Biostatistics, Medical Research, and Medical Ethics

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Talk Outline

I. Basic Biostatistical Methods –
   A. Objectives and Uses
   B. ANOVA
   C. Regression
   D. Analysis of CDA data

II. Medical and Pharmaceutical Research
   A. Phases of Drug Discovery and Testing
   B. A Quick History
   C. Assessing (Actual) Efficacy
   D. Assessing Risk and Safety
   E. Assessing Costs

III. Some Ethical Considerations

IV. Conclusions

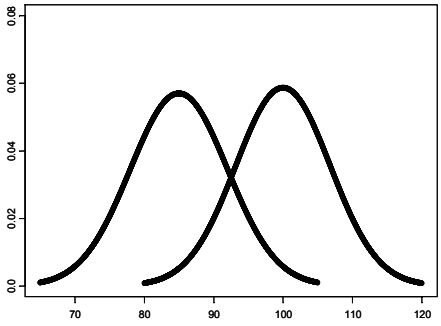
I. Basic Biostatistical Methods

A. Objectives and Uses

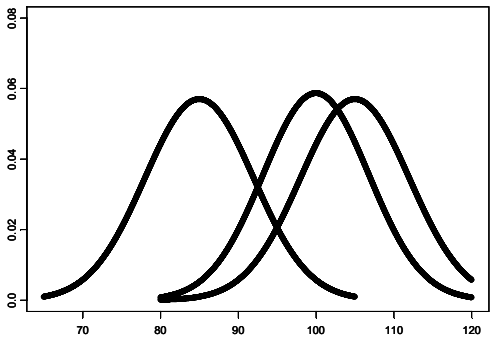
- *Modelling*
- *Estimation*
- *(Hypothesis) Testing*

B. ANOVA

1. 60 pts. and 2 anti-hypertension drugs (A & B), then measure Y = SBP after 24 hours. Could randomize 30 pts. to A and 30 pts. to B. Assume (1) Gaussian dist., (2) equal variances, (3) independent measurements, then do an ***independent sample t-test***.



2. 60 pts. and 3 anti-hypertension drugs (A, B & C), then measure Y = SBP after 24 hours. Could randomize 20 pts. to each drug. Assume (1) Gaussian dist., (2) equal variances, (3) independent measurements, then do a ***one-way ANOVA***.



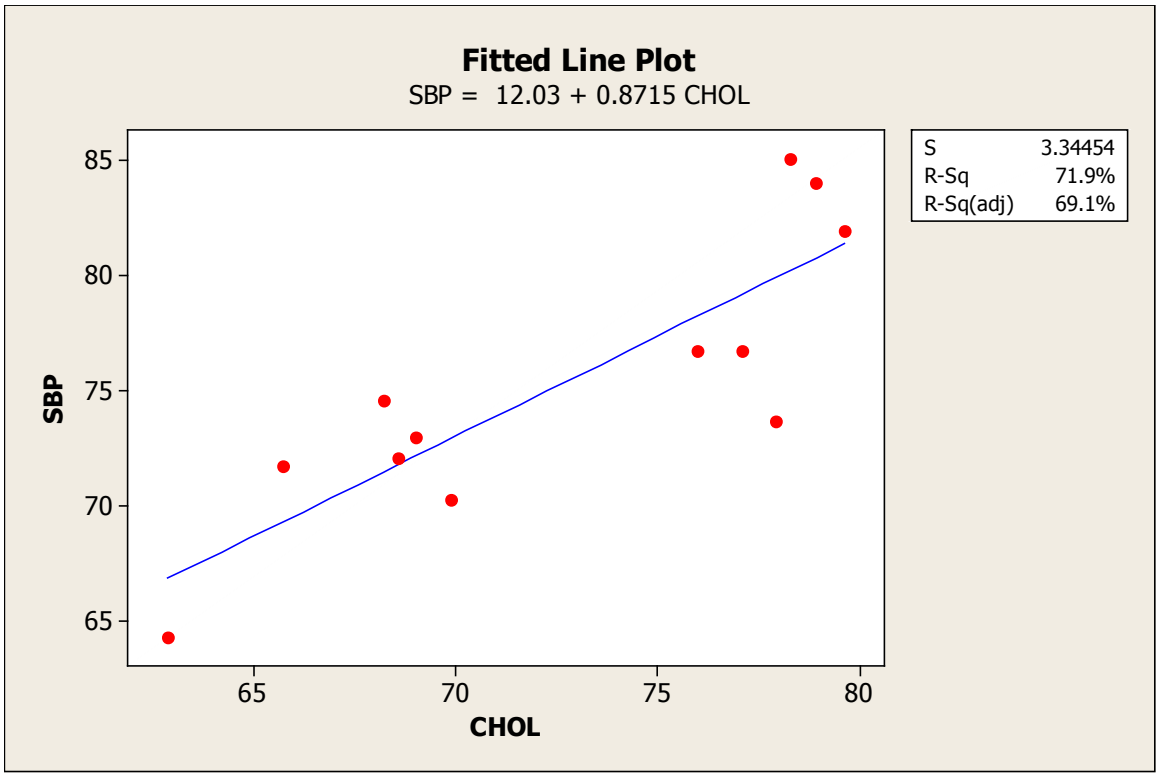
3. Back to 60 pts. and 2 anti-hypertension drugs (A & B) – but now with 30 sets of twins. A set of twins constitutes a "***block***" since the "Experimental Units" (EU's) within a block are typically much more similar than those from two different sets of twins. Other examples of blocking include plots of land in a geographic region, litters of mice, etc. Then, one EU within each block is randomized to each of the treatments. In this instance, we can perform a ***paired t-test*** on the differences of the SBP within the blocks (pairs of twins), assuming Gaussian distribution.

