Putting It All Together in a CER Analysis

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Goal of Presentation

- Illustrate study design, outcomes, covariates and methods principles in CER using Medicare data
  - Incidence of dementia among beneficiaries taking centrally acting vs. non-centrally acting ACEIs
- Set Up Problem
- Present preliminary results
- Respond to your questions to help us improve this analysis

Clinical Question

- Risk factors for cardiovascular disease may be risk factors for Alzheimer's disease & senile dementia
- Hypothesis: Treatment of hypertension and hypercholesteremia may reduce incidence or progression of dementia
  - We focus on hypertension treatment
  - Centrally active (CA) vs. non-CA ACE inhibitors (ACEIs)

Prior Evidence to Support Hypothesis

- Compare ACEI’s crossing blood-brain barrier (thus are “centrally active”)
  - No large RCT evidence to date; one small RCT

- Observational studies in the elderly
  - Non CA ACEIs associated with 73% greater risk of dementia incidence compared to non-ACEI anti-HTNs (Sink. 2009)
    - 1000 subjects followed for up to 6 years
    - Excellent measures of dementia
    - No control for prior exposure
  - CA ACEI (lisinopril) associated with lower risk of dementia & Alzheimer’s incidence compared to non-ACEI anti-HTNs (Li)
    - 800,000 records from the VA followed for 3 years
    - Entry into a nursing home was primary outcome
    - Compared ARBs to lisinopril

Critique of Prior Evidence

- Lisinopril classified as non-centrally active in Li 2010, but Sink classified as centrally active
  - We confirmed with manufacturer that it is centrally active

- Li (2010) study compared groups based on VA claims and groups that were substantially different
  - Mean blood pressures & ethnicity
  - Is ARB vs ACEI a Coke vs Pepsi study?

Purpose of Our (Ongoing) Study

- Compare incidence of diagnosis or treatment of Alzheimer’s or senile dementia among elderly FFS Medicare beneficiaries using CA or non-CA ACEIs
  - Part A & B: Time of first diagnosis (outcome), covariates
  - Part D: Time of first medication, treatment, covariates, and instruments
  - Census: Socioeconomic status proxies, instruments
What Medicare Data Would You Use To Compare CA vs. Non-CA ACEI?

- MCBS
  - Pros: Survey data to supplement claims, rotating panel
  - Cons: Small sample size
- Medicare claims
  - Pros: Large (5%) or huge (100%) sample size
  - Cons: Limited covariate set

What would you choose? Why?

Our Choice for Data

- Medicare claims
  - Very large sample (unlike MCBS)
  - Ability to follow beneficiaries for a long period of time (unlike MCBS)
  - Good (in theory) instruments are available to address unobserved confounding.
  - Good outcomes are available
    - Diagnoses and treatments for dementia
    - Dementia scores on MDS for nursing home residents

Data We Don’t Have As Result of Our Choice

- Marital status
- Disease severity
- History of anti-hypertensive medication use prior to Medicare Part D
- Education
  Proxied by Census data at Zip code level
- Income
  Proxied by Census data at Zip code level and state buy-in
Treatment Group Selection

- What would be your treatment group?
  - Why?

- How would you define your treatment group?
  - E.g., how long do you have to be on a CA ACEI to be in the treatment group
  - Why?

- What inclusion/exclusion criteria would you choose?
  - Why?

Potential Anti-Hypertensive Medication Comparators to CA ACEIs

- Non-CA ACEIs
  - Clinically equivalent for HTN or CHF
  - Most comparable in cost and time on market
  - Coke v. Pepsi: Likely randomness of provider/patient preferences given lack of evidence when we are doing this study

- Angiotensin Receptor Blockers (ARBs)
  - Clinically equivalent (Matchar, 2007 AHRQ report)
  - Higher cost, shorter time on market

- Other anti-HTN medications (Beta-blockers; Calcium channel blockers; diuretics, etc.)

Comparator Selection

- What comparator would you use?
  - Why?

- How would you define your comparison group?
  - Why?

