

# Depression in Children and Adolescents

Diagnosis, Treatment, Suicide Prevention

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# Age and Depression

- Latency                      girls = boys
- By age 14                    girls 2X > boys

Birmhauer 2004



# Adolescent Depression Rates

- 1 out of 10 boys
- 1 out of 5 girls



# Prevalence - I

- n = 1420
- Starting at ages 9-13, interview each year
- End study when each child is 16
- During study:
  - 9.9% anxiety
  - 9.5% depression
  - (36.7%) at least one DSM-IV disorder



# Prevalence II

- Transition to adolescence – girls only  
↑↑ depression and social phobia
- Transition to adolescence – boys and girls  
↑ increase in panic and GAD



# Major Depressive Disorder Genetics

- One parent with major depressive disorder, 2x risk
  - 2 out of 5 girls
  - 1 out of 5 boys
- Two parents with major depressive disorder, 4x risk
  - 4 out of 5 girls
  - 2 out of 5 boys



# Family History

- Poor outcome predicted by paternal MDD (Birmhauer 2004)
- Family history shows overrepresentation of
  - Depression
  - Substance abuse
  - Antisocial disorder



# MDD

- 5 or more of:
  1. Mood
  2. Loss of pleasure
  3. Weight
  4. Sleep
  5. Motor agitation or retardation
  6. Fatigue – energy down
  7. Worthlessness or guilt
  8. Concentration
  9. Thoughts of death -- suicide



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Juvenile Depression	Adult Depression
Irritability	“Down in the dumps,” sad, empty
Reactive	Agitation or retardation
Insidious course	
Worst moods in late afternoon or early evening	Worst moods in early morning to morning



# Onset in Childhood vs. Adolescence

- Similar
  - Duration – mean 17 months
  - Rates of recovery – 85%
  - Recurrence – 40%
  - Severity and depressive symptoms
  - Comorbidity
- Different
  - More melancholic symptoms in teens

Birmhauer 2004



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# Comorbidity in Juvenile Depression

- Larger spectrum
  - Boys – Conduct disorder
  - Girls – Anxiety disorder
  - Manic symptoms “a few years” later in “substantial minority”

Biederman & Spencer 1999



# Diagnostic Difficulties

“Diagnosis (of depression) is greatly complicated by its atypical clinical picture with a reactive mood, fluctuating clinical course, high levels of irritability and aggression, high levels of oppositionalism and anxiety as well as school and behavioral difficulties.”

**Biederman & Spencer,**

**1999**



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# Major Depressive Disorder and Suicide

- Approximately 90% of suicide completers have major depressive disorder
- Substance abuse, including alcohol, worsens prognosis



# Suicide Attempts

- 1% of children under 12
- 34% of adolescent inpatients suicide attempt



# Suicide Rates

- 1,270 high school students
  - 25% of females serious suicidal ideation
  - 14% of males serious suicidal ideation
  - 8% of total attempted suicide once in the year prior
  - 2.6 % of attempts caused need for medical attention



# Methods of Suicide

- Girls more overdose, therefore greater survival
- Boys, violent means – guns, jumping from high places, hanging, car wreck; therefore less likely to survive



# Childhood Environmental Stresses - I

- Adolescent unemployment or not being a student
- Adolescent suspension from school or school drop out
- Adolescent disciplinary crisis
- Frequent moves in childhood (Denmark, June 2009)



# Childhood Environmental Stresses - II

- Family history of suicidal behavior
- Poor communication with mother or father
- Father's problem with police



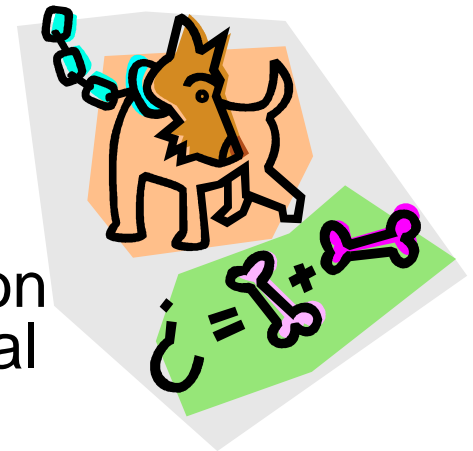
# Completed Suicide

- Suicide rates, age 5-14 years old
    - 0.6/100,000 - 2002
  - Suicide rates, age 15-24 years old
    - 13.6/100,000 – 1977
    - 9.9/100,000 – 2002
- } rate decreasing



