Rare Diseases Forum
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Bayesian Methods Overview

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Outline

- Bayesian approach overview
- Methods for borrowing and Data sources
- Examples
- Conclusion

Key Messages

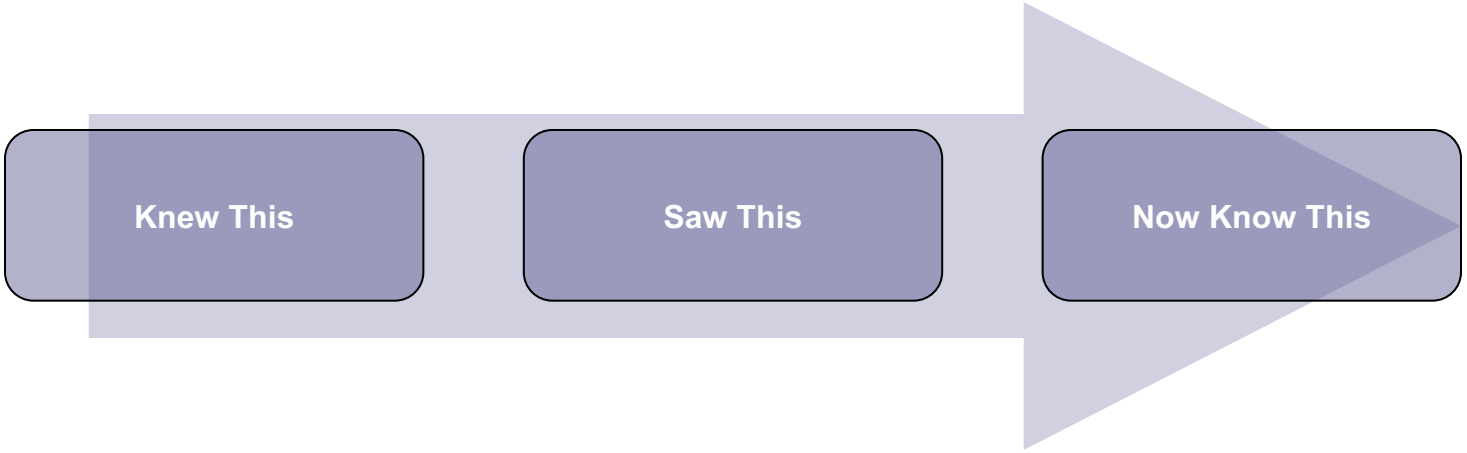
- Rare diseases are in desperate need of innovation
- Bayesian approach
  - Offers an intelligent, complete use of all data to improve decisions
  - Best practices enable transparent evaluation of all data and beliefs
- Bayes is not weakening the standard of evidence
- Bayesian methods can improve the design and analysis of studies for rare diseases

The Bayesian Framework

Bayesian Statistics emulates the way we think

- We all learn from previous experience
  - Personally
  - Scientific decisions
  - Business decisions

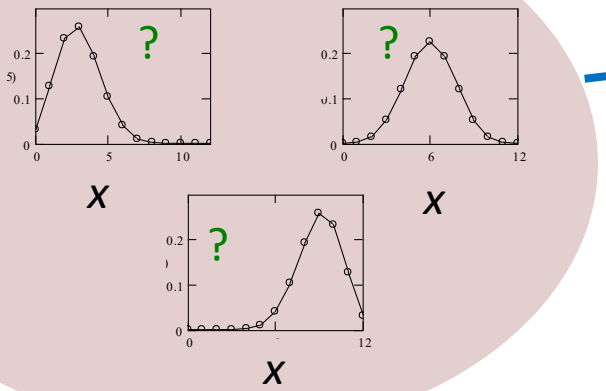
- Pictorially, we can think of this as:



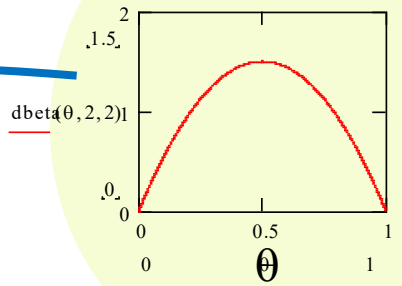
Combining Information

likelihood

$0 < \theta < 1$



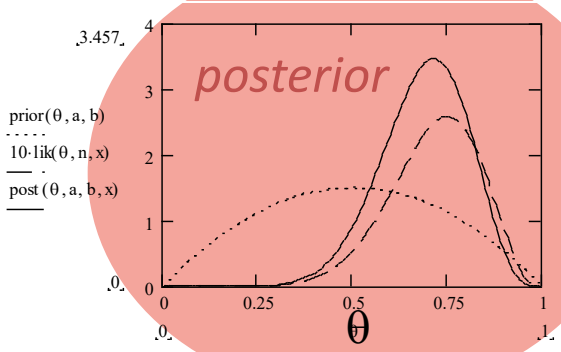
prior



Bayes' Theorem

The likelihood function represents all possible binomial distributions from which the sample might have originated—an infinite, uncountable number of possible distributions, one for each possible value of θ in [0, 1].

posterior



The posterior represents everything we know from prior information and new data.

The prior distribution represents all we know before we obtain the current data. It may be based on past data, expert opinion, or both.

Value of Bayesian Approach

- Emulates how we naturally think (facilitates continual learning)
- Enables probability estimates of questions of interest
- Allows formal use of prior information, including priors built from previous studies
- Great flexibility in modeling and prediction
- Completely transparent

Motivation in Rare Diseases

- Rare diseases need to leverage all available data
- Some rare diseases may be more common in adults
- Some compounds for other indications may be considered for rare diseases, in which case may have:
  - Data on other indications
  - Data on various dose arms (PK/PD, clinical efficacy and safety, etc.)
- Unlikely to be able to fully power phase 3

Borrowing Approaches and Data Sources

Borrowing Approaches

- Borrowing can be on control arm and/or treatment arm(s)
- Static vs Dynamic
  - Static
    - Pooling
    - Single arm trials
    - Power priors
  - Dynamic
    - Hierarchical modeling
    - Mixture priors
- Static vs dynamic can differ for control/treatment

Appeal of dynamic borrowing:
- Borrows more when current data are similar to historical data
- Protects against over-borrowing

See, e.g., Viele, et al., 2014.

