

Expected Value of Research on the Comparative Cost-effectiveness of Antipsychotics Drugs

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Outline

- **Background on Value of Research Methods**
 - **Expected Value of Perfect Information**
 - **Expected Value of Sample Information**
- **Overview of CATIE Cost-effectiveness Results**
- **Aims**
- **Methods (very brief overview)**
- **Results**
 - **Value of Research**
 - **Optimal sample size for a future trial**
- **Conclusions and Discussions**

BACKGROUND

- Value of Research can be best understood via the concepts underlying the value of a diagnostic test.
- Imagine the following scenario:
 - 2 subgroups, A & B each with 50% of the patient population
 - Subgroup A responds to Trt 1 only, producing 5 QALYs, but does not respond to Trt 2, producing 0 QALYS
 - Subgroup B responds to Trt 2 only producing 6 QALYs, but is harmed by Trt 1, producing - 5 QALYS
 - Situation 1: One cannot distinguish between these two subgroups
Trt 1: $0.50*5 + 0.50*0 = 2.5$; Trt 2: $0.50*6 + 0.50*(-5) = 0.5$;
 - Situation 2: Subgroups could be distinguished. The expected value will be:
Trt 1 for A & Trt 2 for B: $0.50*5 + 0.50*6 = 5.5$
 - **Value of a diagnostic test identifying subgroups: 3 QALYs**

BACKGROUND

- Same concepts could be extended to establish the value of future research in a field.
- Today's decision is based on some expected outcomes that carry uncertainties around them – these uncertainties can characterize the error associated with today's decision and therefore the value of future research.
- Example:
- Say the Incr. Value for Pherphenazine vs atypical today = 10
- So, today decision is perphenazine is the optimal treatment, although there is uncertainty surrounding this estimate
- When does future research produce value? Only when it changes today's decision.

BACKGROUND

- What is the value of research if the true level of Incr. Value = 5

$$\Pr(\text{Value}_{\text{True}} = 5) * I(\text{Decision changes} \mid \text{Value}_{\text{True}} = 5) * (\text{Value}_{\text{True}})$$

- What is the value of research if the true level of Incr. Value = -5

$$\Pr(\text{Value}_{\text{True}} = -5) * I(\text{Decision changes} \mid \text{Value}_{\text{True}} = -5) * \text{abs}(\text{Value}_{\text{True}})$$

- Expected Value of Research averages over all possible levels for $\text{Value}_{\text{True}}$

- **Expected Value of Perfect Information** – maximal value of future research – i.e. if future research (with infinite sample size) can fully resolve all uncertainties with outcome what would that research be worth?

- **Expected Value of Sample Information** – Expected value of research with a sample size n .

CATIE CEA

- The Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) was a \$42.6 million, NIMH-funded randomized trial of atypical antipsychotic drugs (A-APDs) and a neuroleptic (perphenazine) in patients with established schizophrenia
- Major findings:
 - Discontinuation rates are similar among those taking the newer A-APDs and perphenazine
 - Perphenazine is the cost-effective first-line treatment in schizophrenia
- Impact
 - Frequently discussed in coverage decisions
 - Some have argued that results should be considered definitive

CATIE CEA

- Limitations
 - Continuation the major endpoint
 - Limited precision in estimates of effectiveness, effects on costs
 - Small differences in effectiveness or effects on costs across many persons could be of great value
- Important to know value of potential future research
 - Help to prioritize individual research opportunities
 - Facilitate rational investment decisions

CATIE Cost-Effectiveness Results

	Monthly Costs	QALY	ICER
	Mean (sd) (\$)	Mean (sd)	(\$/QALY)
Perphenazine	817 (728)	0.722 (0.0064)	-
Olanzapine	1619 (1442)	0.723 (0.0063)	9,624,000
Risperidone	1635 (1457)	0.706 (0.0066)	Dominated
Quetiapine	1680 (1497)	0.721 (0.0065)	Dominated

Ref: Rosenheck et al , 2006; Private Communications with Dr. Rosenheck)

Only statistically significant difference:

$QALY_{\text{Perphenazine}} > QALY_{\text{Risperidone}}$ (p-val < 0.001)

Aims

- Primary Aim: To determine the expected value of more precise determination of effects of AAPDs and perphenazine on costs and QALYs.
- Secondary Aim: To determine the optimal sample size for a future trial of the effects of AAPDs and perphenazine on costs and QALYs

