Comparative Effectiveness Research: What is it and How is it Relevant to Pharmacy?

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Illinois Council of Health-System Pharmacists
2011 Annual Meeting, September 17 2011

The speaker has no conflicts of interest to disclose

Objectives

1) What is it?
- Provide an overview of the factors and initiatives leading to the current national interest in comparative effectiveness.
- Compare the differences between comparative effectiveness studies and traditional efficacy studies.
- Describe the study designs and methods pertinent to comparative effectiveness.

2) How is it Relevant to Pharmacy?
- Discuss the relevance of comparative effectiveness research to pharmacy practice.

  (For example, funding opportunities, patient and system-level decision making, other)

How much do you know about CER?

1. Nothing
2. Little bit
3. Moderate amount
4. A lot

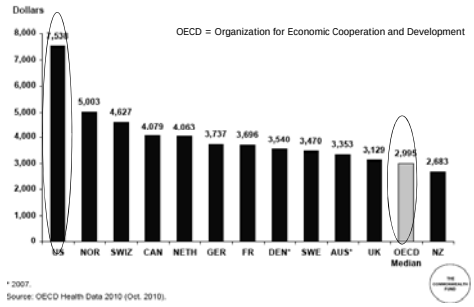
CER: What is it?

- Provide an overview of the factors and initiatives leading to the current national interest in comparative effectiveness.
- Compare the differences between comparative effectiveness studies and traditional efficacy studies.
- Describe the study designs and methods pertinent to comparative effectiveness.

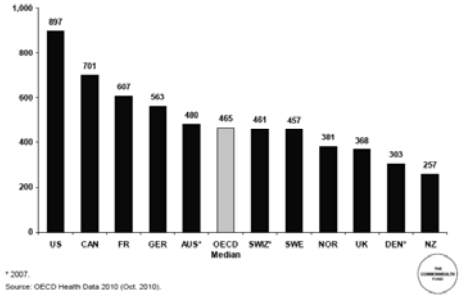
What is the Problem?

- The US continues to spend more on health care than other countries.
- Outcomes of the health care system are not better in the US compared to other developed countries.
- There is much variation in the provision and cost of care between regions of the US.
- Clinicians often do not have necessary evidence on which to base decisions.

Health Spending Per Capita[1]

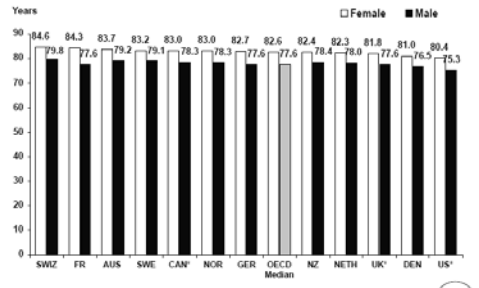


Prescription Spending Per Capita[1]



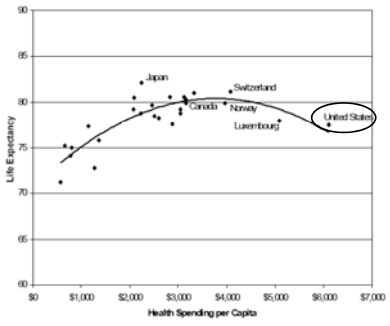
* 2007.
Source: OECD Health Data 2010 (Oct. 2010).

Life Expectancy[1]

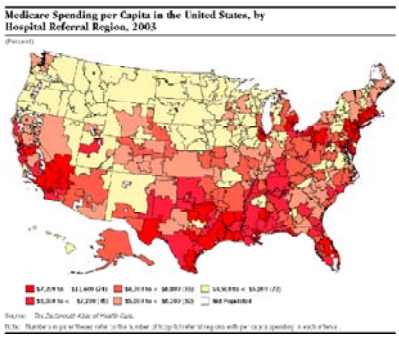


* 2007.
Source: OECD Health Data 2010 (Oct. 2010).

Health Care Spending Per Capita and Life Expectancy[1]



Per Capita Medicare Spending[2]



Information Gap

- Insufficient evidence to support rational decisions about one alternative versus another for the same indication
  - Not studied in same patient population
  - Not compared to true therapeutic alternatives
  - Not studied in actual practice
  - Outcomes of interest not measured
- Illustrated by drug approval process in the US which does not require manufacturers to produce evidence necessary for clinicians or policymakers to choose between drugs for the same indication.

Drug Approval Process

- Safety: Side effects acceptable?
- Efficacy: Can it work? (under optimal conditions)
- Effectiveness: Does it work? (under average or usual conditions)
- Efficiency: Is there sufficient value?

“ [T]here are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know. **”**
—Former US Secretary of State, Donald Rumsfeld

Efficacy

Safety

Effectiveness

What are reasons for the recent interest in CER in the US?

1. High cost of health care in US compared to other countries.
2. Lack of apparent differences in outcomes achieved in US compared to other countries.
3. Lack of information needed to make decisions between alternative treatments.
4. All of above.

CER: What is it?

