

Methodological Issues in PE² PharmacoEPidemiology (PEP) and PharmacoEconomics (PEC)

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What is PharmacoEPidemiology (PEP)?

- A bridge science between pharmacology and epidemiology
- To assess the patterns and appropriateness of drug utilization
- To provide explanations for poor compliance, quantify the frequency and severity of side effects
- To aid in the design and evaluation of interventions to improve drug use and outcomes

Jerry Avorn, The Role of Pharmacoepidemiology and Pharmacoeconomics
in Promoting Access and Stimulating Innovation,
Pharmacoeconomics, 2004;22 Supplement 2 : 81-86

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What is PharmacoEconomics (PEC)?

- A division of Health (Care) Economics
- A tool, not a solution, designed to provide users and decision makers with information about the cost-effectiveness of different pharmacotherapies
- To recommend the most cost-effective agent at achieving a designated outcome in a specific population
- To provide the desired level of efficacy, at achieving an outcome, for the lowest possible costs

Practical Pharmacoeconomics, L.E. Basskin

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Connections of PEP & PEC (PE²)

“Taken pharmacoepidemiology and pharmacoeconomics together, represent the next logical step in the evolution of medication assessment; their judicious deployment can help ensure both access to new medicines and innovation.”

Jerry Avorn, The Role of Pharmacoepidemiology and Pharmacoeconomics
in Promoting Access and Stimulating Innovation,
Pharmacoeconomics, 2004;22 Supplement 2 : 81-86

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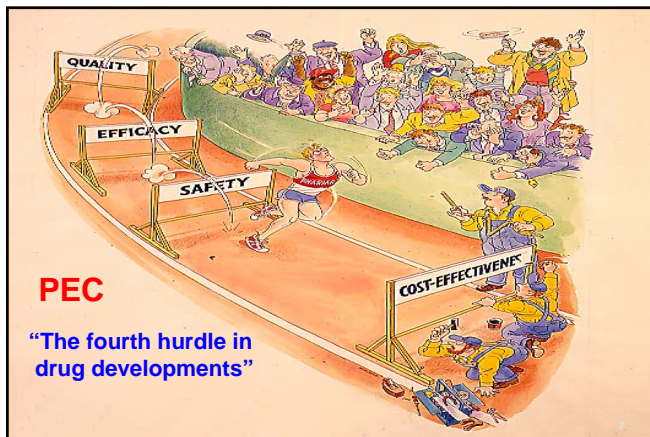
Study Methods in PEP

- Experimental study
phase IV
- Observational cohort study
post marketing surveillance
collaborative group study
- Retrospective case study
chart review in hospitals
- Statistical mining in database
BNHI database extraction

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PharmacoEconomics (PEC) The Fourth Hurdle

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Economics & Health Messages in Biomedical Research

- Costs vs. Health (Effectiveness, Utility)
- Preference of health states
- Disease Burden
- Parameter of the information
- Quantitative Synthesis
- Perspective
- Moral and ethic considerations
- Only for economics message

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Types of PE Analysis

- Cost-minimization Analysis (CMA)
 - Estimates costs of an intervention, but not benefits
 - Appropriate when two pharmacotherapies of equal efficacy are compared
- Cost-effectiveness analysis (CEA)
 - Estimates costs and outcomes of intervention, but the two are measured in different units

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Types of PE Analysis

- Cost-utility analysis (CUA)
 - When the outcomes are measured in utilities, multidimensional scale such as QALYs (Quality Adjusted Life Years)
- Cost-benefit analysis (CBA)
 - Estimate costs and benefits in the same (usually monetary) units

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What Data & When It Happens

- Phase I and II: Incidence and prevalence-based cost of illness
 - Incidence-based: lifetime costs of the disease for a cohort with incident disease
 - Prevalence-based: costs of disease during a given time period for prevalent cases
- Preplanned of phase III economic studies
- Cost / Efficacy studies in clinical trials
 - Provides economic data for registration, pricing, and early use

