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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

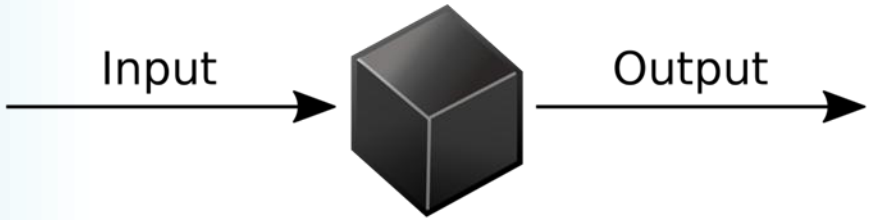
- **Cipriani A, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis.** Lancet. 2016 Aug 27;388(10047):881-90.
- **Interpretation:** When considering the risk–benefit profile of antidepressants in the acute 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.

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

Limitations of Analyses

- 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

Black Box Revision

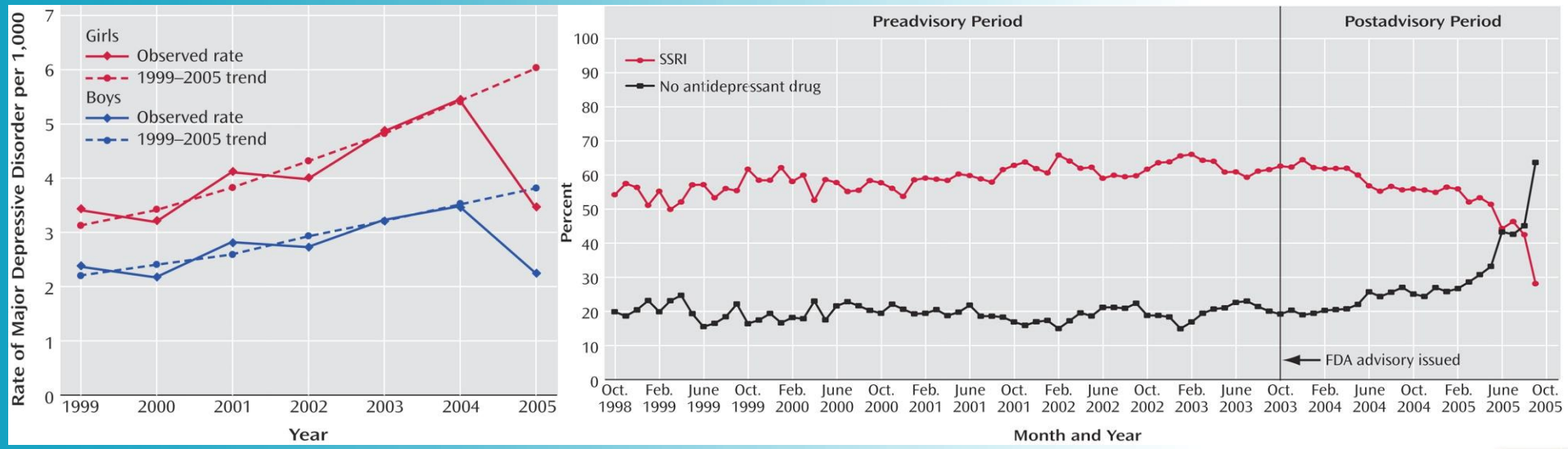
- February 2005
  - FDA altered warning
    - No “causal” relationship had been detected
    - Conclusion based on short-term studies
    - No suicides occurred in any of studies