- What inclusion/exclusion criteria would you choose?
  - Why?
Comparative We’ve Chosen Initially

- Only non-CA ACEIs
  - Most comparable in cost and time on market
  - Coke vs Pepsi: Potentially random provider/patient
    preferences given lack of evidence at time of study (we
    can test this)
  - Propensity score matching is tractable with two groups

- Treatment and Comparator Cohorts To Compare
  - Incident Users satisfying 90 day run-in (N=39,514)

Sample Flow

![Sample Flow Diagram]

New Users or Prevalent Users?

- New users
  - Limited sample (N=39,514)
  - What biases if this group is used?

- Prevalent Users
  - Larger sample (N~100,000)
  - What biases if this group is used?

- Which one would you choose?
  - Why?
How Would You Define the Outcome?

- What would be your primary outcome?
  - Why?

- How would you define it?
  - What data?
  - Why that data?

- Secondary outcomes?

Identification of Medicare Beneficiaries with Alzheimer’s/Dementia

Many mild AD cases may be underdiagnosed or uncoded

Outcomes Defined

- No gold standard in identifying patients with Alzheimer’s and dementia
  - Thus, be inclusive to define incident Alzheimer’s/dementia that should identify majority of incident cases

- Primary outcome: Time until incident diagnosis or treatment via medication
  - Outcome = (Date of 1st Dx or Rx) – Date of End of Run-in

- Secondary outcomes
  - Time until admitted to nursing home with MDS COGS validated dementia
  - Death?
Missing data
What would you do?

- Around 2.5% of patient ZIP codes could not be linked to Census ZCTA measures of SES
- What would you do?
  - Case deletion?
  - Do not use SES measures?
  - Imputation?

What we chose

- Case deletion
  We excluded anyone without a good ZIP code
  SES measures are important and many of these people were in Guam, the Marshal Islands, or other exotic locations
  Retaining the ZIP code allows us to do some distance based IV estimates
  2.5% is not that much

What Analyses Would You Plan?

- What descriptive analyses would you do?
  • Why?
- What regression analyses would you do?
  • Why?
Analysis Plan (Pre-specified)

- Descriptive statistics on unmatched cohort
  - Assess variation in outcome
  - Assess covariate imbalance between treated & controls
- Propensity score matching
- Logistic regression of incidence at one and two years
- Cox regression analysis on unmatched cohort
  - Unadjusted unmatched
  - Adjusted unmatched
  - Unadjusted matched

DESCRIPTION OF OUR ONGOING ANALYSIS

Geographic Dispersion of CA vs. non-CA ACE Inhibitor Use
Geographic Dispersion of CA vs. non-CA ACE Inhibitor Use

Descriptive Statistics of Unmatched CA ACEI and Non-CA ACEI Cohorts

<table>
<thead>
<tr>
<th></th>
<th>CA ACEI Cohort?</th>
<th>Non-CA ACEI Cohort?</th>
<th>P-value</th>
<th>Standardized Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.7</td>
<td>75.8</td>
<td>0.47</td>
<td>2.22</td>
</tr>
<tr>
<td>Female (%)</td>
<td>66%</td>
<td>68%</td>
<td>&lt;0.0001</td>
<td>4.25</td>
</tr>
<tr>
<td>White Race (%)</td>
<td>83%</td>
<td>77%</td>
<td>&lt;0.0001</td>
<td>15.04</td>
</tr>
<tr>
<td>Black Race (%)</td>
<td>7%</td>
<td>9%</td>
<td>&lt;0.0001</td>
<td>7.38</td>
</tr>
<tr>
<td>Baseline AMI (%)</td>
<td>7%</td>
<td>4%</td>
<td>&lt;0.0001</td>
<td>13.19</td>
</tr>
<tr>
<td>Elixhauser Score</td>
<td>5.69 (7.79)</td>
<td>4.66 (6.99)</td>
<td>&lt;0.0001</td>
<td>37.89</td>
</tr>
<tr>
<td>Baseline Expenditures</td>
<td>$7843 (15317)</td>
<td>$5911 (12155)</td>
<td>&lt;0.0001</td>
<td>16.48</td>
</tr>
<tr>
<td>Baseline # Meds</td>
<td>6.7 (3.8)</td>
<td>6.4 (3.6)</td>
<td>&lt;0.0001</td>
<td>17.13</td>
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<tr>
<td>Sample Size</td>
<td>27,692</td>
<td>10,477</td>
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</tbody>
</table>

