Where to find information on adverse effects

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Structure of my presentation

- Why adverse effects matter?
- Why include adverse effects in systematic reviews?
- Where do authors of systematic reviews currently search for information on adverse effects?
- What evidence is available on where we should search for information on adverse effects?
Why do adverse effects matter?

- **Definition**
  - 'A harmful or undesirable outcome that occurs during or after the use of a drug or intervention for which there is at least reasonable possibility of a causal relation' (Chou 2010)

- **Why adverse effects matter**
  - Unpleasant, often serious – hospitalisation, disability, death (USA: 4th to 6th leading cause of death) (Lazarou 1998)
  - Worsen quality of life, make people stop treatment
  - Cost (estimates of cost to UK NHS of £2 billion per year) (Compass 2008)
Why include adverse effects in systematic reviews?

- Need to assess benefit/harm balance

- Detailed evaluation of safety needed when:
  - Narrow margin between benefit and harm (aspirin/CVD)
  - A number of equally effective treatments with different safety profiles
  - When adverse effects cause withdrawal from treatment
Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

- 849 systematic reviews

- Study designs included
  - RCTs (61%) (Included *only* RCTs 33%)
  - Cohort studies (37%)
  - Case-control studies (25%)
  - Case series (8%)
  - Case reports (6%)
Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

- Median number of databases
  - 2 (range 0 to 25)

- Number of sources
  - Increasing over time
  - Greater if information professional involved
Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

Top 5 most popular sources

1. MEDLINE (96%)
2. Reference checking (76%)
3. EMBASE (54%)
4. CENTRAL or Cochrane Library (45%)
5. Contacting experts (22%)
Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

Percentage of reviews over time for MEDLINE, EMBASE, CENTRAL, and Cochrane Library.
Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

- Unpublished data searches
  - Contacting experts (18%)
  - Scanned conference reports (17%)
  - Sought industry data (13%)
  - Clinical trial registries (6%)
  - FDA website (6%)
  - Surveillance data (3%)
  - Databases of unpublished data (3%)
What the evidence suggests we should do

- Search for unpublished data?
- Which sources to search?
- Which study designs to search for?
Should we search for unpublished data?

- Systematic review of the methodological literature
  - 10 included studies

- Availability of unpublished data
  - Case Reports
    - Two out of three studies found more unpublished than published case reports of adverse effects
  - Trials
    - A higher percentage of unpublished trials report adverse effects than published trials
Should we search for unpublished data?

- Differences in unpublished and published data
  - Case reports
    - Unpublished case reports will generate a different picture of the relative frequencies of specific adverse effects
  - Trials
    - No clear evidence that data on adverse effects from published and unpublished trials differed
    - Inclusion of unpublished data could provide information on adverse effects earlier and give more precise risk estimates
Where to search?

The Evidence

A. Systematic review comparing sources of information on adverse effects (Golder et al 2010)

B. Case study systematic review of glitazones and fractures (Golder et al 2012a)

C. Case study systematic review of the safety of spinal fusion (unpublished)
A: Systematic review of previous research (Golder et al 2010)

- **Objective**
  - Summarise all the literature comparing 2 or more sources to identify adverse effects

- **Results**
  - **EMBASE vs MEDLINE**
    - In eight out of ten cases searching EMBASE retrieved more relevant references than MEDLINE
  - **Industry Submissions**
    - In two out of four cases data retrieved from industry submissions retrieved the highest number of relevant records and in each case many records were unique
A: Systematic review of previous research (Golder et al 2010)

- Limitations
  - Over 50 information sources evaluated with little overlap between each study
  - 12 of the 19 studies were published before 1999
  - Many based on poor searches with few evaluations reporting number of relevant records indexed on the databases at time of searching (i.e. potentially missed studies)

- More research needed
B: Case study with a drug intervention (Golder et al 2012)

Long-term use of glitazones and fractures in type 2 diabetes

- Searched over 60 sources (beyond usual practice)
- Used intervention (glitazones) and outcome (fractures) search terms
- No diabetes or study design terms used
- Multiple textwords and indexing
B: Case study with a drug intervention – top databases (Golder et al 2012)
B: Case study with a drug intervention – unique records (Golder et al 2012)
B: Case study with a drug intervention - sources required (Golder et al 2012)

Minimum combination of sources

Science Citation Index
BIOSIS Previews
Medscape DrugInfo
Thomson Reuters Integrity*
AHFS First
Reference checking

