Meta-Analysis for Safety: Context and Examples at US FDA

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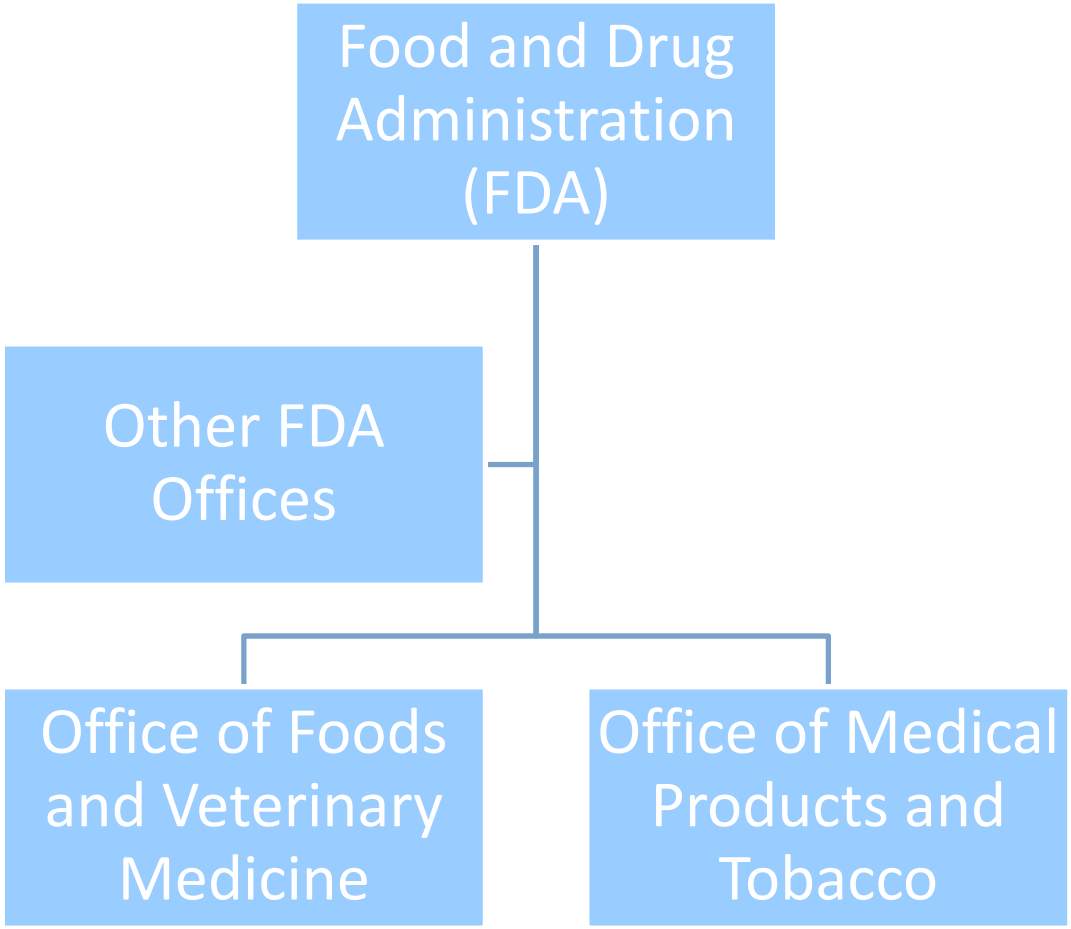
Center for Drug Evaluation and Research

