



UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

PEDIATRIC DEPRESSION AND ANXIETY

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GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

SPEAKER DISCLOSURES

None

OBJECTIVES

Understand clinical presentation, epidemiology
and evidence based treatment approaches of

Pediatric depression

Pediatric anxiety

DEPRESSION

CASE STUDY

- 17 F
- Increased school avoidance and early morning fatigue
- Depressed mood for 3 months with passive SI
- C/o nausea with self induced vomiting for relief. H/O headaches and fatigue
- Familial history of anxiety and eating disorders
- H/o family separation and conflicts with parent; in reconciliation therapy. Not seeing dad for 6 months since separation

PHQ9 A 22 and SCARED 44

EPIDEMIOLOGY

- Adolescent depression affects 12-25% of adolescents
- Onset prior to age 12
- Commonly associated with poor academic, social, and health outcomes; substance abuse, early pregnancy and parenthood, and increased healthcare costs
- Suicide is the 2nd leading cause of death for our youth ages 10-24
- More teenagers and young adults die from suicide than from cancer, heart disease, AIDS, birth defects, stroke, pneumonia, influenza, and chronic lung disease, **COMBINED**
- Despite these statistics, 80 % of adolescents do not receive appropriate treatment

SCREENING TOOLS FOR DEPRESSION

PHQ-9A (Adolescent)

- A Normed for ages 12-18
- Score of 11 has a sensitivity (89.5%) and specificity (77.5%)
 - similar to those in adults
- PHQ-9A scores reflect severity
 - Mild=5-10
 - Moderate=11-14
 - Moderately Severe=15-19
 - Severe>20

Short Mood and Feelings Questionnaire (SMFQ)

- Can be used in children ages 6-17
- Child and parent report in combination have the greatest efficiency in predicting depression severity
- Combined scores (parents+child)>10 concerning for depression
- Individually have concern if:
 - Child score>7
 - Parent score>4

Richardson, L. P., McCauley, E., Grossman, D. C., McCarty, C. A., Richards, J., Russo, J. E., Rockhill, C., & Katon, W. (2010). Evaluation of the patient health questionnaire-9 item for detecting major depression among adolescents. *Pediatrics*, 126, 1117-1123

THE TREATMENT OF ADOLESCENTS WITH DEPRESSION STUDY (TADS)

- Design
 - 12-17 y.o. with MDD
 - Fluoxetine, CBT, combo, or placebo
 - 12 weeks blinded, 24 weeks unblinded
- Results
 - Rates of response (12 weeks):
 - Combo 71.0%>fluoxetine 60.6%>CBT 43.2%>placebo 34.8%
 - Suicidal thinking in 29% at baseline, improved significantly in all 4 groups but **greatest** improvement in combo at 12 wks
 - Suicidal events by 36 weeks:
 - Fluoxetine 14.7%>combo 8.4% or CBT 6.3%

1. TADS Study Team. JAMA 2004;292(7), 807

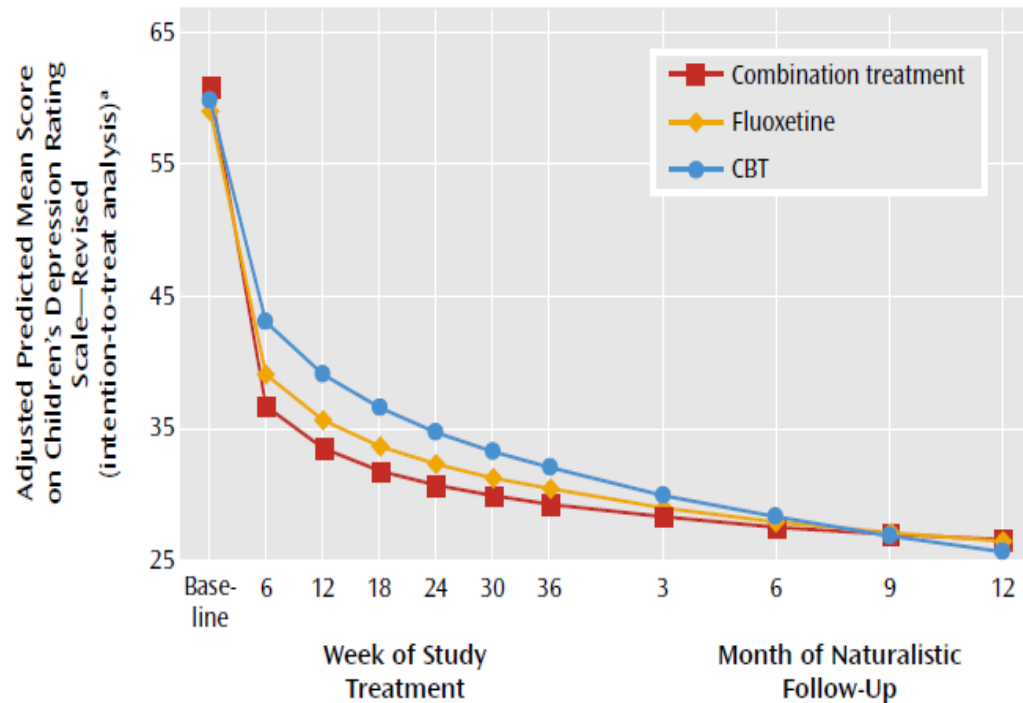
2. March et al. Arch Gen Psych 2007; 64(10):1132

