

The Revised Black Box Warning for Antidepressants and Suicidality

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FDA Psychopharmacologic Drugs Advisory Committee: Antidepressants and Suicidality

FDA PDAC - Reviewed data on fluoxetine in 1991

UK MHRA - Warning for children and adolescents: June, 2003
Risks of A/Ds outweigh benefit (except for fluoxetine)

FDA PDAC - February, 2004: Pediatric Data – 23 RCTs (15 MDD)

- N=4361 (0 deaths)
- 3 of 15 MDD RCTs positive for efficacy

FDA PDAC - September, 2004: Pediatric Data – Suicidality reclassified

- 24 RCTs (16 MDD); N=4582 (0 deaths)
- Meds vs Placebo: Odds Ratio=2.22 (95% CI: 1.40-3.60)
- March, 2005: **FDA Black Box** for pediatric use of A/Ds
 - * Risk/benefit ratio

FDA Psychopharmacologic Drugs Advisory Committee: Antidepressants and Suicidality

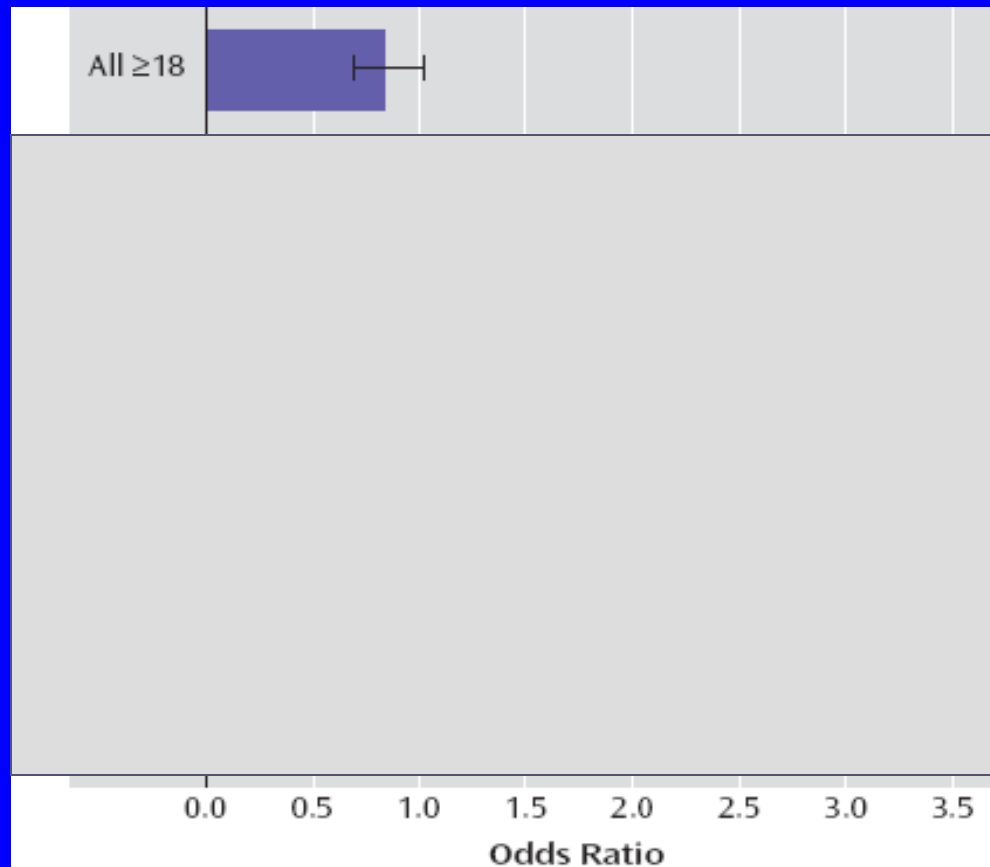
FDA PDAC - December, 2006: Adult Data – 372 RCTs

- N=99,839 (8 deaths: 5 Investigational, 2 PLA, 1 Comparator)
- N=77,382 with MDD & other psych dx -- 295 RCTs

- PDAC voted 6-2 in favor of warning, but with caveat:
 - Warn that untreated MDD is a known risk

