Causal Inference for Medical Decision Making

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OUTLINE

- Regulatory Science
- What is Evidence?
- Assumptions
- Concluding Remarks
1. Medical product entry
   - **Food & Drug Administration**: evaluate medical product safety, efficacy, and quality.
     - Safety assessment relies heavily on observations after market release

2. Medical products/services insurance coverage
   - **Medicare Evidence Development and Coverage Advisory Committee**: evaluates medical literature, technology assessments, etc. on benefits, harms, and appropriateness of medical items and services to make health care coverage recommendations.
     - Clinical trial enrollment of heart attack patients $\geq 75$ year about 9%
       but they comprise 37% of target population (Lee et al., 2001)
     - Must **extrapolate** the treatment benefit to their population ($\geq 65$ yrs)

Therefore, must rely on **observational** data
Manufacturer reformulate existing products to extend product life cycle (1984 Hatch-Waxman Act)

Shift demand for original formulation (soon lose patent protection) to the reformulation

Reformulations involve less frequent dosing, gradual release of active ingredient, or easier to administer

Antidepressant reformulations common (original vs reformulation):
- Celexa vs Lexapro (single isomer); Paxil vs Paxil CR (controlled release); Remeron vs Remeron Soltab (disolvable tablet)

Clinical trial evidence is sparse; mixed at best

Do anti-depressant reformulations decrease medication discontinuation rates compared to original formulations?
What is Evidence?

SCIENTIFIC EVIDENCE FOR MEDICAL DECISIONS

- **Accumulation** of information to support or refute a theory or hypothesis*
- Replication important
- Underlying mechanism important

*Normand, McNeil, 2010

Therefore, **many** designs contribute to evidence base

Source: quoteimg.com Research Evidence Hierarchy Pyramid
1. **ALL** methods make assumptions
   - Either implicit or explicit
   - Statistical and causal assumptions
2. Fewer assumptions better than many assumptions
   - Typically more robust
3. Must assess all assumptions
   - Quantify robustness of results if assumptions are violated
   - **Infrequently** undertaken
CAUSAL ASSUMPTIONS

1. Sample is representative of target population

2. Outcomes for one subject independent of treatment assignment of other subjects and treatments are well-defined & the same for all subjects (SUTVA)

3. Within subpopulations defined by the confounders, treatments are randomly assigned
   - Untestable assumption (sensitivity analysis, multiple comparison groups, control outcomes)

4. There are subjects at every combination of observed confounders so probability of treatment bounded away from zero
   - Structural violations when subjects characterized by specific covariate values cannot possibly get the treatment
   - Practical violations due to finite sample size***
   - Statistically testable

5. Constant Treatment Effect
EXAMPLE: ASSUMPTIONS

Logistic Regression

Bayesian Network

$P(G_1|D) = 30.41$

$P(G_2|D) = 30.43$
## EXAMPLE: ASSUMPTIONS

<table>
<thead>
<tr>
<th>Logistic Regression</th>
<th>Bayesian Network</th>
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<tbody>
<tr>
<td><strong>Statistical</strong></td>
<td>Structured Directed Graph for Joint Probability Distn</td>
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<td>Generalized Linear Model</td>
<td>P(X₁, ⋯, Xₘ) = ( \prod_{j}^{M} P(X_j</td>
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<td>logit(p(X_1 = 1)) = \sum_{j=2}^{M} \beta_j X_j)</td>
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<td>No unmeasured confounders</td>
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<td>( 0 &lt; P(\text{Treatment} \mid \mathbf{X}) &lt; 1 )</td>
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<td>Representative sample</td>
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Logistic Regression

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KEY PRINCIPLES

- Avoid **strong** parametric specifications
  - Likely in settings with many confounders to get model wrong
- Adhere to causal inference **assumptions**
  - Validate assumptions
- Adopt a **design-based** approach
  - Separate treatment from outcome during modeling process
- Reflect all **uncertainty** in estimates
Thank You


- Normand S-LT. Some old and some new statistical tools for outcomes research. Circulation 2008; 118:872-884. PMC2535854

References

- Huskamp H, Busch A, Domino M, Normand S-L. Antidepressant reformulations: Who uses them and what are the benefits? Health Affairs 2009; 28(3):734-745. PMC2752284
