Retrieving and appraising systematic reviews

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Outline

- Information overload
- Evidence based medicine
- Narrative vs. systematic reviews
- Retrieving systematic reviews
- Quality Of Reporting Of Meta analyses (QUOROM) statement
- Overview of QUOROM principles
- Examples

Information Overload

- 1980 Biomedical literature expanding 6-7 % annually, doubling every 10-12 years
- 1998 > 25,000 biomedical journals
  General medicine - 19 articles / day
  - 6,935 articles / year
- New Drugs eg. Hypertension
  - 1972 Original JNC Guidelines - 20 drugs
  - 1998 JNC VI Guidelines - 79 drugs

Evidence-based drug therapy

"Integrating the best evidence, the individual characteristics of the patient, and individual expertise, into a decision-making process which leads to optimal drug therapy"  

Evidence-Based Medicine

- Clinical question
- Search for evidence
- Evaluate evidence
- Apply evidence
- Evaluate outcome

Pharmaceutical Care and EBM

Pharmaceutical Care
- Review of systems
- Drug related problems
- Goals of therapy
- Evaluate alternatives
- Treatment plan
- Monitoring plan
- Evaluate outcomes

Evidence-Based Medicine
- Clinical question
- Search for evidence
- Evaluate evidence
- Apply evidence
- Evaluate outcome

Systematic Review Explosion

- First pooling of studies in 1904
- "Meta analysis" term coined in 1976 by Glass
- Increasing numbers of meta analyses of RCTs
  - 1970s 16
  - 1980s 279
  - 1996 > 500
- Linear explosion of health-related meta analyses reported in the literature

BMJ 1996;312:71-72
Arch Intern Med 1997;157:2413-46
Eval Health Prof 2001;24:327-335.
Definitions

Narrative review (Traditional)
- Reviews on therapy conducted by experts in the field using informal methods to collect and interpret data

Systematic review (EBM)
- Reviews of primary research with an explicit, comprehensive search strategy to identify all relevant studies that are then appraised and synthesized according to a predetermined, rigorous and reproducible methodology
- Meta analyses are quantitative reviews that statistically combine studies to produce a single estimate of effect

Narrative vs. Systematic Reviews

<table>
<thead>
<tr>
<th>Feature</th>
<th>Narrative</th>
<th>Systematic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Broad in scope</td>
<td>Focused clinical question</td>
</tr>
<tr>
<td>Sources/search</td>
<td>Not usually specified, potentially biased</td>
<td>Comprehensive sources, explicit search strategy</td>
</tr>
<tr>
<td>Selection</td>
<td>Not usually specified, potentially biased</td>
<td>Criterion-based selection, uniformly applied</td>
</tr>
<tr>
<td>Appraisal</td>
<td>Variable</td>
<td>Rigorous critical appraisal</td>
</tr>
<tr>
<td>Synthesis</td>
<td>Often a qualitative summary</td>
<td>Quantitative summary*</td>
</tr>
<tr>
<td>Inferences</td>
<td>Opinion, sometimes evidence-based</td>
<td>Evidence-based</td>
</tr>
</tbody>
</table>

*Meta analysis is a quantitative summary that includes a statistical analysis

Retrieving systematic reviews

- Electronic and bibliographic databases
  - MEDLINE, EMBASE, Cumulated Index to Nursing and Allied Health Literature (CINAHL), Health Services Technology Assessment and Research (HealthSTAR), Science Citation Index Expanded (SCI-EXPANDED), Cochrane Database of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), Database of Abstracts of Reviews of Effectiveness (DARE), LILACS Database (English), BioMed Central (BMC) database, Turning Research Into Practice (TRIP) database

Utility of Systematic Reviews

- Enable efficient integration of large amounts of valid information
- Resolve therapeutic controversies from conflicting studies
- Improve statistical power by pooling of smaller studies
- Provide better estimate of precision in effect size or risk
- Determine generalizability of findings and consistency of results by comparing results of difference studies

Discordance - Meta analyses and large RCTs

- Agreement exists in 82-90% of cases
- Early meta analyses of small studies did not predict subsequent results from large RCTs 35% of the time in one study
  - Limitations of pooling small RCTs
  - Publication bias
  - Language bias
  - Heterogeneity

