



# Illuminating the Black Box: Antidepressants, Youth and Suicide

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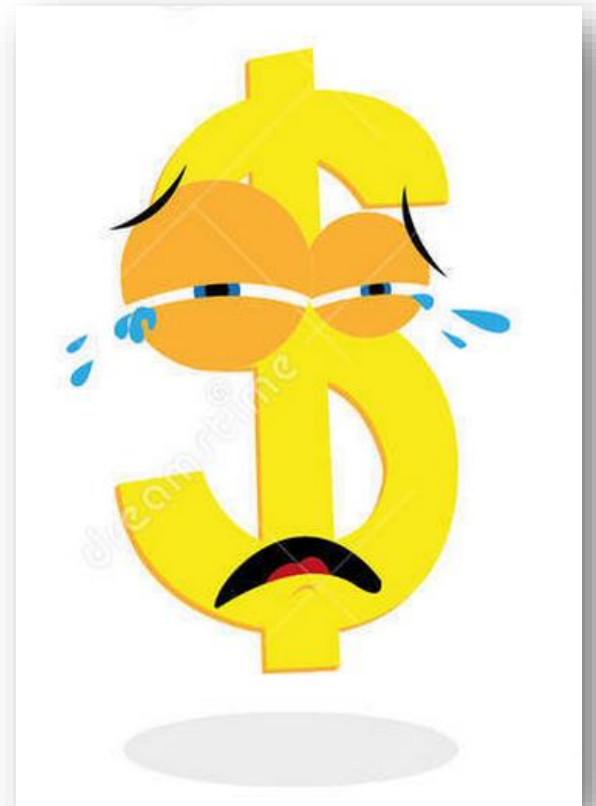
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# Disclosures

- I have no ties to pharmaceutical industries or other corporate entities to disclose.



# Lancet, 27 August 2016

- **Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis**
- **Interpretation:** When considering the risk–benefit profile of antidepressants in the acute treatment of major depressive disorder, these drugs do not seem to offer a clear advantage for children and adolescents. Fluoxetine is probably the best option to consider when a pharmacological treatment is indicated.



# Black Box

# Black Box Warning

“Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies 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...”

# FDA Black Box

- Prompted by warning of increased suicide risk in adolescents treated with ***paroxetine***, by British MHRA in June 2003
- FDA pooled data from 24 studies examining antidepressant use in children for depression and anxiety disorders

# Black Box Analyses

- Examined Suicidality in 4,582 cases in 24 controlled clinical trials on all antidepressants in pediatric patients.
  - Text search with blind recoding
  - Risk ratio for depression trials 1.66
  - Risk difference 0.02 (excess of 1-3 patients/100)

