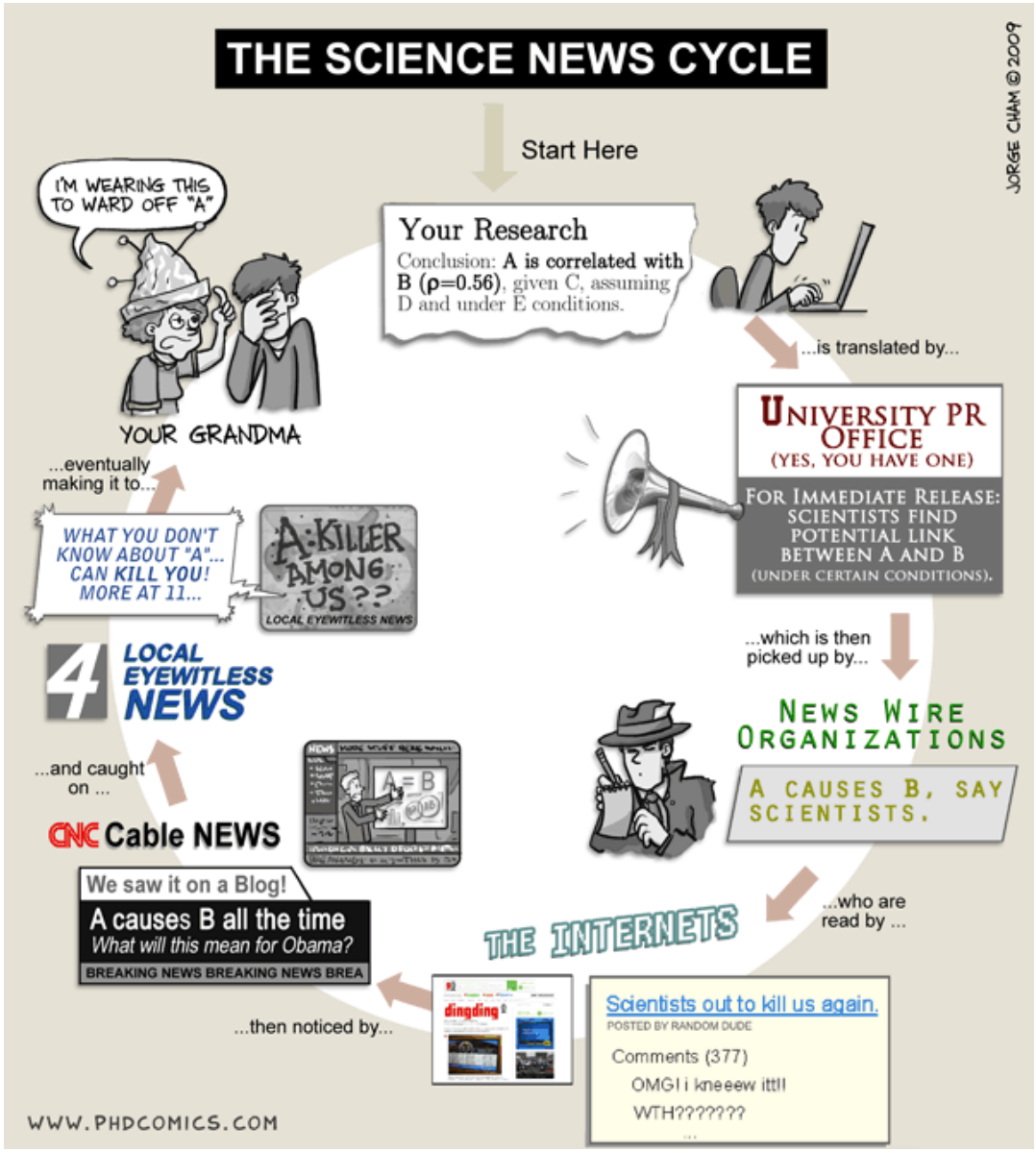
STAT 250

Dr. Kari Lock Morgan

Collecting Data: Randomized Experiments

SECTION 1.3

- Randomized experiments
- Control/comparison group
- Placebo Effect
- Blinding
- Crossover studies / Matched pairs



http://www.phdcomics.com/comics.php?n=1174

Last Class and Lab

- If the explanatory variable is not actively manipulated by the researchers, it is an *observational study*
- Observational studies can almost never be used to determine causality, because of the presence of confounding variables
- By *randomly assigning* the explanatory variable, we can eliminate confounding variables and potentially infer causality

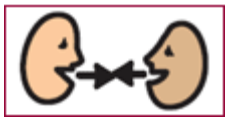
Randomized Experiment

In a ***randomized experiment*** the explanatory variable for each unit is determined randomly, before the response variable is measured

- The different levels of the explanatory variable are known as ***treatments***
- Randomly divide the units into groups, and randomly assign a different treatment to each group
- Medical randomized experiments on humans are called ***clinical trials***

How to Randomize?