Role of Systematic Reviews

- Controversial
- Methodological rigor is paramount
- Hypothesis generating vs. hypothesis testing?
- To generate hypotheses for future RCTs
- To obtain a typical and unbiased estimate of treatment effect and to explore interactions among subgroups

Quality of Systematic Reviews

- Designation as a “systematic review” does not ensure study was conducted or reported well
- Surveys from 1987 to 1992 showed only 28% of meta analyses addressed 6 essential content areas
- Reviews published in “high impact” journals are not of higher methodological rigor
- Reviews in subspecialty literature may not be better
- Cochrane reviews may be more complete than those in print journals, however, 29% still had major flaws
Overview of Quality Assessment

Overview Quality Assessment Questionnaire
- 10 item criteria to assess scientific quality of overview

Users Guides to the Medical Literature
- Are the results of the study valid?
- What are the results?
- Will the results help me in caring for my patient?

Potsdam consultation on meta analysis
- 14 item guideline on conduct and interpretation of meta analyses


QUality Of Reporting Of Meta Analyses (QUOROM)
- Conference of 30 clinical epidemiologists, clinicians, statisticians, editors, researchers
- Identified items that should be included in a checklist of standards to improve the quality of reporting of meta analyses
- Inclusion of checklist items guided by research evidence wherever possible
- 8 of 18 items in checklist proven to contribute to bias in meta analyses


QUOROM Checklist

Title
Abstract
- Objectives, data sources, review methods, results, conclusion

Introduction
Methods
- Searching, selection, validity assessment, data abstraction, study characteristics, quantitative data synthesis

Results
- Trial flow, study characteristics, quantitative data synthesis

Discussion


QUOROM “Top 8 List”

- Structured abstract
- Search techniques
- Publication status
- Language of publication
- Covert duplicate publication
- Assessment of quality of studies
- Blinded abstraction/assessment
- Potential sources of bias cautiously explored
  - Publication, heterogeneity


Searching

- Comprehensive search should include:
  - Computerized bibliographic databases
  - Clinical trial registries
  - Health care agencies
  - Proceedings of conferences and meetings
  - Summaries of dissertations
  - Reference lists of articles
  - Hand searching
  - Contacts with experts in the field
  - Pharmaceutical industry
  - Others?

Searching

Restrictions based on language:
- 1/3 meta analyses have language restriction
- No evidence to support difference in study quality based on language
- Some countries are more likely to publish studies with positive results
- Restriction to English language overestimated the treatment effects by 2%
- Restrictions may be based on logistics


Selection

- Explicit inclusion and exclusion criteria for inclusion of studies to answer focused question
  - Population
  - Intervention
  - Outcomes
  - Study design
- Attempting to include homogeneous data set and strengthen internal validity
- Beware of covert duplicate publication
  - 17% of RCT data may be duplicated
  - Leads to 23% overestimation of treatment

RSS 2002

Quality Assessment

- Extent to which systematic error is minimized (internal validity – "tight" systematic review)
- Extent to which results of trials provide a correct basis for generalization to other circumstances (external validity – "applicability")
- Blinded assessment of trial quality should be performed on trials in a systematic review
- Checklists (qualitative)
- Scales (quantitative)


Pros
- "Garbage in = garbage out"
- Trials with weaker methodologies both overestimate and underestimate effect

Cons
- Assessment tools are complex, time-consuming, may be disease-specific
- Lack of rigorous, validated scales
  - Not based on items proven to reduce bias
  - Subject to inter-rater reliability
- Lack of agreement between scales (23-74%) may affect results depending on scale used

RSS 2002

Quality Assessment

- 90% of methodologists feel quality assessment of RCTs included in meta analysis is very or somewhat important
- A recent report found only 52% of published meta analyses assessed study quality
- Mean quality scores of RCTs included in meta analyses has been about 50% (39-83%)
- Debate exists as to the relative merits and risks of quality assessment of RCTs to be included in meta analyses


Bottom Line Options

- Include only trials meeting a quality threshold
- Use quality score as a weight in estimating the overall effect size (be careful)
- Plot graphs to see if quality affects results, and perform sensitivity analyses by excluding them
- Use key components of design important to your clinical question!
  - Concealment of treatment allocation
  - Proper randomization
  - Appropriate blinding
  - Account for those lost to follow-up

Data abstraction

- Quality assessment and data abstraction under masked conditions to reduce bias
- Independent assessment and abstraction by multiple reviewers in duplicate
- Inter-rater agreement should be reported
- Resolve discrepancies by consensus

