Data sources and search strategies for identifying information on adverse drug effects

Dr Su Golder
su.golder@york.ac.uk
Structure for Today’s Presentation

- Why we should search for information on adverse effects?
- Why information on adverse effects is difficult to search for?
- How we currently search for information on adverse effects?
- How we should search for information on adverse effects?
Why search for information on adverse effects?

- 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 £2 billion per year to UK NHS) (Compass 2008)
- Can be a deciding factor in decision-making
Why is information on adverse effects difficult to identify?

- AEs often treated as **secondary** or even **tertiary outcomes**. **Poor reporting** or absence of adverse effects terms in titles, abstracts and indexing
- Wide range of terms for adverse effects. **Inconsistent terminology and indexing**
- **False hits**: ‘Relative Risk’, ‘Self-harm’, ‘Patient safety’, ‘adverse effects were not considered’
- May wish to identify **all** adverse effects. Hard to predict/plan (specific terms may not be known in advance)
- Relevant adverse effects may come from a **range of study designs**, not just RCTs
- Adverse effects may not be limited to a particular condition
- Many **data sources**: specialist databases, unpublished data, industry funded data, surveillance data, tertiary sources
Where do authors of systematic reviews search for adverse effects?

- **Analysis of 849 reviews of adverse effects** (Golder et al 2013, Golder et al 2014)

- **Number of databases searched**
  - median 2 (range 0 to 25)
  - increasing over time
  - greater if information professional involved
Quiz Time

Q: Which are the top three resources used to identify information on adverse effects?

A: Cochrane Library, MEDLINE and contacting experts

B: MEDLINE, reference checking, and Embase

C: Embase, Derwent Drug File and BIOSIS Previews
Which are the top three resources used to identify information on adverse effects?

1. MEDLINE: 96%
2. Reference checking: 76%
3. Embase: 54%
4. CENTRAL or Cochrane Library: 45%
5. Contacting experts: 22%
How do authors of systematic reviews search for adverse effects?

- 62% search with adverse effects terms
  - 46% with named adverse effect
e.g. headache, bleed, sepsis
  - 5% with generic adverse effect terms
  e.g. adverse effects, side effects, complications etc.
  - 11% with both
The evidence on where to search for adverse effects

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

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

- Case study systematic review of the safety of spinal fusion (unpublished)
Systematic review of previous research (Golder et al 2010)

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

- **Results**
  - 19 included studies
  - 8/10 cases searching Embase retrieved more relevant references than MEDLINE

- **Limitations**
  - Many of the included studies are out of date
  - Little overlap in the sources compared
Case study with a drug intervention (Golder et al 2012a)

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 terms used
- Multiple textwords and indexing
Quiz Time

Q: Which database retrieved the highest number of relevant records for this review on fracture and glitazones?

A: MEDLINE

B: Embase

C: Science Citation Index (SCI)
Case study with a drug intervention: top databases (Golder et al 2012a)

Percentage of all publications retrieved (n=58)
Case study with a drug intervention: unique records (Golder et al 2012a)
Case study with a drug intervention: sources required (Golder et al 2012a)

Minimum combination of sources

Science Citation Index  Embase
BIOSIS Previews  GSK website
Medscape DrugInfo  British Library Direct
Thomson Reuters Integrity*  Conference Papers Index*
AHFS First  Handsearching**
Reference checking

*either database
** ten key journals
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
Case study with a medical device: top databases

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

![Bar chart showing unique relevant records across different databases: Science Citation Index (SCI), Embase, CENTRAL, MEDLINE, PubMed, and ToxFile.]

Centre for Reviews and Dissemination
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
The evidence on how to search for adverse effects

- Analysis of records from 3 systematic reviews of drug interventions (Derry et al 2001)
- Analysis of records from 26 systematic reviews of drug interventions (Golder et al 2012b)
- Analysis of records from case study systematic review of a medical device (unpublished)
Analysis of records from 3 systematic reviews of adverse drug effects (Derry et al 2001)

- **Objective**
  - To assess the presence or absence of adverse effects terms in the title, abstract or indexing of records of articles with adverse effects data

- **Results**
  - 23% of trials that reported adverse effects data had no adverse effects terms in title, abstract or indexing of records in MEDLINE or Embase

- **Guidance**
  - Do not rely on adverse effects terms
  - Check full-text versions of retrieved articles
Analysis of records from 26 systematic reviews of adverse drug effects (Golder et al 2012b)

Objective 1

To assess the presence or absence of adverse effects terms in the title, abstract or indexing of records of articles with adverse effects data published since 2001

Results

8% of articles published after 2001 that reported adverse effects data had no adverse effects terms in title, abstract or indexing of records in MEDLINE or Embase
Database records with any adverse effects terms (Golder et al 2012b)
Quiz Time

Q: Which of the following search terms retrieves the highest number of relevant records in MEDLINE?

