MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Illuminating the Black Box: Antidepressants, Youth and Suicide

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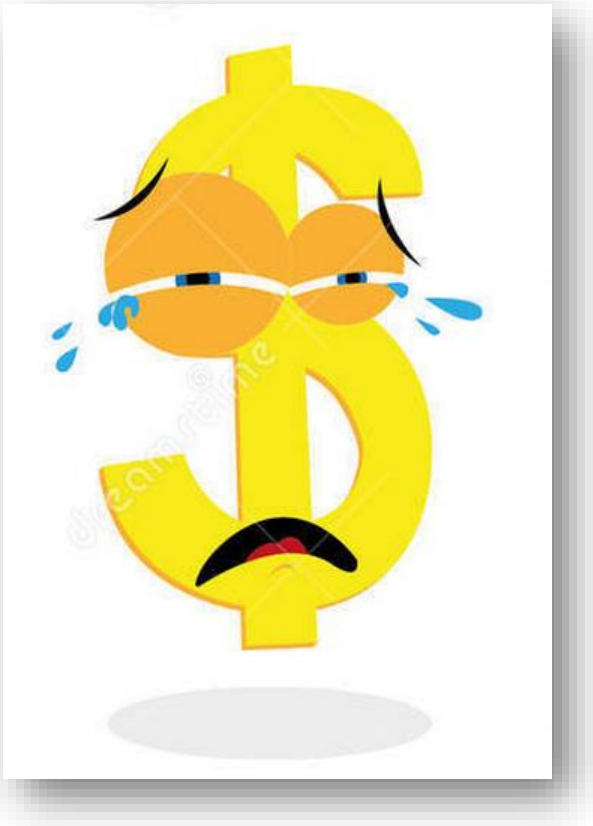
Disclosure

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.

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….

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 v 2.1% on placebo

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)
- No increase in suicidality on clinician rating scales
- Very Few Suicide Attempts and
- 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

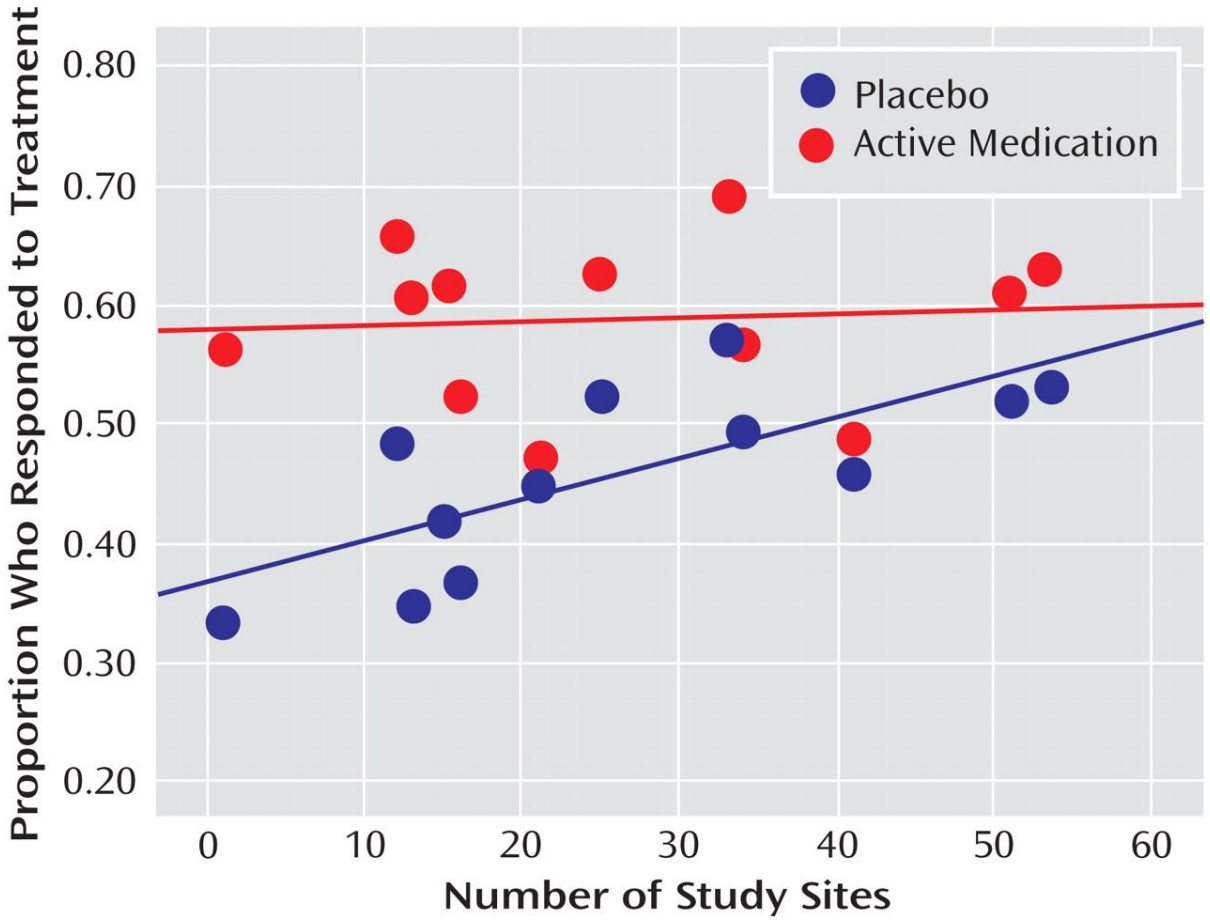
- Post-hoc analyses, multiple sub-analyses
  - ➢ none of original 24 studies were designed to evaluate this
- Few events of “suicidality” (78/4400)
- Substantial differences between studies in classification
- Noncompliance not considered
- Patients with severe pathology excluded