Publication Bias

- Positive studies more likely to be published, important threat to validity
- 50% of meta analyses may have missed studies, but it affects results < 10% of the time
- Look for evidence of publication bias:
  - Inspect funnel plot (< 7% compliance)
  - Determine robustness of meta analysis
- Prospective trial registries may minimize PB

Publication Bias (−)

- Focused question and strict inclusion and exclusion criteria to attempt homogeneity
- Studies are heterogeneous when there is greater variation between their results than is compatible with the play of chance
- Heterogeneity is "noise" that may partially explain the results of the overall analysis and threaten the internal validity of the meta analysis
Heterogeneity

- **Two** types of meta analytic models:
  - Fixed effects model vs. Random effects model
  - Random effects model assumes some underlying heterogeneity, more **conservative**
- Statistical tests to look for heterogeneity should be performed in all meta analyses
- Recent studies show heterogeneity testing done in only **72%** of published meta analyses


### Sensitivity Analysis

- **Multiple analyses to answer** "How sensitive are the results to how the meta analysis was done?"
- Analyses run based on study factors
  - Model (fixed or random), study design (blinded vs. unblinded, lower quality), etc.
- Confident in meta analysis if overall results are the same (robust) and benefits are consistent across factors analyzed
- Hypothesis-generating only, risks are akin to post-hoc subgroup analyses of RCTs


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**Forest plot**

- **Test for Heterogeneity**
  - \( p = 0.29 \)

**Ann Pharmacother 2001;35:1528-1534.**

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**Galbraith plot**

- **Galbraith Plot - Rebleed**
  - \( \text{Log Odds Ratio/SE} \)

**Ann Pharmacother 2001;35:1528-1534.**

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**Heterogeneity**

- **Before you test for statistical heterogeneity, state a priori** what clinical factors may be the cause
- **Clinical heterogeneity** is due to differences in the **characteristics** of the included studies, and may be one contributor to statistical heterogeneity
- If graphical evidence for heterogeneity exists (outliers), re-run the analysis excluding the outliers to see if the results are still the same (robust)

Subgroup Analyses

- Similar to subgroups analyses in RCTs
- Analyses run based on patient factors, should be defined up front, “a priori”
- Post-hoc subgroup testing is not ideal and is subject to bias
- Meta analyses may have more power to examine potential differential effects in subgroups
- Role should always be “hypothesis-generating”

Summary Results

- Quantitative results can be expressed as:
  - Effect sizes (0.2 small, 0.5 mod, 0.8 large)
  - Odds ratio (OR)
  - Relative risk (RR) or relative risk reduction (RRR)
  - Absolute risk (ARR)
- How data is presented affects clinicians perceptions of benefit of therapy
- Summary measure should be converted to NNT or NNH with 95% CI to help determine clinical significance of intervention

Converting ORs to NNTs

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<tr>
<th>OR</th>
<th>NNT</th>
<th>CI</th>
</tr>
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<tbody>
<tr>
<td>0.25</td>
<td>4</td>
<td>2.5-6</td>
</tr>
<tr>
<td>0.50</td>
<td>2</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>0.75</td>
<td>1.33</td>
<td>0.67-2.67</td>
</tr>
<tr>
<td>0.90</td>
<td>1.11</td>
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http://www.cebm.utoronto.ca/practise/ca/therapysr/important.htm

Discussion

- Summarize key findings
- Compared to methodologists, authors more likely to rate conclusions as “positive” or “insufficient/inconclusive evidence”, and less likely to rate conclusions as “no effect”
- Interpret results in context of ALL of the available evidence
- Describe potential limitations and biases
- Suggest future novel or confirmatory studies

Applying the Evidence

- Is our patient so different from those in the study that its results cannot apply?
- Is the treatment feasible in our setting?
- What are our patient’s potential benefits and harms from the therapy
- What are our patient’s values and preferences for both the outcome we are trying to prevent and the side-effects we may cause?

Case #1

Atrial fibrillation

You are the ED pharmacist in Paradise BC. A 63 yo man comes in complaining of “my heart pounding”, “mild dizziness”, and “nausea”. The episode started 8 hours ago, but didn’t go away so he came in to the ED. He is diagnosed with rapid AF of 165 bpm. His rate is controlled to 95 with IV diltiazem, he is hemodynamically stable, but he is still having some symptoms so the EP wants to pharmacologically convert him to NSR. His only PMH is HT x 8 years, and he is taking HCTZ 12.5 mg/d.
Case #1

The EP read a recent meta analysis on IV amiodarone for pharmacological conversion of recent-onset AF, and he says it should be the agent of choice for acute conversion. After reviewing the meta analysis, what would you say?