U.S. Food and Drug Administration

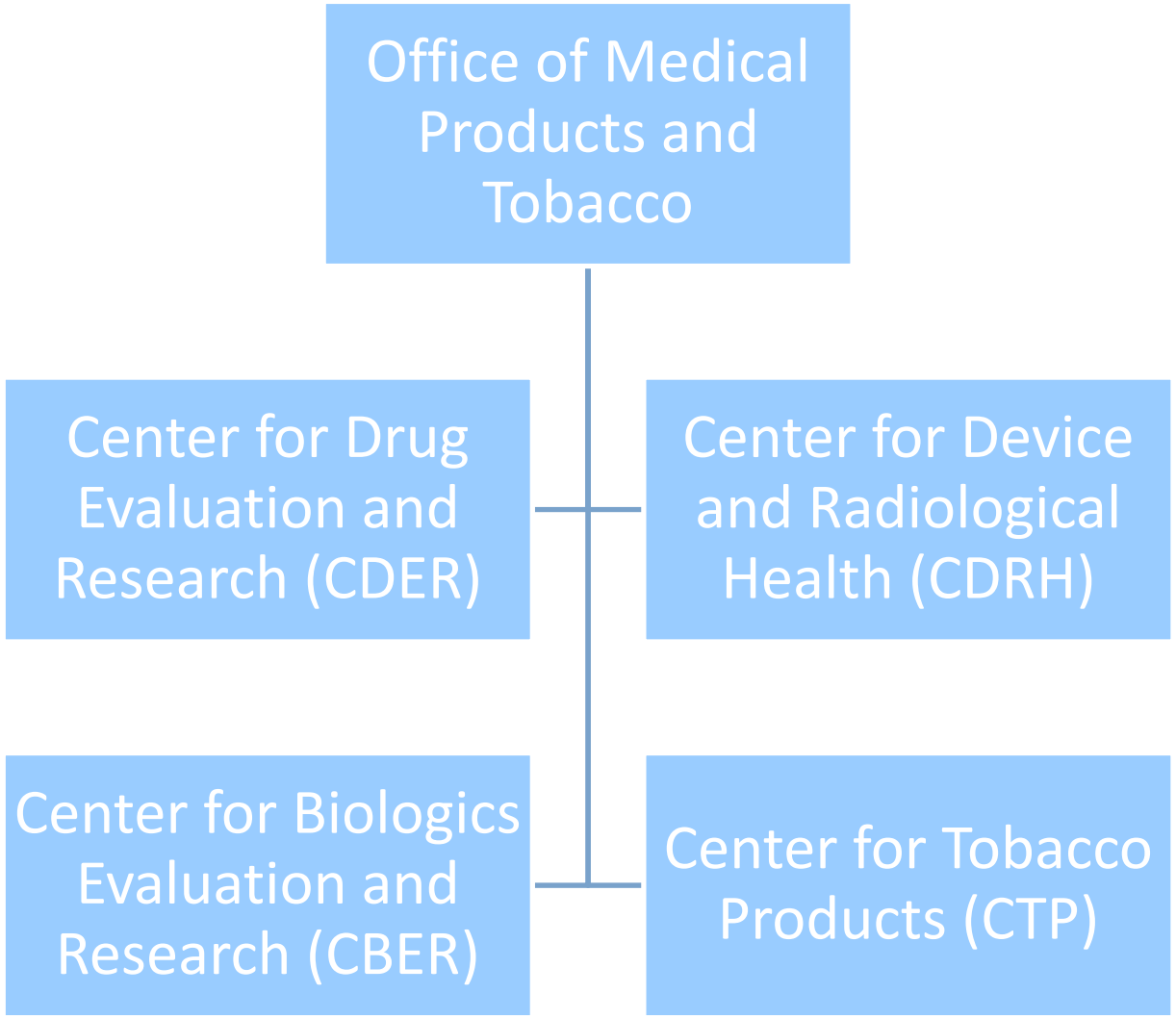
Outline

- Small Background on FDA
- Examples of Meta-Analyses at FDA
  - Antidepressants and suicidal events
  - Cefepime (antibiotic) and mortality
  - Tiotropium (COPD drug) and cardiovascular events
- US FDA Meta-Analysis Guidance