- Option 1: As with random sampling, we can put all the names/numbers into a hat, and randomly pull out names to go into the different groups
- Option 2: Put names/numbers on cards, shuffle, and deal out the cards into as many piles as there are treatments
- Option 3: Use technology



Coming to Class

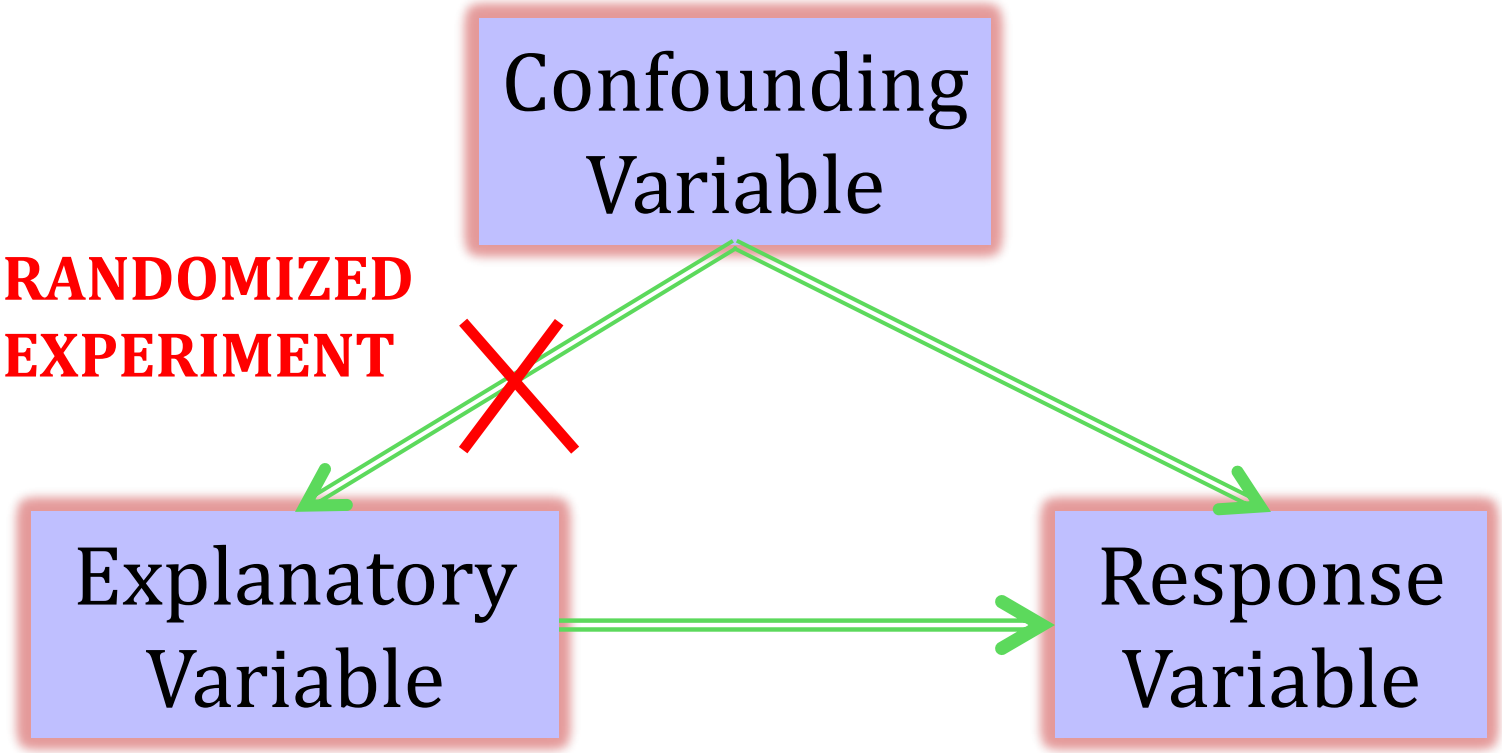
- How much does coming to class every day improve grades on the STAT 250 final exam?
- Cases: students in this class
- Observational study?
  - What would an observational study look like?
  - Why wouldn't this allow us to answer the question?
- Randomized experiment?
  - What would a randomized experiment look like?
  - Why would this allow us to answer the question?
  - Why can't we do this?