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<th>Patient</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>In a patient</td>
<td>...would administering IV amiodarone...</td>
<td>...compared to no antiarrhythmic therapy...</td>
<td>...acutely convert AF to NSR</td>
</tr>
</tbody>
</table>

Case #2

DVT prophylaxis

You are the Ortho pharmacist in Stinkyville ON. A 73 yo man comes in for an elective total hip replacement. His OR 7 days ago was uneventful, and he has been receiving enoxaparin 40 mg SC daily for VTE prophylaxis with no ADRs. His past medical history includes osteoarthritis, type II diabetes, hypertension, and reduce visual acuity. His medications include HCTZ 12.5 mg/d, enalapril 5 mg/d, and glyburide 5 mg bid.

The orthopedics attending wants to send all of his patients home on self-administered enoxaparin 40 mg SC daily to complete a total 6 week course of prophylaxis, and says there is a recent meta analysis to support this. After reviewing the meta analysis, how would you respond?

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<th>Comparator</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>In a patient</td>
<td>...would administering enoxaparin 40 mg SC daily for 6 weeks...</td>
<td>...compared to no DVT prophylaxis...</td>
<td>...prevent symptomatic DVT?</td>
</tr>
</tbody>
</table>

Perspective

“...far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.”

## Useful Electronic Resources for Locating and Retrieving Systematic Reviews

<table>
<thead>
<tr>
<th>Search Engines</th>
<th>URL</th>
<th>Databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Google</td>
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<th>URL</th>
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<tr>
<td>ISI Web of Science</td>
<td><a href="http://woscanada.isihost.com/">http://woscanada.isihost.com/</a></td>
<td>Science Citation Index Expanded (SCI-EXPANDED)</td>
</tr>
<tr>
<td>Cochrane Collaboration</td>
<td><a href="http://www.update-software.com/cochrane/">http://www.update-software.com/cochrane/</a></td>
<td>Cochrane Database of Systematic Reviews (CDSR)</td>
</tr>
<tr>
<td>National Health Services Centre for Reviews &amp; Dissemination (NHS CRD)</td>
<td><a href="http://nhscrd.york.ac.uk/welcome.html">http://nhscrd.york.ac.uk/welcome.html</a></td>
<td>Health Technology Assessment Database (HTA)</td>
</tr>
<tr>
<td>Virtual Health Library (VHL)</td>
<td><a href="http://www.bireme.br/bvs/l/ihome.htm">http://www.bireme.br/bvs/l/ihome.htm</a></td>
<td>LILACS Database</td>
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<td>BioMED Central</td>
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<tr>
<td>Turning Research into Practice</td>
<td><a href="http://www.tripdatabase.com">http://www.tripdatabase.com</a></td>
<td>Turning Research Into Practice (TRIP) Database</td>
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<tr>
<td>Canadian Coordinating Office for Health Technology Assessment (CCOHTA)</td>
<td><a href="http://www.ccohta.ca/">http://www.ccohta.ca/</a></td>
<td>Database of EB reviews of emerging technologies</td>
</tr>
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<tr>
<th>Other sites to identify reviews</th>
<th>URL</th>
<th>Comment</th>
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<tr>
<td>ScHARR Netting the Evidence</td>
<td><a href="http://www.sheffield.ac.uk/~scharr/ir/netting/">http://www.sheffield.ac.uk/~scharr/ir/netting/</a></td>
<td>Links to multiple online databases for EBM articles</td>
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<td>Centre for Evidence Based Medicine (CEBM)</td>
<td><a href="http://cebm.jr2.ox.ac.uk/">http://cebm.jr2.ox.ac.uk/</a></td>
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<td>Evaluations of articles dealing with EBM practice</td>
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<td>American College of Physicians Journal Club (ACP Journal Club)</td>
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<td><a href="http://www.york.ac.uk/inst/crd/ehcb.htm">http://www.york.ac.uk/inst/crd/ehcb.htm</a></td>
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*All included under "EBM Reviews"  
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