

Black Box Warning for Antidepressant Drugs: FDA Perspective

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Antidepressants and Suicidality Meta-Analyses at FDA

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- Chris Holland
- Alice Hughes
- Lisa Jones
- Mark Levenson
- Judith Racoosin
- George Rochester
- Marc Stone

Clinical Psychiatry, by Mayer-Gross, Slater, and Roth, London, 1960, p. 231

- “With beginning convalescence (*following initiation of treatment with tricyclic antidepressants*), the risk of suicide once more becomes serious as retardation fades.”

Pre-Psychotropic Drug References to a Risk of Suicide During the Early Recovery Phase of a Depressive Episode

- Benjamin Rush (1812) – Cautioned about suicide following apparent improvement
- George Savage (1892) – “with the entry on convalescence suicidal attempts are common”

Background on Suicidality Concerns for Antidepressants (Adult Data)

- Teicher paper on fluoxetine and suicidality (1990)
- 1991 PDAC meeting on fluoxetine and suicidality
 - Focus on adult controlled trials data
 - Conclusion: no association
- Subsequent meta-analyses showing lack of association between antidepressant use and suicidality in adults
 - Beasley, et al (1991)
 - Khan, et al (2000)
 - Strosman, et al (2001)
 - Hammad, et al (2003)

Origins of Present Concern About Emergence of Suicidality in Association with Antidepressant Use in Pediatric Patients

- Review of pediatric supplement for Paxil led to finding that events suggestive of possible suicidality were subsumed, along with other events, under preferred term “emotional lability”
- FDA issued request to GSK to separate out verbatim terms suggestive of suicidality
- Resulted in submission of report on paroxetine and pediatric suicidality to FDA, on May 22, 2003
- Report suggested increased risk of suicidality associated with paroxetine use, especially in 1 of 3 studies in pediatric major depressive disorder

Data for Peds Analysis

- 24 trials conducted in pediatric patients (4-16 weeks in duration)
- About 4400 patients overall
- Drugs - number of trials:
 - SSRIs
 - Citalopram (Celexa) - 2
 - Fluoxetine (Prozac) - 5
 - Fluvoxamine (Luvox) - 1
 - Paroxetine (Paxil) - 5
 - Sertraline (Zoloft) - 3
 - Atypical antidepressants
 - Bupropion (Wellbutrin) - 1
 - Mirtazapine (Remeron) - 1
 - Nefazodone (Serzone) - 2
 - Venlafaxine (Effexor XR) - 4

Event Categories for Classifying Possibly Suicide-Related Adverse Events

- 1--Suicide attempt
- 2--Preparatory actions towards imminent suicidal behavior
- 3--Self-injury with intent unknown
- 6--Suicidal ideation
- 10--Injuries without enough information to determine if they represented self-injury or other injury

Main Outcomes Used in the Analysis

Outcomes	Description	Number
Outcome 1	Suicidal behavior, codes 1 & 2	n=33
Outcome 2	Suicidal ideation, code 6	n=45
Outcome 3 (primary outcome)	Suicidal behavior or ideation (codes 1, 2, & 6)	n=78
Outcome 4	<u>Possible</u> suicidal behavior or ideation (codes 1, 2, 6 + 3, 10)	n=109

Robustness of the risk estimates of suicidal behavior or ideation (codes 1,2, & 6) to event ascertainment: results of outcome 4 “possible suicidal behavior or ideation”

Outcomes	Overall RR (95% CI), all trials, all indications	Overall RR (95% CI), SSRI MDD trials
Suicidal behavior or ideation (codes 1,2, & 6)	<u>1.95 (1.28, 2.98)</u>	<u>1.66 (1.02, 2.68)</u>
Possible suicidal behavior or ideation (codes 1, 2, 6 + 3, 10)	<u>2.19 (1.50, 3.19)</u>	1.91 (1.27, 2.89)

Recommendations of Psychopharmacologic Drugs and Pediatric Advisory Committees September 13-14, 2004

- Black box warning regarding suicidality risk for antidepressants in children and adolescents
 - Vote 2:1 in favor of black box
 - No support for contraindication (as done in UK and a few other EMEA countries)
 - For all antidepressants (not limited to those included in meta-analyses)
 - Recommended medication guide
- Look at adult data for antidepressants