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What Data & When It Happens

- Cost-Effectiveness studies in usual care
 - Comparisons made in more realistic settings with more realistic protocols against comparators of interest to individual decision makers
 - Allow decision makers to assess whether results from phase III trials are generalizable to usual care
- Post marketing surveillance studies
 - Observational data to evaluate costs, effectiveness, and adverse experiences related to the drug

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Data Collection : Systematic Review

- Evidence Base Medicine (EBM)
 - Tracking down, Critical appraisal, Integrating, evaluation
 - Well formulated the question in the analysis
 - Patients, Intervention, Comparison, outcomes (PICO)
 - Search for the information from various sources
 - Cochrane database: www.cochrane.org
 - US AHRQ website: www.ahrq.gov
 - GB NICE website: www.nice.org.uk
 - Canada CCOHTA website: www.ccohta.ca
 - Scotland SIGN website: www.sign.ac.uk
 - New Zealand NZGG website: www.nzgg.org.nz
 - Clear queries from web
 - Level of evidence

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Data Collection : Meta Analysis

- Meta Analysis (MA)
 - A quantitative method of combining the results of independent studies and synthesizing summaries and conclusions
 - Used to evaluate therapeutic efficacy

Forest plot



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Data Base Extraction

- Data collection from a pre collected data sources
 - e.g. BNHI data base
- Database layout
- Dictionary of the variables defined
- Technique in data management
- Commercial data base
- Statistical analysis software
- On line query from the database preferred

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Outcomes of Interest in PE Study

- Average Cost-Effectiveness Ratio

$$CE \text{ Ratio} = C / E = \text{Cost} / \text{Effectiveness}$$

- In CEA, effectiveness can be "LY"
- In CUA, effectiveness can be "QALY"
- No alternative is considered

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Outcomes of Interest in PE Study

- Incremental Cost-Effectiveness Ratio (ICER)

$$\Delta C / \Delta E = \text{Cost}_{\text{after}} - \text{Cost}_{\text{before}} / \text{Effectiveness}_{\text{after}} - \text{Effectiveness}_{\text{before}}$$

Incremental costs after an intervention

Incremental effectiveness After an intervention

- In CEA, effectiveness can be "LY"
- In CUA, effectiveness can be "QALY"
- aka Marginal Cost-Effectiveness Ratio

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Decision Tree Analysis

- Purpose:
 - Model diseases in which alternative risks are evaluated and various outcomes are considered in a tree model
- Principles:
 - Disease specific decision are stated, possible outcome are defined with a probability parameters
 - At each possible chance node, cost information are collected
 - At each terminal node of the outcome, utility or effectiveness are defined
 - cost and effectiveness are calculated by a "folding back" calculation method

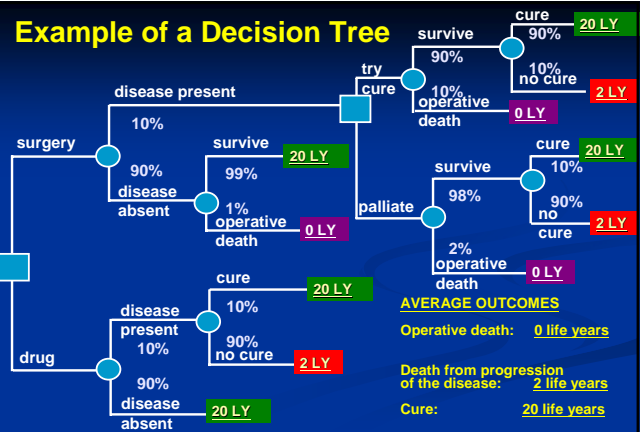
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Example

