

Antidepressants Black Box Warnings

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Black Box Warnings (BBW)

- Medical studies indicate that the drug carries a risk of serious or life-threatening adverse effects
--> FDA can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug
- All antidepressants black box warning
Suicidality in children, adolescents (2004)
Suicidality in young adults < 25 years old (2007)
- Nefazodone black box warning → Hepatotoxicity (2002)
Trade product Serzone not available

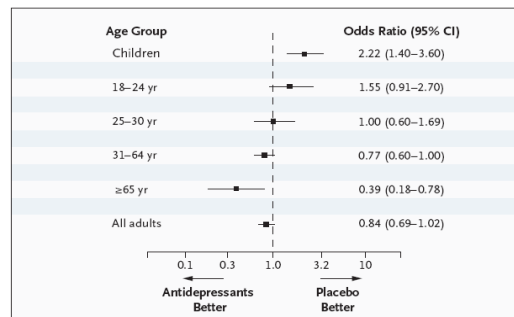
Antidepressants BBW Updates 2007

- [Posted 05/02/2007] FDA proposed that all antidepressant medications update the existing black box warning to include warnings about the increased risks of suicidal thinking and behavior in young adults ages **18 to 24 years old** during the first one to two months of treatment
- The proposed labeling changes also state that scientific data did not show this increased risk in adults > 24 y/o & that adults \geq 65 y/o taking antidepressants have a decr'd risk of suicidality

Expanding the Black Box — Depression, Antidepressants, and the Risk of Suicide

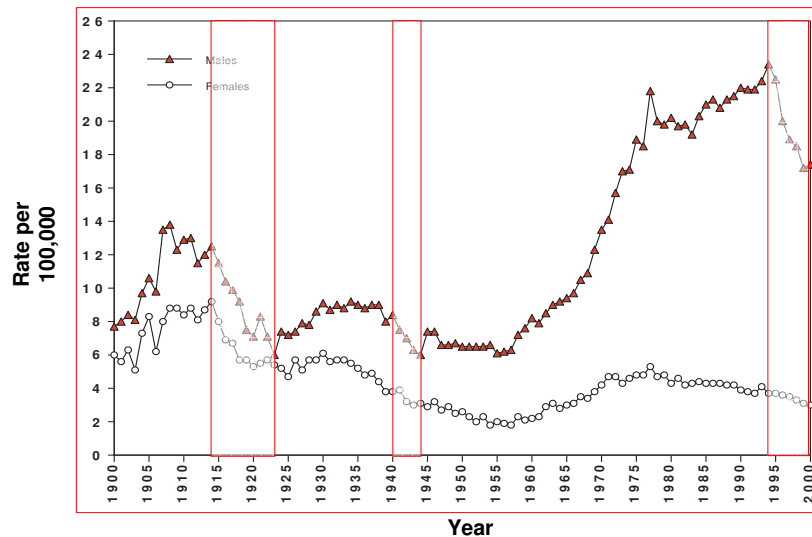
Friedman RA & Leon AC. NEJM 356:2343-2346, June 2007.

“The real killer in this story is untreated depression, and the possible risk from antidepressant treatment is dwarfed by that from the disease.”



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

20th Century Changes In Youth Suicide Rates UNITED STATES, AGES 15-24



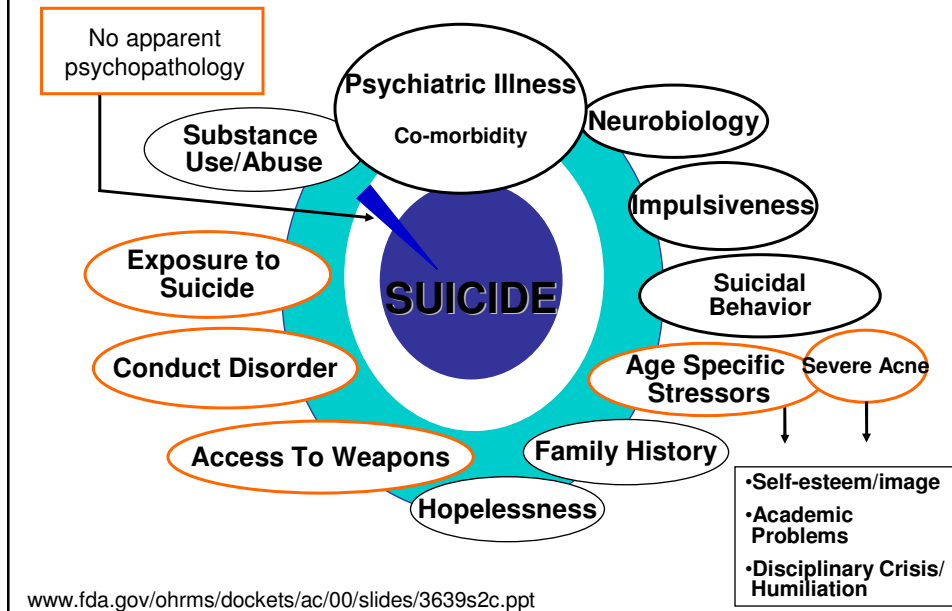
Anderson 2002, CDC Wonder 2003, USDHEW 1956, Vital Statistics U.S. 1954-1978.

