MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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.

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

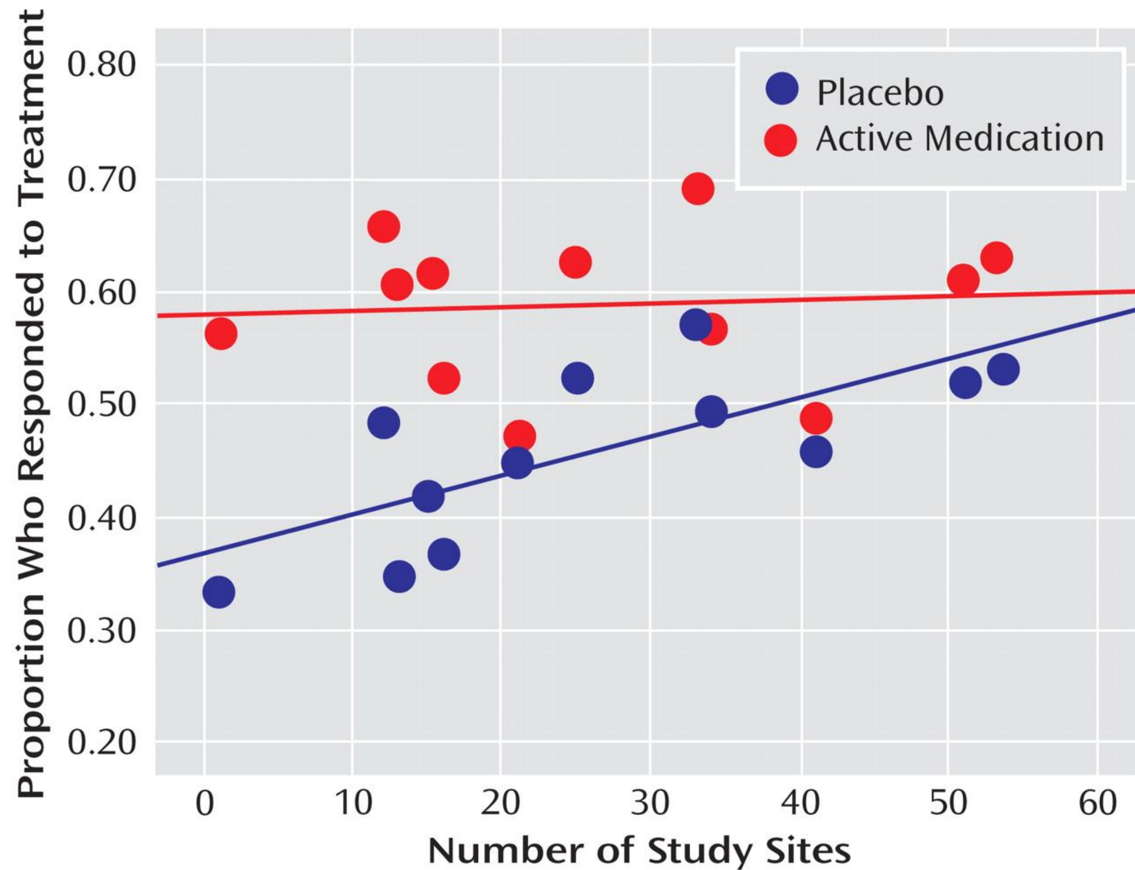
Black Box

- 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

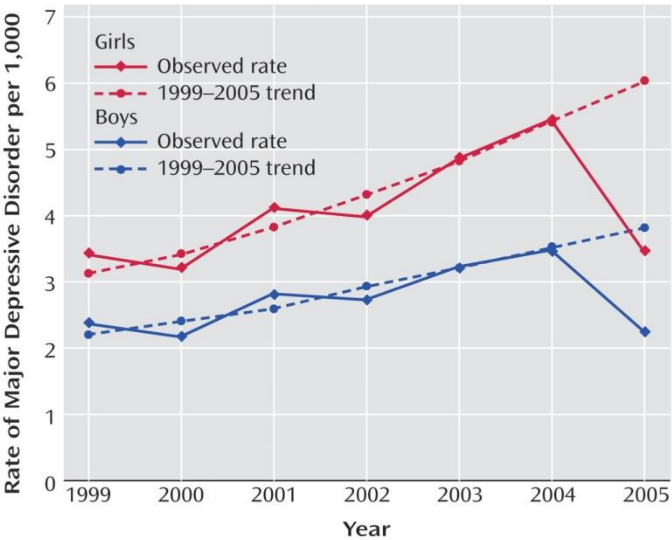
Black Box Revision

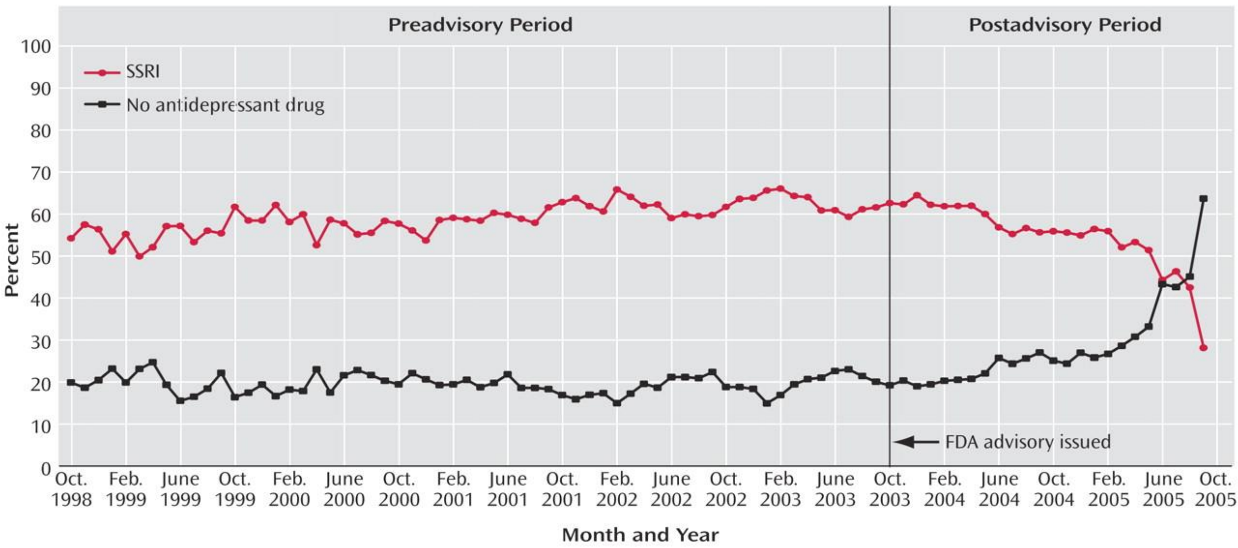
- February 2005
  - FDA altered warning
    - No “causal” relationship had been detected
    - Conclusion based on short-term studies
    - No suicides occurred in any of studies

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?