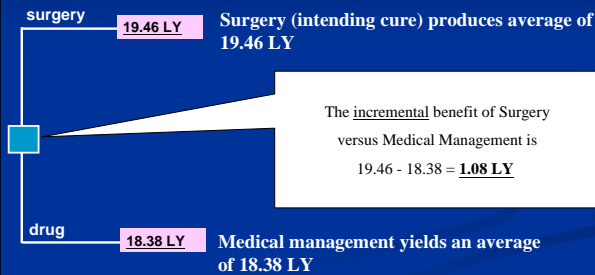
- Symptomatic patient:
 - operate (risky)
 - medical management
- If disease present at surgery, must decide whether try for cure or palliate
- Want to evaluate surgery vs. medical management

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Example of a Decision Tree

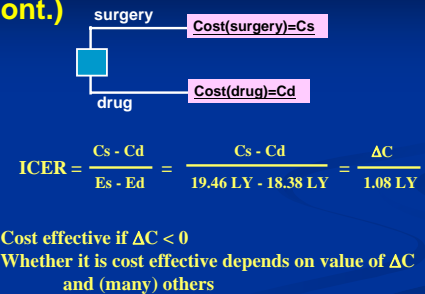


Example of a Decision Tree (cont.)



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Example of a Decision Tree (cont.)



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Cost, Effectiveness Derivation in Decision Tree

- Utilizing of Conditional Expectation in Probability and Statistical Theory

$$E(X) = E(E(X | Y)) = \sum p_y E(X | Y = y) = \sum p_y \sum p_{x|y} X$$

- Apply to both the cost and effectiveness calculation

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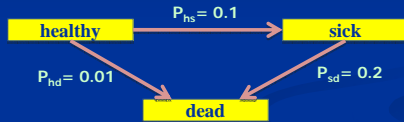
Markov Model

- Purpose:
 - Model diseases in which risks are continuous over time and timing of events is important
- Principles:
 - Disease specific health states are defined, time of evaluation is divided into periods (cycles)
 - At each point in time each patient is in one of the health status
 - During each cycle the patients can move from one health state to another (transition). The risk of this transition is called "transition probability"

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Markov Model (cont.)

- Example: 3 health states (dead, sick, alive)



	Start	after 1 year	after 2 years	after 3 years
healthy	1000	890	792	705
sick	0	100	169	214
dead	0	10	39	81
total	1000	1000	1000	1000

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Markov Model (cont.)

- Transition probability matrix after one cycle

State at the end of every cycle	healthy	sick	dead	total
State at the start of every cycle →				
healthy ↓	0.89	0.1	0.01	1
sick	0	0.8	0.2	1
dead	0	0	1	1

- Transition probability matrix after few cycles

State	healthy	sick	dead	total
State after the first cycle	0.89	0.1	0.01	1
State after the second cycle	0.7921	0.169	0.0389	1
State after the third cycle
State of the k th cycle	P _{hh}	P _{hs}	P _{hd}	1

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Markov Model (cont.)

- Transition probability matrix after one cycle

$$T = \begin{bmatrix} 0.89 & 0.1 & 0.01 \\ 0 & 0.8 & 0.2 \\ 0 & 0 & 1 \end{bmatrix} \begin{matrix} \text{healthy} \\ \text{sick} \\ \text{dead} \end{matrix}$$

- Transition probability matrix after two cycles $T^2 = T * T$
- Transition probability matrix after k cycles $T^k = T * T * ... * T$

$$T^k = \begin{bmatrix} p_{hh} & p_{hs} & p_{hd} \\ 0 & p_{ss} & p_{sd} \\ 0 & 0 & 1 \end{bmatrix} \begin{matrix} \text{healthy} \\ \text{sick} \\ \text{dead} \end{matrix}$$

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Markov Model (cont.)