Time Until Incidence of Alzheimer's or Dementia (Diagnosis or Treatment)
Propensity Score Methods

- Nearest neighbor matching (1-to-1, no replacement)
  - Caliper = 0.013

- Expansive specification
  - 43 main effects (demographic, baseline use, conditions)
  - 119 2-way interactions

- Evaluation of balance (iterative)
  - Standardized differences of pooled cohorts & quantiles

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Propensity Score Balance

![Graph showing propensity score balance]

Descriptive Statistics of Matched CA ACEI and Non-CA ACEI Cohorts

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<thead>
<tr>
<th></th>
<th>CA ACEI Cohort?</th>
<th>Non-CA ACEI Cohort?</th>
<th>P-value</th>
<th>Standardized Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.7</td>
<td>75.8</td>
<td>0.53</td>
<td>2.22</td>
</tr>
<tr>
<td>Female (%)</td>
<td>68%</td>
<td>68%</td>
<td>0.67</td>
<td>0.00</td>
</tr>
<tr>
<td>White Race (%)</td>
<td>78%</td>
<td>77%</td>
<td>0.18</td>
<td>2.39</td>
</tr>
<tr>
<td>Black Race (%)</td>
<td>9%</td>
<td>9%</td>
<td>0.75</td>
<td>0.00</td>
</tr>
<tr>
<td>Baseline AMI (%)</td>
<td>4%</td>
<td>4%</td>
<td>0.49</td>
<td>0.00</td>
</tr>
<tr>
<td>Elixhauser Score</td>
<td>4.72 (7.12)</td>
<td>4.66 (6.98)</td>
<td>0.52</td>
<td>2.26</td>
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<tr>
<td>Baseline Expenditures</td>
<td>$5926 (11756)</td>
<td>$5919 (12224)</td>
<td>0.97</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline # Meds</td>
<td>6.4 (3.6)</td>
<td>6.4 (3.6)</td>
<td>0.96</td>
<td>0.01</td>
</tr>
<tr>
<td>Sample Size</td>
<td>10,422</td>
<td>10,422</td>
<td></td>
<td></td>
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</table>
### Standardized Differences of Quantiles of CA ACEI and Non-CA ACEI Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Quantile #1</th>
<th>Quantile #2</th>
<th>Quantile #3</th>
<th>Quantile #4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-2.22</td>
<td>3.56</td>
<td>-3.81</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Female (%)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>2.05</td>
</tr>
<tr>
<td>White Race (%)</td>
<td>2.39</td>
<td>6.36</td>
<td>3.02</td>
<td>0.00</td>
<td>-8.43</td>
</tr>
<tr>
<td>Black Race (%)</td>
<td>0.00</td>
<td>0.00</td>
<td>-7.84</td>
<td>-6.41</td>
<td>6.41</td>
</tr>
<tr>
<td>Baseline AMI (%)</td>
<td>0.00</td>
<td>2.84</td>
<td>-2.84</td>
<td>0.00</td>
<td>2.76</td>
</tr>
<tr>
<td>Elixhauser Score</td>
<td>2.26</td>
<td>2.46</td>
<td>-4.33</td>
<td>12.07</td>
<td>6.84</td>
</tr>
<tr>
<td>Baseline Expenditures</td>
<td>0.06</td>
<td>1.72</td>
<td>1.62</td>
<td>2.38</td>
<td>1.26</td>
</tr>
<tr>
<td>Baseline # Meds</td>
<td>0.01</td>
<td>-10.61</td>
<td>-5.68</td>
<td>3.95</td>
<td>9.94</td>
</tr>
</tbody>
</table>

