Evidence-Based Practice
Observational studies and more

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An early Clinical Trial

In the late 18th century, King Gustav III of Sweden decided that coffee was poison and ordered a clinical trial.

J Int Med, October 1991:289 -

Study design

- The king condemned a convicted murderer to drink coffee every day.
- Control: another murderer was condemned to drink tea daily.
- Outcome: death.
- Two physicians were appointed to determine the outcome.

Results

- The two doctors died first.
- The king was murdered.
- Both convicts enjoyed long life until the tea drinker died at age 83 (no age was given for the coffee drinker).

Discussion

One should not rely on such a small sample size. Perhaps the end point was too harsh.

The outcome of the trial had no effect on the decision makers. Coffee was forbidden in Sweden in 1794 and again in 1822.
Conclusions

None possible.

External events and other biases may have confounded the result.

Kings should not mess with clinical trials.

The Lancet published a series of papers in 2002 on conducting clinical research:


Comparison

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Quantitative designs

- **Observational**: studies that do not involve any intervention or experiment.
- **Experimental**: studies that entail manipulation of the study factor (exposure) and randomization of subjects to treatment (exposure) groups

Basic principles of study design

- Experimental study
  - Random allocation?
  - Randomized controlled trial
  - Non-randomized controlled trial
  - Analytical study
  - Descriptive study

- Observational study
  - Comparison group?
  - Cross-sectional study

- Case-control study
  - Exposure and outcome at the same time
  - Cohort study
  - Exposure and outcome at different times

- Cross-sectional study
  - Exposure and outcome at the same time

Observational Studies

Dominate the literature

Funai et al.
Distribution of study designs in four major US journals.....
Gynecol Obstet Invest. 2001;51:8-11

Observational Designs

- **Exploratory**: used when the state of knowledge about the phenomenon is poor; small scale; of limited duration.
- **Descriptive**: used to formulate a certain hypothesis: small / large scale. Examples: case-studies; cross-sectional studies
- **Analytical**: used to test hypotheses: small / large scale. Examples: case-control, cross-sectional, cohort.

Descriptive studies

1. Do not feature a comparison (control) group.
2. Often the first foray into a new area of medicine.
3. Describe the frequency, natural history, and possible determinants of a condition.
4. Hypothesis generation about the cause of the disease.
5. Do not allow assessments of causal association.

Descriptive studies

Who, what, why, when, where
1. Who has the disease in question?
2. What is the condition or disease being studied?
3. Why did the condition or disease arise?
4. Where does or does not the disease or condition arise?
Clinical case-series:
- Clinical case-series: usually a coherent and consecutive set of cases of a disease (or similar problem) which derive from the practice of one or more health care professionals or health care setting,
- A case-series is, effectively, a register of cases.

Clinical case series
- Clinical case-series are of value in epidemiology for:
  - Studying predictive symptoms, signs and tests
  - Creating case definitions
  - Clinical education, audit and research
  - Health services research
  - Establishing safety profiles

Case reports

Case series: what to look for
- The diagnosis (case definition) or, for mortality, the cause of death
- The date when the disease or death occurred (time)
- The place where the person lived, worked etc (place)
- The characteristics of the population (person)
- The opportunity to collect additional data from medical records (possibly by electronic data linkage) or the person directly
- The size and characteristics of the population at risk

Conclusions:
- Case reports and case series can be well received, and have significant influence on subsequent literature and possibly on clinical practice.
- Many were followed by clinical trials.
- Often, report rare conditions for which trials may not be feasible.
- Strong publication bias favouring positive results.
Observational Designs

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Analytical Studies

Comparison of the Characteristics of

**Cohort Study** & **Case-Control Studies**

- Usually very expensive
- Complete source population denominator
- Can calculate incidence rates or risks and their differences and ratios
- Convenient for studying many diseases

- Usually less expensive
- Sampling from source population
- Can usually calculate only the ratio of incidence rates or risks
- Convenient for studying many exposures

...... several famous large cohort studies continue to provide important information ......