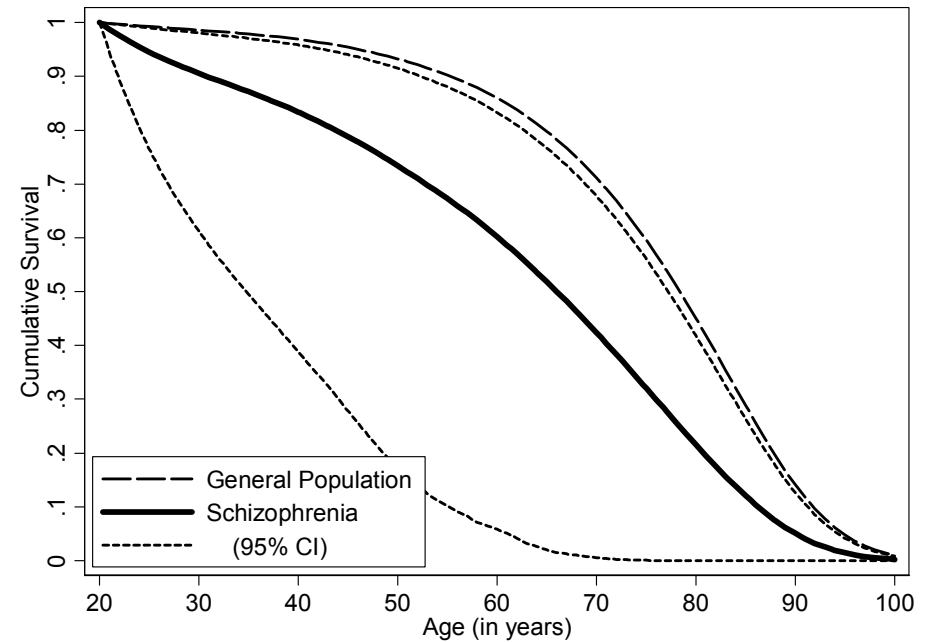
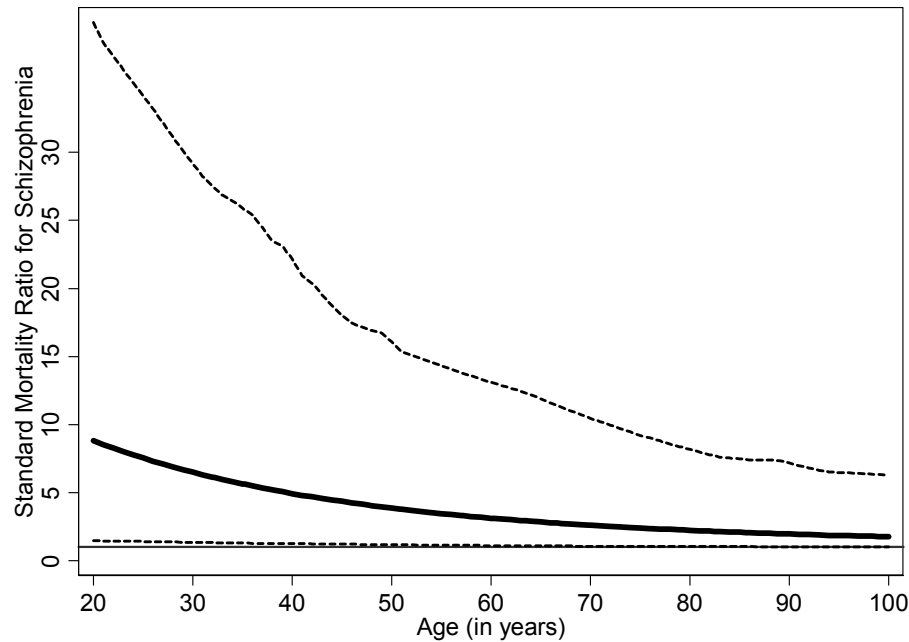
Methods used for Value of Research

Expected value calculated based on the welfare of the prevalent cohort over their lifetimes and the welfare of next 20 incident cohorts over their lifetimes