FDA Requested Labeling Changes Regarding Pediatric Suicidality (for all antidepressants)

- **Boxed warning**
 - Antidepressants increased risk compared to placebo of suicidality.....
 - Anyone considering use.....balance risk and clinical need
 - Monitor appropriately and observe closely...
- **Medication Guide**

Antidepressants and Suicidality in Adults



Antidepressants Studied

<i>SSRIs</i>	<ol style="list-style-type: none">1. Citalopram (Celexa®)2. Escitalopram (Lexapro®)3. Fluoxetine (Prozac®)4. Fluvoxamine (Luvox®)5. Paroxetine (Paxil®)6. Sertraline (Zoloft®)
<i>Non-SSRIs</i>	<ol style="list-style-type: none">7. Bupropion (Wellbutrin®)8. Duloxetine (Cymbalta®)9. Mirtazapine (Remeron®)10. Nefazodone (Serzone®)11. Venlafaxine (Effexor®)

C-CASA Event Classification

<i>Events</i>	<i>Coding</i>
Completed suicide	1
Suicide attempt	2
Preparatory acts	3
Suicidal ideation	4
Self-injurious behavior, intent unknown	5
Not enough information (Fatal)	6
Not enough information (Non-Fatal)	9

The numbering above represents a ranking of event severity, and only the most severe event per patient was submitted in the datasets

Study Indication Groups

1. Major depressive disorder (MDD)
2. Other depressive disorders
3. Other psychiatric disorders
4. Behavioral disorders
5. Other disorders

Non-MDD
Indications

Analysis Populations

Primary: “Psychiatric Indications”

Major depressive disorder

Other depressive disorders

Other psychiatric disorders

Secondary

The indication groups considered individually
(major depressive disorder, other depressive
disorders, other psychiatric disorders,
behavioral disorders, other disorders)

Primary Endpoint

Suicidal Behavior and Ideation

- Completed suicide
- Suicide attempt
- Preparatory acts
- Suicidal ideation

Primary Analysis Method

“Exact method” for common odds ratio

- Stratified method
- Handles low event counts and small trial sizes
- Assumes a common odds ratio across trials
- Does not make use of trials with no events

Subgroup Analysis

Performed on subject- and trial-level characteristics

- Age group
- Gender
- Race
- Drug type: SSRI vs. non-SSRI
- Location: North America vs. other
- Setting: in-patient/out-patient vs. out-patient only

Trial Indication Groups

Indication	Trials	
	n	Subtotal
Major Depressive Disorder	162	162
Other Depressive Disorders	25	187
Other Psychiatric Disorders	108	295
Behavioral Disorders	43	338
Other Disorders	34	372

Psychiatric Indications

Events

Psychiatric Indications

Event	Treatment Group			Total N=77382
	Placebo N=27164	Test Drug N=39729	Active Control N=10489	
Completed suicide	2	5	1	8
Suicide attempt	44	71	18	133
Preparatory acts	3	3	4	10
Suicidal ideation	147	169	42	358
Total Events	196	248	65	509