Treatment Groups

- If the explanatory variable is not randomly assigned, there could be important baseline differences between the treatment groups
- If the explanatory variable is randomly assigned, the treatment groups should look similar in all baseline variables

Randomized Experiments

- Because the explanatory variable is randomly assigned, it is not associated with any other variables. Confounding variables are eliminated!!!



Randomized Experiments

- If a randomized experiment yields a significant association between the two variables, we can establish causation from the explanatory to the response variable

Randomized experiments are very powerful!
They allow you to infer causality.

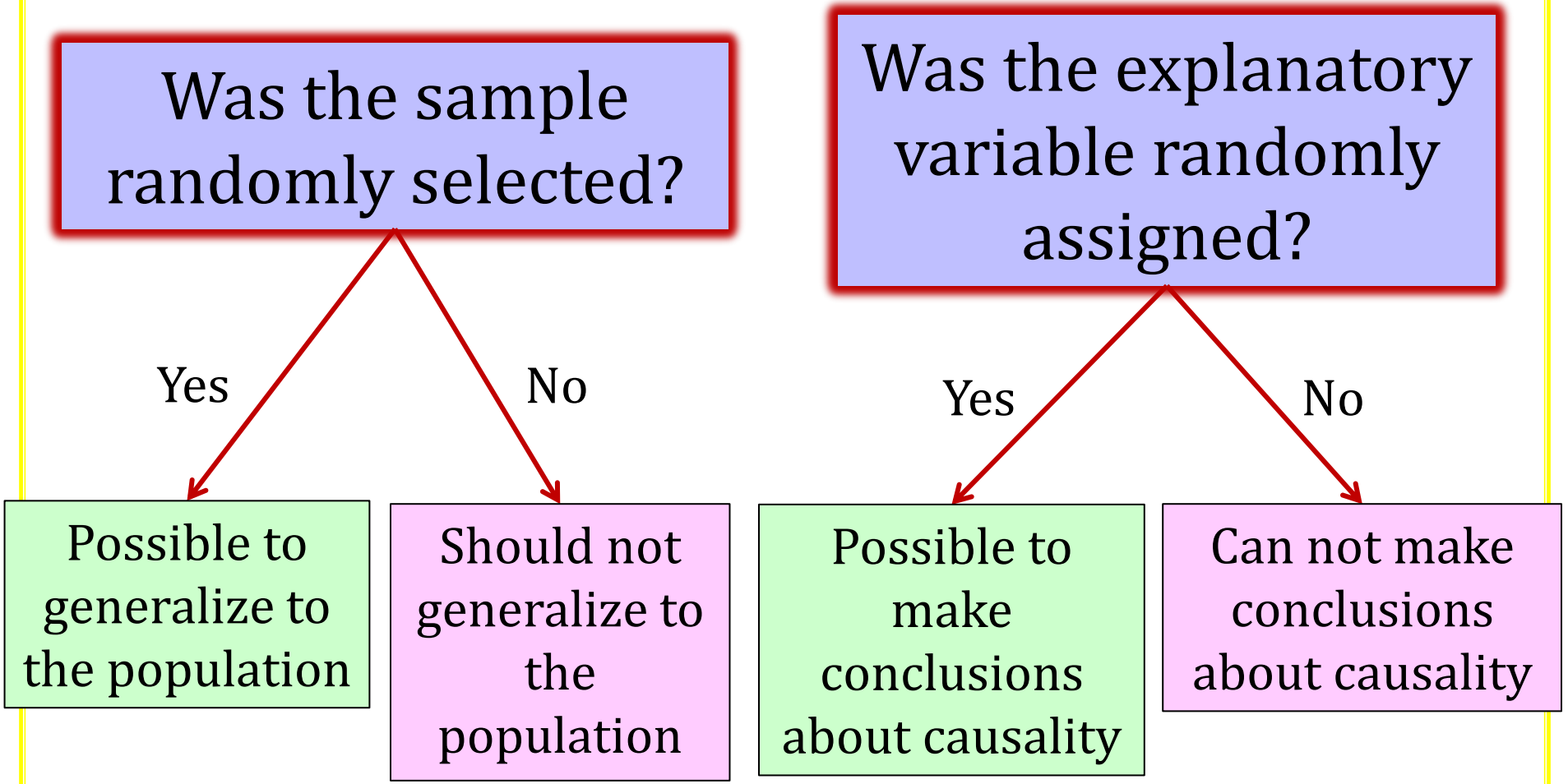
Exercise and Cognition

- A sample of mice were divided *randomly* into two groups. One group was given access to an exercise wheel, the other group was kept sedentary
- "*The brains of mice and rats that were allowed to run on wheels pulsed with vigorous, newly born neurons, and those animals then breezed through mazes and other tests of rodent IQ*" compared to the sedentary mice
- Is this evidence that exercise *causes* an increase in brain activity and IQ, at least in mice?