Embase
GSK website
British Library Direct
Conference Papers Index*
Handsearching**

*either database
** ten key journals
C: Case study with a medical device (unpublished)

Safety of recombinant human bone morphogenetic protein-2 (rhBMP-2)

- Searched 10 databases plus reference checking, contacting authors and automated current awareness service
- Used intervention terms; recombinant human bone morphogenetic protein-2 (rhBMP-2) and spinal fusion
- Multiple textwords and indexing
C: Case study with a medical device – top databases

Percentage of all publications retrieved (n=82)
C: Case study with a medical device – unique records

![Bar chart showing unique relevant records across different databases](chart.png)
C: Case study with a medical device – sources required

Minimum combination of sources

Science Citation Index (SCI)
Embase
CENTRAL
MEDLINE or PubMed
Reference checking
Contacting authors
Automated current awareness service
Which study designs to include? (Golder et al 2011)

- **Objective**
  - Summarise the literature comparing harm estimates from different study designs

- **Analysis**
  - 51 included studies
  - Measured confidence interval overlap
  - Measured occurrence of different answers (significant increase, no significant difference, significant decrease)
  - Compared odds ratios
Which study designs to include? (Golder et al 2011)

<table>
<thead>
<tr>
<th>Study designs compared</th>
<th>Confidence interval overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs vs all ‘observational’ studies</td>
<td>93%</td>
</tr>
<tr>
<td>RCTs vs cohort studies</td>
<td>100%</td>
</tr>
<tr>
<td>RCTs vs case-control studies</td>
<td>90%</td>
</tr>
<tr>
<td>RCTs vs ‘observational’ studies</td>
<td>91%</td>
</tr>
</tbody>
</table>
### Which study designs to include? (Golder et al 2011)

<table>
<thead>
<tr>
<th>Study designs compared</th>
<th>Agreement in findings (direction and significance)</th>
<th>Discrepancy in findings (significance only)</th>
<th>Discrepancy in findings (direction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs vs all ‘observational studies’</td>
<td>64%</td>
<td>34%</td>
<td>2%</td>
</tr>
<tr>
<td>RCTs vs cohort studies</td>
<td>69%</td>
<td>31%</td>
<td>0%</td>
</tr>
<tr>
<td>RCTs vs case-control studies</td>
<td>40%</td>
<td>60%</td>
<td>0%</td>
</tr>
<tr>
<td>RCTs vs observational studies</td>
<td>69%</td>
<td>28%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Which study designs to include? (Golder et al 2011)

<table>
<thead>
<tr>
<th>Study designs compared</th>
<th>Pooled ratio of odds ratios (RORs) and 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs vs all ‘observational studies’</td>
<td>1.03 (0.93-1.15)</td>
</tr>
<tr>
<td>RCTs vs cohort studies</td>
<td>1.02 (0.82-1.28)</td>
</tr>
<tr>
<td>RCTs vs case-control studies</td>
<td>0.84 (0.57-1.23)</td>
</tr>
<tr>
<td>RCTs vs observational studies</td>
<td>1.08 (0.94-1.22)</td>
</tr>
</tbody>
</table>
Which study designs to include? (Golder et al 2011)

- Most confidence intervals overlap between study designs
- Most study designs agree, in terms of finding an increase, decrease or no difference, in adverse effects
- Overall meta-analyses of RCTs agree with meta-analyses of observational studies
Take home messages

- Searching unpublished data retrieves additional useful data
- Searching multiple sources is required
- Observational studies not a major threat to bias
Future

- More reviews are including adverse effects either as secondary outcome (in addition to effectiveness) or as primary outcome

- Better reporting
  - CONSORT Extension for Harms (Ioannidis et al 2004)
  - PRISMA Harms Extension (Zorzela et al 2014)
Guidance

- **Cochrane Handbook**

- **CRD’s Guidance**

- **BMC Paper**
Help and support

Cochrane Adverse Effects Methods Group
http://aemg.cochrane.org/

Discussion List
http://lists.cochrane.org/mailman/listinfo/aemg

Twitter
@CAEMG1
References


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Golder SP, Loke YK, Bland M. Meta-analyses of Adverse Effects Data Derived from Randomised Controlled Trials as Compared to Observational Studies: Methodological Overview. *PLOS Medicine* 2011;e1001026.


Golder S, Loke YK, Zorzela L. Comparison of search strategies in systematic reviews of adverse effects to other systematic reviews. *Health Info Libr J* 2014.