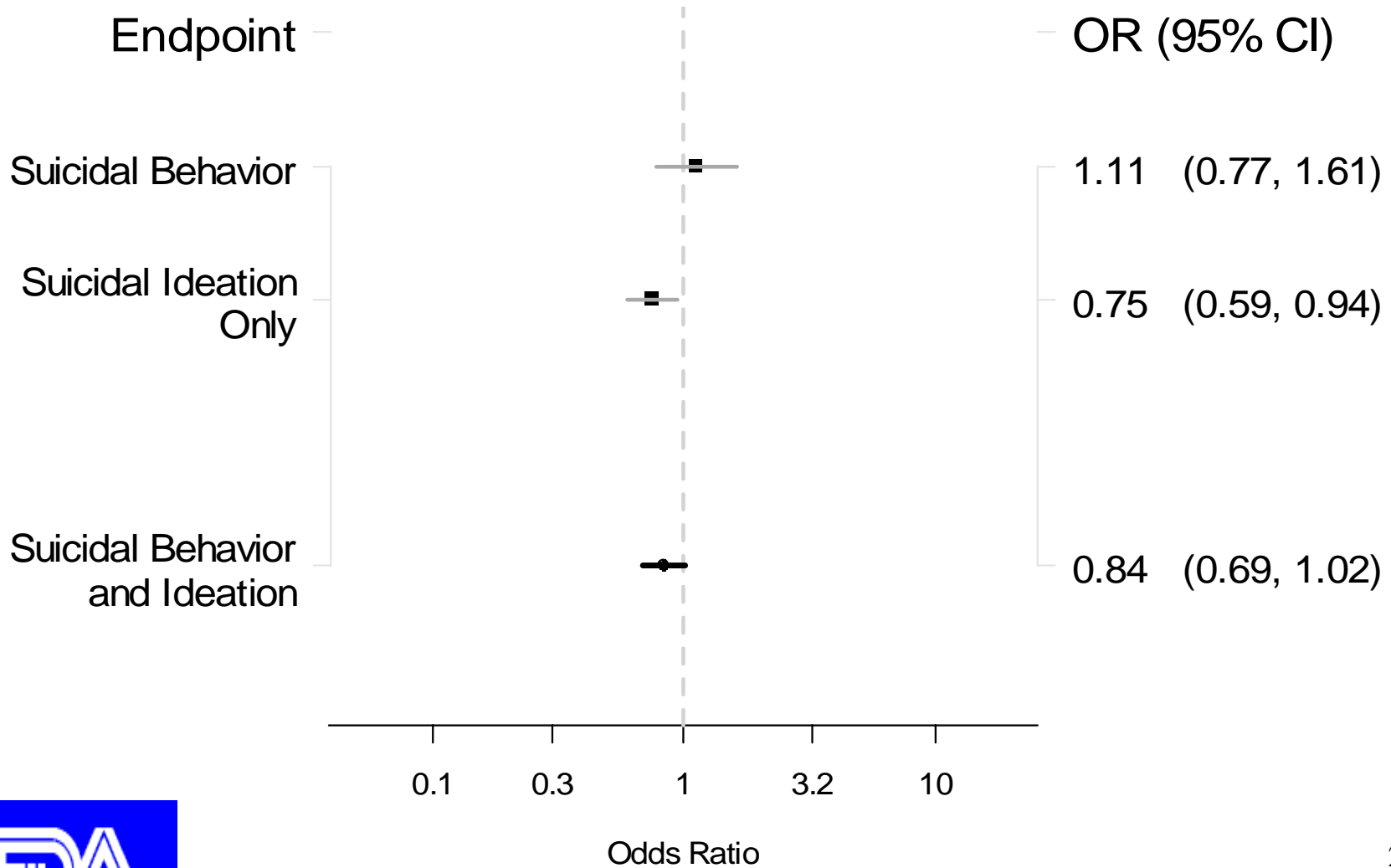
Suicidal Behavior and Ideation Psychiatric Indications