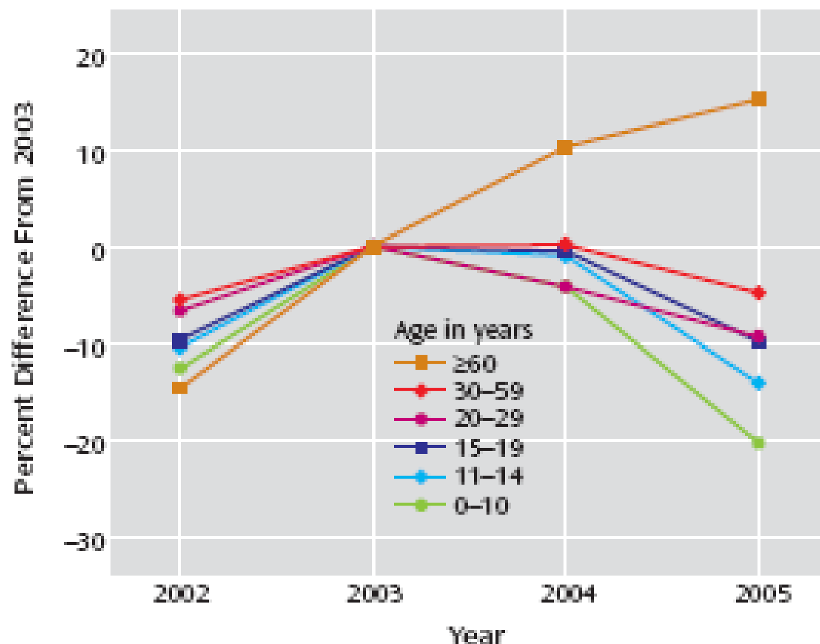


Libby, A.M. et al., Am J Psychiatry 164:884-891, June 2007

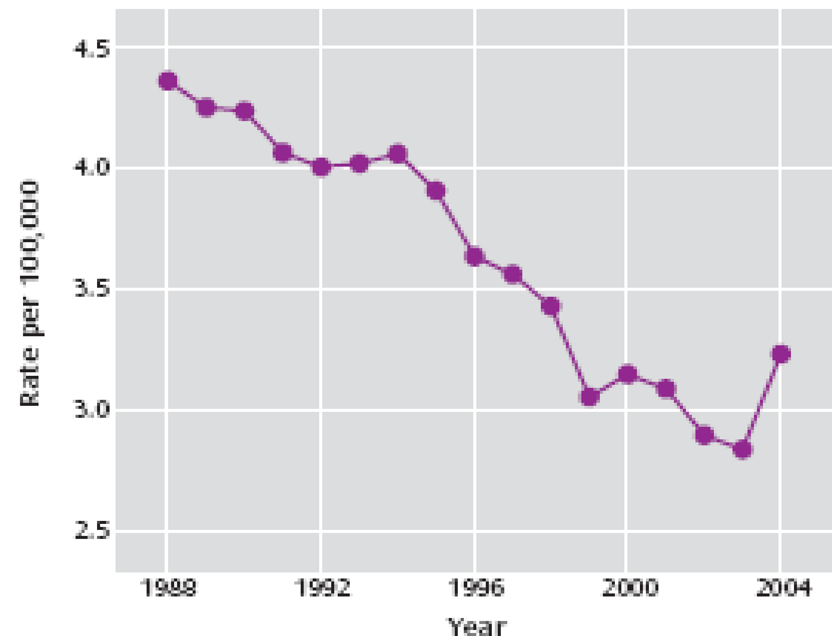
Early Evidence of FDA Mandate on Youth Suicide

- 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

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

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.

Antidepressants

Treatment: Antidepressants

- **SSRIs**
- **Atypical Antidepressants**
- **SNRIs**
- **TCAs**
- **MOAIs**

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

SSRIs

- ***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.

