FIRST DO NO HARM:
AN EBM ODYSSEY

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Learning Objectives

1. Describe the types of studies used to elucidate harm, and when each is appropriate
2. Critically appraise a case control and cohort study for harm (2 for the price of 1!)
3. Describe the difference between risk ratios and odds ratios, and be able to calculate them
4. Calculate a number needed to harm and tell what it means in plain English
5. Apply results from a meta-analysis for harm to a patient
6. Appreciate Homer
Why you should care about Harm Studies

- Counsel patient about risk behaviors
- Everything we do can cause harm
  - Screening
  - Diagnostic testing
  - Treatments
  - Procedures
- Decisions must balance benefits and harms
what types of studies can provide practice-altering information about harm?

1. Systematic reviews
2. Randomized controlled Trials
3. Cohort Studies
4. Case Series
5. 1 and 2
6. All of the above
All study types are needed to elucidate harm

<table>
<thead>
<tr>
<th>When would you use:</th>
<th>Situation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Case series/case control?</td>
<td>1. Dramatic rare effects, long lag time</td>
</tr>
<tr>
<td>2. Cohort study?</td>
<td>2. Unethical to randomize, short-medium lag time</td>
</tr>
<tr>
<td>3. Randomized trial?</td>
<td>3. Relatively common, predictable effect</td>
</tr>
<tr>
<td>4. Systematic review?</td>
<td>4. Rare but serious side effect of established treatment</td>
</tr>
</tbody>
</table>
Name that study -- You wish to determine the risk of major bleeding in patients with atrial fibrillation treated with dabigatran (a direct thrombin inhibitor) for stroke prevention

1. Systematic review
2. Randomized controlled Trial
3. Cohort Study
4. Case Series or Case Control
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

- 18,000 patients with a-fib randomized to warfarin or dabigatran
- Risk of stroke 1.6% vs. 1.5% per year
- Risk of major bleeding 3.4% vs. 2.7% per year (p<0.001)
Name that Study: Your patient asks what the risk of colonic rupture is for the screening colonoscopy you have just ordered

1. Systematic review
2. Randomized controlled Trial
3. Cohort Study
4. Case Series or Case Control
Risk of perforation from a colonoscopy in adults: a large population-based study

Gaurav Arora, MD, Ajitha Mannalithara, PhD, Gurkirpal Singh, MD, Lauren B. Gerson, MD, MS,
George Triadafilopoulos, MD
Stanford, California, USA

**Background:** Previous studies that reported the incidence of perforation from a colonoscopy are limited by small sample sizes, restricted age groups, or single-center data.

**Objective:** To determine the incidence and risk factors of colonic perforation from a colonoscopy in a large population cohort.

**Design:** Retrospective, population-based, cohort study, followed by a nested case-control study.

**Setting:** California Medicaid program claims database.

**Patients:** A total of 277,434 patients (aged 18 years and older) who underwent a colonoscopy during 1995 to 2005, age, sex, and time matched to 4 unique general-population controls.

**Main Outcome Measurements:** Perforation incidence in the 7 days after colonoscopy (or matched index date for controls) with odds ratio (OR); multivariate logistic regression to calculate adjusted ORs for subsequent analysis of risk factors.

**Results:** A total of 228 perforations were diagnosed after 277,434 colonoscopies, which corresponded to a cumulative 7-day incidence of 0.082%. The OR of getting a perforation from a colonoscopy compared with matched controls (n = 1,072,723) who did not undergo a colonoscopy was 27.6 (95% CI, 19.04-39.92),
Name that study: Your mother wants to know whether your little brother, a college football player, is at risk for developing memory loss when he is older.

1. Systematic review
2. Randomized controlled Trial
3. Cohort Study
4. Case Series or Case Control
Association between Recurrent Concussion and Late-Life Cognitive Impairment in Retired Professional Football Players


Abstract

OBJECTIVE: Cerebral concussion is common in collision sports such as football, yet the chronic neurological effects of recurrent concussion are not well understood. The purpose of our study was to investigate the association between previous head injury and the likelihood of developing mild cognitive impairment (MCI) and Alzheimer’s disease in a unique group of retired professional football players with previous head injury exposure.

