the actual threat?
- Does the fear reaction occur with increased frequency and/or remain fixed despite reassurance?
- Is the content of the fear focused on an innocuous situation?
- Does the fear occur spontaneously?
Anxiety Fear Hierarchy

Fear Thermometer (SUDS)

Separation Anxiety Fear Hierarchy

<table>
<thead>
<tr>
<th>Situation</th>
<th>SUDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spending night at friend’s house</td>
<td>10</td>
</tr>
<tr>
<td>Spending 2 hours at friend’s – w/o mom</td>
<td>8</td>
</tr>
<tr>
<td>Spending 30 mins at friend’s – w/o mom</td>
<td>7</td>
</tr>
<tr>
<td>Mom leaving home for 30 minutes</td>
<td>6</td>
</tr>
<tr>
<td>Mom leaving home for 15 minutes</td>
<td>5</td>
</tr>
<tr>
<td>Mom going out to get mail</td>
<td>3</td>
</tr>
<tr>
<td>Mom going in a different room – nighttime</td>
<td>2</td>
</tr>
</tbody>
</table>
Cognitive Behavioral Therapy
Goals of CBT

• Education about anx/dep and CBT
• Training in somatic management
• Changing maladaptive cognitions
• Encouraging proactive behavior
• Extinguishing anxiety/mood reactions
• Solidifying acquired skills
• Promoting generalization
General issues in child therapy

Stage of development can influence the expression of symptoms/disorders

Externalizing problems identified readily; internalizing disorders are often overlooked

Children are vulnerable to multiple influences which will impact upon the nature and severity of their impairments, along with tx response
Elements of CBT Protocols

- Psychoeducation
- Somatic Management
- Cognitive Interventions
- Situational Exposure/Behavioral Activation
- Parent Involvement
- Relapse Prevention
Psychoeducation

• Goals:
  – Normalize the response: What is anxiety/depression and where does it come from?
  – Understand the 3 Component Model
    • What I Think, What I Feel, What I Do
  – Learn the goals and process of CBT

• Diary forms, handouts
Somatic Management

- **Goal:** Develop tolerance of normal, expected levels of anxiety or mood changes

- Breathing Retraining
- Progressive Muscle Relaxation
- Guided Imagery: Spaceship Rides
Cognitive Restructuring

• Goals:
  – Provide corrective information about anxiety, depression and threat
  – Identify automatic thoughts and treat these as hypotheses
  – Develop means to dispute ATs with realistic evidence
  – Develop rational responses to automatic thoughts
Typical Cognitive Distortions

- **All or None Thinking**
  - Either I ace this test, or I fail and I'm a loser.

- **Catastrophizing**
  - This is the worst thing that could happen to me!

- **Disqualifying the positive**
  - A B+ on that test just wasn't very good.

- **Fortune Telling**
  - I know that I won't make friends at that camp.
  - I know something bad will happen to mom.
• **Overgeneralization**
  – That person wasn’t very friendly to me. There just isn’t any nice people around anymore.

• **Mind Reading**
  – I know they think I’m a geek.

• **Shoulds, Can’ts, Won’ts**
  – I should’ve said something different . . .
  – I can’t do this, it is impossible!
  – I won’t ever be able to . . . .

• **Probability Overestimation**
  – I’m absolutely positive that I won’t get into college.
Questions to dispute ATs

- Am I 100% sure that _____ will happen?
- Do I have evidence that ___ will happen?
- How many times has ___ happened before?
- Is ___ really so important that my whole future depends on its outcome?
- What is the likelihood that _____?
- Does ___’s opinion reflect that of everyone else?
- Do I have a crystal ball?
- Am I responsible for this entire conversation?
- What is the worst that could happen?
- What can I do to cope/handle this situation?
World Series, 9\textsuperscript{th} inning, 7\textsuperscript{th} game, 2 outs, the score is tied

- What is Derek thinking when he gets up to bat?
  - “Oh no, I can’t do this.”
  - “My stomach hurts.”
  - “I want to go home.”
  - “If I strike out, I can never play baseball again.”
  - “I’m afraid of that pitcher, he’s mean!”
Derek takes a swing . . . and misses!