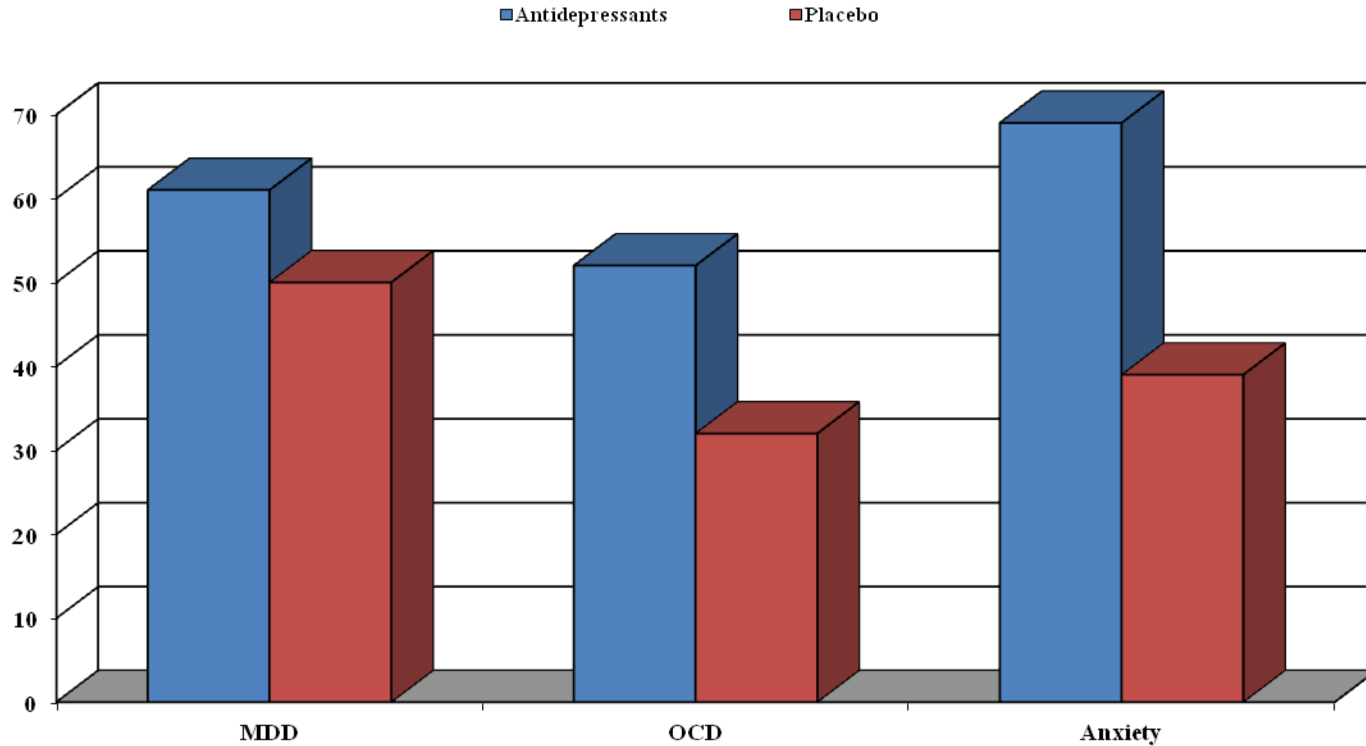
SSRIs

- Recent meta-analysis incorporation of unpublished data gives further support to ***fluoxetine***, while narrowing benfit-to-risk profiles of other agents

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

Efficacy of SSRIs



NNT=10 **NNT=6** **NNT=3**

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

Meta-Analysis of Overall Rate of Emergent Suicidality: All Types of Antidepressants

Diagnosis	Number Needed to "Harm" (NNH)
MDD	112
OCD	200
Anxiety	143

OCD, obsessive compulsive disorder.
MDD, major depressive disorder.

Bridge JA, et al. *JAMA*. 2007;297:1683-96.

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

TCAs

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

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

Treatment of Adolescents with Depression Study (TADS)

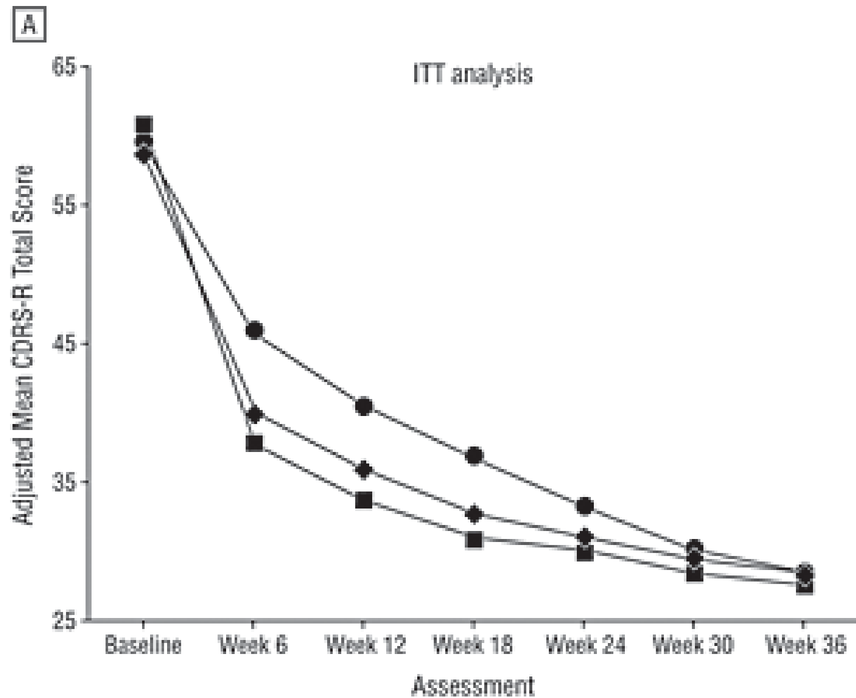
- NIMH sponsored multi-center controlled clinical trial
  - 13 sites
- 12-17 year olds with MDD
  - N=439
- Aim to compare efficacy of fluoxetine, CBT, combination, & placebo over 36 weeks with 1 year follow-up.
  - Fluoxetine 10-40 mg/day