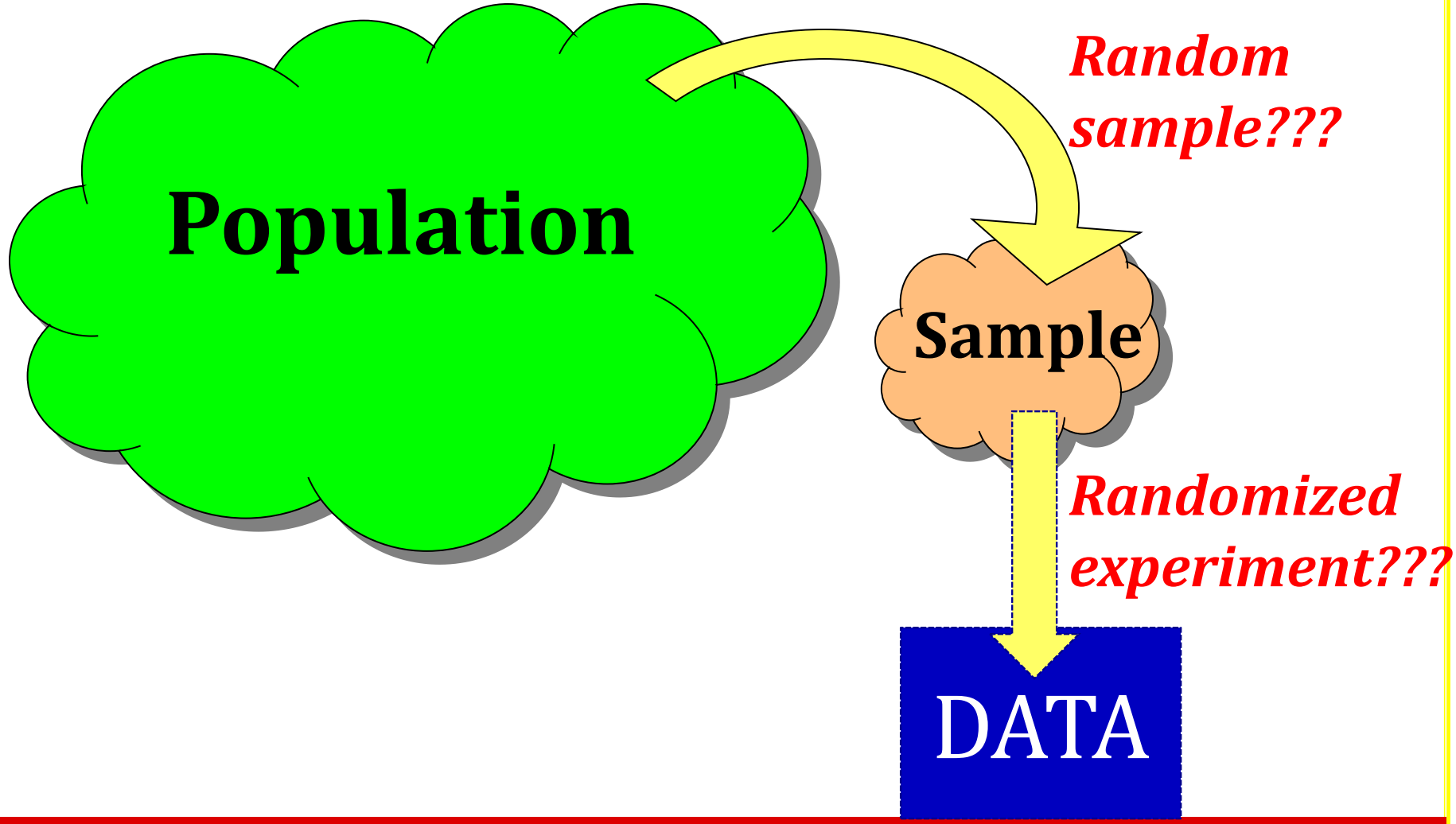
(a) Yes (b) No

Reynolds, "Phys Ed: Your Brain on Exercise", *NY Times, July 7, 2010.*

Randomization in Data Collection



Two Fundamental Questions in Data Collection



Randomization

- Doing a randomized experiment on a random sample is ideal, but rarely achievable
- If the focus of the study is using a sample to estimate a value for the entire population, you need a random sample, but do not need a randomized experiment (example: election polling)
- If the focus of the study is establishing causality from one variable to another, you need a randomized experiment and can settle for a non-random sample (example: clinical trials)

Knee Surgery for Arthritis

Researchers conducted a study on the effectiveness of a knee surgery to cure arthritis. It was randomly determined whether people got the knee surgery. Everyone who underwent the surgery reported feeling less pain.

Is this evidence that the surgery causes a decrease in pain?

(a) Yes

(b) No

Placebo Effect

- Often, people will experience the effect they think they should be experiencing, even if they aren't actually receiving the treatment. This is known as the ***placebo effect.***

- One study estimated that 75% of the effectiveness of anti-depressant medication is due to the placebo effect

- A review of 15 clinical trials with different diseases found that 35% of patients were satisfactorily relieved by the placebo alone (The Powerful Placebo)

- For more information on the placebo effect (it's pretty amazing!) read The Placebo Prescription or listen to Radiolab's podcast Placebo

Study on Placebos

- Blue pills are better than yellow pills
- Red pills are better than blue pills