Hammad et al. AGP, 2006

Simon et al., Am J Psychiatry 163:41-47, January 2006

Bridge, J. A. et al. JAMA 2007;297:1683-1696

# FDA

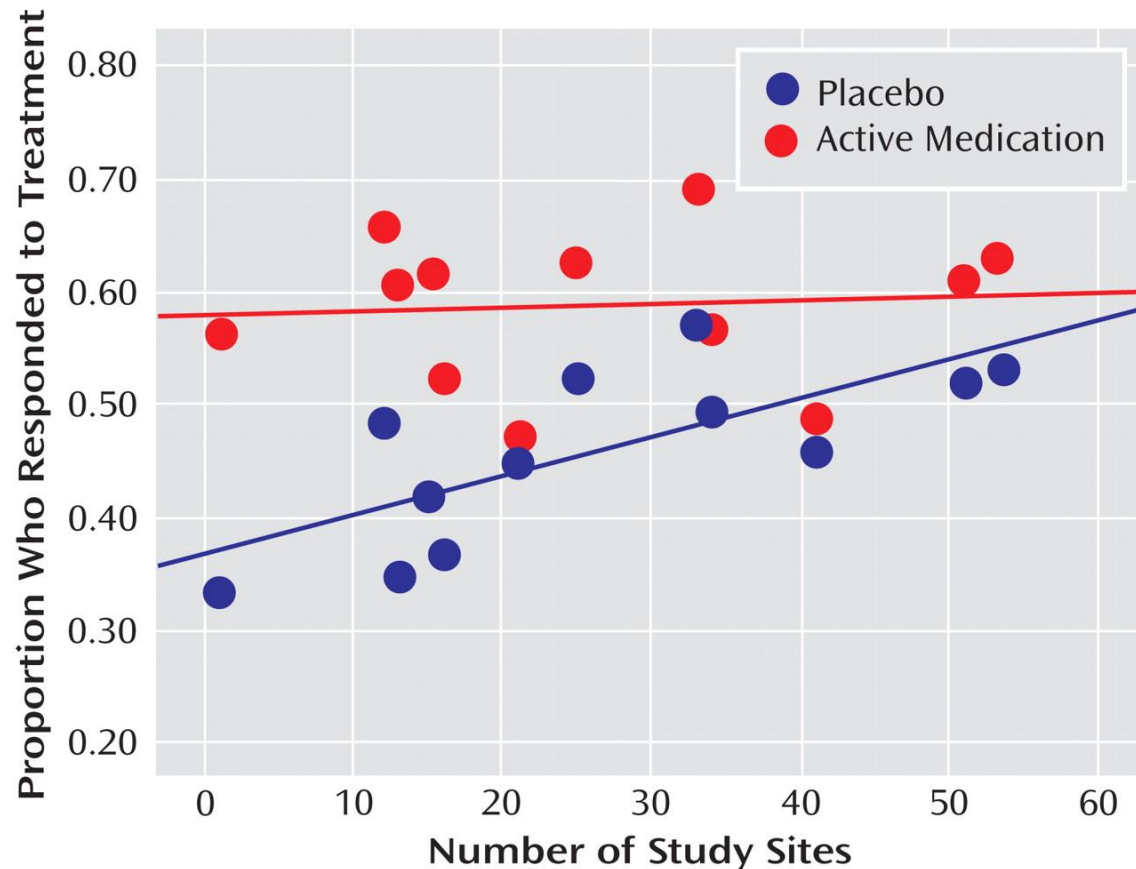
- September 2004, FDA reported increase in *suicidality*
  - Defined as
    - new onset SI
    - worsening of SI
    - new or increased suicidal behaviors
  - 3.8% on SSRIs v 2.1% on placebo



# FDA

- Limitations
  - Post-hoc analyses, multiple sub-analyses
    - none of original 24 studies were designed to evaluate this
  - Few events of “suicidality” (78/4400) despite threshold
