Anxiety and Depression in Children and Adolescents: Pharmacology

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# Disclosures

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Introduction

• Anxiety medication treatment
• Depression medication treatment

• Behavioral treatment of anxiety and depression
Anxiety Disorders

- Specific Phobia
- Obsessive compulsive disorder
- Separation Anxiety Disorder
- Generalized Anxiety Disorder
- Social Anxiety Disorder
- Acute Stress Disorder
- Post-traumatic stress disorder
- Panic Disorder
Anxiety is not a great term

- Home sickness (separation)
- “Worry worts” (generalized)
- Self-conscious or shyness (social anx)
- Excessive interpersonal sensitivity
- Fear
- Apprehension
- Dread
- Worry
- Stressed out
Characteristics Common to All Anxiety Disorders

- Hypervigilance
- Reactivity to novel situations
- Biased interpretation of experiences as threatening
- Avoidance coping
- Catastrophic reactions
- Parental accommodation
- Midline physical symptoms
Tension headache
Dizziness
Perioral tingling (hyperventilation)
“lump in the throat”
can’t swallow pills
worry about gagging, choking, swallowing, vomiting
“can’t catch his/her breath”
shortness of breath
hyperventilating
chest pain
abdominal pain
Bowel and bladder urgency
Tingling in finger tips
(hyperventilation)
Other symptoms

- Problems with falling asleep and middle of the night awakening,
- Eating problems – over and under
- Excessive need for reassurance – bedtime, school, storms, bad things happening
- Inattention and poor performance at school
- Explosive outbursts
- Avoidance of outside and interpersonal activities – school, parties, camp, sleepovers, safe strangers
- Not necessarily pervasive
Ages of Onset Risk

- ASDs – 0-3 years or later for mild
- ADHD - 4-7 or later for mild, but differential is broader
- Anxiety – 6-12 years
- Depression – 13-16 years
- Bipolar and psychosis - > 16 years
- Panic Disorder 16-25 years
- Disruptive behavior – almost anytime
Specific Phobia

- Animals, insects etc.
- Environmental - thunder, water, heights
- Blood, injection or other suspected painful event
- Situational - tunnels, bridges, elevators
- 70% have another anxiety disorder
Separation Anxiety Disorder

- Excessive concern regarding separation from home or from attachment figures
  - Bad things happening to parent and or child
  - Cannot be alone
  - Avoidance  S, M, L, XL, XXL
  - Difficulty falling asleep or sleeping with loved ones
  - Physical aches and pains
  - Accommodation by adults S, M, L, XL, XXL

- Impairment or distress.
Generalized Anxiety Disorder

- Excessive worry and apprehensiveness
  - Restless, keyed-up or on edge.
  - Fatigued at end of school day
  - Concentration problems “choking on tests”
  - Sleep problems (falling asleep)
  - Tense and irritable
- Unable to control the worry
- Impairment or distress
Social Anxiety Disorder

- Fear of social or performance situations
  - Specific
  - Generalized
    - “slow to warm up” socially
    - anxious about being with other people
    - reticent to talk in social settings (short answers, soft spoken)
    - self-conscious and anticipate being embarrassed
    - anticipate that others will judge them
    - worry before an event where other people will be
    - avoid places where there are other people
    - blush, sweat, or tremble around other people
    - feel nauseous or sick to their stomach when with other people
    - depersonalize or derealize when with other people
Selective Mutism

- Young children
- Ability to speak
- Not speaking in social situations
- Not part of another disorder

- Mild variant (single words, soft spoken, not spontaneous social speech)
Acute Stress Disorder

- True stressful event – life threatening
- Re-experiencing the event
- Avoidance and numbing
- Increased arousal
- Negative thoughts, feelings and moods
- Time limited
Post-traumatic Stress Disorder

- True stressful event – life threatening
- Re-experiencing the event
- Avoidance and numbing
- Increased arousal
- Negative thoughts, feelings and moods
- Risks for enduring symptoms
  - Pre-existing or genetic risk for mental disorder
  - Proximity
  - Post-traumatic environment
  - Stuck in unhelpful narrative about trauma
The Trauma Narrative

- Failure to progress through the stages of trauma
- Victim – validation of trauma
- Survivor – trauma is never forgotten but it is in the “rearview mirror”
- Heroic living – trauma is a source of energy for giving and living freely
Panic Disorder