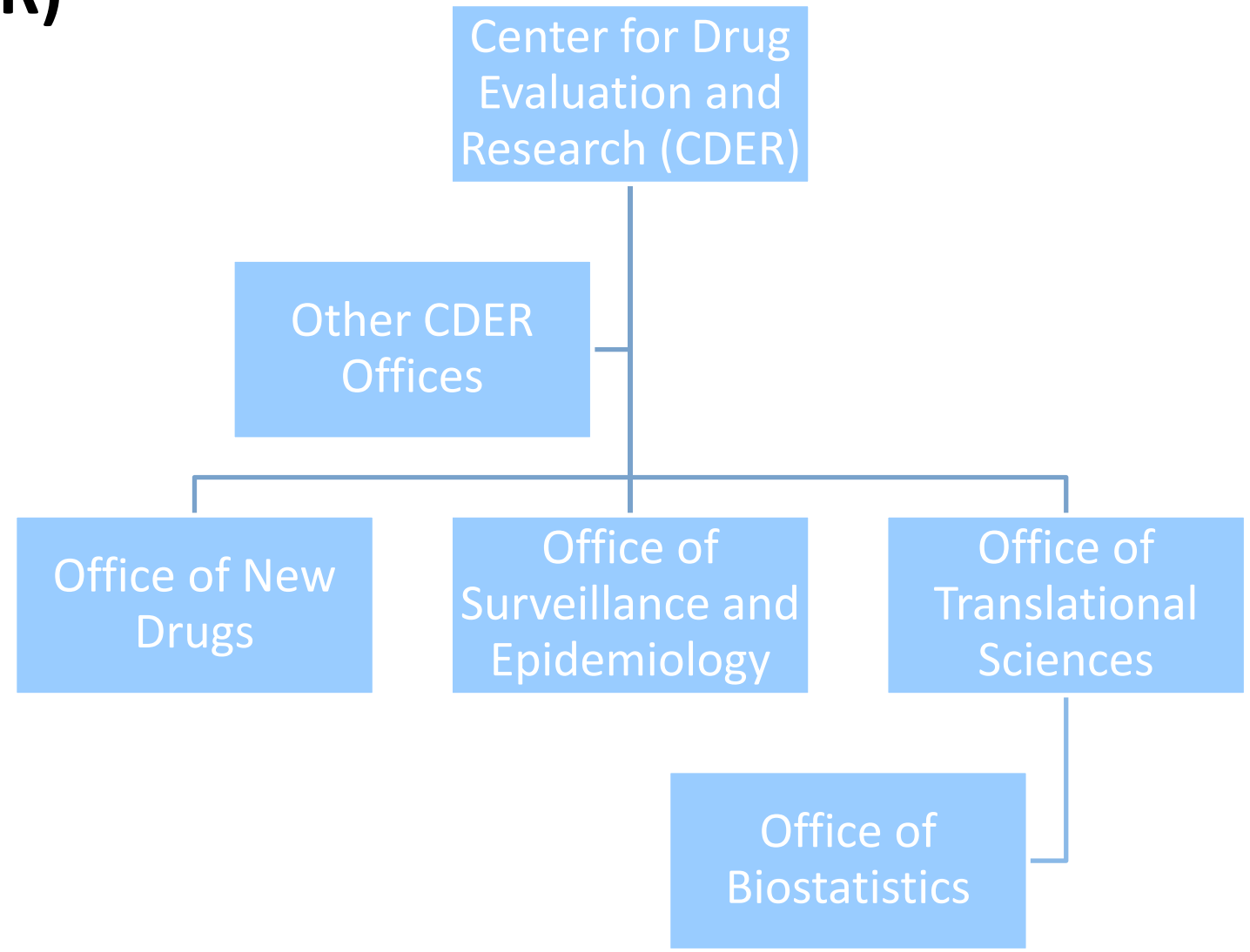
United States Food and Drug Administration