METHODS: A general health questionnaire was completed by 2552 retired professional football players with an average age of 53.8 (±13.4) years and an average professional football playing career of 6.6 (± 3.6) years. A second questionnaire focusing on memory and issues related to MCI was then completed by a subset of 758 retired professional football players (≥50 yr of age). Results on MCI were then cross-tabulated with results from the original health questionnaire for this subset of older retirees.

RESULTS: Of the former players, 61% sustained at least one concussion during their professional football career, and 24% sustained three or more concussions. Statistical analysis of the data identified an association between recurrent concussion and clinically diagnosed MCI ($X^2 = 7.92, df = 2, P = 0.02$) and self-reported significant memory impairments ($X^2 = 19.75, df = 2, P = 0.001$). Retired players with three or more reported concussions had a fivefold prevalence of MCI diagnosis and a threefold prevalence of reported significant memory problems compared with retirees without a history of concussion. Although there was not an association between recurrent concussion and Alzheimer’s disease, we observed an earlier onset of Alzheimer’s disease in the retirees than in the general American male population.
Name that study: Your patient with advanced Alzheimer’s has agitated behavior interfering with his care, but his family is concerned about the pharmacist’s warning that risperidone may increase his risk of death

1. Systematic review
2. Randomized controlled Trial
3. Cohort Study
4. Case Series or Case Control
Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia
Meta-analysis of Randomized Placebo-Controlled Trials

Lon S. Schneider, MD, MS
Karen S. Dagerman, MS
Philip Insel, MS

A majority of elderly patients with dementia develop aggression, delusions, and other neuropsychiatric symptoms during their illness course. Antipsychotic medications are commonly used to treat these behaviors, along with psychosocial and environmental interventions. They have been the mainstay of psychopharmacological treatment for this purpose during the last several decades despite their clear overuse in the 1980s and federal regulations implemented in the early 1990s requiring their oversight and monitoring in nursing homes.1

During the last decade, the newer atypical antipsychotic drugs (ie, risperidone, olanzapine, quetiapine, and aripiprazole, in order of introduction) have largely replaced the older conventional or first-generation antipsychotic drugs (eg, haloperidol and thioridazine) and have been considered preferred treatments for these behaviors. Context Atypical antipsychotic medications are widely used to treat delusions, aggression, and agitation in people with Alzheimer disease and other dementia; however, concerns have arisen about the increased risk for cerebrovascular adverse events, rapid cognitive decline, and mortality with their use.

Objective To assess the evidence for increased mortality from atypical antipsychotic drug treatment for people with dementia.

Data Sources MEDLINE (1966 to April 2005), the Cochrane Controlled Trials Register (2005, Issue 1), meetings presentations (1997-2004), and information from the sponsors were searched using the terms for atypical antipsychotic drugs (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), dementia, Alzheimer disease, and clinical trial.

Study Selection Published and unpublished randomized placebo-controlled, parallel-group clinical trials of atypical antipsychotic drugs marketed in the United States to treat patients with Alzheimer disease or dementia were selected by consensus of the authors.

Data Extraction Trials, baseline characteristics, outcomes, all-cause dropouts, and deaths were extracted by one reviewer; treatment exposure was obtained or estimated. Data were checked by a second reviewer.

Data Synthesis Fifteen trials (9 unpublished), generally 10 to 12 weeks in duration, including 16 contrasts of atypical antipsychotic drugs with placebo met criteria (aripiprazole [n = 3], olanzapine [n = 5], quetiapine [n = 3], risperidone [n = 5]). A total of 3353 patients were randomized to study drug and 1757 were randomized to placebo. Outcomes were assessed using standard methods (with random- or fixed-effects models) to calculate odds ratios (ORs) and risk differences based on patients randomized and relative risks based on total exposure to treatment. There were no differences in dropouts. Death occurred more often among patients randomized to drugs (118 [3.5%] vs 40 [2.3%]). The OR by meta-analysis was 1.54; 95% confidence interval [CI], 1.06-2.23; P = .02; and risk difference was 0.01; 95% CI, 0.004-0.02; P = .01). Sensitivity analyses did not show evidence for differential risks for individual drugs, severity, sample selection, or diagnosis.
Today’s Odyssey: Evaluating Possible Harms in Osteoporosis Literature