TADS 1 YR FOLLOW-UP

At one year follow-up benefits persisted

TADS TEAM

FIGURE 1. Depression Scores From Baseline to End of Naturalistic Follow-Up for 327 Adolescents With Major Depressive Disorder Treated With Fluoxetine, Cognitive-Behavioral Therapy (CBT), or a Combination



^a Derived from the random coefficients regression model with adjustments for fixed and random effects.

TADS - CONCLUSIONS

- Treatment of depression with fluoxetine alone or in combo with CBT accelerates response
- Adding CBT to meds enhances the safety of meds
- Therefore, combined treatment superior to monotherapy

INITIAL TREATMENT OF DEPRESSION

- Mild/uncomplicated/brief
 - Psychoeducation
 - Supportive management - active listening and reflection, restoration of hope, problem solving, coping skills, and strategies for maintaining participation in treatment
 - Case management – environmental stressors in family and school
- Moderate
 - CBT (or IPT)
 - Consider SSRI – not responding, not ready for therapy
- Severe/suicidal ideation
 - CBT (or IPT) and SSRI

WHICH SSRI TO START WITH?

- Fluoxetine – multiple positive RCTs, FDA approved 8 and up
 - Very little SI signal in controlled studies
 - Long half life means no withdrawal symptoms from missed doses
 - Covered by all plans, and available generic
 - Available in once a week dosing:
 - Start patient on short acting fluoxetine and stabilize at 20 mg dose
 - Then stop fluoxetine 20 mg/day and start fluoxetine 90 mg/week capsule 7 days after last 20 mg dose
 - Caution: Medication interactions

WHICH SSRI TO START WITH? (CONT.)

- Sertraline* – 1 positive RCT
- Citalopram* – 1 positive RCT
 - Caution: QT prolongation, doses over 40 mg not recommended and caution advised with other QT prolonging medication or meds/conditions that would decrease citalopram metabolism
- Escitalopram – 1 mixed result RCT (only adolescent subset positive), FDA approved 12 and up

* Not FDA approved for depression treatment <18

MEDICATING MAJOR DEPRESSION

- Start low, go slow
- Change one medicine at a time
- Use the full dose range, wait 4-6 weeks before each increase

PREDICTORS OF POOR RESPONSE

- Depression severity and chronicity
- Hopelessness
- Suicidal ideation
- Family conflict
- Functional impairment
- History of abuse
- Non-suicidal self injury (NSSI)
- Older age and lower family income (TADS study)
- Comorbidity (TADS)

TREATMENT OF RESISTANT DEPRESSION IN ADOLESCENTS (TORDIA)

- Design
 - 12-18 y.o. with MDD that had not responded to 2 mo on SSRI
 - Switch to: (1) 2nd SSRI, (2) 2nd SSRI and CBT, (3) venlafaxine, (4) venlafaxine and CBT
 - 12 weeks blind, 12 more open
- Results
 - Rates of response (12 weeks):
 - CBT plus either med 54.8% > med alone 40.5%
 - No difference in response between 2nd SSRI and venlafaxine
- Adverse Effects
 - No differential treatment effects on SI
 - More AEs with venlafaxine
 - increase diastolic BP and pulse
 - skin problems
 - associated with a higher rate of self-harm adverse events in those with higher SI

1. Brent et al. JAMA 2008;299(8):901
2. Emslie et al. Am J Psychiatry 2010; 167:782–791
3. Brent et al, *Am J Psychiatry* 2009; 166:418–426

TORDIA - CONCLUSIONS

- For adolescents with depression not responding to first SSRI:
 - Continued treatment results in remission in approximately 1/3 of patients
 - Eventual remission is evident within the first 6 weeks in many
 - Earlier intervention may be important
 - Switch to 2nd SSRI just as efficacious as a switch to venlafaxine
 - SSRI had fewer adverse effects
 - Combo of CBT + new med > new med alone