3% discounting was used

RESULTS ON VALUE OF RESEARCH

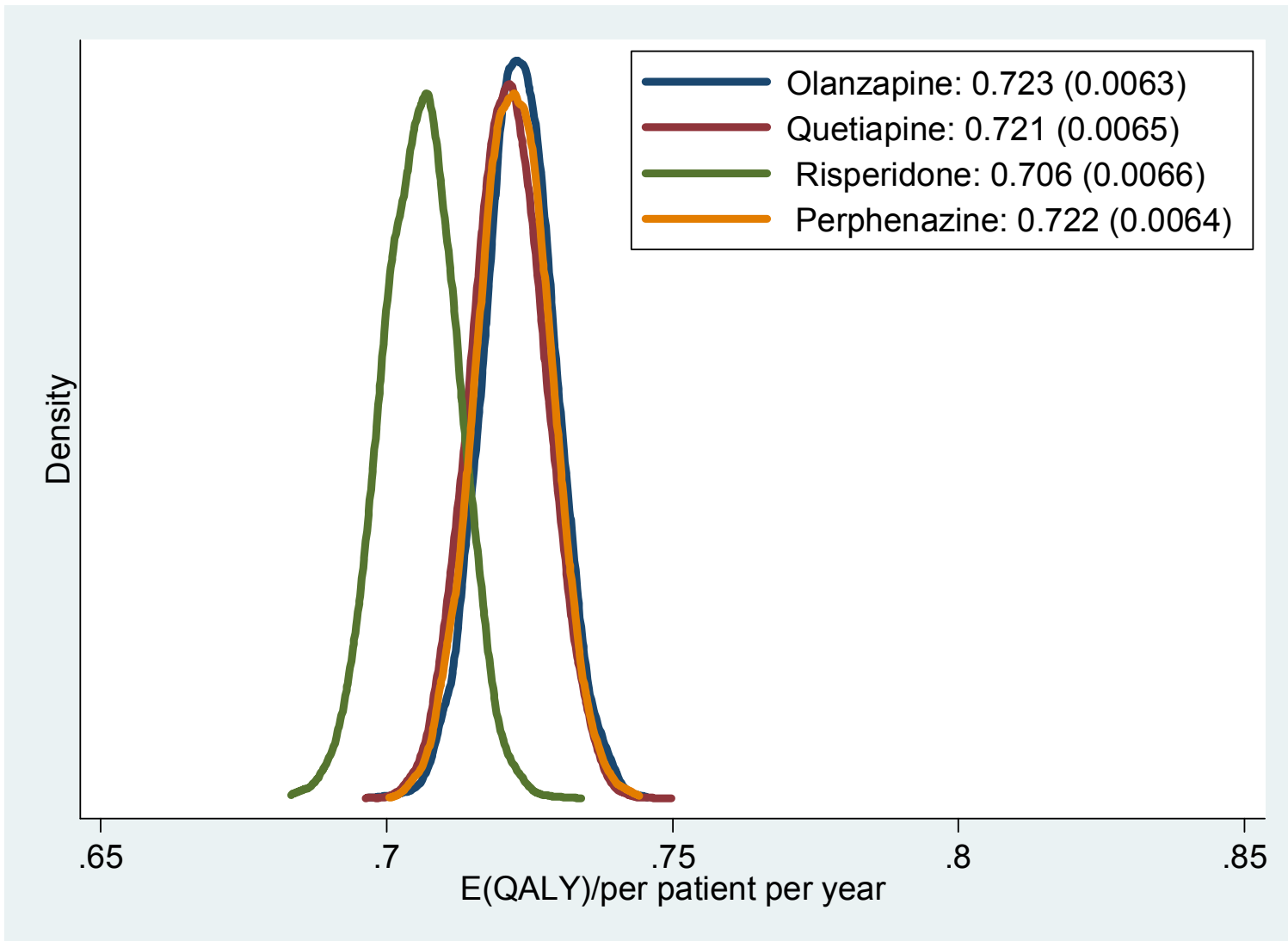
Posterior mean and 95% CCI of age-specific SMR and survival fractions for the schizophrenia population