  - Substantial differences between studies in classification
  - Nonadherence not considered
  - Patients with severe pathology excluded
  - Increasing number of sites rapidly to accelerate trial
  - Aggressive advertising to recruit patients
  - Age of participants
  - No increase in suicidality on clinician rating scales
  - No patients committed suicide or seriously harmed self

# Placebo Response in Pediatric MDD Trials



Bridge JA et al., Am J Psychiatry 2009; 166:42-49

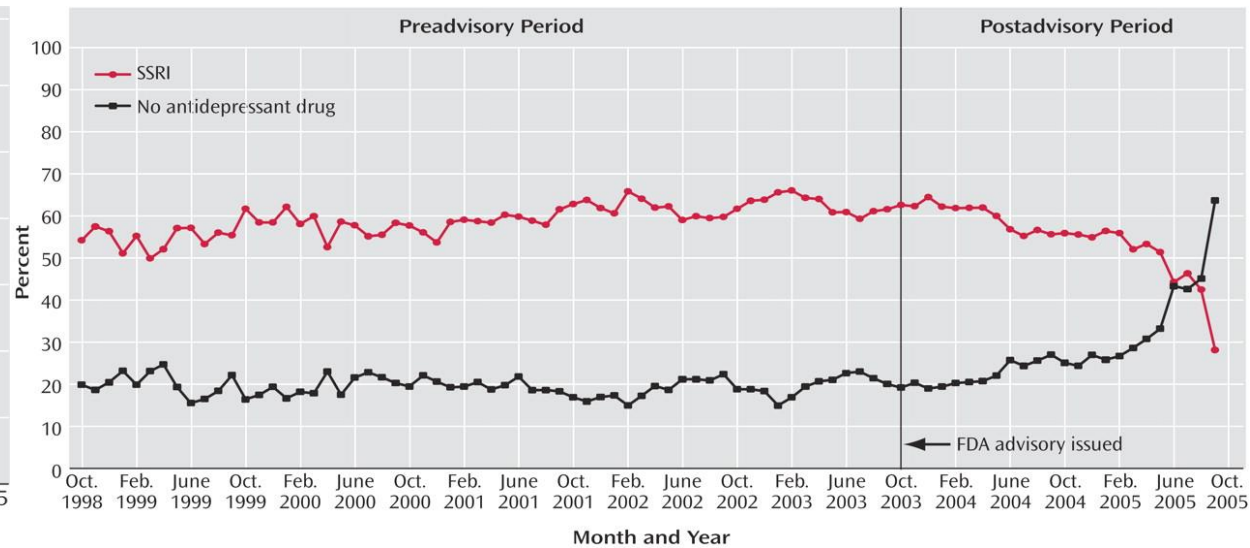
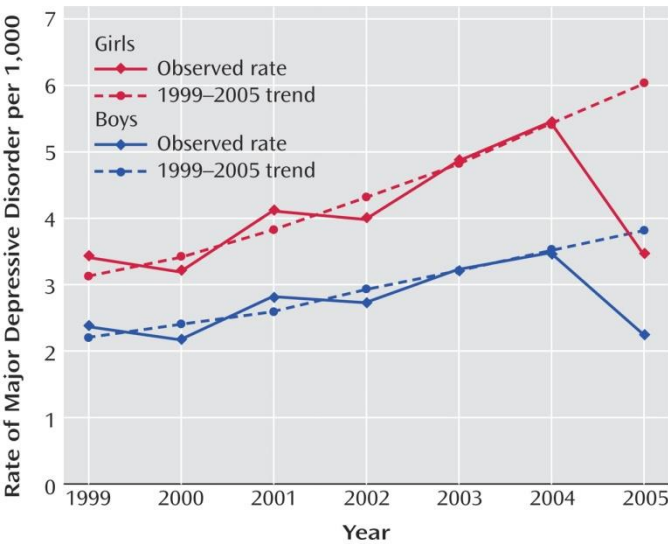
# Black Box Revision