- Data

	Cost per cycle	Utility level
healthy	\$5,000	0.8
sick	\$50,000	0.6
dead	0	0

- Calculation of the cost at the first cycle
after one cycle, cost = \$5000 x 0.89 + \$50000 x 0.1
 - Calculation of the cost at the second cycle
after two cycle, cost = \$5000 x 0.7921 + \$50000 x 0.169
 - Calculation of the utility at the first cycle
after one cycle, utility = 0.8 x 0.89 + 0.6 x 0.1
 - Calculation of the cost at the second cycle
after two cycle, utility = 0.8 x 0.7921 + 0.6 x 0.169
- Continue to derive the costs and utility till the end of study cycle

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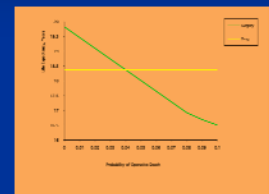
Sensitivity Analysis

- Helps to
 - Decide what matters & what does not
 - What to worry about in the decision
 - What level of data precision is required
- Allows decision maker to attack specific issues and solve the right problem
- Reexamine the issue:
 - “What is fundamentally important and makes a difference?”

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One-Way Sensitivity Analysis

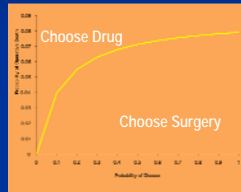
- Makes graph that varies a single variable from a low-to high-end range and shows output as a function of variable
- The resulting graph shows how “sensitive” the answer is to changes in the one variable



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Analysis

- Shows a 2-dimensional plot of what happens when change of 2 variables at once
- Graph generated is a “frontier” of feasible options between two variables



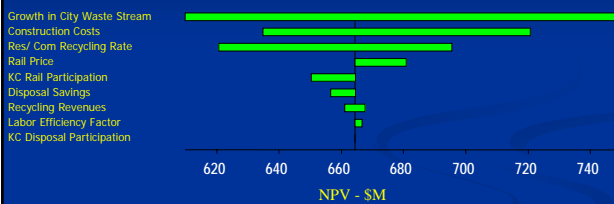
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Tornado Diagrams

- To compare one-way sensitive analyses for many input variables at once (one changes while all others held constant)
- Length of bars tells how sensitive output is to each variable
 - Bigger bar = more sensitive
 - Ideally to demonstrate from most to least
 - Looks like a tornado
- Spider diagrams are similar

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Tornado Diagrams



A Tornado Diagram evaluates the impact of each uncertainty by varying it from its best to worst state, while fixing all other uncertainties to their base (most likely) state. The width of the bar shows the impact on total option cost.

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Discounting Rate

- All costs and/or effectiveness should discounted to the present value

$$\text{present value} = \frac{\text{future amount}}{(1+r)^{t_i}}$$

where “ t_i ” is the time ahead of the present and “ r ” is the discount rate

- Annual discount rate, r , of 3% is commonly used
- Inflation to the current value may need to be considered

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Does the Choice of the Discount Rate Matter?

Annual net benefits and net present values for three alternative projects

Year	Project A	Project B	Project C
0	-80,000	-80,000	-80,000
1	25,000	100,000	0
2	25,000	5,000	0
3	25,000	5,000	0
4	25,000	5,000	0
5	25,000	5,000	140,000
NPV (no discount)	45,000	40,000	60,000
NPV (discount rate = 2%)	37,836	36,705	46,798
NPV (discount rate = 5%)	28,360	32,125	29,690
NPV (discount rate = 10%)	14,770	25,318	6,929

NPV: net present value

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Discussion

- PEC is (or should be) about two dimensions: cost & health
- More incentive needed to encourage cost effective health care (= the cost effective use of cost effective technologies)
- Disincentive to discourage non cost effective care
- Still have lots of methodological issues
- CEA is just one criteria for decision making
- Need for more studies (should be in legal requirement) and incorporating results in clinical guidelines

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Health Economics.... A New Toxicity?



"The drug itself has no side effects - but the number of health economists needed to prove its value may cause dizziness and nausea"

Another hurdle?!

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Thank You!

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