Meta-Analysis

Pharmacy 309: Quantitative Methods I

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Outline

• Definition, History and Relevance
• Methods
  1. Systematic review
  2. Quantitative synthesis
  3. Evaluate studies
• Examples
  1. Efficacy of antiseptic-impregnated catheters
  2. Pharmacist clinical services

Definition

• Meta-analysis is a quantitative approach to systematically combining the results of previous research in order to arrive at a conclusion about a body of literature.
  – Examples:
    1) Questions of Efficacy:
       Antiplatelet Trialists Collaboration - "Whether or not to prescribe an antiplatelet drug for patients with transient ischemic attacks to prevent stroke."
    2) Questions of Safety:
       Health risks of work in the nuclear industry. Incidence of drug-related adverse consequences.

History

• Termed coined in 1976 by G. Glass:
  Meta (transcending) Analysis
• Development of meta-analysis was driven by the perception that narrative literature reviews were selective in their inclusion of studies and subjective in their weighting of studies.
• Need became especially acute in the social sciences when many studies existed on the same topic.
• Both of the above apply to the medical literature:
  1971-1985 1 meta-analysis in top 4 medical journals
  1986-1990 32 meta-analyses
Relevance

• Widespread use of meta-analysis has coincided with increased focus on randomized controlled trials (RCTs)

• It has benefited (or been harmed!) from concern about the interpretation of small and individually inconclusive clinical trials.

• Meta-analysis is not confined to synthesis of data from RCTs. Methods for the quantitative synthesis of "nonexperimental" data have been developed.

• Meta-analysis can be used in combination with decision analysis and cost-effectiveness analysis.

Method

• Performing a meta-analysis is complex for real world applications. However, the method involves a limited number of discrete steps and simple steps.

• The main goal of meta-analysis is to combine the results of previous studies to arrive a summary conclusion about a body of research. It is most useful in summarizing prior research when individual studies are too small to yield a valid conclusion.

Early Examples

Problem
Use of thrombolytic agents after acute MI was controversial in the early 1980s. Of the eight published studies, 2 found higher risk, 5 found lower risk, and 1 found essentially the same risk of mortality in streptokinase treated patients compared to controls.

Solution
In a meta-analysis based on these trials, Stampfer et al (1982) estimated the pooled relative risk of mortality in patients treated with streptokinase to be 0.80 (95% CI 0.68 - 0.95).

Validation
Subsequently, the Studies of Intravenous Streptokinase After Acute MI (GISSI 1986) confirmed the conclusion of the meta-analysis.

Early Examples

Problem
The effect of exposure to environmental tobacco smoke on lung cancer risk is a topic of considerable public health importance. By 1991, there were 19 case-control studies of lung cancer in which information on exposure to environmental tobacco smoke was available.

Fifteen studies found an elevated risk, 3 found a decreased risk, and 1 found no risk difference in women who never smoked but were exposed to environmental tobacco smoke.

Solution
A meta-analysis by the EPA estimated the relative risk of lung cancer to be 1.42 (95% CI 1.24 and 1.63). These data served as the basis for the EPA to designate environmental tobacco smoke as a carcinogen.
9-Step Method

1. Define the question
2. Identify search terms/keywords
3. Determine inclusion and exclusion criteria
4. Identify potential studies via Medline search
5. Exclude ineligible studies
6. "Abstract" data from studies
7. Describe studies and data
8. Analyze data statistically
9. Report findings

Systematically identify studies

- Steps in identifying studies
  - Literature search
    - In Medline, use keyword and MESH heading searches
    - Search conference proceedings, Government pubs, theses, etc.
    - Contact authors
  - Develop inclusion/exclusion criteria
    1. Patients
    2. Intervention
    3. Effectiveness measures
  - Identify relevant studies
    - Read abstracts online
    - Retrieve and read relevant studies
    - Include/exclude studies based on criteria

Quantitatively analyze studies

1. Fixed Effects Model
   - Assumes differences within studies
   - Accounts for effect of intervention in each study
   - Mantel-Haenszel method
   - "Did the treatment produce benefit "on average" in the studies at hand?"

2. Random Effects Model
   - Assumes differences within and between studies
   - Accounts for differences in studies
   - DerSimonian and Laird method
   - "Will the treatment produce benefit "on average"?"
Limitations

1. **Heterogeneity of studies**
   - How similar are the studies?
   - Consider patients, intervention, and outcomes measured
   - Studies conducted on similar populations using similar protocols and similar treatments would be reasonable to combine
   - Combining results from heterogeneous studies can lead to 'incorrect' or misleading results

2. **Study quality**
   - Generally all identified studies are included
   - Inclusion/exclusion criteria can be used to eliminate studies with (generally obvious) poorer quality
   - But evaluation of quality is subjective, and difficult to do
   - A properly conducted meta-analysis will help identify poor quality studies

3. **Publication bias**
   - Studies with ‘negative’ results tend to not be published
   - This can lead to an overestimate of the benefits of an intervention
   - Try to identify by looking for lack of small studies that have ‘negative’ results or trends

Example 1
Efficacy of antiseptic-impregnated central venous catheters: a meta-analysis


**Catheter-related bloodstream infection (CR-BSI)**

- 3 million central lines used per year in U.S.
- 3-7% of central lines lead to CR-BSI
- Approx. 150,000 cases per year in U.S.
- 10% to 25% attributable mortality rate
- Increased hospitalization and costs

**CR-BSI: pathogenesis**

- Primarily due to skin organisms
- Local infection
- Catheter colonization
- Bloodstream infection (CR-BSI)

**CR-BSI: prevention**

- Aseptic insertion techniques
- Routine catheter replacement
- Antiseptic/Antibiotic catheters
Antiseptic-impregnated catheters

- Chlorhexidine
  - broad spectrum antiseptic used for disinfection, irrigation
- Silver sulfadiazine
  - bactericidal and fungicidal action, used for prolonged periods in burn treatment

Are antiseptic catheters effective?