• “I knew I was a loser!”
• “I’m so embarrassed!”
• “I’m gonna get fired.”
• “Now Mr. Torre will really be mad at me.”
• “The guys hate me, I just know it.”
Derek Jeter’s REAL Thoughts

• “Okay, so, he’s throwing me a slider.”
• “I’ve been here before, I know what to do.”
• “This is what I practice for and I’m ready.”
• “I’m going to send this ball straight into the left field bleachers.”
Helpful Coaching Style

- Focus on effort, not outcome
- Evaluate the situation realistically
- Think about what you know and what you’ve done in the past
- Focus on coping: How will I handle this?
- Give opportunities for practice
- Reward (praise) all efforts, no matter how small
Behavioral Exposures

• Goals:
  – Provide experience performing in and managing difficult situations
  – Practice and refine cognitive, social, somatic management, and problem solving skills
  – Gather evidence to refute ATs
  – Habituation to anxiety
Exposure suggestions

• Fear and Avoidance Hierarchy
  – Provides target situations
• Graduated exposure to increasingly challenging situations (imaginal/in-vivo)
• Decreased use of “safety signals”
• Contingent reinforcement
Exposure Procedures

- Define the situation
- Define observable goals
- Generate Automatic Thoughts
- Dispute AT’s
- Choose Rationale Response
- Conduct 10 minute exposure
- (Therapist) tracks SUDS and goals
Exposure: “Starting a conversation”
• **Goals:**
  – Introduce myself
  – Ask 3 questions
  – Speak up in a louder voice
• **ATs:**
  – I won’t know what to say!
  – She thinks I’m a geek
• **Rational Response:**
  – “I’m only responsible for 50% of this conversation”
Processing the Exposure

- Review goals & determine goal attainment
- Review occurrence of AT’s
- Review use of cognitive coping skills
- Examine SUDS ratings and their relationship to AT’s
- Access feedback from group
- Assign homework
Typical Habituation Curve
Behavioral Activation Tasks

• Depression leads to withdrawal from reinforcing activities
  – Social: with peers, family
  – Success: studying, working
  – Physical: organized sports, bowling, aerobics
  – Relaxing/Self soothing: music, reading for pleasure, yoga
Activity Scheduling

• Depression leads to withdrawal from reinforcing activities
• Keep track of mood rating in relation to activity level
  – Social: with peers, family
  – Success: studying, working
  – Physical: organized sports, bowling, aerobics
  – Relaxing/Self soothing: music, reading for pleasure, yoga
Healthy diet and exercise

• Eating healthy improves overall physical and mental health

• Physical exercise (walking, dancing, jogging) improves mood

• Exercise with a friend

• Journals help to keep track of healthy habits
Parents in the Treatment Process

- Parents often are inadvertently drawn into the cycle of negative affective
- Provide model of negative affect and education
- Examine maintaining variables
- Contingency management training
- Parents as “coaches”
- Transfer of control
Considerations for parental involvement:

- Cognitive-developmental level of child
- Degree of anxiety pathology and interference in functioning
- Comorbidity, especially with externalizing disorders
- Parental psychopathology
- Degree of family dysfunction
Family Cognitive Behavior Therapy

Family Techniques

Teach parents to:

Reward child’s courageous/active behaviors
Extinguish child’s fear/withdrawal behaviors
Control their own (parent’s) anxiety/mood
Communicate, cope, and problem-solve
Level of Parental Involvement

CONSULTANT
provide information

CHEERLEADER
provide encouragement

COACH
supervise/administer treatment components

CLIENT
target of specific aspects of intervention
Contingency Management Procedures

- Symptoms are maintained by reinforcement from the environment
  - missing school, tangible items, attention
- Alter existing contingencies to allow extinction to occur
- Differential reinforcement of adaptive behavior
- Parent training
Relapse Prevention

• Goal: Transfer of responsibility for treatment

• Development of relapse prevention plan:
  – How do you spell relief? EXPOSURE!
  – When do you call for help?