Overview of Potential Data Sources

- Expert opinion / Caregiver insights
- Natural history studies
- Summary level data (RCTs, observational)
- Individual-level patient data
- PK/PD modeling
- Pre-clinical data

Need to assess relevance of historical data to new data: similar indications, patient population, time since data collection, relevance of endpoints, timepoints, etc. (exchangability)

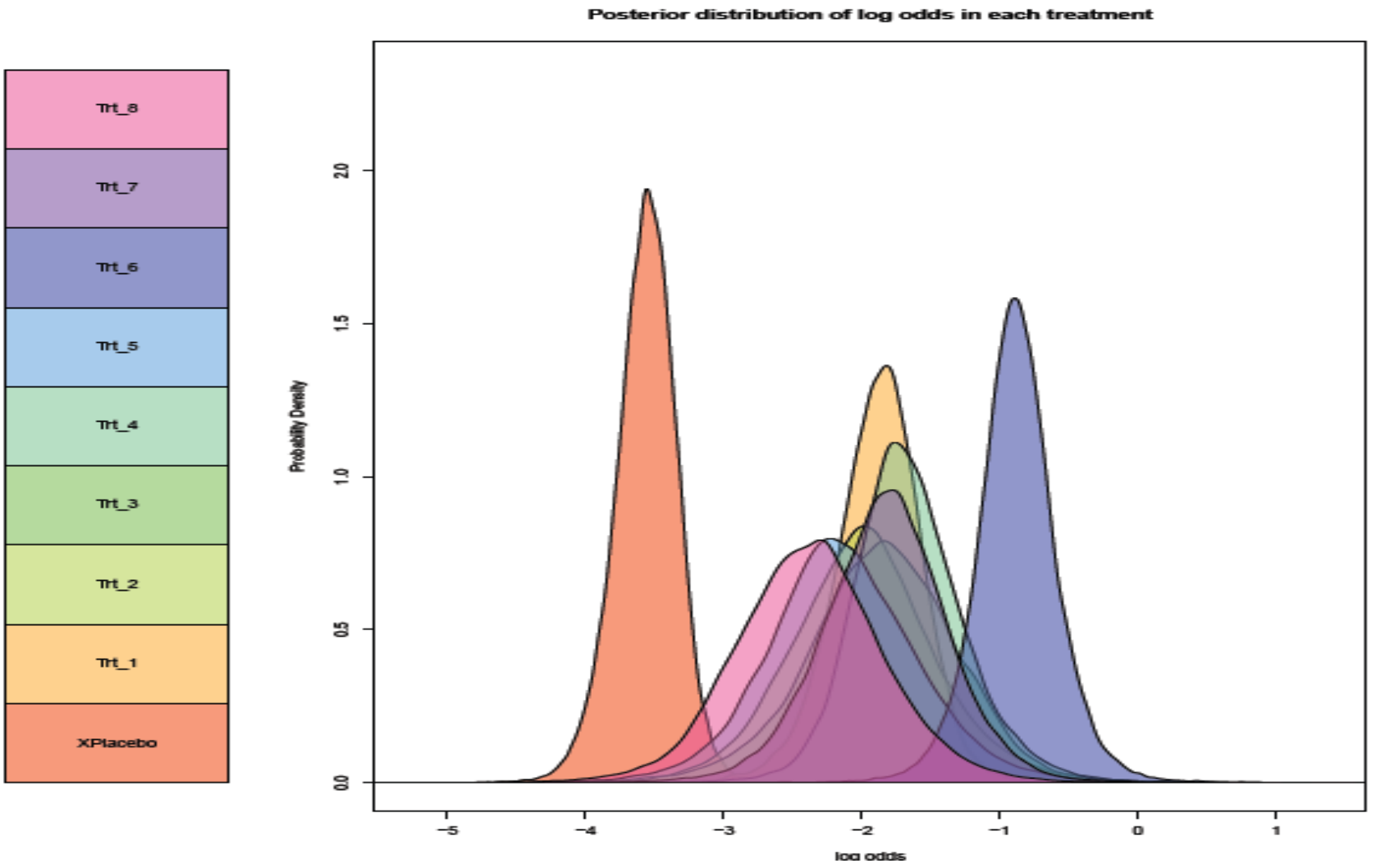
Note on Expert/Caregiver Opinion

- Can elicit distributions of belief about key efficacy/safety endpoints
  - Not required to fully borrow elicited distribution
  - May be used as portion of prior or down-weighted
- Can use to elicit distributions about belief in relationships between endpoints, doses, populations, etc.
- Can use to inform about relevance of historical information

Note on Expert Opinion, cont.

- Need to develop protocol ahead of elicitation
  - Endpoints to elicit
  - Populations to elicit
  - Questions that will be asked
  - Individual vs group
  - Who are the experts?
- Large literature on this topic
- Examples available (see, e.g., MYPAN)

Bayesian Synthesis of Data



General Comments about Borrowing

- How much to borrow?
  - ✓ What data is eligible to be included in the prior
  - ✓ Currently need to simulate operating characteristics
  - ✓ Consider “prior effective sample size” and “prior probability of success”
  - ✓ Should assess prior to posterior sensitivity
- May borrow different amounts for different treatments, based on medical need, etc.
- Note, borrowing may ‘dampen’ the effect in current trial (so borrowing does not always favor Sponsor)