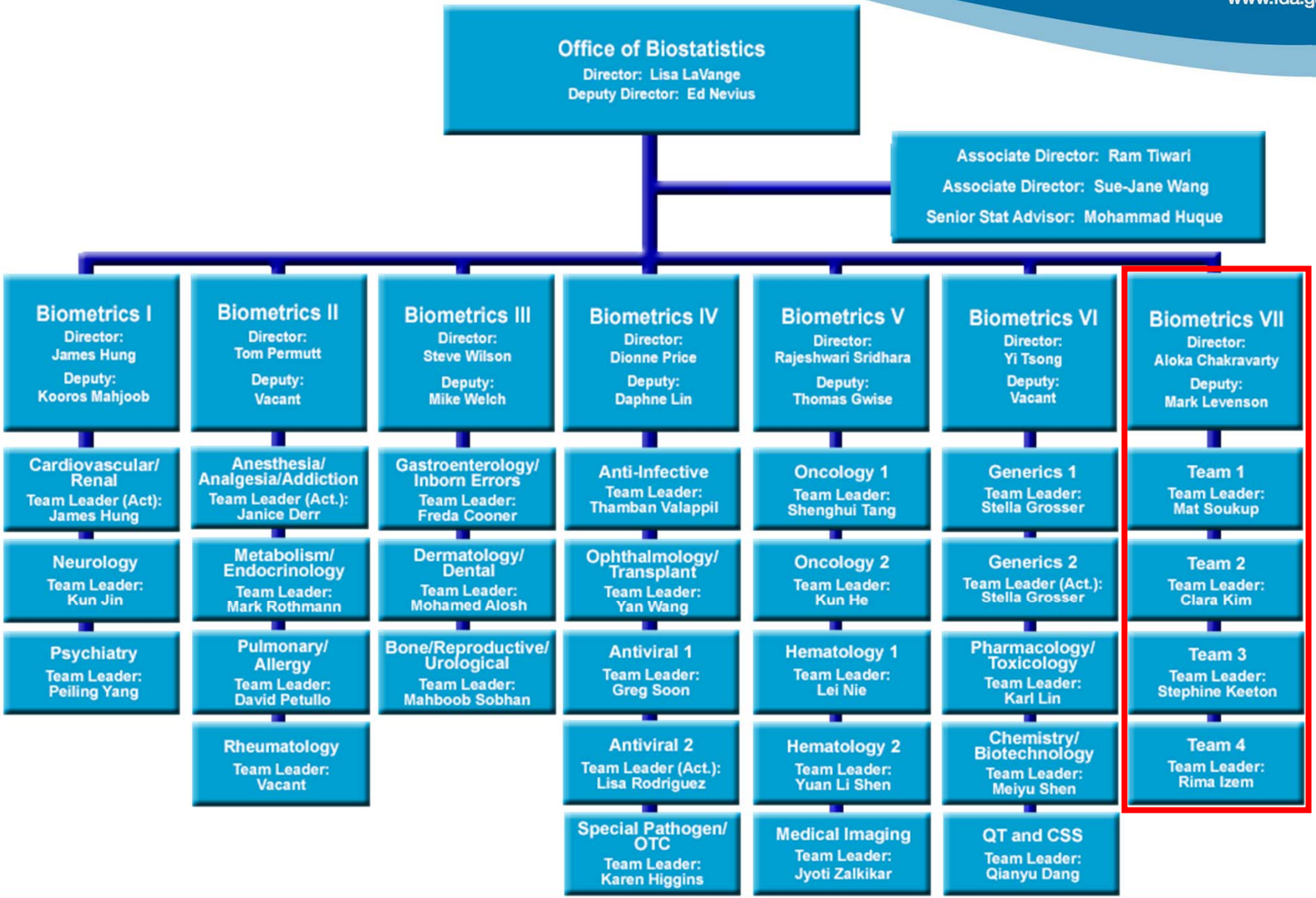


United States Food and Drug Administration



Center for Drug Evaluation and Research (CDER)

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Antidepressants and suicidal events in adults

Antidepressants meta-analysis: Motivation and objective

Motivation

FDA meta-analysis of pediatric trials showed an association between antidepressants and suicidal events

Primary Objective

To estimate the effect of antidepressant drugs on suicidal events in adults in placebo-controlled, randomized control trials

Antidepressants meta-analysis: Data source

- FDA requested all placebo-controlled, randomized trials
  - sponsored by manufacturers of antidepressants
  - with available patient-level data

Antidepressants meta-analysis: Outcome definition

- FDA provided instructions to companies on the identification of potential events and the adjudication of events
  - All serious adverse events and adverse events based on a predefined search criteria of verbatim terms identified
  - Potential events blindly adjudicated by experts based on Columbia C-CASA system

Antidepressants meta-analysis: Analysis plan

- Prespecified
  - Data source
  - Trial and patient inclusion criteria
  - Outcome definition and adjudication
  - Primary and secondary objectives
  - Primary analysis methods
  - Sensitivity analyses
  - Subgroup definitions