AFTER TWO SSRIS DON'T WORK - DEPRESSION

- Venlafaxine*
 - Combo of 2 RCTs (2ndary analysis) showed positive effect for adolescents
- Cymbalta*
 - 1 open label safety study
- Bupropion*
 - Open label positive studies in adolescents
- Mirtazapine*
 - Open label positive study in adolescents
- Tricyclic antidepressants*
 - Serious side effects, fatal in overdose
 - Meta-analysis – not superior over placebo in kids
- Other augmenting agents*

SWITCHING ANTIDEPRESSANTS

- Cross taper vs. switch over
- Potential concerns:
 - Discontinuation syndrome
 - Relapse of partially treated symptoms
 - Side effects to new medication
 - Medication interactions
 - Serotonin syndrome
 - P450 2D6
 - fluoxetine and paroxetine strongly inhibit it, most commonly used antidepressants are substrates
 - Time to get to therapeutic dose of new med
 - Complexity of instructions

ALTERNATIVE TREATMENTS

- Exercise
 - 2006 Cochrane review found 28 RCTs, 4 highest quality showed small benefit for adults with MDD
 - J Consult Clin Psychol 2010; 78: 268-272
 - Prospective longitudinal study on youth with MDD: increased physical activity in teens (11-15 y/o) decreased risk for subsequent MDD by 16% for each additional type of activity
 - Ment Health Phys Act 2009; 2: 76-85
 - 15 adolescents with history of MDD randomized to aerobic vs stretching for 12 weeks, 80% of those in exercise group responded by 12 weeks vs. 60% of stretchers
- Bright light therapy
 - Recent study in JAMA Psychiatry 2016;73(1):56-63
 - Bright light therapy effective in adults with non-seasonal MDD both as monotherapy and in combination with fluoxetine
 - Small RCT in Int J Psychiatry Clin Pract 2012; 12(3): 233-7
 - 28 adolescents in RTC improved on BDI with light therapy compared to placebo
- Omega-3 fatty acids
 - RCT in Am J Psychiatry 2006; 163(6): 1098
 - 20 patients showed improvement with omega-3 monotherapy

ALTERNATIVE TREATMENTS CONT.

- St. John's wort (hypericum) www.nccam.nih.gov/health/stjohnswort/
 - Inconsistent data in adults only, no RCT's in youth
 - Drug interactions: can potentiate serotonergic drugs and increase risk of serotonin syndrome, must stop prior to SSRI trial
- SAM-E: one positive systematic review in adults, no RCT's in youth
- 5-Hydroxytryptophan (5HTP): mixed results in adults, no RCT's in youth
- Glutamine: no RCT's in youth
- Vitamin D: no RCT's in youth
- Reiki: Positive RCT in Psychiatry Research 2016; 239: 325-330
 - 188 teens in Iran, compared CBT, Reiki and waitlist, and showed CBT > Reiki > waitlist

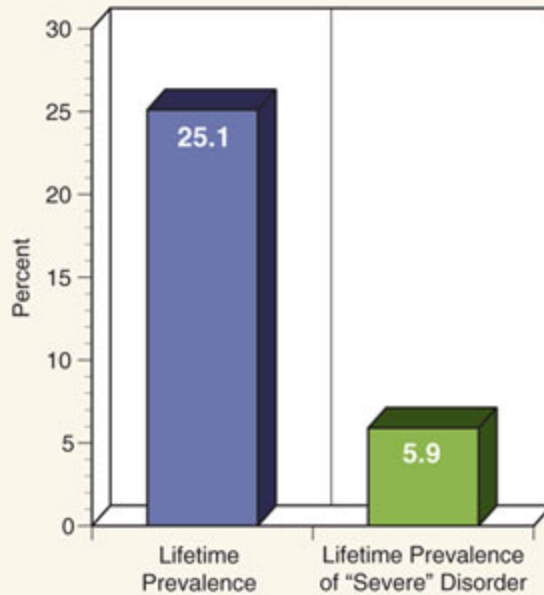
ONCE THINGS STABILIZE. . .

- Treatment should be continued for 6 to 12 months during the continuation phase
 - Patients typically seen at least monthly, depending on clinical status, functioning, support systems, environmental stressors, motivation for treatment, and the presence of comorbid psychiatric or medical disorders.
- General rule of thumb: the longer it takes to recover or the higher the # of recurrences, the longer the period of maintenance.
 - ≥ 2 episodes of depression, 1 severe episode, or chronic episodes should have maintenance treatment for > 1 yr.