- February 2005
  - FDA altered warning
    - No “causal” relationship had been detected
    - Conclusion based on short-term studies
    - No suicides occurred in any of studies

# SSRIs

- 1998 to 2002
  - 9% increase in juvenile SSRI prescriptions
- Began to drop since first quarter of 2004 after FDA and MHRA warnings

# Unintended Effect of Black Box Warning?

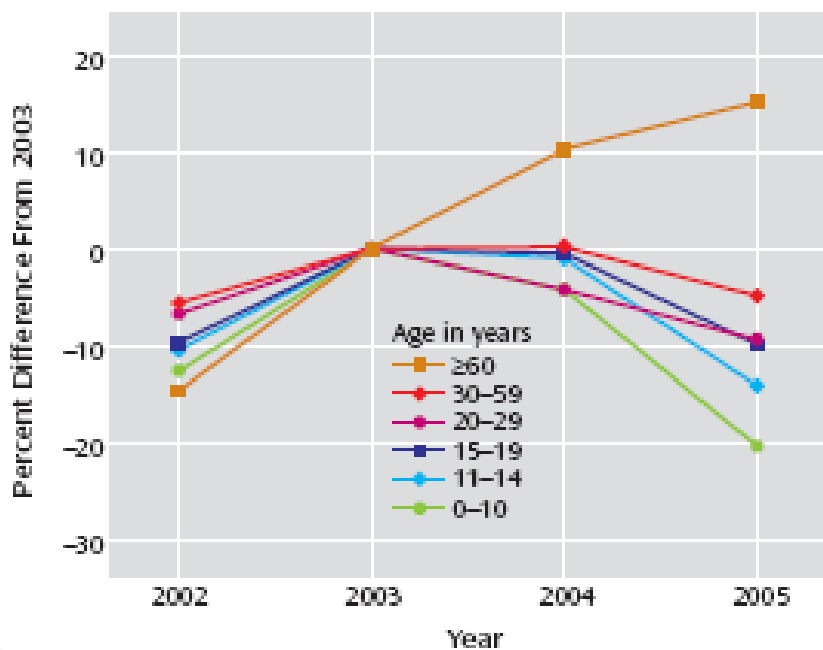


Libby, A.M. et al., Am J Psychiatry 164:884-891

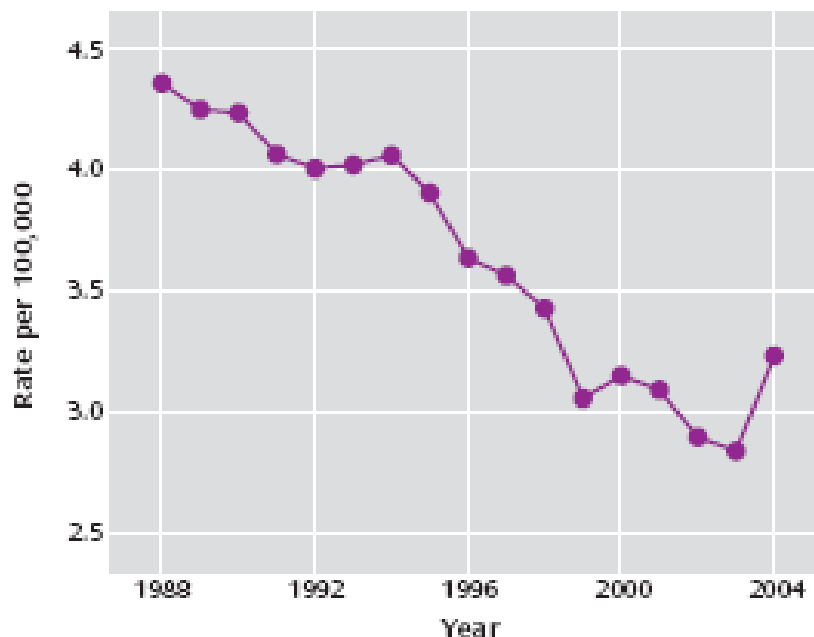
# Early Evidence of FDA Mandate on Youth Suicide

- Evaluation of large pharmacy claims database
- Determined SSRI use by age
- Compiled suicide data from the CDC

SSRI Prescription Rates by Age



Suicide Rates in Children and Adolescents





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PSYCHIATRY ACADEMY

# Youth

# Complications of Depressive Disorders

- Academic, interpersonal, and family difficulties
- Increased risk for suicide and other psychiatric problems (e.g., conduct problems, use/abuse of nicotine, alcohol and drugs)
- Increased risk for suicidal behaviors 10- to 50-fold
- 80% of attempters and 60% of completers are depressed



# Diagnostic Considerations: Bipolar

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- Rates of manic switching peak ages 10-14.
- No antidepressant uniquely “safe.”
- BPAD risk factors

# Risk of Converting to Bipolar Disorder

- 20-40% of youth with MDD convert to Bipolar Disorder if they have:
  - Psychosis
  - Family History of Bipolar Disorder
  - Pharmacologically induced hypomania/mania
- BUT,
  - Not all youth who are activated by antidepressants have bipolar disorder



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PSYCHIATRY ACADEMY

# Suicide

# Assessment of Suicidal Youth

- Characteristics of Suicidality
- Current and Lifetime Psychopathology
- Psychological Characteristics
- Family and Environmental Factors
- Availability of Lethal Means
- Use of Self-Report Instruments (e.g., Suicidal Ideation Questionnaire, Suicide Probability Scale) (Huth-Bocks et al., 2007)