Antidepressants meta-analysis: Data summary

- 11 drugs
- 9 companies
- 295 trials (met inclusion criteria)
- 66,893 patients (met inclusion criteria)
- 444 primary events

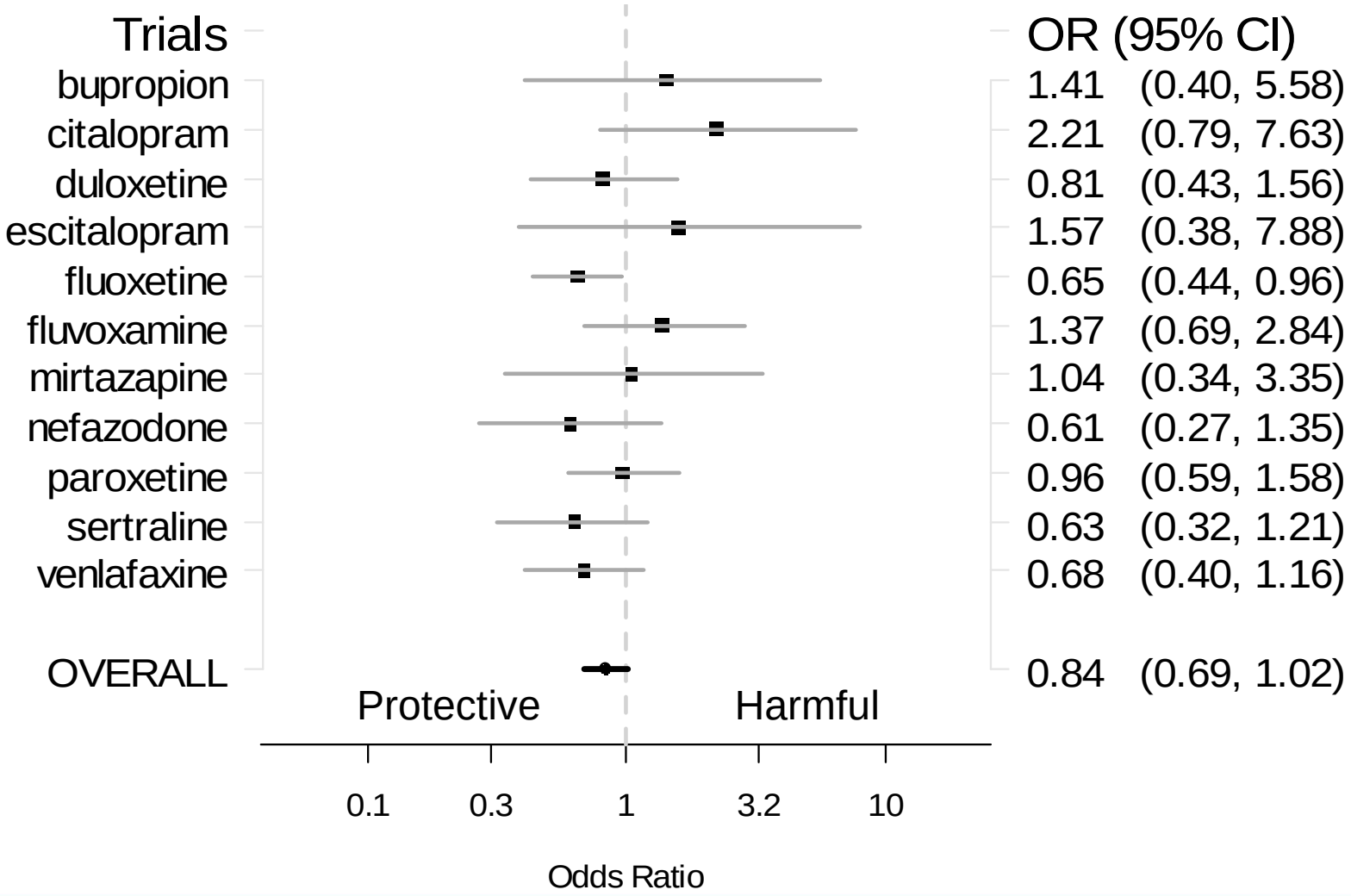
Antidepressants meta-analysis: Outcome event rates