- Attacks of anxiety (Physical Symptoms)
  - Heart rate, pounding heart, palpitations
  - Hyperventilation, shortness of breath
  - Choking sensation
  - Chest discomfort or pain
  - Abdominal pain
  - Some psychological symptoms
- Worry about the next one
- Avoidance behavior related to the attacks
- Agoraphobia....
Obsessive Compulsive Disorder

- Prominent obsessions or compulsions
  - Dirt, germs, or other contamination
  - Ordering and arranging
  - Checking
  - Repetitive acts
- Impairing or time consuming
Infection-triggered Childhood Onset Conditions

- Neuropsychiatric disorders associated* with infections
  - PANDAS (Strep)
  - PANS (acute onset with other infectious agents)
Epidemiology

- Very common up to 8-10% of kids
- Under diagnosed
- Under treated
- Probably the most common childhood disorder and the prepubertal disorder associated with changes in mood and emotion regulation
Course of Anxiety

- Onset in childhood - “Prepubertal affective illness”
- Adolescence - symptoms + accumulated disability
  - Intense symptoms “burn out” ..... sometimes
  - Generalized anxiety
  - Poor adaptation and coping – easily flooded and overwhelmed by typical life and developmental expectations
  - **Some morph to depression**
  - School drop out (fade away)
- Young adulthood – symptoms + failure in major roles
  - Work inhibition
  - Fail to leave home or stay in college
  - Evolution into panic disorder
  - Evolution to recurrent depression and risk for bipolar disorder
  - Substance abuse
Anxiety and Treatment

- Evidence base for children established in 2009 (Walkup et al., 2008)
- Combination treatment most effective - 80% response rate
  - SSRIs and CBT are both effective – 55-60%
  - Placebo response rate is less than 25%
- Outcomes more clearly positive than for teen depression
Assessment Strategies

- Global scales with anxiety subscales
  - Child Behavior Checklist
  - Behavioral Assessment System for Children
- MASC
- SCARED
  - Child version
  - Parent on child version
Serotonin Reuptake Inhibitors FDA Approvals

- Approved for OCD
  - Clomipramine ≥ 10 yrs
  - Fluvoxamine ≥ 8 yrs
  - Sertraline ≥ 6 yrs
  - Fluoxetine ≥ 7 yrs

- Approved for Depression
  - Fluoxetine ≥ 8 yrs
  - Escitalopram ≥ 12 yrs

- Approved for Non-OCD Anxiety
  - Duloxetine ≥ 7 yrs GAD
The Treatment of OCD
Treatment of OCD

- Cognitive-behavioral treatment
- SRIs effective for OCD
  - Clomipramine (TCA)
  - Fluvoxamine
  - Paroxetine
  - Sertraline
  - Fluoxetine
  - Citalopram likely effective
  - Escitalopram likely effective
- All permutations
- Brain stimulation
Pediatric OCD Treatment Study - POTS

- N = 112
- Ages 7-17 years
- 3 sites, 12 weeks
- CBT, Sertraline, COMB and placebo
CY-BOCS ITT Outcomes

PBO < SER = CBT < COMB

Week 0

Week 12

PBO
SER
CBT
COMB

Pediatric OCD Study Team (2004) JAMA.
Site x Treatment Interaction

Pediatric OCD Study Team (2004) *JAMA.*
SRI Efficacy for Non-OCD Anxiety Disorders

- SAD, GAD and SoP
  - Fluvoxamine – RUPP, 2001
  - Fluoxetine – Birmaher et al, 2003

- SoP
  - Paroxetine - Wagner et al, 2004
  - Fluoxetine - Beidel et al 2007
  - Venlafaxine - March et al, 2007

- GAD
  - Sertraline - Rynn et al., 2001
  - Venlafaxine, Rynn et al., 2007
  - Duloxetine, Strawn et al 2015
  - Buspirone in GAD, unpublished negative trial
Child/Adolescent Anxiety Multimodal Study (CAMS)

- NIMH-funded
- SAD, GAD and SoP, N=488
- 12 weeks; COMB vs Med vs CBT vs PBO

Results
- COMB 81%
- CBT 59%
- SRT 56%
- PBO 24%  (Walkup et al., NEJM 2008)
Other CAMS Outcomes

- Younger kids with anxiety do best with all treatments.
- Medication is well tolerated, but younger kids also have more side effects – endpoint dose sertraline 130-40 mg/day (highest safe dose).
- Technical expertise required for optimal dosing or risk under treatment and poor outcome.
- Adolescents likely require psychosocial rehab.
Depression Medication Treatment

