Formulary Considerations - Use of Experimental and Observational Data

Raulo Frear, Pharm.D.
Director, Pharmacy Services
The Regence Group
May 15, 2009
2:45pm – 3:05pm
Overview

- Evolution in Medication Reviews
- Formulary Decisions
  - Identifying useful scientific data
  - Critically appraising the data
  - How data is considered
  - What data is considered
- P & T Committee Philosophy
Evolution in Medication Reviews

Low Quality

- Formulary kits
- Abstracts
- Some published literature

Best Practice

- Dossier
  - Evidence Tables
  - PE Modeling
- FDA dockets
- Primary/Secondary Literature
- Practice Guidelines
- Identify/use of “quality” data
- Key research questions
- Systematic methods
- Critical Appraisal
- Reproducibility
- Transparency

Formulary Decisions

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# Conducting Medication Reviews

**Is everyone aligned?**

<table>
<thead>
<tr>
<th>Best Practice</th>
<th>FDA¹</th>
<th>Cochrane Library²</th>
<th>Clinical Evidence³</th>
<th>NICE⁴</th>
<th>AHRQ⁵</th>
<th>CADTH⁶</th>
<th>Health Plans &amp; PBM’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined Review Topic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Predefined Scope; Key research questions</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ / -</td>
</tr>
<tr>
<td>Reproducible, systematic literature search</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ / -</td>
</tr>
<tr>
<td>Critical appraisal of evidence</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ / -</td>
</tr>
<tr>
<td>Grading system for level/quality of evidence</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ / -</td>
</tr>
<tr>
<td>Transparent</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ / -</td>
</tr>
</tbody>
</table>

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**Sources:**  Peer Reviewed Journal, Dossiers, FDA dockets, Secondary Sources, Unpublished Information

- Randomization
- Blinding
- Concealment
- Intent to treat
- Statistical methods
- Adherence

**Critical Appraisal**

- Power
- Handling of Missing data
- Clinically Relevant Measures
- Validated Endpoints
- Drop-outs
- Valid Conclusions

**“Reliable” evidence**

**Formulary Considerations**

- Inferior Value
- Equivocal Value
- Superior Value
Evidence Based Medicine Decision-Making
Critically Appraising the Literature℠

Uncertainty

- Abstract
- Published Journal Article
- Accept Author’s Conclusion
- Review Methods & Results
- Accept / Modify Author’s Conclusion
- Low Reliability

Best Practice

- Systematic Review
- Audit Study Data
- Weigh Evidence
- Best Information
  - Efficacy, Safety & Value Conclusions for Formulary Decisions
- High Reliability

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Determining “Reliable” Evidence Critical Appraisal Tool

EBM Checklist

<table>
<thead>
<tr>
<th>PAPER SECTION And tool</th>
<th>Item</th>
<th>Description</th>
<th>Reported on page</th>
<th>Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE &amp; ABSTRACT</td>
<td>1</td>
<td>How participants were allocated to interventions (e.g., “random allocation” “randomised” or “randomly assigned”).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTRODUCTION Background</td>
<td>2</td>
<td>Scientific background and explanation of rationale.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>METHODS Participants</td>
<td>3</td>
<td>Eligibility criteria for participants and the settings and locations where the data were collected.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>4</td>
<td>Present details of the interventions intended for each group and how and when they were actually administered.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objectives</td>
<td>5</td>
<td>Specific objectives and hypotheses.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>6</td>
<td>Clearly defined primary and secondary outcome measures and, when applicable, any methods used to address (e.g., multiple observations, training of observers).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>7</td>
<td>How sample size was determined and, when applicable, proportion of randomization and stopping rules.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization -- Sequence generation</td>
<td>8</td>
<td>Method used to generate the random allocation sequence; incl. details of any restrictions (e.g., blocking, stratification)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization -- Allocation concealment</td>
<td>9</td>
<td>Method used to conceal the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization -- Implementation</td>
<td>10</td>
<td>Who generated the allocation sequence, who divulged treatment, and who assigned participants to their groups.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>11</td>
<td>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12</td>
<td>Statistical methods used to compare groups for primary outcomes, such as subgroup analyses.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESULTS Participant flow</td>
<td>13</td>
<td>Flow of participants through each stage (a diagram is strongly recommended) for each group (number of participants randomly assigned, excluding intended treatment, completing the study protocol, and analyzed for the primary outcomes).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitment</td>
<td>14</td>
<td>Details defining the period of recruitment and follow-up.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descriptive data</td>
<td>15</td>
<td>Provide demographics and clinical characteristics of each group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbers analyzed</td>
<td>16</td>
<td>Number of participants (demographics) by analysis groups submitted in each analysis and whether the analysis was by “intention-to-treat”.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17</td>
<td>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those supplementary.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>19</td>
<td>All important adverse events or side effects in each intervention group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DISCUSSION Interpretation</td>
<td>20</td>
<td>Interpretations of the results, linking into account study hypothesis, sources of potential bias or imprecision and the inferences associated with multiple analyses and outcomes.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalizability</td>
<td>21</td>
<td>Stated generalizability, including any caveats in findings.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall evidence</td>
<td>22</td>
<td>General interpretation of the results in the context of current evidence.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference: www.consort-statement.org/Downloads/Checklist.doc