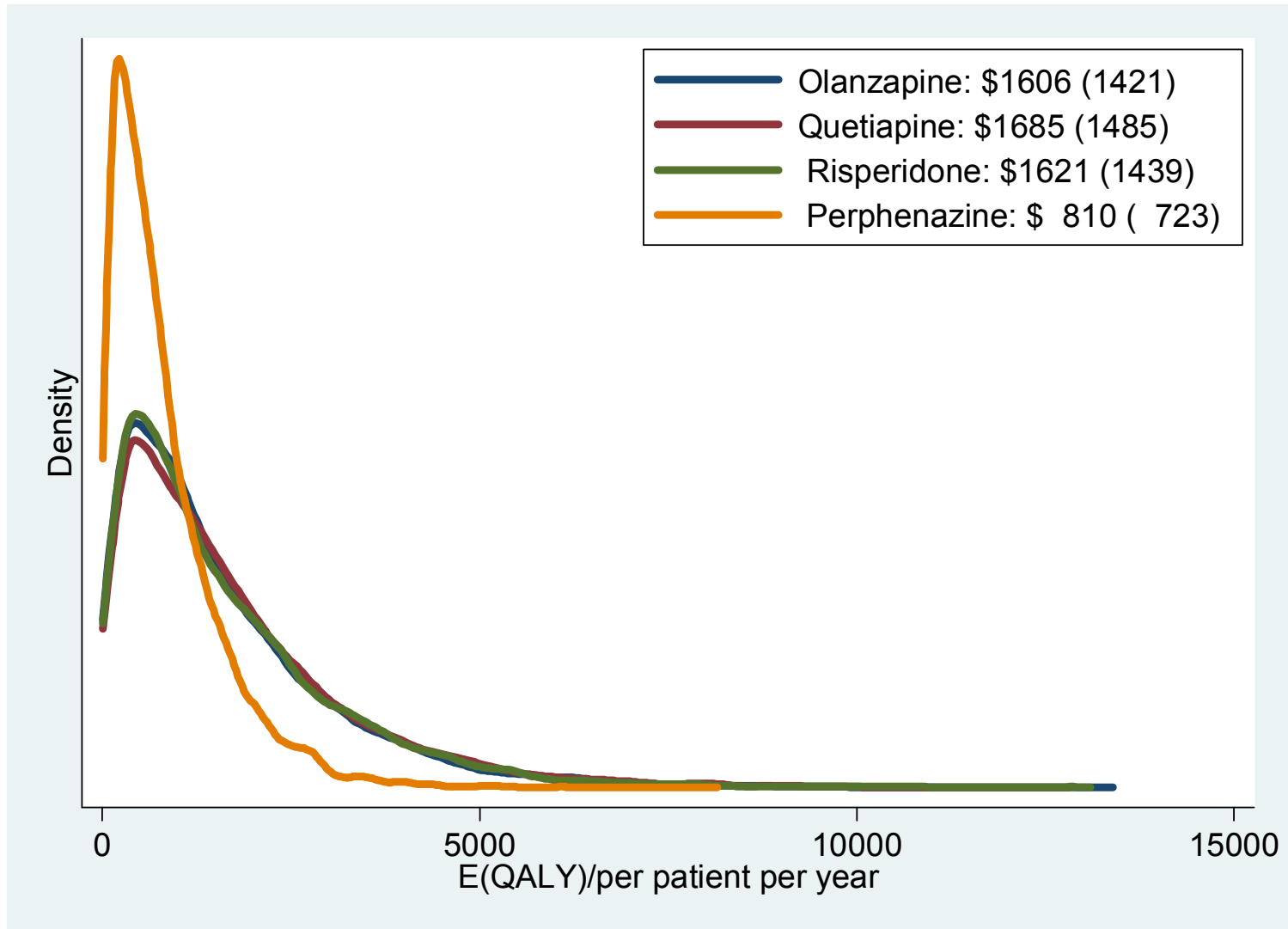
Avg. life expectancy for general population @ age 20 = 56 yrs.

Avg. life expectancy for schizophrenia population @ age 20 = 43 yrs (SD = 9.93).

Simulated distribution of Mean QALYS (based on uncertainty around CATIE results)