- 2 pills are better than 1 pill
- 4 pills are better than 2 pills
- And shots are the best of all!

Placebo Effect

Should doctors be allowed to prescribe placebos?

Placebo-controlled studies

- Control groups should be given a ***placebo***, a fake treatment that resembles the active treatment as much as possible

- This allows researchers to separate effect of treatment itself from effect of the placebo effect

- Often instead of a placebo, new treatment is compared to the existing standard treatment (not ethical to not help a patient in need)

Double-Blind Experiments

- If possible, randomized experiments should be ***double-blind***: neither the participants or the researchers involved should know which treatment the patients are actually getting
- The participants should be blinded because of the placebo effect
- The researchers should be blinded to avoid conscious or unconscious bias of the results

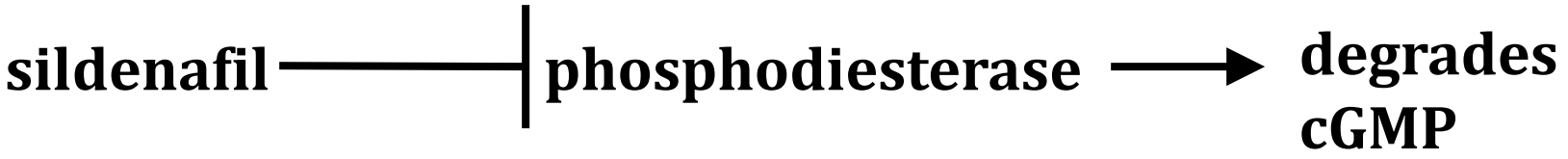
Question of the Day

What is the effect of Sildenafil as a drug?

Sildenafil and cGMP

The molecule cGMP is a natural *vasodilator*: it increases blood flow by relaxing muscle in the walls of blood vessels.

Sildenafil inhibits phosphodiesterase (an enzyme), which degrades cGMP.



Sildenafil

- **1980s:** Pfizer develops sildenafil citrate, which inhibits phosphodiesterase, hoping to increase blood flow in the coronary arteries of individuals with heart disease.
- **1991:** Phase I clinical trials are begun.
- **1992:** Pfizer gets reports of an unexpected "side effect" in men.
- **1994:** After sildenafil fails to show any cardiac benefit, Pfizer begins pilot studies
- **1998:** FDA approves sildenafil for ED.

