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Illuminating the Black Box: Antidepressants, Youth, and Suicide

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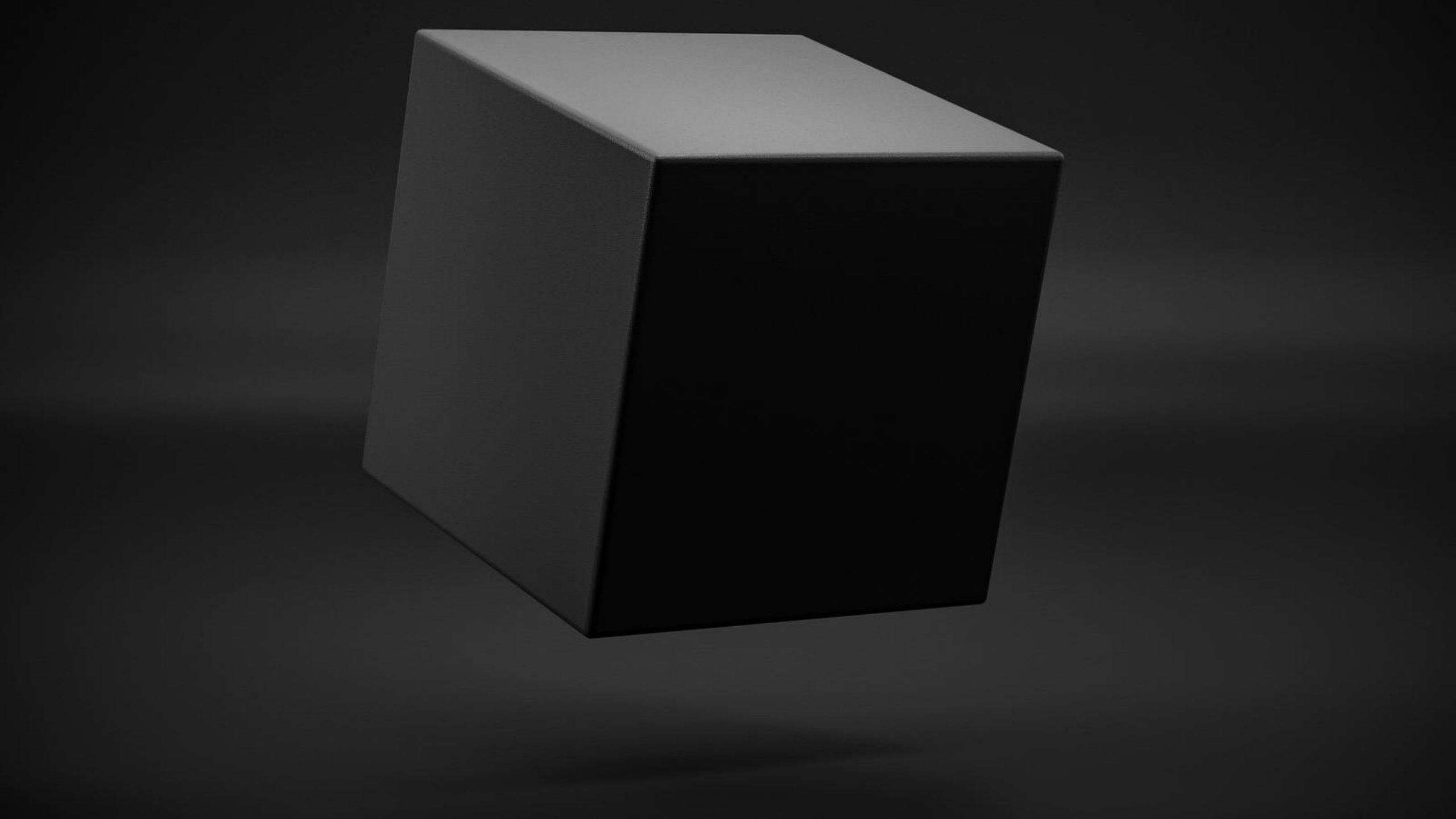
Disclosure

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest 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.

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The Black Box

A **black box warning** is the strictest and most serious type of warning that the FDA gives a medication, meant to draw attention to a medication's serious or life-threatening side effects or risks

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….

Black Box Warning – Cont'd

The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

No suicides occurred in these trials.