A: ‘adverse effects’ as a subheading

B: ‘adverse adj3 event$’ in title or abstract

C: ‘safety’ in title or abstract
### Top search terms in MEDLINE (Golder et al 2012b)

<table>
<thead>
<tr>
<th></th>
<th>Search Term</th>
<th>Location</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>‘adverse effects (ae)’</td>
<td>Floating subheading</td>
<td>51%</td>
</tr>
<tr>
<td>2</td>
<td>‘adverse adj3 event$’</td>
<td>Title or abstract</td>
<td>32%</td>
</tr>
<tr>
<td>3</td>
<td>‘safety’</td>
<td>Title or abstract</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>‘adverse adj2 events’</td>
<td>Title or abstract</td>
<td>29%</td>
</tr>
<tr>
<td>5</td>
<td>‘risk’</td>
<td>Title or abstract</td>
<td>28%</td>
</tr>
<tr>
<td>6</td>
<td>‘drug effects (de)’</td>
<td>Floating subheading</td>
<td>27%</td>
</tr>
<tr>
<td>7</td>
<td>‘complications (co)’</td>
<td>Floating subheading</td>
<td>18%</td>
</tr>
</tbody>
</table>
### Top search terms in Embase (Golder et al 2012b)

<table>
<thead>
<tr>
<th></th>
<th>Search Term</th>
<th>Location</th>
<th>Accuracy</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>‘adverse drug reaction(ae)’</td>
<td>Floating subheading</td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>‘side effect(si)’</td>
<td>Floating subheading</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>exp drug safety/</td>
<td>Emtree indexing term</td>
<td>38%</td>
</tr>
<tr>
<td>4</td>
<td>‘adverse adj3 event$’</td>
<td>Title or abstract</td>
<td>32%</td>
</tr>
<tr>
<td>5</td>
<td>‘safety’</td>
<td>Title or abstract</td>
<td>28%</td>
</tr>
<tr>
<td>6</td>
<td>‘adverse adj2 events’</td>
<td>Title or abstract</td>
<td>28%</td>
</tr>
<tr>
<td>7</td>
<td>‘risk’</td>
<td>Title or abstract</td>
<td>27%</td>
</tr>
</tbody>
</table>
Analysis of records from 26 systematic reviews of adverse drug effects (Golder et al 2012c)

- **Objective 2**
  - The second objective of this analysis was to measure the performance of suggested adverse effects search filters/hedges
Average sensitivity of adverse effects search filters in 26 systematic reviews (Golder et al 2012c)
Analysis of records from case study systematic review of a medical device (unpublished)

- **Objective**
  - To assess the presence or absence of adverse effects terms in the title, abstract or indexing of records of articles with adverse effects data

- **Results**
  - 4% of articles that reported adverse effects data of a medical device had no adverse effects terms in title, abstract or indexing of records in MEDLINE or Embase
## Top search terms for adverse effects of a medical device in MEDLINE

<table>
<thead>
<tr>
<th>Rank</th>
<th>Search Term</th>
<th>Location in MEDLINE</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>‘adverse effects (ae)’</td>
<td>Floating subheading</td>
<td>47%</td>
</tr>
<tr>
<td>2</td>
<td>‘complication$’</td>
<td>Title or abstract</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>‘postoperative complications/’</td>
<td>MeSH indexing term</td>
<td>27%</td>
</tr>
<tr>
<td>4</td>
<td>‘safety’</td>
<td>Title or abstract</td>
<td>20%</td>
</tr>
<tr>
<td>5</td>
<td>‘safely’</td>
<td>Title or abstract</td>
<td>20%</td>
</tr>
<tr>
<td>6</td>
<td>‘blood loss’</td>
<td>Title or abstract</td>
<td>20%</td>
</tr>
</tbody>
</table>
## Top search terms for adverse effects of a medical device in Embase

<table>
<thead>
<tr>
<th></th>
<th>Search Term</th>
<th>Location</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>'complication (co)'</td>
<td>Floating subheading</td>
<td>49%</td>
</tr>
<tr>
<td>2</td>
<td>'complication$'</td>
<td>Title or abstract</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>'pseudarthrosis/'</td>
<td>Emtree indexing term</td>
<td>24%</td>
</tr>
<tr>
<td>4</td>
<td>'adverse drug reaction (ae)'</td>
<td>Floating subheading</td>
<td>22%</td>
</tr>
<tr>
<td>5</td>
<td>'postoperative complication/'</td>
<td>Emtree indexing term</td>
<td>20%</td>
</tr>
<tr>
<td>6</td>
<td>'blood loss'</td>
<td>Title or abstract</td>
<td>18%</td>
</tr>
<tr>
<td>7</td>
<td>'bleeding/'</td>
<td>Emtree indexing term</td>
<td>18%</td>
</tr>
<tr>
<td>8</td>
<td>'dysphagia/'</td>
<td>Emtree indexing term</td>
<td>18%</td>
</tr>
</tbody>
</table>
Take home messages

- Including adverse effects in systematic reviews is important so that clinicians, patients and policy makers can make balanced decisions and minimise harm.

- Searches of multiple databases and non-database sources are required in systematic reviews of adverse effects.

- Searching only MEDLINE may miss over 40% of the relevant references.
Take home messages

- Adverse effects terms increasingly prevalent in title, abstract or indexing
- Searchers may cautiously rely on adverse effects search terms
- Indexing terms for adverse effects much more prevalent in Embase
- Subheadings particularly useful in Embase and MEDLINE
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/](http://aemg.cochrane.org/)

- Discussion List
  [http://lists.cochrane.org/mailman/listinfo/aemg](http://lists.cochrane.org/mailman/listinfo/aemg)

- Twitter
  [@CAEMG1](https://twitter.com/CAEMG1)
Any questions?
References


Golder S, McIntosh HM, Duffy S, Glanville J. Developing efficient search strategies to identify reports of adverse effects in MEDLINE and EMBASE. Health Info Libr J. 2006 Mar;23(1):3-12.

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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.


