Greatest Hits:

Top Ten Cognitive Optical Illusions in Clinical Research

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Examples of Everyday Intellectual Illusions

- You're in a footrace and you pass the person in second place. What place are you in?
- A pencil and an eraser together cost $1.10. The pencil is $1 more than the eraser. How much is the eraser?

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- A pencil and an eraser together cost $1.10. The pencil is $1 more than the eraser. How much is the eraser?

- Answers:
  - Second place
  - 5 cents

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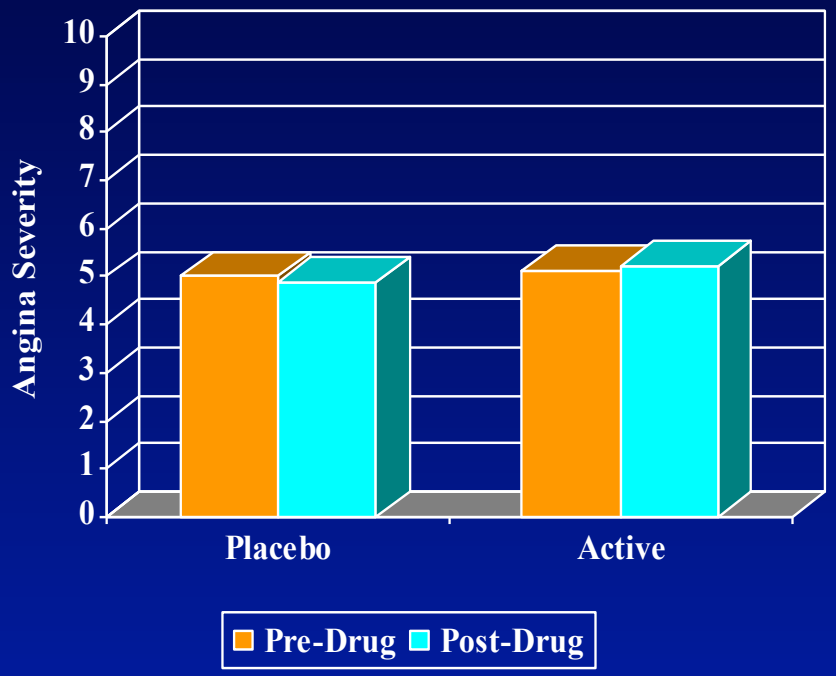
Intellectual Optical Illusions

- Primate brains are not hardwired to process aggregate data properly
- There is natural tendency to use heuristic processing, which is usually adequate for anecdotal data encountered in everyday life
- But this can lead to wrong conclusions when processing statistical information

Illusion 1: Regression to the Mean

- A promising drug for patients with depression is being developed
- Unfortunately, it fails to meet the primary endpoint (symptom severity) in the Phase 2 study



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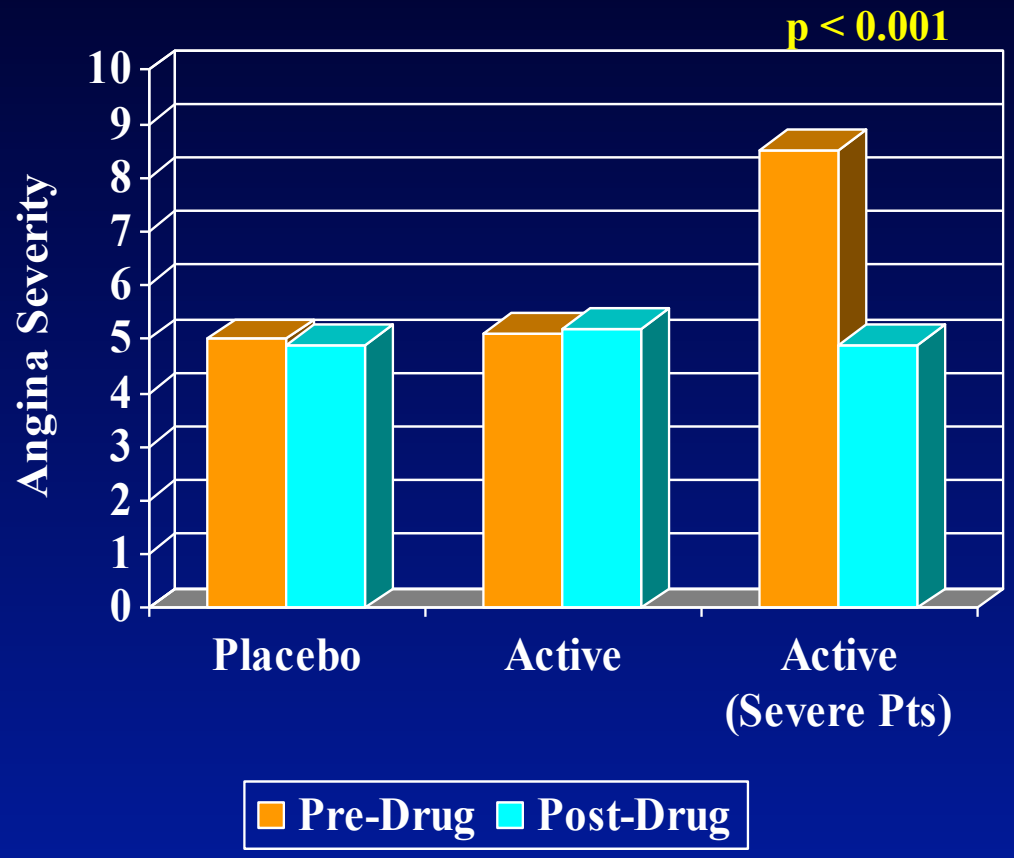
Illusion 1: Regression to the Mean

- But, preclinical data suggest that only the more severe patients would benefit because the drug affects receptors that are the most upregulated in severe disease
- So, a subgroup analysis is performed on the 50% most severe patients

In severe patients, the drug shows clear benefit



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The drug is advanced into Phase 3 for the more severe patients and it fails