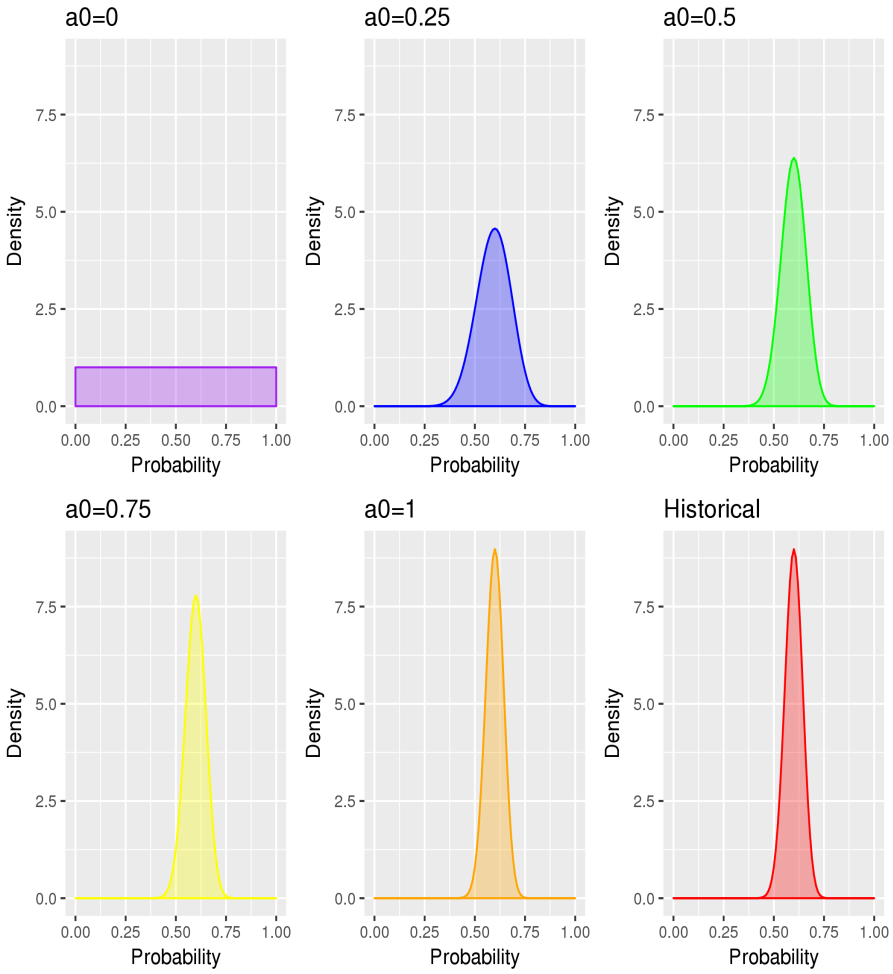
Suggestions available in CDRH/CBER Bayesian Guidance document

Examples

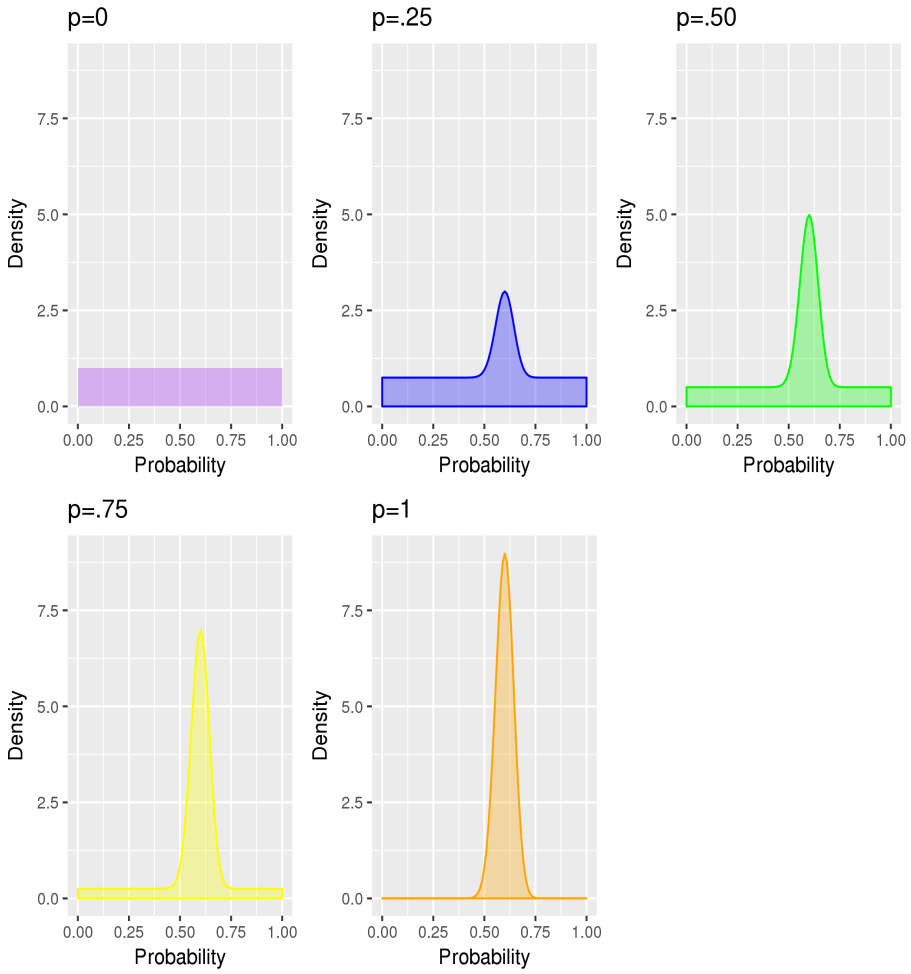
Example 1: Difference between power prior and mixture prior

- Previous data is available on the control group.
  - Specifically, a trial with 120 subjects and 72 responses.
  - Thus the historical rate is 60%.
- This historical information is kept constant throughout the simulation.
- The sample sizes for the current study are 70 for the controls and 140 for the new treatment.