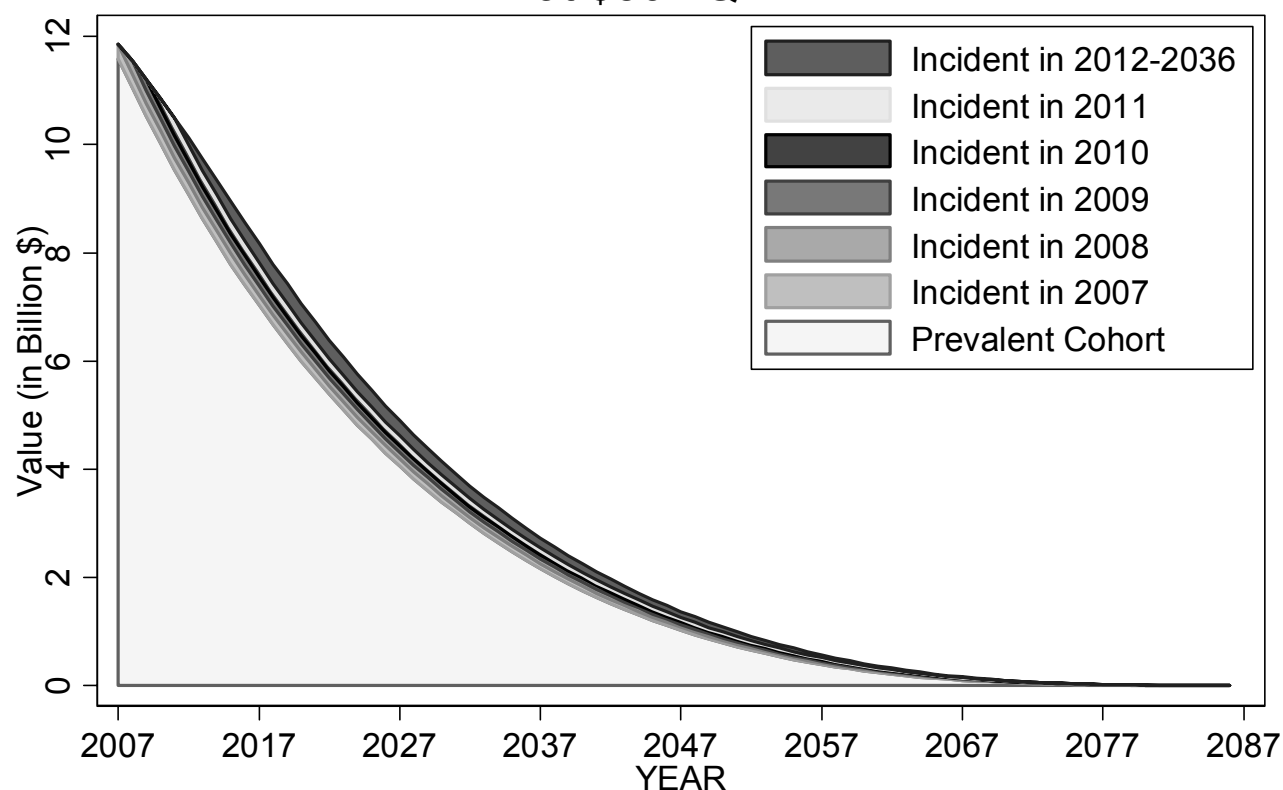


Simulated distribution of Mean Costs (based on uncertainty around CATIE results)