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

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 vs 2.1% on placebo

Black Box *Analyses*

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- 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)
- No increase in suicidality on clinician rating scales
- Very Few Suicide Attempts
- No patients committed suicide or seriously harmed self

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

Black Box *Limitations*

- Post-hoc analyses, multiple sub-analyses
  - none of original 24 studies were designed to evaluate this
- Few events of "suicidality" (78/4400)
- Substantial differences between studies in classification
- **Noncompliance not considered**
- Patients with severe pathology excluded

Black Box *Limitations (continued)*

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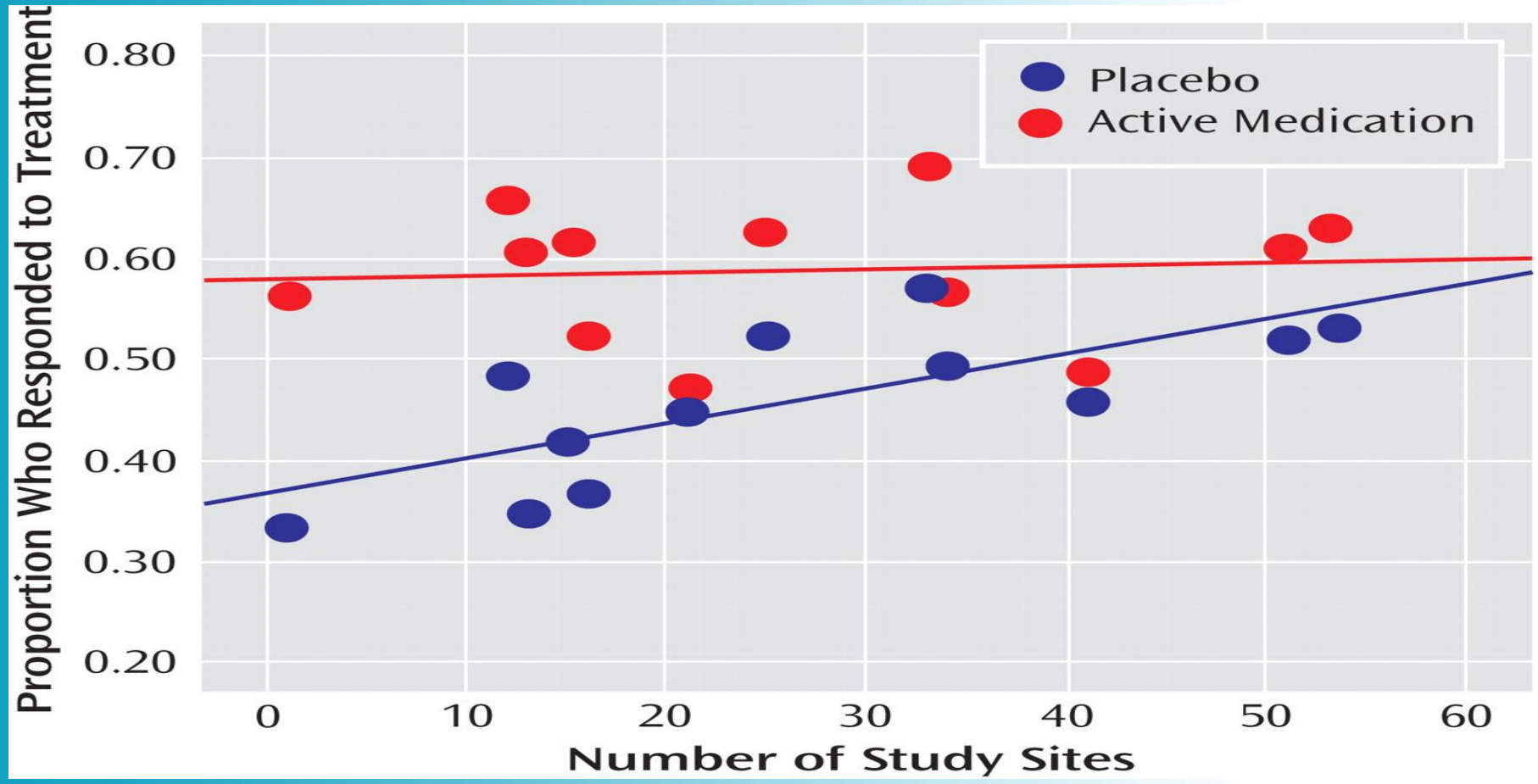
- Increasing number of sites rapidly to accelerate trial
- Aggressive advertising to recruit patients

Placebo Response in Pediatric MDD Trials



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

Black Box Revision *February 2005*

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FDA altered warning…

- ***No "causal"*** relationship had been detected
- Conclusion based on short-term studies
- **No suicides occurred in any of studies**

