Introduction to Biomedical Research Designs

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Presentation Outline

- Why a course in Biomedical Research Design?
- Case Studies
- Course Objectives
- Lectures and Lecturers

Why a Course in Biomedical Research?

- Monthly, 6000 articles enter Medline
  - Many more in the grey literature
  - Biomedical research is the primary method for generating new information on medical interventions.
- Studies have shown that poor quality biomedical research appears even in top-tier journals.
- You are the expert regarding biomedical information about pharmaceuticals.
  - You are expected to excel at critical appraisal of published literature.

EBM: A Practical Definition

- When there is evidence of benefit and value, do it.
- When there is evidence of no benefit, harm or poor value, don’t do it.
- When there is insufficient evidence to know for sure, be conservative.
- (And whatever we do, do it right!)
  - David Eddy

Evidence-Based Medicine

- Bases action on best evidence synthesis
- Rejects individual bias
- Focuses on populations, not individuals
- A new paradigm:
  - The old way: “This patient is sick; I’ve got to prescribe something.”
  - The new way: “Don’t prescribe a drug unless reasonably sure it will actually help.”

Grade the Evidence
(Example McMaster Grading System)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Large, well-designed randomized controlled clinical trials</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Small, or not-so-well-designed controlled clinical trials</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Non-randomized prospective cohort studies</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Non-randomized historical cohort studies, case-control studies</td>
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<tr>
<td>Grade 5</td>
<td>Case series</td>
</tr>
<tr>
<td>Grade 6</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
People who live in the areas in which the study was conducted

People with headaches

People with migraine

Excluded
- bed rest
- vomiting

20% of the time

Whole US Population

Included
- IHS criteria
- > 18yr old
- good health

Actual Study Subjects

Example: Demographics of a Headache Study

Risk Reduction and NNT

Diabetes—Intensive insulin therapy to prevent neuropathy – 6 year trial

<table>
<thead>
<tr>
<th>control</th>
<th>treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Relative risk reduction = (10% - 3%) / 10% = 70%

Absolute risk reduction = 10% - 3% = 7%

NNT = 1 / (7%) = 14 patients for 6 years to prevent 1 case of neuropathy.

Encainide, Flecainide

Twice the risk of death (all cause & CAD) if post-MI patient has ventricular premature beats (VPCs)


Flecainide

Suppresses >90% VPCs

“Highly effective and well tolerated... for long-term treatment of serious arrhythmias”


Encainide and Flecainide increased mortality in patients (after MI) with asymptomatic or mildly symptomatic VPCs


Active drug: cardiac deaths & arrests 8%

Placebo: cardiac deaths and arrests 3% (p<0.001)

ARI = 5%, NNH = 20


Exclusion

Case Studies
**Encainide, Flecainide: Summary**

- New warning flecainide
  - Can cause new or worsened arrhythmias; use with great caution in view of CAST trial results, reserving for patients not controlled by other agents
  - Encainide not available

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**HOPE Trial**

- HOPE trial (Heart Outcomes Prevention Evaluation Study)
  - RCT studying effect of both ACE inhibitor (ramipril) and Vitamin E on cardiac events
  - Patients (N = 9541)
    - Age over 55 with:
      - History of CVD event or DM and additional CVD risk factor
      - Lipids, HTN, smoking, microalbuminuria

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**HOPE Trial**

- Intervention
  - Ramipril 10 mg daily or placebo
- Outcomes
  - Primary: MI, CVA, or CV death
  - Secondary: total mortality, revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes.
  - Mean f/u 4.5 years

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**HOPE Trial Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NNT (5YRS)</th>
<th>MI, Stroke, Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

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**HOPE Trial Adverse Events**

- Adherence
  - 65% at 4 years
- Cough
  - NNH (number needed to harm) for cough = 20
  - For every 20 patients treated there is one patient who had to stop ramipril because of cough

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**HOPE Trial Clinical Importance Benefits, Harms, Costs**

- For every 10,000 patients eligible
  - Potential to prevent approximately 500 cardiovascular events within 5 years
  - 350 Myocardial infarctions
  - 150 Revascularizations
- Potential to avoid approximately $4,000,000 in variable costs over 5 years by avoiding the cost of poor quality
Exclusions in Analysis: Anturane Reinfarction Trial

- Randomized, double-blind, multicenter clinical trial
- Subjects:
  - Patients with recent documented MI
- Intervention:
  - Anturane (sulfinpyrazone) 200 mg four times daily compared to placebo
- Primary Outcome:
  - Cardiac mortality

Exclusions in Analysis: Anturane Reinfarction Trial

- Authors excluded 7 patients in the analysis because of ineligibility.
  - 6 pts in treatment group excluded, 1 pt in placebo group excluded (additional pts could have been declared ineligible on the basis of similar criteria, but were not).
  - Authors excluded 2 deaths in the treatment group and one death in the placebo group - the authors labeled these pts as "non-analyzable" because of poor compliance.

