

“Proof” in Medicine: The Role of Research Synthesis

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**What Can Be Learned from Public Health
on the Role of Research for
Policy Purposes?**

PROBLEM:

Generating and evaluating evidence
about drug safety

Not unlike the problem of generating
and evaluating evidence to establish
a causal link between

smoking and lung cancer

Jerry Cornfield

"If we ask for "proof" in medicine
we may be asking for something that
does not exist."

". . . [T]he evidence for a causal
relationship can be made strong but
can not be regarded as proved."

Public Health Model

Evidence for “Cause-and-Effect” Relationships Includes:

- **Strength of Association**
- Dose-Response relationship
- **Plausibility** – plausible biological mechanism
- **Consistency** – replication in different settings using different methods
- Elimination of **alternative explanations** for the observed association

(Hill, 1965)

Alternative Explanations:

“If important alternative hypotheses are compatible with available evidence, then the question is unsettled *even if the evidence is experimental*.

But, if only one hypothesis can explain all the evidence, then the question is settled, *even if the evidence is observational*.”

Cornfield

THE ROLE OF RESEARCH SYNTHESIS

- Every scientific investigation takes place in the context of uncertain evidence about a question of interest
- Rarely does one study produce an unequivocal and durable result.
- Research synthesis plays a central role in this process by providing a systematic approach to the **accumulation** and **evaluation** of evidence

Case Study

Do Antidepressants Cause Suicidality in Children?

- I. Summary of the FDA Evidence
- II. Alternative Explanations
- III. Other Source of Evidence

Introduction

October 2004 FDA issued a **black box** warning re use of antidepressants

“caution[ed] . . . about an increased risk of suicidal thinking and behavior in children and adolescents . . . who are taking antidepressant medication”

