Background

- There is a large and growing literature on the economics of obstructive sleep apnea, its diagnosis, and its treatment
  - Cost of OSA
  - Potential cost offsets associated with treatment
  - Cost-effectiveness
- Little of this literature is clinical trial-based
  - Well known problems with determining causality
- In what follows I review this literature

Cost of Undiagnosed Sleep Apnea

- Several observational studies have reported on the cost of undiagnosed obstructive sleep apnea
- Kapur et al.
  - Undiagnosed OSA may add $1,335 per year (1996 U.S dollars) in medical costs compared with age and gender matched controls
  - Nationally, it may cause $3.4 billion in additional medical costs
- Ronald et al.
  - Undiagnosed OSA may add as little as $427 per year (1985 through 1995 Canadian dollars) to physician claims and hospitalization cost
Potential Savings from Treatment of Sleep Apnea

• Several observational studies have attempted to estimate potential savings that may be result from treatment for OSA
  
  • Peker et al.
    – Treatment may reduce cardiovascular and pulmonary disease costs by $2800 per year (measured in Swedish Kroner, but expressed in U.S. dollars)
  
  • Bahamman et al.
    – Treatment may reduce physician claims and hospitalization cost by $655 (1990 through 1996 Canadian dollars)

Potential Savings from Treatment (2)

• The Winnipeg studies
  
  – Series of pre/post + control group observational studies of medical service use
  
  - Leading up to the diagnosis of OSA
  
  - From before diagnosis to after diagnosis
  
  – Evaluated changes in # of physician visits and physician fees
  
  – Regularly found higher costs / service use in the OSA group and greater reductions in costs / service use after diagnosis
  
  • In one article, the authors indicated some of the changes may be due to regression to the mean

<table>
<thead>
<tr>
<th>Change in Physician Claims, Pre / Post *</th>
</tr>
</thead>
<tbody>
<tr>
<td>YR -3 to -1</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>All OSAS</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>CPAP Comp</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Noncomp</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Wgt Loss</td>
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<td>Control</td>
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Change in Physician Claims After Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>OSA *</th>
<th>Control *</th>
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<tbody>
<tr>
<td>All, Mean</td>
<td>-37.96</td>
<td>24.68</td>
</tr>
<tr>
<td>SE</td>
<td>21.35</td>
<td>7.97</td>
</tr>
<tr>
<td>CPAP TC, Mean</td>
<td>-20.96</td>
<td>28.11</td>
</tr>
<tr>
<td>SE</td>
<td>26.60</td>
<td>12.20</td>
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<tr>
<td>Non Comp, Mean</td>
<td>-72.20</td>
<td>-21.33</td>
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<tr>
<td>SE</td>
<td>45.91</td>
<td>32.94</td>
</tr>
<tr>
<td>Weight Loss, Mean</td>
<td>-46.78</td>
<td>27.76</td>
</tr>
<tr>
<td>SE</td>
<td>51.83</td>
<td>10.48</td>
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</tbody>
</table>

* †2nd year after diagnosis – year before diagnosis

Change in Physician Claims After Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>OSA *</th>
<th>Control *</th>
<th>Diff</th>
<th>p-value</th>
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<td>24.68</td>
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<td>~0.006</td>
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<tr>
<td>SE</td>
<td>21.35</td>
<td>7.97</td>
<td>-22.78†</td>
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<tr>
<td>CPAP TC, Mean</td>
<td>-20.96</td>
<td>28.11</td>
<td>-49.07</td>
<td>~0.09</td>
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<tr>
<td>SE</td>
<td>26.60</td>
<td>12.20</td>
<td>-29.26†</td>
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<tr>
<td>Non Comp, Mean</td>
<td>-72.20</td>
<td>-21.33</td>
<td>-50.87</td>
<td>~0.37</td>
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<tr>
<td>SE</td>
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<td>32.94</td>
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<td>SE</td>
<td>51.83</td>
<td>10.48</td>
<td>-52.88†</td>
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* †2nd year after diagnosis – year before diagnosis

† SE_E = (SE_{OSA}^2 + SE_{Control}^2)^1/2

Cost-Effectiveness Analyses by Year
### 5-Year Cost and QALYs, Nothing vs CPAP

<table>
<thead>
<tr>
<th></th>
<th>( C_{\text{No}} )</th>
<th>( C_{\text{CPAP}} )</th>
<th>( \Delta C )</th>
<th>( Q_{\text{No}} )</th>
<th>( Q_{\text{CPAP}} )</th>
<th>( \Delta Q )</th>
<th>( C/Q )</th>
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<tr>
<td>Mar '03 (( \epsilon ))</td>
<td>55</td>
<td>2719</td>
<td>2664</td>
<td>3.39</td>
<td>3.73</td>
<td>0.34</td>
<td>7861</td>
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<td>Ayas (( $ )) *</td>
<td>1659</td>
<td>4177</td>
<td>2518</td>
<td>1.47</td>
<td>2.22</td>
<td>0.75</td>
<td>3354</td>
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<tr>
<td>Mar '06 (( \epsilon ))</td>
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<td>-</td>
<td>6000</td>
<td>-</td>
<td>-</td>
<td>1.09</td>
<td>5480</td>
</tr>
<tr>
<td>Guest (( \£ ))</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-5000</td>
</tr>
<tr>
<td>Tan (( \text{SC} )) *</td>
<td>266</td>
<td>2983</td>
<td>2717</td>
<td>1.47</td>
<td>2.22</td>
<td>0.75</td>
<td>3636</td>
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<tr>
<td>Sadatsafavi</td>
<td>4126</td>
<td>6401</td>
<td>2185</td>
<td>3.34</td>
<td>3.50</td>
<td>0.16</td>
<td>13698</td>
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</tbody>
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* Ayas and Tan represent US and Canadian versions of the same model