Exclusions in Analysis: Anturane Reinfarction Trial

Did these exclusion affect results?

Exclusions in Analysis: Anturane Reinfarction Trial - Summary

- FDA refused to approve a claim that sulfinpyrazone (Anturane) was effective in the prevention of sudden death during the first six months after myocardial infarction.

FDA Review Anturane

- 2yr, double-blind, randomized, multicenter trial
- ~1600 patients
- Designed to compare effect of sulfinpyrazone (200 mg qid) with placebo in preventing recurrent infarction and death in patients who had well documented acute MI (25-35 days earlier)
- Study reported
  - Statistically significant reduction in early sudden death (74% RRR in the sulfinpyrazone group) in months 2-7 following MI (24 vs 6 pts, P=0.003)

FDA Review Anturane

- FDA audited half case records of patients with focus on
  - assigned cause of death
  - Pts who died but were subsequently excluded from the analysis
FDA Review Anturane

- FDA review of study as reported by authors
  - Nearly significant reduction in total and early cardiac mortality
    - 32% RRR for the entire study
    - 62 vs 43 patients, P=0.058
  - 43% RRR in sudden death
    - 37 pts vs 22 pts, P=0.041
  - 51% RRR in total and cardiac mortality
    - 35 vs 17 pts, P=0.021

FDA conclusion after audit

"We do not believe that either reported outcome [cardiac mortality or total mortality] can be accepted for the following reasons."

Reasons FDA did not accept conclusions presented in NEJM

- Assignments of patients were often inaccurate and failed to conform to the criteria set forth at the outset of the study
  - FDA: "the reported statistically significant reduction in sudden death is thus invalid."
  - Errors in assignment nearly all favored the conclusion that sulfinpyrazone decreased sudden death
- The assignment of cause of death made it apparent that the classification scheme had no clear logic (did not divide death into meaningful or discrete groups)
  - Identical histories could lead to classification as sudden death, acute MI, or other cardiac death

Cox-II Inhibitors Case Studies

- Cox-2 inhibitors are marketed as drugs for treating arthritis (~$6 billion sales/yr) with the advantage over NSAIDs of fewer upper GI adverse effects
- Rationale
  - Cox-2s should reduce ulcer complications by selectively blocking cyclo-oxygenase-2
  - Symptom relief (arthritis) from Cox-2 blockage without adverse GI side effects - (Cox-1 remains protective of gastric mucosa because it is not blocked by Cox-2 inhibitors)

A common theme from clinicians -

- "I read a couple of good studies about COX-2s. They look like good drugs. The incidence of UGI adverse events is approximately 50-65% when compared to traditional NSAIDs."
- But...clinicians frequently get the evidence wrong
Vigor Trial - Rofecoxib vs Naproxen in Pts with Rheumatoid Arthritis

- Double blinded, multicenter RCT
  - N = 8076
  - Subjects: RA pts (average age 58) receiving long-term NSAIDs or steroids. Pts taking ASA were excluded.
  - Intervention: Comparison of Rofecoxib 50mg/d (Vioxx) to naproxen 500mg bid
- Primary outcome: Clinically evident upper GI events (gastroduodenal perforation, obstruction, and upper GI bleeding)
  - Follow-up: median f/u period of 9 months


Results from NEJM article

<table>
<thead>
<tr>
<th>GI events/100 Pt-Yrs</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib 2.1</td>
<td>0.4 percent</td>
</tr>
<tr>
<td>Naproxen 4.5</td>
<td>Relative Risk=0.5</td>
</tr>
<tr>
<td></td>
<td>95%CI (0.3 to 0.6)</td>
</tr>
<tr>
<td></td>
<td>P=0.005</td>
</tr>
<tr>
<td></td>
<td>0.1 percent</td>
</tr>
<tr>
<td></td>
<td>Relative Risk=0.2</td>
</tr>
<tr>
<td></td>
<td>95%CI (0.1 to 0.7)</td>
</tr>
</tbody>
</table>

Other Adverse Events in VIGOR Trial

- Increased Adverse Events With Vioxx:
  - Elevated BP, renal, hepatic, heart failure, stroke, sudden death, TIA

Authors’ Conclusions

- "In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor. The two drugs had similar rates of clinical effectiveness."

Conclusions From Critical Appraisal

- Vioxx (rofecoxib)
  - Vioxx is not more clinically effective than naproxen in treating rheumatoid arthritis
  - NNT for avoiding 1 clinically significant upper GI event: 125
  - NNH for thrombosis: 103
  - Despite a small improvement in adverse GI events, the absence of increased efficacy and increased risk of MI and thrombosis indicate that rofecoxib does not offer significant advantages compared to naproxen, a non-COX2 selective agent