- Provide an overview of the factors and initiatives leading to the current national interest in comparative effectiveness.
- Compare the differences between comparative effectiveness studies and traditional efficacy studies.
- Describe the study designs and methods pertinent to comparative effectiveness.

Definition of CER[3]

Comparative effectiveness research is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings.

From Federal Coordinating Council 2009

Purpose of CER[4]

The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.

From Institute of Medicine 2009

Essential Elements

- Comparison of two or more drugs, devices, surgeries, diagnostic tools, care management strategies, or other approaches to care that are considered true therapeutic alternatives.
- Examines effects/outcomes in actual practice (i.e., effectiveness).

Comparison to Traditional RCTs

	Efficacy (Can it work?)	**Effectiveness** (Does it work in routine care?)
Placebo comparison (or usual care)	Most RCTs for drug approval	
Active comparison (head-to-head)		Goal of CER

Differences Between Efficacy and Effectiveness Drug Studies[5]

Table 1.
Comparison of Traditional Phase III Randomized Clinical Trials (RCTs) and Phase IV Comparative Effectiveness Studies

Characteristic	Traditional Phase III RCT	Comparative Effectiveness Study
Research question	Can the drug work?	Does the drug work in normal practice, and how does it compare to therapeutic alternatives?
Comparison group	Placebo or inferior treatment	True therapeutic alternatives (e.g., head-to-head) based on current choices available to health care professionals
Population	Narrowly selected, usually healthier than patients who will eventually use the drug	Patients who actually use the drug once marketed
Setting	Controlled	Normal or actual practice
Compliance	Strictly enforced	As in normal practice
Outcomes	Often short-term, surrogate, or intermediate endpoints	True outcomes that are relevant to decision-making at the clinical level, policy level, or both
Validity	High internal validity but low external validity, not widely generalizable	Lower internal validity than RCT but higher external validity

From: Schumock. AJHP 2009

Types of CER

- Primary comparative effectiveness
  - Prospective observational studies (aka "large simple clinical trial," "pragmatic clinical trials")
  - Cluster randomized studies
  - Registry-based studies
  - Retrospective observational studies (case control or cohort studies)
- Secondary comparative effectiveness
  - Systematic review and meta-analyses
  - Modeling and decision-analysis

Which of the following is most true about CER?

1. Compares true therapeutic alternatives in actual practice setting.
2. Is not randomized.
3. Does not include a placebo comparator.
4. Is usually retrospective.

CER: What is it?

- Identify rationale/need for comparative effectiveness research.
- Review the basic purpose, definitions, and methods involved in comparative effectiveness research.
- Provide examples of primarily and secondary comparative effectiveness research.

Example: CER - Primary Prospective[6]

- Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)
- Patients:
  - Schizophrenia
- Intervention:
  - Drug treatment (antipsychotics)
- Comparators:
  - Olanzapine, perphenazine, quetiapine, risperidone, ziprasidone
- Endpoint/outcome
  - Treatment failure (time to discontinue)

Other Examples: ALLHAT, WHI


The NEW ENGLAND JOURNAL of MEDICINE

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

CATIE Impact[7]

- CATIE found little difference between the effectiveness of older, cheaper antipsychotics and that of more expensive “second-generation” drugs.
- If reimbursement policies had been changed in response and Medicaid had stopped paying for the more costly drugs, it would have saved $1.2 billion out of the $5.5 billion that it spent on these medications in 2005.

Philipson, 2011

Advantages and Disadvantages of Prospective CER

- Allows for inclusion of outcomes that might not be available in a retrospective database.
- Can be randomized.
- However, it is an unrealistic expectation that we will have head-to-head randomized trials...
  - for every intervention and
  - its combinations
  - in every patient subgroup
  - that exactly mimic **routine** care.
- Prospective studies are expensive and take time to conduct.

Example: CER - Primary Retrospective[8]

- Patients:
  - Adults with COPD
- Intervention:
  - Drug regimens containing theophylline
- Comparators:
  - Drug regimens not containing theophylline
- Endpoint/outcome
  - Death
  - COPD exaccerbations
  - COPD hospitalizations

Mortality Risk in Patients Receiving Drug Regimens with Theophylline for Chronic Obstructive Pulmonary Disease

Advantages of retrospective CER

- Are more representative of **routine** care
  - Spectrum of disease severity
  - Spectrum of co-morbidities
  - Co-medications
  - Real world adherence
- Have very large sample sizes, good for
  - Infrequent exposure, recently marketed medications
  - Many subgroups to study treatment effect heterogeneity
- May allow Long follow-up
  - With hard clinical endpoints
- Produce results fast, inexpensive

Disadvantages of retrospective CER

- Not randomized therefore subject to bias
  - Confounding by indication (selection bias)
- Important outcomes may not be present in data
  - Clinical outcomes, quality of life

Example: CER – Secondary[9]

- Patients:
  - Chronic obstructive pulmonary disease (COPD)
- Intervention:
  - Drug therapy (anticholinergics)
- Comparators:
  - Ipratropium or tiotropium vs. control (placebo or active comparator)
- Endpoint/outcome
  - Death
  - Myocardial infarction (MI)
  - Stroke
- Many meta-analyses may not be easily characterized as "secondary CER" as are often based on clinical trials setting not actual practice

Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients With Chronic Obstructive Pulmonary Disease

A Systematic Review and Meta-analysis

Which of the following is a potential disadvantage of retrospective CER?