# Treatment for Adolescents with Depression Study (TADS)

- To evaluate the effectiveness of 4 treatments for teens with MDD (N = 439)  
12 weeks of:
  - CBT plus fluoxetine (10-40 mg/d)
  - Fluoxetine alone (10-40 mg/d)
  - CBT alone
  - Placebo
- Outcome measures: Children's Depression Rating Scale-Revised (CDRS-R) & Clinical Global Impressions (CGI) Improvement score

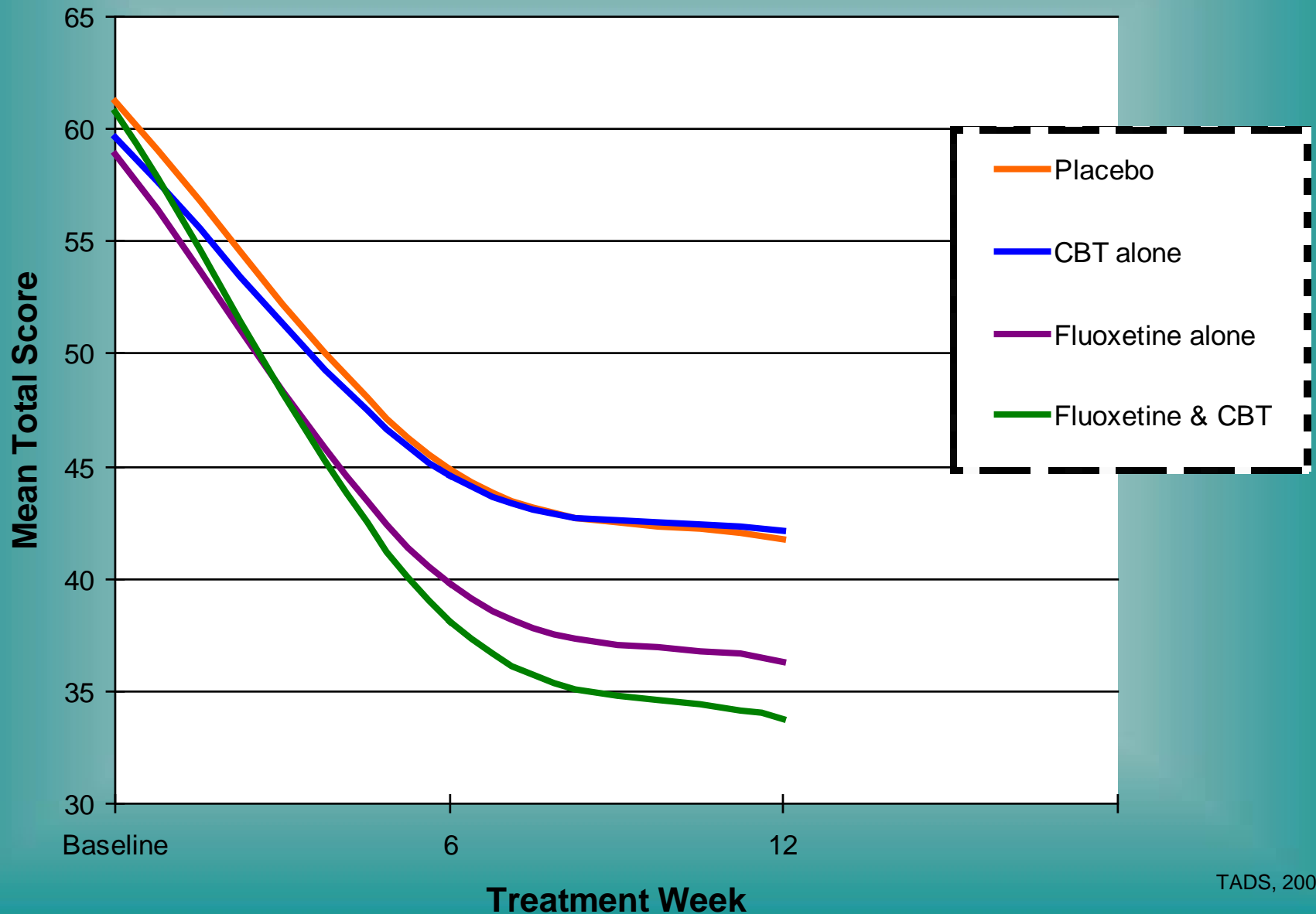


**TADS Team, JAMA, 2004**



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# Children's Depression Rating Scale Scores in the Treatment for Adolescents with Depression Study



# TADS Conclusions

- Fluoxetine + CBT was most effective in treating depressive symptoms
- Fluoxetine alone was effective, but not as effective as fluoxetine + CBT
- CBT alone was less effective than fluoxetine and not significantly better than placebo
- Suicidal ideation decreased with all treatments, improvement was greatest for fluoxetine + CBT and least for fluoxetine alone; CBT may be protective



# Suicide – Treatment

- SSRIs
- Reasons for close monitoring
  - Activation of thinking before improvement in mood
  - Mechanism of SSRIs lowering serotonin, increasing aggression



# Activation vs. Bipolar Switching

<u>Side Effect</u>	<u>Time Frame</u>	<u>Description</u>	<u>Treatment</u>
Activation	Early in treatment	↑ motor activity	Taper or discontinue
Bipolar Switching	Later in treatment after clinical benefit	↑ motor activity, mood, & impulse problems	Mood stabilizer

2001

Walkup & Labellarte,



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# Suicide Rates & Antidepressants



- Analysis of pediatric antidepressant use in a US pharmacy database
- Correlation between  $\uparrow$  regional prescribing of antidepressants and  $\downarrow$  suicide rates in 10-19 year olds