Selective Serotonin Reuptake Inhibitors - Change in Prescribing

- From 1998 to 2002
  - 9% increase in juvenile SSRI prescriptions

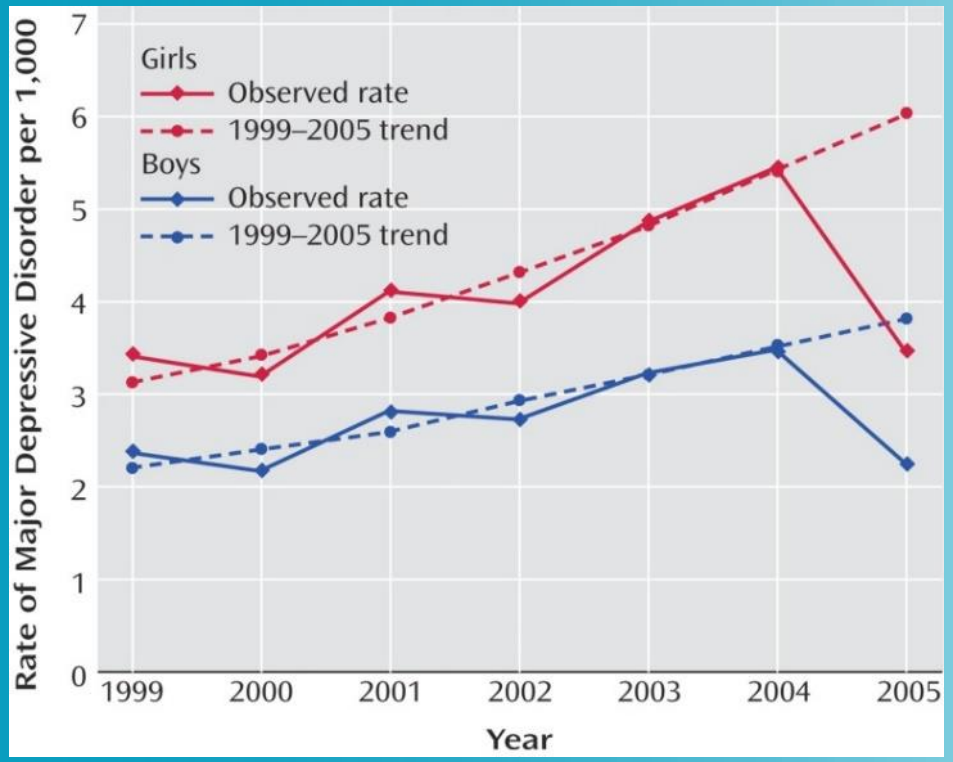
- Began to drop since first quarter of 2004 after FDA and MHRA warnings

