HETEROGENEITY IN CER: THE CASE OF SCHIZOPHRENIA TREATMENTS IN MEDICAID

Anirban Basu, PhD
University of Washington, Seattle
National Bureau of Economic Research, MA

Comparative Effectiveness: A Real-world User’s Guide
March 14-15, 2012
• The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

• These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
BACKGROUND

- Patient-centered comparative effectiveness research implies a focus on personalization.
- Personalization / individualization is a process of identifying subgroups of patients whose marginal benefits / harms from treatment (compared to an alternative) is greater / lower than average.
- Personalization has a strong economic foundation in generating value in health care settings.
- Average results are often misleading!
TWO TYPES OF PERSONALIZATION

• Active personalization
  • Research to identify new genotypical / phenotypical markers for incremental effectiveness or harm
  • Translation of evidence into practice

• Passive Personalization (for existing treatments)
  • Learning-by-doing, N-of-1 trials, adaptation.
  • Study factors driving such processes.
  • Disseminate such learning broadly across practices.
WHAT HAPPENS WHEN PATIENTS ARE HETEROGENEOUS?

Patients who benefit from Red Pill (Group 2)

Patients who benefit from Blue Pill (Group 1)

Efficacy of Red Pill

Efficacy of Blue Pill

Value of Red Pill to Group 2

Pop. Value of Red Pill

Value of Blue Pill to Group 2

Pop. Value of Blue Pill

Value of Blue Pill to Group 2

Equal Efficacy
OUTLINE

• Highlight levels of passive personalization in CER

• Comparative effectiveness of first-line treatment in schizophrenia
  • Novel Instrumental variable analyses of Medicaid data

• Conclusions
BACKGROUND

• Schizophrenia
  • Chronic psychiatric disorder and serious public health issue
  • Lifetime prevalence ~ 1.3%
  • Standardized Mortality Ratio = 151
  • No known cure

• Treatable primarily with drug-therapy
  • Second-generation antipsychotics available since early 1990’s
  • e.g., olanzapine, risperidone, quetiapine etc
  • Risperidone now available as a generic

• Medicaid spends $1.3 billion annually on antipsychotics
ANALYSES GOALS

1. Establish heterogeneity in treatment response between generic atypical and all other atypicals

2. Show that response cannot be easily predicted by subgroups

3. Compare patients outcomes for three policies governing atypical use:
   - Status quo
   - Generic-first policy – i.e, risperidone first
   - Assignment using clinical model

(JOINT WORK WITH ANUPAM JENA (HARVARD), ROBERT DUBOIS (NPC); TOMAS PHILIPSON (U CHICAGO) AND DANA GOLDMAN (USC))
STUDY DESIGN

• Retrospective Medicaid claims data analysis for 24 States, 2002-2005 (claims through 2008 soon available)

• Identified a cohort of patients initiating atypical therapy:
  • Schizophrenia diagnosis (ICD-9= 195.xx)
  • Treatment: initiate monotherapy on risperidone versus any other atypical (olanzapine – 43%, quetiapine – 32%, aripiprazole – 14% or ziprasidone – 10%)

• Other restrictions:
  • No anti-psychotic use in prior 6 months
  • Continuously eligible (1 year prior and subsequent to diagnosis)
  • Ineligible for Medicare
  • Survived at least 12 months after diagnosis
DATA

• **Outcome:** No. of hospitalizations (all-cause & schizophrenia-related)

• **Covariates:**
  - Demographics – age, gender, race
  - Elixhauser’s comorbidity indicators
  - Prescriber characteristics – categories for # of AAD Rx written in last 6 months
  - Treatment history: Any inpatient admission (schizophrenia-specific, psychiatric, all-cause) in past year; any monotherapy or polytherapy of AAD in past year

• **Instruments (to create quasi-randomization):**
  - Provider’s (prescriber) rate of risperidone use
  - Zip-code specific rates of risperidone use
Unobserved confounder: Fundamental problem of evaluation