ANXIETY

Lifetime Prevalence of 13 to 18 year olds

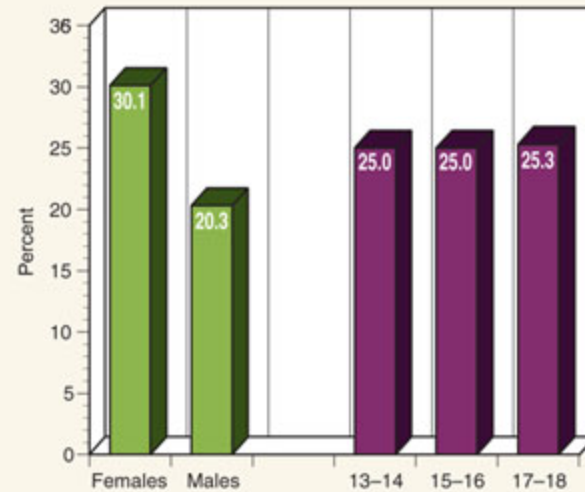
- **Lifetime Prevalence:** 25.1% of 13 to 18 year olds
- **Lifetime Prevalence of “Severe” Disorder:** 5.9% of 13 to 18 year olds have “severe” anxiety disorder



¹Merikangas KR, He J, Burstein M, Swanson SA, Avenevoli S, Cui L, Benjet C, Georgiades K, Swendsen J. *Lifetime prevalence of mental disorders in U.S. Adolescents*. Under review.

Demographics (for lifetime prevalence)

- **Sex:** Statistically different
- **Age:** Not statistically different



- **Race:** Statistically significant differences were found between non-Hispanic whites and other races

EPIDEMIOLOGY

- An estimated 15% to 20% of youth in the United States meet criteria for any anxiety disorder (i.e., SAD: 2.8% to 8%, SP: 10%, SOC: 7%, panic disorder: 1%–3%, GAD: 4.3%) ([Beesdo, Knapp, & Pine, 2009](#)), and approximately 1 in 5 youth will have an episode of MDD by age 18

THE NATURAL HISTORY OF ANXIETY

- Harvard/Brown Anxiety Research Project
 - Adult patients of psychiatric clinics
 - Remission at one year
 - Panic disorder - ~40%
 - Panic disorder with agoraphobia - ~15%
 - Social phobia - ~7%
 - GAD - ~10-15%
 - Remission at 8 years
 - Panic disorder - ~70-75%
 - Panic disorder with agoraphobia - ~35-40%
 - Social phobia - ~30%
 - GAD - ~45-55%

THE NATURAL HISTORY OF ANXIETY

- Cumulative Probability of Relapse after 8 years
 - Panic disorder - ~20-65% (gender variable)
 - Panic disorder with agoraphobia - ~40-50%
 - Social phobia - ~30%
 - GAD - ~40%

- Important points
 - Anxiety disorders are chronic in majority of men and women
 - Patients who experienced remission were more likely to improve during first 2 years

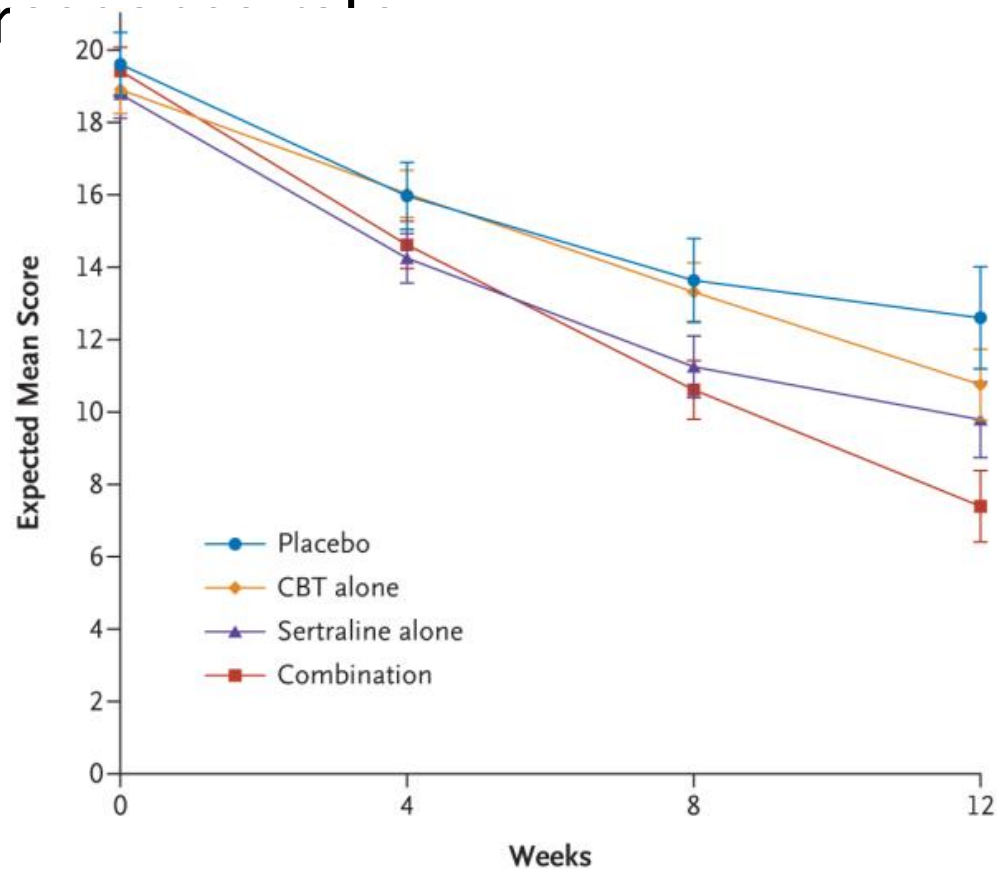
Yonkers et al; Depression and Anxiety 17:173 (2003)