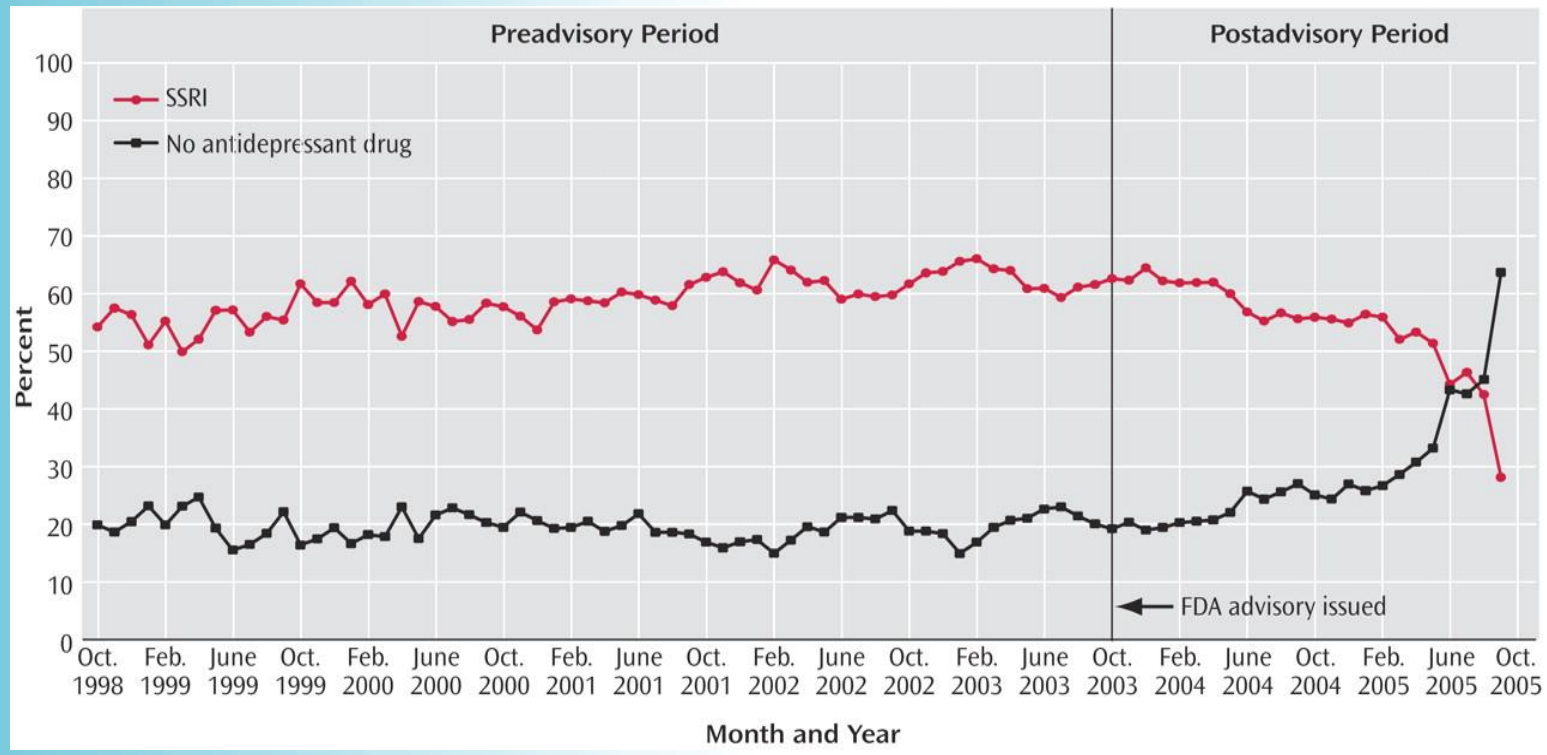
SSRIs

- The decrease in juvenile suicide has correlated with availability of SSRIs

- Systematic examinations of large databases have supported inverse relationship between SSRI prescriptions and suicide, particularly for ages 15-19

Unintended Effect of Black Box Warning?





Libby, A.M. et al., Am J Psychiatry 164:884-891, June 2007

Early Evidence of FDA Mandate on Youth Suicide

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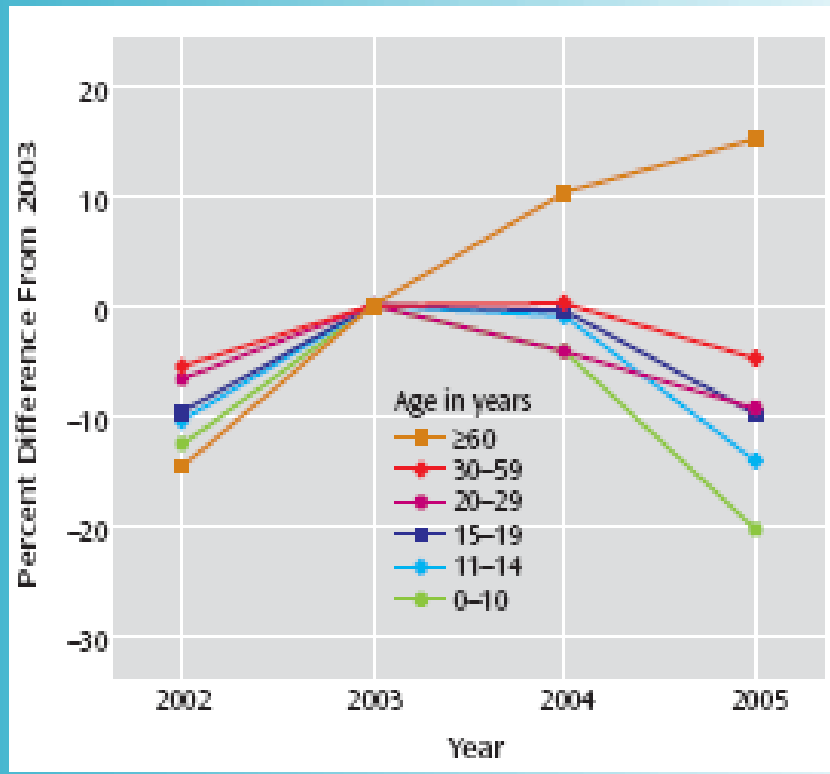
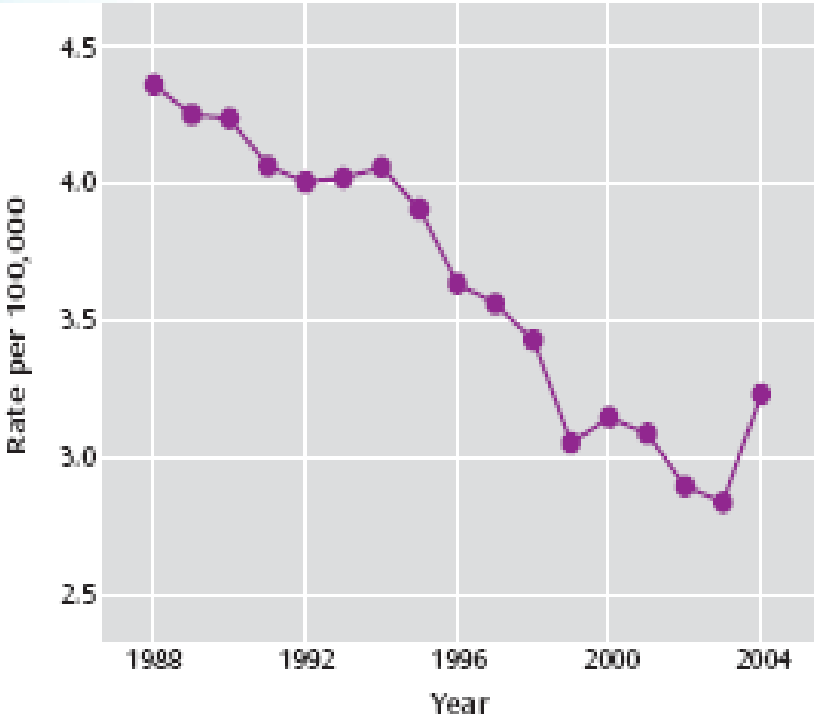
- Evaluation of large pharmacy claims database
- Determined SSRI use by age
- Compiled suicide data from the CDC

SSRI Prescription Rates by Age



Suicide Rates in Children and Adolescents



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

Ecological Studies in USA Comparing Trends in Suicide Rate and Antidepressant Prescribing

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Common finding

Increases in SSRI prescribing associated with decreases in absolute suicide rates

Caution!