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## Grading of the Evidence

### Delfini™ Validity & Usability Grading Scale

<table>
<thead>
<tr>
<th>Grade A: Useful</th>
<th>The evidence is strong and appears sufficient to use in making health care decisions; it is both valid and useful.</th>
</tr>
</thead>
</table>

### Grade “High to Low B”: Possibly Useful
- **High B**: Evidence is strong enough to conclude that results are probably valid and useful; however, study results from multiple studies are inconsistent, or studies may have some (but not lethal) threats to validity.
- **Low B**: Evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that evidence cannot fully reach a high Grade B and uncertainty is not great enough to fully warrant a Grade U.

<table>
<thead>
<tr>
<th>Grade U:</th>
<th><strong>Uncertain</strong> – There is sufficient uncertainty so that caution is urged regarding the use of the information in making health care decisions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Grade UV:</td>
<td><strong>Uncertain Validity</strong> – perceived methodological weaknesses</td>
</tr>
<tr>
<td>- Grade UU:</td>
<td><strong>Uncertain Usefulness</strong> - methodology appropriate but applicability of results uncertain</td>
</tr>
<tr>
<td>- Grade UVU:</td>
<td><strong>Uncertain Validity and Usefulness</strong> – combination of the above</td>
</tr>
<tr>
<td>- Grade UA:</td>
<td><strong>Uncertainty of Author</strong> – author uncertain about findings</td>
</tr>
</tbody>
</table>

| Grade X: | **Not Useful** - studies are so poorly done and are so potentially misleading that the strongest caution is urged about their quality |

Grade U and X evidence is not considered by P&T Committee.

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About 10% of studies after critical appraisal deemed reliable.
Scientific Validity (RCT’s)
- Common Problems

- Transparency in methods
  - Randomization
  - Concealment of allocation
  - Blinding Methods

- Large numbers lost to follow-up

- Problematic choices of outcomes

- Lack of intent-to-treat analysis

- Non-significant findings from underpowered studies

- Post-hoc analysis
## Scientific Evidence (RCT’s)
### Medication - Without Critical Appraisal

<table>
<thead>
<tr>
<th></th>
<th>Seizures</th>
<th>Nerve Pain</th>
<th>Fibromyalgia</th>
<th>Anxiety</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Trials</strong></td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td><strong>Total Patients</strong></td>
<td>1,397</td>
<td>3,124</td>
<td>2588</td>
<td>1,027</td>
<td>8136</td>
</tr>
<tr>
<td><strong>Author’s Conclusions</strong> (Published studies)</td>
<td>Effective compared to placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Scientific Evidence (RCT’s)
**Medication - With Critical Appraisal**

<table>
<thead>
<tr>
<th>Health Plan Conclusions</th>
<th>Seizures</th>
<th>Nerve Pain</th>
<th>Fibromyalgia</th>
<th>Anxiety</th>
<th>Total</th>
</tr>
</thead>
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<td>12</td>
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<td>1,397</td>
<td>3,124</td>
<td>2,588</td>
<td>1,027</td>
<td>8,136</td>
</tr>
<tr>
<td>Uncertain</td>
<td>3</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>Possibly Useful</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- Treatment value in seizures over placebo.
- Unknown if better than other seizure medication options.
- Uncertain evidence about value in conditions, other than seizures, where its use is likely to be.
Scientific Evidence (RCT’s)
Fibromyalgia Class Review - With Critical Appraisal

<table>
<thead>
<tr>
<th></th>
<th>milnacipran</th>
<th>duloxetine</th>
<th>pregabalin</th>
<th>gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Trials</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total Patients</td>
<td>2095</td>
<td>1,081</td>
<td>2588</td>
<td>150</td>
</tr>
<tr>
<td>Possibly Useful</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Uncertain</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Health Plan Conclusions

- Uncertain evidence for medications used for fibromyalgia.
- No evidence to define superiority for one over another.
- Modest benefit (if at most) among medications for reducing fibromyalgia pain symptoms.


