

What Me Worry? Anxiety Disorders in Youth
(Generalized Anxiety Disorder , Separation Anxiety
Disorder, Social Phobia)

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Question 1

Behavioral Inhibition

A-is a clinical syndrome

B-is associated with increased risk of developing separation anxiety disorder in adulthood

C-is associated with increased risk of developing social phobia

D-is associated with increased risk of developing depression in adulthood

E- is associated with increased risk of developing selective mutism

Question 2

Social phobia

- A-develops in mid teens and is associated with overachievement
- B-develops at puberty and is associated with underachievement, alcoholism and school drop-out
- C-develops in early 20s and is associated with substance abuse
- D-develops in mid teens and is associated with underachievement and alcoholism
- E-none of the above

Question 3

RUPP study of fluvoxamine in youth with anxiety disorders show:

- A- Drug has no efficacy compared to placebo
- B-Placebo responders outperformed active medication
- C-Higher levels of depression associated with poorer outcome
- D-High incidence of AEs of sexual side effects
- E-High incidence of AEs of cognitive confusion

Question 4

Which of the following is a true statement about paroxetine in youth?

- A-It is FDA-approved for the treatment of OCD
- B-It has linear pharmacokinetics
- C-It has non-linear pharmacokinetics
- D-It is not associated with drug interactions
- E-None of the above

Question 5

Which of the following statements is true about CBT of anxiety disorders in youth?

- A-Individual CBT is less efficacious than treatment with buspirone
- B-CBT has not been shown to be efficacious
- C-CBT should not be combined with pharmacotherapy
- D-Only group CBT has been shown to be effective
- E-CBT is an effective therapy

Teaching Points

- Anxiety disorders in childhood are frequently missed by clinicians
- Stranger anxiety is usually first evident by ~8 months while separation anxiety starts in toddler years
- In the RUPP study with anxiety disorders, Fluvoxamine showed significant in symptoms compared to placebo

Plan of Lecture

- Review of developmental considerations
- Genetics of anxiety disorders
- What normal kids worry about
- Assessment of Anxiety Disorders
- Classification of Anxiety Disorders
- Importance of Co-morbidity
- GAD, SAD, Social Phobia
- CBT
- Pharmacotherapy

Anxiety: Developmental Considerations

- Developmentally appropriate types of anxiety
 - Stranger anxiety
 - Usually first evident by ~8mos
 - Self/other □ mother /other
 - Separation anxiety
 - Starts in toddler years
 - Various fears and phobias
 - Preschool, school age children
 - Dark, bodily injury / integrity, animals, performance

Anxiety: Development or Disorder?

Key distinctions

- Impaired daily living & distress
- Particularly school attendance and performance
- Children may exhibit marked anxiety with minimal impairment
- Prevalence rates highly dependent on impairment criteria (~10x variation)
- 5-18% range in epidemiological studies
 - Typically transient
 - 80+% of adults with anxiety disorders had as children

Anxiety: Development *into* Disorder

- ü Heritability-of general predisposition, rather than of specific type
- ü Question of whether separating out diagnoses critical (Ferdinand et al 2006)
- ü Behavioral Inhibition and social phobia
 - Strongest continuity from child to adulthood
 - Behavioral inhibition (BI) to the unfamiliar (Kagan and Snidman 1999)
 - Withdrawal reactions on facing novelty,--->a percentage dev. social anxiety as teen
- ü Parents with panic disorder are at high risk for having children with behavioral inhibition (Hirshfeld-Becker et al 2004)
- ü Is Separation Anxiety Disorder (SAD) a predictor for early adult panic disorder? (Klein 1964)
 - Retrospective support from adults with Panic Disorder and Social Phobia both equal rates of childhood SAD (Otto et al 2001)
- * SAD may be marker for many anxiety disorders: specific phobia, OCD, PTSD, acute stress disorder (Aschenbrand et al 2003)

Anxiety: Development *into* Disorder?