Instrumental variable

Exposure/Treatment

IV methods

Outcomes

Confounding

IV methods
Unobserved confounder:
Fundamental problem of evaluation

Instrumental variable

Exposure/Treatment

Outcomes

IV methods

Confounding
METHODS

- Propensity score weighting
- Traditional IV approach
  - Two-stage residual inclusion (Terza et al, 2008)
- Local instrumental variables approach
  - Estimates expected treatment effects conditional on a patient’s observed and distribution of unobserved confounders
  - Pioneered by Heckman and others (Heckman & Vytlacil, 1999; Heckman et al, 2006; Basu et al, 2007)

- Note: Both instruments are highly predictive of treatment choice, with a z>9 for each in a logistic regression. The joint Wald test chi-squared statistic is 727 (p<.001), and the other covariates are closely balanced across the quintiles of the instruments.

- Regression $R^2 = 0.18$
## SAMPLE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risperidone (N = 24,028)</th>
<th>Other AAD (N = 54,503)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg. age, y (sd)</td>
<td>40.8 (11.9)</td>
<td>40.4 (11.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>16.8</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>11.7</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>68.9</td>
<td>65.4</td>
<td></td>
</tr>
<tr>
<td>Health care utilization prior to index start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>date of AAD, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any prior AAD mono-therapy</td>
<td>11.7</td>
<td>12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any prior AAD poly-therapy</td>
<td>0.9</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Co-morbidities, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. No. Elixhauser indicators (sd)</td>
<td>1.99 (2.2)</td>
<td>2.02 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>2.6</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, uncomplicated</td>
<td>18.9</td>
<td>18.1</td>
<td>0.010</td>
</tr>
<tr>
<td>Hypertension, complicated</td>
<td>1.8</td>
<td>1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic Pulmonary disease</td>
<td>14.5</td>
<td>15.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes without complications</td>
<td>11.1</td>
<td>9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>1.6</td>
<td>1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>6.9</td>
<td>6.5</td>
<td>0.042</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>18.5</td>
<td>19.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>24.2</td>
<td>26.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychoses</td>
<td>26.3</td>
<td>27.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>11.2</td>
<td>12.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## RESULTS (UNADJUSTED)

<table>
<thead>
<tr>
<th></th>
<th>Risperidone</th>
<th>Other AAD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 24,028)</td>
<td>(N = 54,503)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication adherence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patientsdiscontinuing AAD, %</td>
<td>80.0 (79.5–80.5)</td>
<td>79.1 (78.7–79.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Avg. no. of months treated with an AAD</td>
<td>5.02 (4.97–5.07)</td>
<td>5.24 (5.21–5.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients hospitalized, %</td>
<td>60.4 (59.9–61.2)</td>
<td>60.2 (59.8–60.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Avg. no. of hospitalizations</td>
<td>1.81 (1.77–1.86)</td>
<td>1.84 (1.82–1.87)</td>
<td>0.25</td>
</tr>
<tr>
<td>Patients hospitalized for schizophrenia, %</td>
<td>37.0 (36.4–37.6)</td>
<td>35.3 (34.9–35.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Avg. no. of schizophrenia hospitalizations</td>
<td>0.77 (0.75–0.79)</td>
<td>0.73 (0.72–0.75)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Worried about unobserved confounding due to symptom severity – affects hospitalizations, also may be correlated with receipt of risperidone*
## RESULTS

### (EFFECT OF RISPERIDONE VS OTHER AAD)

<table>
<thead>
<tr>
<th>Group</th>
<th>All hospitalizations</th>
<th>Schizophrenia-related hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>All patients</td>
<td>0.98 (0.54 – 1.42)</td>
<td>0.60 (0.36 – 0.84)</td>
</tr>
<tr>
<td>Patients initiating therapy with risperidone</td>
<td>0.34 (0.04 – 0.64)</td>
<td>0.12 (0.01 – 0.24)</td>
</tr>
<tr>
<td>Patients initiating therapy with other AADs</td>
<td>1.26 (0.72 – 1.80)</td>
<td>0.70 (0.41 – 0.99)</td>
</tr>
<tr>
<td>Alternative models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propensity score weighting</td>
<td>-0.02 (-0.08 – 0.04)</td>
<td>0.03 (-0.05 – 0.11)</td>
</tr>
<tr>
<td>Traditional IV</td>
<td>1.47 (-3.20 – 6.13)</td>
<td>0.82 (-0.68 – 2.32)</td>
</tr>
</tbody>
</table>
TREATMENT EFFECT HETEROGENEITY