CHILD/ADOLESCENT ANXIETY MULTIMODAL STUDY (CAMS)

- Design
 - 488 7-17 y.o. with SAD, GAD or SP
 - 14 sessions of CBT, sertraline, combo, or placebo
 - 12 weeks
- Results
 - Very much or much improved:
 - 80.7% combo
 - 59.7% CBT
 - 54.9% sertraline
 - 23.7% placebo
 - Pediatric anxiety rating scale, similar results
 - SI no more frequent in sertraline than placebo, no suicide attempts

CAMS - CONCLUSION

- CBT and sertraline both work, combo of the two has superior r



CAMS - CONCLUSION

- CBT and sertraline both work, combo of the two has superior response rate

SCREENING MEASURES FOR ANXIETY–SCARED (CHILD AND PARENT VERSIONS)

- Free, ages 9-17
- Broad screen for global anxiety
- Also has subscales for specific anxiety diagnoses
- Brief version for tracking over time
- Available in several languages

Triggering is contingent on child respondent age ≥ 8 and ≤ 18

Subscale	Trigger subscale when score \geq	Trigger respondent
Panic Disorder	7	Child; Parent (if account exists)
Generalized Anxiety	9	Child; Parent (if account exists)
Separation Anxiety	5	Child; Parent (if account exists)
Social Anxiety	8	Child; Parent (if account exists)
School Avoidance	3	Child; Parent (if account exists)

• Triggers are based on cutoff scores developed by Birmaher and Colleagues
See: Birmaher, B., Brent, D.A., Chiappetta, L., Bridge, J., Monga, S., & Baugher, M. (1999). Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): A replication study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38 (10),1230-6

ADDITIONAL SCREENERS FOR ANXIETY

- SPENCE Children's Anxiety Scale <http://scaswebsite.com>
 - Free, has child, parent and teacher scales
 - Ages 3-17
 - Available in many (28+) languages
 - 44 item measure for child and 38 item measure for parent
 - Screens for somatization, panic, GAD, separation anxiety and social phobia
- GAD7
 - Free
 - Brief, only 7 questions
 - Validated for ages 14 and up
 - Scores 0-21 with >5 (mild), >10 (moderate), >15 (severe)
 - Total score >10 should trigger extended evaluation

INITIAL TREATMENT OF ANXIETY

- Mild
 - CBT (or other therapy)
- Moderate
 - CBT
 - Consider SSRI— esp. if not responding, not ready for therapy
- Severe
 - CBT and SSRI

AFTER TWO SSRIS DON'T WORK - ANXIETY

- Venlafaxine* (Effexor XR) – 2 positive RCTs combined in one to get benefit
 - Side effect profile makes this a 2nd tier option
- Mirtazapine* (Remeron) – no controlled trials
 - Consider if need sedation and appetite stimulation
- Buspirone* (Buspar) – 2 negative RCTs in youth with GAD
- Benzodiazepines*
 - Have not shown efficacy in RCTs with youth
 - Risk of tolerance and dependence
 - When used for severe anxiety - adjunctively & short term
- Beta-blockers*- no controlled trials
 - Used for performance anxiety
- Antihistamines- no controlled trials
 - Hydroxyzine used for as adjunctive, often for insomnia/anticipatory anxiety
- Tricyclic antidepressants
 - Clomipramine shown to be efficacious in OCD, FDA approved ≥ 10 yo
 - Anticholinergic side effects, cardiac monitoring, risk of fatality with overdose