Placebo: 0.72% of patients with event

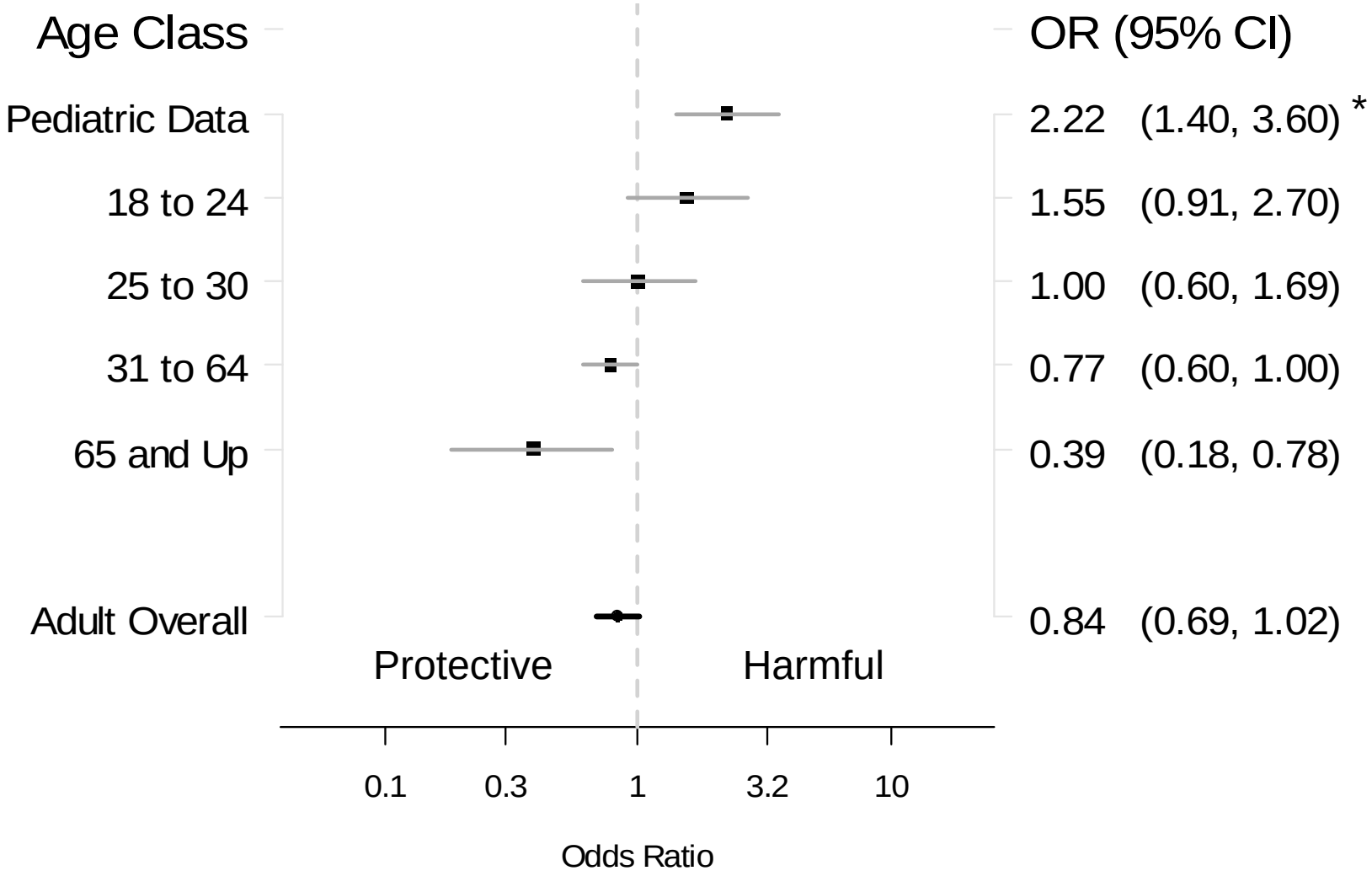
Test Drug: 0.62% of patients with event

174/295 = 59% trials had reported events

Suicidal Behavior and Ideation
Psychiatric Indications
Odds Ratio



Suicidal Behavior and Ideation
Psychiatric Indications
Odds Ratio



Antidepressants meta-analysis: Key points

- Selection of trials
  - Not exhaustive (company trials only)
  - Not prone to publication bias
- All events rigorously and consistently defined
- Overall approach provided good internal validity, but results apply to short-term usage only
- Action not based on strict p-value
- Resource intensive study
- FDA uniquely positioned to perform this MA

