Gathering Adequate Clinical Trial Data for the Postmarketing Safety Database

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1. Code adverse events properly

Keller et al. *J Am Acad Child Adolesc Psychiatry* 2001 Study 329

- Randomized, double-blind, placebo-controlled trial
- 275 adolescents with major depression
- 8 weeks of double-blind paroxetine, imipramine, or placebo
- "Paroxetine was generally well tolerated in this adolescent population, and most adverse effects were not serious…"
- "Serious adverse effects occurred in 11 patients in the paroxetine group…Of the 11 patients, only headache (1 patient) was considered by the treating investigator to be related to paroxetine treatment."

Keller et al.
J Am Acad Child Adolesc Psychiatry 2001
Study 329

Adverse Effect	Paroxetine (n=93)		Placebo (n=87)	
Nervous system	n	%	n	%
Dizziness	22	23.7	16	18.4
Emotional lability	6	6.5	1	1.1
Hostility	7	7.5	0	0
Insomnia	14	15.1	4	4.6
Nervousness	8	8.6	5	5.7
Somnolence	16	17.2	3	3.4
Tremor	10	10.8	2	2.3
Headache	32	34.4	34	39.1

GSK analysis of suicidal events in paroxetine pediatric clinical trials

- GSK conducted an electronic search of their clinical trial database for AE descriptions included the following text strings:
  - attempt, cut, gas, hang, hung, jump, mutilat, overdos, self damag, self harm, self inflict, self injur, shoot, slash, suic
  - overdose other than accidental
- included events up to 30 day after treatment

Results of GSK re-analysis of suicidal adverse events in pediatric trials (including Study 329, top)

(Mosholder & Willy, J Child Adolesc Psychopharmacol, 2006)

Drug	*Indication*	*Study*	*N drug*	*Drug patient years*	*Drug serious suicidal events*	*Pbo n*	*Pbo patient years*	*Pbo serious suicidal events*
	MDD	329	93	13	7	88	13	1
	MDD	377	181	41	7	95	21	4
Paroxetine	MDD	701	104	16	3	102	17	1

Conclusion: To define the safety profile properly, adverse events:

- Need to be classified appropriately
- Need to be reported whether considered drug-related or not

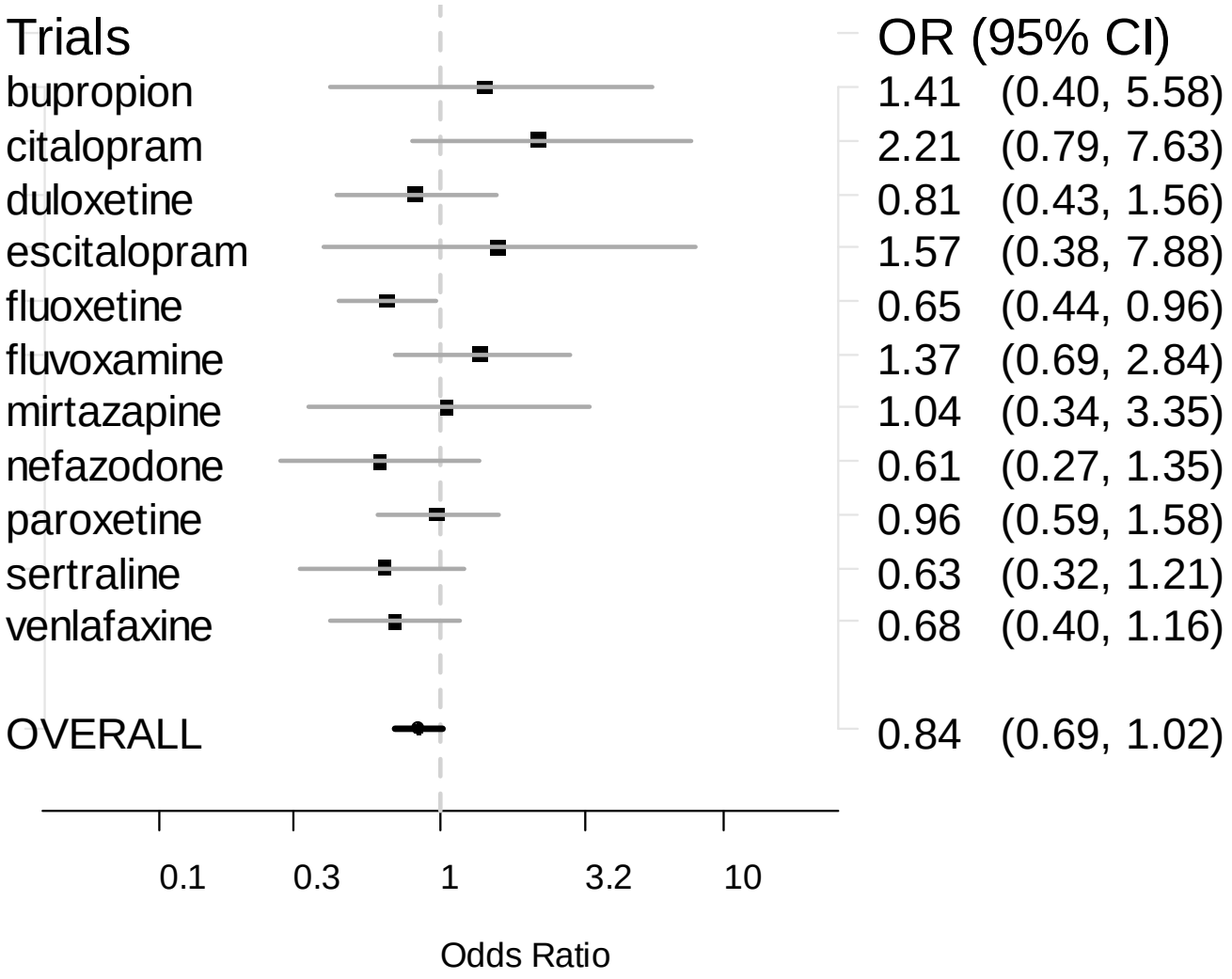
2. Sample from relevant age groups, so the safety profile can be analyzed by age (avoiding extrapolation)