Example 1: Power Prior vs Mixture Priors

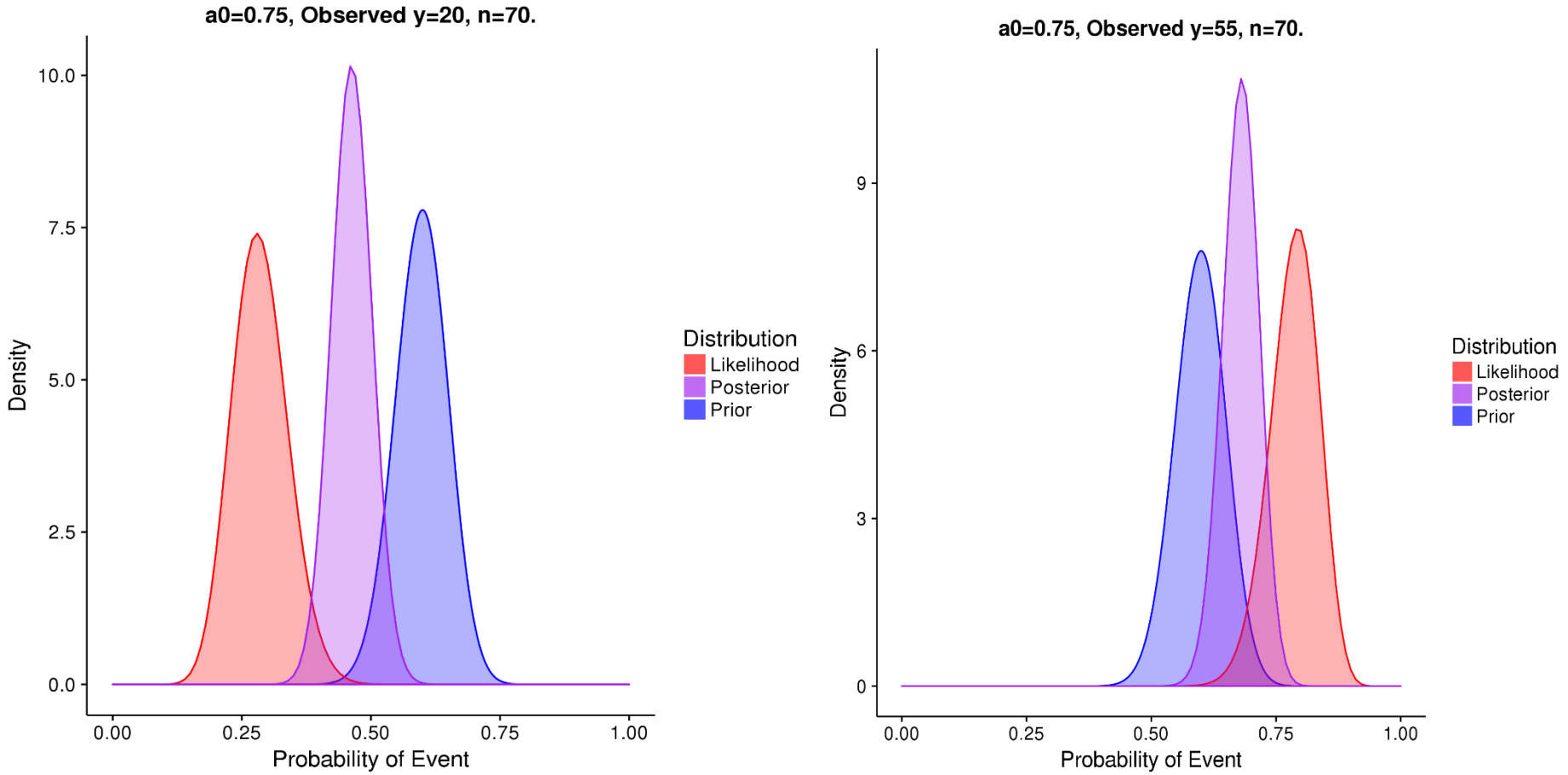


Power prior with various α_0 values



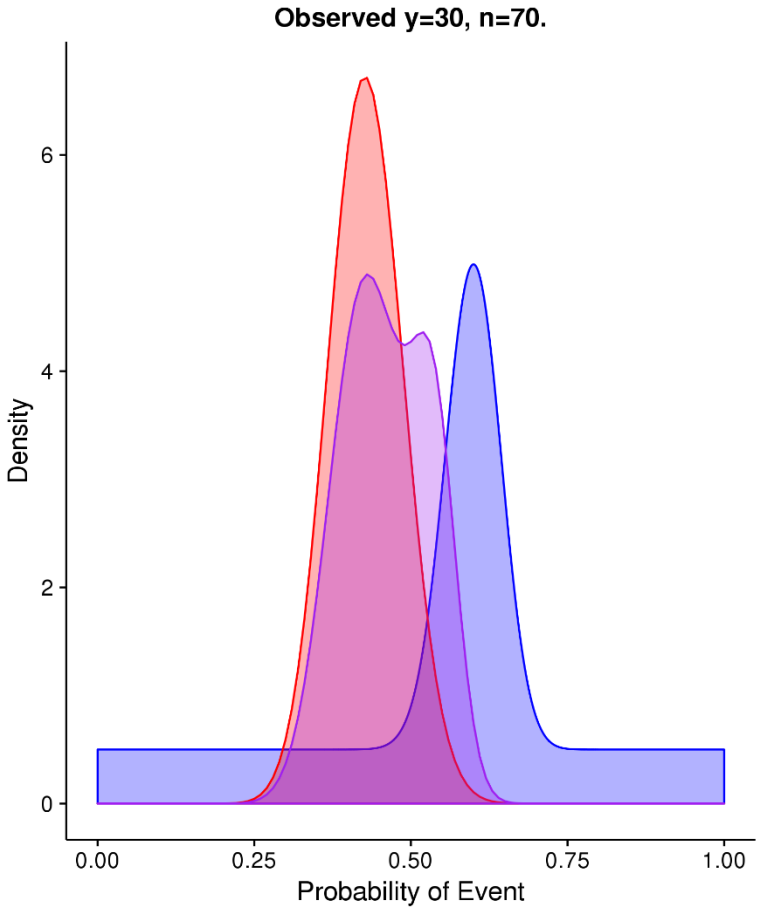