4. Other ANOVA's includes the analysis of ***repeated measures***, ***crossover designs***, etc.

C. Linear Regression

Simple Linear Regression – For example,

$$\mathbf{SBP = \alpha + \beta * CHOL + \varepsilon}$$



Need to assume: (a) line is correct; (b) Gaussian distribution; (c) constant variance; (d) independent measurements.

Multiple Linear Regression – Could include (on the RHS) other potentially useful explanatory variable(s) in the model. For example,

$$\mathbf{SBP = \alpha + \beta * CHOL + \gamma * AGE + \varepsilon}$$

D. Analysis of Categorical Data

First example:

		Infected?	
		Yes	No
Gender	Male	13	12
	Female	5	20

π_M = Probability of Infection for Males; $p_M = 0.52$
π_F = Probability of Infection for Females; $p_M = 0.20$

- can test $\pi_M = \pi_F$ using a χ^2 test
- can estimate RR = $\frac{\pi_M}{\pi_F}$ and test RR = 1
- can estimate OR = $\frac{\pi_M /(1-\pi_M)}{\pi_F /(1-\pi_F)}$ and test OR = 1

Second example (popular with epidemiological studies):

		Neural Tube Defects	
		Case	Control
Genotype	TT	73	83
	CC	151	439

π_{TT} = Probability of Case for TT; $p_{TT} = 0.4679$
π_{CC} = Probability of Case for CC; $p_{CC} = 0.2559$

➔ 95% CI for OR is (1.78,3.68)

Caveat – these methods lack power for tables like:

Pain Relief	Drug A	Drug B
None	3	7
Some	7	11
Substantial	10	5
Complete	5	2
Total	25	25

The (incorrect) commonly-used χ^2 statistic here gives a p-value of 14.2% and the FET p-value is 16.2%. On the other hand, the (correct) Mantel-Haenszel χ^2 p-value is 2.8% – thereby indicating the superiority of Drug A over B.

Biostatistician's Challenge – beyond the challenge of modeling, is to match the correct "statistical tool" to the problem at hand, so as to answer the relevant question(s) via estimation and/or testing.

