

Institute of Medicine
CNS Clinical Trials: Suicidality and Data
Collection

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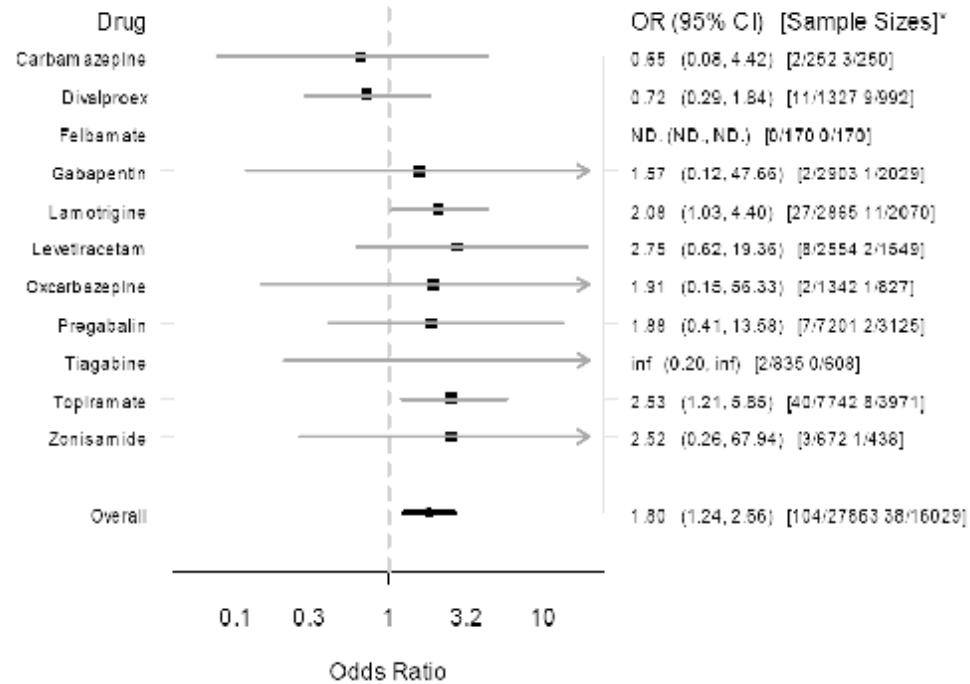
Key Problems – Suicide Surveillance

- Rare event – ideation, attempts, completion
- Suicide elevated in patients receiving tx
- Suicidality leads to tx – does tx lead to it?
- Regression towards the mean
- Natural course of illness
- Very few specific statistical methods

Anti-Epileptic Drugs and Suicidality

- January 31 2008 – FDA Alert
- July 10 2008 – FDA Scientific Advisory Committee Hearing – Black Box Warning?

