Antidepressants in Children and Adolescents: The Good, The Bad & The Ugly

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Objectives

At the conclusion of this presentation, the participant will be able to:

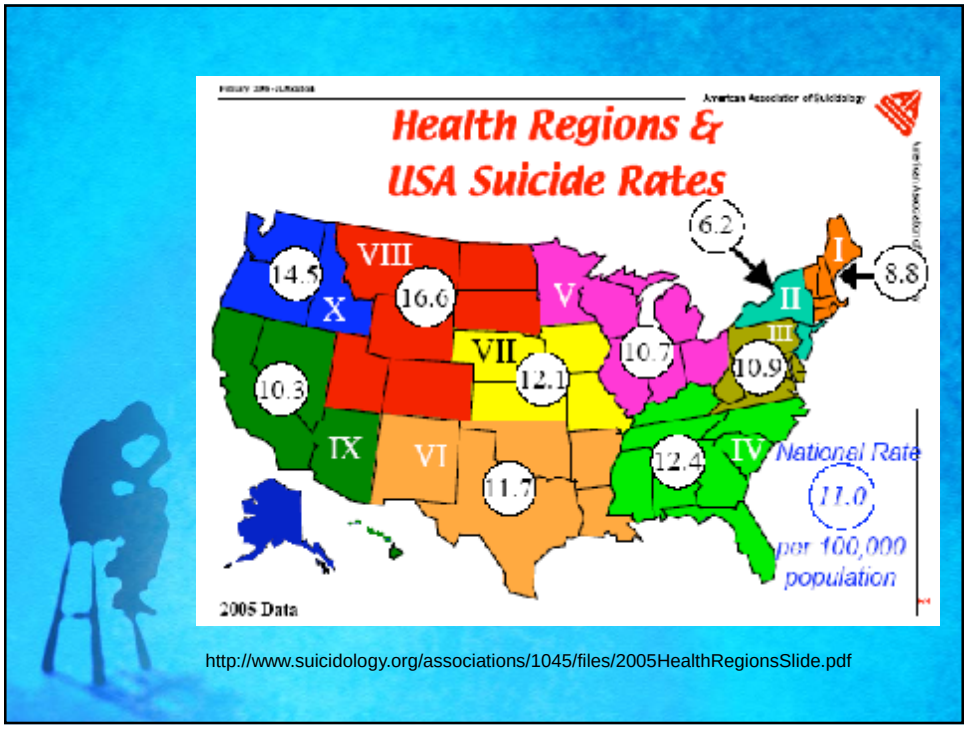
- **Explain to patients and families the meaning and ramifications of FDA warnings regarding antidepressants.**
- **Appropriately monitor patients on antidepressants.**
- **List factors to consider when initiating antidepressants.**
- **List risks of using second generation antipsychotics in children and adolescents.**