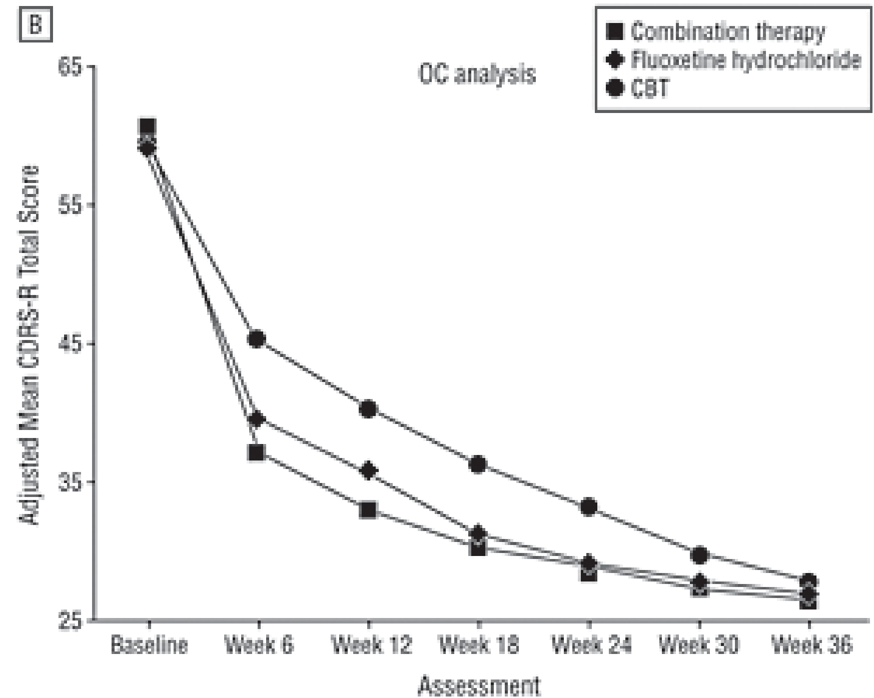
March et al., JAMA, (2004) 292 (7):807-820

TADS

- TADS Response Rates
  - Fluoxetine+CBT 71%
  - Fluoxetine 61%
  - CBT 43%
  - Placebo 35%

Adjusted mean Children's Depression Rating Scale-Revised (CDRS-R) total scores





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

Using Medications for Pediatric Depressive Disorders

- **May increase every one or two weeks by:**
  - **Fluoxetine*@ (Prozac) @ 5-10 mg QD**
  - **Sertraline*(Zoloft) 12.5-25 mg QD**
  - **Citalopram (Celexa) 5-10 mg QD**
  - **Paroxetine** (Paxil) 5-10 mg QD or 12.5 mg CR**
  - **Fluvoxamine* (Luvox) 12.5-25 mg QD**
  - **Venlafaxine (Effexor) 12.5-25 mg IR or 18.75-37.5 XR**
  - **Bupropion (Wellbutrin) 37.5 mg IR or 100 mg SR**
  - **Mirtazapine (Remeron) 3.75-7.5 mg QHS**
  - **Escitalopram@ (Lexapro) 2.5-5 mg QD**
  - **Duloxetane (Cymbalta) 20 mg QD**