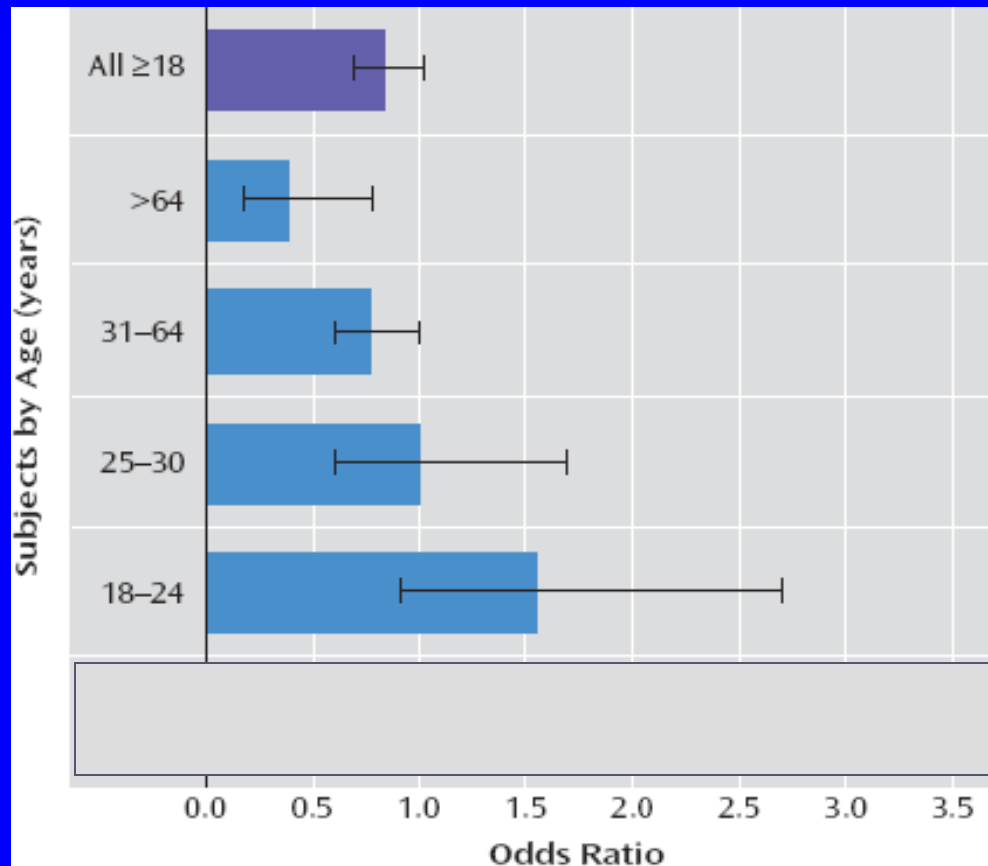
- * May, 2007: **FDA Black Box** extended to young adults