Boxed Warning

Suicidality and Antidepressant Drugs

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 (MDD) and other psychiatric disorders. Anyone considering the use of XXX or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. …

Cefepime and mortality

Cefepime meta-analysis: Background and motivation

Background

- Cefepime is broad-spectrum antibiotic
- Only antibiotic approved as monotherapy for febrile neutropenia (FB)

Motivation

- Published article by an independent researcher on a systematic review and meta-analysis showed an association of cefepime and mortality

Cefepime meta-analysis: Yahav systematic review and meta-analysis

- Compared cefepime to other β-lactam antibiotics
- Primary outcome was 30-day all-cause mortality
- Searched: literature databases, trial registries, references in published studies, FDA documents
- Contacted study investigators for unreported outcome data
- Evaluated study quality using standard criteria

Cefepime meta-analysis: FDA meta-analysis

- Patient-level and trial-level data was searched from drug company and publications
- Trial inclusion broader for comparator drug than Yahav
- Conducted patient-level and trial-level meta-analyses
- Analysis plan prespecified
- Reviewed case report forms for mortalities in febrile neutropenia trials for trials submitted to FDA

Cefepime meta-analysis: Meta-analysis comparison

Yahav

- 38 trials with mortality, 16 without mortality
- Significant findings
  - Overall
  - Febrile neutropenia
- Gomez FB trial interim included and significant

FDA (trial-level)

- 88 trials with mortality (includes 38 and 11/16 Yahav trials)
- Not significant findings
  - Overall
  - Febrile neutropenia
- Gomez FB trial final included and not significant

Cefepime meta-analysis : Key points

- Available trials affects MA results
- Resource intensive but important public health question
- Based on experience with MA, FDA would likely provide instructions to the drug company to perform such a MA

Drug Safety Communication

Cefepime (marketed as Maxipime) Safety Review: An Update

6/17/2009

FDA has finished its analysis of a possible risk of higher death with cefepime, an antibiotic, following publication of a study that suggested a higher rate of death in patients treated with this drug, as compared to patients treated with similar drugs. FDA has determined that the data do not indicate a higher rate of death in cefepime-treated patients. Cefepime remains an appropriate therapy for its approved indications.

Tiotropium and adverse cardiovascular events

Tiotropium: Background

- Tiotropium is long-acting anticholinergic bronchodilator for COPD (approved 2004).
- Sponsor pooled analysis of adverse events showed an increase in the rate of stroke (Nov. 2007)
- Published systematic review of inhaled anticholinergics showed significantly increased risk of adverse cardiovascular (CV) events (Sept. 2008)
- Large, long-term, trial UPLIFT did not show increased risk of adverse cardiovascular events (Oct. 2008)
- FDA Advisory Committee meeting (Nov. 2009)