*=FDA approved to treat Pediatric OCD

@=FDA approved to treat Pediatric Depression

**=currently FDA recommends NOT using to treat Pediatric 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

Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

Brent et al. JAMA 2008

- 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

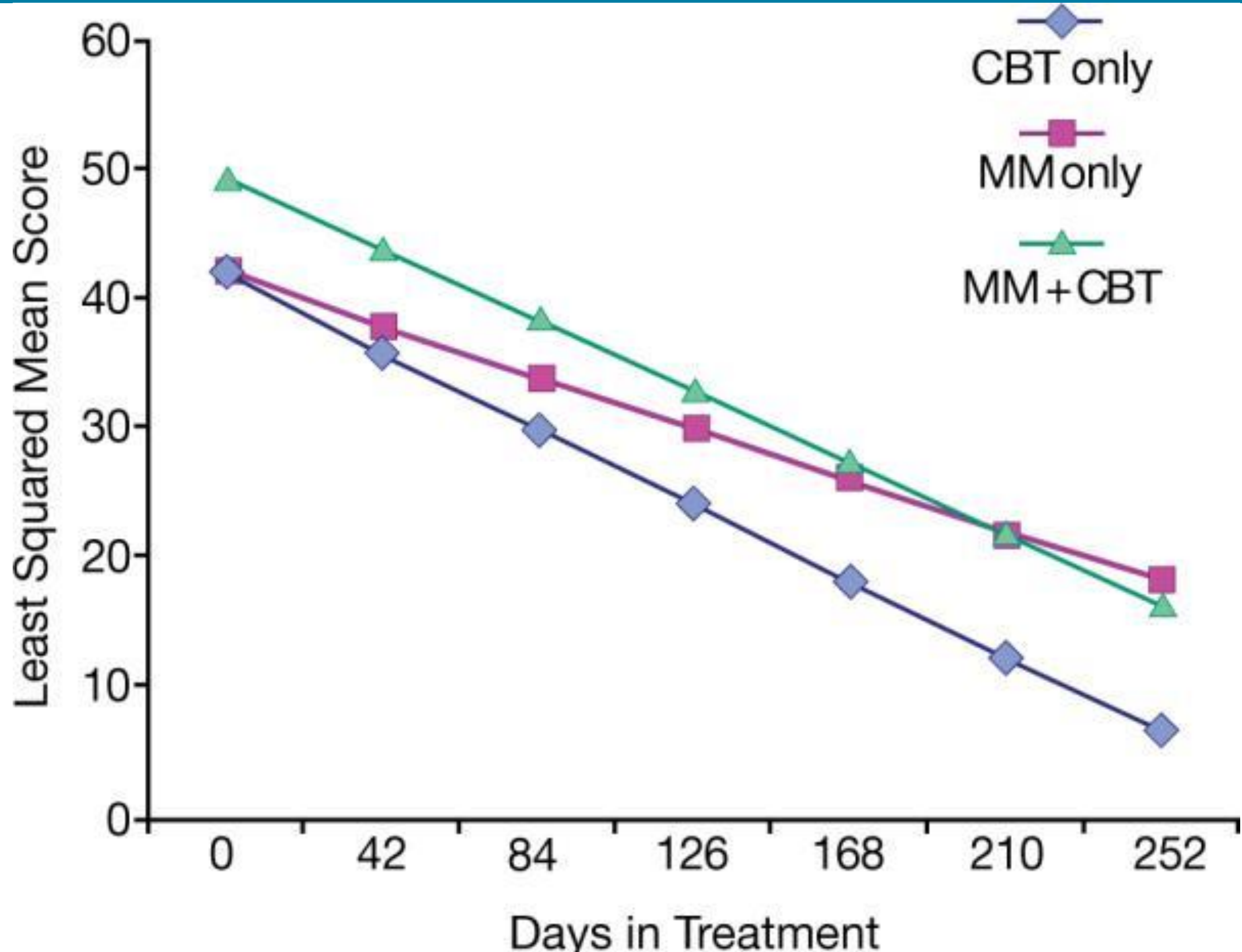
Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

Brent et al. JAMA 2008

- 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

Depressive symptoms and clinical status during the Treatment of Adolescent Suicide Attempters (TASA) Study

Child Depression Rating Scale-Revised Scores Over Time



Vitiello B et al., JAACAP 2009 Oct;48(10):997-1004.

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% or attempters and 60% of completers are depressed

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

Suicide

Incidence of Suicide in Perspective

- Worldwide, there are about 1 million suicides annually.
- In the last 25 years, approximately 750,000 people committed suicide in the US, and suicides outnumber homicides by at least a 3 : 2 ratio.
- Deaths from suicide exceeded deaths from AIDS by 200,000 in the past 20 years, and
- Four times as many Americans died as a result of suicide than in the Vietnam war during the same time period.

Gibbons & Mann Drug Saf 2011; 34 (5): 375-395

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.

Leading Causes of Death 10-14 yo in United States

	2009			2008		
Causes	**n**	**%**	**Rate**	**n**	**%**	**Rate**
Accidents	891	28.5	4.5	1024	32.5	5.1
Cancer	426	13.6	2.1	433	13.8	2.2
Suicide	259	8.3	1.3	215	6.8	1.1
Assault	201	6.4	1.0	207	6.6	1.0
Congenital	161	5.3	0.8	161	5.1	0.8

Annual Review of Vital Statistics Pediatrics (2012) Vol. 129 No. 2: 338 - 348

Leading Causes of Death 15-19 yo in United States

	2009			2008		
Causes	n	%	Rate	n	%	Rate
Accidents	4758	41.5	22	5541	44.7	25.8
Assault	1893	16.5	8.8	2095	16.9	9.7
Suicide	1656	14.4	7.7	1604	12.9	7.5
Cancer	654	5.7	3.0	685	5.5	3.2
Heart	325	2.8	1.5	363	2.9	1.7

Annual Review of Vital Statistics Pediatrics (2012) Vol. 129 No. 2: 338 - 348

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.