Outline

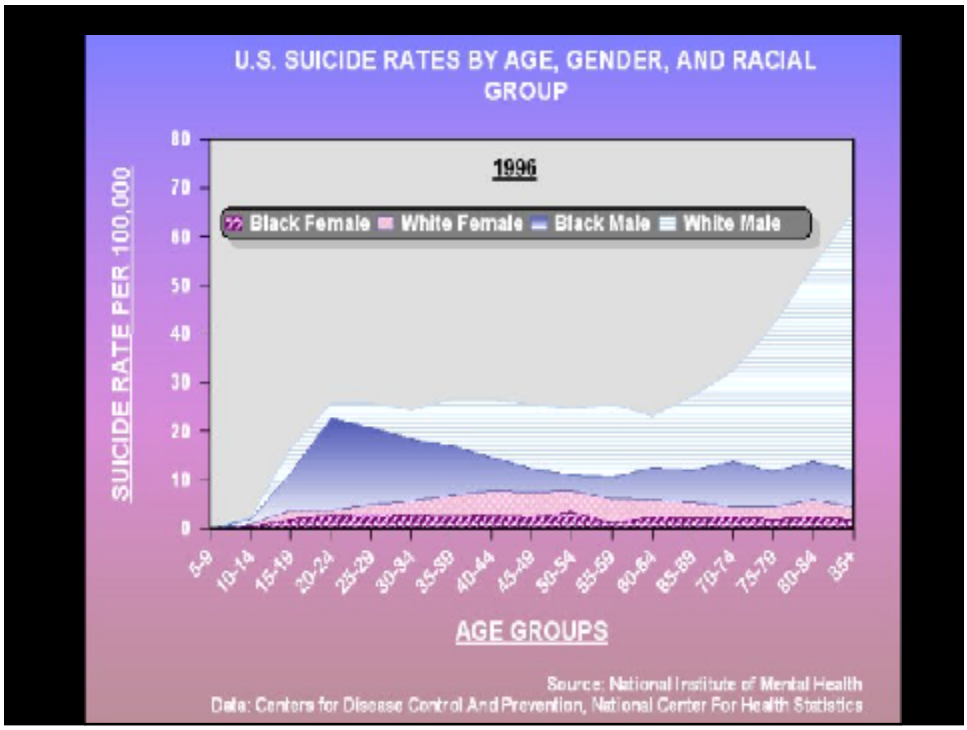
- Suicide
  - Everything you didn't want to know
- The FDA black box warning
- Monitoring and prevention
- The emerging use of second generation antipsychotics (SGAs)

Suicide - The Common Theme

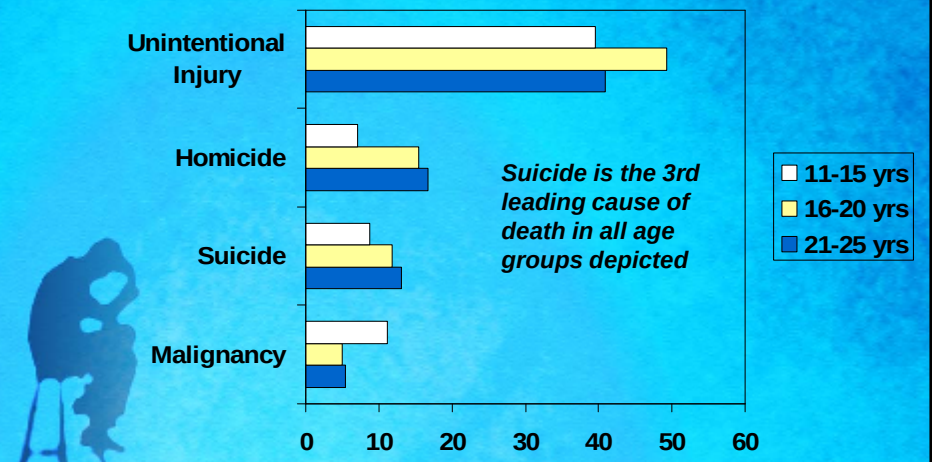
- The common purpose is to seek a solution.
- The common goal is cessation of consciousness.
- The common stimulus is intolerable psychological pain.
- The common stressor is frustrated psychological needs.
- The common emotion is hopelessness - helplessness.



http://www.suicidology.org/associations/1045/files/2005HealthRegionsSlide.pdf



10 Leading Causes of Death as Percent of Total United States, 1999 - 2005, All Races, Both Sexes



Centers for Disease Control and Prevention, National Centers for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS) [online]. (2005) cited 4/24/2008 Available from: www.cdc.gov/ncipc/wisqars

2005 U.S. Youth Risk Behavior Survey

- Grades 9-12
  - surveyed regarding the past 12 months
- 28.5% felt sad or hopeless
  - almost every day for >2 weeks with impact on activities
- 16.9% seriously considered suicide
- 13% made a plan
- 8.4% made an attempt
- 2.3% required treatment for attempt

CDC, MMWR 2006;55(SS-5), 51-53

History

- 2003 – FDA issues warnings about paroxetine use in youth
- 2004
  - FDA changes labeling to warn about risk for 10 antidepressants
  - Advisory panel debates black box warning; votes to endorse
  - Specific data about youth included in labeling
  - Patient information sheet
  - Black box
- 2006
  - – Black box updated to reflect new data on all ages and extend specific warnings to ages 18-24 years