Bridge et al., (2006) *J Child Psychol Psychiatry* 47 (3-4): 372-394

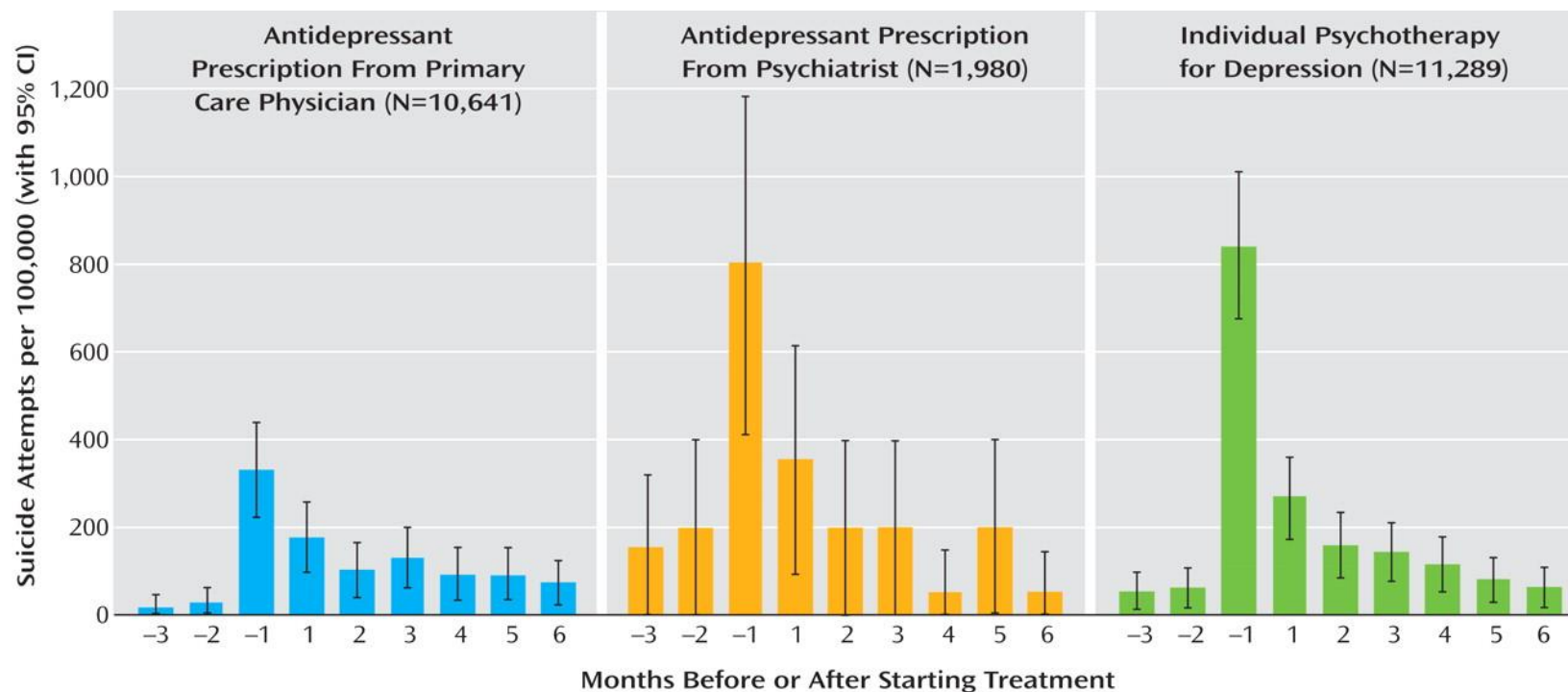
# Youth Suicide

- Male adolescents die by suicide at a rate 4 × higher than females
  - Of all suicide completions, 80% are male
  - 75% are white males
- Female adolescents attempt suicide at a rate 3 × higher than males
  - Asian-American females aged 14-24 years have the highest suicide rate (not attempts) of all females of ethnicity
- Gay, lesbian, bisexual, transgender, questioning have a 4 × greater risk of suicide attempts than heterosexuals

# Diagnostic Considerations: Suicide

- Juvenile suicide
  - increased markedly from the 1950s through the 1980s
  - decreased since early 1990s
- 8% of high school students make suicide attempts every year.
- 7% of youth with untreated depression complete.