Siren song and the subtrochanteric fracture case-control and cohort

Aeolus’ bag of winds and a-fib in zoledronic acid RCT

Break on Calypso’s island

Scylla and Charybdis and calcium supplement meta-analyses
Mrs. S

- 75 year old African American woman
- Generally healthy and active
- Osteoporosis diagnosed on screening DXA
Osteoporosis Treatment Benefits

• Bisphosphonates - first line therapy
  • Reduce vertebral fractures 50%
  • Reduce hip fracture 35%
  • NNT 20-80
  • Improve quality of life
  • Highly cost effective

• Antiresorptive agents
  • Suppress bone turnover
Odysseus and the Sirens
The Siren Song of Subtrochanteric Fractures

- In 2007-2008, 3 case series of 10-15 patients published
  - Unusual appearance and clinical presentation
  - All had long term bisphosphonate use
  - Bone biopsies with very low/absent bone turnover
- Number of case reports 200+ by 2010
- Widespread media coverage
What do you tell Mrs. S?

1. The benefits of treatment almost certainly outweigh the risks – keep taking your medicine
2. The risks are unclear, stop taking your medicine until additional information is available
3. The risks are unclear, continue taking your medicine until additional information is available
4. Stop the medicine and consider whether another treatment is indicated
Buzz Group – 5 minutes

- Design a study to help clarify the risks of subtrochanteric fractures in bisphosphonate users
Case Control and Cohort Study of Bisphosphonate Use and Atypical Femoral Fractures

- 12,777 femur fractures in Sweden, 2008
  - Examined most of the 1271 subtrochanteric fractures
  - 59 atypical fractures
  - 263 control cases of ordinary subtrochanteric fractures selected
Cohort study

- All 1.5 million women over age 55 in Sweden
  - 83,311 bisphosphonate users
  - Age in categories of 5 year increments
  - Duration of use categories

BP use Y/N

Atypical fracture Y/N

1.5 million Swedish women

Jan, 2008

December, 2008
Case Control Study

- 59 cases of atypical fractures
- 263 controls with ordinary fractures in a similar location
- Controlled for:
  - Duration of use
  - 6 other drugs impacting fracture risk
  - Co-morbidity score

Look for prior bisphosphonate exposure

Jan-Dec, 2008

59 atypical fracture cases

263 similar controls
Validity of Harm Case Control and Cohort Studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Our Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment?</td>
<td>• Table 3 p. 1734</td>
</tr>
<tr>
<td></td>
<td>• Analysis adjusted for:</td>
</tr>
<tr>
<td></td>
<td>• Age</td>
</tr>
<tr>
<td></td>
<td>• 6 other medications that impact fracture risk</td>
</tr>
<tr>
<td></td>
<td>• Co-morbidity score</td>
</tr>
</tbody>
</table>
Validity of Harm Case Control and Cohort Studies

2. Were treatments/exposures and clinical outcomes measured in the same ways in both groups?
   - Objective?
   - Blinded to exposure?

Our Study

- Outcome: pg. 1729-1730
  - Fracture classified based on established radiographic criteria
  - Unclear if blinded to BP treatment
  - Random subset classified by second rater, 100% agreement

- Exposure: pg. 1731
  - National drug registry data
Validity of Harm Case Control and Cohort Studies

<table>
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<tbody>
<tr>
<td>3. Was the follow-up of study patients complete and long enough? (cohort studies)</td>
<td>• 1 year of observation</td>
</tr>
</tbody>
</table>
Measures of Harm

Cohort Study: Risk Ratio or "Relative Risk"

<table>
<thead>
<tr>
<th></th>
<th>Atypical Fx</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP use</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>None</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

- Risk of fx in BP users: \( \frac{a}{a+b} \)
- Risk of fx in non-users: \( \frac{c}{c+d} \)
- Risk Ratio: \( \frac{a}{a+b} \) \( \frac{c}{c+d} \)

Case Control Study: Odds Ratio

<table>
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<td>a</td>
<td>b</td>
</tr>
<tr>
<td>None</td>
<td>c</td>
<td>d</td>
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</table>