[Scatter plot showing hospitalizations with Risperidone and hospitalizations with other atypical antipsychotic drugs]

Hospitalizations with Risperidone

Hospitalizations with other atypical antipsychotic drugs
SELECTION IN PRACTICE

- Predicted proportion who would benefit from risperidone: 28%
- Observed proportion who starts on risperidone: 31%
- Proportion predicted to benefit from risperidone among risperidone starters: 50%
- Proportion predicted to benefit from risperidone among non-risperidone starters: 18%
**WHAT EXPLAINS TREATMENT EFFECT HETEROGENEITY?**

<table>
<thead>
<tr>
<th>Sub-group</th>
<th># of subgroups</th>
<th>Variance in treatment effects explained by subgroups (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Race</td>
<td>4</td>
<td>1.8</td>
</tr>
<tr>
<td>Age</td>
<td>47</td>
<td>2.6</td>
</tr>
<tr>
<td>Elixhauser indicator combinations</td>
<td>6,086</td>
<td>73.0</td>
</tr>
</tbody>
</table>

In other words…
A CER trial with 6,086 treatment groups would only explain 73% of variation in effects.
## POLICY IMPLICATIONS

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Average annual number of hospitalizations (95% CI)</th>
<th>% change from Status-quo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status-quo</td>
<td>1.83 (1.81 – 1.85)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>All patients started on AAD besides risperidone</td>
<td>1.73 (1.63 – 1.93)</td>
<td>-5.5</td>
<td>0.026</td>
</tr>
<tr>
<td>All patients started on risperidone</td>
<td>2.71 (2.33 – 3.09)</td>
<td>48.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All patients started on optimal predicted therapy</td>
<td>1.57 (1.53 – 1.61)</td>
<td>-14.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Notes: P-values reflect comparisons of average annual number of hospitalizations under various scenarios to status quo.

Currently 31% of patients start on risperidone; model indicates that 28% would optimally be started.
IMPLICATIONS FOR CER

• Individual patient differences of crucial importance
  • Tying decision making – i.e., coverage or clinical guidelines – to average results may be marginally beneficial at best, substantially harmful at worst
  • Studying heterogeneity over broad subgroups may not be useful

• Learning-by-doing works well, at least in some contexts

• Algorithmic predictions may be a promising way to guide clinical decision-making
  • Large, observational data sets can be valuable resources to explore and generate such algorithms, which can be later validated using confirmatory studies
CONCLUSIONS

• A paradigm shift in the design of CER studies is needed

• Need to develop the recognition that heterogeneity in effects is the most relevant information in CER

• Establishing extensive margins in comparative health outcomes is necessary to truly mimic market-based outcomes
  • Essential for maximizing patient welfare
  • Necessary for efficient translation of evidence to policy

• Need to align information to decision making at the individual level
ACKNOWLEDGEMENTS

• Ryan Conrad (USC) for research assistance

• This research was funded by the National Pharmaceutical Council with additional support from the National Institute on Aging through its support of the RAND Roybal Center for Health Policy Simulation (7P30AG024968).