Placebo: 0.72% of subjects with event

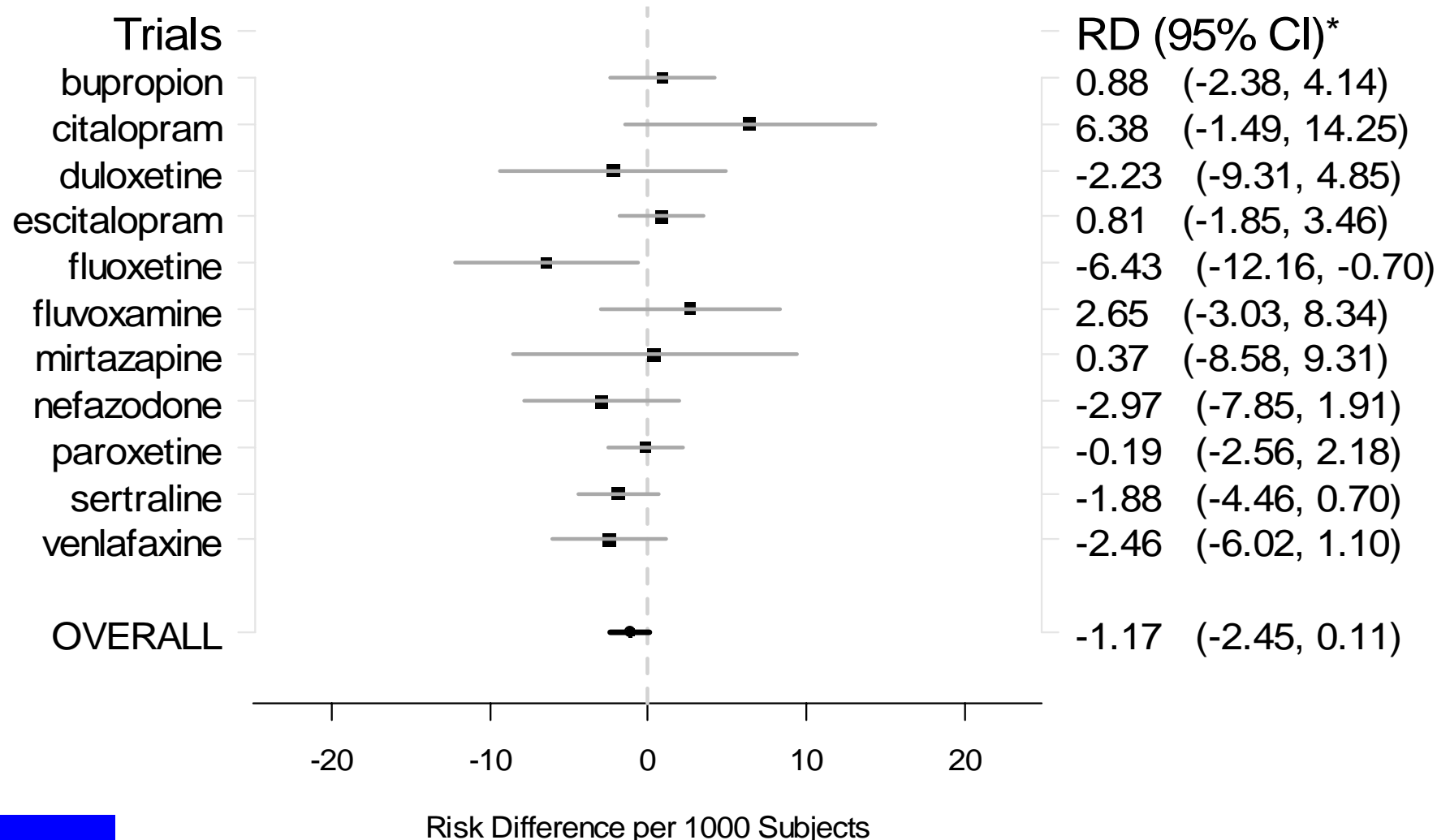
Test Drug: 0.62% of subjects with event

$174/295 = 59\%$ trials had reported events

Psychiatric Indications Odds Ratio

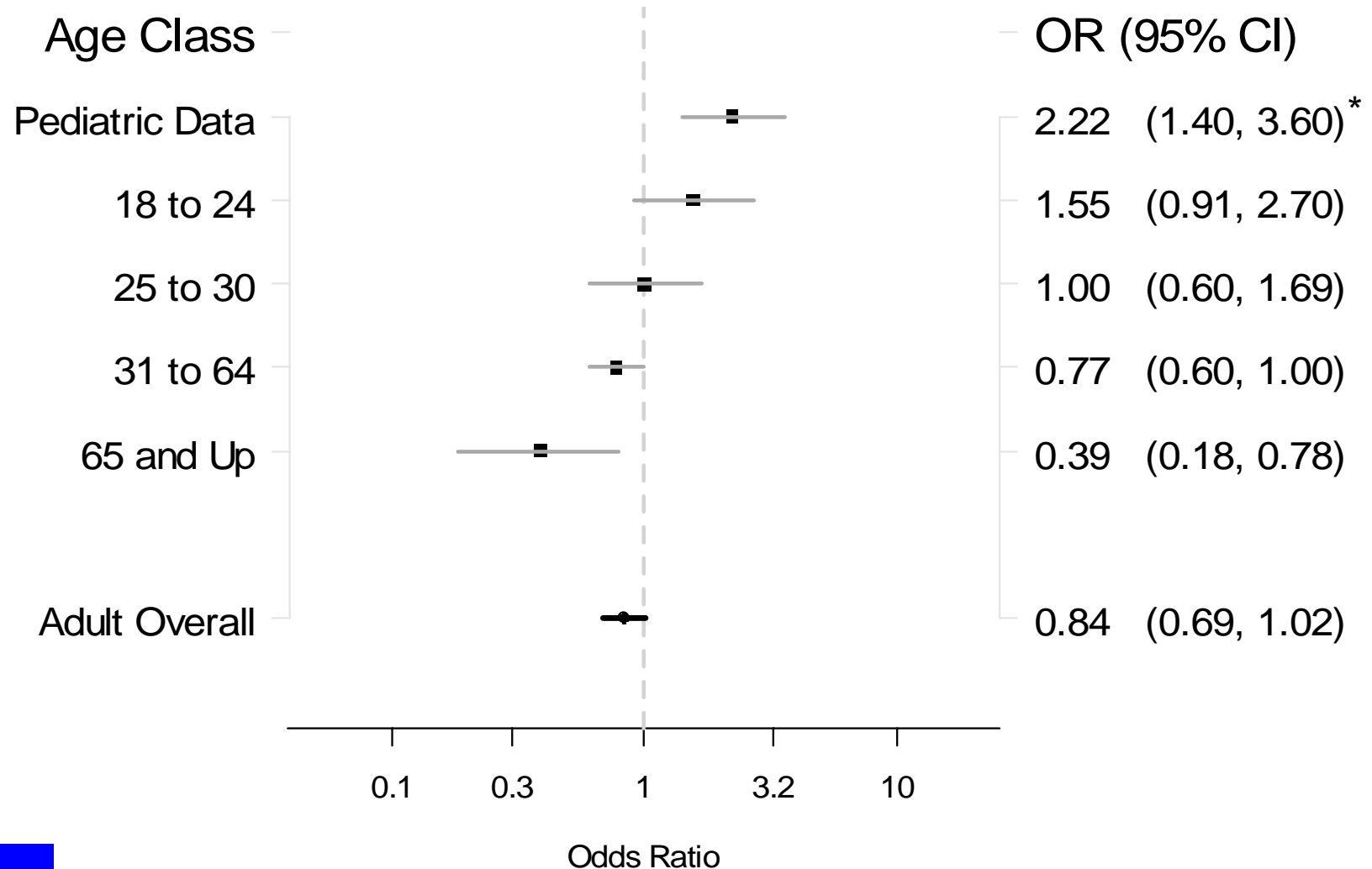


Suicidal Behavior and Ideation Psychiatric Indications Risk Difference



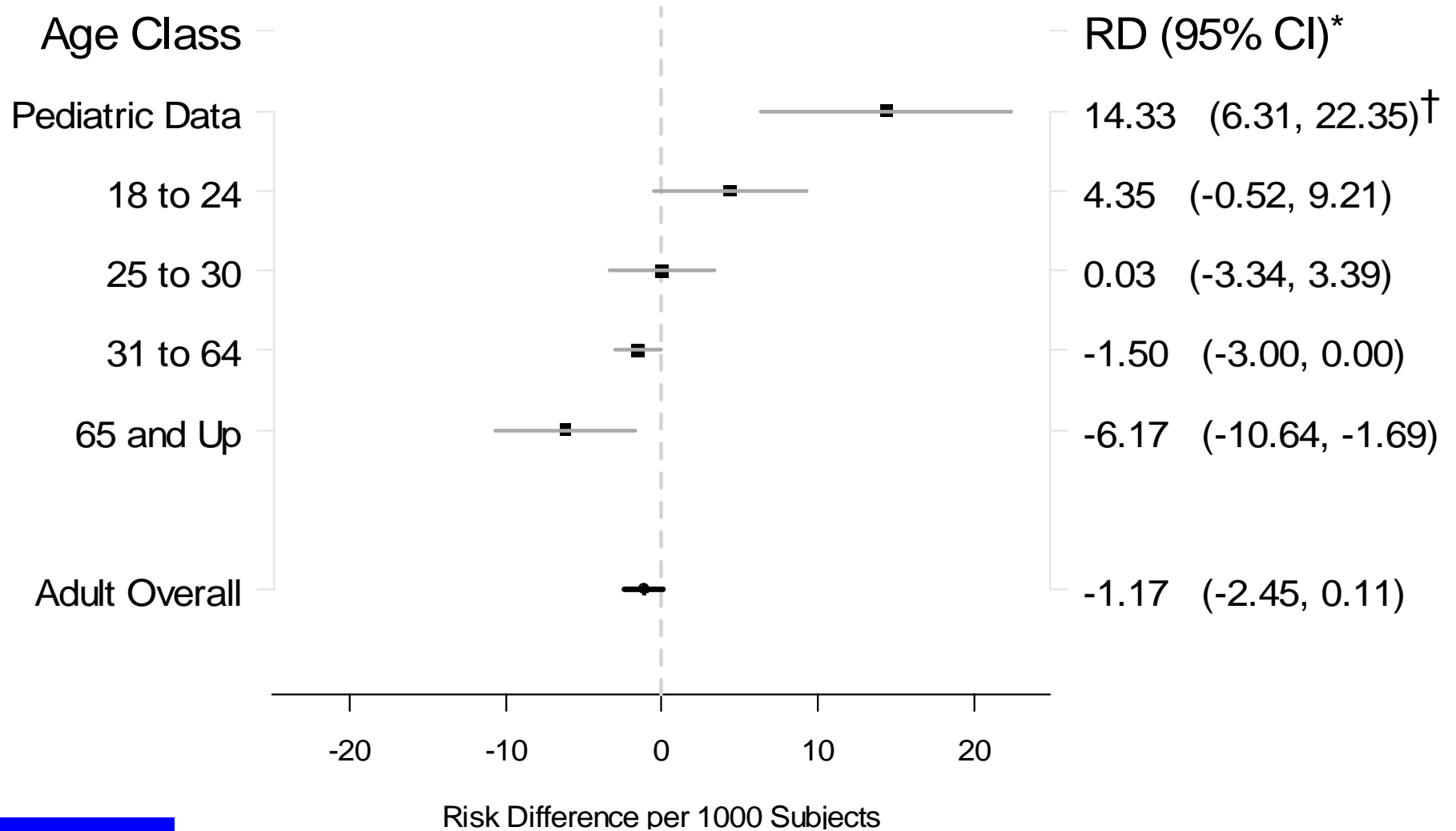
* Per 1000 subjects

Suicidal Behavior and Ideation Psychiatric Indications Odds Ratio



* Reanalysis of FDA/Hammad 2004 data

Suicidal Behavior and Ideation Psychiatric Indications Risk Difference



* Per 1000 Subjects. † Reanalysis of FDA/Hammad 2004 data.

Additional Subjects with Suicidal Behavior and Ideation (Per 1000 Subjects)

Age Class	Estimate	95% Interval
Pediatric Data	14	(6, 22)
18 – 24	4	(-1, 9)
25 – 30	0	(-3, 3)
31 – 64	-2	(-3, 0)
65 and up	-6	(-11, -2)
Adult Overall	-1	(-2, 0)

Summary of Adult Analysis

- Primary analysis population and endpoint