Mixture priors with beta(72, 48) and beta(1,1) at various mixing proportions

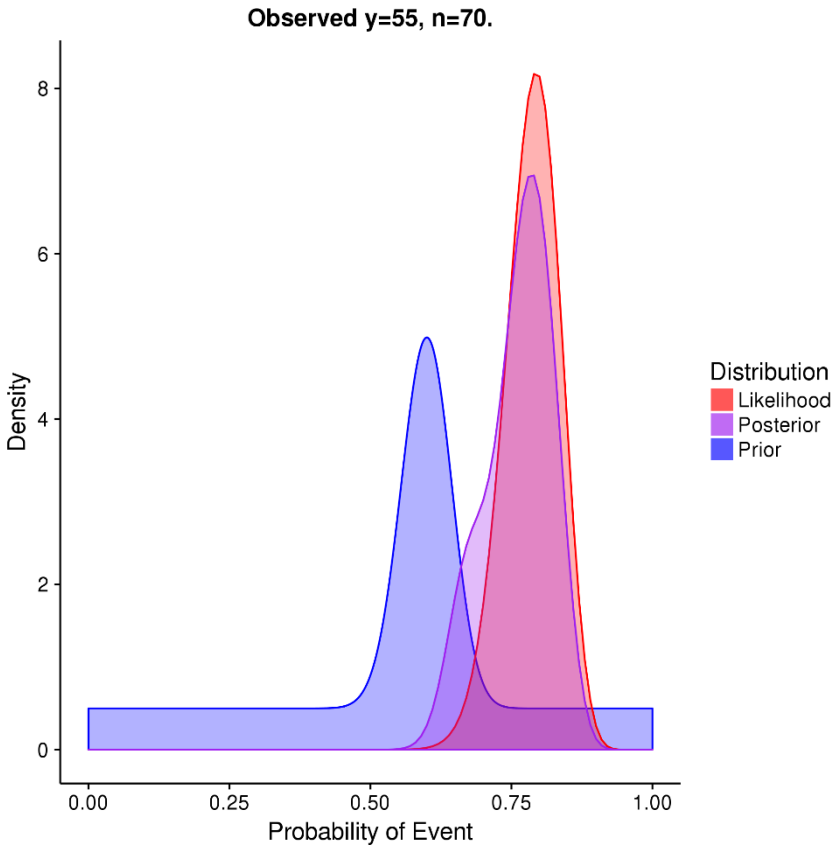
Example 1: Impact of Borrowing with Power Prior