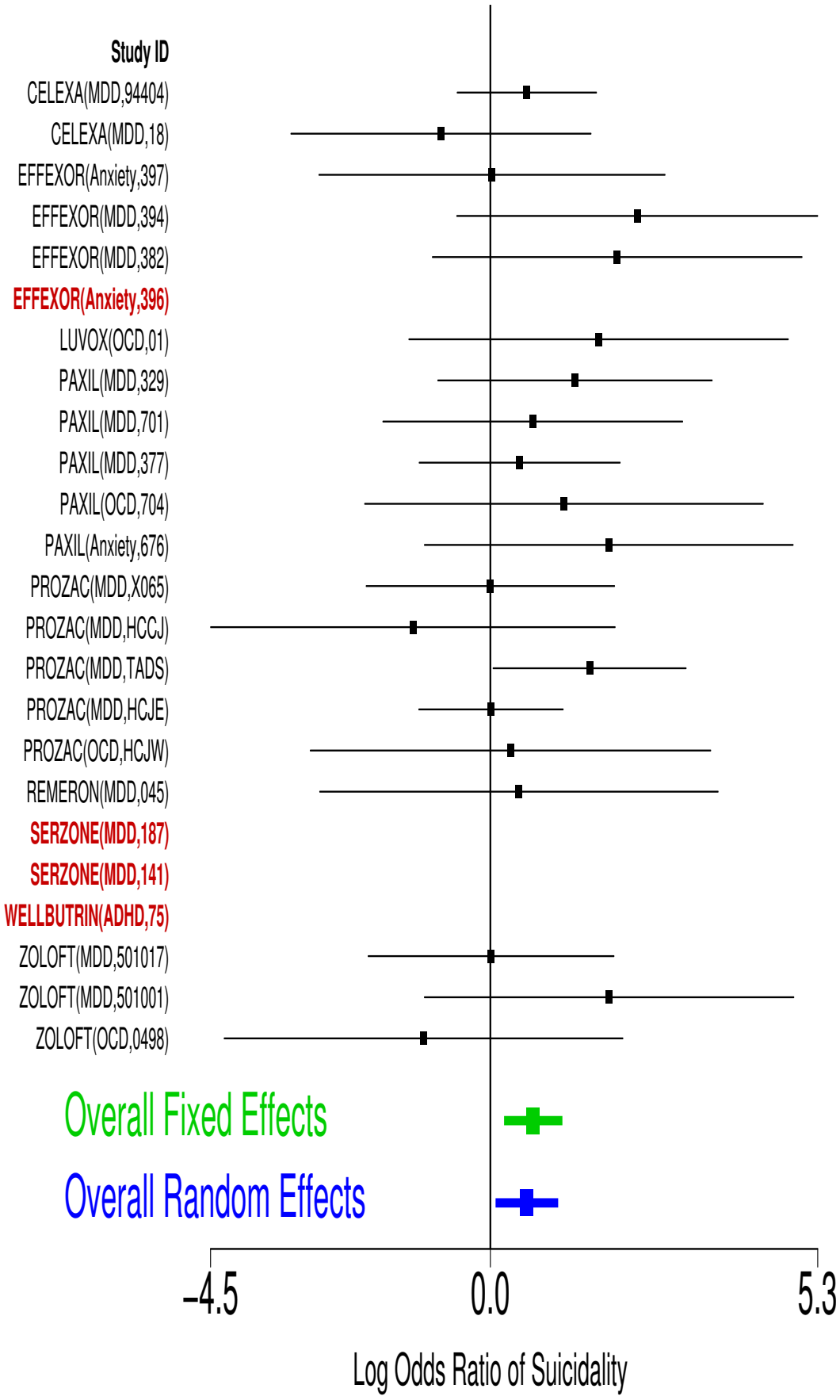
I. FDA Meta-Analysis

FDA Database

- 24 Randomized Placebo-Controlled Trials
 - 23 industry sponsored efficacy trials
 - 1 NIMH multi-site trial - TADS
- 4,582 total children and adolescents studied
- Outcome
 - **No completed suicides**
 - FDA outcome: Suicidality = Suicidal Behavior and/or Ideation (n = 87)
 - Retrospectively assessed

Study-Level Characteristics

Drug Class	# Studies	Diagnosis	# Studies
SSRI	16	MDD	16
Celexa	2	OCD	4
Luvox	1	Anxiety	3
Paxil	5	ADHD	1
Prozac	5		
Zoloft	3		
Atypical	8	Trial Length (4-16 wks)	# Studies
Effexor	4	≤ 8 weeks	13
Remeron	1	≥ 9 weeks	11
Serzone	2		
Wellbutrin	1		



FDA Results*

<u>Model</u>	<u>Odds Ratio</u>	<u>95% Confidence Interval</u>
Fixed Effects	2.0	[1.3, 3.1]
Random Effects	1.8	[1.1, 2.9]

*Excludes all studies with 0 events

FDA Meta-Analysis - Conclusions

FDA Scientific Advisory Committee (Leslie et al. 2005)

“. . . there is a **causal link** between newer antidepressants and pediatric suicidality”

FDA issues **black box** warning

THE ROLE OF META-ANALYSIS

STRENGTHS

- Pooling of Results Across Studies

When outcomes are rare, no single study is large enough to provide enough events

- Cross-study Heterogeneity

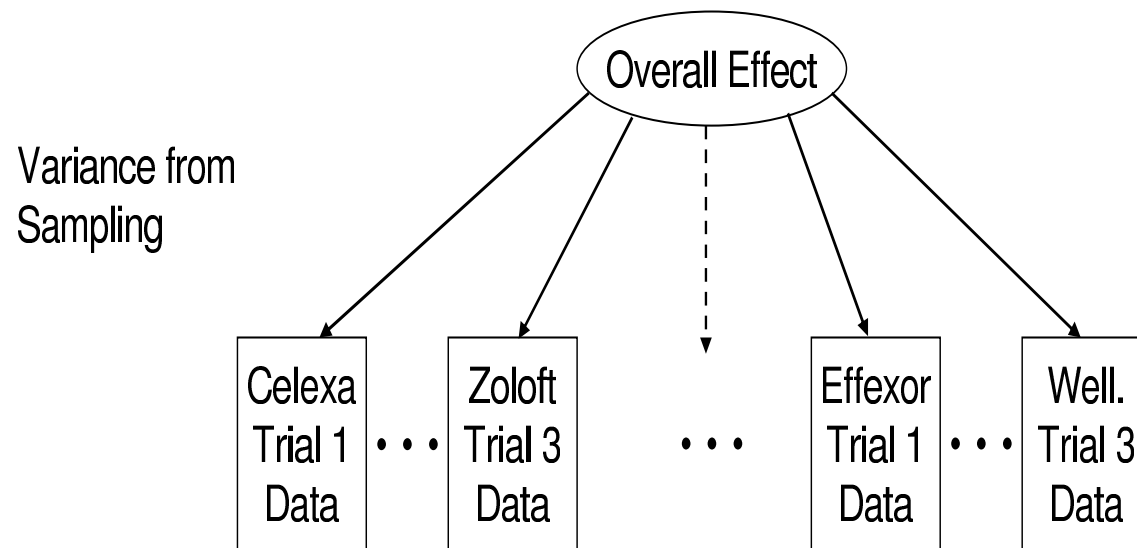
Ability to study how the effect varies across study-level covariates

THE ROLE OF META-ANALYSIS (con't)

LIMITATIONS

- Meta-analysis is an **observational study**
 - *e.g.*, Can not randomly assign studies to different subgroups
- What we can learn from a meta-analysis is defined solely by the underlying primary studies
 - *e.g.*, RCTs typically have restrictive inclusion/exclusion criteria, limitations on generalizability, and narrowly focused questions
- FIXED EFFECTS MODEL implies that each study is a random sample from the same population of studies and subjects, and that any differences in effect sizes across studies is due to sampling variability.