• Dr. Basu acknowledges financial support from the National Institutes of Health grants R01MH083706, RC4CA155809 and R01CA155329.
REFERENCES


Heckman JJ, Vytlacil EJ. Local instrumental variables and latent variable models for identifying and bounding treatment effects. Proc Nat Acad Sci 1999; 96(8): 4730-34


BACKUP
Individualized CER (i-CER)
Conceptual model for the development of the Potential for Benefit Scale (PBS). *Kaplan et al. 2010*
DOES IVS REDUCE IMBALANCE?
**DOES IVS REDUCE IMBALANCE?**

<table>
<thead>
<tr>
<th>Drug</th>
<th>P(Z) &lt; Median</th>
<th>P(Z) &gt; Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>43%</td>
<td>44%</td>
</tr>
<tr>
<td>Aripripazole</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

p-value = 0.19
CATIE – COMPARATIVE EFFECTIVENESS STUDY OF ANTIPSYCHOTIC DRUGS

- NIMH Sponsored $50 mill study
  - Looked at the direct head-head comparison on the effects of initial assignment of alternative antipsychotic drugs on a variety of outcomes
  - Compared one typical versus atypicals
- Results presented in 2005/2006.
CASE OF ANTIPSYCHOTICS

- CATIE – found initializing with first vs second generation antipsychotics produced similar effectiveness over an 18-month period.
  - Lead to no major change in clinical practice (Chen et al., 2008)
  - Post CATIE, 40% of the state-run Medicaid programs have instituted prior authorization (PA) restrictions on some 2nd gen. drugs (Polinski et al, 2007)
  - Manufacturers are seen to have waning commitments to invest in developing new drugs in neuroscience (Reuters, Feb 2011)
ISSUES OF GENERALIZABILITY

• CATIE recruited patients, most were continuing to receive an AAD.
  • % with exacerbation of symptoms in past 3 mo = 28%
  • % not using any drug at baseline = 28%
• A first-line PA policy would apply to initiators or clean starters – do CATIE results apply?
• Compare with clean starters in Medicaid (no AAD in past 6 months)
  • % of patients hospitalized annually due to schizophrenia related symptoms: CATIE: 7-14%; MEDICAID: 36%
  • Avg. number of hospitalizations per patient in a year among those initiated with risperidone: CATIE: 0.20. MEDICAID: 0.75.
Dr. Basu is an associate professor in the Departments of Health Services and Pharmacy at the University of Washington, Seattle. He is also a faculty research fellow at the National Bureau of Economic Research. Dr. Basu received his MS in Biostatistics from the University of North Carolina, Chapel Hill in 1999 and his PhD in Public Policy from the University of Chicago in 2004.

Dr. Basu's research interests lie in revealing heterogeneity in clinical and economic outcomes in order to establish the value of individualized care. His work has focused on translating such information for public policy using innovative methods in comparative effectiveness and cost-effectiveness research. Dr. Basu has developed methods dealing with issues related to modeling health expenditure data, which is renowned for its idiosyncrasies and the difficulties it poses for applied health services researchers. He has also worked on methods used for making causal inferences using observational data. His applied work spans many dimensions that include analyzing the cost-effectiveness of prostate cancer treatments, establishing the value of individualized care based on patient preferences, developing models to predict quality of life of patients with multiple comorbidities, measuring the effect of patients’ health on the quality of life of their partners, developing novel methods to estimate long-term costs of prostate cancer therapies, estimating the future value of research in diagnosing and finding a cure for Duchenne muscular dystrophy, developing simulation models for evaluating the cost-effectiveness of pharmacological treatment algorithms in schizophrenia, and comparative effectiveness research on the dynamic intensification of glucose lowering therapies in diabetes.

Dr. Basu is an Associate Editor for both Health Economics and the Journal of Health Economics and has taught courses on decision analysis, cost-effectiveness analysis and health services research methods. He has received numerous recognitions for his work throughout his career and for which he remains grateful to his mentors and peers: the NARSAD Wodecroft Young Investigator Award (2005), the Research Excellence Award for Methodological Excellence (2007) and the Bernie O'Brien New Investigator Award (2009) from the International Society for Pharmacoeconomics and Outcomes Research, the Alan Williams Health Economics Fellowship (2008) from the University of York, UK and the Labelle Lectureship in Health Economics (2009) from McMaster University, Canada.