Plots of example posterior distributions for control arm, based on different trial outcomes, using power prior (α_0 = .75)

Example 1: Impact of Borrowing with Mixture Prior





Plots of example posterior distributions for control arm, based on different trial outcomes, using mixture prior (p = .5)

Example 2: Dynamic Borrowing of Adult Data to Pediatrics

- We are considering a pediatric rare disease trial in 50 patients: 40 active, 10 placebo (pbo)
- Primary Endpoint is binary response variable
- We want to use all relevant information
  - ✓ Network Meta-Analysis
  - ✓ Drug of Interest was featured in one study in adults
- We consider the new trial successful if

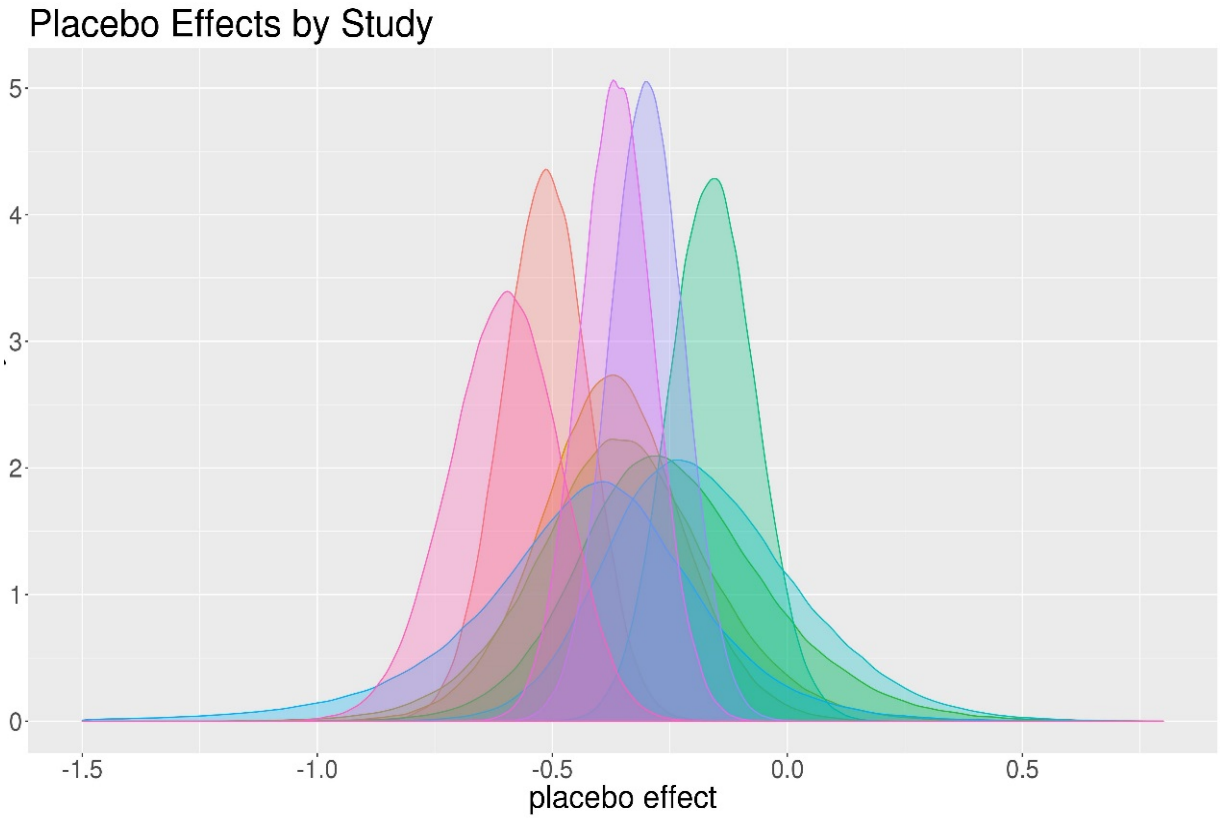
$$P(\text{effect} > 0.4) > 80\%$$

Could be based on medical impact of disease, patient/presciber input

where effect is difference in log odds for drug vs pbo

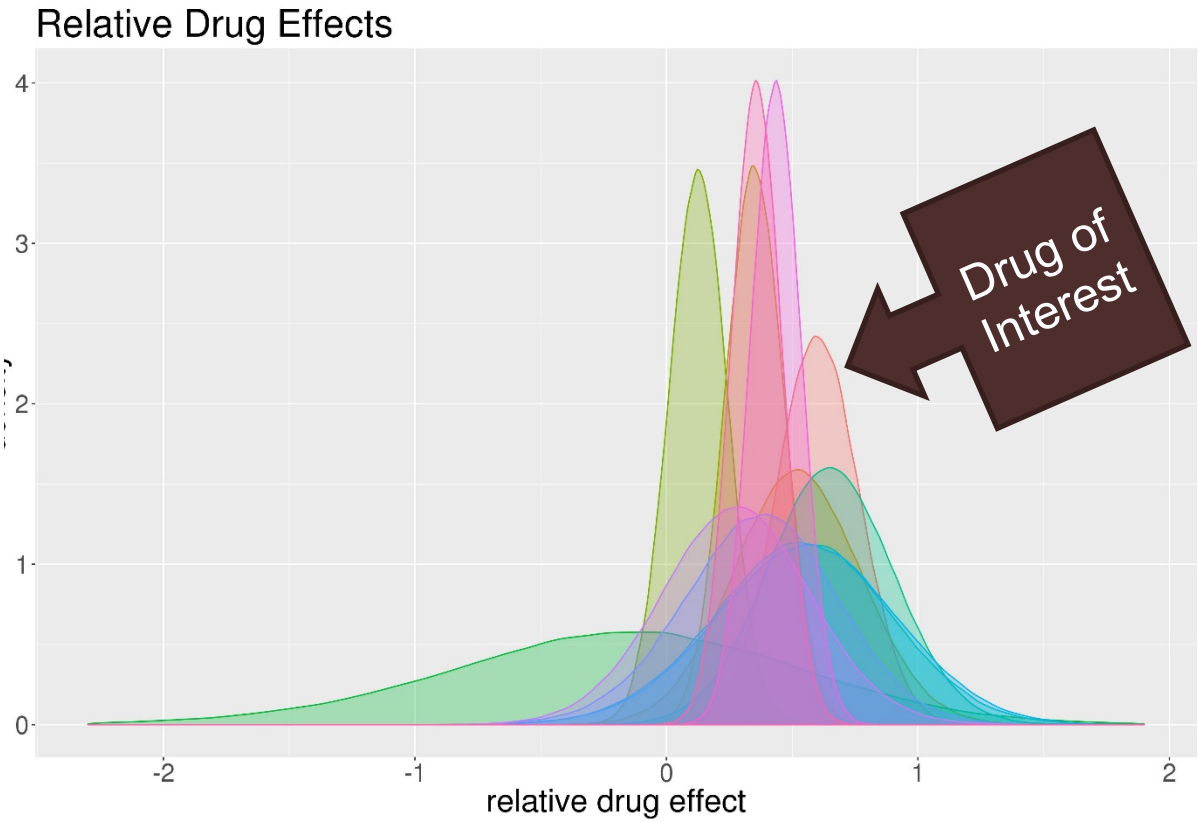
Example 2: Historical Adult Placebo Data

- 10 relevant studies (all controlled).
- 13 different dose / treatments.
- Average Control Rate = 0.4 (*n*=1853)

