Therapy

April 12th, 2016

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Larry Young, MD
Objectives

✓ The evidence-based medicine cycle
✓ Start with a case scenario
✓ Ask the clinical question
✓ Critical appraisal
  • Allocation concealment
  • Intention-to-treat
  • Blinding
  • Follow-up
✓ Results: making the math simple!
The 5 A's

ASSESS

ASK

ACQUIRE

APPLY

APPRAISE

Evidence-based Medicine Cycle

THE PATIENT
Case scenario

✓ A 67-year-old man presented with productive cough and fever for 3 days

✓ Past medical history of coronary artery disease, with a myocardial infarction two years prior

✓ Heavy smoker, 2 packs of cigarettes per day for 50 years (100 pack-year)
Bad pneumonia!
Case scenario

✔ Also had a new myocardial infarction

- Echocardiogram with a drop in ejection fraction to 46% and new segmental wall motion abnormality
All I want for Christmas is for Dad to Quit Smoking
If I get 2 million likes
my Dad says
he'll quit smoking!
His daughter’s request

“Please start something for my father to quit smoking before he goes home, otherwise he will just go back to it right after discharge.”
This sounds like PICOTT...

Yes, this is “PICOTT”able!

Can we PICOTT this?
Clinical question formation

**PICOTT**
- Population
- Intervention
- Comparison
- Outcome
- Type of Question
- Type of (ideal) study design
Clinical question

Smokers admitted to the hospital

Inpatient strategies for smoking cessation

No/other strategies

Quit rate, pneumonia, myocardial infarction

Therapy question

Randomized controlled trial
Search strategy
Search ACP Journal Club

 smoking cessation

Results 1 - 10 of about 83 for smoking cessation.

2007 - An intensive smoking cessation intervention reduced ...

Telling smokers their "lungs age" promoted successful smoking ...

2005 - A smoking cessation program plus inhaled ipratropium ...

2004 - Review: Bupropion and nortriptyline each increase ...

Review: Preoperative smoking cessation interventions reduce ...

A personalized, cellular phone text-messaging program ...

Cytisine increased smoking cessation in adults | Annals of ...

Review: Cytisine increases smoking abstinence | Annals of ...

Nicotine patch plus nicotine lozenges increased smoking ...

Extended-duration transdermal nicotine therapy was more ...
Intensive Smoking Cessation Intervention Reduces Mortality in High-Risk Smokers With Cardiovascular Disease*

Syed M. Mohiuddin, MD, FCCP; Aryan N. Mooss, MD, FCCP; Claire B. Hunter, MD; Timothy L. Grollmes, MPA; David A. Cloutier, BS; and Daniel E. Hilleman, PharmD

Purpose: To compare an intensive smoking cessation intervention against usual care in hospitalized high-risk smokers with acute cardiovascular disease.

Methods: A total of 209 hospitalized smokers were randomized to the intensive intervention (n = 109) or to usual care (n = 100). Usual care consisted only of counseling and printed educational material provided prior to hospital discharge. Intensive treatment consisted of a minimum of 12 weeks of behavior modification counseling and individualized pharmacotherapy provided at no cost to the participant. Smoking status in all subjects was confirmed biochemically (ie, by measuring expired carbon monoxide) at 3, 6, 12, and 24 months after randomization. Outcomes included point prevalence and continuous abstinence smoking cessation rates, hospitalizations, and all-cause mortality.

Results: At each follow-up interval, point prevalence and continuous abstinence smoking cessation rates were significantly greater in the intensive-treatment group compared to the usual care group. At 24 months, continuous abstinence smoking cessation rates were 33% in the
<table>
<thead>
<tr>
<th>Users’ Guide:</th>
<th>Article:</th>
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<tbody>
<tr>
<td>Are the Results Valid?</td>
<td></td>
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<tr>
<td>Did experimental and control groups begin the study with a similar prognosis?</td>
<td></td>
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<tr>
<td>Were patients randomized?</td>
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<tr>
<td>Were patients analyzed in the groups to which they were randomized?</td>
<td></td>
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<tr>
<td>Were patients in the treatment and control groups similar with respect to known prognostic factors?</td>
<td></td>
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Goals of randomization

- To keep all known and unknown prognostic variables evenly distributed between the groups

Diagram:
- Treatment
- Control
- Prognosis X
- Outcome A
- Outcome B
<table>
<thead>
<tr>
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<table>
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<tr>
<th>Did experimental and control groups retain a similar prognosis after the study started?</th>
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<tbody>
<tr>
<td>Were 5 important groups (patients, caregivers, collectors of outcome data, adjudicators of outcome, data analysts) aware of group allocation?</td>
</tr>
<tr>
<td>Aside from the experimental intervention, were groups treated equally?</td>
</tr>
<tr>
<td>Was follow-up complete?</td>
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</table>
Allocation concealment
Our population

YOU!
List generation

Head: Allowed to ask questions (A)

Tail: NOT Allowed to ask questions (NA)
Allocation concealment

✓ The person who is enrolling participants cannot know, predict, or manipulate the list

✓ Trials with inappropriate allocation concealment are associated with larger estimates of treatment effect
Allocation concealment

Diagram: P → R → O
- List generation
- Allocation concealment
Intention-to-treat

✓ AKA: Were patients analyzed in the groups to which they were randomized?

✓ Teaching method 1
Intention-to-treat

Teaching method 2

Cerebrovascular disease

ASA

Surgery + ASA

Surgery

100

100

10

10

Stroke

Stroke

Per Protocol

10/90 = 11%

RD = 9%

20/100 = 20%

ITT

20/100 = 20%

RD = 0%
Intention-to-treat... Why??