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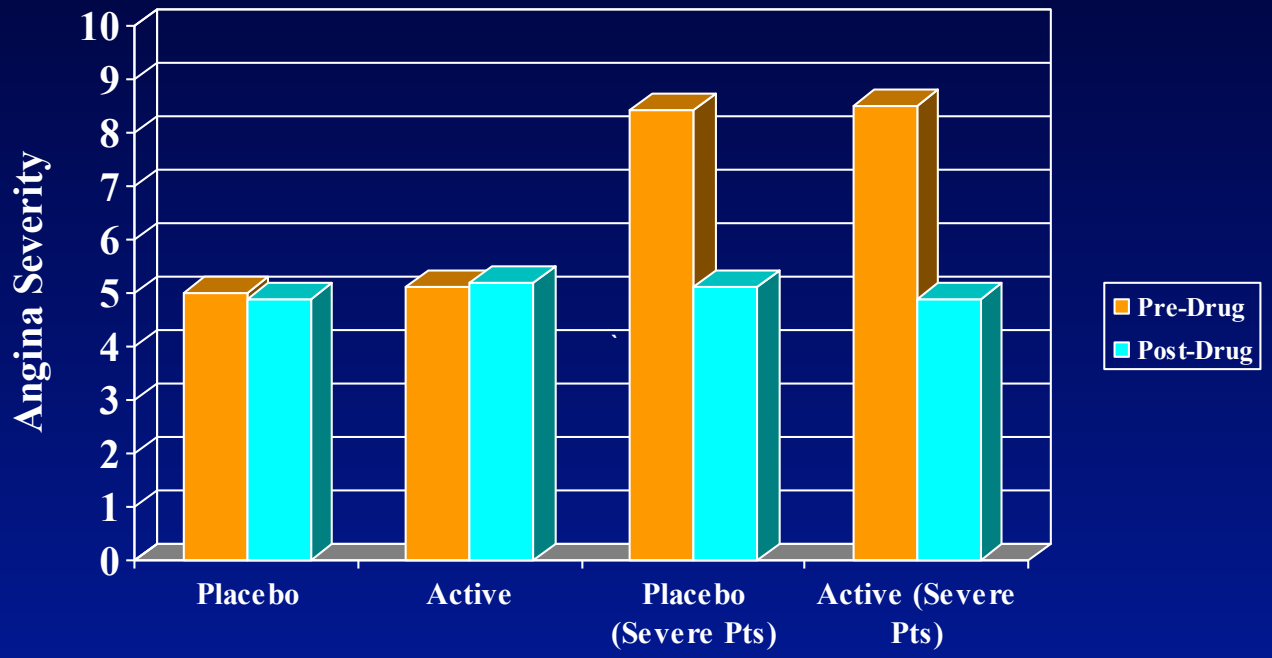
Illusion Explained

- In a waxing and waning diseases, all patients will have good periods and bad
- Taking only the patients who are having worse than usual days will result in patients appearing to improve on repeat measurement

Illusion Explained

- In the Phase 2 study, even the placebo patients appear to do well if only the severe patients are considered



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Solution

- Never compare subgroup in one arm against the entire group from the other arm
- Stratification by severity at time of randomization can protect against regression to the mean

Other Common Instance of Regression to the Mean

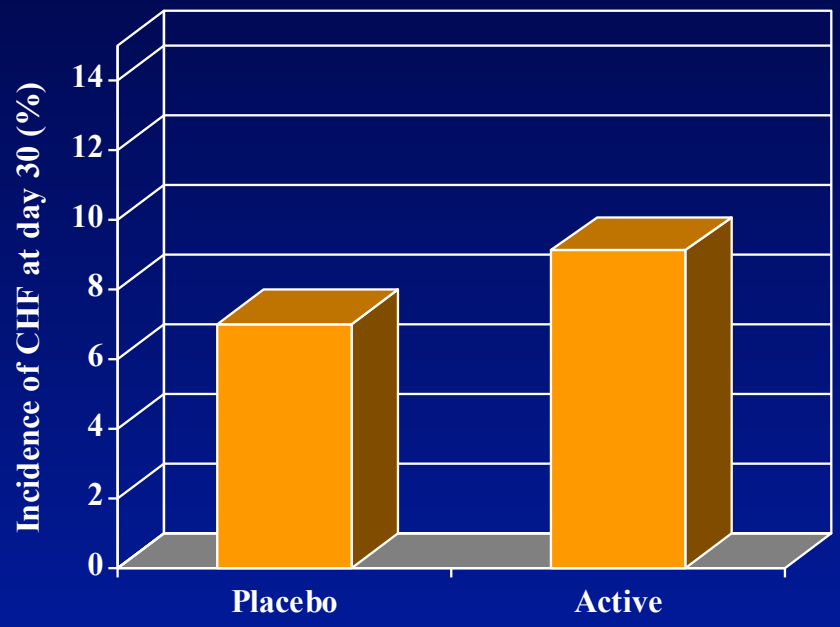
- Often, a Phase 2 study will yield spectacular results, and the subsequent Phase 3 will be less impressive. Given the number of Phase 2 studies that are conducted and given that only a subset proceed into Phase 3, it would be expected that in general, Phase 3 results will be less impressive than Phase 2.
- Often, a trial will fail due to "higher than expected placebo arm response." This is in some cases because patients who were having flares of disease or having a particularly bad day were enrolled.

Illusion 2: Survivor Bias

- A new anticoagulant is being developed for heart attack (MI) patients
- It is expected to decrease damage to the heart, lowering deaths and severity of the MI
- Two most common sequelae of MI are deaths and congestive heart failure (CHF)
- CHF is more common than death, so in order to increase the power of the study, CHF is selected as the primary endpoint

Illusion 2: Survivor Bias

- Contrary to expectation, CHF is increased rather than decreased in the treated group



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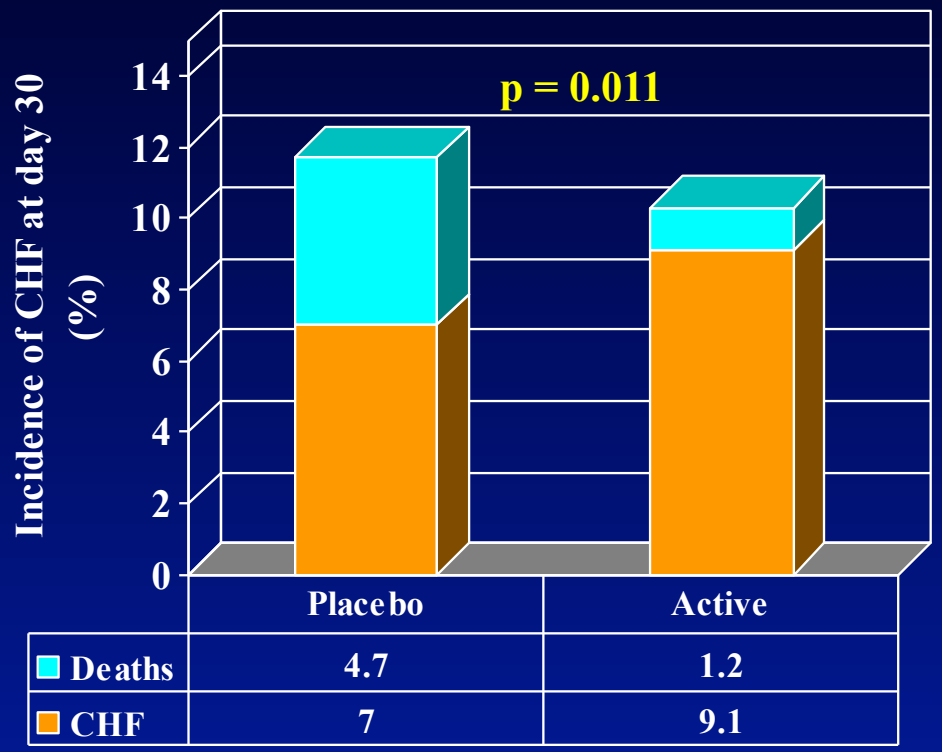
However, Death + CHF was decreased in the active group



Death + CHF is significantly decreased in the treated group.