*Not FDA approved for anxiety treatment <18

OTHER COMMON CONCERNS AND RECENT UPDATES

SLEEP TROUBLES

- Commonly impacted by both depression and anxiety
- Impact from SSRI's
 - Serotonergic REM suppression may cause decreased dream frequency
 - Increased periodic limb movements of sleep
 - Vivid dreams
- Sleep hygiene
- CBT-Insomnia
- Sleep meds: no medication labeled for insomnia in children by FDA
 - Melatonin: 3-5 mg, 1 hour before bedtime
 - Diphenhydramine: 12.5-25 mg starting dose, max 50 mg QHS, short term only
 - Trazodone: 25-50 mg QHS, max 200 mg QHS
 - inhibits CYP 2D6, use with caution with fluoxetine or paroxetine, it may decrease their effect

SSRI RISK BENEFITS

TABLE 7 SSRI Side Effects

Side Effect	Management
Gastrointestinal distress	Typically self-resolves Symptomatic care
Headache	Typically self-resolves Symptomatic care
Appetite change	Counsel on healthy nutrition
Sedation	Administration at bedtime
Sleep disturbance	Administration in morning Counsel on sleep hygiene Consider melatonin as needed
Diaphoresis	No action if mild
Sexual side effects	Consider medication change
Activation (disinhibition, agitation, irritability, silly)	If persistent and significant, discontinue medication
Platelet dysfunction (rare)	Discontinue medication

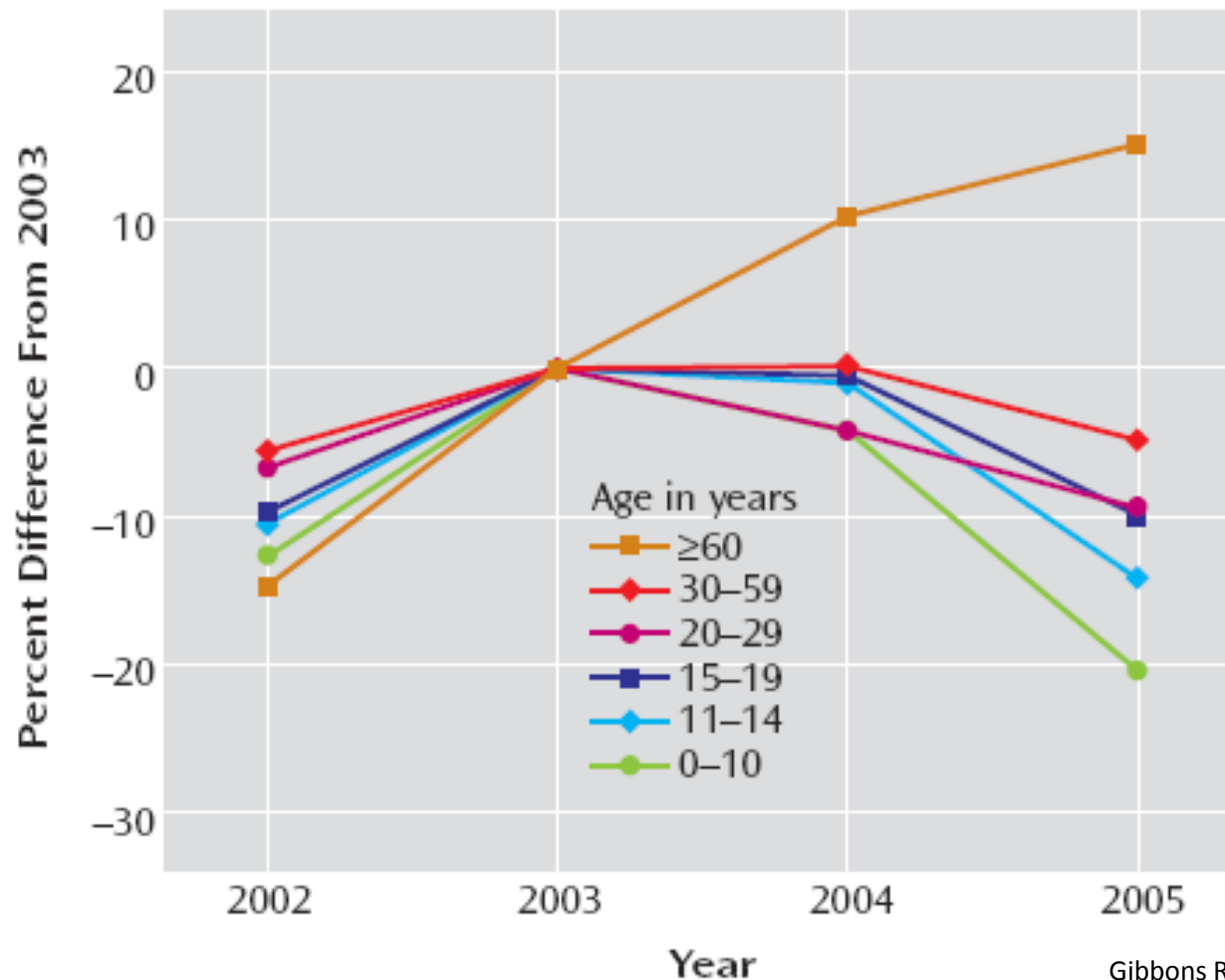
If any symptoms are severe, prescriber may decrease medication dose or switch to another.