REALIZATIONS OF VALUE OF RESEARCH OVER TIME

Value of Future Research to Prevalent and Incident Cohorts
at \$50k/QALY

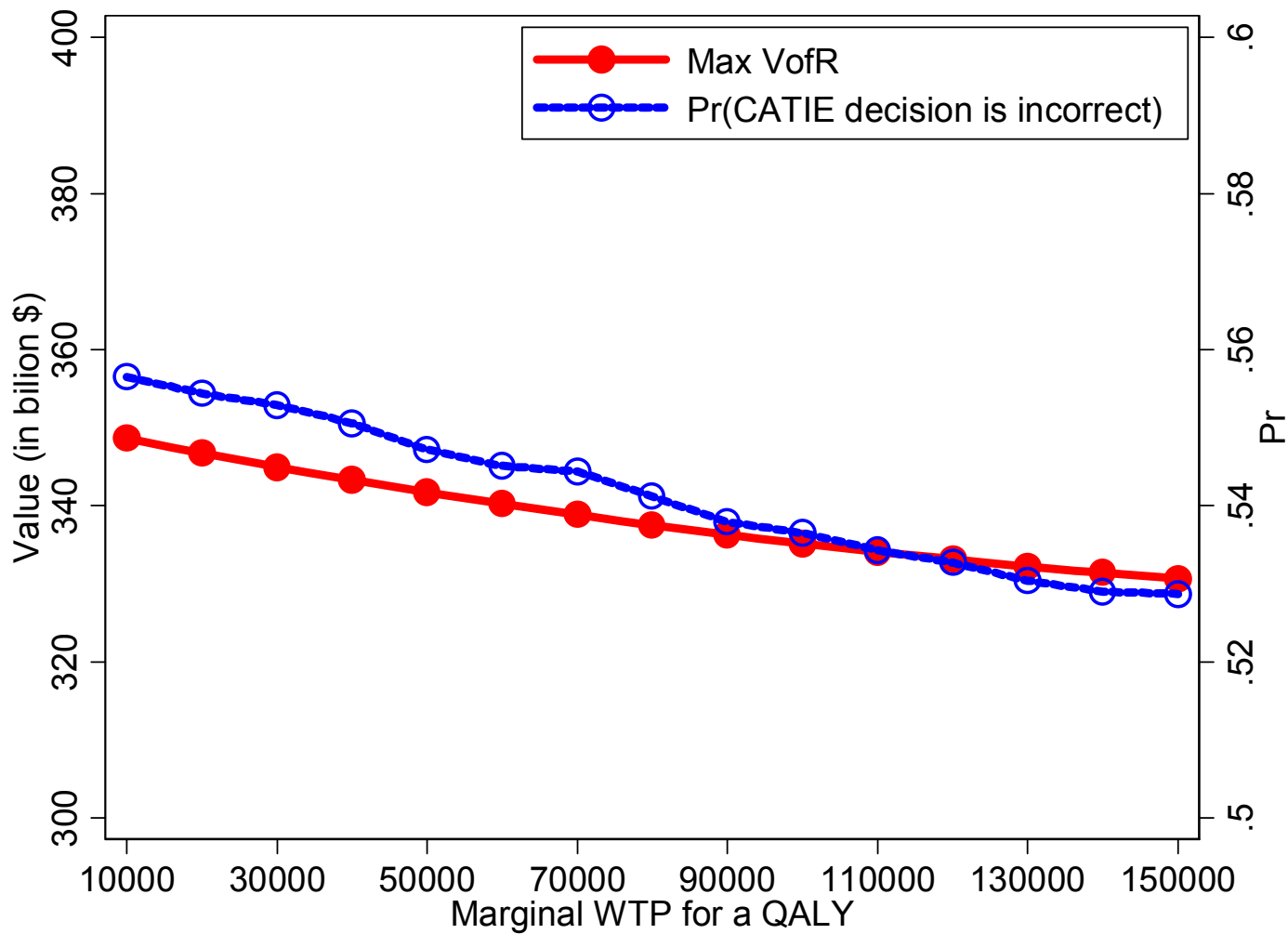


TOTAL VALUE TO PREVALENT COHORT: \$207 billion

TOTAL VALUE TO EACH INCIDENT COHORT: \$6.6 billion

TOTAL VALUE TO PREVALENT & NEXT 20 INCIDENT COHORTS:
\$342 billion

VALUE OF RESEARCH AND ACCEPTABILITY PROFILE



Methods for Optimal Design for Future Research on Comparative CEA

- Approach 1: Traditional deterministic power calculations conditional on estimates effect size and variance
- Approach 2: Fully Bayesian Expected Value of Sample Information (EVSI)
 - Establish the maximal expected value of research, not for perfect information, but for the information potentially generated by a trial of size n (each arm).
 - Calculate net expected value of research by subtracting the costs of conducting a trial of size n (each arm).
 - The trial size n , at which the net expected value gets maximized, is the optimal sample size for a future trial.

