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# Illuminating the Black Box: Antidepressants, Youth and Suicide

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# Disclosures

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





# Recent Studies of the BBW

- **Cipriani A, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis.** Lancet. 2016 Aug 27;388(10047):881-90.
- **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.
- Similar arguments have been made with the newer antidepressants: **Hetrick SE, et al. New generation antidepressants for depression in children and adolescents: a network meta-analysis.** Cochrane Database of Systematic Reviews 2021, Issue 5.



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# 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*. Jan. 2006;163:41-47.

Bridge JA 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



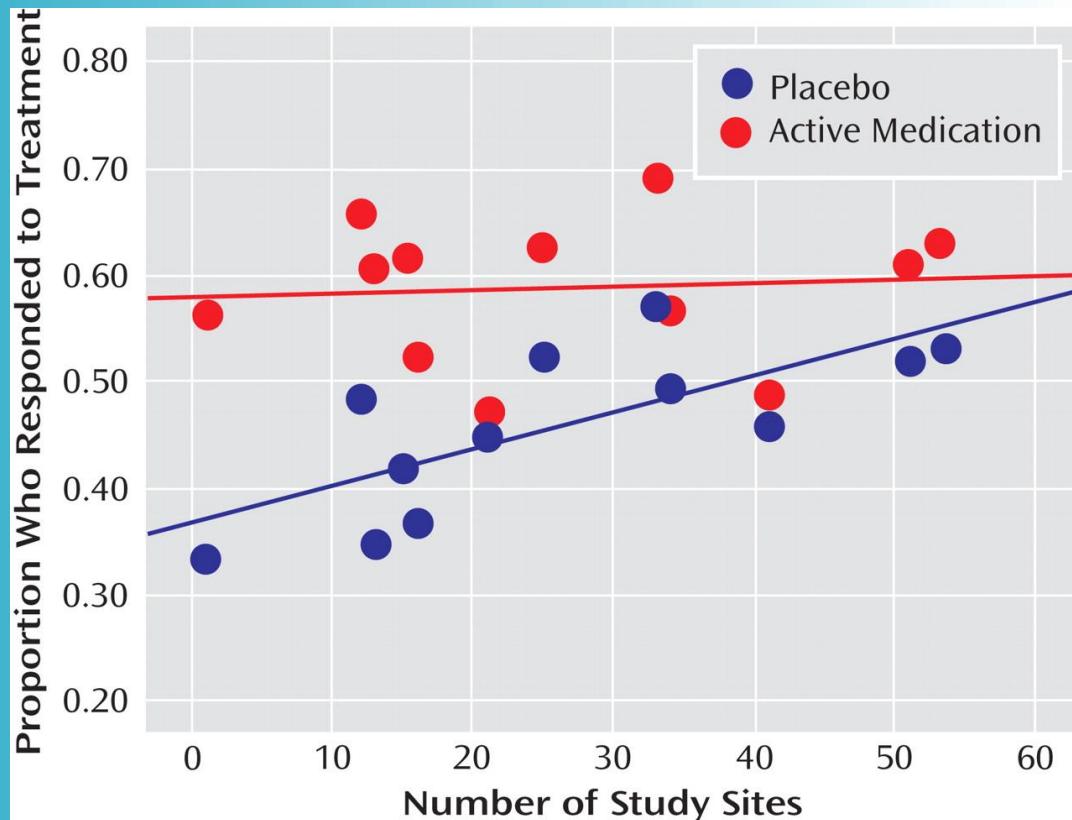
# FDA

- 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



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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