- Parental contribution: if they have an anxiety disorder and parenting style
- Early life experience and adverse life events
- Look for anxiety in youth with asthma
(asthma causes anxiety, treat it, Rietveld and Creer 2003))

Anxiety: Diagnostic & Treatment Barriers

- Developmental continuum
 - All anxiety “normalized” and impairment underappreciated
- Silent suffering-especially in younger children
 - Difficulty communicating internal states
 - Uncommonly leading to obvious difficulties
- Measurement difficulties-there is only moderate consensus on instruments (Muris P et al 2002)

***In primary care, neither screening or diagnosis of anxiety is routine (Wren et al 2003)

What do normal kids (8-13 years) worry about?

- School performance 21%
- Dying and illness of others 16%
- Getting sick 12%
- Being teased 8%
- Making mistakes 7%
- Appearance 7% (Muris et al 1998)

Above age 7, children identify palpitations, shakiness and breathing difficulties as signs of anxiety (Muris et al 2004)

Anxiety: Assessment I

- Subjective anxiety rarely the presenting complaint
 - Physical sxs common (headaches, GI, palpitations)
 - If you don't take a temperature you can't find a fever
- Rule out medication side effects
 - Pimozide: school phobia and separation anxiety (Linnet 1985,
 - Diet pills, sympathomimetics, asthma agents (incl. steroids)

Anxiety Disorders: Classification

- Generalized Anxiety Disorder
- Social Anxiety/Selective Mutism
- Separation Anxiety Disorder
- Panic Attacks / Panic Disorder
- Specific Phobias
- Post Traumatic Stress Disorder
- Obsessive Compulsive Disorder

Co-morbidity of Anxiety Disorders

- More than 2/3 of diagnosed children meet criteria for 2 other anxiety disorders (Reinblatt and Walkup 2005)
- Children- 25%ADHD (Bernstein 2005)
- Teens-MDD co-morbidity on 1/3 - to -2/3, Substance Abuse, Bipolar (anxiety precedes it)

Remember co-morbidity effects presentation, outcome and treatment

Generalized Anxiety Disorder

- 6 month criteria of excessive anxiety and apprehensive expectation more days than not
- Difficult to control anxiety
- 1 additional symptom in children:
Restlessness, easy fatigue, irritability, difficulty concentrating, muscle tension or aches, disturbed sleep (Kendall and Pimental 2003)
- Not occur in relation to another disorder
- Anxious about performance in school or sports; punctuality, catastrophes, seek reassurance
- Chronic and fluctuating, interfere with functioning

Sample of GAD youth and comorbidity

- Depressive disorder was the most frequent comorbidity, being present in 56% of the patients. Comorbid anxiety disorders were present in about 75% of the patients, and 21% showed externalizing disorders (Masi et al 2004)

Panic Attacks

At Least 4 Symptoms, Peak in 10 Minutes

1. Palpitations, pounding heart, or accelerated heart rate
2. Chest Pain or discomfort
3. Shortness of breath
4. Feeling of choking
5. Feeling of dizzy, unsteady, lightheaded or faint
6. Paresthesias (numbness or tingling sensations)
7. Chills or hot flushes
8. Trembling or shaking
9. Sweating
10. Nausea or abdominal stress
11. Derealization or depersonalization
12. Fear of losing control or going crazy
13. Fear of dying

A decision tree



- If cued or situational, then it is a social anxiety disorder or a specific phobia
- If un-cued, “comes out of the blue” then consider Panic Disorder

Panic Disorder: DSM-IV Criteria

- **Both (1) and (2)**
 1. Recurrent unexpected panic attacks
 2. At least one of the attacks followed by 1 (or more) months of one (or more) of the following
 - a) Persistent concern about additional attacks
 - b) Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack etc.)
 - c) Significant change in behavior related to the attacks
- **With (or Without) Agoraphobia**

Fear of being alone and unable to get help or trapped and unable to escape in the event of having panic or panic-like symptoms

Watch out for Panic Disorder and Depression in adults (55.6%, Kessler 1989)

-longer duration, more severity and
higher danger of suicide in adults



“The human brain is a wonderful thing. It operates from the moment you’re born, until the first time you get up to make a speech”