Fixed Effects Model



Do antidepressants **cause** suicidality in children?

Based on the meta-analysis of RCTs we *may* have evidence for an association between antidepressant use and suicidality but is there sufficient evidence for a cause-and-effect relationship?

Part II. Alternative Explanations

Part III. Other Sources of Evidence

II. ALTERNATIVE EXPLANATIONS

Selection Effects - E.g., RCT Exclusion Criteria

Issue: Patients at high risk of suicide were excluded from the RCTs

- Generalizability?

Is the target population different from the RCT population?

- Impact on Evidence?

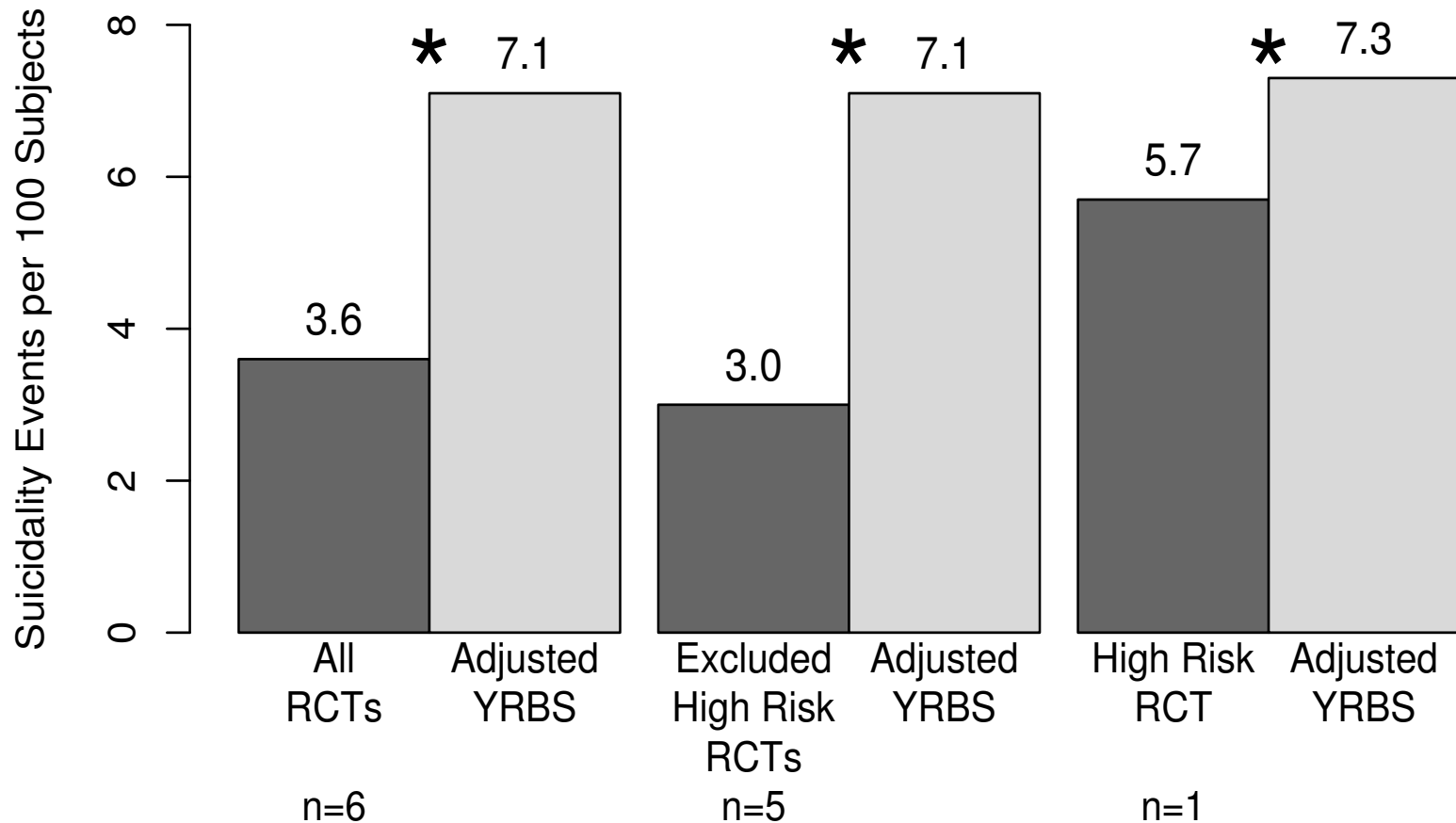
Generalizability

Youth Risk Behavior Surveillance System (YRBSS)

- Includes a complex probability survey of 9th-12th graders in public and private schools conducted by CDC biennially since 1991
- Monitors health-risk behaviors among youth and young adults, including behaviors that contribute to unintentional injuries, violence, and suicidality
- **OUR GOAL:** To compare the suicidality rates in the FDA RCT database to that of a nationally representative sample, using the
 - 1999 YRBSS
 - RCTs of adolescents (9-12th graders)

YRBSS: Generalizability

8 Week Suicidality Rates: RCTs vs. Adjusted YRBS



* The difference in suicidality rates is statistically significant, $p < 0.001$.