Olfson et al., 2003

- $\downarrow$  suicide rate in US in past 10 years due to gun control, better assessment and treatment of suicidal youth, and  $\uparrow$  prescribing of SSRIs in teens

Brent, *NEJM*, 2004



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# Persisting Decline in Depression Treatment after FDA Warnings

## Timeline

- October, 2003 – FDA Warning – Increased risk of suicide with antidepressants.
- February, 2005 – Boxed Warning and package insert – Pediatric
- May, 2007 – Warning extended to 18-24 year old young adults



# What is the Black Box?

- 2004 – FDA
  - Most serious warning placed in the labeling of a prescription medication
  - Requires physician to warn patients and families of the risk of suicidal thoughts & behavior when treating children & adolescents with antidepressants
  - Close monitoring (weekly in first month then biweekly in second month, then at 3 months)
  - Patient Medication Guide to be given out by pharmacist

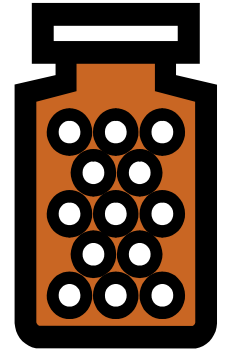


# Warning extended to young adults

- May 2006, the warning was voluntarily amended by GSK to include young adults (ages 18-24) taking paroxetine
- Based on new meta-analysis in adults including 8958 on paroxetine & 5953 on placebo
- Frequency of suicidal behavior was 2.19% on paroxetine & 0.92% on placebo



# FDA Meta-Analysis



- 21 randomized, short-term, double-blind, placebo-controlled trials of 8 drugs
- 2,298 children on drug, 1,952 on placebo
- Suicidal adverse events identified via
  - electronic search PLUS
  - blinded manual review of all serious adverse events
- Events included up to 30 days post discontinuation
- Data combined and analyzed by Mantel-Haenszel method