Pre- Black Box

- Juvenile SSRI Prescriptions
  - 9% increase 1998-2002

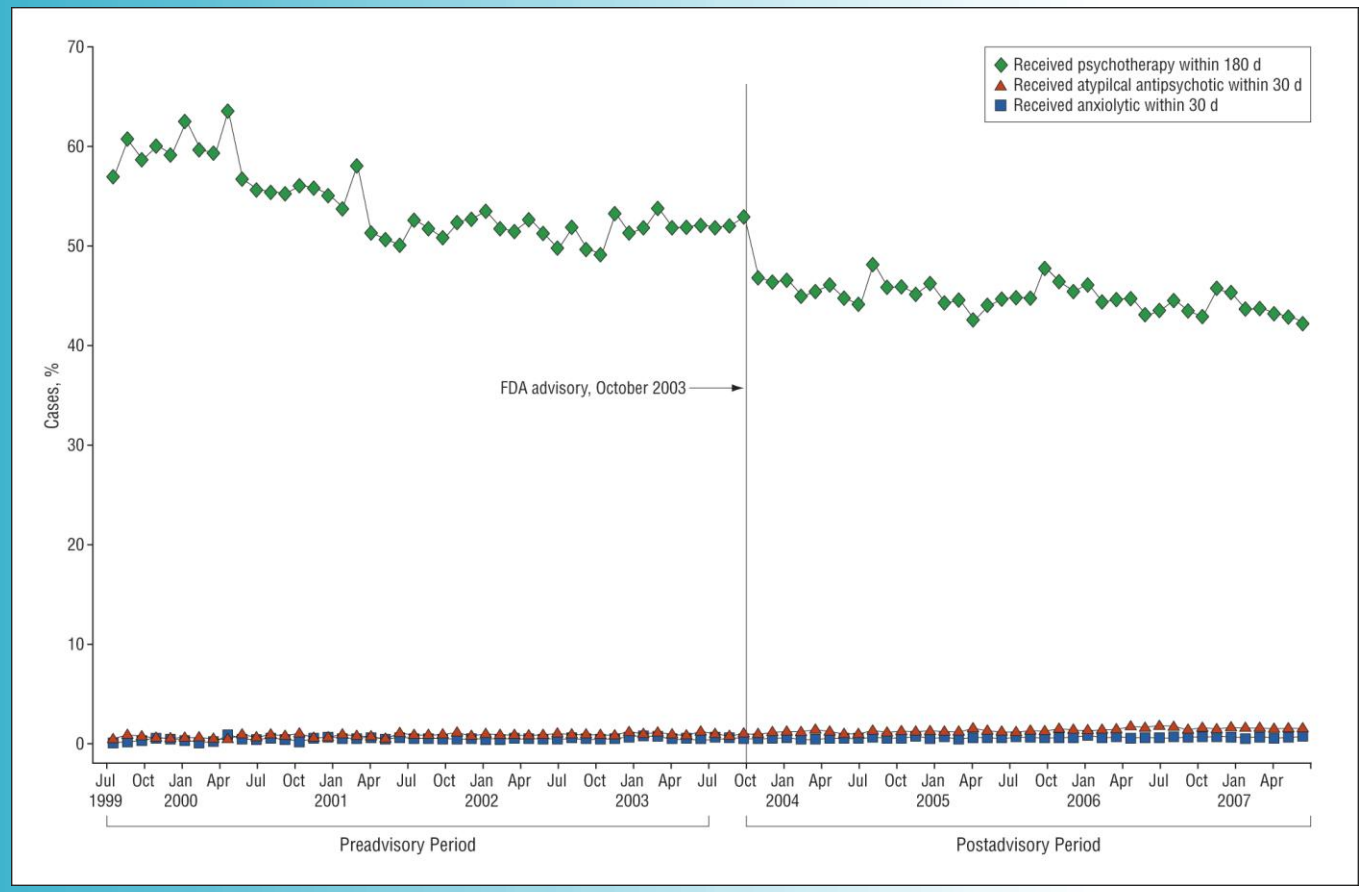
- Juvenile suicide
  - increased markedly from the 1950s through the 1980s
  - Decreased steadily starting in the early 1990s

Unintended Effect of Black Box Warning?



Libby AM. et al. *Am J Psychiatry*. 164:884-891.

Unintended Effect of Black Box Warning?



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

Early Evidence of FDA Mandate on Youth Suicide

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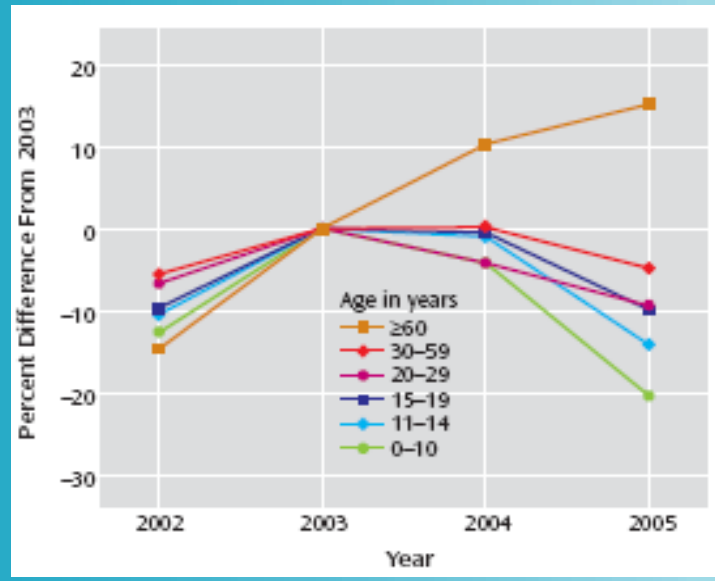
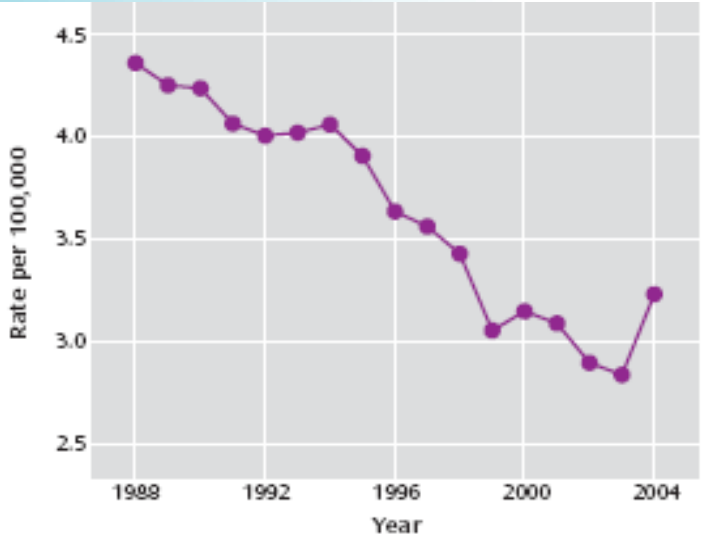
- Evaluation of large pharmacy claims database
- Determined SSRI use by age
- Compiled suicide data from the CDC