Cannot reach conclusion about causality

Grunebaum MF, et al. J Clin Psychiatry. 2004;65:1456-62;
Gibbons RD, et al. Arch Gen Psychiatry. 2005;62:165-72;
Gibbons RD, et al. Am J Psychiatry. 2006;163:1898-904;
Milane MS, et al. PLoS Med. 2006;3:e190.

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Youth

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AAP-AACAP-CHA Declaration of a National Emergency in Child and Adolescent Mental Health

Pediatricians, Child and Adolescent Psychiatrists, and The Children's Hospital Association Declare National Emergency in Children's Mental Health and call on All Policymakers to Act Swiftly to Address Mental Health Crisis
- October 19, 2021

… This worsening crisis in child and adolescent mental health is inextricably tied to the stress brought on by COVID-19 and the ongoing struggle for racial justice and represents an acceleration of trends observed prior to 2020.

https://www.aacap.org/aacap/zLatest_News/Pediatricians_CAPs_Childrens_Hospitals_Declare_National_Emergency_Childrens_Mental_Health.aspx

A New Surgeon General's Advisory – U.S. Surgeon General Dr. Vivek Murthy

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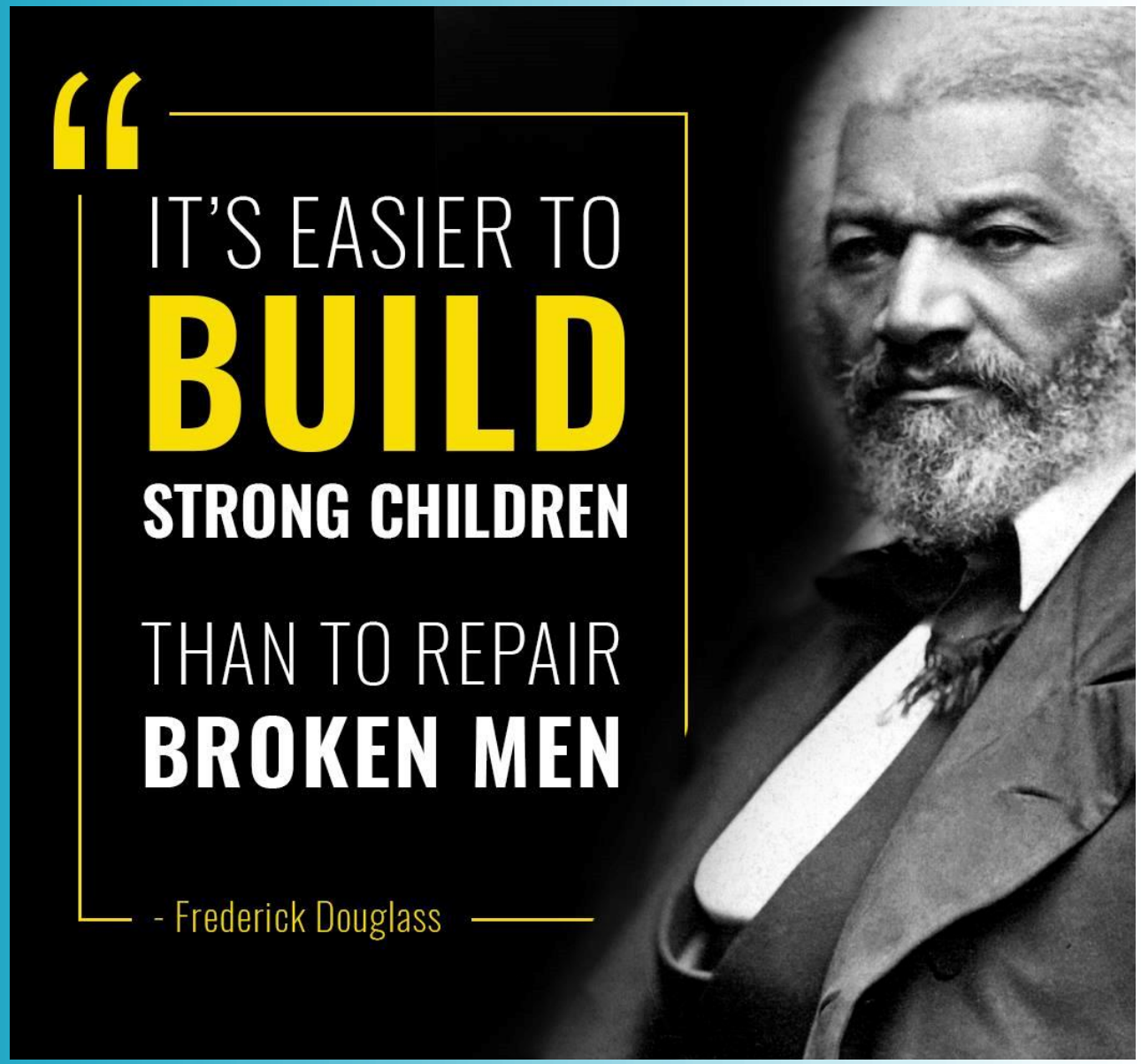
U.S. Surgeon General Issues Advisory on Youth Mental Health Crisis Further Exposed by COVID-19 Pandemic - December 7, 2021