Mosholder & Willy, *JCAP*, 2006



# Combined Incidence Rate Ratios for Serious Suicidal Events

<u>Drug</u>	<u># Trials</u>	<u>Incidence Rate Ratio (CI)</u>
Paroxetine	5	2.19 (0.92-5.24)
Sertraline	2	2.52 (0.49-13.01)
Venlafaxine	4	1.80 (0.52-6.20)
Fluoxetine	4	0.88 (0.32-2.44)
Citalopram	2	2.54 (0.91-7.05)
Mitrazapine	1	*
Nefazodone	2	*
Fluvoxamine	1	*
MDD Trials	14	1.95 (1.19-3.21)
Non-MDD Trials	7	1.31 (0.26-6.72)
<b>All Trials</b>	<b>21</b>	<b>1.89 (1.18-3.04)</b>

\* Ratio undefined due to zero events in placebo group

Mosholder & Willy,

2006



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# Findings

78 serious suicidal adverse events

54 on drug, 24 on placebo

No completed suicides

Rate ratio of 1.89 (95% CI = 1.18-3.04)

Risk is 4% on drug and 2% on placebo

Mosholder & Willy, 2006



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# Black Box Warning is changing how antidepressants are being prescribed

- 20% ↓ in pediatric prescriptions for antidepressants
  - Positive: more care in prescribing (attention to diagnosis, use of nonpharmacologic treatments, careful monitoring including attempts to standardize the classification of adverse events)
  - Negative: children not receiving needed medications



**Rosack, *Psych News*, 2005**



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# Ambulatory Patients Studied – National Database

	Pediatric (<18)	Young Adult (18-24)	Adult
Reduction in new diagnosis of depression (2009 vs. 1999-2004)	44%	37%	29% (not targeted)

Therefore: Not only children and young adults, but **also** adults are affected by the warning.

Libby, Arch Gen Psychiatry, June 2009



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# Suicide Rates – Affected by FDA Warning

- Marked increase in 10-19 year old suicide rates in 2004. This is **NOT** a fluctuation (Bridge).
- Suicide rates among 10-19 year olds “significantly higher” than predicted based on 1996-2003 levels (CDC).

Bridge, JAMA 2008  
CDC, July 2008



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# Suicide Rates – Affected by FDA Warning

<b>Adults Mid-40s – 50s</b>			
<b>Year</b>	<u>1999</u>	<u>2002</u>	<u>2005</u>
<b>Rate</b>	12.52/100,000	13.94/100,000	16.56/100,000

Bridge, JAMA 2008

CDC, July 2008



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# AACAP Response to Black Box

- 2004 – AACAP
  - Opposed the Black Box Warning
  - Black Box would discourage families from seeking treatment and physicians from prescribing
  - URGED CHILD PSYCHIATRISTS TO CONTINUE TREATING YOUTH WITH ANTIDEPRESSANTS - USE WITH CAUTION
  - Recommended that MDs explain warning & implement FDA schedule of monitoring
  - Consider who is treating, choice of medication (fluoxetine has the most empirical evidence in youth), and how it is administered (caution in initial period, with dose change, and during taper & discontinuation)



# What explains the increased rate of suicidal events on antidepressants?



- Precursor events: activation, agitation, disinhibition, irritability, akathisia
- Induction of mania or mixed mood state
- Drug withdrawal phenomena
- Compliance issues
- More common in depressed than anxious youth
- Note: None of the trials balanced risk factors for suicidality (e.g., family history of suicidal behavior) between drug and placebo groups



# Psychological Risk Factors

- Increased rates of suicide amongst first degree relatives and second degree relatives
- First degree relatives antisocial personality disorder, assaultive behavior, substance abuse



# Long-term Factors

- Psychiatric hospitalization – nine fold higher rate of suicide in following years
- Mood disorders risk factor
- Prior suicide attempt
- Substance abuse



# Family Factors in Suicide

- Scapegoating
- Family sees the suicide as a rational solution



# Suicide – Treatment

- Psychoeducation of the family and staff
- Result – improved outcomes, lowered parental emotional distress, and enhanced family cohesion