MOST COMMON PSYCHIATRIC DIAGNOSES IN TEENS WHO SUICIDE

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

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

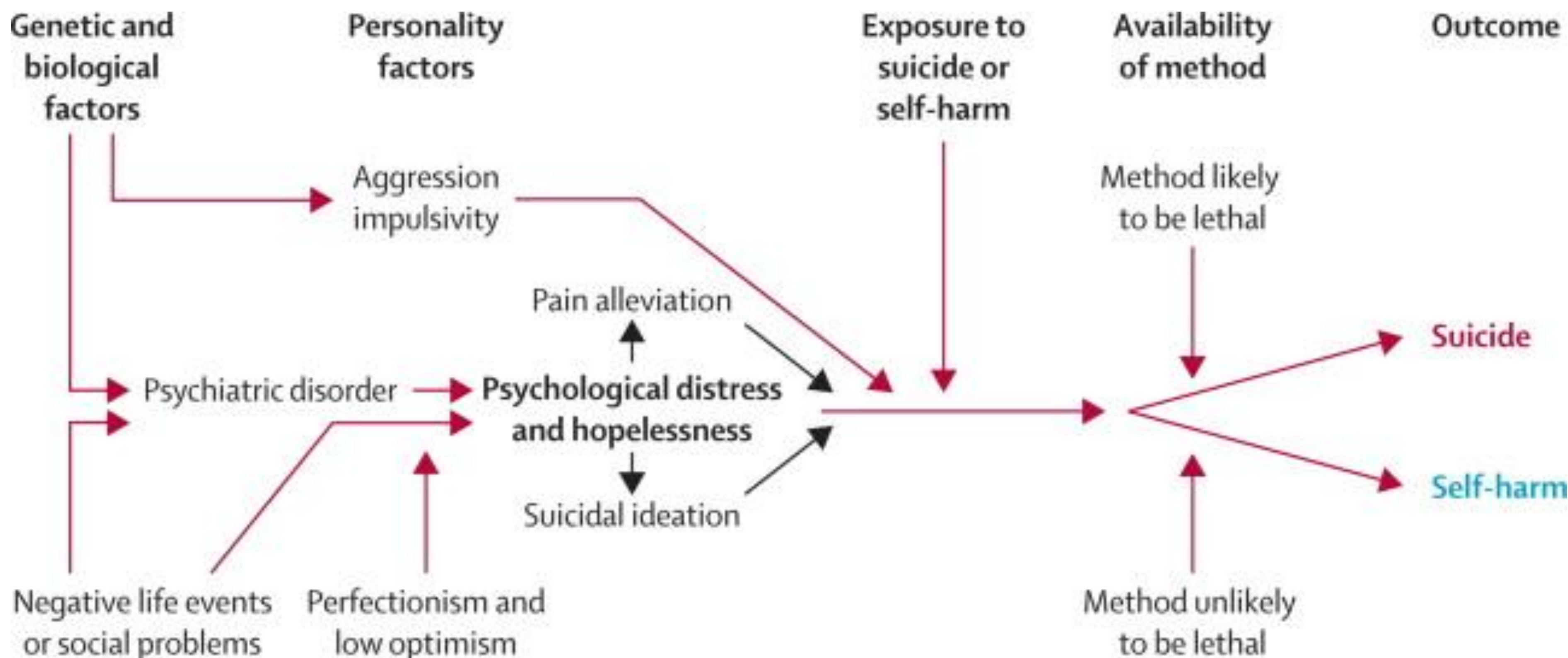
Brent et al. 1999, Shaffer et al. 1996

David Jobes' "Truisms"

- Most suicidal people do not want an end to their biological existence;
  - rather, they want an end to their psychological pain
- Most suicidal people tell others (including mental health professionals) that they are thinking about suicide as a compelling option for coping with their pain.
- Most suicidal people have psychological problems, social problems, and poor methods for coping with pain –
  - all things that mental health professionals are usually well trained to tackle.

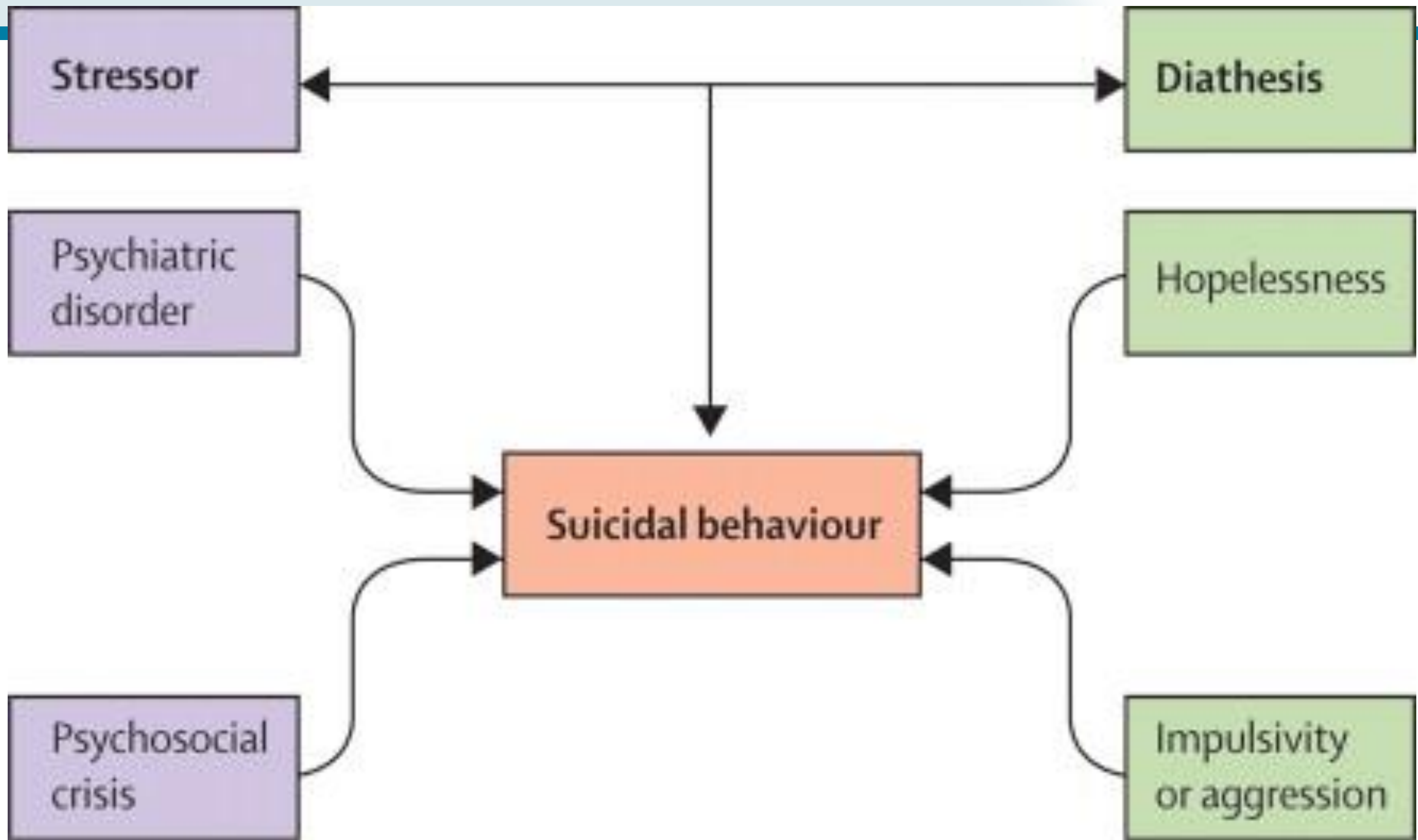
David Jobes, *Managing Suicidal Risk: A Collaborative Approach*, 2006