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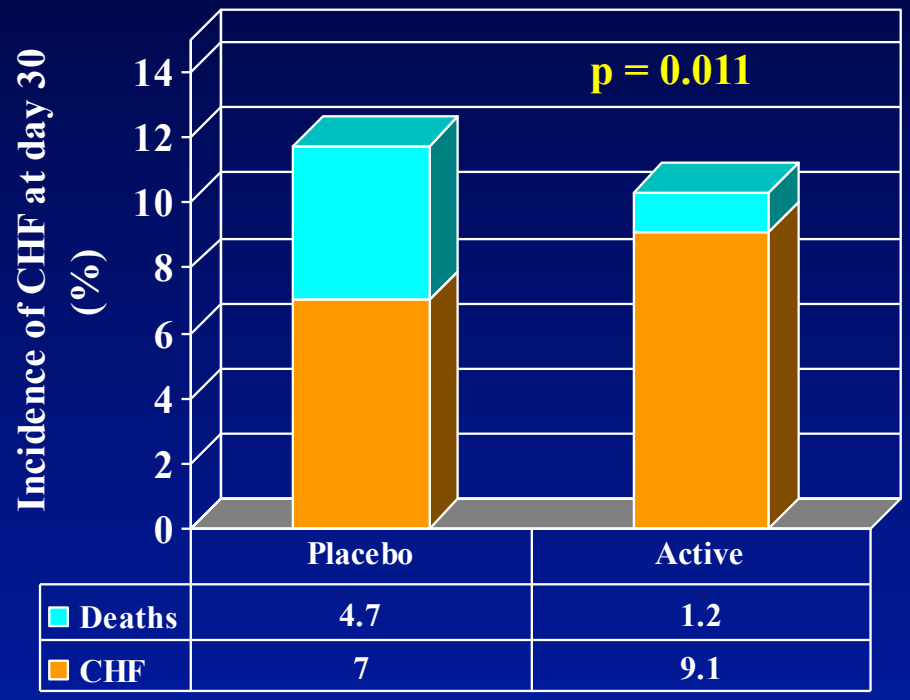
Illusion Explained

- The drug was very effective in preventing deaths
- The patients who would have died on placebo survived, but with enough damage that they developed CHF



Death + CHF is significantly decreased in the treated group.

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Solution

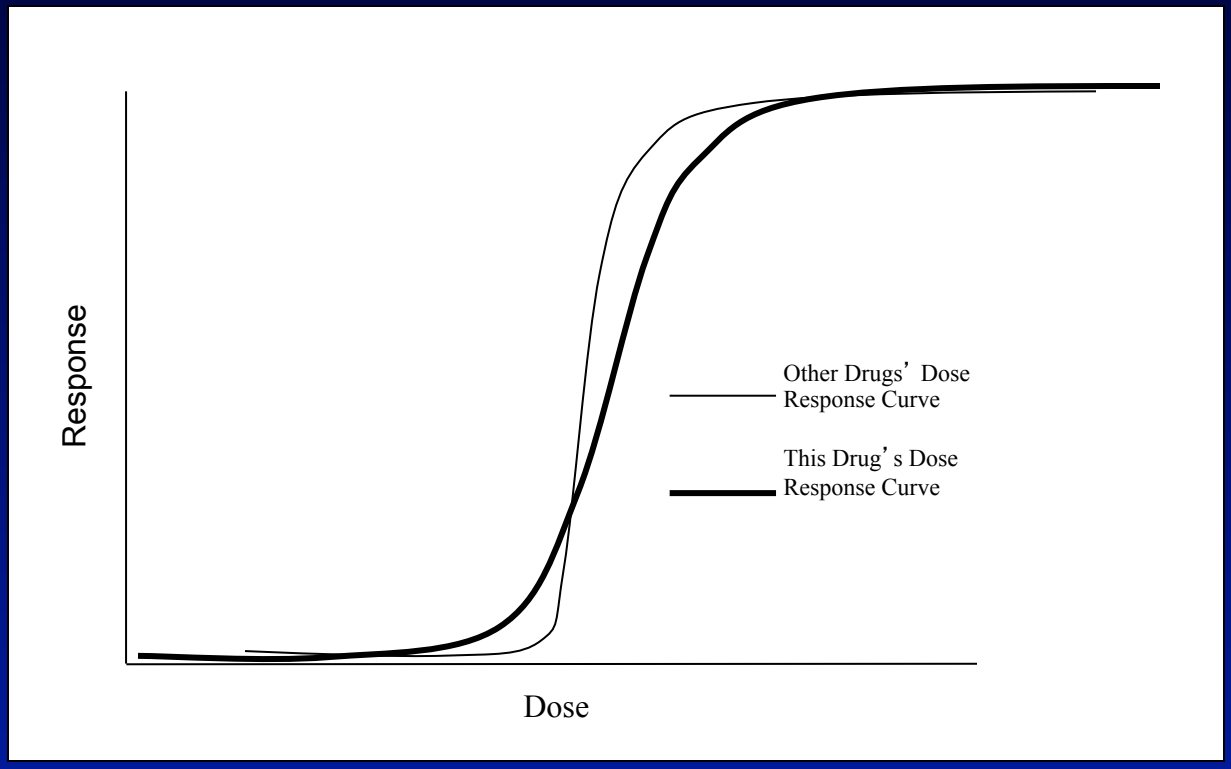
- When selecting endpoints, make sure that all critical endpoints are included
- Consider using composite endpoints instead of single endpoints if power needs to be increased

Illusion 3: Doses in Groups vs. Individuals

- A novel drug is being developed for seizures
- Unlike many other drugs, this drug appears to possibly have an extremely gradual dose-response curve that could lead to a wide therapeutic index
- A phase 2 study is conducted to test this hypothesis