Suicide: Risk Factors

SAD PERSONS - assessing suicide risk:

- **S**ex (male)
- **A**ge (elderly or adolescent)
- **D**epression
- **P**revious suicide attempts
- **E**thanol abuse
- **R**ational thinking loss (psychosis)
- **S**ocial supports lacking
- **O**rganized plan to commit suicide
- **N**o spouse (divorced > widowed > single)
- **S**ickness (physical illness)

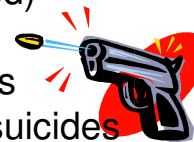
Suicide: A Multi-Factorial Event - Adolescent



USC

Suicide Among the Youth

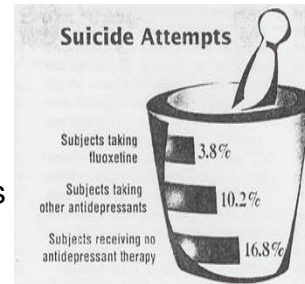
- Suicide ⇒ 6th leading cause of death for 5-14 y/o and 3rd leading cause of death for 15-24 y/o
- Adolescents age 15-19 ⇒ completed suicide = .008% (0.4-0.5% if depressed)
 - * Other studies = average 7% with depression
- Suicide attempts = 8.8% (35-55% if depressed)
Suicidal ideation = 19% (higher if depressed)
- Availability of guns is the paramount risk factor for younger, impulsive individuals
- Among ages 15-19 years, firearm-related suicides accounted for 62% of the suicide rate over the last few decades



Gould MS, et al. JAACAP 2003;42:386-405.

Revisiting the Link Between SSRI Use and Suicidal Behavior

- Re-analysis of multiple clinical studies → no correlation
- SA: no AD tx = 16.8%, other ADs = 10.2%, SSRIs = 3.8%
- Leon et al. reported a prospective, naturalistic 15-yr f/u study from the NIMH Collaborative Depression study found no correlation
- Possible reason for suicidal behavior is nonresponse to SSRIs with worsening of depressive sx's and emergence of SI/ suicidal behavior; or improved energy >> mood --> suicide after drug therapy begins
- Solution = careful monitoring/evaluation in 1-2 mo of treatment



Stimmel GL. Mental Health Econ 1999;12:3-4. Leon AC et al. Am J Psychiatry 1999;156:195-201.

History of FDA Actions Regarding Antidepressants in Youth

6/19/03 → FDA issues warning about Paxil and increased suicidal behavior.

- Recommendation: **NOT** to use Paxil in youth

3/04/04 → FDA issues a public warning requiring 10 antidepressants to *add warning about worsening depression and the emergence of suicidality*

- Fluoxetine ■ Sertraline ■ Paroxetine
- Fluvoxamine ■ Citalopram ■ Escitalopram
- Bupropion ■ Venlafaxine ■ Nefazodone
- Mirtazapine

Source: www.fda.gov

History of FDA Actions Regarding Antidepressants in Youth (2)

9/16/04 → *Increased risk of suicidality to all antidepressants in children & adolescents.*

- Split decision regarding black box warning: 15 → YES 8 → NO
 - Based on 4% antidepressant-related suicidal events with no fatalities vs. 2% placebo.
- Provide patient information sheet with all prescriptions + results from controlled pediatric trials included in labeling.

10/15/04 → *Mandates all antidepressants include black box warning:*

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need.