- Odds of BP use in cases: \( \frac{a}{c} \)
- Odds of BP use in controls: \( \frac{b}{d} \)
- Odds Ratio: \( \frac{a}{c} = \frac{ad}{bc} \) \( \frac{b}{d} \)
Risk Ratios vs. Odds Ratios

• Clinicians tend to think in terms of risk rather than odds, but often odds ratios are reported
  • Case control studies can ONLY give you odds ratios
  • Cohort or RCTs may report odds ratios when they are using logistic regression to adjust for confounders
• Odds ratios approximate relative risk when the event rate is low
• If the event is frequent, then odds ratio will be an overestimate of true relative risk
Measures of Harm for our Study

Cohort Study: Risk Ratio or “Relative Risk”

<table>
<thead>
<tr>
<th></th>
<th>Atypical Fx</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP use</td>
<td>46</td>
<td>83,265</td>
</tr>
<tr>
<td>None</td>
<td>13</td>
<td>1,437,807</td>
</tr>
</tbody>
</table>

• Calculate the risk of atypical fractures in exposed and unexposed women
• Calculate the Risk Ratio

Case Control Study: Odds Ratio

<table>
<thead>
<tr>
<th></th>
<th>Atypical Fx (cases)</th>
<th>None (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP use</td>
<td>46</td>
<td>26</td>
</tr>
<tr>
<td>None</td>
<td>13</td>
<td>237</td>
</tr>
</tbody>
</table>

• Calculate the odds of BP use in cases and controls
• Calculate the Odds Ratio
## Validity of Harm Case Control and Cohort Studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Our Study</th>
</tr>
</thead>
</table>
| 4. Do the results satisfy some “diagnostic tests for causation”? | • Exposure clearly preceded outcome  
• Greater risk with longer duration  
• Conflicting results with other population studies, but these did not separate typical from atypical fractures  
• Biologic sense |
| • Clear that exposure preceded outcome? | |
| • Dose-response gradient? | |
| • Dechallenge-rechallenge study? | |
| • Consistent from study to study? | |
| • Makes biologic sense? | |
What was the magnitude of the harm?

- 5 additional cases per 10,000 patient years

- Number needed to harm 2000 per year of use
  - “If I treat 2000 women with bisphosphonate for 1 year, I will cause 1 additional atypical femur fracture”
What do you tell Mrs. S.?

1. The benefits of treatment almost certainly outweigh the risks – keep taking your medicine
2. The risks are unclear, stop taking your medicine until additional information is available
3. The risks are unclear, continue taking your medicine until additional information is available
4. Stop the medicine and consider whether another treatment is indicated
Odysseus Takes a Break with Calypso (and so do we)
Odysseus and Aeolus’ Bag of Winds
Unexpected Harms in RCTs – Cause for worry or “bag of winds”?

- Large RCT zoledronic acid for osteoporosis
- 3889 subjects
- RR vertebral fractures 0.30
- RR hip fracture 0.59
- Significant increase serious atrial fibrillation
Was this a valid “harm” study?

<table>
<thead>
<tr>
<th>Harm Criteria (Designed for Cohort/Case Control)</th>
<th>Randomized Controlled Trial Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Similar groups</td>
<td>1. Follow-up sufficient</td>
</tr>
<tr>
<td>2. Exposure/outcome measured in same way</td>
<td>2. Randomization</td>
</tr>
<tr>
<td>3. Follow-up sufficient</td>
<td>3. Intention to treat</td>
</tr>
<tr>
<td>4. Causation tests</td>
<td>• NOT IN HARM QUESTIONS</td>
</tr>
<tr>
<td></td>
<td>– per protocol analysis</td>
</tr>
<tr>
<td></td>
<td>4. Similar baseline</td>
</tr>
<tr>
<td></td>
<td>5. Blinding</td>
</tr>
<tr>
<td></td>
<td>6. Equal treatment</td>
</tr>
</tbody>
</table>
Buzz Group

- Calculate the absolute risk increase (risk difference) for a-fib with ZOL
- Calculate the Risk Ratio for a-fib with ZOL
- Calculate the Number Needed to Harm (NNH) with ZOL