Atenonol: A randomized experiment

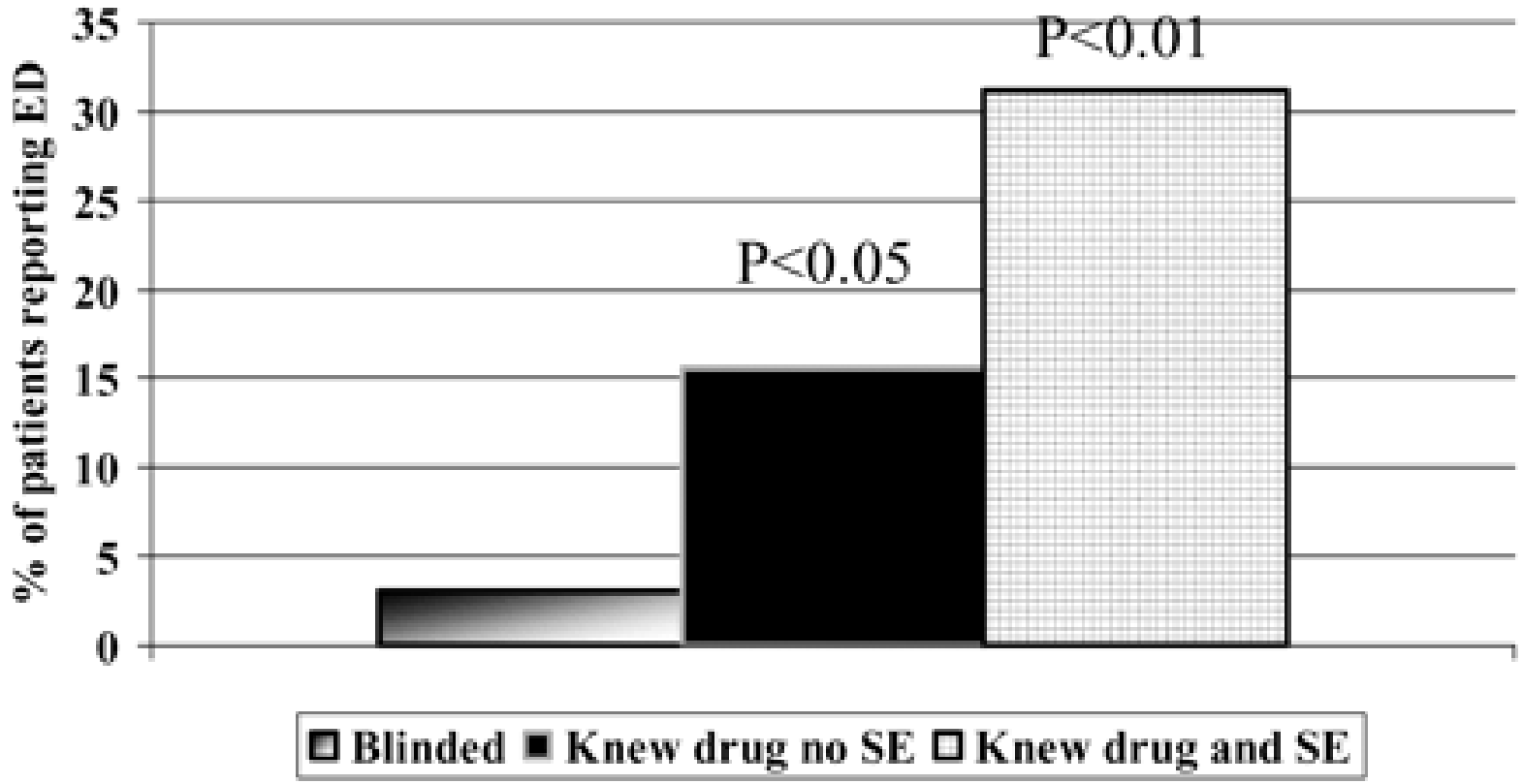
Silvestri et al assigned 96 men to take atenolol, a heart drug which can cause ED as a side effect:

- 32 men were told they were taking either atenolol or placebo
- 32 were told only that they were taking atenolol
- 32 were told that they were taking atenolol, *and* that it can cause ED as a side effect.

After 3 months, the researchers asked men to report any experience of ED.

•Silvestri A, Galetta P, Cerquetani E, Marazzi G, Patrizi R, Fini M, Rosano GM. Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. Eur Heart J. 2003 Nov;24(21):1928-32.