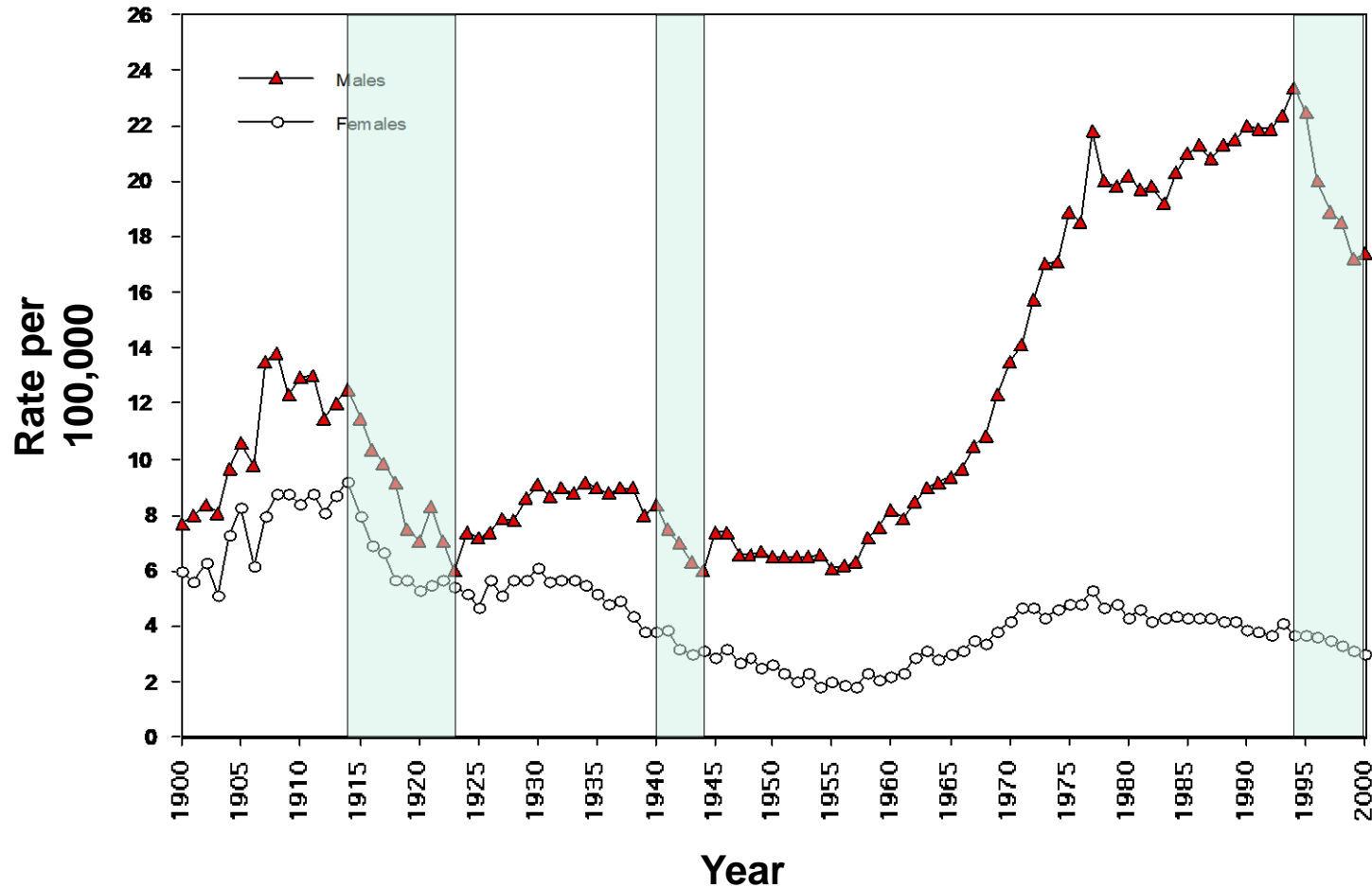
# Risk of Suicide Attempt Before and After Starting Treatment <25 yrs



**Simon GE and Savarino J (2007) Am J Psychiatry 164:1029-1034**

# CHANGES IN YOUTH SUICIDE RATES

— UNITED STATES, AGES 15–24 —





# MOST COMMON PSYCHIATRIC DIAGNOSES IN TEENS WHO SUICIDE

	MALE (N=213)	FEMALE (N=46)
<b>Depression</b>	<b>50%</b>	<b>69%</b>
<b>Antisocial</b>	<b>43%</b>	<b>24%</b>
<b>Substance Abuse</b>	<b>38%</b>	<b>17%</b>
<b>Anxiety</b>	<b>19%</b>	<b>48%</b>

***66% of 16- to 19-Year-Old Male Suicides  
Have Substance/Alcohol Abuse***

Brent et al. 1999, Shaffer et al. 1996

# Suicidality and SSRIs

- “Activation”
  - correlates with 7-fold increase in suicidality
- “Manic Switching”
- “Joy Returns Last”
  
- Specific “suicidal” effects on serotonergic pathways, “withdrawal syndrome” not supported.

# Autopsy Studies of Suicide Victims

- 151 youth suicides studied in Utah
  - Of 137 with toxicology, only 4 with detectable levels of AD, AP, or MS
- 41 youth suicides studied in NYC, 1999-2002
  - Of 36 with toxicology, only 1 AD detected
- 1419 adult suicides studied in NYC, 2002-2004
  - 13.9% of young adults (18-24 years) had AD present on toxicology

**Gray DB, et al. *J Am Acad Child Adolesc Psychiatry*. 2002;41:427-34;**  
**Leon AC, et al. *J Am Acad Child Adolesc Psychiatry*. 2006;45:1054-8;**  
**Leon AC, et al. *J Clin Psych*. 2007;9:1399-403.**



# Conclusions

# Impact on Treatment Guidelines

- Informed Consent
- Frequency of visits
- Reserve for moderate to severe cases
- SSRIs remain first line
- Diligent attention to deteriorations in mood/  
manic switching