Surgeon General's Advisory to highlight the urgent need to address the nation's youth mental health crisis.
… outlines the pandemic's unprecedented impacts on the mental health of America's youth and families, as well as the mental health challenges that existed long before the pandemic.

https://www.hhs.gov/about/news/2021/12/07/us-surgeon-general-issues-advisory-on-youth-mental-health-crisis-further-exposed-by-covid-19-pandemic.html



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Depression in young people is a disabling and stigmatizing illness. It is the leading cause

of suicide, which climbed by about 50 percent among adolescents between

2003 and 2016.

Depressive Disorders and the Risk of Not Treating

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- 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% or attempters and 60% of completers are depressed

Long-Term Consequences

- Academic underachievement
- Employment difficulties
- Increased risk for poorer health
- Poverty

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Antidepressants

Treatment: Antidepressants

- ***TCAs*** generally avoided due to potential lethality and side effect burden

- ***MAOIs*** 80% of adolescents do not comply with dietary restrictions

- ***SSRIs, SNRIs, Atypical Antidepressants*** favored in practice due to relative safety in overdose and lower side effect burden

Selective Serotonin Reuptake Inhibitors

- ***Fluoxetine*** and ***citalopram***
  - controlled trials demonstrating benefit over placebo
- ***Escitalopram***
  - trial showed statistically significant benefit when subgroup analysis of adolescents was performed

Evidence: Antidepressants

- **Fluoxetine** and **Escitalopram** are the only FDA approved agents.

- Controlled data, published and unpublished now readily availably.

SSRIs

- The decrease in juvenile suicide has correlated with availability of SSRIs

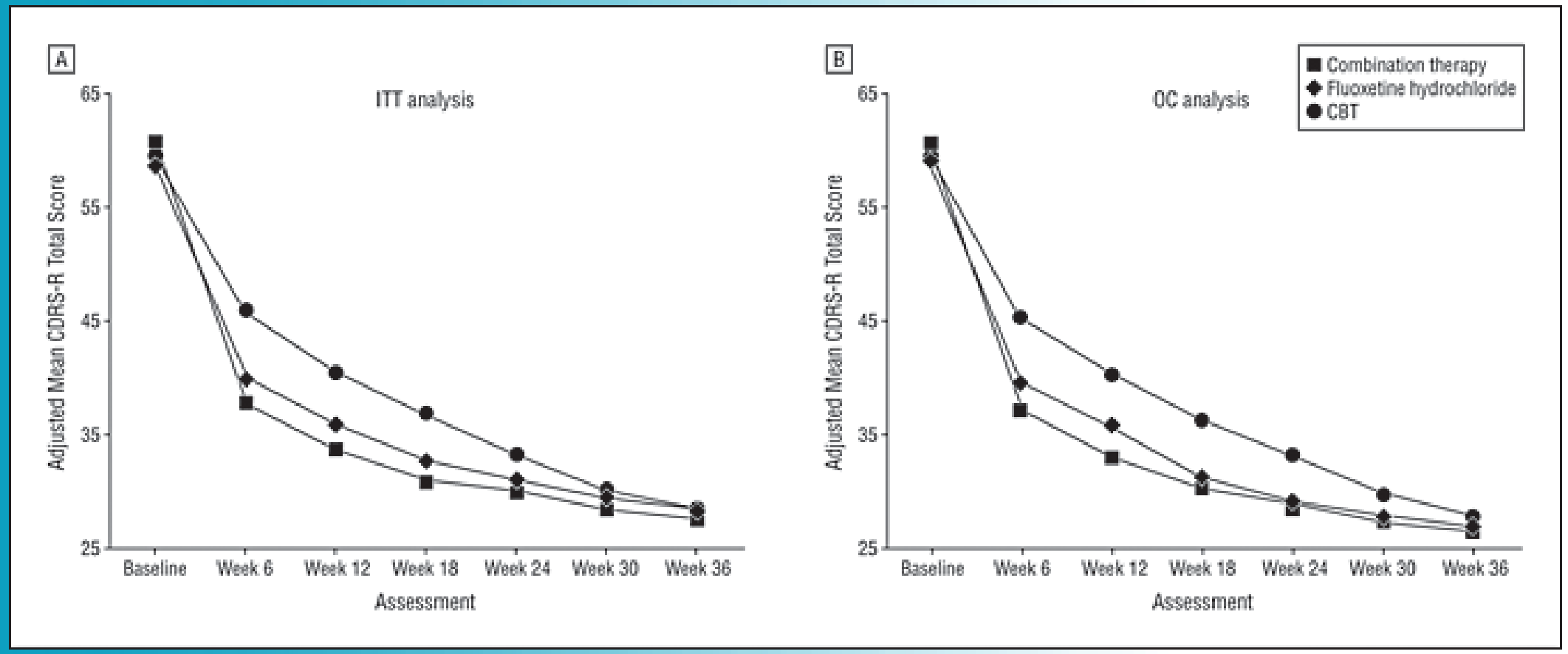
- Systematic examinations of large databases have supported inverse relationship between SSRI prescriptions and suicide, particularly for ages 15-19

