Meta-analyses of clinical dose response

N. Thomas[1] D. Roy, V. Somayaji, and K. Sweeney

[1]Pfizer Inc
445 Eastern Point Road
Groton, CT 06340

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Outline

1. Meta-analyses of Pfizer data
   - Compounds/studies
   - Study designs
   - Exemplar of dose response data
   - Summarizing $\mathrm{E}_{\mathrm{max}}$ model fits

2. Meta-analyses of FDA-approved compounds (2009-2014)

Compound/study sampling frame

Sampling frame

- Identified all phase 2 studies with reports completed between 1998-2009
- Repository represented approximately 10% of pharmaceutical R&D spending
- Repository represented 13 of 17 TAs

Compound/study inclusion/exclusion criteria

Compound criteria

- Excluded oncology compounds
- Small molecules only
- To be included, a compound must differentiate from placebo based on review of study reports

Study criteria

Phase 2 studies. Phase 3 studies were included if they had $\geq$ 3 dose groups

Compound/study counts

- 33 compounds (29 distinct molecules)
- 76 studies

Outline

Study designs

Study structure

Parallel groups. Only 2 cross-over designs.

Data types

- 27 were continuous
- 6 were binary
- No time-to-event or (ordered) categorical outcomes

Dosing designs

Dose groups (including placebo) per compound

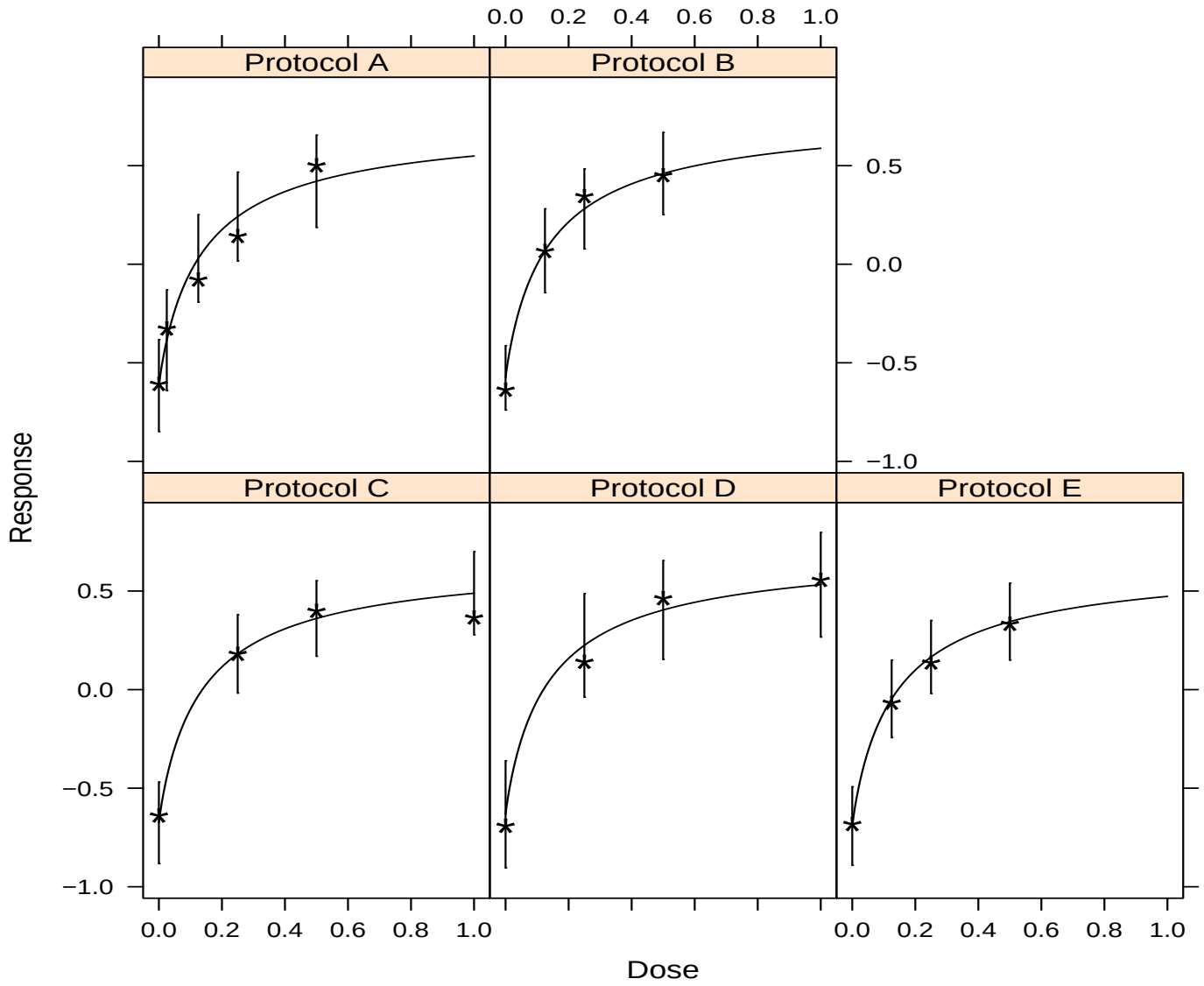
Number of Compounds	Number of Dose Groups
9	4
4	5
10	6
7	7
3	8 – 10