Impact on Evidence (Weisberg et al, 2009)

Effect of the exclusion of high risk patients:

- (i) **Deflate** placebo group response rate
 - (ii) No effect on treated group response rate
- ⇒ EFFECT: Observed increased RR may be due to a **selection effect**

Model:

π_{targ}^c Target Probability Response – Placebo Group

π_{obs}^c Observed Probability Response – Placebo Group

γ Degree of selection favors those who would **not** experience an event if assigned to placebo group

SELECTION MODEL: PLACEBO RESPONSE RATE

$$\pi_{obs}^c = \frac{\pi_{targ}^c}{\pi_{targ}^c + \gamma(1 - \pi_{targ}^c)}$$

$$\gamma = 1 \Rightarrow \pi_{obs}^c = \pi_{targ}^c \quad RR_{obs} = RR_{targ}$$

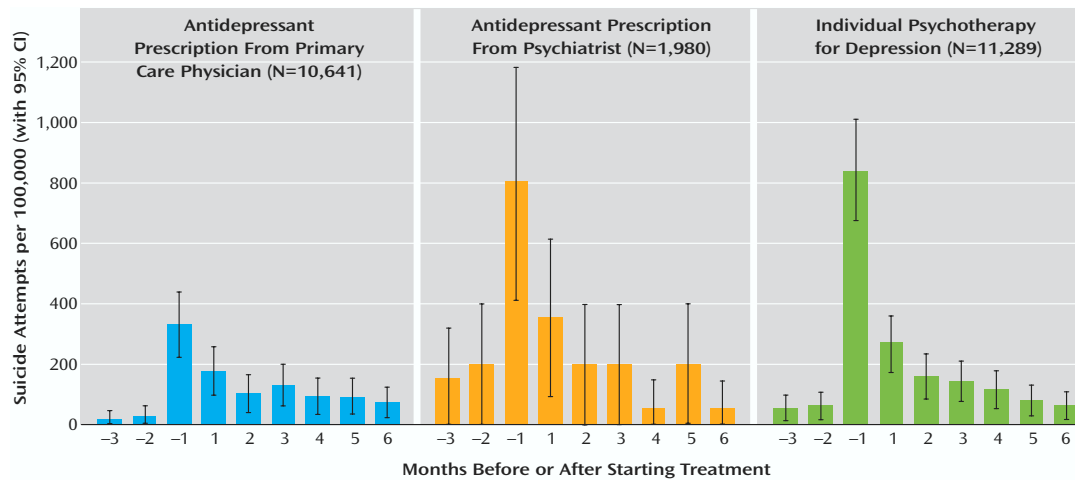
$$\gamma > 1 \Rightarrow \pi_{obs}^c < \pi_{targ}^c \quad RR_{obs} > RR_{targ}$$

III. OTHER SOURCES OF EVIDENCE

EXAMPLES:

- Bridge et al (*AJP*, 2005) psychotherapy trial
- Bridge et al (*JAMA*, 2007) risk/benefit analysis
- Claims Data
 - Valuck et al (25,000 new MDD, children \leq 18 yo)
 - Simon et al (65,000 treatment episodes)

FIGURE 2. Risk of Suicide Attempt or Possible Suicide Attempt Before and After Starting Treatment Among Adolescents and Young Adults (age less than 25 years) Receiving New Antidepressant Prescriptions From Primary Care Physicians, Receiving New Antidepressant Prescriptions From Psychiatrists, or Starting Individual Psychotherapy for Depression



THE ROLE OF RESEARCH SYNTHESIS CONCLUDING REMARKS

Methodology

1. Meta-Analysis is an observational study - **Use with caution**
2. Research synthesis can help make “**the evidence for a causal relationship strong**” by
 - (a) the systematic accumulation and integration of evidence, and
 - (b) by facilitating the investigation of
 - moderating variables
 - generalizability
 - alternative explanations
3. For the study of causes of rare adverse events the synthesis of evidence from **multiple data sources** is an important emerging methodological approach.

Challenges

- Pharma

- Monitor and report accurately adverse events

- Epidemiology/Statistics

- Establish the public health impact of “*suicidality*”
- Identify subgroups at risk
- Understand and communicate better issues for statistical models for low event rates

- FDA

- Improve post-marketing surveillance and methods for identifying adverse events
- Consider *Risk/Benefit* analyses in regulatory decisions
- *What further scientific evidence is needed to remove the black box warning?*

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