-Howard Goshorn

Facts about Social Phobia

- Feel they will be embarrassed or judged in public speaking, being in social situations, writing, eating, using bathrooms in public
- Prevalence 3-13% lifetime
- Onset in mid-teens and usually chronic course
- High incidence of underachievement, poor social networks, alcoholism, school drop-out



Youth Generalized Social Phobia

- Not lack social skills, appear more nervous (Cartwright-Hatton et al 2003)
- Look for it in Turners and Fragile X (Lesniak-Karpiak et al 2003)
- School-based treatment of group CBT (Masia et al 2001)
- Youth less responsive to SSRIs than adults (Ameringen et al 2004)

Social Phobia (Social Anxiety Disorder) DSM-IV Criteria

- Persistent fear in one or more social or performance situations
- Exposure leads to a cued panic attack or significant symptoms
- Situations are avoided or endured with distress
- For youth, 6 month criteria, generalized

Separation Anxiety Disorder (SAD)

- Excessive anxiety and distress when leave home or significant others, may be at bedtime
- More than 4 weeks , not developmentally appropriate
- May have nightmares and physical complaints (e.g., head aches, stomach aches, nausea, vomiting in anticipation or visual illusions or panic if older)
- May have fears of kidnapping, death or dying
- Increased MDE or DD

Separation Anxiety Disorder-2

- More common in younger children
- SAD prevalence is 4%, may be more common in lower SES (Masi et al 2001)
- Not a consequence of actual trauma (Bandelow et al 2001)
- SAD associated other anxiety diagnoses and specific phobias (Verdun et al 2003)
- Diagnosis not same as “school refusal”
- School refusal may be based on fears of being bullied , teens with MDE and/or anxiety disorders, avoidant disorder, hallucinations

SAD-Children v Parents

- Parents and children rarely agree about the presence of any level of child separation anxiety. A symptom ...indexes diagnoses based on interview with only one informant, but the relative validity of such diagnoses remains unclear (Foley et al 2004)

What happens to SAD

- 80% children with SAD in a community setting are well 18 months later. A minority of children with persistent SAD are at significantly increased risk of a new depressive disorder, especially those with a history of oppositional defiant disorder, impairment associated with symptoms of attention deficit hyperactivity disorder, or parental marital difficulties.(Foley et al 2004)

What happens to SAD?

- ‘Most children experience a dissipation of SAD symptoms in young childhood but that some children continue to experience stable, significant distress. The results are consistent with prior research on older children that SAD remits for many but not all youth and suggest that parent and family variables may have much to do with cases of poor remission in this population.’ (Kearney et al 2003)

Anxiety: Psychosocial Treatment I

Four general components

- Exposure: graded exposure & “fear hierarchy”, systematic desensitization, relaxation techniques
- Contingency management: external factor reinforcement, shaping, extinction
- Cognitive strategies: internal factor self instruction, problem solving
- Modeling: appropriate behavior in anxiety situation

CBT for Youth with Anxiety Disorders

- Efficacy demonstrated (Muris et al 2002, Barrett et al 2001)
- Individual and group CBT have equal outcomes (Manassis et al 2002)
- Adding a parent not change child's outcome (Nanta et al 2003, only useful when parent is anxious (Cobham et al 1999))
- Parent only group - parents act as therapists for kids (Thienemann et al 2006)

CBT vs Medication-Based Modalities

- Despite results from CBT, there has been a shift toward medication-based outpatient treatment modalities (Rietveld and Creer 2003)