<table>
<thead>
<tr>
<th></th>
<th>Serious a-fib</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOL treatment</td>
<td>50</td>
<td>3826</td>
</tr>
<tr>
<td>Placebo</td>
<td>20</td>
<td>3847</td>
</tr>
</tbody>
</table>
Risk Difference, Risk Ratio, NNH

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<td>20</td>
<td>3847</td>
</tr>
</tbody>
</table>

- Risk in ZOL: $\frac{50}{50+3826} = 0.013$
- Risk in Placebo: $\frac{20}{20+3847} = 0.005$
- Risk Difference: $0.013 - 0.005 = 0.008$
- Risk Ratio: $\frac{0.013}{0.005} = 2.6$
- NNH: $\frac{1}{0.008} = 125$
Causation Test Criteria?

- Clear that exposure preceded outcome?
- Dose-response gradient?
- Dechallenge-rechallenge study?
- Consistent from study to study?
- Makes biologic sense?
What do you tell Mrs. S who is considering Zoledronic acid?

- Practice “harm talk” with your neighbor
Subsequent Studies

- 2 large cohort studies
  - 1 negative, 1 protective
- 3 “systematic reviews”
  - 1 negative
  - 1 with 50% risk increase
  - 1 inconclusive
- FDA review
  - No clear association

- Real harm or “bag of wind”? 
Odysseus, Scylla and Charybdis
Sailing between benefits and harms

- Calcium and vitamin D supplements recommended for bone health
  - Reduce fractures
  - Reduce falls
  - Given concomitantly in all trials of osteoporosis therapy
- Recent concerns about cardiovascular safety
# Meta-analysis to answer harm questions

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>• Increase sample size (power) to detect rare events</td>
<td>• Included trials were designed to answer other questions</td>
</tr>
<tr>
<td>• Greater precision of effect size estimate</td>
<td>• May not measure harm outcome accurately, on all subjects</td>
</tr>
<tr>
<td>• Enhance generalizability</td>
<td>• Many applicable trials may be excluded</td>
</tr>
</tbody>
</table>
Meta-analysis of Calcium with or without Vitamin D and Cardiovascular events

Bolland et al., *BMJ* 2011;342:d2040
What questions should you be asking to assess the validity of this finding?

Harm Validity Questions

1. Similar groups?
2. Exposure/outcome measured in same way?
3. Follow-up sufficient?
4. Causation tests?

Systematic Review Validity Questions

1. All relevant studies included?
2. Included studies similar enough to be combined?
3. Included studies high quality?
## Weigh the potential benefits and harms

<table>
<thead>
<tr>
<th>Benefits</th>
<th>RR</th>
<th>Harms</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture</td>
<td>0.88</td>
<td>CV event</td>
<td>1.15</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>0.94</td>
<td>Renal stone</td>
<td>1.17</td>
</tr>
<tr>
<td>Falls</td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

But how do I apply these RRs to my patient?

• Need to estimate the patient’s expected event rate (PEER)
  • Validated risk calculator (e.g., FRAX, Framingham)
  • Population rate
  • Clinically educated guess

• Use equation
  Risk Difference = |1-RR| x PEER
  NNT or NNH = 1/Risk Difference

• Or use pre-populated table from EBM references
Practice on Mrs. S

75 year old with osteoporosis, normal BP and cholesterol

- 10 year risk of major fracture by FRAX = 0.24

- 10 year risk of CV event by Framingham = 0.04
Mrs. S’s Benefits and Harms

Fracture Risk Reduction

• Risk Difference
  \[(1-0.88) \times 0.24 = 0.03\]

• NNT = \[1/0.03 = 33\]

CV Event Risk Increase

• Risk Difference
  \[(1.15-1) \times 0.04 = 0.006\]

• NNH = 167
Learning Objectives

1. Describe the types of studies used to elucidate harm, and when each is appropriate
2. Critically appraise a case control and cohort study for harm
3. Describe the difference between risk ratios and odds ratios, and be able to calculate them
4. Calculate a number needed to harm and tell what it means
5. Apply results from a meta-analysis for harm to a patient
6. Appreciate Homer
Odysseus Arrives Home in Ithaca