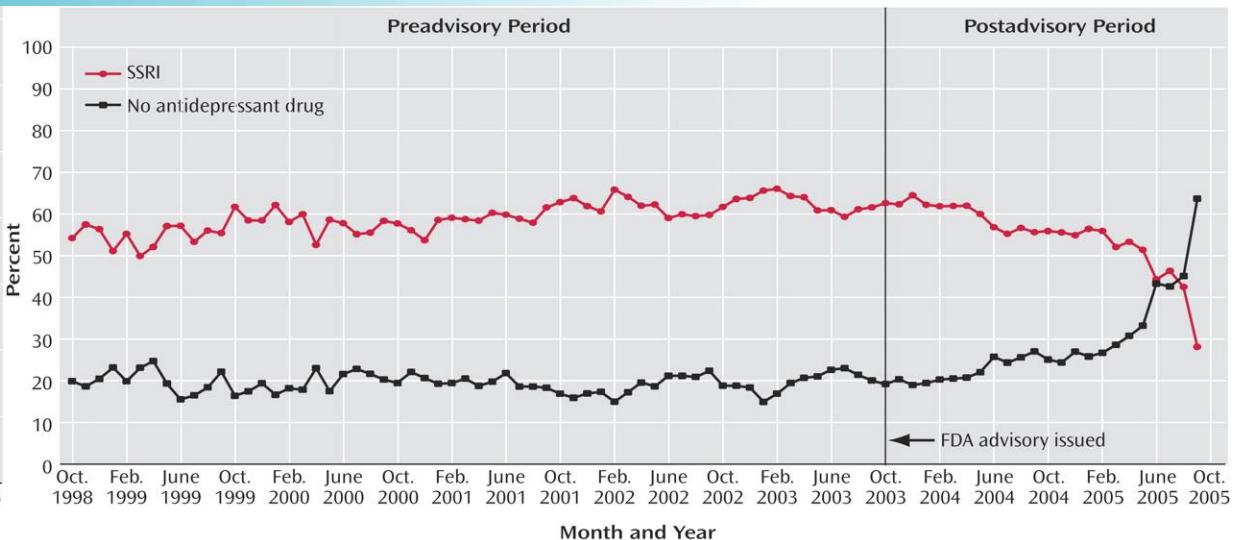
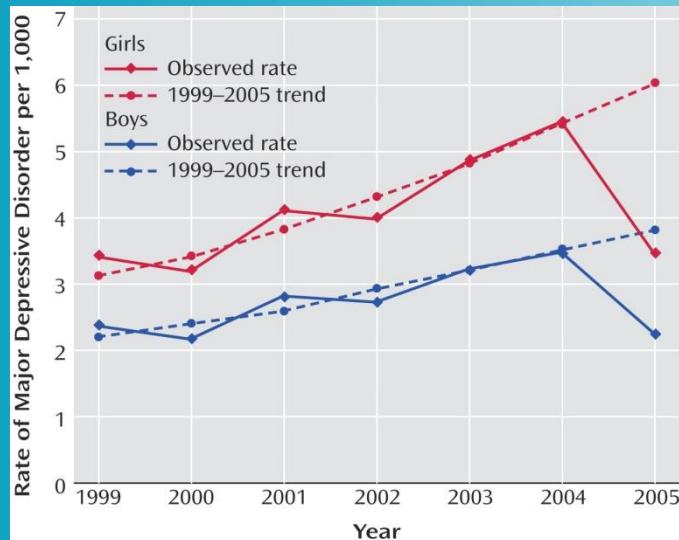


# SSRIs

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



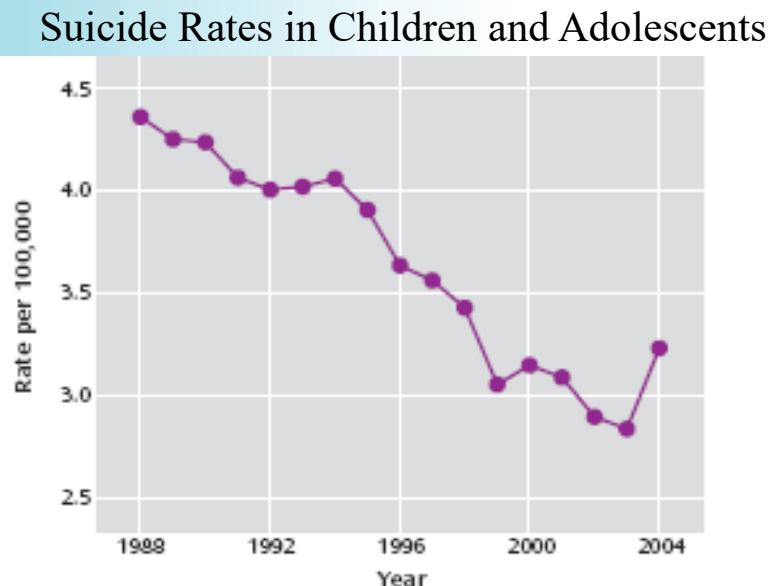
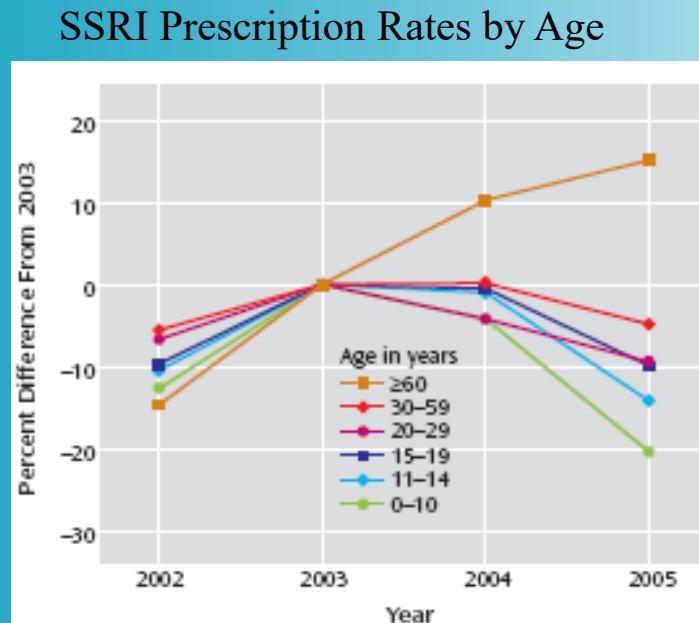
# Unintended Effect of Black Box Warning?