### Lifetime Cost and QALYs, Nothing vs CPAP

<table>
<thead>
<tr>
<th></th>
<th>( C_{\text{No}} )</th>
<th>( C_{\text{CPAP}} )</th>
<th>( \Delta C )</th>
<th>( Q_{\text{No}} )</th>
<th>( Q_{\text{CPAP}} )</th>
<th>( \Delta Q )</th>
<th>( C/Q )</th>
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<tbody>
<tr>
<td>Mar '03 (( \epsilon ))</td>
<td>591</td>
<td>7902</td>
<td>7311</td>
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<td>14.38</td>
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<td>Guest (( \£ ))</td>
<td>10645</td>
<td>9672</td>
<td>-973</td>
<td>7.22</td>
<td>8.09</td>
<td>0.87</td>
<td>DOM</td>
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<tr>
<td>Weatherly (( \£ ))</td>
<td>8140</td>
<td>9301</td>
<td>1061</td>
<td>11.93</td>
<td>12.39</td>
<td>0.46</td>
<td>2524</td>
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</table>

### 5-Year Cost and QALYs, Other Comparisons

<table>
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<tr>
<th></th>
<th>( C_0 )</th>
<th>( C_1 )</th>
<th>( \Delta C )</th>
<th>( Q_0 )</th>
<th>( Q_1 )</th>
<th>( \Delta Q )</th>
<th>( C/Q )</th>
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<tbody>
<tr>
<td>Home Diagnosis (0) vs In-Lab (1)</td>
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<tr>
<td>Chervin '99 (( $ ))</td>
<td>2939</td>
<td>3799</td>
<td>860</td>
<td>3.955</td>
<td>4.019</td>
<td>0.064</td>
<td>13431</td>
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<tr>
<td>Deutsch '06 (( $ ))</td>
<td>4096</td>
<td>4886</td>
<td>790</td>
<td>2.23</td>
<td>2.33</td>
<td>0.10</td>
<td>7900</td>
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<tr>
<td>Oral Devices (0) vs CPAP (1)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Sadatsafavi '09 (( $ ))</td>
<td>4484</td>
<td>6401</td>
<td>1917</td>
<td>3.427</td>
<td>3.496</td>
<td>0.070</td>
<td>27540</td>
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<tr>
<td>Weatherly '09 (( \£ )) (lifetime)</td>
<td>8797</td>
<td>9301</td>
<td>504</td>
<td>12.26</td>
<td>12.39</td>
<td>0.13</td>
<td>3899</td>
</tr>
</tbody>
</table>
Probabilistic Cost-Effectiveness Analyses by Year

Year
1999 2003 2005 2006 2008 2009
Number of studies
1 1 1 3 3 2 2 2

Probabilistic Cost-Effectiveness Analysis
• Substitutes distributions of variables for point estimates
  – e.g., substitute the distribution of the mean cost of CPAP for the point estimate of the mean cost
• Repeatedly run the model (at least 1000 times)
• In each repeated “run,” draw a sample mean from each of the distributions
• Average out the resulting tree (same as deterministic CEA)
• Similar to running a bootstrap on primary data, we evaluate the results of the repeated samples and draw statistical conclusions such as whether or not the difference in cost or the difference in effect is significant.

Ayas Cost-Effectiveness Plane
p-value for costs: ???
p-value for QALYs < 0.001
Probabilistic Cost-Effectiveness Analysis (2)

- Fairly new technology
  - Pioneering work by David Eddy in the 1980s
- Same rapid expansion in the mid-2000s observed in OSA research common in most medical fields
- Software now available makes it very easy to do
- Even the best of the published guides in the field don’t identify simple mistakes that can lead to biased estimates of standard errors for the differences and thus of statistical significance
  - My view: The mistakes we are seeing are the responsibility of the PCEA thought leaders and our educational programs; can’t expect people to avoid mistakes if we haven’t warned them

Probabilistic Cost-Effectiveness Analysis (3)

- Recognizing that I don’t think it is their responsibility, 2 of Dr. Ayas’ and colleagues’ studies report results that are indicative of the problem
- Shouldn’t presume these are the only 2 studies in which the problem arose
  - The others simply did not provide sufficient detail in their results to allow us to know whether or not the problem exists

Ayas Statistical Results

- No Therapy / CPAP Costs:
  - 1659, 95% CI, 283 to 3936
  - 4177, 95% CI, 2804 to 6057