Initial FDA Review

- 24 trials, > 4400 patients
- 0.6 % attempted suicide
- 4% on medication exhibited suicidal thinking or behavior
- 2% on placebo exhibited suicidal thinking or behavior
- Greater risk in first few months of treatment
- Suicidal thinking or behavior more frequent in study non-completers
- no successful suicides

http://www.fda.gov/CDER/Drug/antidepressants/SSRIPHA200410.htm

Hammad TA, Laughren T, Racoosin J. Arch Gen Psychiatry. 2006;63:332-339

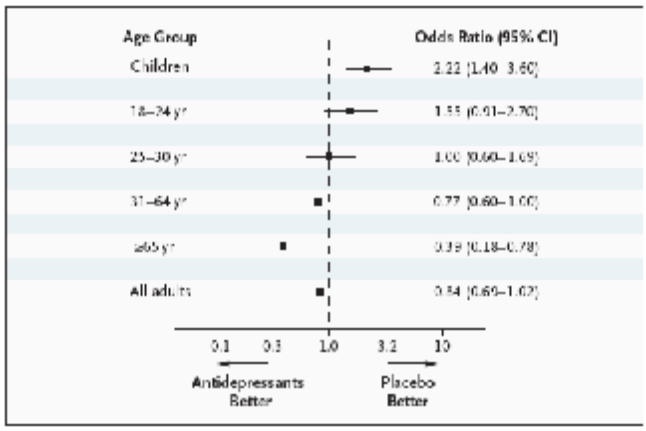
FDA Analysis of Antidepressant Trials

Summary of Overall Risk Estimates for Definitive Suicidal Behavior or Ideation, by Drug

Drug	Overall Relative Risk (95% CI) All trials, all indications	Overall Relative Risk (95% CI) MDD trials
Fluoxetine	0.92 (0.39, 2.19)	0.89 (0.36, 2.19)
Paroxetine	2.65 (1.00, 7.02)	2.15 (0.71, 6.52)
Sertraline	1.48 (0.42, 5.24)	2.16 (0.48, 9.62)
Citalopram	1.37 (0.53, 3.50)	1.37 (0.53, 3.50)
Venlafaxine	4.97 (1.09, 22.72)	8.84 (1.12, 69.51)
Mirtazapine	1.58 (0.06, 38.37)	1.58 (0.06, 38.37)

Hammad TA, Laughren T, Racoosin J. Arch Gen Psychiatry. 2006;63:332-339

. . . and wait! There's more!



Odds Ratios for Suicidal Behavior and Ideation among Patients Treated with Antidepressants for Psychiatric Indications, as Compared with Placebo.

Data are from the Summary Comments of the December 13, 2006, meeting of the FDA's Psychopharmacologic Drugs Advisory Committee. CI denotes confidence interval.

Friedman RA, Leon AC. N Engl J Med 2007;356:2343-2346

FDA Black Box Warning (1)

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 Drug X 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.

FDA Black Box Warning (2)

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.

Labeling (1)

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug versus placebo), however, were relatively stable within age strata and across indications.

Labeling (2)

Age in Years	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
< 18	14 additional
18-24	5 additional
25-64	1 fewer
>64	6 fewer