Libby AM. 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



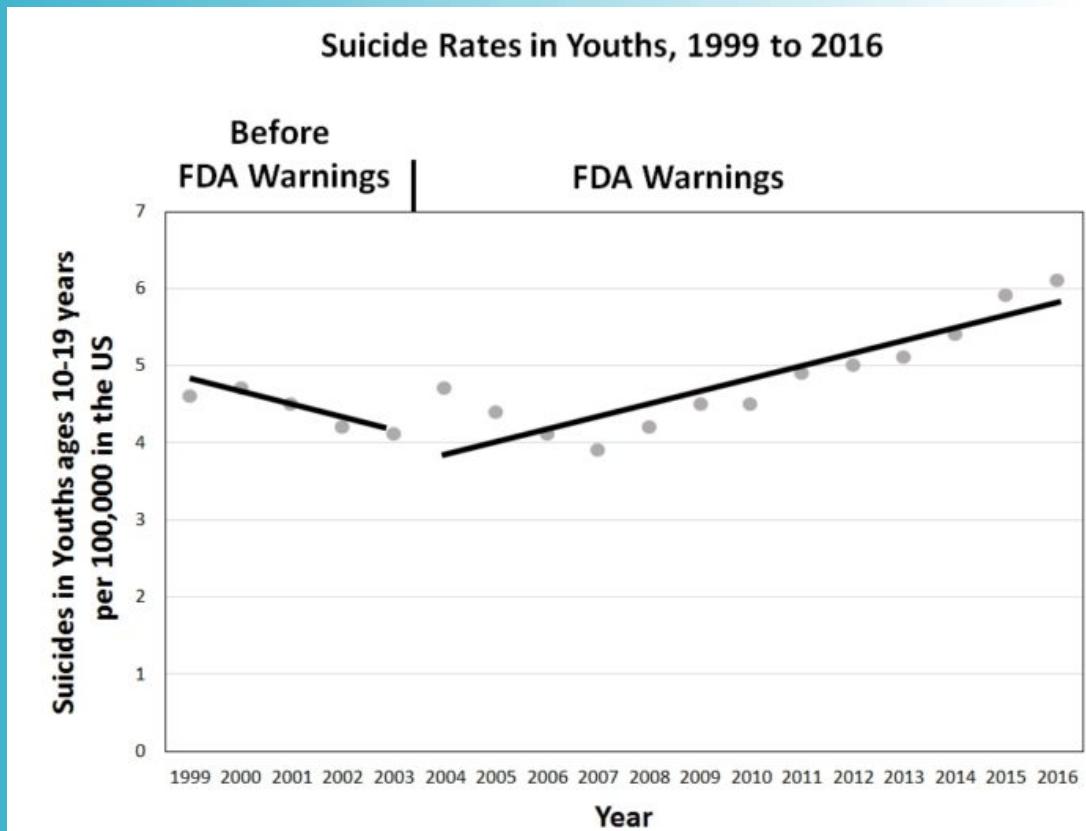
Gibbons et al. *Am J Psy.* 2007;164:1356-63.