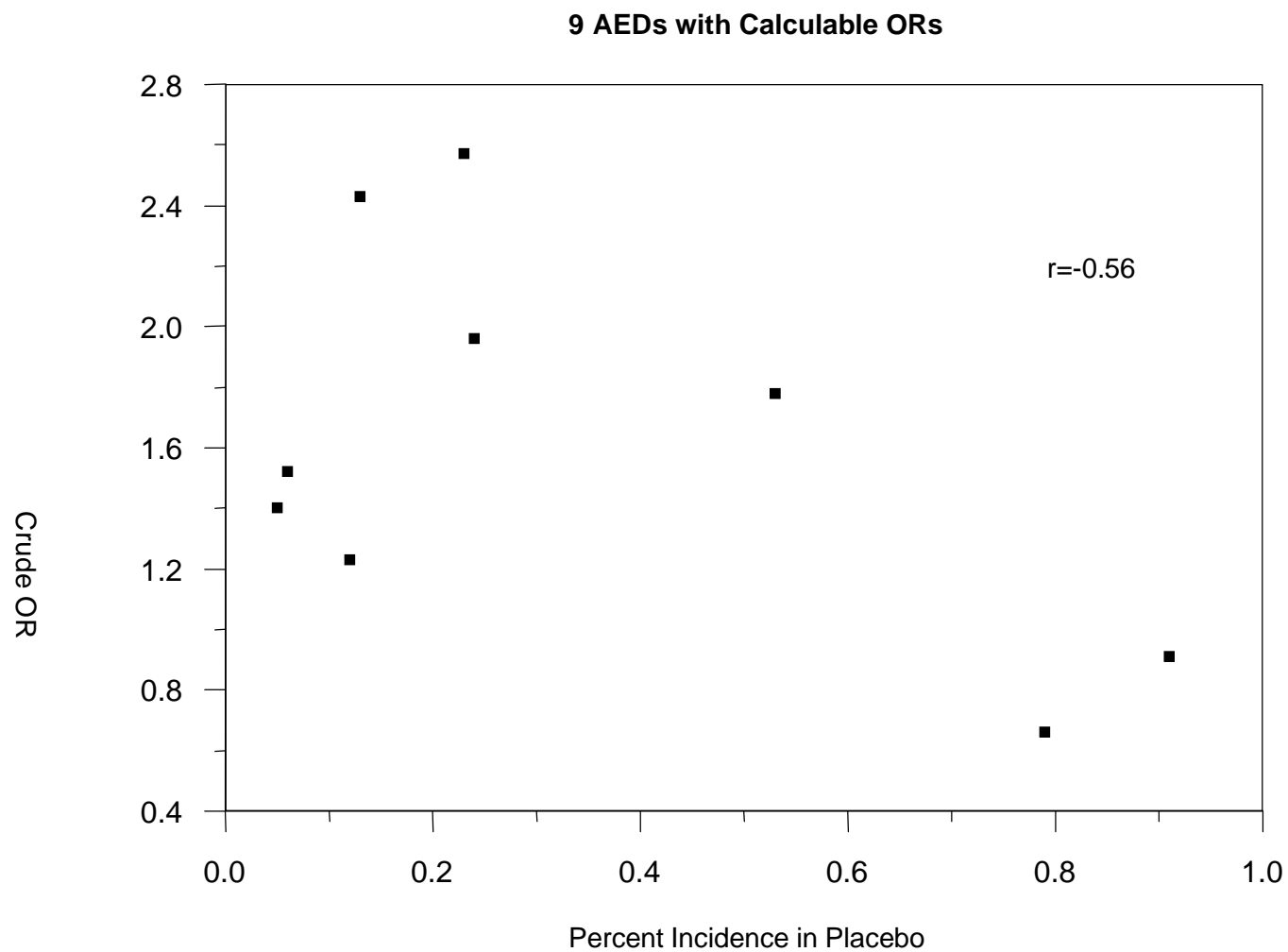
Odds ratios for 11 AEDs



*[Treat. Events/Treat. n Plac. Events/Placebo n]

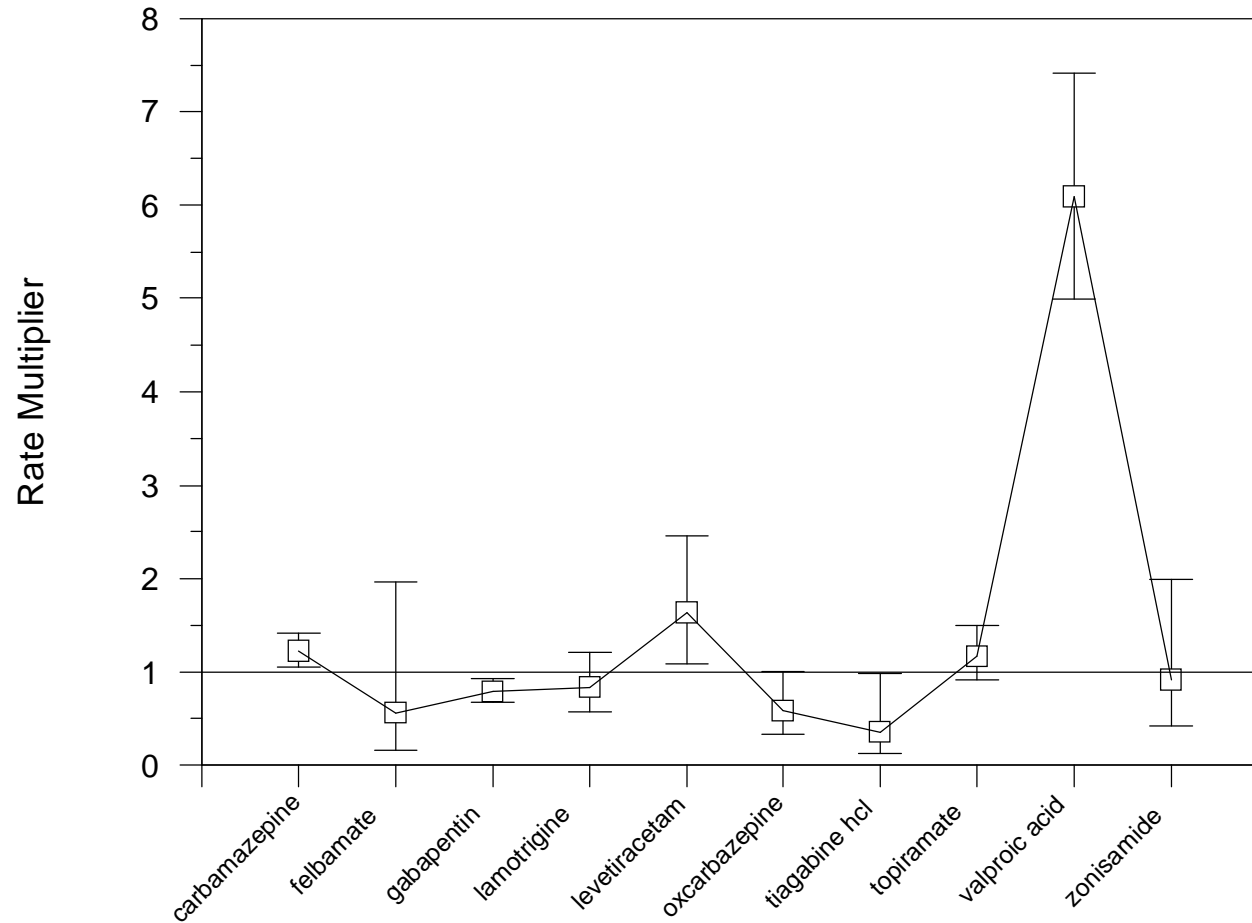
Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials.