• Fading sessions

• Videotaped commercial

• Booster groups/planned sessions at times of high stress
Pharmacological Treatment of Pediatric Major Depressive Disorder
Why Treat Depression?

- Annual prevalence: 2% children, 9% adolescents (girls > boys)
- Cumulative prevalence: 20% in adolescence but less than ½ receive any treatment
- Depression is the most common risk factor for suicide; 2x rate of substance abuse
- Suicide = 2nd leading cause of death in adolescents in Westernized countries (3rd in US)
- More adolescent deaths (>1500) from suicide than almost all medical conditions combined!
- CDC: 17% of teens reported suicidal thoughts, 9% acted on them, 3% needed medical attention because of self harm event
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name®</th>
<th>FDA Max per day</th>
<th>FDA Approved for Major Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>60 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Cymbalta</td>
<td>60 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Velanfaxesine</td>
<td>Effexor</td>
<td>225 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>Effexor XR</td>
<td>225 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Selegine</td>
<td>Emsam patch</td>
<td>12 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro</td>
<td>30 mg</td>
<td>Children &amp; Adol (12-17); Adults</td>
</tr>
<tr>
<td>Fluvaxamine CR</td>
<td>Luvox CR*</td>
<td>300 mg</td>
<td>No</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil, Pexeva</td>
<td>50 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Paroxetine CR</td>
<td>Paxil CR</td>
<td>62.5 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Pristiq</td>
<td>400 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>60 mg</td>
<td>Children &amp; Adol (8-17); Adults</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Remeron</td>
<td>45 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Sarafem*</td>
<td>80 mg</td>
<td>No</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Silenor*</td>
<td>6 mg</td>
<td>No</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>Viibryd</td>
<td>40 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Wellbutrin</td>
<td>30 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Bupropion SR/XR</td>
<td>Wellbutrin SR/XR</td>
<td>300 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Brand Name®</td>
<td>FDA Max per day</td>
<td>FDA Approved for Major Depression</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Anafranil</td>
<td>250 mg</td>
<td>No</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Sinequan</td>
<td>300 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Desyrel</td>
<td>300 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Amitryptiline</td>
<td>Elavil</td>
<td>300 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Nortryptiline</td>
<td>Pamelor</td>
<td>200 mg</td>
<td>Adults</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tofranil</td>
<td>300 mg</td>
<td>Adults</td>
</tr>
</tbody>
</table>
Selective Serotonin Reuptake Inhibitors (SSRIs)

• Most commonly prescribed antidepressants
• Primary effect is inhibition of 5HT reuptake by blocking the transporter
• Different SSRIs have different pharmacodynamics (how they effect other neurotransmitters) and pharmacokinetics (half life, metabolic pathways)
• Some are potent inhibitors of NE and 5HT
• Newest meds are reformulations of older meds
• NE associated with better pain relief in adults but possibly more side effects in children
• 5HT for OCD/bulimia (compulsive behaviors)
How do Antidepressants Work?

- **First**: boosts monoamine transmitters (NE, DA, 5HT): in depression there is a 1/3 increase in enzyme MAO-A, which breaks down monoamines, so less amines available in the synapse to stimulate receptors
- Tricyclics primarily block NE and DA reuptake while SSRIs primarily block serotonin (5HT) reuptake
- However, this effect happens quickly and does not correlate with onset of symptom relief
- **Second**: Increased neurotransmitters causes receptor down regulation- see more 5HT receptors in completed suicides
- **Third**: change in synthesis of critical proteins like BDNF that cause structural changes in the brain
- Hippocampal atrophy in MDD while fluoxetine promotes nerve growth in hippocampus
Monoamine Theory of Depression

(Meyer et al., Arch Gen Psych, 2006)

(a = normal, b = depressed, c/d = effects depend on # of receptors)
Monoamine Theory for SSRI Treated Major Depressive Episode

ANTIDEPRESSANTS MOST PRESCRIBED U.S. DRUG - NEWS ITEM

YOU'RE IN A GOOD MOOD, OSCAR...