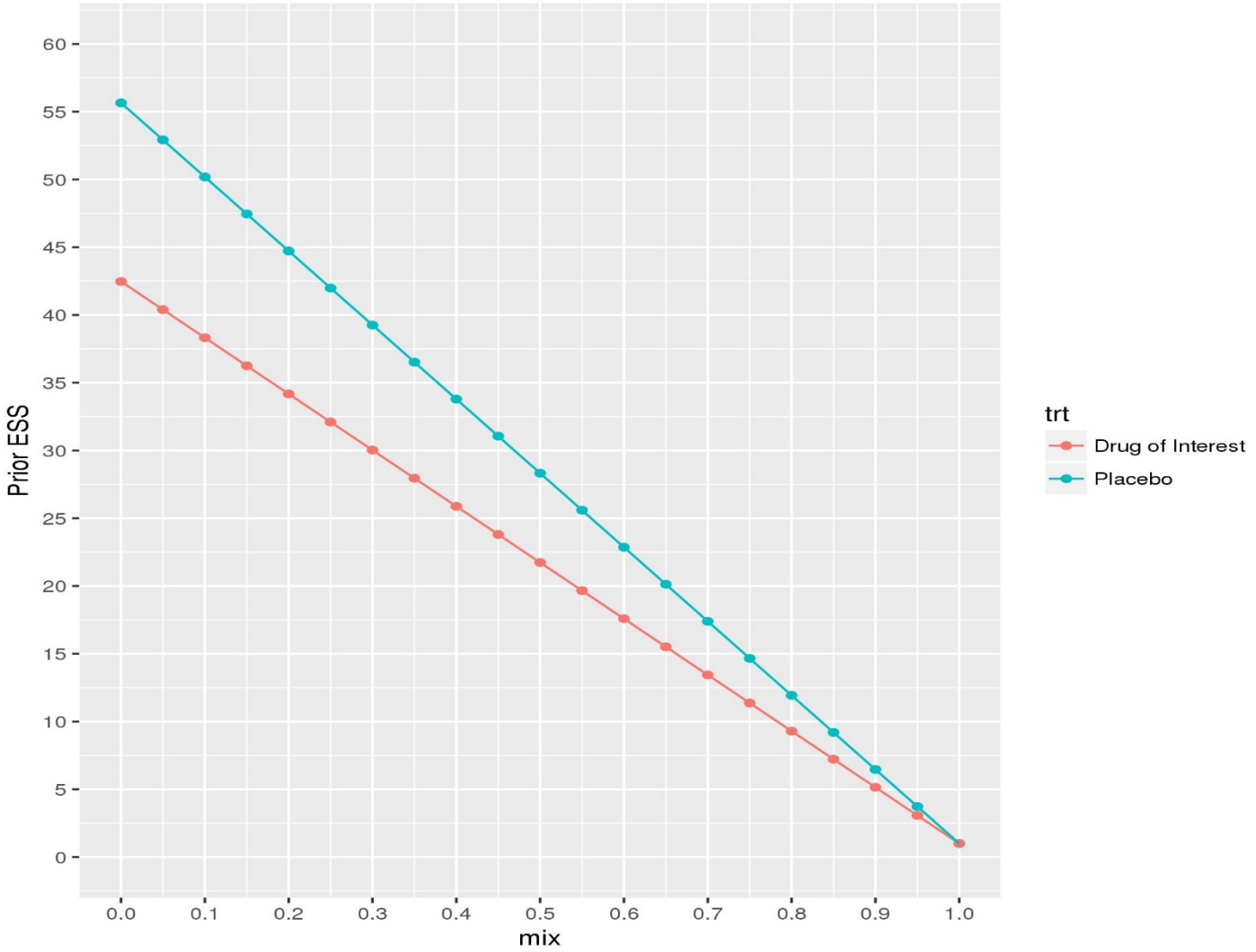


Example 2: Historical Adult Active Drug Data

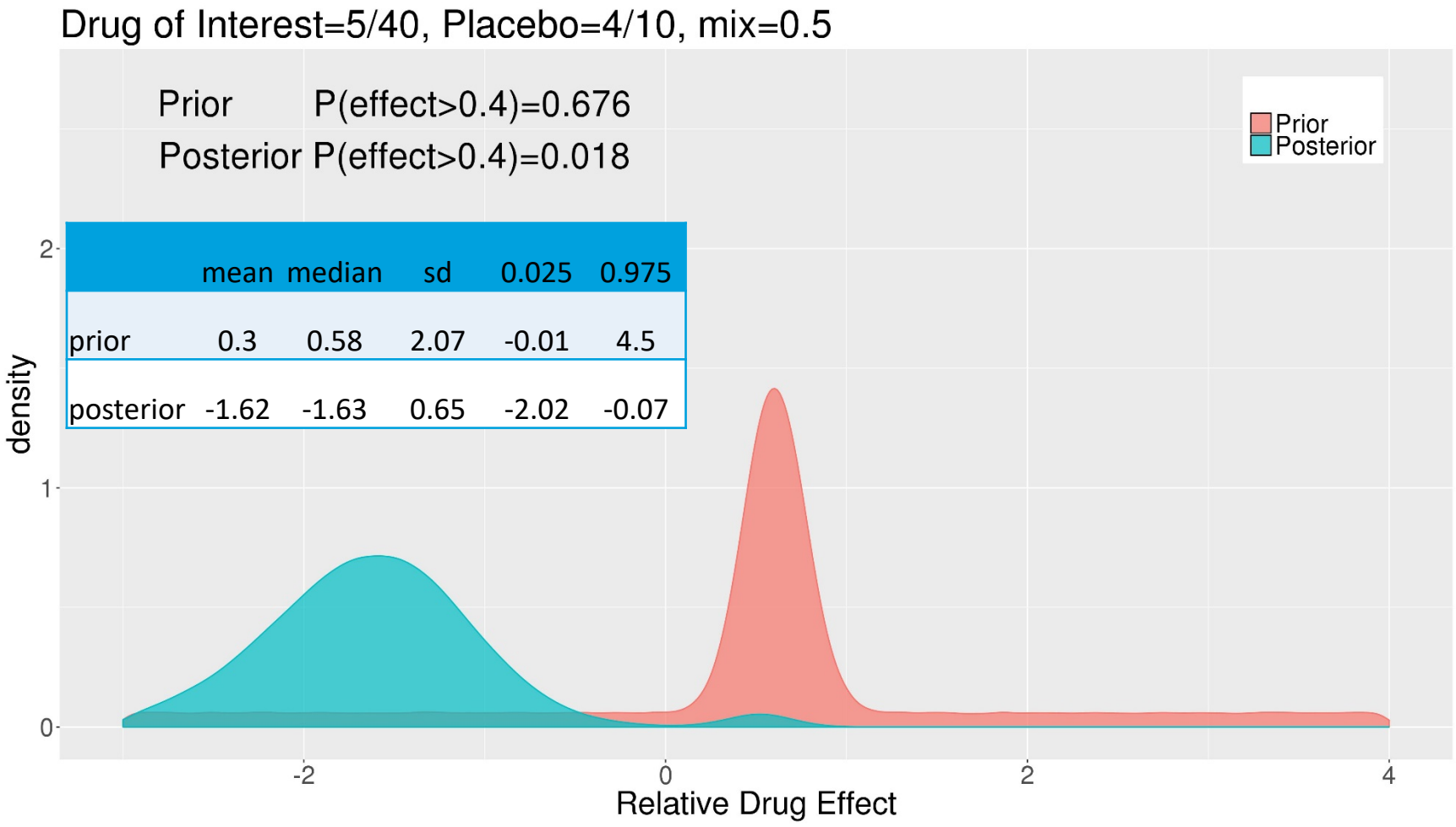
- 10 relevant studies (all controlled)
- 13 different dose / treatments
- Drug of interest rate = 0.5 (*n*=300)