SSRI Prescription Rates by Age

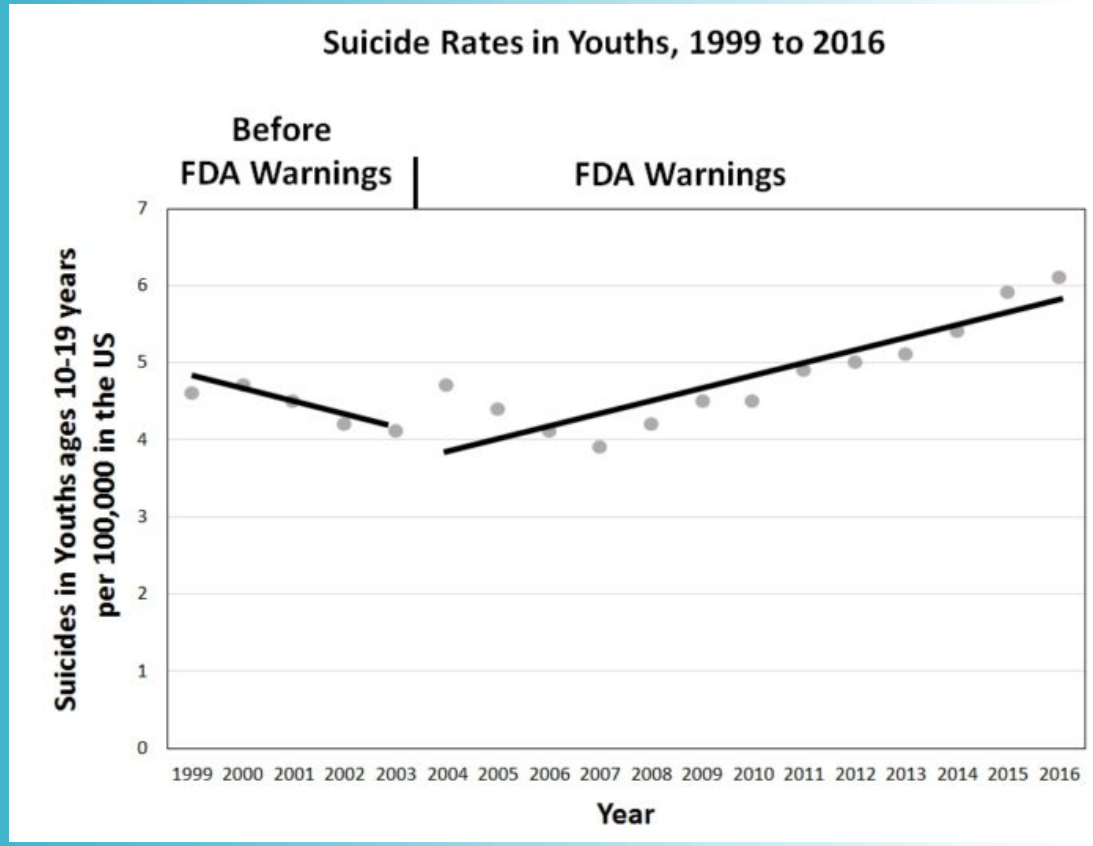


Suicide Rates in Children and Adolescents



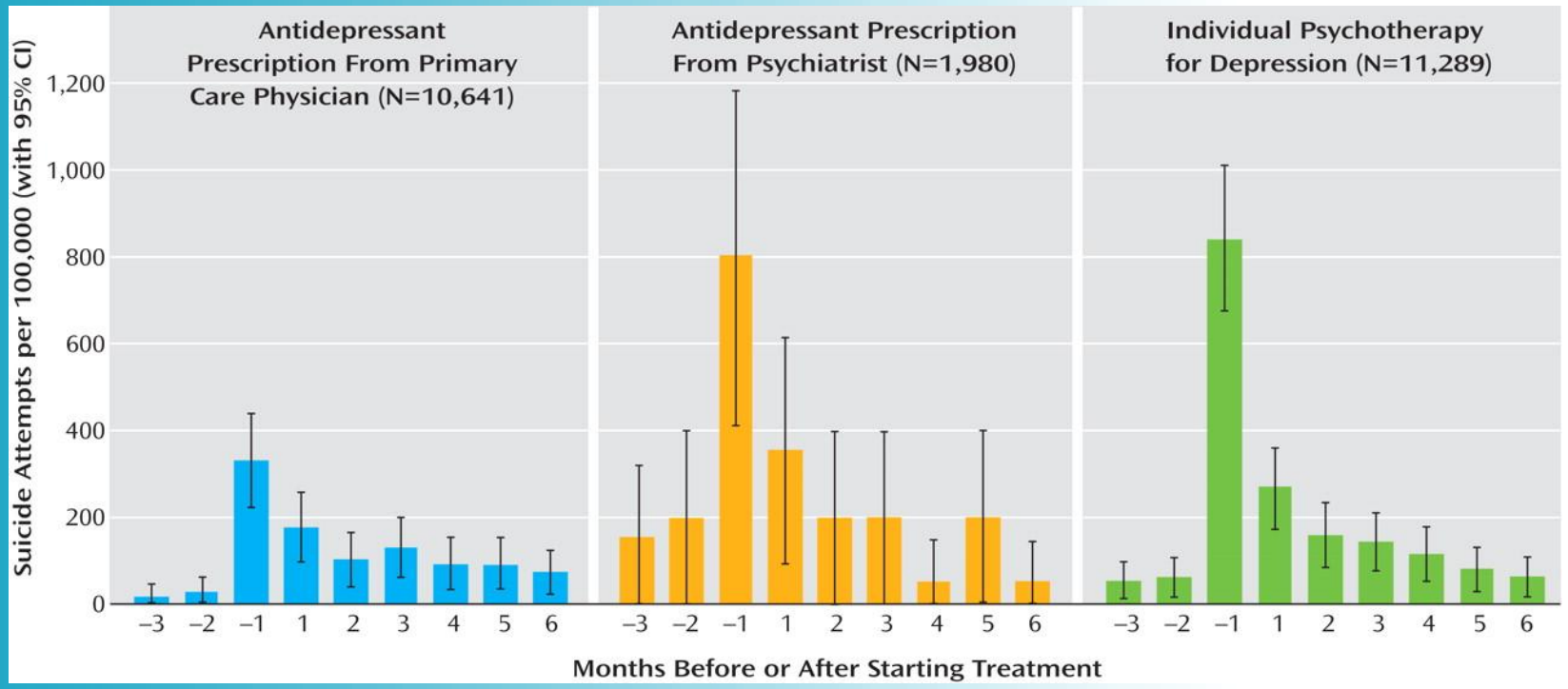
Gibbons et al. *Am J Psy*. 2007;164:1356-63.

Unintended Effect of Black Box Warning?



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

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



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

Autopsy Studies of Suicide Victims

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- 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.

Suicidality and SSRIs

- "Activation"
  - correlates with 7-fold increase in suicidality
- "Manic Switching"
  - Peaks in 10-14 age range, switch rates up to 20-40%
  - No antidepressant uniquely "safe"
- "Joy Returns Last"
- Specific "suicidal" effects on serotonergic pathways, "withdrawal syndrome" not supported.

CDC Youth Suicide Risk Factors, Feb 2022

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- Individual factors, such as:
  - Previous suicide attempts
  - Mental health conditions, such as depression
  - Social isolation
  - Substance use
- Relationship factors, such as:
  - Adverse childhood experiences
  - Bullying
  - Family history of suicide
  - Family or peer conflict
- Community and Societal factors, such as:
  - Barriers to health care
  - Stigma associated with mental health or help-seeking
  - Access to lethal means
  - Unsafe media portrayals of suicide
  - Systemic trauma or marginalizing experiences based on socioeconomic factors, race/ethnicity or gender/sexual identity

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

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Thank You!