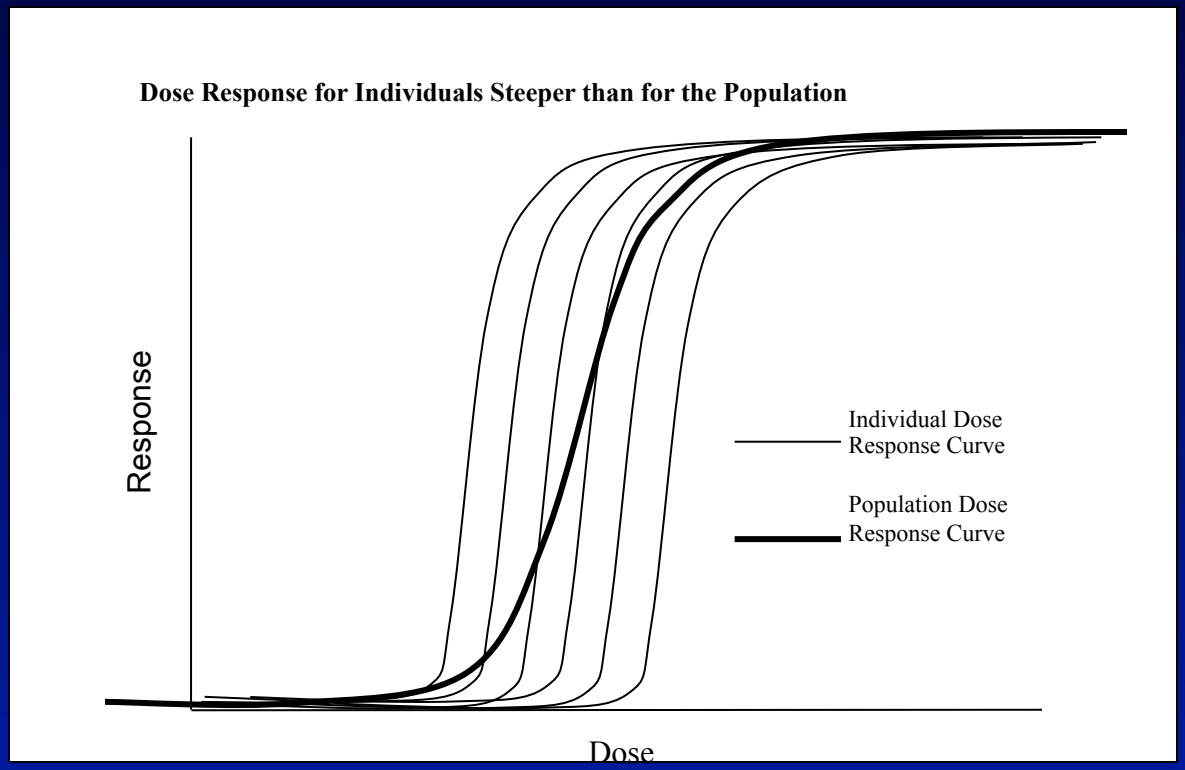
Illusion

- As expected, the dose response curve is very gradual
- This seems to be great news until a pharmacokineticist explains the data



Illusion: Doses in Groups vs. Individuals

- The gradual population dose-response curve does not necessarily translate into gradual individual dose-response curve



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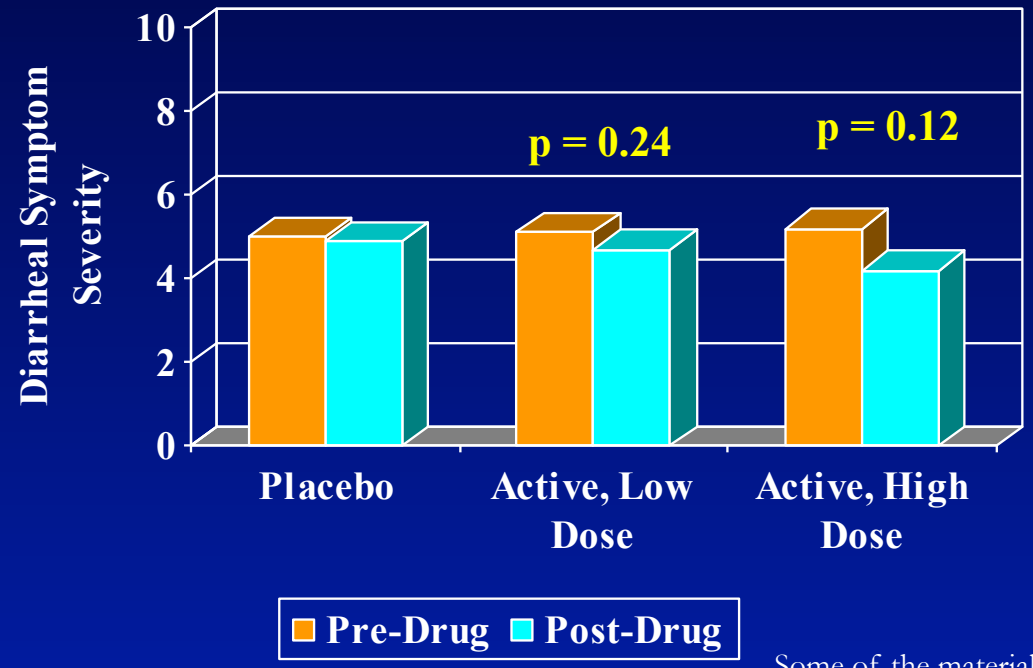
Illusion 4: Shifty Subgroups

- Subgroup analysis can often be useful, but unless interpreted correctly, it is a minefield of intellectual optical illusions
- Three most common illusions are:
  - Misuse of dependent variables
  - Completer analysis
  - Responder analysis (Mercedes in Chile phenomenon)

Confounded Dependent Variable

- A promising drug for gastroenteritis is being developed
- The study misses primary endpoint of diarrheal symptom severity, but there does seem to be some effect at the higher dose