OR = 0.84 (95% CI: 0.69, 1.02)
- Clear pattern in the estimates with increasing age
- Other subgroups (gender, race, location, setting, drug class) do not have notable effect
- Results are not sensitive to method

An Additional Exploratory Finding From Adult Data

- A suggestion of an even stronger signal of suicidality in the < 25 group coming from the non-depressed psychiatric patients (mostly for behavior)
- Clinical Implication: Important to observe for suicidality in younger patients getting antidepressants for other psychiatric indications (anxiety disorders, etc) or any other indication, as well as depression

Does Not Appear to be Ascertainment Bias

- **Argument:** Patients who get antidepressants talk more about their suicidality or are detected because of other AEs
- **Counter-Arguments:**
 - May also expect placebo bias
 - Age-relatedness of finding
 - Stronger finding in non-depressed psychiatric patients
 - Finding is stronger for behavior than for ideation
- We think these findings are real (even though public health implications and mechanism unclear)

Recommendations of Psychopharmacologic Drugs Advisory Committee December 13, 2006

- Add new information to warnings:
 - Suicidality risk extends to young adults (<25)
 - No net effect ages 25-65
 - Reduced suicidality in > 65 group
- Emphasize in warning statement that depression itself is a strong predictor of suicide
- Changes implemented in 2007

Controversial Environment for Considering Antidepressant Suicidality Data

- Emotionally charged atmosphere at FDA advisory committees (both 2004 & 2006)
- Attacks on FDA in various media
- Attacks from patient “advocacy groups”
- Continuous propaganda from plaintiff’s bar
- Political theater in congressional hearings
 - Energy and Commerce Committee: 9-23-04