1. Takes a long time to conduct.
2. Expensive
3. Subject of confounding
4. Not representative of actual practice

CER: How is it Relevant to Pharmacy?

- Discuss the relevance of comparative effectiveness research to pharmacy practice.
  - Lots of opportunities for funding CER in pharmacy.
  - Pharmacists can serve as stakeholders to inform CER.
  - CER can inform policy and patient care decisions.

CER Funding[10]

- Medicare Moderization Act 2003
- Patient Protection and Affordable Care Act
  - Section 6301: Patient-Center Outcomes Research (previously known as CER)
  - Patient-Center Outcomes Research Institute (PCORI)

PCORI Funding (millions)

Year	Gov Rev	Medicare	Private	Total	Less DHHS
2010	$10.0			$10.0	
2011	$50.0			$50.0	
2012	$150.0	$50.2	$179.0	$379.2	$318.6
2013	$150.0	$104.0	$364.0	$618.0	$519.1
2014	$150.0	$107.1	$370.0	$627.1	$526.7
2015	$150.0	$110.1	$374.0	$634.1	$532.7
2016	$150.0	$113.2	$382.0	$643.3	$540.3
2017	$150.0	$116.5	$382.0	$648.5	$544.8
2018	$150.0	$119.9	$382.0	$651.9	$547.6
2019	$150.0	$123.4	$382.0	$655.4	$550.5

IOM CER Priorities[11]

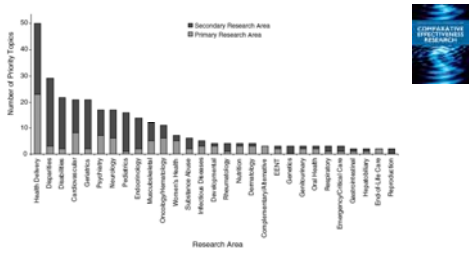


FIGURE 5-1 Distribution of the recommended research priorities by primary and secondary research areas

IOM CER Priorities

- Compare the effectiveness of treatment strategies for atrial fibrillation including surgery, catheter ablation, and pharmacologic treatment.
- Compare the effectiveness of primary prevention methods, such as exercise and balance training, versus clinical treatments in preventing falls in older adults at varying degrees of risk.
- Compare the effectiveness of upper endoscopy utilization and frequency for patients with gastroesophageal reflux disease on morbidity, quality of life, and diagnosis of esophageal adenocarcinoma.
- Compare the effectiveness of comprehensive care coordination programs, such as the medical home, and usual care in managing children and adults with severe chronic disease, especially in populations with known health disparities.
- Compare the effectiveness of different strategies of introducing biologics into the treatment algorithm for inflammatory diseases, including Crohn's disease, ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis.
- Compare the effectiveness of various screening, prophylaxis, and treatment interventions in eradicating methicillin resistant *Staphylococcus aureus* (MRSA) in communities, institutions, and hospitals.
- Compare the effectiveness of strategies (e.g., bio-patches, reducing central line entry, chlorhexidine for all line entries, antibiotic impregnated catheters, treating all line entries via a sterile field) for reducing health care associated infections (HAI), including catheter-associated bloodstream infection, ventilator associated pneumonia, and surgical site infections in children and adults.

Prioritizing Topics for CER: Stakeholder Input

- Importance of stakeholder input.
- Examples of stakeholders:
  - Physicians
  - Pharmacists
  - Payers
  - Policy-makers
  - Patients

Application of CER

- CER data can be used to help inform:
  - individual patient care decisions/recommendations (patient-level)
  - Population or system-level decisions (e.g., formulary decisions)
- CER data can add to body of evidence on:
  - effectiveness of one drug compared to another
  - safety of one drug compared to another
- Outcomes from CER studies provide inputs for cost-effectiveness analyses and decisions analysis

What Should Pharmacists Do?

- Understand study design and methods used in comparative effectiveness research.
- Understand differences between efficacy and effectiveness studies and their strengths and weaknesses.
- Monitor literature for results of comparative effectiveness studies.
- Integrate evidence from these studies with existing knowledge base relevant to patient and system-level decision making.

Which of following is not a current use of CER?

1. Individual patient care decisions.
2. FDA drug approval decisions.
3. Policy-level decisions.
4. Input to cost-effectiveness analyses.

Conclusion

- We need comparative effectiveness data in order to make more informed decisions in health care.
- CER compliments efficacy data.
- There are various study designs and methods to conduct CER that the pharmacist should understand.
- CER results can be very relevant to the daily patient care and policy-level decisions that pharmacists are involved in.

How much do you know about CER now?

1. Still nothing
2. Little bit
3. Moderate amount
4. A lot

References and Supplemental Reading

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