RESULTS ON OPTIMAL SAMPLE SIZE FOR A FUTURE TRIAL

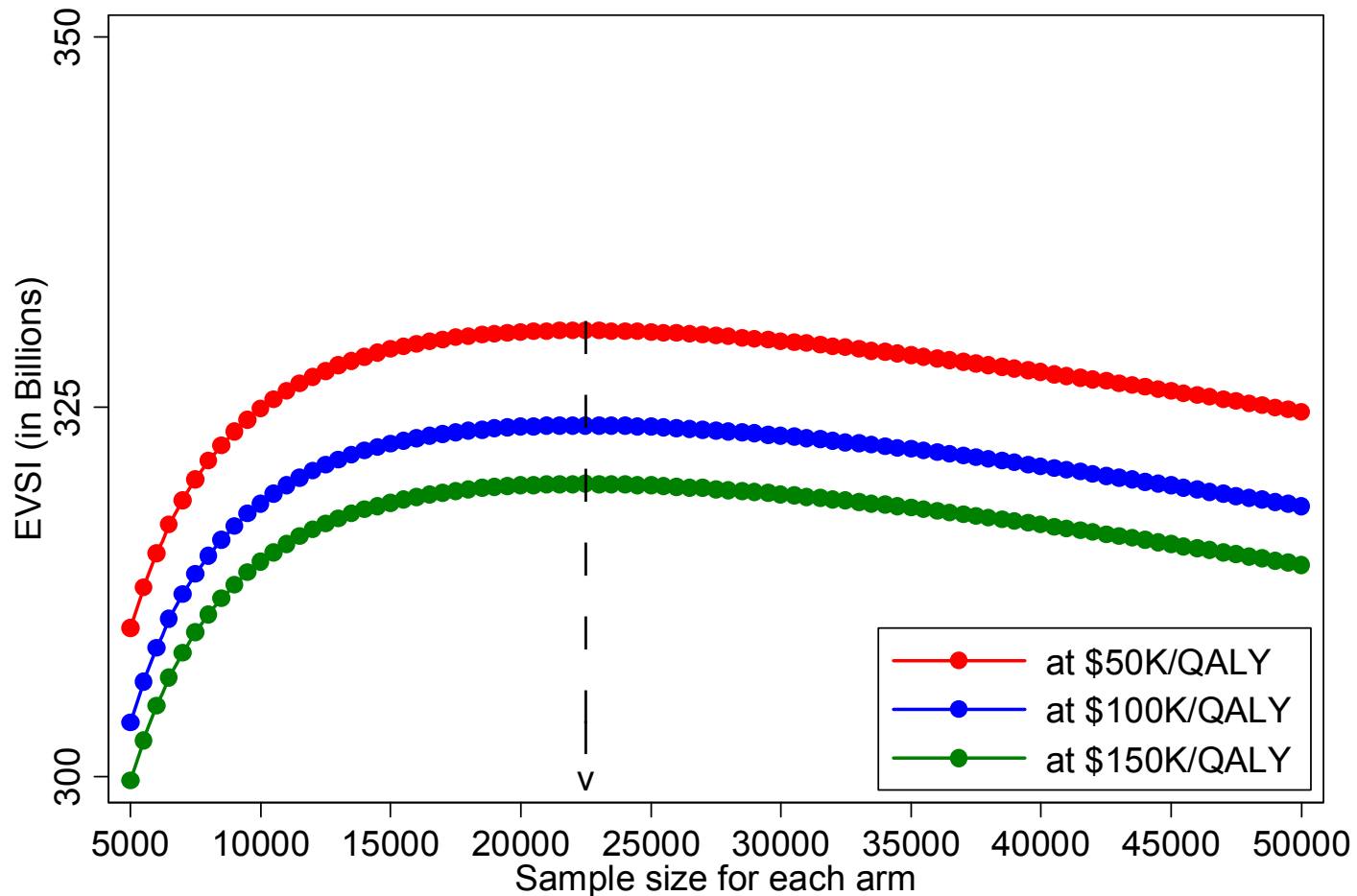
TRADITIONAL (DETERMINISTIC) POWER CALCULATIONS (at \$50K/QALY)

Largest effect size in NMB between
a atypical & perphenazine based on CATIE results:
15,680 (sd=315,000) vs 26,296 (sd=140,000)

Sample size required for $\alpha = 0.05$ & power = 0.80:
8,300 for each arm

Power associated with n of CATIE = 400/arm & $\alpha = 0.05$:
10%

NET EXPECTED VALUE OF SAMPLE INFORMATION (at \$50K, \$100K and \$150K/QALY)



Cost of Research: \$3 mill + (sample size*4)*(\$5000/month)*18 months

Optimal sample size for each arm = 22,500

LIMITATIONS

- SMR based on older data from pre-atypical period
- Value of information for specific domains of outcomes may provide a more useful guide to the value of specific studies
- Results could be sensitive to distributional assumptions
- Analysis only examine first-line treatment assignment, and neglects algorithmic approaches to treatment assignment

CONCLUSIONS

- The value to more precisely establishing the cost-effectiveness of typical/atypical antipsychotics is enormous.
- The results of CATIE should not be viewed as definitive.
- Further studies of the comparative cost-effectiveness of typical/atypical antipsychotics with adequate sample size to answer such questions are needed.
- Optimal sample sizes may be exceptionally large, raising interesting questions as to how clinical trials on such a scale might be executed.
 - Large scale social experiments may provide an interesting model for such studies.