- Preserves balance between the groups
- Reflects real life
Blinding

2 volunteers!

Patient

Researcher
Shhhhhhhh!!
Trials with inappropriate blinding are also associated with larger estimates of effect, but not as much as with inappropriate allocation concealment.
<table>
<thead>
<tr>
<th>Allocation Concealment</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Who?</strong></td>
<td><strong>Patients, caregivers, data collectors, adjudicators, analysts</strong></td>
</tr>
<tr>
<td><strong>Allocation Concealment</strong></td>
<td><strong>What?</strong></td>
</tr>
<tr>
<td>Enroller</td>
<td><strong>The list</strong></td>
</tr>
<tr>
<td><strong>Group assignments</strong></td>
<td><strong>After randomization</strong></td>
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</tbody>
</table>
Follow-up

✓ Patients who are lost often have different prognoses from those who are retained

✓ Strategies to deal with lost to follow up: last observation carried forward, worst-case scenario

✓ The best solution is to assure a good follow up
An intensive smoking cessation intervention reduced mortality in high-risk smokers with cardiovascular disease


Clinical impact ratings: GIM/FP/GP ★★★★★☆ Hospitalists ★★★★★☆☆ Cardiology ★★★★★☆☆ Pulmonology ★★★★★★☆☆

Question
In high-risk smokers hospitalized for cardiovascular disease, does an intensive behavioral plus pharmacotherapy smoking cessation intervention after discharge plus usual care reduce mortality and hospital admissions more than usual care alone?

Methods
Design: Randomized controlled trial.
Allocation: [Not concealed]†.*
Blinding: Unblinded.*
Follow-up period: 2 years.
Setting: Coronary care unit in a university hospital in Nebraska, USA.
Patients: 209 patients 30 to 75 years of age (mean age 55 y, 63% men) who were admit-included written self-help materials and a 30-minute counseling session before discharge.

Outcomes: Point prevalence (no smoking since the previous follow-up visit) and continuous abstinence (no smoking since the first follow-up visit) quit rates (both confirmed by measurement of expired carbon monoxide), mortality, and hospital admission.

Patient follow-up: 96% (intention-to-treat analysis).

Main Results
The intensive-intervention group had higher quit rates than the usual-care group throughout the follow-up period and at 2 years (Table). The intensive intervention led to fewer hospital admissions and lower all-cause mortality (Table).

Conclusion
In high-risk smokers hospitalized with cardiovascular disease, an intensive smoking cessation intervention reduced hospital admissions and all-cause mortality more than usual care only.

Source of funding: State of Nebraska Cancer and Smoking Disease Research fund.

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*See Glossary.
†Information provided by author.
All-cause hospital admissions

Step 1:
- Intensive: 23%
- Usual: 41%

Step 2: Subtract: 41% - 23% = 18%

Step 3: Divide: 23% / 41% = 0.56

Risk difference: 18%
Risk ratio: 0.56
Number Needed to Treat

✓ What is the risk difference of 18% telling you?

In order to save 18, you needed to treat 100.

In order to save 1, how many do you need to treat?

Formula

NNT: 100 / RD
Number Needed to Treat

✓ Formula: \[ \text{NNT} = \frac{100}{RD} \]
  \[ \text{NNT} = \frac{100}{18} = 5.5 \]
  \[ \text{NNT} = 6 \]

✓ You needed to treat 6 patients in order to prevent one extra hospitalization in 2 years
Relative Risk Reduction

✅ Teaching method 1

By how much (in %) did I reduce?

Answer: 25%
All-cause hospital admissions

Step 1:

Step 2: Subtract: 41% - 23% = 18%

Step 3: Divide: 23% / 41% = 0.56

Risk difference

Risk ratio
Relative Risk Reduction

✓ Teaching method 2

Formula: 

\[ \text{RRR} = 1 - \text{RR} \]

Intensive: 23%  
Usual: 41%

\[ \frac{23\%}{41\%} = 0.56 \]

Risk ratio
Relative Risk Reduction

Teaching method 2

- Intensive: 41%
- Usual: 41%

Risk ratio:
- 41% / 41% = 1
- 23% / 41% = 0.56

Formula:
$$ RRR = 1 - RR $$
Relative Risk Reduction

Teaching method 2

Formula:

$$RRR = 1 - RR$$

$$RRR = 0.44 \ (44\%)$$

Risk ratio

23% / 41% = 0.56
Math time!
Mortality

Risk difference: 9.2%
Risk Ratio: 0.23
NNT: 11
RRR: 0.77 (77%)
Take-home points

✓ The evidence-based medicine cycle: everything starts and ends with a patient
✓ Improper allocation concealment can overestimate the effect size
✓ For therapy papers, ITT is preferred to per-protocol analysis
✓ Look for who was blinded in the study
✓ Make the math simple! Remember to subtract and divide!
Teaching Take-home Points

- What strategies did we use to teach these concepts?
Teaching Take-home Points

✓ Real clinical case - start with a patient.
✓ Clinical question related to different specialties, and even non-medical learners
✓ Group activities
✓ Pre-mark article - saves time; reduces stress
✓ Imperfect articles (you can teach with them)
✓ Interactivity
✓ Different teaching strategies (visual learners, math lovers)
✓ Simplicity: one step at a time, with “no man left behind”
✓ Triage: you can’t do it all
Back to our patient...

✓ One year after discharge:
Thank you!