# Unintended Effect of Black Box Warning?



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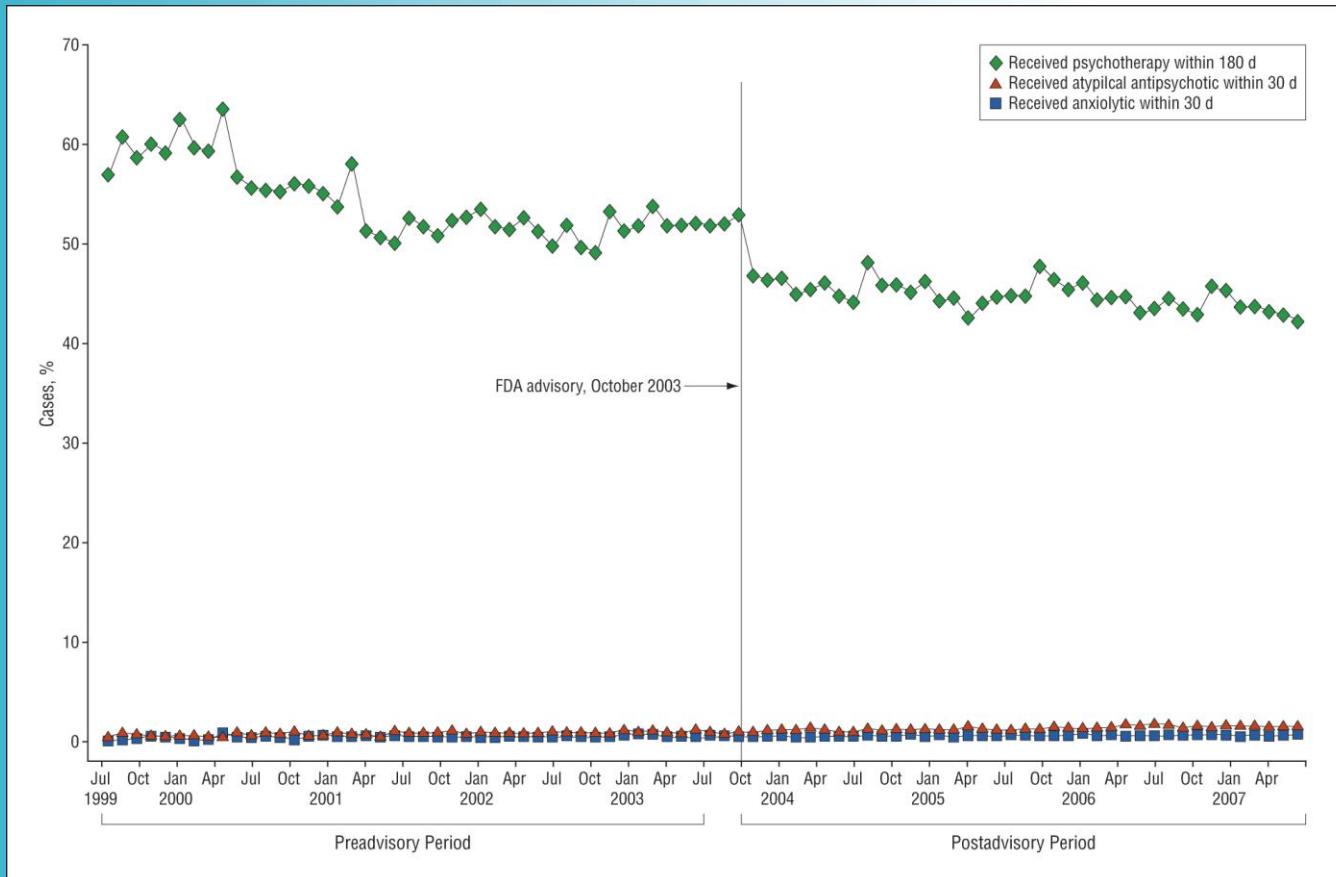
Data from the National Vital Statistics Reports, June 1, 2018 as visualized by Soumerai & Koppel (2018) *StatNews*.



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# Unintended Effect of Black Box Warning?



Libby AM, Orton HD, Valuck RJ. *Arch Gen Psychiatry*. 2009;66(6):633-639.



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# Youth



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# 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 those who attempt suicide and 60% of those who die by suicide are depressed



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# Diagnostic Considerations: Bipolar

- 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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# 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)



# Youth Suicide

- Male adolescents die by suicide at a rate 4 × higher than females
  - Of all suicide deaths, 80% are male
- Female adolescents attempt suicide at a rate 3 × higher than males
  - In 2019, 9% of high school students reported attempting suicide during the previous 12 months. Suicide attempts were reported most frequently among girls compared to boys (11% vs. 6.6%) and among non-Hispanic American Indian/Alaska Native students (25.5%).