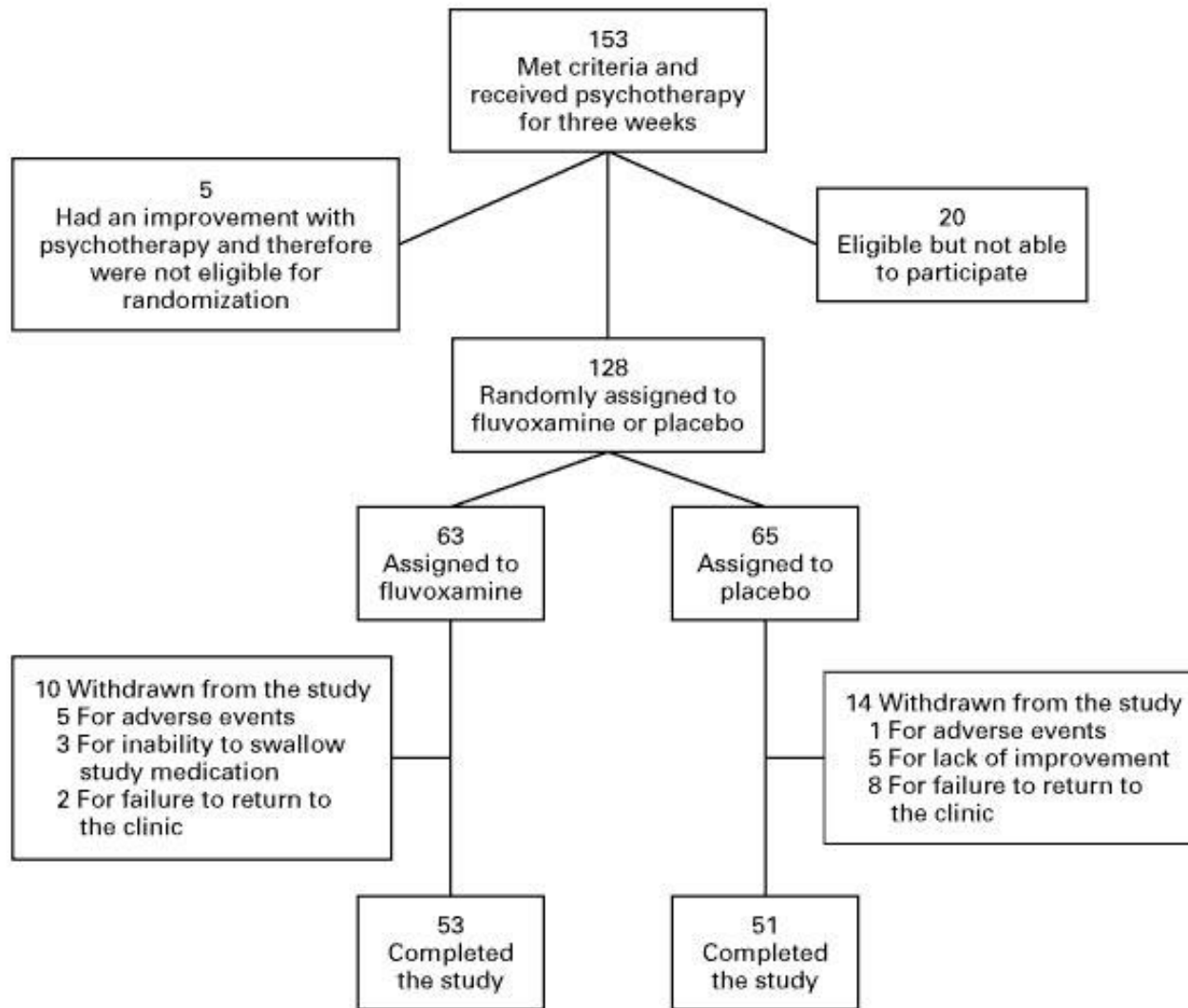
Medications-DBPC Studies: Fluvoxamine

Black Box warning for suicidality for all antidepressants in youth, regardless of disorder being treated

Fluvoxamine (RUPP studies 2001, extension 2002) with 50- 300 mg, 8 wks, n=128 in 6-17 yrs, GAD, SAD, Social Phobia after 3 wks supportive psychotherapy n=128