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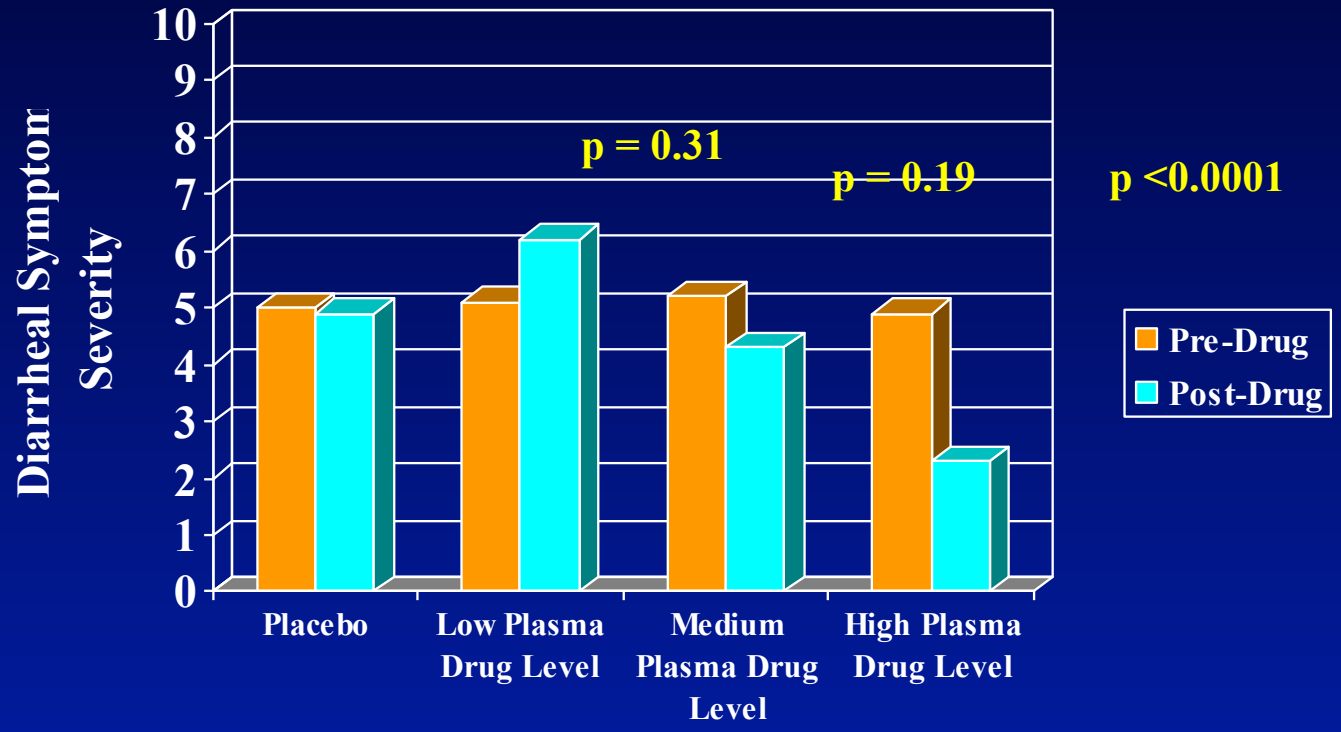
Confounded Dependent Variable

- One of the formulation experts thinks that the drug may not have been absorbed well in these patients with diarrhea
- If drug is not absorbed, then it can't be expected to work
- So, perhaps patients who absorbed the drug did well

Confounded Dependent Variable

- So a new analysis is performed. Patients are divided into 3 groups based on the drug levels in plasma
- There is a profound decrease in symptom score in patients who absorbed the drug best



The drug is advanced into large Phase 3 study with high dose, and the study is negative

Illusion Explained

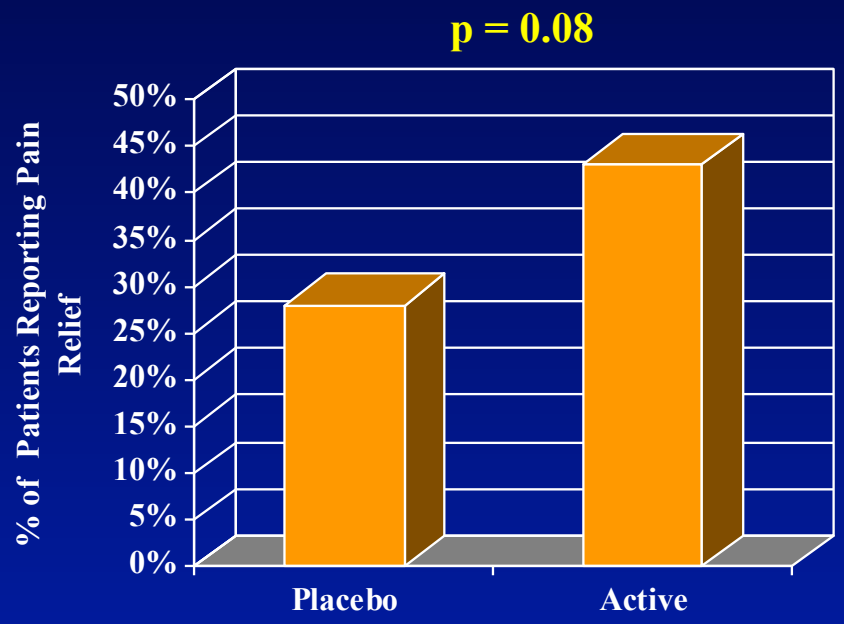
- Patients who were destined to improve had less severe form of gastroenteritis
- As a result, they were able to absorb drug better
- So, they absorbed drug better because they were in a subgroup with better prognosis, not the other way around
- Using any variable that changes during the course of the study (PK, PD, etc.) can lead to erroneous, confounded conclusions

Illusion Variation: Improper Imputation

- A promising new therapy for arthritis is being developed
- It appears to be highly effective in some patients
- Unfortunately, it causes severe itching in some patients that can lead to discontinuation
- Phase 2 is conducted, and as expected, dropouts are significant (about 30%)
- The results are therefore analyzed looking only at patients who completed the study (completers)

Completer Analysis

- The results among those patients who tolerated the drug and completed the study look promising, though statistical significance is not reached



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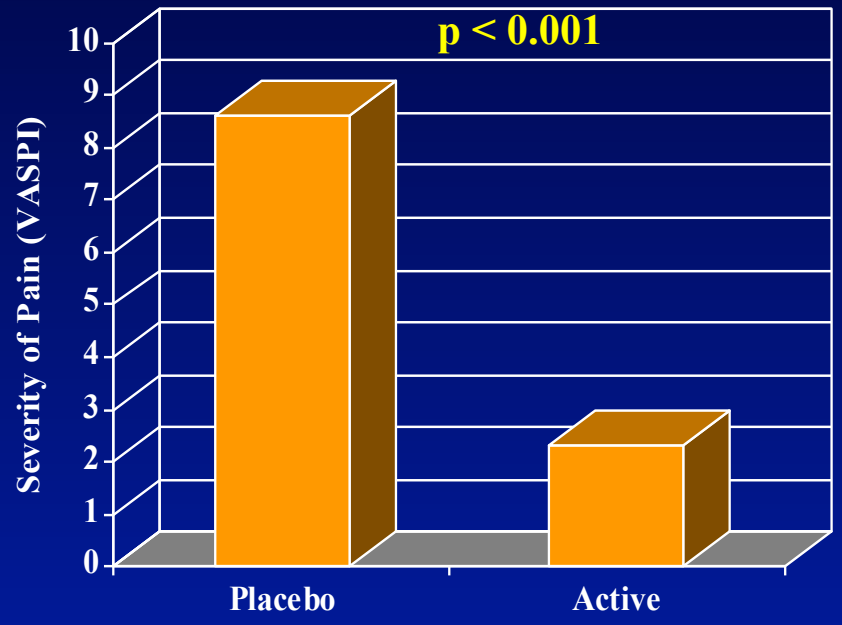
Responder Analysis