- The studies
- The evidence base
- Dosing
- Adverse events
  - Managing “the activation syndrome”
  - Is it Bipolar disorders
  - What is the suicide risk?
Teens and Depression

- 3-6% of teens suffer from depression at any point in time
- Up to 20% over a lifetime
- Most with depression do not get appropriately assessed or treated
- Depression is highly responsive to treatment
Treatment of Depressed Teens

- Treatment for Adolescents with Depression Study (TADS)
- Treatment of Resistant Depression in Adolescents (TORDIA)
- ADAPT
- Treatment of Adolescent Suicide Attempters (TASA)
Treatment of Teen Depression

- Psychological treatments
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Therapy (IPT)

- Medications
  - SSRIs and atypical antidepressants
  - TCAs and MAOIs

- Treatment of Adolescents with Depression Study (TADS)
Antidepressant Trials

- 2 NIMH-funded
  - Demonstrated efficacy
  - Low placebo response rates
  - Many quality indicators

- 17+ industry-funded (FDAMA)
  - Multiple sites
  - High placebo rates
  - No quality indicators
  - FDAMA exclusivity
  - No investment in outcome
Placebo Response in C&A Antidepressant Trials

- Bridge et al. 2009
- 12 Studies – published and unpublished
- Placebo response correlated with number of sites
- Baseline severity inverse predictor of placebo response
- Younger subject had higher PBO response rate
e.g. Sertraline

- Wagner et al., 2003
- Pooled data of two multisite trials
- N=376 (Sites = 63)
- Ages 6-17 years
- 10 week, double-blind, placebo controlled trial
- Drug > placebo
- CDRS Responder 69% vs. 59%
- CGI-I Responder 63% vs. 53%
What is depression?

- Lets go back a step

- Normal human sadness
- Demoralization
- Sadness without cause

- Horwitz and Wakefield...Loss of Sadness
What is depression?

- Depression before DSM-III
  - Sadness with cause
  - Sadness without cause
    - Black bile
    - “Groundless despondency”
    - Melancholy

- Depression after DSM-III
  - Change in mood
  - Other depressed symptoms
  - Context and quality of mood irrelevant
What is depression?

- Normal human sadness
  - Common
  - Expectable reaction to certain events
  - Can be severe, if event is severe
  - Time limited, but not episodic - moving on is expected

- Can progress to an autonomous, excessive and disproportionate sadness
What is depression?

- Sadness without cause
  - Depression with anhedonia
  - Many physical manifestations
  - Disproportionate and unexpected as to cause
  - Mood is distinct from normal sadness
  - Autonomous course – unaffected by changes in life circumstances
What is depression?

- Demoralization
  - Chronic unhappiness due to adverse circumstances
  - Depressive symptoms, but not anhedonia
  - Can be severe
  - Treated with a change in circumstances
Treatment of Adolescents with Depression Study (TADS)

- JAMA August 18, 2004
- N=439 teens at 13 sites
- Ages 12-17 years
- Treatment Comparisons
  - Meds (fluoxetine)
  - Cognitive-behavioral therapy (CBT)
  - Combination of medication + CBT
  - Medical Management with placebo
- Treatment duration - 12 weeks
TADS Response Rates

- COMB: 71%
- FLX: 61%
- CBT: >43%
- PBO: 35%
Treatment for Adolescents with Depression Study (TADS)

- Longer term outcome
  - Week 18
    - COMB 85%
    - FXT 69%
    - CBT 65%
  - Week 36
    - COMB 86%
    - FXT 81%
    - CBT 81%
ADAPT Trial

- Goodyer et al. 2006
- N=249
- MDD to age 17 years
- Design
  - Brief intervention (n=164)
  - SSRI vs SSRI + CBT (n=208)
- Result wk 12
  - Brief intervention - 25%
  - SSRI 45%
  - SSRI+CBT 43%
ADAPT Longer Term Outcomes

- Total of approximately 80% responded
- Approx 20% no change or worse by endpoint
- Approx 10% persistently refractory
- Some new onset responders between 12-28 weeks
ADAPT Suicidal Adverse Events

- No increased events in either arm
- 15-20% had no baseline risk
- 45% had no risk at wk 6
- 65% had no risk at wk 28

- No between group differences
Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) Trial