Examples: The Framingham study.

- Began in 1948 with 5,209 participants
- ~5,123 spouses and children added in 1971
- Selection not based on exposures, but on
  stable population, wide spectrum of
  occupations,
- Single hospital, annual updated population
  list
- Allowed calculation of incidence rates and
  other descriptive measures for many
  outcomes

Source: Stanaway et al. (1994) European Journal of
  Clinical Epidemiology, 47, 477-486.
Catching my eye today is this roll of toilet paper called, "Hemo Roll".

It's a product of Slovakia, made by a company named "Tento".

The paper is infused with herbal compounds that are claimed to help prevent hemorrhoid inflammation with continued use. According to the product's website...

**RCT: Well conducted ➔ no bias**
- 5 patients with haemorrhoids received Hemo-Roll
- 5 people received placebo
- 4 out of 5 with Oximax got better
- 2 out of 5 with placebo got better

**Participants are not convinced…**
"It could have happened by chance!"

- So how many would you want before you believe the results?
- 10 in each arm?
- 20?
- 100?

**The “Null Hypothesis”**

It could have happened by chance and nothing was really going on

**The p-value**

- What does a p-value of 5 tell us?
Hypothermia vs. control

Proportion responding in treatment arm

Proportion responding in control arm

p-value

Hypothermia vs. control

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p-value
Natural frequency approach

Trial of Hemo-Roll 2

Control group

Intervention group

200 people

200 people

40 people have haemorrhoids

20 people have haemorrhoids

20% 10%

Natural frequencies

Control 100

Intervention 100

20 10

Natural frequencies

Control 100

Intervention 100

20 10

Natural frequencies

Control 100

Intervention 100

20 10

Natural frequencies

Control 100

Intervention 100

20 10

Natural frequencies

Control 100

Intervention 100

20 10
Summary

It could have happened by chance and nothing was really going on

Relative risk - divide

Risk difference – take away

Natural frequencies how many in a 100

Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial

Summary

Background Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability to prevent type 2 diabetes in individuals at high risk of developing the condition.

Methods 5309 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 23 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily); metformin (1000 mg) or placebo (104) and followed for a median of 3.3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT0095056.

Findings At the end of study, 27 individuals had dropped out from the rosiglitazone group and 46 from the placebo group. 100 (1.9%) of the 5298 individuals given rosiglitazone developed the composite primary outcome (hazard ratio [HR] 0.48 [95% CI 0.35–0.64]; p<0.001). 113 (2.4%) of the 4836 individuals in the metformin group and 176 (3.6%) in the placebo group became normoglycemic (p=0.51). 157 (3.1%) died of cardiovascular events in both groups, although 16 (0.3%) participants in the rosiglitazone group and two (0.1%) in the placebo group developed heart failure (p=0.05).

Interpretation Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.
Prevention of diabetes

Drug trials show promising results, but have limitations

Diabetes affects one in 10 adults worldwide, and WHO estimates that 380 million people are living with diabetes in 2010. Treatment can prevent some of the complications of diabetes, including blindness, kidney failure, and heart attacks. However, more research is needed to fully understand and prevent diabetes.

The Diabetes Research Group (DRG) reports that lifestyle interventions, such as weight loss and increased physical activity, can reduce the risk of developing diabetes. The DRG has conducted numerous studies on the effectiveness of these interventions and finds that they are effective in reducing the risk of diabetes.

Combination therapy has also been shown to be effective in the prevention of diabetes. A combination of medication and lifestyle changes has been found to be more effective than either treatment alone. The DRG recommends a combination approach for individuals at high risk for diabetes.

Drug trials are ongoing, and more research is needed to fully understand the effectiveness of these interventions. The DRG encourages researchers to continue studying these treatments and to work towards finding a cure for diabetes.