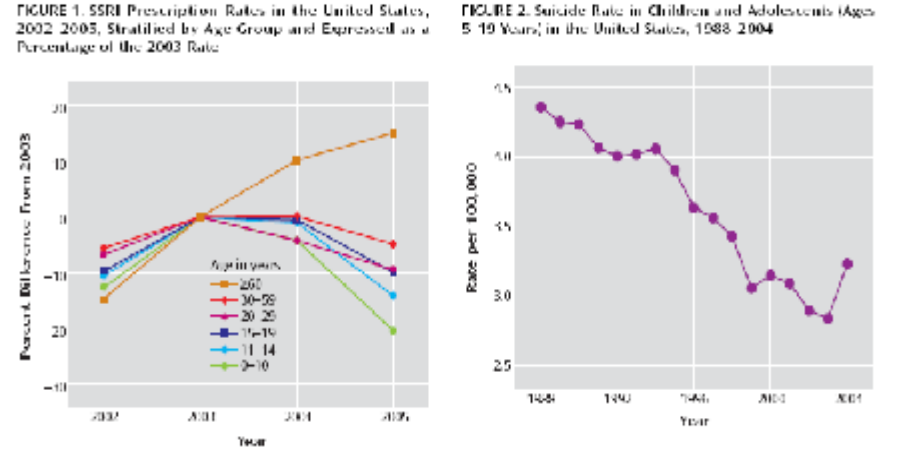
Potential Mechanisms

- Antidepressants are given to depressed people
- Activation of undiagnosed bipolar disorder
- Increased level of energy
  - Too depressed to plan or act
- Increased frustration
  - Don't work quickly, cause side effects
- Drug induced anxiety
- Akathisia

Was the FDA wrong?

Suicide Trend Data for Adolescent Population, Ages 15-24

Suicide and SSRI Prescription Rates



Gibbons RD, Brown CH, et al. Am J Psychiatry 2007; 164:1356–1363

Suicide and SSRI Prescription Rates

"In both the United States and the Netherlands, SSRI prescriptions for children and adolescents decreased after U.S. and European regulatory agencies issued warnings about a possible suicide risk with antidepressant use in pediatric patients, and these decreases were associated with increases in suicide rates in children and adolescents."

Gibbons RD, Brown CH, et al. Am J Psychiatry 2007; 164:1356–1363

On the Other Hand . . .

- Case control study using Medicaid data
  - Suicide attempts resulting in hospitalization
  - Completed suicides
- Children and Adolescents (ages 6-18)
- Increase risk of suicide attempts
  - OR, 1.52; 95% CI, 1.12-2.07
- Increase risk of completed suicide
  - OR, 15.62; 95% CI, 1.65-infinity
- No significant risk in adults

Olfson M, Marcus SC, Shaffer D. Arch Gen Psychiatry. 2006;63:865-872

A Moderate View

The real killer in this story is untreated depression, and the possible risk from antidepressant treatment is dwarfed by that from the disease. Still, clinicians need to tell their depressed patients that some people who take antidepressants have an increase in suicidal symptoms, especially early in treatment, and they need to follow their patients very closely during the first 4 to 6 weeks of treatment.

Friedman RA, Leon AC. N Engl J Med 2007;356:2343-2346

Time Relationship to Suicide Risk

- 6,976 in UK database aged 10 – 19 years
- Controls were matched by age and gender
- No completed suicides in adolescents
- Time relationship
  - Risk for suicidal event is greatest in the first 9 days of antidepressant therapy

Jick H, Kaye JA, Jick SS. JAMA 2004;292(3):338-343

Compliance

- Utah Youth Suicide Study
- 151 suicides (137 toxicology samples)
- Only 4 positive for psychotropic (2 SSRIs)
- 49 family interviews
- 14 indicated prescriptions for psychotropics
- All 14 had negative toxicology reports

Gray D, Achilles J, Keller T, et al. *J Am Acad Child Adolesc Psychiatry.* 2002;41:427–434.

Gray D, Moskos M, Keller T. Proc Am Assoc Suicidology; April 25, 2003.