Source: www.fda.gov

SUICIDALITY IN CHILDREN AND ADOLESCENTS

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. [Drug Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here]. (See Warnings and Precautions: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

American Academy of Child & Adolescent Psychiatry
AACAP Recommendations & Press Releases

6/16/04 → Decision to call for a national registry of clinical trials making data of all trials available.

9/30/04 → Urges FDA not to put black box for antidepressants to avoid risk of reluctance to prescribe antidepressants.

- Emphasizes frequent monitoring, esp. early in the course of treatment & when meds are changed or dosages adjusted.
- *Putting a black box warning by the FDA may be misinterpreted by some practitioners or families to mean antidepressants cause children and/or teens to commit suicide.*

American Psychiatric Association
APA Response & Press Releases

10/15/04 → We restate our continued deep concern that a *“black box” warning on antidepressants may have a chilling effect on appropriate prescribing for patients. This would put seriously ill patients at grave risk.* Recent prescription data suggest the current controversy over antidepressants has already lowered treatment rates; the new black box warning may further negatively impact treatment rates...Lastly, *we are concerned that publicity around the new warning may cause some successfully treated patients to stop taking antidepressants. An abrupt withdrawal could compound the problem by producing serious side effects.*

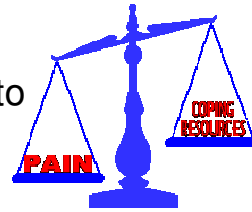
Suicidality and Antidepressant Drugs (2007 BBW update)

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 [Insert established name] 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. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).



Altered Response to Antidepressants?

- Immature brain development ... neural pruning till early-mid 20s ⇒ altering connections & synapses
 - Last area to finish pruning is prefrontal cortex
 - ⇒ helps with planning & judgment
 - ⇒ poor impulse control & coping skills to psychosocial factors
- Inadequate/ineffective treatment
- Activation from antidepressants
 - ⇒ irritability, impulsivity, hypomanic/manic sx



Pediatric Onset Bipolar Disorder

- Watch for “behavioral activation” in children/teens taking antidepressants...20-50% incidence of restlessness, irritability, jitteriness, insomnia (up to 10% may be an isolated drug effect)
- 20-40% of youth w/MDD develop Bipolar disorder within 5 yrs of the onset of MDD
- Prodromal symptoms (episodes of depressed mood or hopelessness & excessive mood lability) seen in youths who later were diagnosed with bipolar disorder
- Antidepressants may induce “switch” to hypomania/mania within days; need to stop antidepressant if this occurs

Patient/Caregiver Education

- ✓ Individuals currently taking antidepressants should not stop taking them & should notify their healthcare professional if they have concerns
- ✓ Delayed onset for mood elevation – increased energy before mood. Risk of suicidal behaviors greatest in the first 9 days, up to 3 months. More frequent monitoring
- ✓ Report any behavioral activation, agitation, “severe restlessness,” impulsivity, hostility, insomnia, irritability, or worsening depression
- ✓ Report any ADRs & avoid abrupt self-d/c --> w/d sx
- ✓ Watch for substance abuse in an attempt to escape “overwhelming emotional pain”

Patient/Caregiver Education

- During the first four weeks of treatment, a child or adolescent should be seen by the provider prescribing the medication at least once a week, with face-to-face contact with the family (weeks 1-4);
- In weeks five through eight of treatment, a child or adolescent should be seen every other week by the treating provider, with face-to-face contact (weeks 5-8);
- A child or adolescent should then be seen again by the treating provider at week 12, with face-to-face contact (weeks 9-12); and
- A child or adolescent should be seen by the treating provider as clinically indicated after 12 weeks of treatment (weeks 13+).

Nefazodone Black Box Warning: Hepatotoxicity

- Black box warning on nefazodone was added in 2001
- Cases of life-threatening hepatic failure have been reported in patients treated with Serzone. The reported rate in the United States is about 1 case of liver failure resulting in death or transplant per 250,000- 300,000 patient-years
- Treatment with nefazodone should not be initiated in individuals with active liver disease or with elevated liver serum transaminases

Nefazodone Black Box Warning: Hepatotoxicity

- Patients should be advised to be alert for s/sxs of liver dysfunction (jaundice, anorexia, etc) and to report them immediately if they occur
- Nefazodone should be discontinued if clinical s/sxs suggest liver failure. Patients with increased serum LFTs (AST or ALT) levels $\geq 3x$ the upper limit of normal should d/c nefazodone