Meta-analysis of antidepressant clinical trials (all age groups)

- Data source:
  - 295 antidepressant placebo-controlled trials in psychiatric disorders
  - 39,729 drug patients
  - 27,164 placebo patients
- Outcome: suicidal behavior/ideation, adjudicated by expert panels
- Method: Patient-level data meta-analysis

Levenson and Holland, FDA Psychopharmacologic Drugs Advisory Committee, 12-13-06.
www.fda.gov/ohrms/dockets/ac/06/slides/2006-4272s1-00-index.htm

Suicidal Behavior and Ideation
Psychiatric Indications
Odds Ratio



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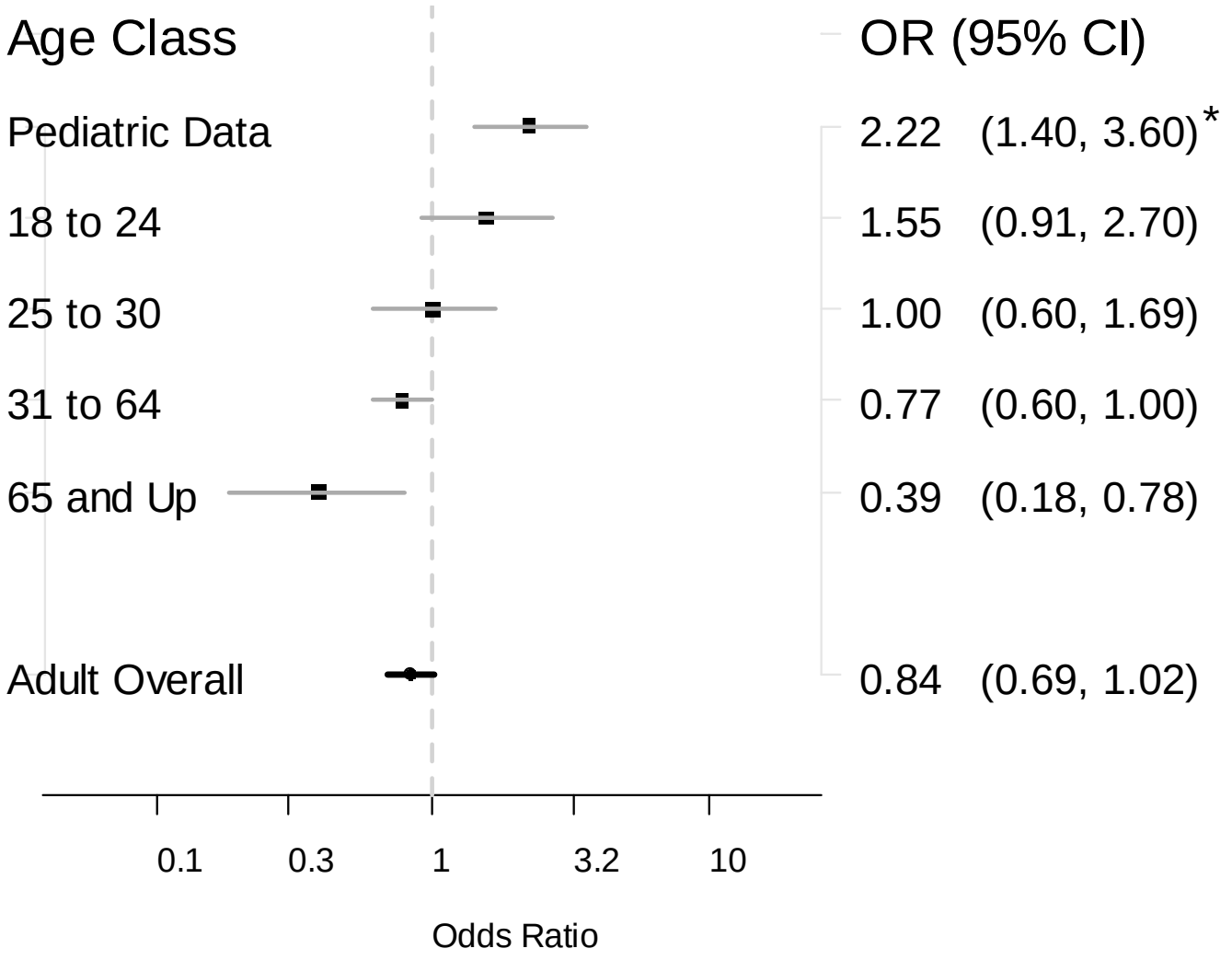


* Reanalysis of FDA/Hammad 2004 data

Updated analysis

Stone et al. BMJ 2009

- 372 double blind trials of antidepressants, roughly half in depression
- Odds ratio for suicidal events declined 2.6% per year of age (p=0.0001)