Results from NEJM article and FDA

2. FDA Cardiovascular, Safety Review, NDA 21-042, S-007
   www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.doc

Other Adverse Events in VIGOR Trial

<table>
<thead>
<tr>
<th>Complicated Upper GI Events</th>
<th>Myocardial Infarction</th>
<th>All Thrombotic Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib</td>
<td>0.6%</td>
<td>0.4 %</td>
</tr>
<tr>
<td>N=434</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.4%</td>
<td>0.1 %</td>
</tr>
<tr>
<td>N=4205</td>
<td>RR=0.499</td>
<td>Relative Risk=0.2</td>
</tr>
<tr>
<td></td>
<td>95%CI (0.2-0.8)</td>
<td>95%CI (0.1 to 0.7)</td>
</tr>
<tr>
<td>ARR (ARI)</td>
<td>0.8%</td>
<td>(0.3%)</td>
</tr>
<tr>
<td>NNT (NNH)</td>
<td>125</td>
<td>(333)</td>
</tr>
</tbody>
</table>

www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.doc
CLASS
(Celecoxib Long-term Arthritis Safety Study)

- Prospective, double-blind, randomized trial
  - 8059 pts with OA or RA
  - Celecoxib (400mg twice daily) compared to ibuprofen 800mg three times daily and diclofenac 50mg three times daily
- Primary outcome
  - Incidence of upper GI toxic effects (upper GI ulcer complications (perforation, gastric outlet obstruction, and upper GI bleeding).
  - 6 month treatment period


Results from CLASS as reported in *JAMA*

- “For all patients” annualized incidence rates of upper GI ulcer complications and symptomatic ulcers
  - Celecoxib 2.08%
  - NSAIDs 3.54% (P=.04)

Authors’ Conclusions

“In this study, celecoxib, at dosages greater than those indicated clinically, was associated with a lower incidence of symptomatic ulcers and ulcer complications combined, as well as other clinically important toxic effects, compared with NSAIDs at standard dosages.”

Key Problem with the CLASS Trial

- CLASS
  - Published trial included only the first 6 months worth of trial data
  - Important benefit/harm data not reported
  - FDA sites includes full trial data

Annualized Incidence UGI Events

<table>
<thead>
<tr>
<th>Adverse Ulcer Events</th>
<th>Celecoxib</th>
<th>Diclofenac</th>
<th>Ibuprofen</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>20/3987</td>
<td>11/1996</td>
<td>13/1985</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(0.43%)</td>
<td>(0.50%)</td>
<td>(0.55%)</td>
<td></td>
</tr>
</tbody>
</table>

From FDA Statistical Reviewer Briefing Document NDA20-998
www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_04_stats.doc

FDA Conclusions

FDA Panel finds no safety benefit for Celebrex.

- “For upper GI Safety, and also for global safety, there does not appear to be any meaningful advantage for Celebrex”

Scrip World Pharm New. Feb 9,2001;No.2616:19
What is the difference in cost between COX-2 inhibitors and traditional NSAIDs?

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Relative Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib</td>
<td>12.5-25mg qd</td>
<td>8.2</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100-200mg bid</td>
<td>9.5-15.9</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>75mg bid</td>
<td>3.5</td>
</tr>
<tr>
<td>Etodolac</td>
<td>400mg bid</td>
<td>1.6</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>800mg tid</td>
<td>1</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>1500mg/day</td>
<td>2.8</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500mg bid</td>
<td>1</td>
</tr>
</tbody>
</table>

Cox-2s Benefits, Harms, Cost

- Insufficient evidence to conclude that Cox-2 drugs are more effective than older NSAIDs
- Celebrex (celecoxib) does not prevent clinically significant upper GI events (gastroduodenal perforation, obstruction, bleeding)
- Vioxx (rofecoxib)
  - NNT for avoiding 1 clinically significant upper GI event: 125
  - NNH for thrombosis: 103
- Cox-2s are more expensive (factor of 8-16)
  - $3million-$4million per year additional costs for HMO of 500,000 pts.

Course Objectives

- Introduce you to common biomedical research designs in order to:
  - Provide an understanding of drug development
  - Make you a better consumer of clinical information
  - Create a culture of critical appraisal – not passive acceptance
- Expose you to the complicated language of the biomedical researcher.
  - Statistical versus clinical significance
  - Intention to treat versus completer analysis
  - Case-control study, randomized controlled double-blind trial

Lectures and Lecturers

- The drug and device development process – Hazlet
- Experimental methods – Blough
- Reporting results – Blough
- Observational methods – Boudreau, Gardner
- Early clinical studies - Thummel
- Using the literature –
  - Meta-analysis – Veenstra
  - Pharmacoeconomics – Garrison
  - Population-level decisions - Watkins

Montelukast versus Beclomethasone:
Mean FEV1, Response

[Graph showing Montelukast vs. Beclomethasone percent change from baseline]

DA-SNG 10(1). Available on request from Merck & Co., Inc.

Course Objectives

- Present approaches to synthesizing and using the literature to support individual and population-level decisions
  - Meta-analysis and systematic reviews
  - Pharmacoeconomic analyses
- Prepare you for:
  - Pharm 479 – Biostatistical Methods
  - Pharm 509 – Literature Evaluation
  - Your clinical clerkships