- 334 adolescents with major depression resistant to \( \geq 8 \) weeks of SSRI treatment
- Randomized to one of four treatments:
  - Switch to alternate SSRI (Paroxetine then Citalopram)
  - Switch to alternate SSRI + CBT
  - Switch to venlafaxine
  - Switch to venlafaxine plus CBT
- 12 week trial
- Unique context

(Brent et al, JAMA 2008;299:901-913)
TORDIA Wk 12 Outcomes

- Results
  - Antidepressant only - 50% response
  - Combo – 60% response
TORDIA Adherence

- Blood levels
  - Low and high did worse
  - Medium did better

- Pill Counts (>30% of pills remaining)
  - Adherent did better 63% vs. 47%
  - Some 51% had evidence of nonadherence
TORDIA: Week 24 Outcomes

- Week 12 Non-responders didn’t do more
- Responders tailored their treatment even further between week 12 and 24

- Response breeds additional interest in treatment
Treatment of Depressed Adolescent Suicide Attempters

- Brent et al., 2009
- N= 124
- Open trial

Results

- Depression – 72% responded
- Suicidal events – 19%
- Suicide attempts – 12%
- Median time to event – 44 days
Longer Term Outcomes

- **TADS**
  - All active treatment converge – 80-85%

- **ADAPT**
  - Estimated 80+% responded; 10% persistently refractory

- **TASA**
  - 72% response

- **TORDIA**
  - 60% remitted

- **The earlier the response the better**
Moderators for Poor Outcome

- More Severity
- Longer Duration
- More Comorbidity
- More Family Issues
- More Drugs and alcohol
- Poor Adherence
Suicide Summary

- Treatment reduces risk – even placebo
- Lack of response increases risk
  - Slow depression response
  - Predictors of poor response
Dosing of SSRIs

- Use clinical trials for timing of dose changes and maximum safe doses e.g.
  - Fluoxetine up to 40 mg by week 12 (TADS, 2004)
  - Fluvoxamine 100-150 mg by week 10 (RUPP, 2001)
  - Sertraline 100-150 mg by week 8 (CAMS, 2009)
  - Paroxetine 40-50 mg by week 10 (Geller, 2004)
Adverse Events of SSRIs

- Activation is common 10-15%
  - Early in course or after dose change – think diphenhydramine
  - Younger kids
  - “Minimal brain dysfunction”
- Bipolar switches uncommon <1% - later
- Frontal lobes symptoms at higher doses
- GI issues early
- Easy bruising and bloody noses
- Some case reports about growth
Suicidality – Benefit/Risk

- % Difference for Efficacy
  - MDD - 11.0% = NNT of 10 (3 for NIH Studies)
  - OCD - 19.8% = NNT of 5
  - Non-OCD anxiety disorders - 37.1% = NNT of 3

- % Difference for Suicidality
  - 1-2% = NNH 50-100 (Hammad et al., 2006)
  - 0.7% = NNH 143 (Bridge et al., 2007)
  - But not for individual disorders
    - MDD - 0.9%; NNH ~100
    - OCD - 0.5%; NNH ~200
    - non-OCD anxiety disorders - 0.7%; NNH ~140
What to do about activation?
What to do about activation?

- Psychoeducation
  - Early in treatment or right after dose change 24-72 hours (think diphenhydramine)
  - Late activation? Prob unrecognized early activation
- Stop immediately
  - Doesn’t go away with time
  - Won’t get to treatment dose
  - False alarms
What to do about activation?

- **Switch**
  - Second SSRI
  - Non-activating antidepressant
  - No evidence that any non-antidepressant will be useful
Non-activating Antidepressants*

- Mirtazapine (Remeron)
- Duloxetine (Cymbalta)
- Nefazadone* (Serzone)
- TCAs
  - Nortriptyline (Pamelor)
  - Clomipramine (Anafranil)
  - Desipramine (Norpramin)

* With some exceptions - NE reuptake inhibitors may cause an initial anxious reaction that goes away with time
Bottom Line

- Antidepressants work extremely well
  - SSRIs medication of choice for anxiety and depression
  - Atypical antidepressant should be considered second line, but considered
  - Limited data for long term use of benzodiazepines for anxiety
  - No reason to expect that buspirone or bupropion should be effective for anxiety
  - To do a good job will have to prescribe ‘off label’
- CBT also extremely effective when done by an experienced professional
- Outstanding med management and CBT principles are wonderfully complementary