- Someone on the team recalls that comparing average scores (continuous endpoint) rather than looking just at success/failure (dichotomous endpoint) can increase the power of the study
- Also, the biology of the drug suggests that it will only work in some patients
- Therefore, the average pain score among those who reported pain relief is examined (responder analysis)

Responder Analysis

- In the responder population, the results are overwhelmingly positive
- In other words, it looks like the drug only works in some patients but in those where it works, it works astonishingly well



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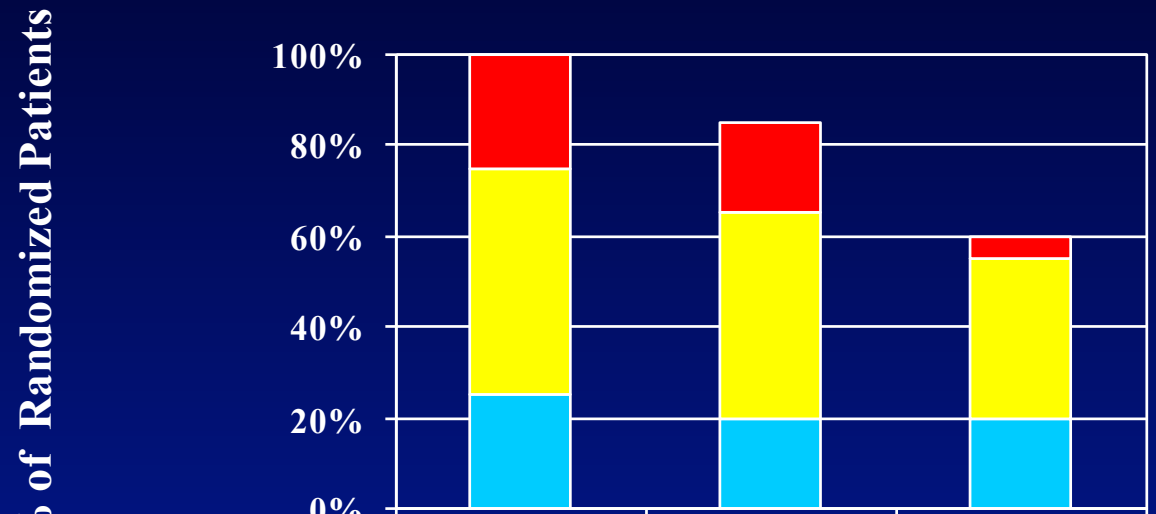
Bad Decision

- The drug is advanced into Phase 3
- It fails to show a benefit in Phase 3

Illusion

- The drug was most likely to cause itching in patients with worst arthritis
- Most patients in the active group who had the most severe arthritis dropped out



	All Randomized Patients	Placebo Completers	Active Completers
Severe Patients	25%	20%	5%
Moderate Patients	50%	45%	35%
Mild Patients	25%	20%	20%

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Completer Illusion

- The numerator is similar between the groups, but denominators change, because more patients drop out in the active group
- The sicker patients are the ones who tend to drop out
- The healthier patients are the ones most likely to improve spontaneously

	Placebo	Active
Responder	27	26
Completer	82	61
Response Rate	33%	43%

Responder Illusion

- Among the responders in the placebo, some patients are from the severe group, who had higher pain scores to start with
- Among the responders in the active group, almost none are in the severe group because they nearly all dropped out
- The pain scores from the severe group skews the mean score in the placebo group

Mercedes in Chile

- Using only responders to gauge the efficacy of a drug is like trying to determine whether Chile or the U.S. is richer by using average income of Mercedes owners in each country
- Very small proportion of the people in Chile own a Mercedes but their average income is higher than Mercedes owners in the U.S.
- That doesn't mean that the average Chilean is richer than an average American
- Nor does it mean that the GNP of Chile is higher than U.S.'s

Solution

- Be very cautious with subgroup analysis
- Use intent-to-treat analysis whenever possible
- If subgroup analysis is important
  - use baseline variables, not variables that can change during the course of the study
  - stratify at randomization by the baseline variable
- Alternatively, titrate the drug to the dependent variable
  - For example, rather than a study with placebo/low dose/high dose, conduct a study with placebo/low target plasma level/ high plasma level

Illusion 5: Puzzling Proportions

- A company claims that its new drug reduces mortality by 90%
- Another drug is supposed to reduce mortality by 9%
- Yet another claims to reduce mortality from 10% to 1%
- Another company says that survival is increased from 90% to 99%.
- All of these claims are equivalent

Illusion

- The difference between 1% and 10% is the same as the difference between 90% and 99%
  - 1% mortality = 99% survival
  - 10% mortality = 90% survival
- The difference between 0% and 90% is comparable to the difference between 90% and 99%
  - 10% to 100% is tenfold difference
  - 1% to 10% is tenfold difference

Definitions

- Absolute difference: mathematical difference when one subtract one number from another
  - 100% - 90% = 10%
- Relative difference: absolute difference in relation to the baseline value
  - 25% - 20% = 5% -> 5%/25% = 20%
- Odds ratio: relative odds
  - 25%/75% ÷ 20%/80% = 1.33

Illusion 6: Post-hoc Analysis

"If you torture the data long enough, it will confess to anything"

- A Phase 3 trial of a drug for pulmonary fibrosis has completed
- It has missed the primary endpoint of walk distance
- But on a post-hoc exploratory analysis, a subgroup of patients with longstanding disease has demonstrated convincing improvement in mortality, from 10% to 2%, with $p < 0.001$
- Another phase 3 study is conducted, with all cause mortality as the endpoint
- The trial fails

Post-hoc Analysis

- Given enough time and enough analysis, a compelling subgroup and/or endpoint can be found for virtually any study
- In general, these findings are spurious and almost never repeatable.