Acknowledgement

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Slides posted on:

<http://home.uchicago.edu/~abasu>

APPENDIX

Methods used for Value of Research

1. Account for uncertainty in survival estimates by Bayesian meta-analysis of age-specific SMR in schizophrenia → converted to a distribution of survival curves.
2. Estimate incidence rate given distribution of survival curves and a steady-state lifetime schizophrenia prevalence of 1% (estimated to be 13 per 1000 incident 20 year olds ~4047740 incident cases per year)
3. Establish best decision with current information based on expected values

Today's decision, based on mean incremental benefits $\Delta\bar{q}$ and mean incremental costs $\Delta\bar{c}$ from CATIE, favors using perphenazine as the first-line of treatment since

$$INMB(\Delta\bar{q}, \Delta\bar{c}) < 0 \text{ for all atypicals compared to perphenazine}$$

4. Generate a distribution of values for Δq and Δc based on uncertainty around the estimates of CATIE results

- Assume mean costs under each drug follow a Gamma distribution with expected value and variance based on CATIE results
- Assume mean QALYs under each drug follow a Normal distribution with expected value and variance based on CATIE results

5. Calculate incremental net monetary benefits given a specific level of incremental benefit (Δq) and incremental costs (Δc) of an atypical versus perphenazine:

For Prevalent Cohort:

$$INMB_{PREV}(\Delta q, \Delta c) = \int_{s \in S} \left[\sum_{a=20}^{100} p_a \cdot \sum_{A=a}^{100} \left(\beta^{(A-a)} \cdot s(A) \cdot \{\Delta q \cdot \lambda - \Delta c\} \right) \right] ds$$

p_a = Prevalence at age a ; $s(A)$ = Deterministic survival fraction at age A ;
 S = Distribution of survival functions; λ = Maximum societal willingness-to-pay for a QALY; β = Discount Factor

For Each Incident Cohort: Similar calculations, but:

$$INMB_{INC}(\Delta q, \Delta c) = \int_{s \in S} \left[\sum_{a=20}^{100} i \cdot (\beta^{(a-20)} \cdot s(A) \cdot \{\Delta q \cdot \lambda - \Delta c\}) \right] ds$$

i = # of incident cases of schizophrenia per year (incident at 20 years).

Total Net Present Incremental Value

$$INMB_{TOT}(\Delta q, \Delta c) = INMB_{PREV}(\Delta q, \Delta c) + \sum_{t=1}^{20} \beta^{(t-1)} \cdot INMB_{INC}(\Delta q, \Delta c)$$

6. Calculate the Maximal Net Present Value of Future Research

- Calculate the expected value of changing decisions over all values of incremental benefit (Δq) and incremental costs (Δc) of an atypical versus perphenazine.
- Value of future research is positive only when that research produces new information that will change our current decision, otherwise it is zero.

$VALUE_{TOT} =$

$$\int_{\Delta c \in \Delta C} \int_{\Delta q \in \Delta Q} \left[I \{ \max\{INMB_{TOT}(\Delta q, \Delta c)\} \leq 0 \} \cdot 0 + I \{ \max\{INMB_{TOT}(\Delta q, \Delta c)\} > 0 \} \cdot \max\{INMB_{TOT}(\Delta q, \Delta c)\} \right] d\Delta q \cdot d\Delta c$$

- $VALUE_{TOT}$ can be further decomposed into a $VALUE_{PREV}$ & $VALUE_{INC}$
- Probability that future research produces new information that will change our current decision is given by $E(I \{ \max\{INMB_{TOT}(\Delta q, \Delta c)\} > 0 \})$

Specifics of EVSI Method

- For every true level of incremental QALY Δq and incremental costs Δc , a future trial of size n , will produce sample means Δq_n and Δc_n
- Therefore, the future posterior means, $\Delta q'$ and $\Delta c'$, will be a weighted average of the mean CATIE results and the mean results from the future trial, where the weights will be dependent on the size n of the trial.
- Future decision will be made based on these posterior means. Therefore, the future trial would be valuable if the future posterior means based on the results of that trial would change today's decision
- EVSI is calculated similarly as Value of Research calculations described above, where deviates of incremental QALY Δq and incremental costs Δc are replaced with $\Delta q'$ and $\Delta c'$ respectively