Treatment of Adolescents with Depression Study (TADS)

- NIMH sponsored multi-center controlled clinical trial
  - 13 sites
- 12-17 year olds with MDD
  - N=439
- Aim to compare efficacy of fluoxetine, CBT, combination, & placebo over 36 weeks with 1 year follow-up.
  - Fluoxetine 10-40 mg/day

March et al., JAMA, (2004) 292 (7):807-820

Adjusted Mean Children's Depression Rating Scale-Revised (CDRS-R) Total Scores



The TADS Team, Arch Gen Psychiatry October 2007;64:1132-1143.

TADS Response Rates

- Fluoxetine + CBT 71%
- Fluoxetine 61%
- CBT 43%
- Placebo 35%

Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

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- Adolescents (12-18) who failed 8 weeks of SSRI
  - N=334 patients; 6 centers
- Randomized to 12 weeks of switch to
  - Another SSRI
    - - Paroxetine, citalopram or fluoxetine (20-40 mg)
  - Another SSRI + CBT
  - Venlafaxine (150- 225 mg)
  - Venlafaxine + CBT
- CBT 9 times in 12 weeks

Brent et al. JAMA 2008

Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

- Higher response rate to switch to
  - New Medication + CBT (54.8%) vs.
  - New Medication alone (40.5%)
- No difference in response rate to switch to
  - Venlafaxine (48.2%) vs.
  - Second SSRI (47%)
    - No difference between the SSRIs
- No difference between treatments in
  - Adverse events
  - Self harm or suicidal adverse events
  - 17 subjects attempted suicide; no completers

Brent et al. JAMA 2008

Atypical Antidepressants/ SNRIs

- No controlled trial data has shown statistically significant benefit of any of these agents (with exception of ***nefazadone***) over placebo

- ***Venlafaxine***
  - positive effect for adolescent subgroup

Tricyclic Antidepressants (TCAs)

- ***Clomipramine*** v. ***paroxetine***
  - single multicenter trial
  - showed benefit for both agents

- No other study or meta-analysis has supported TCAs for juvenile depression

Using Medications for Pediatric Depressive Disorders

- Start low, go slow?
- After initiation of pharmacotherapy make plan for regular follow-up & emergency access
- Educate family
  - delay in onset of action
  - worsening depression/anxiety/sleep
  - negative behavior change
  - Discontinuation Syndrome
  - Potential for increase in 'Suicidality'
  - Symptoms of mania, hypomania & mixed episodes
  - www.parentsmedguide.org

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Suicide

SUICIDE

2nd leading cause of death among young people ages 10-24

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.

Data and Worries: Harvard Study

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- 2000-2017: Suicide rate rose by ***47% among teens ages 15-19*** and 36% among those 20-24
- Among **males** 15-19: suicide rate jumped 14.2% yearly from 2015-17
- This is more than ***6,200 suicides*** among 15-24 year-olds

First study in which male suicides are greater than females*

Miron,MA et. al: JAMA 2019; 321(23): 2362-3

Suicide

- Suicide was the ***tenth*** leading cause of death overall in the United States, claiming the lives of over 47,500 people.

- Suicide is the ***2nd*** leading cause of death among all children and adolescents in the United States, including ages **10 to 24 years** (CDC WISQARS; 2019)

CDC: Trending Data 2011-2021

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3 in 5 girls experienced persistent sadness or hopelessness (36%-57%)

More than 1 in 4 girls seriously considered suicide (19%-30%)

1 in 5 teen girls experienced sexual violence 2017-2021: Significant increase

LGBTQ Youth

- 1 in 4 experiences sexual violence
- 1 in 4 bullied in school
- 50% seriously considered suicide
- 1 in 4 attempted suicide
- 3 in 4 were persistently sad or depressed

Source: https://www.cdc.gov/nchhstp/newsroom/fact-sheets/healthy-youth/sadness-and-violence-among-teen-girls-and-LGBQ-youth-factsheet.html

Suicide Among Black Youth

- Suicide rate is growing fastest among Black individuals ages 13-30, with a 55% increase from 2010-2019

- To what factors can we attribute these rising rates, and what are some things to consider when looking at this data?