Illusion 7: Surrogates

"I am not a doctor but I play one on TV."

- Many patients die of irregular heart rhythm (arrhythmias) after a heart attack (MI)
- The patients with the greatest number of premature ventricular contractions (PVC's) are clearly the highest risk of death
- Several drugs were developed to prevent PVC's, and they were believed to be effective in preventing life-threatening arrhythmias.

CAST

- CAST was a study of antiarrhythmic drugs designed to demonstrate that the drugs lowered mortality
- It was initiated amidst controversy, because many physicians thought it was unethical to randomize patients to placebo
- Unfortunately, the drugs did not prevent the arrhythmias
- They rather caused a proarrhythmic side effect that led to deaths
- The drugs increased mortality and CAST was terminated early by the DSMB

TNF Inhibitors

- There is overwhelming data proving that in congestive heart failure (CHF) patients, higher the level of TNF, more likely they are to die
- Because of this a large study was conducted to reduce mortality by administering TNF inhibitor
- The study showed that blocking TNF increased mortality

Illusion Explained

- Biomarkers that are correlated with a disease can sometimes be
  - a good surrogate if they are in the causal pathway
  - a good drug target if they are in the causal pathway between the drug action and clinical outcome
- However, they are more often
  - An epiphenomena – not in the causal pathway
  - Caused by the disease, rather than causing the disease
  - A protective counter-regulatory response to the disease
- A surrogate can be helpful if used correctly, but they must be validated first

Illusion 8: Statistical Flukes

- A new drug is being developed for wound healing
- The Phase 2 results are convincing, with 30% wound healing in placebo and 63% in active group (p = 0.002)
- However, one of the sites displays a worrisome effect. There, there were 60% wound healing in placebo and only 25% in active.
- An investigation is launched to determine what happened at the site, whether the randomization codes were mixed up, etc.

Illusion Explained

- With enough sites, one or more sites will show reversal of effect, just by chance
- The table below shows the probability of at least one site showing reversal of effect (alpha of 0.05, 80% power)

Probability of At Least One Center Showing Treatment Reversal								
Number of Centers	1	2	3	4	5	6	7	8
Probability of Treatment Reversal	.003	.05	.15	.29	.43	.56	.67	.75

Illusion Part 2

- The drug is taken into Phase 3
- Just to be sure, 4 identical Phase 3 studies are conducted rather than just 2. These studies have the exact same design as Phase 2.
- Despite being identical, 3 of the studies meet the primary endpoint, while the fourth one misses it with p=0.13
- Though pleased with the positive results, many people are puzzled why the fourth one was an anomaly.

Illusion Explained

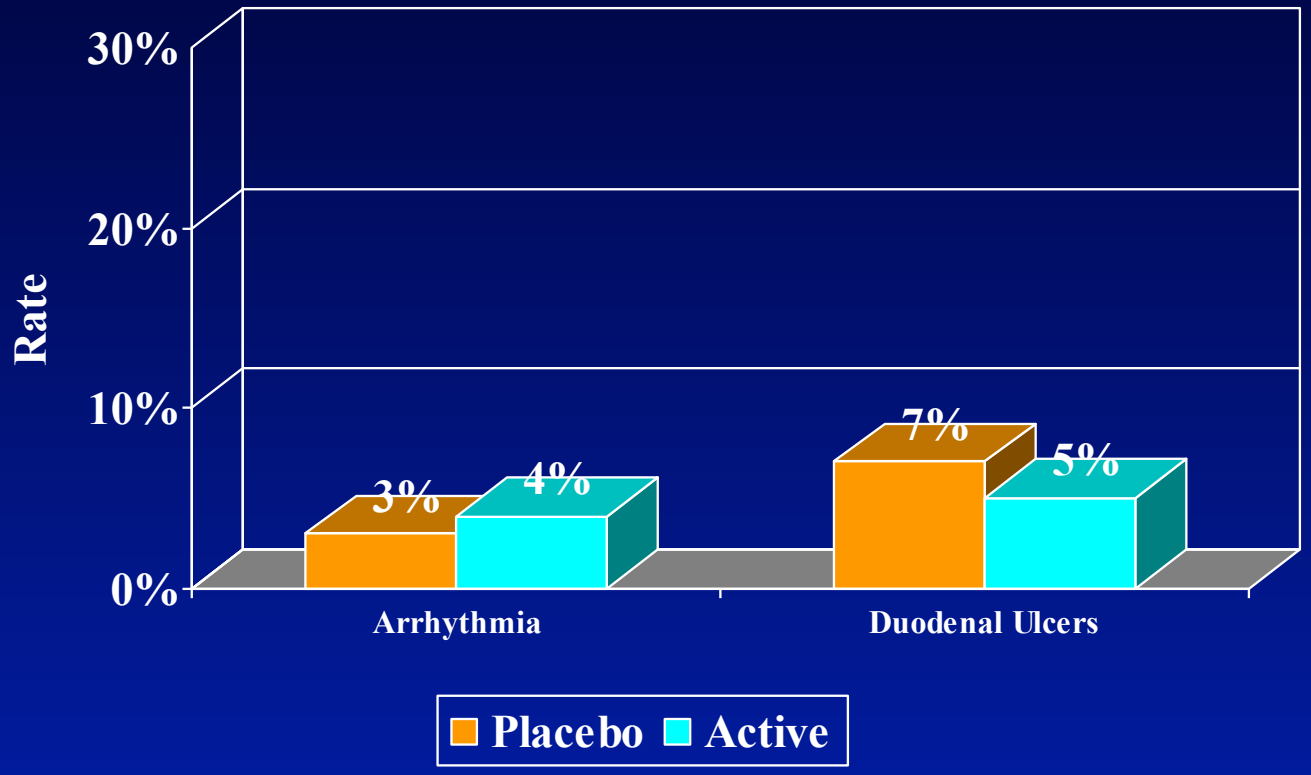
- Even with 90% power, and even with identical study designs, the results are not likely to be exactly the same
- The likelihood of 5 out of 5 studies meeting the primary endpoint is 0.9 x 0.9 x 0.9 x 0.9 x 0.9 = 0.59
- With 80% percent power, the likelihood is 0.8 x 0.8 x 0.8 x 0.8 x0.8 = 0.33
- Even with an active drug, if enough studies are conducted, one or more will eventually fail to show an effect

Illusion 9: Safety Shuffle

- A promising drug for refractory seizures is being developed
- Unfortunately, it appears to have two drawbacks
  - Potential to cause arrhythmias
  - Potential to cause duodenal ulcers
- Therefore, the Phase III safety data is carefully examined to assess potential signal in those two categories