Black Box

Limitations (continued)

- 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

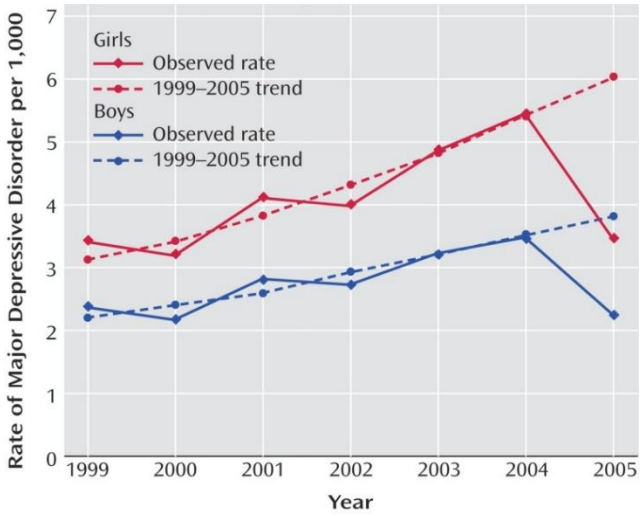
February 2005

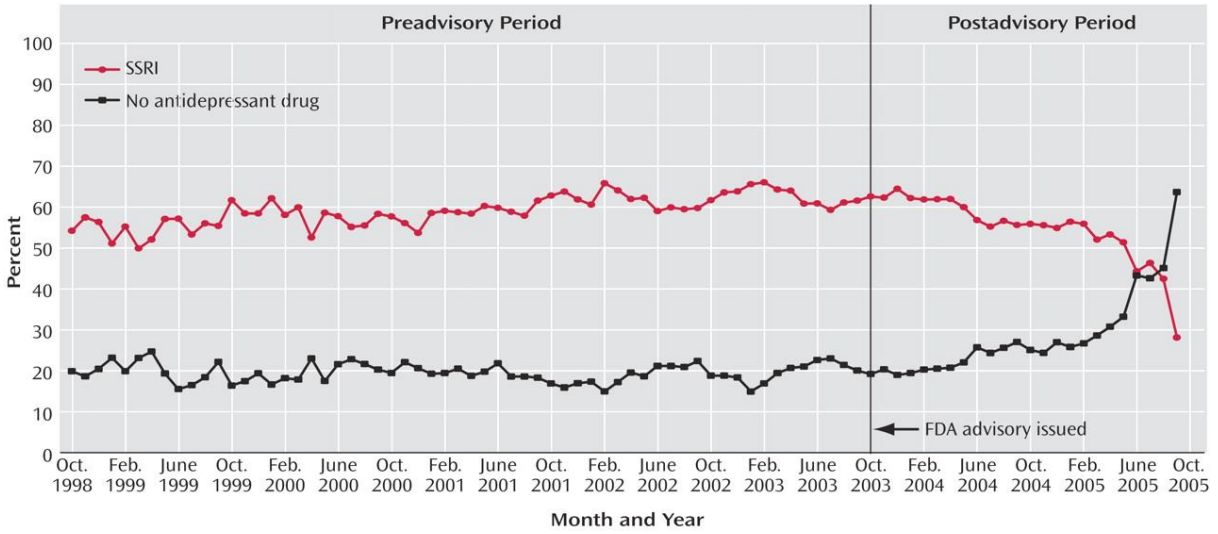
- FDA altered warning
  - No “causal” relationship had been detected
  - Conclusion based on short-term studies
  - No suicides occurred in any of studies