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***.

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

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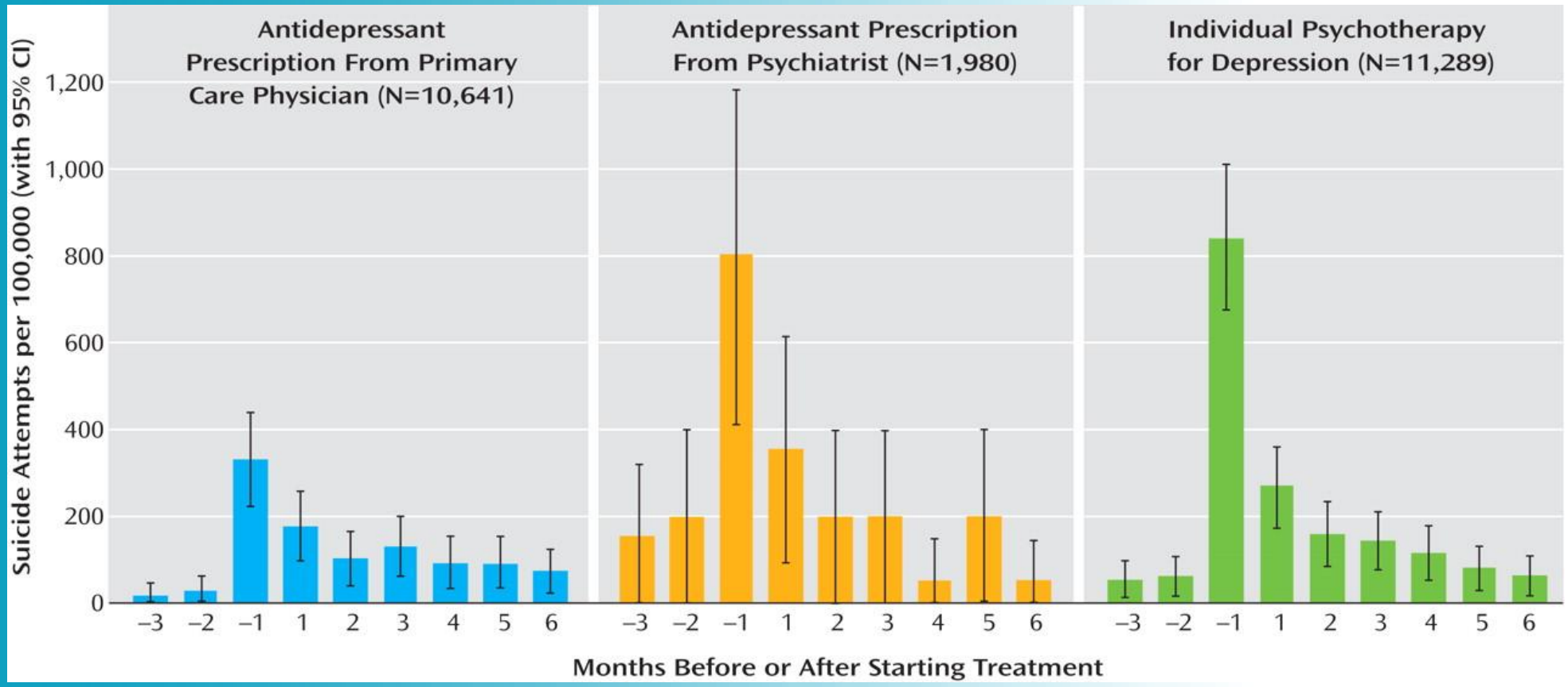

Simon GE and Savarino J (2007) Am J Psychiatry 164:1029-1034

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.

In Conclusions

Managing Depression in Children and Adolescents

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- Depression in children & adolescents is common, identifiable and treatable

- Psychotherapy acceptable/emphasized as a first line in mild/moderate MDD

- Based on FDA meta-analysis, share with families
  - there is a 2-4% of SI vs. 1-2% on placebo.
  - TADS study shows 60-70% chance of improvement of MDD with medication treatment

Managing Depression in Children and Adolescents – Cont'd

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- Fluoxetine and Escitalopram are FDA approved to treat Depression in Children and Adolescents (although may have good reason to use others)

- Educate families to watch for and report
  - increase in agitation or uncharacteristic behavior change or Suicidal/Self-Injurious Thoughts/Behaviors and how to get help if concerned

- Weekly visits- not always practical- judge on case-by-case basis, qualified staff contacts acceptable

… know that the risk posed by untreated depression — in terms of morbidity and mortality — has always been far greater than the very small risk associated with antidepressant treatment.

N Engl J Med 2014; 371:1666-1668 DOI: 10.1056/NEJMp1408480

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THANK YOU