Example 2: Effective Sample Size

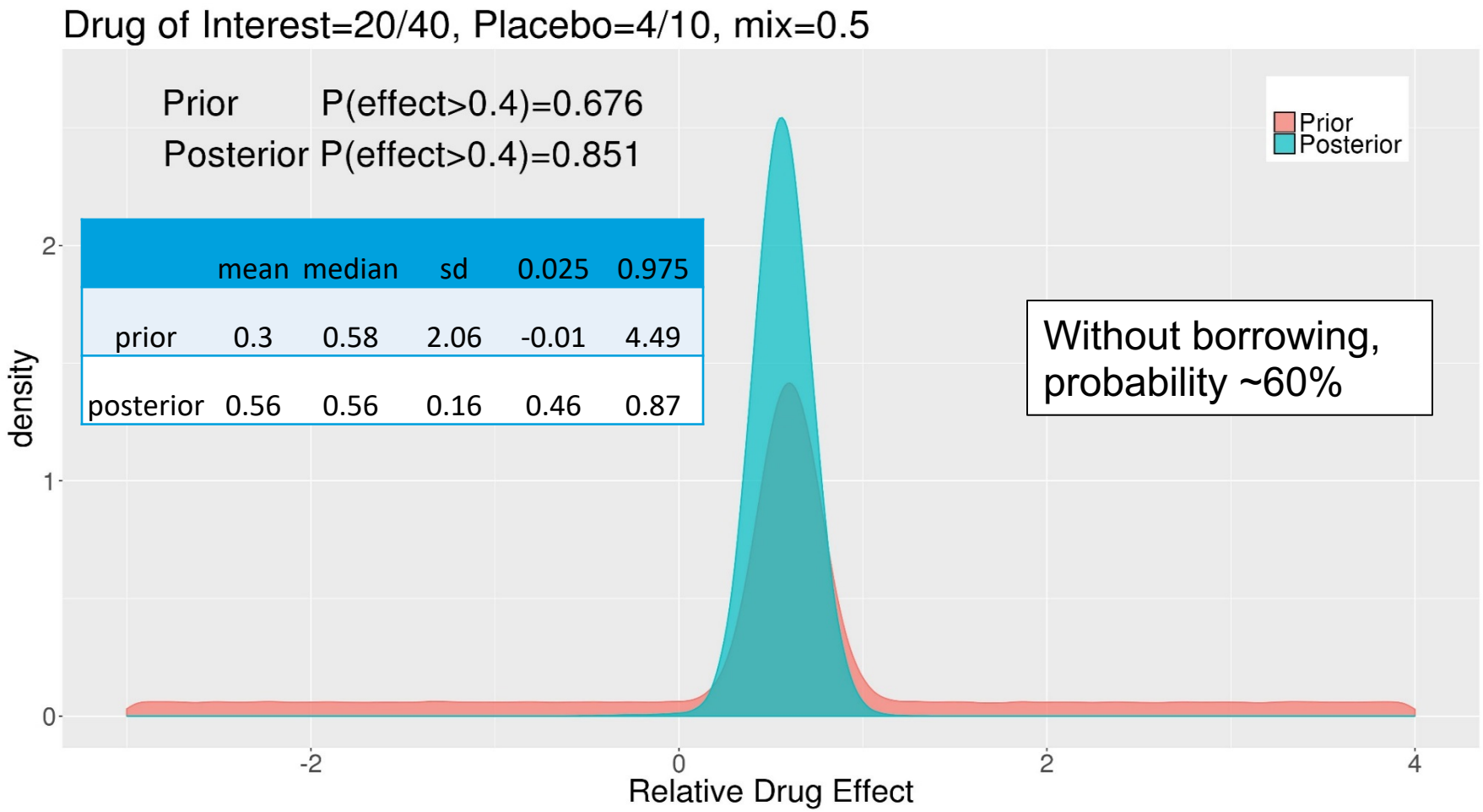


Example 2: An example outcome



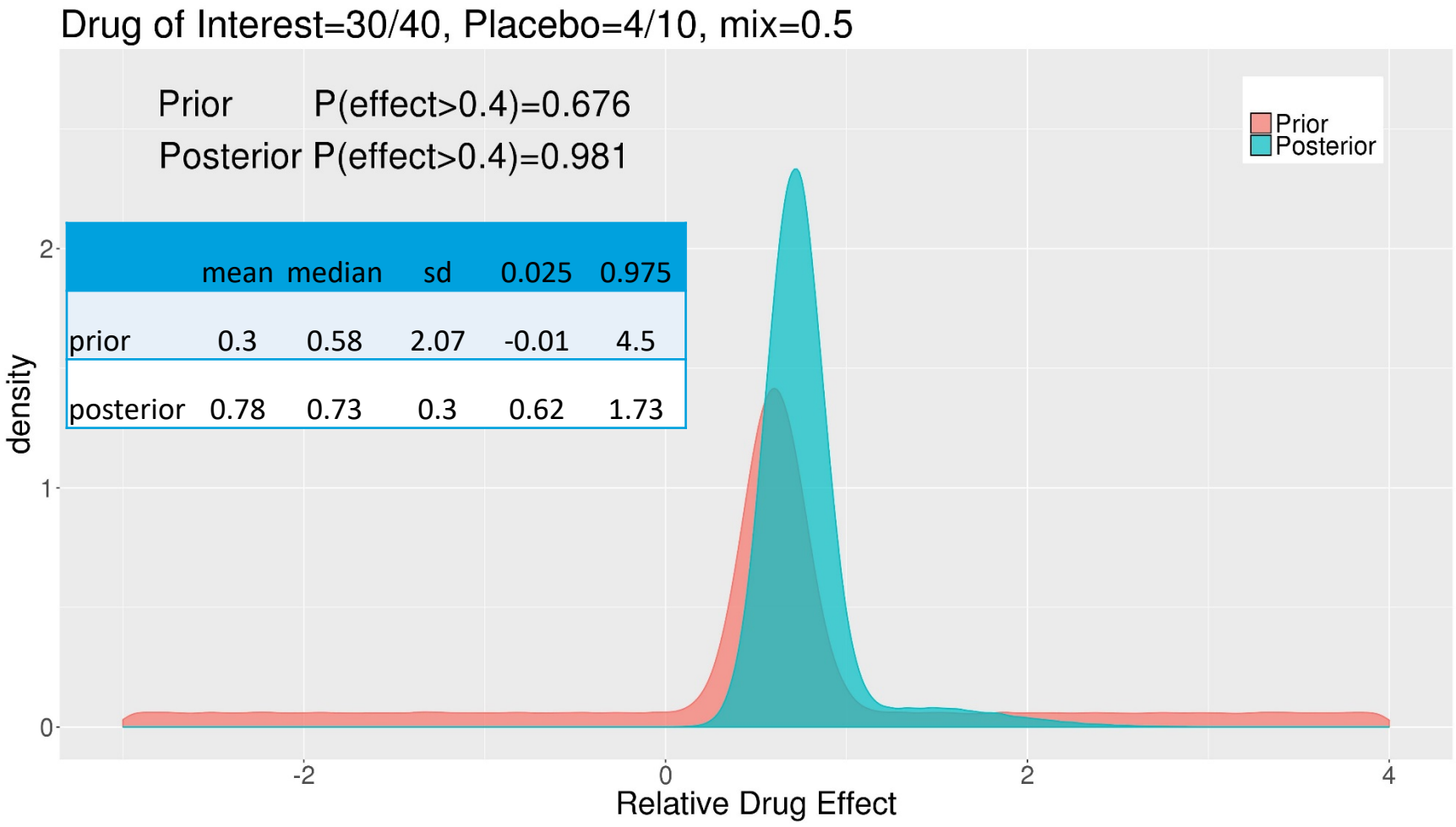
	mean	median	sd	0.025	0.975
prior	0.3	0.58	2.07	-0.01	4.5
posterior	-1.62	-1.63	0.65	-2.02	-0.07

Example 2: An example outcome



	mean	median	sd	0.025	0.975
prior	0.3	0.58	2.06	-0.01	4.49
posterior	0.56	0.56	0.16	0.46	0.87

Example 2: An example outcome



	mean	median	sd	0.025	0.975
prior	0.3	0.58	2.07	-0.01	4.5
posterior	0.78	0.73	0.3	0.62	1.73

Conclusion

- Patients with rare diseases are in desperate need of innovation
- Need to leverage ALL sources of information
- Great flexibility in methods for borrowing
- Can incorporate patient/caregiver preferences and set thresholds accounting for unmet need, etc.
- Requires a shift in thinking from 2 studies $p<0.05$ to continual learning via Bayesian approach

Thank you!