DISCUSSING THE BLACK BOX WARNING

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

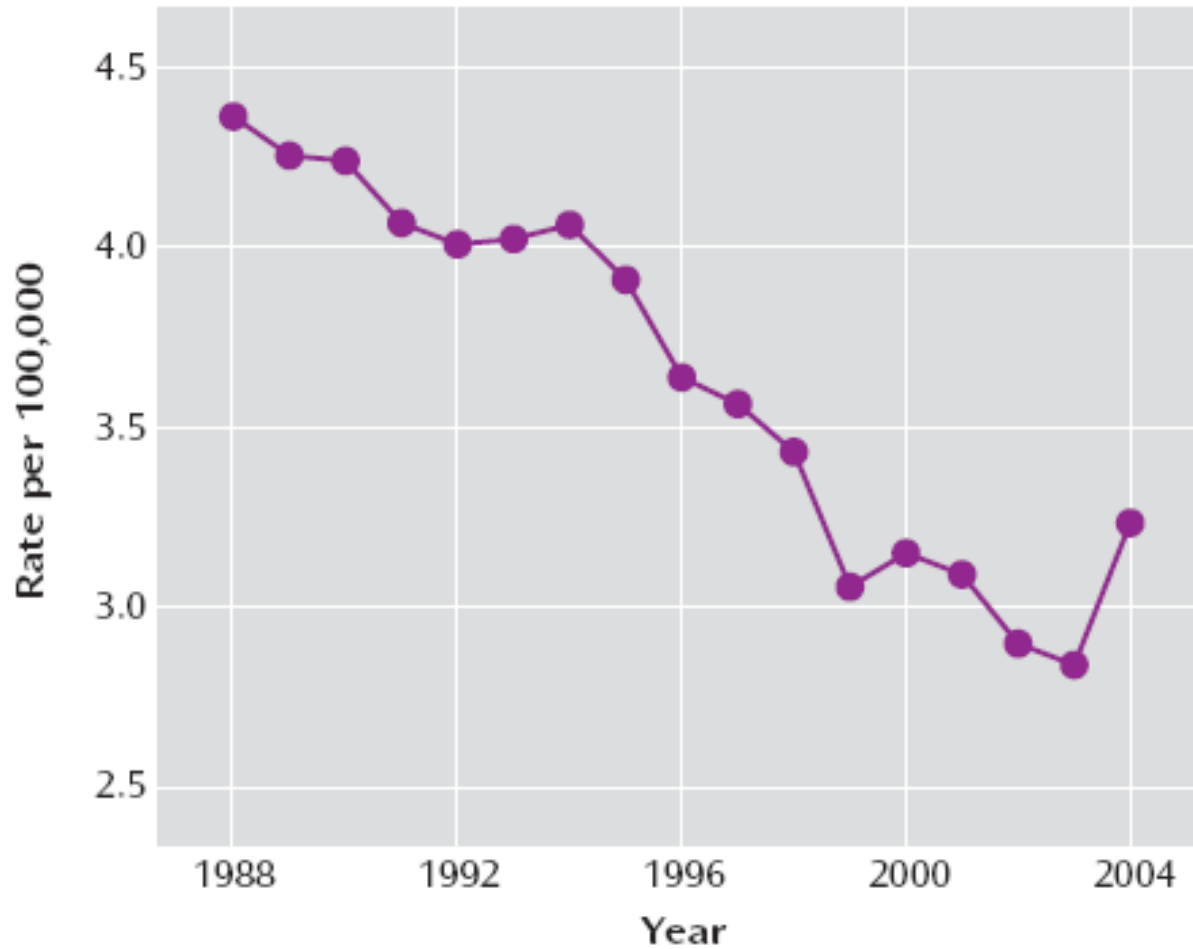
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PROZAC or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PROZAC is approved for use in pediatric patients with MDD and Obsessive Compulsive Disorder (OCD).