Odds of Suicidal Ideation or Behavior



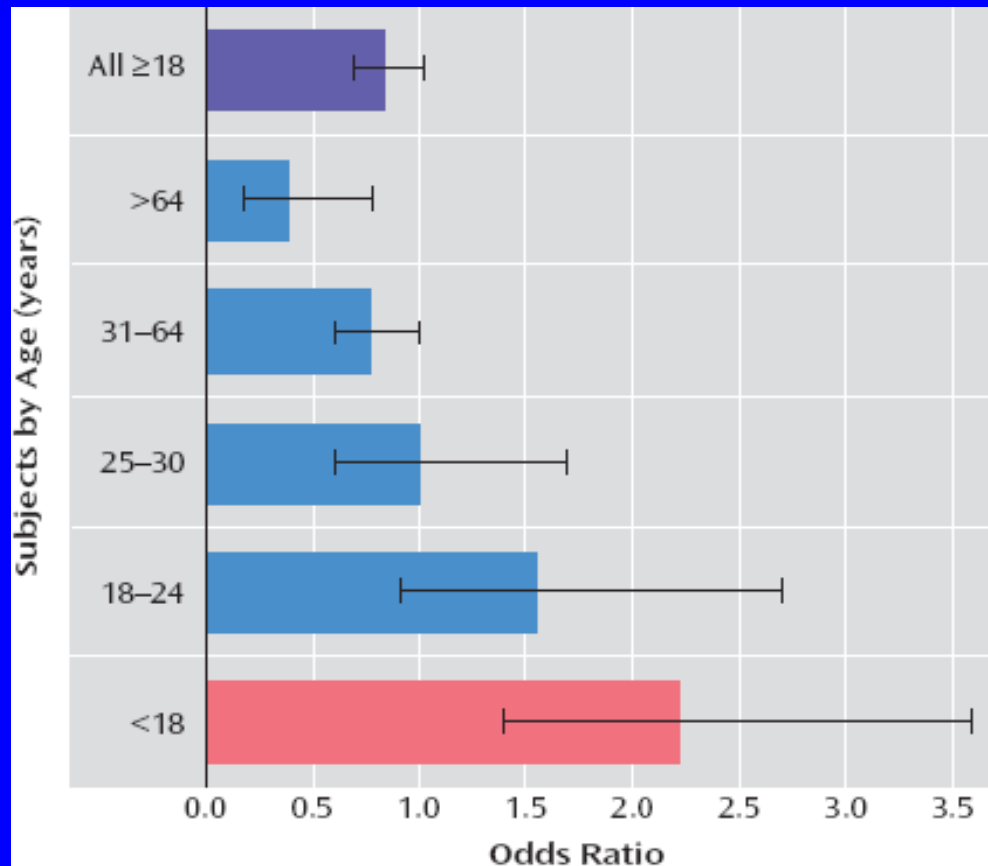
Odds of suicidality among Ss randomized to antidepressants relative to placebo. FDA, 2006

Odds of Suicidal Ideation or Behavior



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FDA's Challenge

Balance

- Risks of mandating black box warning
- Benefits of black box warning - a *class warning*

Fear an unintended consequence

- Reduced antidepressant use
- Increase in suicides - that black box was to prevent

Excerpt from the Revised Labeling for Antidepressant Use in
Children, Adolescents, and Adults (US FDA, 2007)

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders.

Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must **balance this risk with the clinical need**. ... **Depression** and certain other psychiatric disorders are themselves **associated with increases in the risk of suicide**.

Patients of all ages who are started on antidepressant therapy should be **monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.

Strengths of FDA Analyses

- Safety Analyses of rare events require broad medication exposure (N=77,382 with MDD & other psych dx were randomized)
- Pattern of risk across the age groups looks real
- Convergence of results from 2 independent analyses:
 - FDA Safety and FDA Biometrics groups used different statistical approaches
- Extensive Sensitivity Analyses
 - Sensitivity of results to alternative data analytic assumptions

Threats to the Validity of FDA Analyses

- Confounding by Indication
- Suicidality assessed with spontaneous A/E reports
 - Ascertainment bias
- Limited generalizability
 - 4-8 week RCTs
 - Restrictive inclusion criteria - inapplicable to those with subthreshold dx, comorbidity or other meds

Rationale for Mandating a Black Box for 18-24 yr

- Do data provide clear evidence of risk of suicidality?
- Do data provide evidence that risk can be ruled out?
- FDA erred on side of caution
 - Let the *informed* prescriber and patient beware
- Is there consensus?

Impact of Black Box is Uncertain

- No dispute about need for monitoring
 - Dispute centers on method to promote monitoring
- No ideal data to predict impact of black box
 - RCTs provide best available

CDC: US Suicide Data

	<u>2004</u>	<u>2005</u>	<u>change</u>
All ages	32,439	32,637	+0.6%
5 to 14	285	272	-4.6%
15 to 24	4316	4212	-2.4%
25 to 44	11,712	11,540	-1.5%
45+	16,115	16,605	+3.0%

CDC, WISQARS, Feb. 2008

Is the Black Box Warning Appropriate?

- Clinical Considerations
- Role of Meta-Analysis for Safety and Efficacy
- Patient and Family experience
- Legal Implications
- Regulatory Basis