Tiotropium: Systematic review and UPLIFT

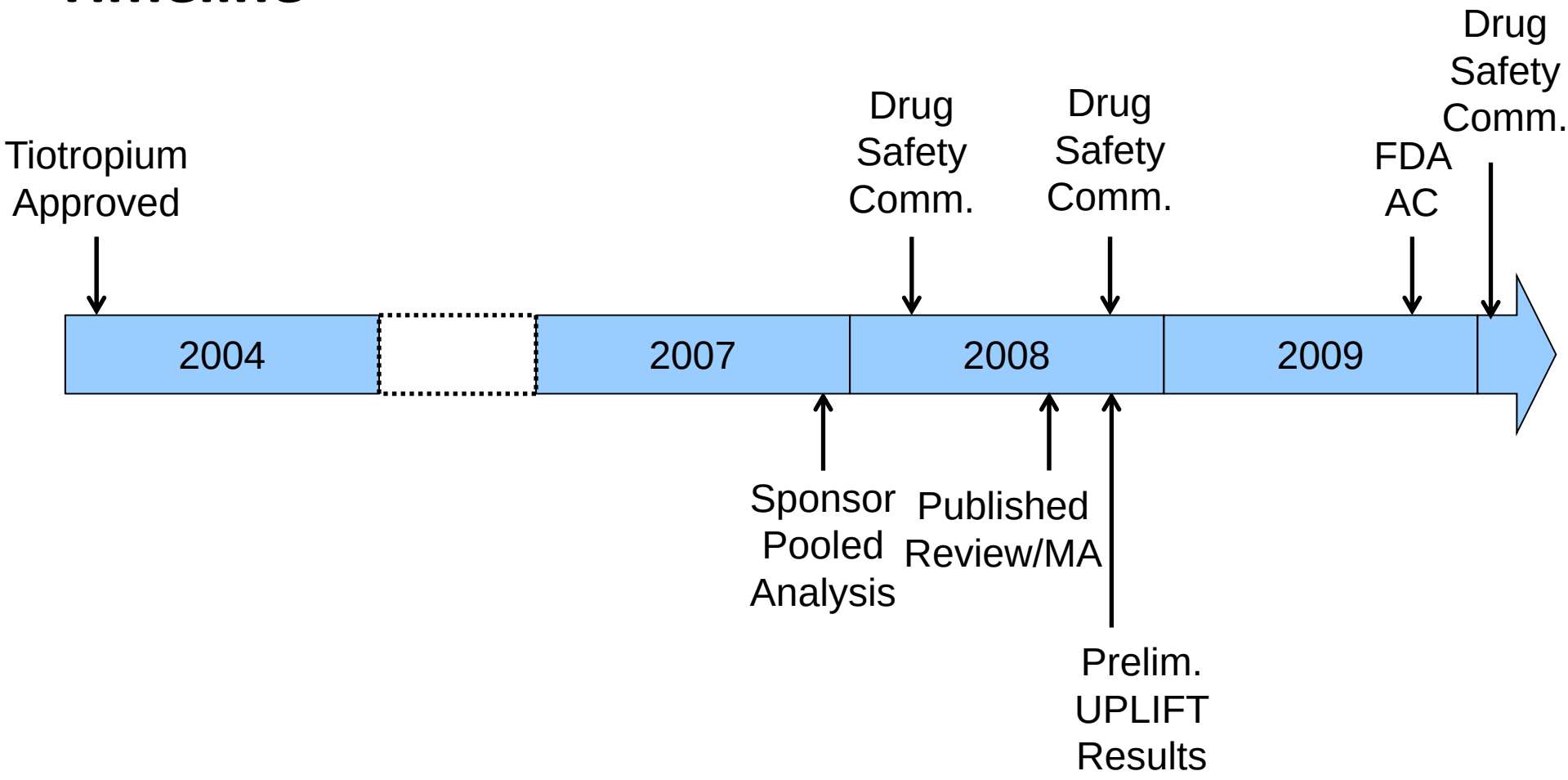
Systematic review

- Possible publication bias of using studies that report CV events
- Differential discontinuation rates
- Heterogeneity of trial designs: anticholinergic, comparator, duration, population

UPLIFT

- Mortality and adverse events systematically collected
- Large study and long-term follow-up

Tiotropium: Timeline



Tiotropium: Key points

- Even carefully designed and conducted systematic reviews and meta-analysis can provide apparently contrary conclusions to a single large trial
- FDA must act to ensure safe and effective use based on best information available at the time

US FDA Meta-Analysis Guidance

PDUFA V Goals:
Advancing the Science of Meta-Analysis Methodologies

- Develop a dedicated review team for meta-analysis in the FDA regulatory context
- Hold a public meeting to obtain input on the use of meta-analyses in the FDA regulatory context
- Publish a draft guidance on FDA's intended approach to the use of meta-analyses in the FDA's regulatory review process (by end of FY 2015)
- Publish a final or revised draft guidance within 1.5 years of the close of the public comment period

Conclusions

- Meta-analyses require a high-level of rigor to support regulatory decisions
- Meta-analyses may produce contrary finding to each other and to relevant trials
- Carefully designed and conducted meta-analyses can provide important input to FDA regulatory decisions