ZOLOFT!

EVERYBODY'S COLUMN
Recent Prevalence Data

Figure 1. Percentage of persons aged 12 and over who take antidepressant medication, by age and sex: United States, 2005–2008

1Significantly different from age group 18–39. 2Significantly different from age groups 40–59 and 60 and over. 3Significantly different from females. 4Significantly different from age group 60 and over.

NOTE: Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db76_tables.pdf#1.

FDA Approved Antidepressants

- Best data is for fluoxetine: 2 controlled studies that led to FDA approval for depression (ages 8+)
- Only drug used in largest teen MDD study (TADS)
- FDA approval for OCD down to age 8
- Fluoxetine studies were designed to reduce placebo response rates and enrolled sicker patients
- Fluoxetine has linear pharmacokinetics with long half life that makes for predictable dosing with little concern over withdrawal due to missed doses
- Escitalopram (Lexapro) approved for depression in children ages 12-17 (2 studies)
- Citalopram and sertraline have one controlled study each showing efficacy in children
What’s going on with the FDA?

- Pharma companies rushed to do trials of antideps in children to extend patent life, not primarily to prove efficacy
- Led to a host of negative trials that were not published
- Primary issue is high placebo response rates
- Best predictor of negative trial is # of sites enrolled not the drug used in the study
- Newer studies designed to reduce placebo response by enrolling sicker subjects are finding better medication effects
What’s going on with the FDA?

- Signal of increased agitation/depression first seen in trials of paroxetine for pediatric depression.
- FDA reviewed all controlled depression studies in youth (4,000 individual cases)- NO COMPLETED SUICIDES.
- 95 cases identified as true suicidal events (2/3 were serious).
- 4% of children experienced adverse emotional responses.
- 1.6X risk with medication vs. placebo (one child gets worse for every ten that get better).
- No risk seen with same meds in pediatric anxiety studies suggesting risk relates to use in depression.
- FDA created med guide and **BLACK BOX**
Black Box Impact?
(Libby et al 2009 Archives of Gen Psych)

- Examined antidepressant scripts for youth in large managed care database (643, 313) before and after warning (1999 vs. 2007)
- After warning: rate of diagnosis of MDD decreased by almost half in boys and girls
- MDD rates: children is 1-2% and 5-9% in teens
- 10% decline in antidepressant usage in new MDD cases
- Declined more for primary care than psychiatry
- No increase in other treatments (psychotherapy still under 50% of cases)
- Large increase in no treatment: from 19% to 64%
PHARMetrics Patient Centric Database population rates of major depressive disorder (actual and predicted) by age group (male and female individuals combined)

US SSRI Prescription Rates by Age

(Gibbons et al., 2007 Am J Psychiatry, Volume 164(9), p 1358)
Persons Aged 10 to 17 Years and 18 to 19 Years in the United States, Suicide rates from 1996 Through 2005

- Rates increased 18% from 2003 to 2004
- 2005 rate dropped 5% but still > than 2003 rates
- Rates declined in 2006, 2007 then have increased in 2008, 2009 to near 2004 levels (economic downturn)
- No decrease in youth suicide rates post Black Box

The Best Study: TADS

- Randomized trial of 439 depressed teens with chronic, moderate to severe depression
- Goal was to compare different initial treatments
- Real world patients with high rates of ADHD and anxiety
- Excluded imminently suicidal youth
- 4 arms: fluoxetine (FLX), Cognitive Behavioral Therapy (CBT), FLX +CBT, placebo
- FLX started at 10mg and could go to 40mg (mean of 28mg)
- 12 weeks active treatment- reassessed every 6 weeks
TADS Results