II. Medical and Pharmaceutical Research

A. Phases of Drug Discovery and Testing

- Non-clinical (compound(s) in a Petri dish)
- Pre-clinical (studies in rats)
- Clinical

- Phase I (PK, healthy volunteers, how drug metabolizes)
- Phase II (dosing, safety, MTD)
- Phase III (large-scale clinical trial for efficacy)
- Phase IV (post-marketing, other indications)

(often now, drug companies "buy" promising compounds from biotech companies, and then just do the clinical testing)

B. A Quick History (*Avorn, Ch. 2*)

- Old days: potions; aspirin from willow bark, etc.
- Giving government clout: FDA since 1962
- Scientific Evolution: shift from anecdotal evidence to Randomized controlled trials (RCT's); important to show an improvement over the placebo effect:

  My doctor gave me these pills and my symptoms were gone in a week! A good thing – otherwise the problem would have taken seven days to resolve.

- Placebo effects are observed through MRI's
- Biostatistical revolution and p-values.

Avorn: each drug represents a triangle with 3 faces representing ***healing, hazards, and costs***.

C. Assessing *(Actual)* Efficacy

- Is challenging because drug companies/FDA continued to resist head-to-head drug comparisons with other similar drugs.
- An inspiring exception: the ALLHAT study (see below).

> ***The net effect, though, is that drugs have been tested and approved based on relatively short randomized controlled clinical trials; later, numerous serious adverse experiences have surfaced.***

D. Assessing Risk and Safety

- "All medicines are poisons .. the right dose differentiates a poison from a remedy." Avorn, p.72 (Med. School)
- "Every drug has at least two effects: the one you intended and the one you didn't."
- Once drugs are approved, cannot rely on (profit-focused) drug companies nor the (overwhelmed) FDA to monitor AE's (adverse experiences, or side-effects).
- Once drugs have been approved and marketed to the public, risks can only be assessed using epidemiological tests such as ***case-control studies***, and these (***observational studies***) are often marred by confounding factors and "confounding by indication."

- Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) – head-to-head comparison (RCT) of anti-hypertensive drugs – showed the less-expensive diuretics safest and equally efficacious. This study contradicted the indications from previous case-control studies!

E. Assessing Costs

- very challenging: is illness in a 92-year-old "worth less" than the same illness in a 29-year-old? Is ED "worth the same" as a heart attack? What fraction? Who decides? How do we discount to present value a heart attack in 20 years?
- very important since the financial strain on State and Federal Medicare and Medicare programs is very great.
- felt most dearly by the elderly, who are often forced to travel to foreign lands or the Internet to fill drug prescriptions.
- Some hope – Avorn's anecdote: "Academic detailing" (NEJM, 1983) under the auspices of the U.S. government.

III. Ethics (Drug Testing in the Third World)

- "The Constant Gardener" and "The Body Hunters" focus on drug testing in Africa and Asia
- The former is based on (true story): Pfizer tested its antibiotic Trovan in Kano, Nigeria, which was subsequently withdrawn: "after less than two years on the market, there were over a hundred reports that the drug produced liver toxicity, causing several deaths, and it is no longer available."
- The latter story was the *Washington Post* 6-part series on drug testing in Africa and ethical concerns: http://www.washingtonpost.com/wp-dyn/world/issues/bodyhunters/
- Movie and article (p.2) address:
  - how drug companies distort research to make their drugs look safer and more effective than they are,
  - how they can get away with this more easily in poor regions of the world,
  - and how they use their vast wealth to influence governments and the medical profession and any other institutions that might interfere with their single-minded pursuit of profits.
- Angell: ".. it was unethical to test an experimental drug orally in the midst of an epidemic." These tests and others conducted in the third world are "inherently exploitative."

- In the U.S.,
  - NDA's must be filed with the FDA
  - IRB's (Institutional Review Boards) must be established to monitor safety and side-effects
  - IC (informed consent) must be obtained and continuously updated (IC is a dialogue rather than a form to sign)
- No IRB was set up for the Pfizer study and IC was dubious at best.
- AZT versus placebo studies in Africa and Thailand to test HIV transmission from mother to child!

IV. **Some Conclusions and Hope**:

- Given our capitalistic system, can we really blame drug companies? Avorn lays a good deal of the blame on MD's who compromise their striving to provide better health-care for financial gain. Equally culpable: politicians (even within FDA) for the same reason.
- All is not hopeless given Avorn's successes and our dire need!