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Scientific Evidence (RCT’s)
Sorafenib - With Critical Appraisal

<table>
<thead>
<tr>
<th></th>
<th>Unresectable hepatocellular carcinoma</th>
<th>Advanced renal cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Trials</strong></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total Patients</strong></td>
<td>602</td>
<td>834</td>
</tr>
<tr>
<td><strong>Reliable</strong></td>
<td>1 (602 patients)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Uncertain</strong></td>
<td>0</td>
<td>2 (834 patients)</td>
</tr>
<tr>
<td><strong>Health Plan Conclusions</strong></td>
<td><strong>Improves survival by about three months over placebo (i.e. best supportive care).</strong></td>
<td><strong>Uncertain value in advanced renal cell carcinoma</strong></td>
</tr>
</tbody>
</table>

Critique of Study: Not Useful (Grade X)

-- Summary of “fatal flaws”

Therapeutic Class Review
Treatments for Fibromyalgia
May 2009

Critique of Study: Not Useful (Grade X)

--- Summary of “fatal flaws”

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Pharmacoeconomic Data
– Where is this considered?

**FOUNDATIONAL**
Model based on reliable, critically appraised evidence

**Critical Appraisal**
- Relevance
- Sensitivity analysis
- Reasonable assumptions
- Reasonable options compared
- Valid cost data
- Transparency
- Limitations
- Bias
- Time horizon

**Useful**
Observational Studies
- Considerations to use in formulary considerations

- Potential safety signals
- Additional areas for study/specific patient populations

Limitations:
- Not able to draw reliable cause and effect conclusions.
- Removed early at level of systematic search.
Real World Data
– Considered in Formulary Decisions?

- How medication performs in “real world”
  - Medication adherence
  - Achieving expected outcomes

- Appropriate medication use
  - Practice standards adherence
  - Conditions where there is reliable evidence

- Medical cost offsets

- Quality of life/productivity benefit
Pharmacy and Therapeutics Committee

Philosophy

- Determine formulary status of medications
- Stewards of the healthcare dollar
- Best Practice
  - EBM philosophy
  - Consistent EBM decision-making
  - Use of critically-appraised scientific evidence
  - Medication value based on improving health outcomes.
    - Supported by clinically meaningful outcomes/improved health.
    - Return on investment -- Weigh efficacy, clinical benefits, safety risks, practice/community standards, and cost.
Regence P & T Committee

Checks and Balances

Regence P & T Committee Formulary Decisions
n = 218

Evidence-Based Decisions
186 / 218 (85%)

Add
36/186 (19%)

Not Add
150/218 (81%)

Judgment Decisions
32 / 218 (15%)

Add
30/32 (94%)

Not Add
2/32 (6%)

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## P & T Committee Decisions
### Medications Approved (1999 to Present) & Withdrawn from Market

<table>
<thead>
<tr>
<th>FDA Approval</th>
<th>Medication</th>
<th>Year Withdrawn</th>
<th>Reason</th>
<th>Regence P &amp; T Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Rofecoxib</td>
<td>2005</td>
<td>Heart attack and strokes</td>
<td>Non-formulary/PA</td>
</tr>
<tr>
<td>2000</td>
<td>Alosetron</td>
<td>2000 (2002- restricted access)</td>
<td>Ischemic colitis</td>
<td>Non-formulary/PA</td>
</tr>
<tr>
<td>2001</td>
<td>Valdecoxib</td>
<td>2005</td>
<td>Severe skin reactions</td>
<td>Non-formulary/PA</td>
</tr>
<tr>
<td>2004</td>
<td>Hydromorphone ER</td>
<td>2005</td>
<td>Potentially fatal overdose if taken with alcohol.</td>
<td>Non-formulary/PA</td>
</tr>
<tr>
<td>2006</td>
<td>Inhaled insulin</td>
<td>2007</td>
<td>Production discontinued due to poor sales.</td>
<td>Non-formulary/PA</td>
</tr>
<tr>
<td>2002</td>
<td>Tegaserod</td>
<td>2007</td>
<td>Heart attack and stroke.</td>
<td>Non-formulary/PA</td>
</tr>
<tr>
<td>2009</td>
<td>Efalizumab</td>
<td>2009</td>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Non-formulary/PA</td>
</tr>
</tbody>
</table>

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Formulary Considerations

- Align what data are used

- Commitment to EBM philosophy/resources
- Timely information
- Critical appraisal (consistently/accurately)
- Proper accounting of results
- Managing areas of complexity
- Transparency
- P & T Committee Philosophy
Thank you

References:
2. Cochrane Collaboration: http://www.cochrane.org/
4. Clinical Evidence: http://clinicalevidence.bmj.com
5. Agency for Healthcare Research and Quality http://www.ahrq.gov/
8. The Delfini Group: http://www.delfini.org