- No Therapy / CPAP QALYs
  - 1.47, 95% CI, 0.28 to 3.08
  - 2.22, 95% CI, 0.86 to 3.89
Ayas Statistical Results

- No Therapy / CPAP Costs:
  - 1659, 95% CI, 283 to 3936, ~ SE, 913
  - 4177, 95% CI, 2804 to 6057, ~ SE, 813
  ~ SE for difference: $(913^2 + 813^2)^{0.5} = 1223$
  ~ $z = 2518 / 1223 = 2.059; ~ p = 0.02$

- No Therapy / CPAP QALYs:
  - 1.47, 95% CI, 0.28 to 3.08, ~ SE, 0.7
  - 2.22, 95% CI, 0.86 to 3.89, ~ SE, 0.7575
  ~ SE for difference: $(0.7^2 + 0.7575^2)^{0.5} = 1.03$
  ~ $z = 0.75 / 1.03 = 0.728; ~ p = 0.47$

Tan Issues Almost Identical

Ayas Summary

- Based on the reported cost-effectiveness plane:
  - Differences in QALYs were significant
  - We can be 95% confident of good value if we are willing to pay ~40,000 to 50,000 per QALY
  - Probably due to some modeling decisions that “shrank” the standard errors
- Standard errors calculated by use of common formulas suggest that the difference in cost is significant, but the difference in QALYs is not
- Using these revised estimates to calculate a confidence interval for the CER suggests we should ONLY be 95% confident of value IF we are willing to pay at most ~$300 per QALY; for higher values of WTP, can’t be confident
Guest Statistical Results

- No Therapy / CPAP Cost:
  - 10,645, 95% CI, 7988 to 14,098, ~ SE, 1528
  - 9672, 95% CI, 8057 to 12860, ~ SE, 1201
  - SE for difference: \((1528^2 + 1201^2)^{0.5} = 1943\)
  - \(z = \frac{973}{1943} = 0.500; ~ p = 0.69\)

- No Therapy / CPAP QALYs
  - 7.22, 95% CI, 6.48 to 7.93, ~ SE, 0.3625
  - 8.09, 95% CI, 7.17 to 8.44, ~ SE, 0.3175
  - SE for difference: \((0.3625^2 + 0.3175^2)^{0.5} = 0.482\)
  - \(z = \frac{0.87}{0.482} = 1.805; ~ p = 0.07\)

Guest Summary

- The paper reports: “CPAP has a 0.99 probability of being cost-effective for a threshold of £20,000 per QALY” (implies we can be 2-tailed 98% confident of being cost-effective)
- Standard errors calculated using the common formula suggest that neither the difference in cost \((p=0.69)\) nor the difference in QALYs \((p=0.07)\) are significant
- Nevertheless, this is one of the uncommon analyses in which even though neither the difference in cost nor the difference in effect is significant, we can be ~95% confident that the therapy is cost-effective for a threshold of £20,000 per QALY
  - How can this be???

Deutsch *

- Based on the results reported in the article:
  - FN-PSG costs significantly more than home study \((p<0.01)\) and is significantly more effective \((p<0.02)\)
  - Neither SN-PSG’s cost \((p=0.14)\) nor its effect \((p=0.12)\) is significantly different from home studies’
  - Neither FNPSG’s cost \((p=0.36)\) nor its effect \((p=0.48)\) is significantly more than SN-PSG’s
- No standard errors reported so no assessment of the degree of “shrinkage” possible

* FN-PSG = full night polysomnography; SN = split night
No standard errors that would allow assessment of the degree of “shrinkage” are reported, but...

Do We Know What We Need to Know?

• Given the large number of studies, why hasn’t the question been satisfactorily answered?
  – Little to no direct controlled observation of benefit
    • Shares with health problems such as obesity the fact that while it “makes sense” that treatment should avoid outcomes such as heart attacks and stroke, but no trial has ever demonstrated that treatment actually avoids these outcomes

Why Hasn’t the Question Been Satisfactorily Answered? (2)

• Inputs needed for modeling analyses are uncertain
  – New tools for addressing some of this uncertainty have been introduced (e.g., PCEA)
    • May be too early in the technological development to be routinely confident in these results
  – In both the OSA and broader literature should require better reporting of results
    • SE’s for the costs and outcomes in each treatment group as well as the SE’s for the differences
Why Hasn’t the Question Been Satisfactorily Answered? (3)

• Inputs needed for modeling analyses are uncertain (cont)
  – No attempt has been made to address the potential bias introduced from borrowing data from multiple studies and assuming they can all be combined in a new study
  • If you were doing a clinical study, but hadn’t measured something, would you call up a colleague and say, “you measured that; send me the data and I’ll include it in my study as well”?

Summary

• There is a large literature on the cost-effectiveness of diagnosing and treating OSA
  – The point estimates from this literature almost all indicate that treatment of OSA is cost-effective
  – It is less clear that we can be 95% confident of these results
• Little to none is based on direct observation of different methods of diagnosis and treatment
• Hoping the new trial-based evidence will address these uncertainties