Key risk factors for adolescent self-harm and suicide



Keith Hawton, Kate EA Saunders, Rory C O'Connor. Self-harm and suicide in adolescents. Lancet, Volume 379, Issue 9834, 2012, 2373–2382

A stress–diathesis model of suicide Adapted from Mann 2003



Keith Hawton, Kees van Heeringen. Suicide. Lancet, Volume 373, Issue 9672, 2009, 1372–1381

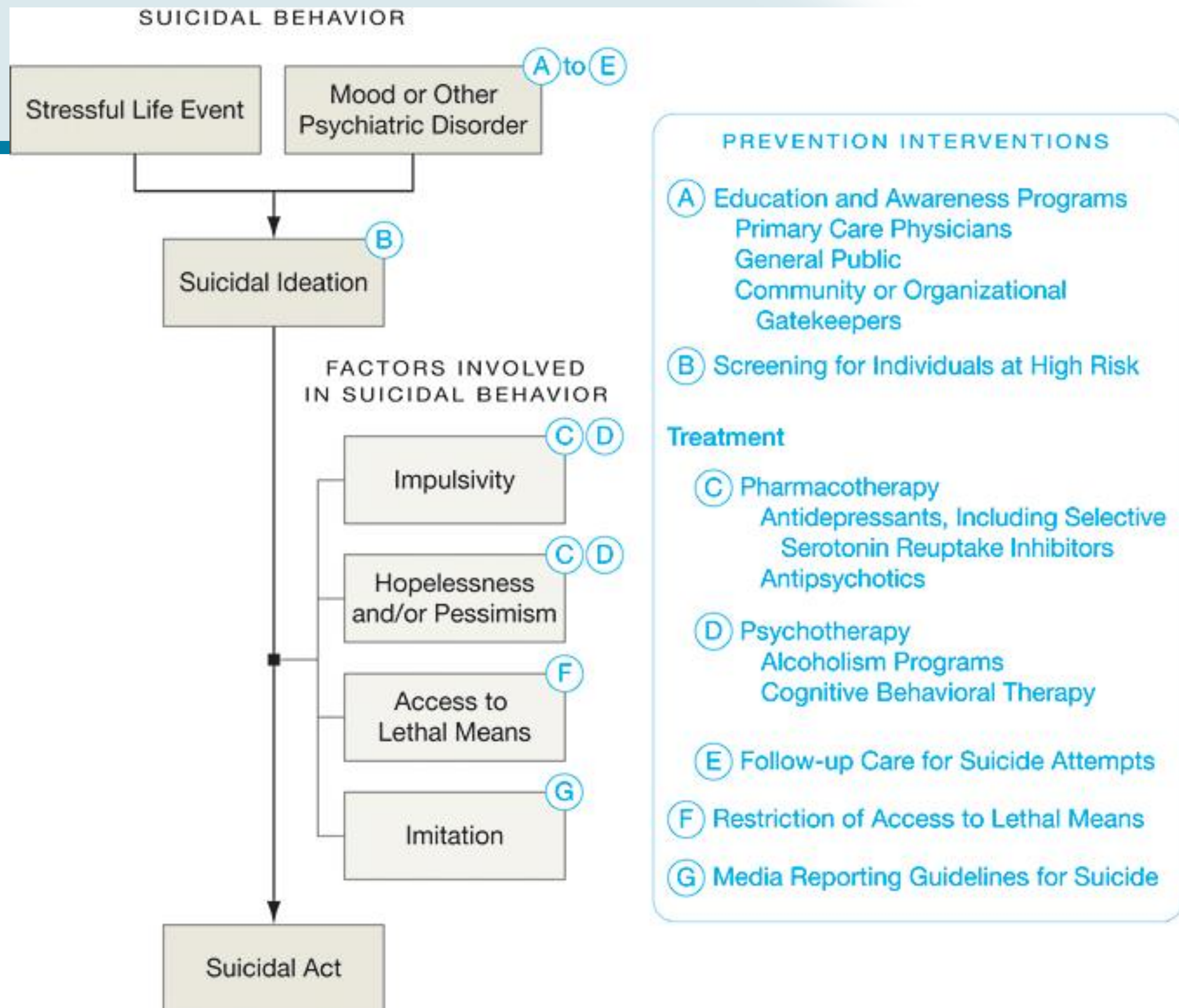
www.mghome.org

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

Targets of Suicide Prevention



Mann, J. J. et al. JAMA 2005;294:2064-2074

www.mghcme.org

Suicide Rates Reduced By:

- Educating Health Care Professionals about recognizing and treating depression.
- Restricting access to lethal methods.
- Other interventions need more evidence of efficacy.
- Ascertaining which components of suicide prevention programs are effective in reducing rates of suicide and suicide attempts is essential in order to optimize use of limited resources.