Crude OR versus Incidence in Placebo Arm



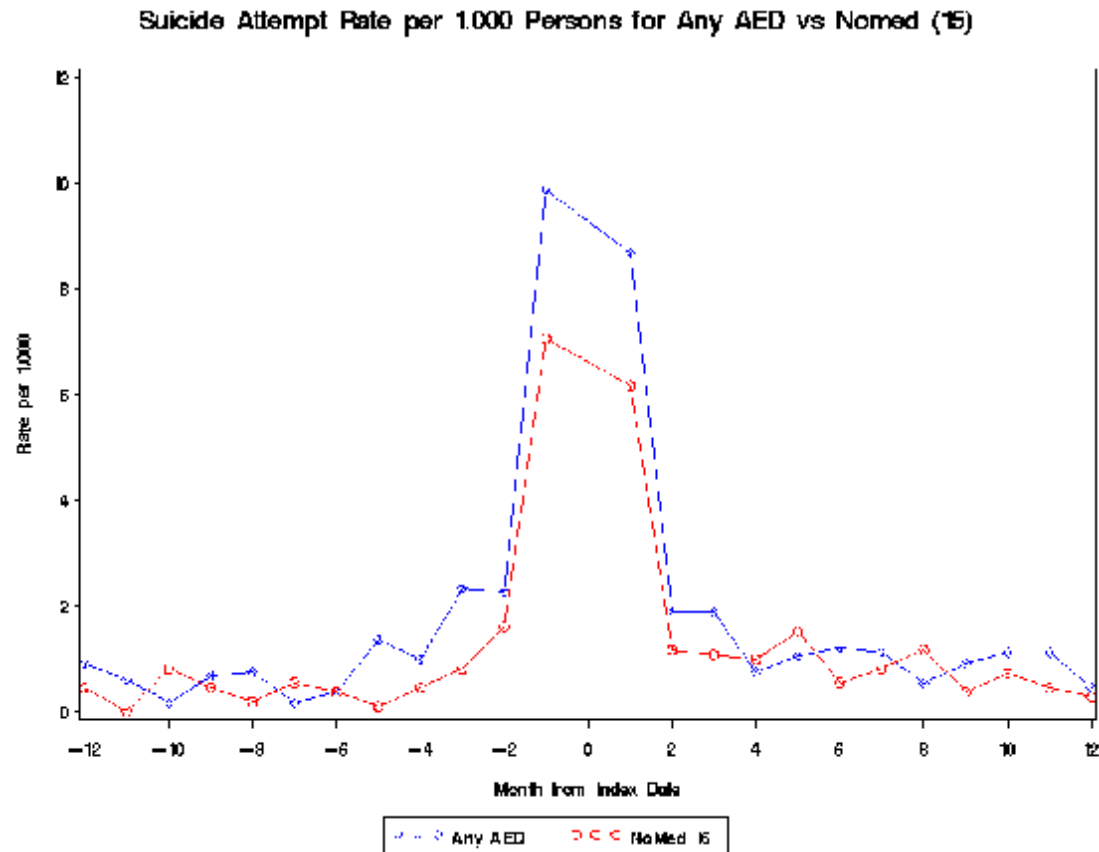
FDA AERS Data for Completed Suicide

10 Antiepileptic Drugs on the Market from 2000-2005
Empirical Bayes Rate Multipliers



See Gibbons et.al., 2008, *Statistics in Medicine*, 27, 1814-1833.

Suicide Attempt Rates Before and after BP Index Date in Treated and Non-Treated Pts.



Comparison of Approaches

Method	Pros	Cons
RCTs	Randomized	Generalizability
AERS	Large Samples	No denominator, media
Ecological	Large Samples	Not person-level
Medical Claims	Large Samples	Prescriptions and DXs
Between Subject	Person-level, drug vs. no drug	Confounding by indication
Within Subject	Subject own control	Temporal effects
Person-time	Adjusts for time effects	Carry-over effects
Propensity Score + Time Matching	Adjusts for confounds and time	May not eliminate baseline risk difference
Case-Control	Adjusts for some confounds	Cases are still more severely ill

Does Suicidal Ideation Lead to Suicidal Behavior?

- Obtain all RCT data for 372 adult antidepressant studies for weekly HAMD item 3 and AE reports of suicide attempts.
- Predict attempts from HAMD ideation ratings using mixed-effects Poisson regression model (ideation is a time-varying covariate).
- Design a large new study with longer term follow-up and prospective suicidality measurements.