### Descriptive Statistics of Treated Folks In Common Support and Not In Support

<table>
<thead>
<tr>
<th></th>
<th>In Common Support</th>
<th>Not In Support</th>
<th>P-value</th>
<th>Standardized Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.8</td>
<td>75.7</td>
<td>0.21</td>
<td>3.70</td>
</tr>
<tr>
<td>Female (%)</td>
<td>68%</td>
<td>65%</td>
<td>&lt;0.0001</td>
<td>6.36</td>
</tr>
<tr>
<td>White Race (%)</td>
<td>78%</td>
<td>86%</td>
<td>&lt;0.0001</td>
<td>-20.94</td>
</tr>
<tr>
<td>Black Race (%)</td>
<td>8%</td>
<td>6%</td>
<td>&lt;0.0001</td>
<td>7.84</td>
</tr>
<tr>
<td>Baseline AMI (%)</td>
<td>5%</td>
<td>8%</td>
<td>&lt;0.0001</td>
<td>-12.19</td>
</tr>
<tr>
<td>Elixhauser Score</td>
<td>4.7</td>
<td>6.2</td>
<td>&lt;0.0001</td>
<td>-55.79</td>
</tr>
<tr>
<td>Baseline Expenditures</td>
<td>$6095</td>
<td>$8882</td>
<td>&lt;0.0001</td>
<td>-23.10</td>
</tr>
<tr>
<td>Baseline # Meds</td>
<td>6.4</td>
<td>7</td>
<td>&lt;0.0001</td>
<td>-31.01</td>
</tr>
<tr>
<td>Sample Size</td>
<td>10,442</td>
<td>17,250</td>
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<td></td>
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</tbody>
</table>

### Logistic Regressions of Incident Diagnosis or Medication for Alzheimer’s or Dementia at One Year

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted, Unmatched</td>
<td>1.24 (1.15, 1.34)</td>
</tr>
<tr>
<td>Adjusted, Matched</td>
<td>1.27 (1.16, 1.39)</td>
</tr>
</tbody>
</table>
Incident Diagnosis or Medication for Alzheimer’s or Dementia

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted, Unmatched</td>
<td>1.01 (0.94, 1.10)</td>
</tr>
<tr>
<td>Adjusted, Unmatched</td>
<td>1.00 (0.92, 1.08)</td>
</tr>
<tr>
<td>Unadjusted, Matched</td>
<td>0.95 (0.86, 1.05)</td>
</tr>
</tbody>
</table>

Instrumental variable analysis

- Top map shows observed geographic distribution of high/low use of treatment ZIP codes (blue=high)
- Lower graph: high/low instrument ZIP codes after DACC adjustment.

Incident Diagnosis or Medication for Alzheimer’s or Dementia within 1 year

<table>
<thead>
<tr>
<th>Model</th>
<th>Change in the probability of the outcome attributable to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logit unadjusted</td>
<td>2.6 (95% CI, 2.0 to 3.3)</td>
</tr>
<tr>
<td>Logit adjusted</td>
<td>1.8 (95% CI, 1.2 to 2.4)</td>
</tr>
<tr>
<td>2SLS</td>
<td>4.1 (95% CI -6.6 to 14.9)</td>
</tr>
<tr>
<td>2SRI</td>
<td>2.2 (95% CI -6.1 to 10.6)</td>
</tr>
<tr>
<td>Bivariate probit</td>
<td>0.6 (95% CI -5.6 to 6.8)</td>
</tr>
</tbody>
</table>
Next Steps?

- Additional year of follow-up
- Examine additional outcomes
  - Time until nursing home admission
  - Death?
- Compare ACEI cohorts to other cohorts?
  - ARB cohort
  - Other anti-HTN cohorts
- Expand beyond incident user cohorts?
  - Prevalent users of anti-hypertensives

Takeaway Points

- CER takes as much effort in thought as in action
  - Why?
    - "It is not possible to put right with statistics what has been done wrong by (study) design"
      - Cook & Steiner 2010 Psych Methods
  - Three choices are critical
    - Covariates for adjustment or matching
    - Comparator for valid counterfactual
    - Outcomes for evidence of treatment effect

References & Resources