Ratio of the highest dose to the lowest (non-placebo) dose

- 25^{th} percentile is 8
- 50^{th} percentile is 16
- 75^{th} percentile is 30
- Maximum dosing ratio was 588

Outline

PDE5 inhibitor (ID 31)for erectile dysfunction



$$\hat{\lambda} = 0.93$$

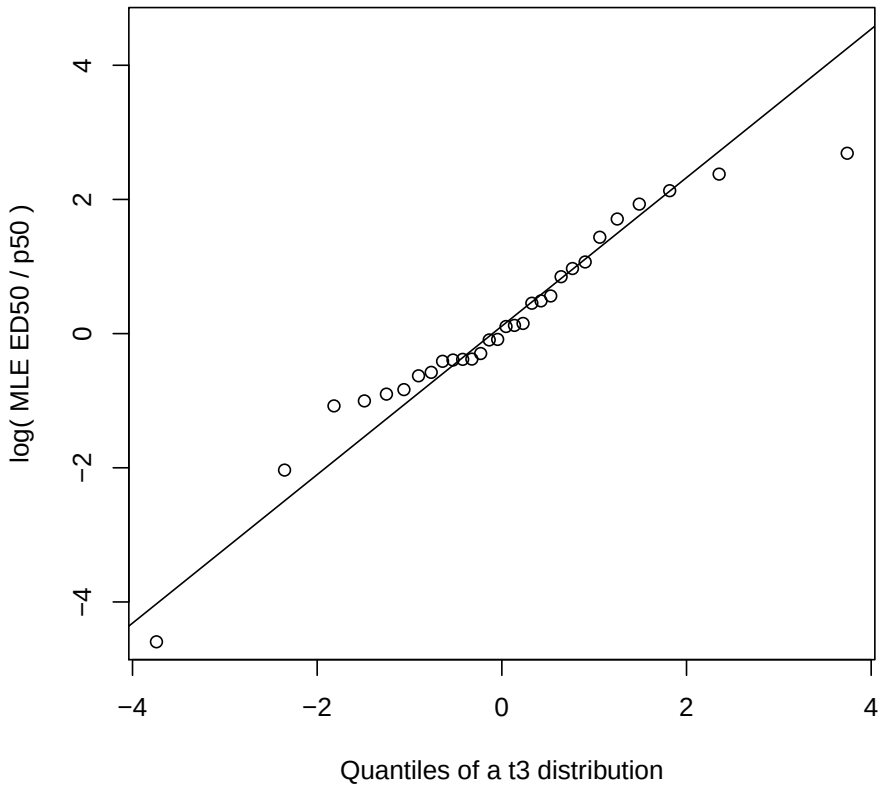
Outline

Summarizing the MLE of the Hill (λ)

Distribution of Hill (λ) parameter estimates

- 25^{th} percentile is 0.85.
- 50^{th} percentile is 1.13.
- 75^{th} percentile is 1.61.

Quantile plot of $\log(\widehat{\mathrm{ED}}_{50}/\mathrm{P}_{50})$



90% of the compounds satisfied $(-2 < \log(\widehat{\mathrm{ED}}_{50}/\mathrm{P}_{50}) < 2)$ or equivalently, $(0.14\mathrm{P}_{50} < \widehat{\mathrm{ED}}_{50} < 7.4\mathrm{P}_{50})$.

Summarizing the magnitude of effects

Standardized treatment estimates

Percentile	Standardized Effect
25	0.53
50	0.96
75	1.66

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Compound/study inclusion/exclusion criteria

Compounds/studies

- Excluded oncology compounds
- Small molecules only
- Other criteria similar to the Pfizer data

Compound/study counts

- 66 compounds (62 distinct molecules)
- 105 studies

Dosing designs

Dose groups (including placebo) per compound

Number of Compounds	Number of Dose Groups
19	≤ 3
23	4
10	5
11	6
2	7

Ratio of the highest dose to the lowest (non-placebo) dose

- 25^{th} percentile is 3
- 50^{th} percentile is 4
- 75^{th} percentile is 8
- Maximum dosing ratio was 33

Dose response curves

High-level overview

- Limited information for many compounds. Linear segments, plateaus.
- Dose response for compounds with better dosing designs were well-described by Emax models
- One compound with potential non-monotone response

Summary

What do clinical dose response curves look like?

Most look like hyperbolic $\mathrm{E}_{\max}$ curves.

How well were they determined by the studies conducted?

- The answer varies due to controllable and uncontrollable reasons.
- Dosing ranges are too narrow.

Are there consistent quantitative trends in clinical dose response across unrelated diseases and compounds?

- Yes
- Distributions of likely parameter values are important in both design and analysis of dose response studies.

Reference

Thomas, N., Sweeney, K., and Somayaji, V. (2014). Meta-analysis of clinical dose response in a large drug development portfolio. To appear in Statistics in Biopharmaceutical Research, doi: 10.1080/19466315.2014.924876.