- 12 week results: treatment works
  - Response rates: 71% combo, 61% fluox, 43% CBT and 35% placebo
  - Effect sizes: Combo .98, flx .68, CBT 0
  - Suicidal Ideation reduced in all 4 groups (29% at base to 10% at week 12)
- Week 18: Combo, FLX>CBT
- Week 24: Combo>CBT (?FLX)
- Week 30: all treatment the same (CBT catches up)
- 36 week response rates: Combo=86%, 81% FLX, 81% CBT
TADS 36 Month Results
(Arch Gen Psych 64(10): 1138)
TADS Conclusions

- Meds work quicker than CBT (better at 12 weeks)
- CBT gains efficacy after 4-6 months of active therapy so by 36 weeks they look the same
- Suicidal ideation improves with either treatment (CBT>med)
- 1 in 10 treated teens with MDD experience prominent suicidal ideation
- CBT may protect against the risks of a self harm event in youth on antideps
- Depression is treatable with meds, therapy or both
- Meds work quicker but have more side effects
Comorbidity Findings

• MDD severity had more impact than comorbidity
• No evidence of differential treatment responses within groups although power was a bit low for this
• Anxious class responded better than those with severe disruptive behaviors
• MDD+ anx: flx almost as good as combo
• When add ODD/ADHD, combo becomes more effective
• High rates of comorbidity, suggests we need to provide treatment that target multiple realms
TORDIA
(Brent et al., 2008 JAMA)

• Similar to TADS but specifically looked at adolescents with suicidal thoughts who had failed at least one med for depression (NEXT STEP)
• Compared switching meds (SSRI vs. mixed NE 5HT drug venlafaxine) vs. adding CBT
• 50% got better with next treatment
• Switching meds and adding therapy improved more subjects more than just switching med
• Different meds worked the same but venlafaxine (5HT plus NE) was harder to tolerate
• Stick with the SSRIs and refer for therapy
Practical Medication Tips

- **Fluoxetine (Prozac):** most studied and is FDA approved for pediatric MDD, so is best first choice
- Long ½ life is good for compliance; watch for drug (2D6) interactions and poor metabolizers
- **Escitalopram (Lexapro):** FDA approved ages 12+, shorter ½ life and less drug interactions than fluoxetine but less data & more cost; QTc concerns
- **Sertraline (Zoloft):** some MDD data, easy to titrate and OCD approval; watch for GI side effects
- **Citalopram (Celexa):** some MDD data but QTc concerns; generic dual isomer version of escitalopram which is approved for children
- **Paroxetine (Paxil):** OCD approval but poor MDD data and higher rate of paradoxical reactions so would NOT use
- **Fluvoxamine (Luvox):** Good anxiety data but not much data for MDD; sedating and drug interactions (3A4)
- **Others:** Duloxetine (Cymbalta), Venlafaxine (Effexor), Bupropion (Wellbutrin- data for ADHD but not MDD)
SSRI SIDE EFFECTS

- no adverse effect on major organs; (caution with serotonergic meds- Serotonin Syndrome)
- Slight delay in clotting times (good post MI)
- agitation/suicidal thoughts
- insomnia or fatigue/sedation- most common
- Headache- 2nd most common
- Physical hyperactivity
- manic “switch”
- GI (nausea, diarrhea): little wt gain for most
- cognitive (“spacey”, weird dreams)
- sexual side effects (quite common in adults)
Switching into Mania

- SSRIS cause mild physical restlessness
- This is not manic activation
- Mania: decreased sleep need, dangerous impulsivity, persistent irritability, aggression
- If mild, occurs in first 1-2 weeks and resolves soon after drug stopped then less likely to be mania
- Reasonable to try 2nd antidep then (some children just emotionally allergic to antideps)
- Mania: often gets better initially than worse, about 3 months after drug onset and stays bad off meds; don’t retry antidepressant alone
- Data in adults with Bipolar found that antideps only risky if have active manic symptoms (didn’t help MDD though)
General Advice