Mann, J. J. et al. JAMA 2005;294:2064-2074

Risk Management in Treatment of Depressive Disorders in Youth

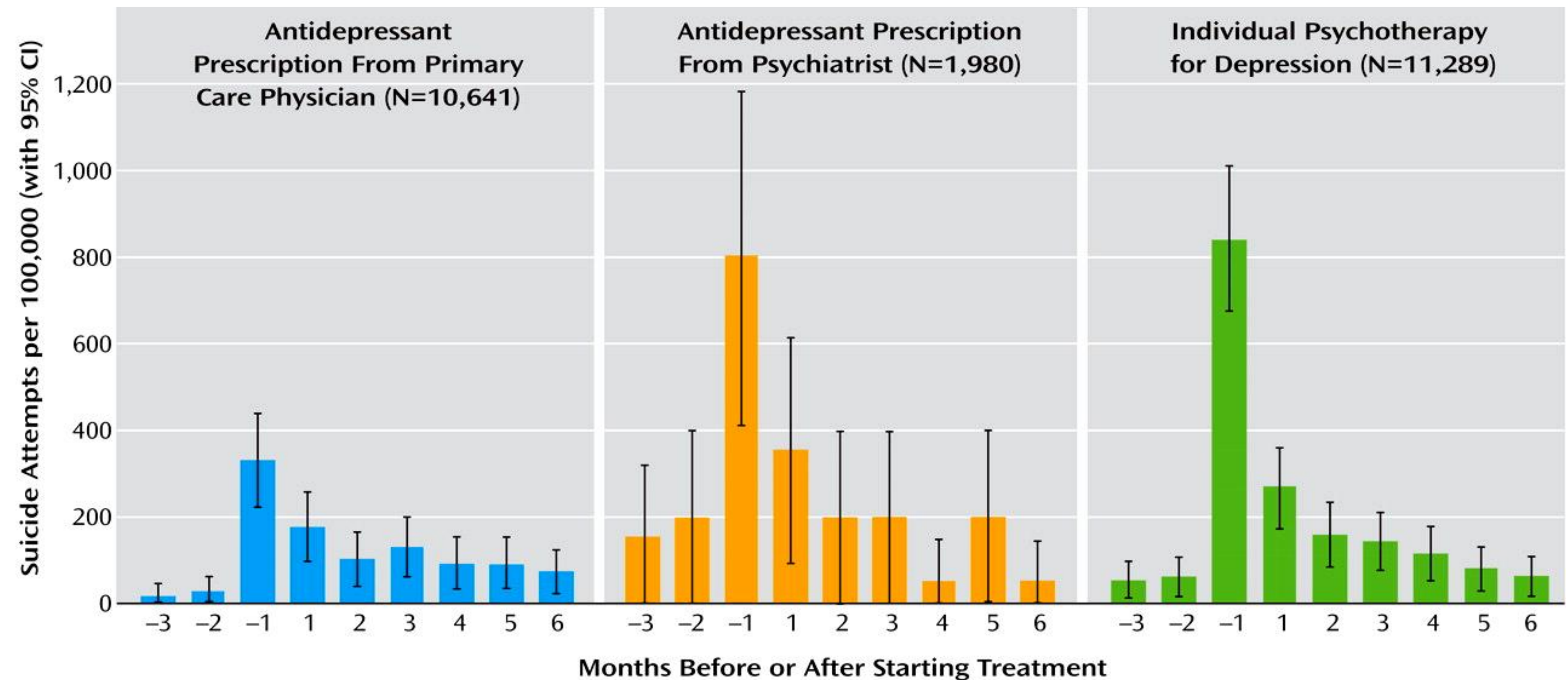
- Education is the foundation of successful treatment
  - **Correct information about depression to patient, parents, educators and others involved in the development of child**
    - **Clinical manifestations**
    - **Course and Prognosis**
    - **Treatment(s): Importance of Adherence**
  - **Remove GUNS from home**
  - **Identify available supports and how to access**
  - **Together with parents (or guardians) and patient formulate and agree on a treatment plan (including a safety plan. Consider PRACTICING this plan)**

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.

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



Simon GE and Savarino J. *Am J Psychiatry*. 2007;164:1029-34.

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

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

Supports for Clinicians, Patients & Families

- **American Psychiatric Association** **www.psych.org**
- **American Academy of Child and Adolescent Psychiatry** www.aacap.org
- American Academy of Pediatrics
- American Society for the Prevention of Suicide www.afsp.org
- **National Alliance for the Mentally Ill** www.nami.org
- **The American Association of Suicidology** **www.suicidolgy.org**
- **Mental Health Screening** www.mentalhealthscreening.org
- www.samaritains.org
- **National Suicide Prevention Lifeline 1-800-273-TALK**
- **National Adolescent Suicide Hotline** 800-621-4000
- www.suicidehotlines.com/national.html