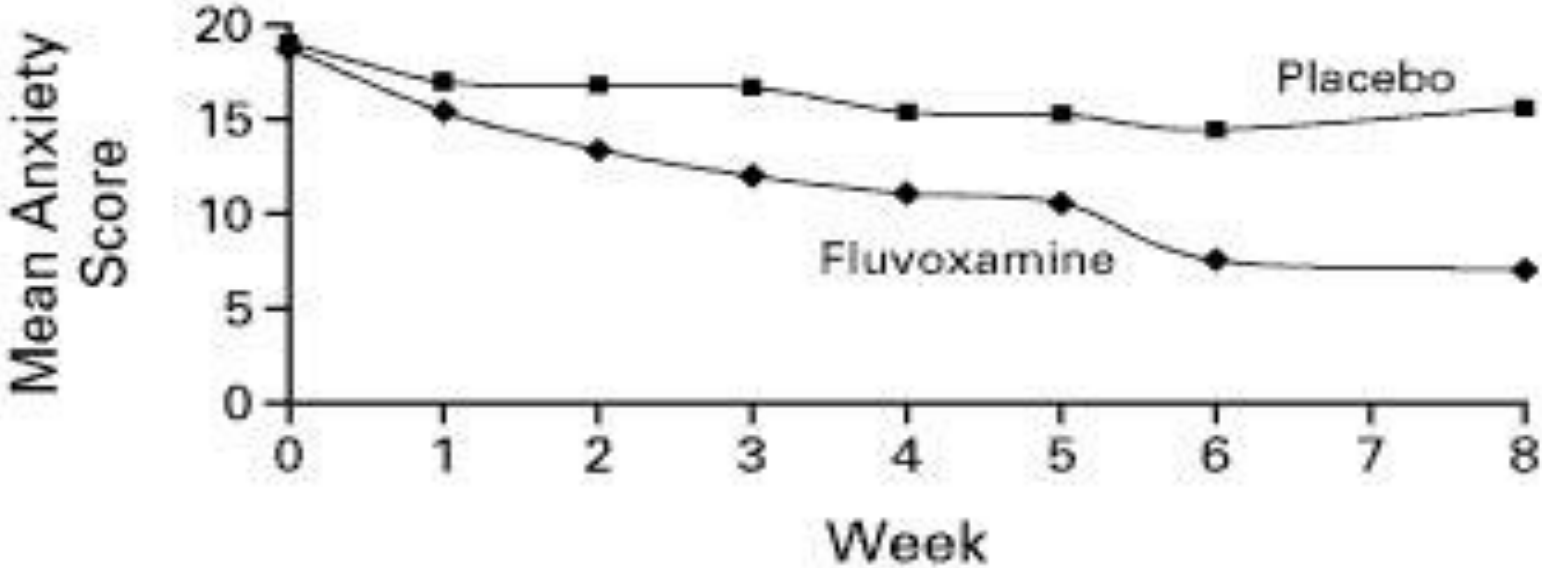
- ✓ CGI and PARS= FLVX 76% v 29% placebo
- ✓ Adverse effects= stomachache, motor activation 28% v 12% placebo
- ✓ 6 mo open label extension-94% continued remission; fluvox non-responders-> Fluoxetine (n=14) 20-40 mg 71% response by clinician rating and PARS
- ✓ Higher level of depression, SP and severity of illness- less drug efficacy;
- ✓ ES=1.1 largely because of low placebo response

Take home message: If no response from first SSRI, try a second one



Flvoxamine study 2001

Mean Total Score on the Pediatric Anxiety Rating Scale in the Fluvoxamine and Placebo Groups during the Eight-Week Trial



Sertraline study

- **Sertraline** to 50 mg (low dose), n=22, 9 wks, 5-17 yrs, primary GAD (actually had other anxiety dxs
-> no significant AEs
- Drug effect by 4 wks (Rynn 2001)

Fluoxetine Studies

- ❖ (Birmaher et al 2003) **Fluoxetine** at 20 mg, 12 wks, 7-17 yrs, n=74. SAD, GAD, SP
 - CGI 61v 35% by wk 9 significant differences (only a trend for SAD)
 - AEs= headache and gi- 5/74 significant akathisia; more mild, reduce dosing
 - severity at start and family anxiety disorder predicted poorer outcome
- ❖ **Fluoxetine** increased to 0.6mg/kg/day 12 wks, n=15, selective mutism->improved but still symptomatic (Black and Uhde 1994)