Recommended Frequency for Follow-up Visits

- Weekly face-to-face visits for first 4 weeks
  - (Amer Acad Pediatrics endorses phone follow up)
- Biweekly visits for second 4 weeks
- Visit at week 12
- As clinically indicated beyond 12 weeks
- Recommends face-to-face visits, with additional contact by telephone as needed

Pediatrics 2007;120;e1313-e1326

Risk Factors for Suicide and Attempted Suicide - Adults

Suicide

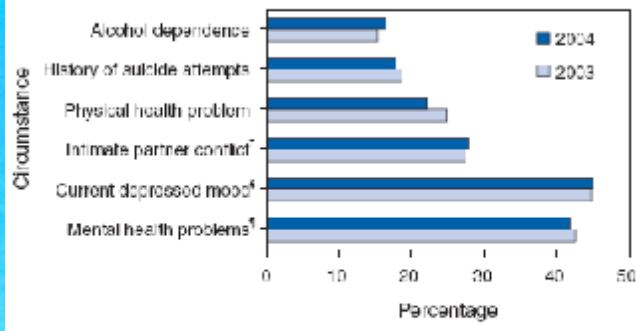
- male gender
- >= 60 years old
- widowed or divorced
- White or Native American
- living alone
- unemployed or finance problems
- recent loss (job, death)
- clinical depression or schizophrenia
- substance abuse
- other psychiatric diagnoses
- h/o suicide attempt
- anhedonia, hopelessness

Attempted Suicide

- female gender
- age <= 30 years old
- perceived threat to intimate relationship
- living alone
- unemployed or finance problems
- recent loss (job, death)
- clinical depression or personality disorder
- substance abuse

Hirchfeld RMA, NEJM 337:910, 1997

FIGURE 1. Percentage of suicide cases, by selected circumstances — National Violent Death Reporting System, United States, 2003 and 2004*



* Percentages might total to more than 100% because certain incidents involve multiple circumstances.
† Includes separation, major argument, or violence.
§ Current depressed mood was based on the family or friends' impression of the decedent's mood.
¶ Includes any mental illness diagnosis of the decedent (e.g., clinical depression, dysthymia, bipolar disorder, or schizophrenia).

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5526a1.htm

Adolescents

- **Previous psychiatric diagnosis**
- **Substance abuse**
- **Precipitating Events**
  - **disciplinary crises**
  - **loss of face with peers**
  - **arguments with parents**
  - **broken romance**
  - **school difficulties**
- **“girls try, boys die”**

Suicide – Is Path Warm?

I	Ideation
S	Substance Abuse
P	Purposelessness
A	Anxiety
T	Trapped
H	Hopelessness
W	Withdrawal
A	Anger
R	Recklessness
M	Mood Change

Suicide – What to do!

- Be direct.
  - Talk openly and matter-of-factly about suicide.
- Be willing to listen.
  - Allow expressions of feelings.
  - Accept the feelings.
- Be non-judgmental.
  - Don't debate whether suicide is right or wrong, or whether feelings are good or bad.
  - Don't lecture on the value of life.
- Get involved.
  - Become available.
  - Show interest and support.

Suicide – What to do!

- Don't dare him or her to do it.
- Don't act shocked.
  - This will put distance between you.
- Don't be sworn to secrecy.
  - Seek support.
- Offer hope that alternatives are available but do not offer glib reassurance.
- Take action.
  - Remove means, such as guns or stockpiled pills.
- Get help from persons or agencies specializing in crisis intervention and suicide prevention.

Monitor for Worsening Depression or Indications of Suicidality

- Anxiety
- Agitation
- Panic attacks
- Insomnia
- Irritability
- Unusual changes in behavior
- Hostility
- Impulsivity
- Akathisia
- Hypomania
- Mania

For your consideration . . .

- Who will be monitoring and when
- Bipolar disorder
- Substance abuse
- Anxiety
- History of violence or suicide attempt
- Other mental health / physical issues
- Recent events

And what about SGAs?

- Increasing use
- Changing indications
- Metabolic syndrome
- Prolactin elevation
- EPS
- Unknown ramifications of long term use

The Good, the Bad & the Ugly

- The Good
  - Antidepressants work in many patients
  - The risk appears to diminish with time
  - We can monitor and intervene
- The Bad
  - There is a risk in children and adolescents
  - There are multiple mechanism by which antidepressants can increase risk
  - Some choose not to use antidepressants because of the risk
- The Ugly
  - Suicide rates are increasing
  - The data is far from clear
  - More drugs (even for non-psychiatric indications) may increase suicide risk

Questions and Comments