FIGURE 1. SSRI Prescription Rates in the United States, 2002–2005, Stratified by Age Group and Expressed as a Percentage of the 2003 Rate



Gibbons RD, Brown CH, et al 2007

FIGURE 2. Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004



Gibbons RD, Brown CH, et al 2007

BLACK BOX WARNING, RECENT META-ANALYSES

- Bridge et al, JAMA. 2007;297:1683-1696
 - Meta-analysis of 27 RCTs for antidepressants relative to placebo for pediatric MDD and anxiety (OCD and non-OCD)
 - Results:
 - Overall small but increased risk of treatment-emergent suicidal ideation/suicide attempt.
 - Pooled risk of suicidal ideation/suicide attempt for each indication were all **less than 1%**.
 - Depending on treatment indication, **NNT ranges from 3 to 10, while NNH via emergence of suicidal ideation/suicide attempt ranges from 112 to 200**

BLACK BOX WARNING, RECENT META-ANALYSES (CONT.)

- Conclusions:
 - Relative to placebo, antidepressants are efficacious for pediatric MDD and anxiety disorders
 - Effects strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD.
 - Benefits of antidepressants appear to be much greater than risks from SI/suicide attempt across indications
 - Comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.
 - “We believe that the strength of evidence presented here supports **the cautious and well monitored use** of antidepressant medications as one of the first-line treatment options”

BLACK BOX WARNING, RECENT META-ANALYSES

- Sharma et al. BMJ. 2016; 352:i65
 - Looked at meta-analysis of data from clinical study reports on double blind placebo controlled trials of SSRI medications
 - included 70 studies of duloxetine, fluoxetine, paroxetine, sertraline and venlafaxine
 - included 18,526 patients, both adult and teen data was included.
 - mortality, suicidality, aggressive behavior and akathisia were outcome measures
 - No deaths in children or teens in the study
 - Odds ratios were 2.39 (1.31 –4.33) for suicidality, 2.79 (1.62-4.81) for aggression and 2.15 (0.48-9.65) for akathisia.
 - Values >1 indicate higher risk with drug than placebo
 - In children and adults, the **risk of suicidality and aggression doubled**
 - Argued morbidity data missing and misreported from reports likely underestimates potential harms

REFUSAL TO ENGAGE IN THERAPY

- Help him/her learn more about what therapy really is
 - http://www.dartmouthcoopproject.org/TeenMental/Cognitive_Behavioral2_PT.html
- Educate patient and family on the benefits of therapy
- Remind him/her that therapists are different, therapies are different, and the future experience may be nothing like the past
- Suggest starting with self-guided therapy
- Take a motivational stance

SELF-GUIDED THERAPY (DEPRESSION AND ANXIETY)

- For parents:
 - Helping Your Anxious Child: A Step-by-Step Guide for Parents (Rapee et al).
 - Freeing Your Child From Anxiety: Powerful, Practical Solutions to Overcome Your Child's Fears, Worries, and Phobias. (Tamar Chansky)
 - Freeing Your Child From Negative Thinking: Powerful, Practical Strategies to Build a Lifetime of Resilience, Flexibility and Happiness. (Tamar Chansky)
 - The Depressed Child: Overcoming Teen Depression (Kaufman)
- For children:
 - What to Do When You Worry Too Much: A Kid's Guide to Overcoming Anxiety (Huebner and Matthews).
 - What to Do When Your Brain Gets Stuck (Huebner)
 - Taking Depression to School (2002), (Kathy Khalsa)
 - Where's Your Smile, Crocodile? (Clair Freedman)

SELF-GUIDED THERAPY (DEPRESSION AND ANXIETY)

- For adolescents/young adults:
 - Mastery of Your Anxiety and Worry: Workbook (Craske and Barlow)
 - Mastery of Your Anxiety and Panic: Workbook (Barlow and Craske)
 - Riding the Wave Workbook (Pincus et al)
 - Feeling Good: The New Mood Therapy (David Burns)
 - Relaxation Exercises
 - http://www.dartmouthcoopproject.org/TeenMental/using_relaxation_TN.html
 - http://palforkids.org/docs/Care_Guide/Anxiety_Care_Guide.pdf (Relaxation Therapy Tip Sheet)
 - Depression Self Care
 - <http://www.dartmouthcoopproject.org/TeenMental/teen-resources.html>

USEFUL APPS: MOOD AND ANXIETY

- **Positive Penguins:** educational app to help kids understand why they feel the way they do and help them challenge their negative thinking
– <http://positivepenguins.com/>
- **Breathe2Relax:** app designed by the National Center for Telehealth & Technology to teach breathing techniques to manage stress
- **Worry Box:** app to track worries
- **Bellybio:** interactive, guided deep breathing
- **Optimism:** mood tracking app

USEFUL APPS: SLEEP

- **Bedtime meditations for kids:** guided meditations
- **Deep Sleep with Andrew Johnson:** guided progressive muscle relaxation to target anxiety and insomnia
- **isleep:** guided meditations with music for sleep

QUESTIONS?