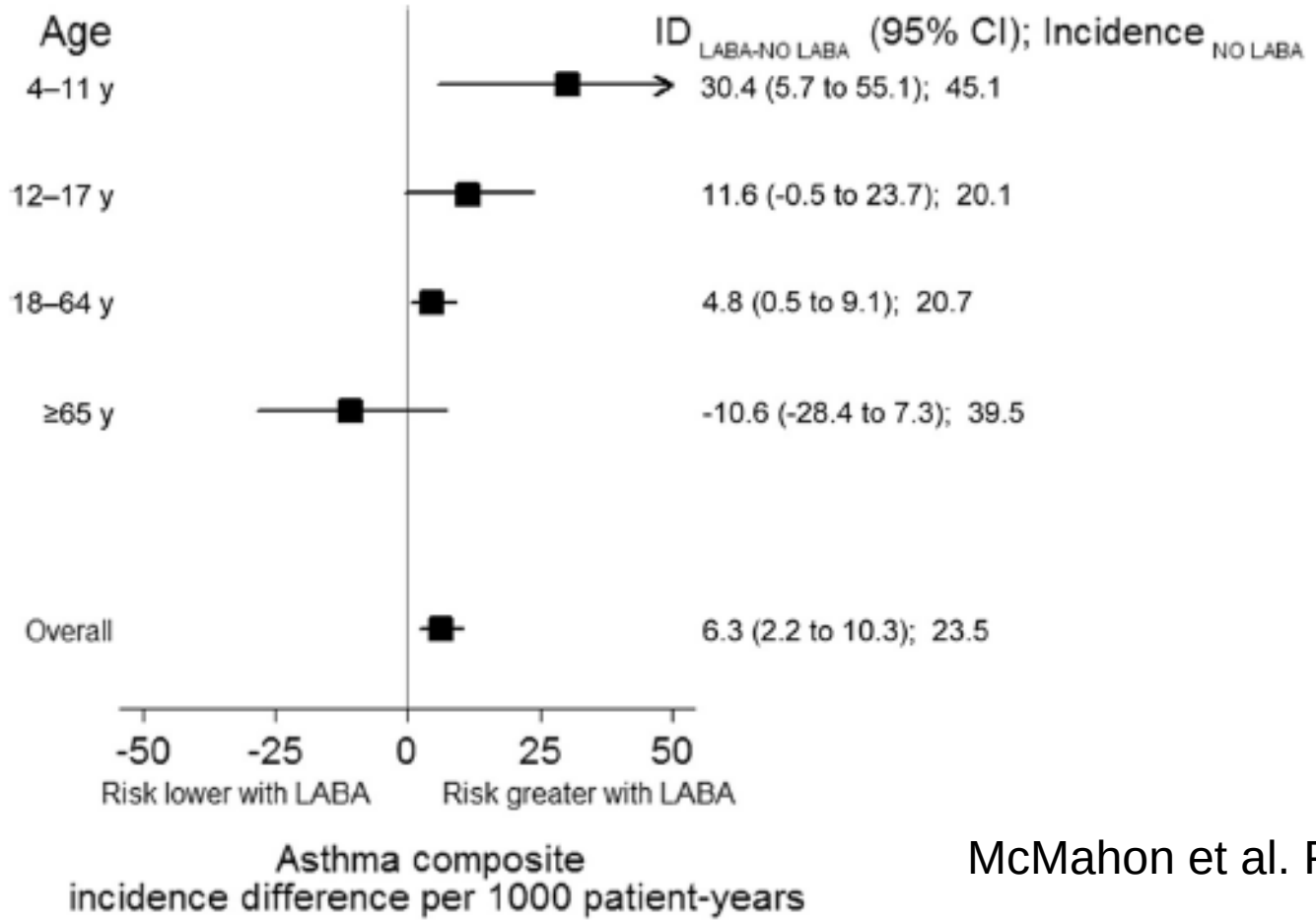
Age group	OR
<25	1.6 (1.0-2.7)
25-64	0.8 (0.6-1.0)
65+	0.4 (0.2-0.8)

- Conclusion: risk strongly age dependent, benefit increases with age (esp. 65+)

FDA Safety Meta-Analysis of LABAs for Asthma

McMahon et al. Pediatrics 2011

- Purpose: characterize pediatric risk of serious asthma events with long acting beta agonist (LABA) treatment
- Experts blind to treatment assignment reviewed all “serious” adverse events for
  - Asthma hospitalizations
  - Asthma-related intubations
  - Asthma deaths
- Manufacturers of LABA products provided patient- and trial-level datasets from asthma trials
- Meta-analysis of serious asthma events conducted



McMahon et al. Pediatrics 2011

FIGURE 2

Incidence difference for asthma composite index according to age for LABA versus no-LABA therapy. The asthma composite index includes asthma-related hospitalizations, deaths, and intubations. ID indicates incidence difference per 1000 patient-years; $\text{Incidence}_{\text{No LABA}}$ indicates incidence in No LABA group per 1000 patient-years.

3. Strive for a large denominator and combine data from multiple trials (meta-analysis) to assess uncommon reactions

Using the "Rule of 3" approximation to interpret zero numerators

"This 'rule of three' states that if none of n patients shows the event about which we are concerned, we can be 95% confident that the chance of this event is at most three in n (i.e., 3/n).

In other words, the upper 95% confidence limit of a 0/n rate is approximately 3/n."

-Hanley & Lippman-Hand, JAMA 1983

Hypothetical Example of Rule of 3

- A certain adverse event has been reported in adults with the study drug
- Open label safety trial in 100 children
- None of the children have that event
- Conclusion: 95% statistical confidence the pediatric risk is no more than ~3%

Summary

1. Code adverse events properly and report them whether considered drug-related or not
2. Analyze adverse event rates by age when feasible
3. Strive for large denominators
4. Combine data from multiple trials (meta-analysis) to assess uncommon reactions

Questions?