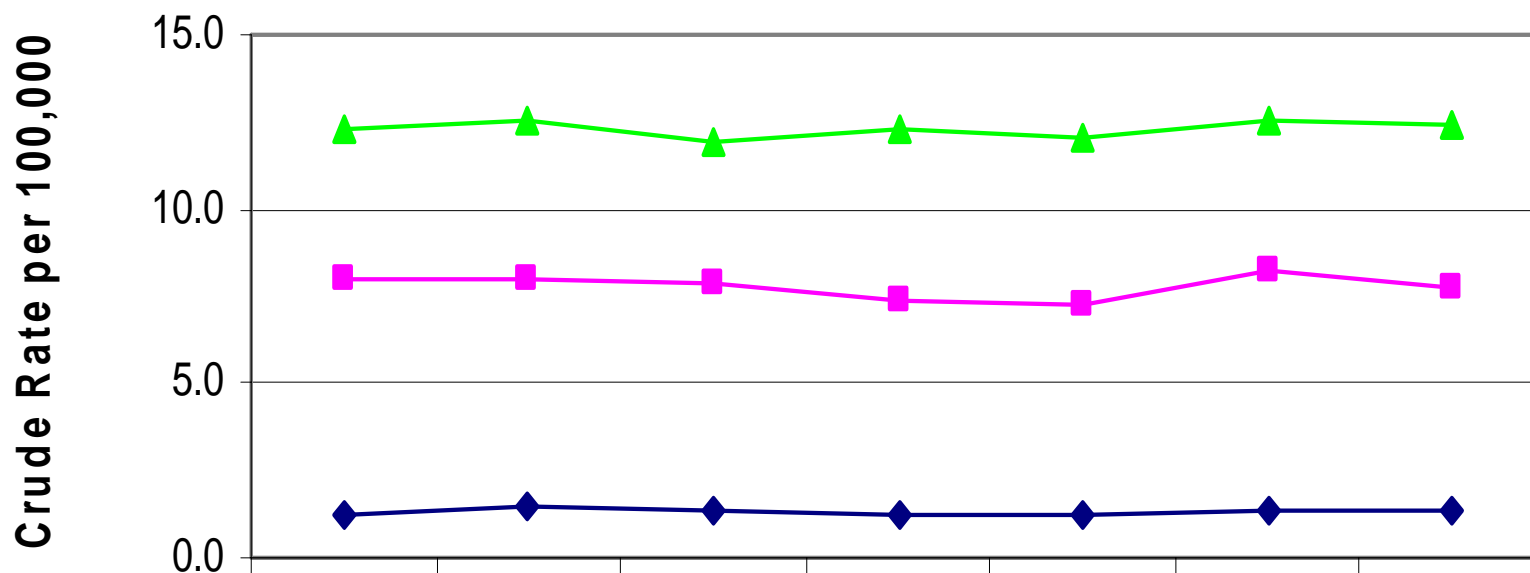
FDA's Decision to Implement Black Warning for Antidepressants