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?



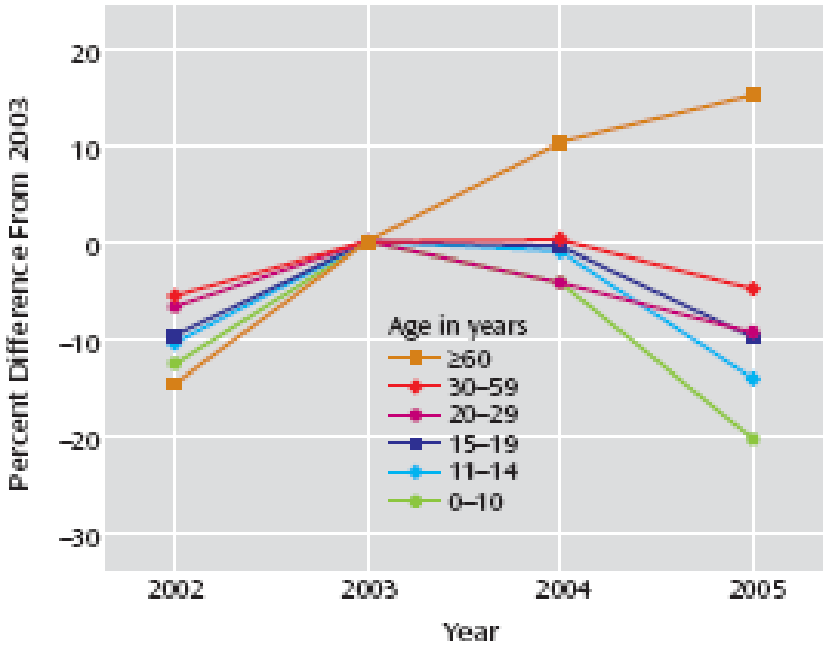


Libby, A.M. et al., Am J Psychiatry 164:884-891, June 2007

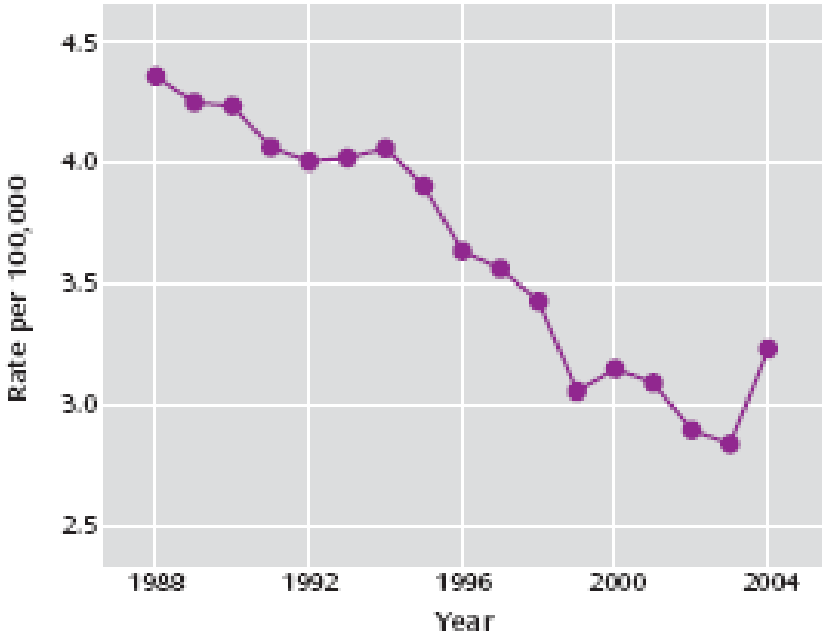
Early Evidence of FDA Mandate on Youth Suicide