• FDA did not ban antidepressants in youth
• Should consider therapy first +/-drug
• Use fluoxetine (Prozac) first or possibly escitalopram (Lexapro) unless have reason not to-
• See back in a week (could be phone), review warning signs and FDA guidelines
• First episode: continue med for 6+ months after improvement, then taper off
• No identified risks of medication use on development but data is limited so goal should be short term usage
• Recurrent episodes may need maintenance therapy
Prescribing Principles

- Start low with ½ dose of smallest pill; increase in 7 days to get to initial target dose
- Full effects of each dose can take 4+ weeks
- If no response in 6 weeks, try other SSRI; usually cross taper so symptoms could worsen some
- If no response to second SSRI, reevaluate diagnosis and consider referral
- Comorbid conditions: okay to treat ADHD first; anxiety may improve with MDD; always treat Bipolar Disorder and psychoses first; ?substance
- Other strategies: combining antidepressants (bupropion); augmentation with Lithium, thyroid, buspirone, atypical antipsychotics
Pharmacological Treatment of Pediatric Anxiety Disorders
General Info

- Prevalence: phobia, sep anxiety, social anxiety, GAD, OCD, panic, PTSD (most to least)
- Most common psychiatric disorder in children
- Waxing and waning course
- 42% of children with anxiety will have anxiety disorder as adults
- 3 main categories:
  1. Sep Anxiety, social phobia, GAD, panic
  2. OCD
  3. PTSD
General Info

• Group 1 responds well to SSRIs and TCAs except for social phobia (not TCAs)
• Group 2 (OCD) high comorbidity rate with tics, ADHD and is related to Basal Ganglia dysfunction
• Group 3 (PTSD) is correlated with HPA Axis dysfunction
• Frequently have more than one anxiety disorder
• Anxiety is at risk to evolve into depression
Role of Medications

• Trial of psychotherapy for approximately 3 months first; if unsatisfactory response, then consider SSRIs as first line medication

• Exceptions (when to use meds early):
  – Severe symptoms and impairment
  – Family unwilling/unable to access therapy
  – Child unwilling/unable to benefit from therapy
Selective Serotonin Reuptake Inhibitors (SSRIs)

- Citalopram (Celexa and generic)
- Escitalopram (Lexapro)
- Fluoxetine (Prozac and generic)
- Fluvoxamine (Luvox)
- Sertraline (Zoloft)
- Paroxetine (Paxil): generally should not be used in children and adolescents
- Some data on buspirone (buspar) and venlafaxine (Effexor XR)
The Clinical Question

Weighing the risks and the benefits of using medications must be posed vs. the risks and benefits of NOT using medications.
The FDA and Antidepressants in Children: Do they work?
(Bridge et al JAMA 297(15))

- Recent Meta-analysis of all controlled trials
- 6 for nonOCD anxiety, 6 for OCD, 15 for MDD
- OCD: drug response was 52% vs. 32% placebo for NNT of 6
- Non OCD anxiety: 69% response for drug vs. 39% for placebo for NNT of 3
- MDD: 61% drug and 50% placebo for NNT of 10
- For anxiety, children responded as well as teens but for MDD response was lower if <12 years
The FDA and Antidepressants in Children: Are the Safe?
(Bridge et al JAMA 297(15))

- Looked at all reported cases of voiced suicidal ideation or self harm attempts (no completions)
- OCD: drug rate was 1% vs .3% placebo for NNH of 200
- NonOCD anxiety: 1% for drug vs. .2% for placebo for NNT of 143
- MDD: 3% drug and 2% placebo for NNH of 112
- Authors concluded that there was a small risk of paradoxical response that was outweighed by the benefits, especially for children with anxiety and teens with anxiety/depression
- Degree of drug induced risk was same for depression vs. anxiety but there is a higher base rate of self harm in depression
SSRIs Trials

• Several small studies but the largest are the CAMS and RUPP study for mixed anxiety and POTS for OCD
• RUPP Anxiety Study: 128 children with social, sep or GAD randomized to placebo or fluvoxamine
• Doses up to 250mg produce significant response in 76% vs. 29% placebo \textit{(NEJM 2001)}
• It took up to 6 weeks to see effect and no reliable predictors of who responds
• In RUPP study, 10/14 non-responders did well with fluoxetine (Prozac)
• Side effects: tiredness, hyperactivity
Pediatric OCD Treatment Study (POTS)