[https://www.cdc.gov/suicide/facts/disparities-in-suicide.html#race\\_ethnicity](https://www.cdc.gov/suicide/facts/disparities-in-suicide.html#race_ethnicity)



# Youth Suicide

- Almost a quarter (23.4%) of high school students identifying as lesbian, gay, bisexual, transgender, or questioning reported attempting suicide in the prior 12 months. This rate is nearly four times higher than the rate reported among heterosexual, cis-gendered students (6.4%).
- The rate of self-reported suicide attempts in the prior 12 months among sexual minorities decreases with age, from 5.5% among people ages 18-25 to 2.2% among people ages 26-49.

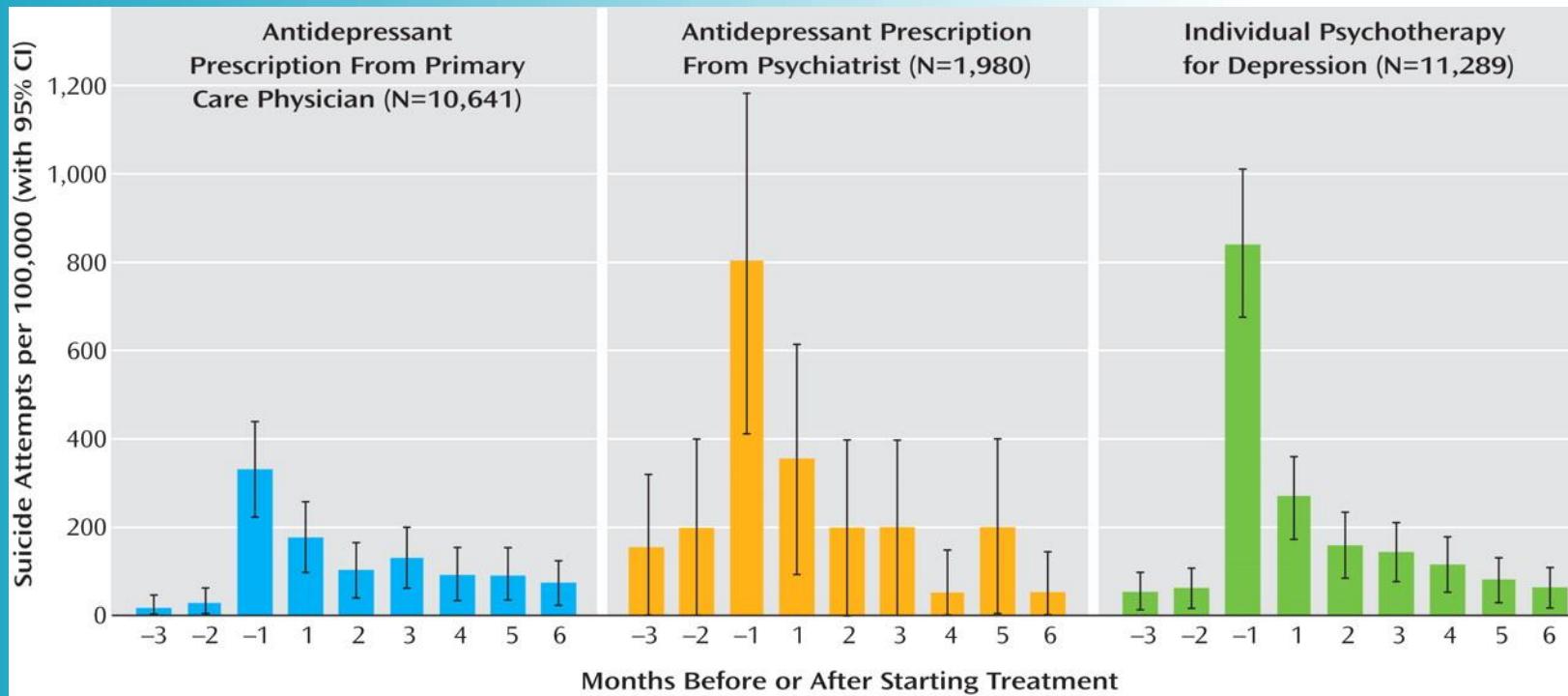
[https://www.cdc.gov/suicide/facts/disparities-in-suicide.html#race\\_ethnicity](https://www.cdc.gov/suicide/facts/disparities-in-suicide.html#race_ethnicity)



# Diagnostic Considerations: Suicide

- Juvenile suicide
  - increased markedly from the 1950s through the 1980s
  - decreased since early 1990s
- 9% of high school students make suicide attempts every year.
- 7% of youth with untreated depression die by suicide.

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



Simon GE and Savarino J. *Am J Psychiatry*. 2007;164:1029-1034.



# 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.



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# 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