- Preliminary reports published in 1994
- Maki study (1997) indicated significant decrease in CR-BSI
- Several other studies reported non-significant decreases in CR-BSI

Meta-analysis

- What?
  - Method for summarizing the results of independent studies
- How?
  - Systematic literature search, data abstraction, and statistical pooling of results
- Why?
  - evaluate discrepant results
  - provide greater statistical power
  - determine sources of heterogeneity

Study search strategy

- Medline databases 1966 to 1998
- Bibliographies of retrieved articles
- Authors of studies and manufacturer contacted for additional information
Inclusion/Exclusion Criteria

- Published or unpublished studies
- Any language
- Randomized controlled trials
- Catheter colonization or CR-BSI confirmed by catheter culture

Data abstraction

- Two abstractors, one blinded
- Data collected
  - sample size
  - patient population
  - catheter duration, type, etc.
  - methodology

Search results

Initial search: 215 studies

24 studies

191 non-comparative or non-human

9 not randomized

15 studies

2 no catheter culture

13 studies

Studies Retrieved: I

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<th>Outcomes</th>
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<td>Tennenberg ('97)</td>
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<td>CC, CR-BSI</td>
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<td>Maki ('97)</td>
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<td>van Heerden ('96)</td>
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<td>CC</td>
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<td>Hannan ('96)</td>
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Studies Retrieved: II

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<td>Trazzera ('95)</td>
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<td>George ('97)</td>
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<td>Transplant</td>
<td>CC, CR-BSI</td>
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Summary of studies

- 12 studies reported catheter colonization
- 11 studies reported CR-BSI
- 90% of catheters triple-lumen
- Mean catheter duration: 8 days

Statistically summarizing results

- Calculated summary odds ratio using Mantel-Haenszel fixed-effects model
- Statistically evaluated homogeneity of studies

Results: catheter colonization

![Odds Ratio Graph]

P heterogeneity = 0.005
Potential sources of heterogeneity

- Differences in patient population
- Different outcome definitions
- George et al:
  - immunosuppressed patients
  - less stringent definition of colonization
  - 71% colonization in control group

Results: bloodstream infection (CR-BSI)

CR-BSI: Publication bias?

Catheter colonization: heterogeneity

P heterogeneity = 0.010

P heterogeneity = 0.005

P heterogeneity = 0.100
Sensitivity analyses

- Increased variance if >1 catheter per patient
- “Truly randomized” studies only
- Triple-lumen catheters only
- Clinical symptoms of sepsis
- Include study that used paired blood cultures

Example 2

Evaluation of Studies Investigating the Effectiveness of Pharmacists’ Clinical Services

Morrison and Wertheimer AJHP 2001:58:569-577
Background

“Pharmacists in ambulatory care and inpatient settings provide education, counseling, drug-use review, and other ‘cognitive services’ to patients as well as to physicians and other health care professionals.”

“The effectiveness of these services has been investigated for decades, but many studies in this field have been of poor quality; for example, only 23 of 104 studies in ambulatory care settings…incorporated a control group.”

Research Question

Are clinical interventions by pharmacists effective?

Methods: Literature Search

MEDLINE search of English-language articles published from 1965 to May 1999

MeSH (Medical Subject Heading) terms (“pharmaceutical services” or “pharmacy services”) and “patient education” and “comparative study” and then the keywords “randomized” and “control” in any field and “pharmacist” in the text field.
Study inclusion/exclusion

- Inclusion
  - Randomized or quasi-randomized controlled trials
- Exclusion
  - Intervention by a group of providers
  - <10 subjects
  - previously published

Results

- 74 studies found in literature search
- 32 met inclusion/exclusion criteria and were used in analysis
- What more details would be helpful in regard to above?

Interventions

- Categorized as
  - counseling of patients only
  - counseling of both patients and their physicians
  - counseling of physicians only
  - patient care by the pharmacist
- What are the pros and cons of categorizing?

Outcomes

- Compliance
- Patient knowledge
- Blood cholesterol
- Blood pressure
- Blood sugar
- Adverse events
- Symptoms
Pooling of Study Results?

“We did not compute pooled summary statistics for groups of studies; we did not believe that the conceptual criteria for pooling were strictly met, because of heterogeneity in study outcomes and other characteristics.”

Conclusions

“An evaluation of pharmacists’ clinical services showed that counseling of patients and their physicians by pharmacists can improve patient outcomes. The evidence that counseling of patients alone improved patient outcomes was good, though weaker because of suboptimal trial design.”

References