- Basis for Decision
 - Data from meta-analyses
 - Advisory committee votes

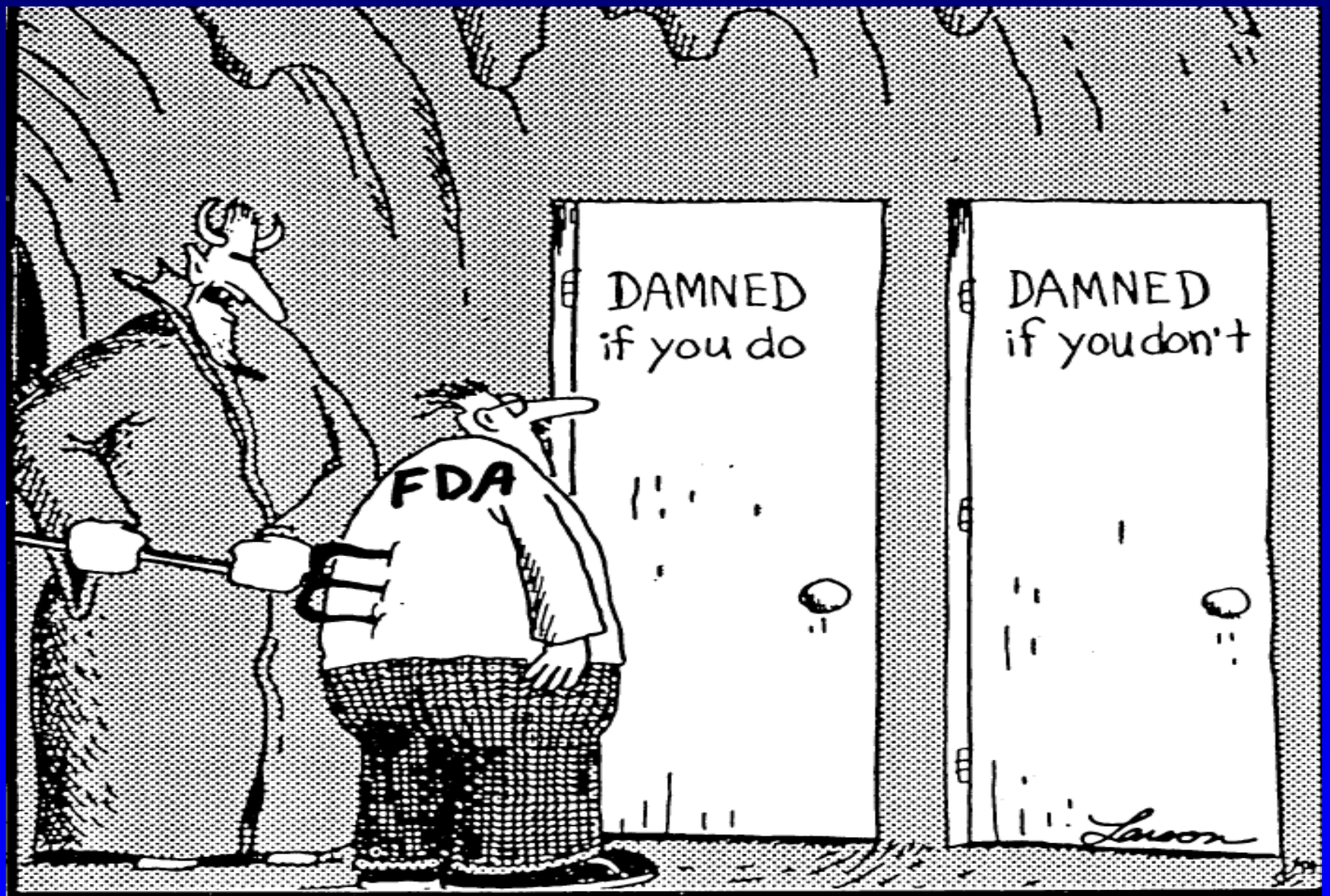
Current Concerns in Psychiatric Community

- Antidepressant prescribing in pediatric patients has declining somewhat
- Appears to some decline in diagnosing of pediatric depression
- CDC adolescent suicide data:
 - Uptick in 2004 for first time in 15 years
 - 2005 data still slightly above 2003, but down from 2004

United States Suicide Rates 1999 - 2005



	1999	2000	2001	2002	2003	2004	2005
◆ Ages 10-14	1.2	1.5	1.3	1.2	1.2	1.3	1.3
■ Ages 15-19	8.0	8.0	7.9	7.4	7.3	8.2	7.7
▲ Ages 20-24	12.3	12.5	11.9	12.3	12.1	12.5	12.4



“C’mon, c’mon—it’s either one or the other.”

What Is FDA Doing to Monitor Impact of Black Box Labeling Actions for Antidepressants?

- Monitor suicidality data from CDC, scientific literature, and other sources
- Monitor antidepressant use data (large FDA effort currently underway to try to track and better understand changes in prescribing)

What Would Influence FDA to Further Modify Antidepressant Black Box Labeling?

- New evidence
 - E.g., Black box modified in 2007 to add data from adult analysis, including mention of beneficial effect in elderly and emphasis on risks associated with depression itself

Implications of Recent Suicidality Findings for Ascertainment for Suicidality in Future Drug Trials

- FDA is in process of revising policy regarding what is needed to ascertain for suicidality in trials for psychiatric drugs
- For trials involving antidepressants we have asked for some approach beyond spontaneous reporting, e.g., Columbia-Suicide Severity Rating Scale (C-SSRS)
- These requirements will likely be extended to other psychiatric drug classes and indications