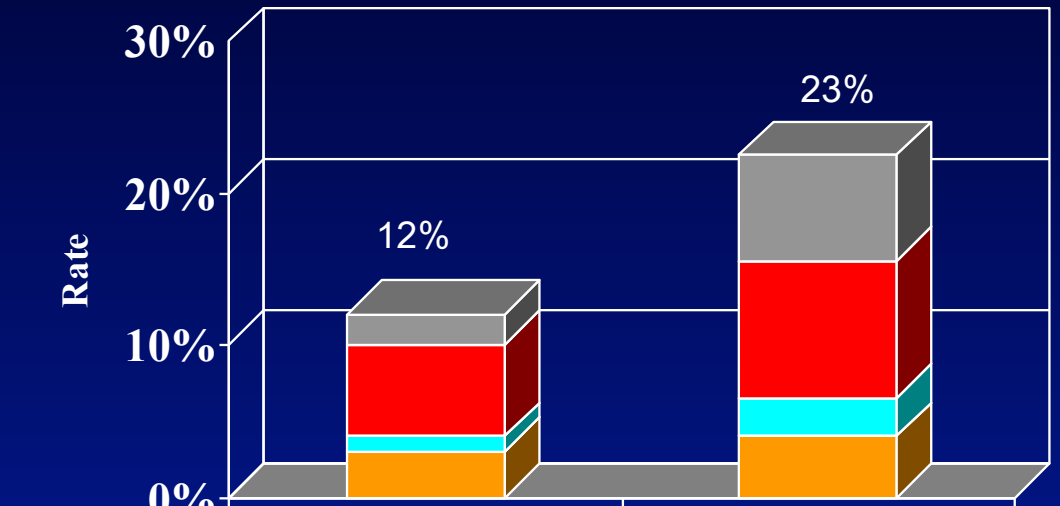
Initial reading

- Fortunately, neither concern seems to have been justified, as no signal is apparent



Illusion: Lumping

- Unfortunately, if the net for arrhythmias is cast more widely to include not just the term, “arrhythmia” but also “sudden death,” “palpitations,” “syncope,” (which can be other presentations of arrhythmia) then a signal becomes apparent



	Placebo	Active
Syncope	2%	7%
Palpitations	6%	9%
Sudden Death	1%	3%
Arrhythmia	3%	4%

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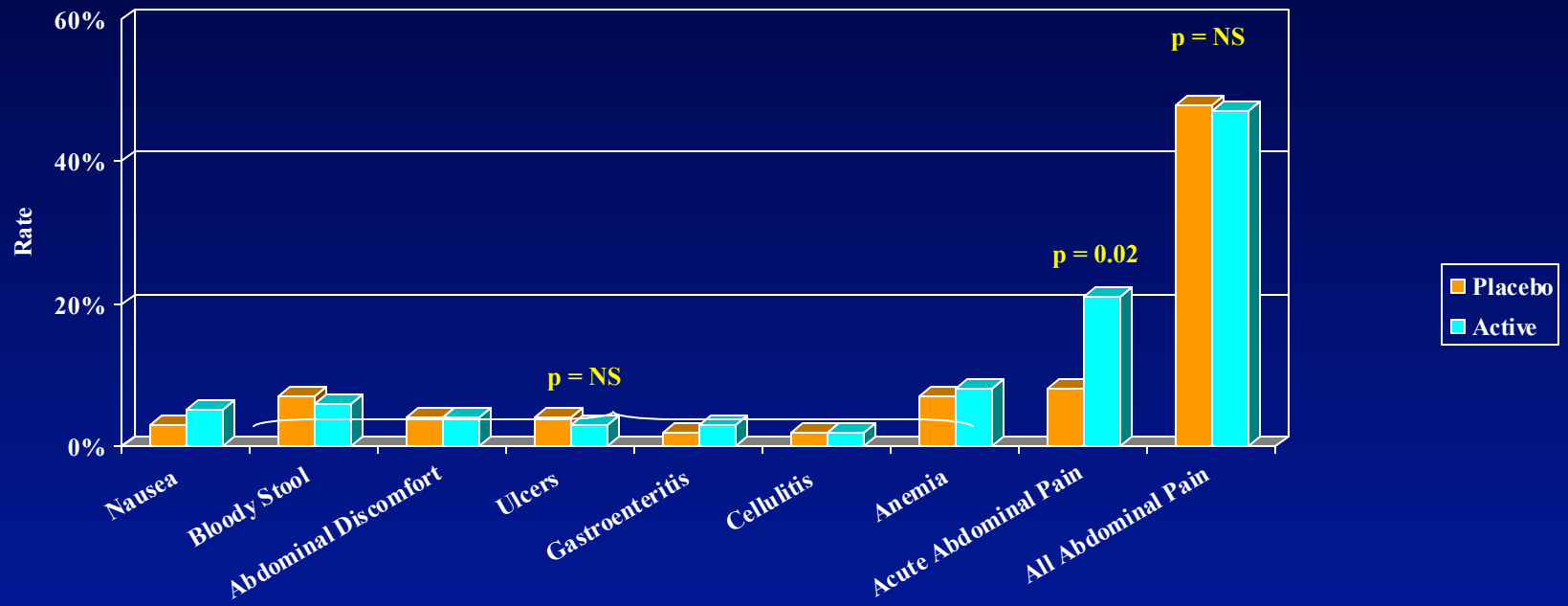
Lumping and Splitting

- For ulcers, no signal is apparent if the data is split too much or lumped too much
- But if we zoom to the right level, a clear signal comes into focus



Illusion 10: Playing with p Values

- Two companies are neck and neck in racing to develop a therapy for a congenital storage disease
- Their drugs are similar but when the two companies announce their Phase II results nearly simultaneously, the results appear quite different
  - The first company announces a successful study with a p=0.0001
  - The second announces a successful study with p=0.04
- What happened? Did the second company make a mistake in their trial design? Is the first company's drug more likely to work?

Illusion

- No, the drugs worked similarly, and to a similar magnitude in the two studies
- The first company's studies had 300 patients, the second had 80
- P values reflect 2 things: how well the drug works and how large the sample size is
- Impressive p values don't necessarily mean that a drug works better, if the studies are not equivalent in design and size

Other Things to Remember about p Values

- The bar is different for efficacy and safety
  - Bar for efficacy is $p<0.05$
  - Bar for safety is far less. Even a safety signal that does not come close to $p=0.05$ must be taken seriously.
- When looking at multiple endpoint, there must be adjustments for multiple comparisons.
- Any p values derived from post hoc analysis is nominal. It represents what would have been the p value, but it is not a real p value.

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