Paroxetine (Wagner et al 2004)

- 16 wk multicenter, industry sponsored, 8-17 yrs with social anxiety disorder, n=322
- Paroxetine 10-50 mg /day found superior to placebo 78% v 39%
- AEs insomnia, decreased appetite and V

New Pharmacokinetic Findings in Children

- Sertraline in teens, 50 mg, initial half-life = 26 hrs, but at steady state, half life 15 hrs; should be bid; non-linear, but at 100-150 mg, initial half-life 26 hrs and at steady state = 20 hrs, therefore dose once, but C_{max} at steady state is 35% higher than expected. Watch out for discontinuation syndromes (Axelson 2002)
- Citalopram in teens; initial and steady state half life 17-18 hrs and linear (Axelson 2003)
- Mirtazapine children have higher C_{max} and require only once/day dosing (Findling 2003)
- Nefazodone- (Findling 2003) children have more mCPP metabolite, but it means nothing clinically.
- Paroxetine in children, half life = 11 hours, but steady state by 1 week; saturable state; non-linear pharmacokinetics--- 10mg is probably best dose. When increase to 20 mg->blood levels increases to approximately 70 mg (Findling 2003)
Discontinuation syndrome can be profound.

Buspirone and Venlafaxine

- Buspirone JAMA August 2003- FDA
Not effective in treatment of anxiety in children
- Venlafaxine drug company sent out letter that this drug is not effective in anxiety in children, with possible increased risk of suicidal ideation

TCA and Benzodiazepines

- TCAs
 - SAD: 1971 report of IMI > PLA (n=35)
 - Not replicated by same group in 1992 (n=21, SAD)
 - Role in resistant or co-morbid (e.g. ADHD) cases
 - Concerns over cardiotoxicity: EKG monitoring
- Benzodiazepines
 - 2 DBPC studies, both negative- CNZ with disinhibition: 3/15 (Graae 1994) alprazolam (Simeon 1992)

Benzodiazepines- Comparisons

Drug (*sub-lingual)	(mgs) Equiv	absorption	important metabolites	1/2 life (hrs)	Dose comments/metabolism
*Diazepam (valium) min age 6 mo	10	fastest	desCH3DZ	20-100 long	high addictive potential <CYPs 3A4, 2C19>
Alprazolam (xanax) min age 18 years	1	intermed	no	10-24 intermed	high abuse, rage reaction <CYP 3A4 et al>
*Lorazepam (ativan) min age 12 years	1.5-2	intermed	no	10-20 short	IM, glucuronidated
Clonazepam (klonopin) min age not specified	0.50	slow	mod	18-60 intermed	anti-seizure<CYP 3A >+ ketoreduction/acetylation

Bupropion

- SR and XL lower incidence of seizures than bupropion
- CYP2B6-is major cytochrome pathway and CYP 3A4 is a minor pathway
- 22 x>one of the active metabolites in relation to parent bupropion > in kids than adults; may be the active part of the drug
- 6mg/kg/day recommended in bid dosing
- XL and SR have different absorption and distribution, but half-life and clearance remain the same
- Is a potent CYP2D6 inhibitor
- Metabolite AUC decreased by OCs (Palovaara et al 2003)
- AEs- watch out for serum sickness
- Overdose-- seizures dose dependent, rare, tachycardia and QTc prolonged

Child/Adolescent Anxiety Multimodal Treatment Study (CAMS)

- Multicentric study comparing sertraline, CBT, combination and pill placebo in treatment of anxiety disorders (Jan 2003-May 2007)
- Subjects aged 7-17 years with DSM-IV criteria for separation anxiety disorder, social phobia, or generalized anxiety disorder included
- Phase I: Participants randomly assigned to receive sertraline, CBT, combination or placebo for 12 weeks.
- Phase II: 6-month maintenance period for participants that respond to any of the three active treatments.
- Results awaited

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Answers

- 1- C
- 2- D
- 3- C
- 4- C
- 5- E