- 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



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

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

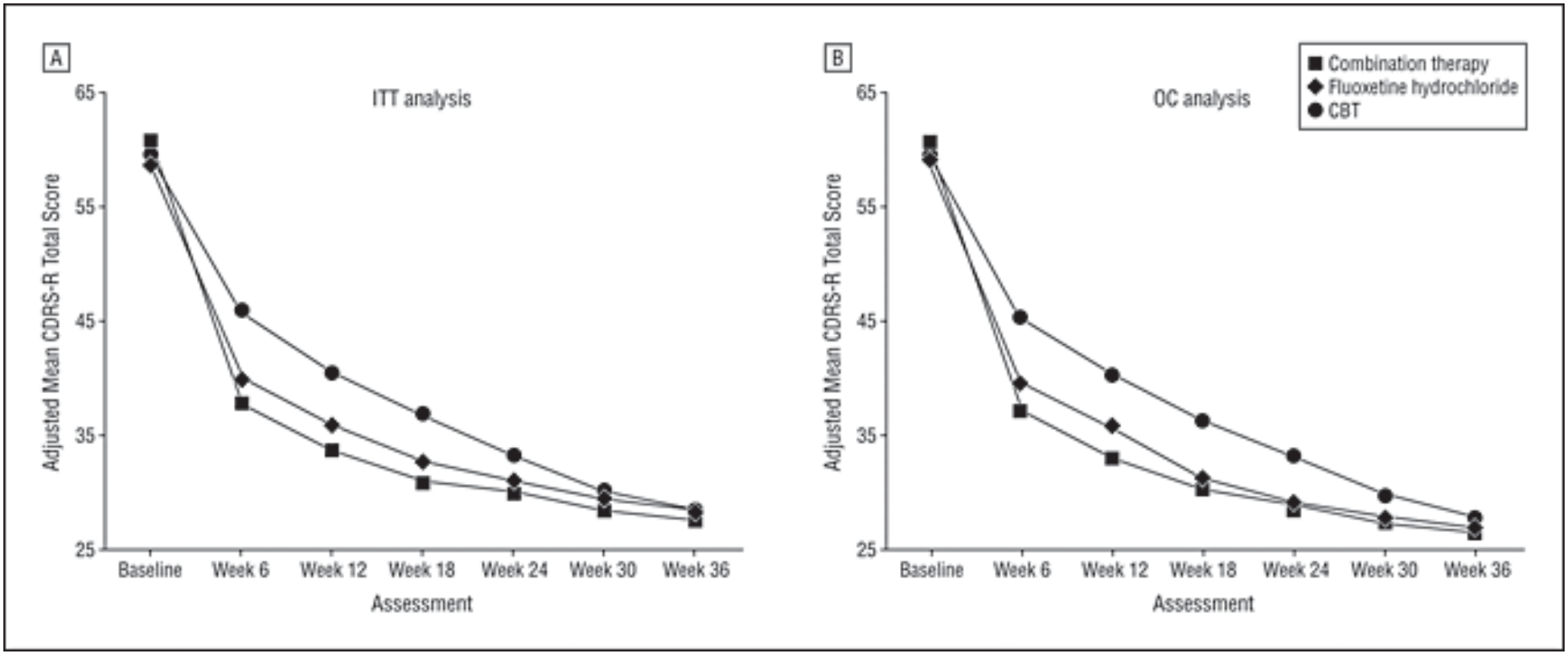
Antidepressants

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.

Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

- 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

Youth

Complications of Depressive Disorders/ Risk of Not Treating

- 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

Suicide

Youth Suicide

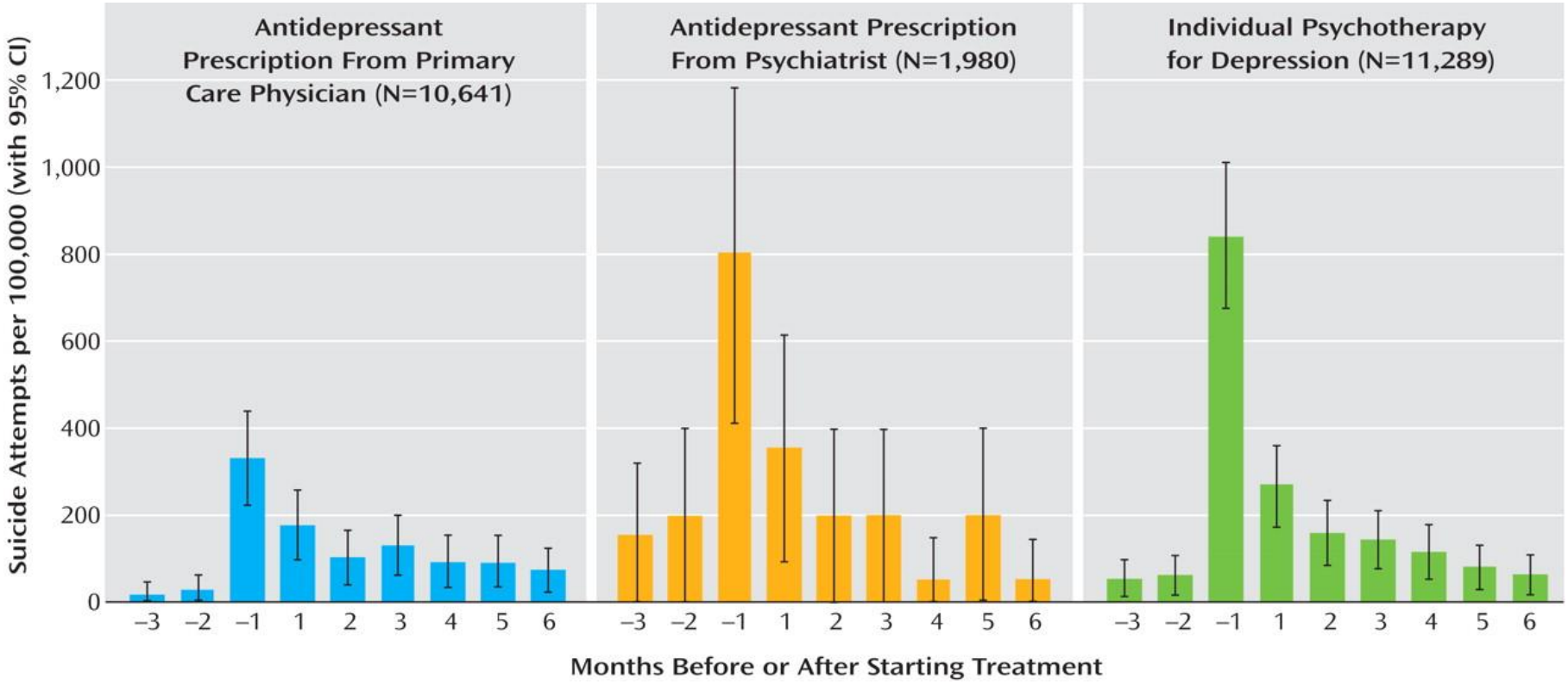
- Male adolescents die by suicide at a rate 4 × higher than females
  - Of all suicide completions, 80% are male
  - 75% are white males
- Female adolescents attempt suicide at a rate 3 × higher than males
  - Asian-American females aged 14-24 years have the highest suicide rate (not attempts) of all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

Available at: http://www.cdc.gov/ViolencePrevention/pdf/Suicide-DataSheet-a.pdf.

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

Suicidality and SSRIs

- "Activation"
  - ➢ correlates with 7-fold increase in suicidality
- "Manic Switching"
- "Joy Returns Last"

- Specific "suicidal" effects on serotinergic 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

Managing Depression in Children and Adolescents

- 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
- 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