Beta-blockers and Report of ED

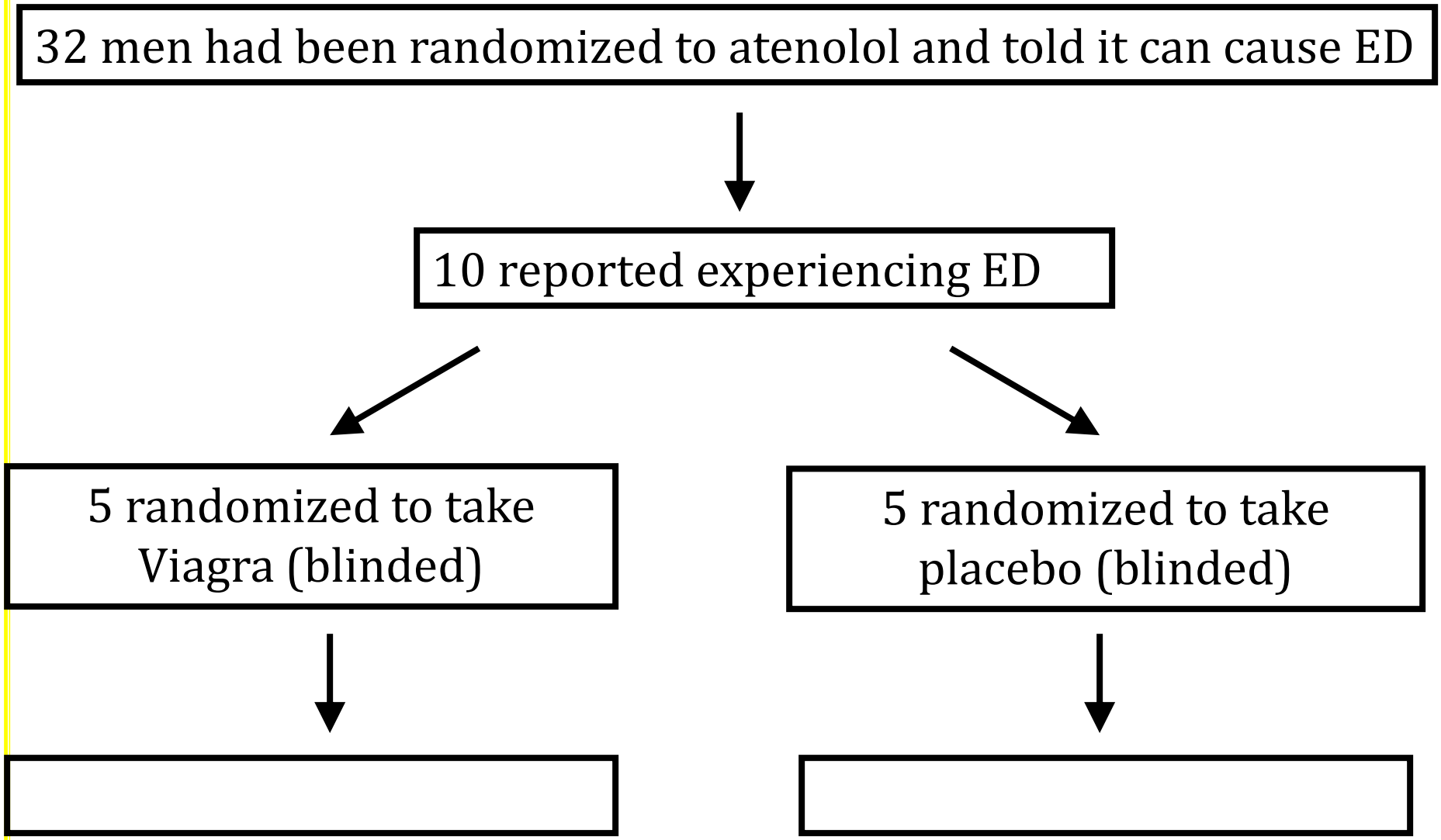


They were all on the *same* drug!

Sildenafil: A Randomized Experiment

The researchers then assigned all men who'd experienced ED to either 50mg sildenafil or placebo. The men were blinded regarding this treatment.

After a week the researchers asked the men if their ED had improved. Any guesses what the men reported?


32 men had been randomized to atenolol and told it can cause ED
10 reported experiencing ED
5 randomized to take Viagra (blinded)
5 randomized to take placebo (blinded)

Trustworthy Clinical Trials

- To assess the trustworthiness of results from clinical trials (or any medical result), ask…
  - Was the treatment randomly assigned?
  - Was the control group given a placebo or other treatment?
  - Was the study double-blind?