12 week multi-center randomized parallel group study for OCD

CBT alone (14 sessions), sertraline (25-200mg), both or placebo meds

112 subjects ages 7-17, could have ADHD/tics but not mood disorders

Subjects on stimulants were allowed

Primary measure was CYBOCS
POTS Results

- 87% completed the study, mean drug dose was 133 (combined) 170mg (alone); good CBT attendance
- CYBOCS: Combined was better than all others; CBT=drug>placebo
- Remission: combo 54%, CBT 39%, drug 21%, placebo 4%
  - NNT: combo 2, CBT 3, drug 6
- Conclusion: both treatments work but CBT was a bit better than drug alone, so either start with combo or CBT
Design: 124 youth ages 7 - 17 with OCD randomly assigned to MEDS alone, MEDS plus CBT or Meds plus CBT instructions

All participants were partial med responders

Meds: un-blinded maintenance treatment with 7 visits over 12 weeks

CBT: 14 visits over 12 weeks of manualized CBT

CBT lite: physician prescriber integrated basic CBT principles into 45 min visit plus two phone check-ins

Response rates: defined as 30% reduction in symptom scores

- CBT full 69%, CBT lite 34% and meds only 30% (CBT full significantly better)
- NNT of full CBT vs meds only was 3

Full course of CBT helpful for partial med responders but integration of basic CBT principles in medication sessions did not impact outcome
• 488 children ages 7-17 with anxiety (not OCD/PTSD)
• CBT, sertraline or both for 12 weeks
• Improvement: 81% combo, 60% CBT, 55 % med, 24% placebo (all better than placebo) (NNT: 1.7, 32., 2.8)
• All treatments worked but combo most effective
• Serious adverse events were not more likely with med
• More tiredness, restlessness and sleep delay with med than with therapy
• Conclusions: therapy has lower side effect rates so start with it except for more severe cases, then go to combo
Benzodiazepines

- Benzos are classified as controlled substances
- Clonazepam (Klonopin) and lorazepam (Ativan) most commonly used, with concerns over alprazolam (Xanax) due to rebound and addiction concerns
- No good controlled studies in children
- The one controlled trial of alprazolam for social phobia was negative
- Concerns over higher rates of disinhibition and cognitive dulling in kids that may affect school performance
- Used while waiting for antidepressants to take effect
- Link use to achievable increase in functioning
What is a Treatment Success?

• Rare to get total remission with meds alone
• Good goal is visible improvement in function (i.e. school attendance)
• Medication targets all anxieties even those that may be beneficial but meds do not seem to impair inhibition on neuropsych tasks (Gunther, 2005)
• May see child act more defiant, less academically motivated once anxiety is reduced, especially if comorbid ADHD/ODD
• Less likely with CBT interventions?
Length of Treatment

• Long term effects of exposure to SSRIs during neurodevelopment is still not 100% known
• Group 1 Anxiety disorders tend to remit
• Reasonable to try slow med taper after 6+ months of stable functioning
• Continue treatments longer if comorbid depression, OCD or possibly PTSD (little data)
I used to hate writing assignments, but now I enjoy them.

I realized that the purpose of writing is to inflate weak ideas, obscure poor reasoning, and inhibit clarity.

With a little practice, writing can be an intimidating and impenetrable fog! Want to see my book report?

"The dynamics of interbeing and monological imperatives in Dick and Jane: A study in psychic transrelational gender modes."

Academia, here I come!
For more information, please go to the main website and browse for more videos on this topic or check out our additional resources.

**Additional Resources**

**Websites:**
1. The Columbia University Clinic for Anxiety and Related Disorders: http://www.anxietytreatmentnyc.org/index.html

**Books:**

**Peer Reviewed Journal Articles:**