Sildenafil, a novel effective oral therapy for male erectile dysfunction

http://onlinelibrary.wiley.com/doi/10.1046/j.1464-410X.1996.10220.x/epdf

M. BOOLELL*, S. GEPI-ATTEE, J.C. GINGELL and M.J. ALLEN*

*Department of Urology, Southmead Hospital, Westbury on Trym, Bristol, and *Pfizer Central Research (Early Clinical Research Group), Sandwich, UK*

Objectives To determine the efficacy and safety of sildenafil, a novel orally active inhibitor of the type-V cyclic guanosine monophosphate-specific phosphodiesterase (the predominant isoenzyme in the human corpus cavernosum) on penile erectile activity in patients with male erectile dysfunction of no established organic cause.

Patients and methods Twelve patients (aged 36–63 years) with male erectile dysfunction of no established organic cause were entered into a double-blind, randomized, placebo-controlled, crossover study which was conducted in two phases. In the first phase (four-way crossover), treatment efficacy was evaluated by measurements of penile rigidity using penile plethysmography during visual sexual stimulation at different doses of sildenafil (10, 25 and 50 mg or placebo). In the second phase (two-way crossover), efficacy was assessed by a diary record of penile erectile activity after single daily doses of sildenafil (25 mg) or placebo for 7 days.

Results The mean (95% confidence interval, CI) duration of rigidity of >80% at the base of the penis was 1.3 min (0.4–3.1) in patients on placebo, 3.5 min (1.6–7.3; $P = 0.009$) on 10 mg, 8.0 min (3.7–16.7; $P = 0.003$) on 25 mg and 11.2 min (5.6–22.3; $P < 0.001$) on 50 mg of sildenafil. The mean (95% CI) duration of rigidity of >80% at the tip of the penis was 1.2 min (0.4–2.7) on placebo and 7.4 min (2.4–8.5; $P = 0.001$) on 50 mg sildenafil. From the diary record of daily erectile activity, the mean (95% CI) total number of erections was significantly higher in patients receiving sildenafil was 6.1 (3.2–11.4), compared with 1.3 (0.5–2.7) in those on placebo; 10 of 12 patients reported improved erectile activity while receiving sildenafil, compared with two of 12 on placebo ($P = 0.018$). Six patients on active treatment and five on placebo reported mild and transient adverse events which included headache, dyspepsia and pelvic musculo-skeletal pain.

Conclusion These results show that sildenafil is a well tolerated and effective oral therapy for male erectile dysfunction with no established organic cause and may represent a new class of peripherally acting drug for the treatment of this condition.

Keywords Sildenafil, penile erection, penile plethysmography

Crossover Studies and Matched Pairs

In a ***crossover study***, each unit gets both treatments.

This is a special case of a ***matched pairs study***, in which either each unit gets both treatments or units are paired and each pair gets both treatments.

- For randomized experiments, the order of treatment or treatment assignment within a pair is randomly determined

Genes or Choices?

- A study examined 10 male identical twins in their mid-30s, in which one twin engaged in regular physical activity and the other was more sedentary.
- The journal article reports: "According to pairwise analysis, the active twins had lower body fat percentage" and also "brain grey matter volumes were larger … in active twins compared to those in inactive co-twins."

Rottensteiner M, et al., (2015) "Physical activity, fitness, glucose homeostatis, and brain morphology in twins," *Medicine & Science in Sports & Exercise*, 47(3), 509-518.

Crossover/Matched Pairs

- Compare a unit to itself or a very similar unit
- Analyze by looking at differences in response within the pair
- Useful in experiments when the response variable varies a lot from unit to unit
- Useful in observational studies to help reduce confounding variables

Why not always randomize?

- Randomized experiments are ideal, but sometimes not ethical or feasible
- Ethics: Can't force someone to partake in a treatment known or suspected to cause harm
- Feasibility: Often, randomized experiments are simply not feasible (cost, time, and practical issues are limiting factors)
- Often, you have to do the best you can with data from observational studies

Takeaway #1

Randomized experiments are important because they…

a) Eliminate confounding variables
b) Allow for causal conclusions
c) Create similar, comparable treatment groups
d) All of the above

Takeaway #2

Use of a control group, placebo, and blinding are important because…

a) Confounding variables exist in observational studies, preventing causal conclusions
b) People may experience the effect they think they should, even without the active treatment
c)They allow the results to generalize from the sample to the population

Takeaway #3

In matched pair designs…

a) Each unit or pair gets both treatments and thus has two response values
b) The difference between responses is analyzed
c) Identical twins are often used
d) Each person often gets both treatments
e) All of the above

To Do

- HW 1.3 due Wednesday, 1/25