Search strategies and data sources for adverse effects reviews

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• Research referred to in this workshop was undertaken as part of an MRC fellowship.

• The views expressed in this presentation are those of the author and not necessarily those of the MRC.

• CRD is part of the National Institute for Health Research (NIHR) and is a department of the University of York, UK.
Introductions

- Background
  - Any information specialists?
  - Reviewers?

- Experience of adverse effects reviews?
Format of the workshop

• Introduction (10 mins)
• Group work using real systematic reviews (30 mins)
• Feedback and discussion (20 mins)
• What the research evidence tells us about the most effective search strategies and data sources (20-30 mins)
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 should we do systematic reviews of adverse effects?

• **Need to assess benefit/harm balance**
  - Considering benefits alone leads to bias

• **Detailed evaluation needed when:**
  - Narrow margin between benefit and harm
  - Other effective treatments have different or unknown safety profiles
  - When adverse effects make people stop treatment
Why is searching for adverse effects difficult?

- AEs often treated as secondary or even tertiary outcomes. Poor reporting in titles and abstracts and indexing

- 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 (may not know which adverse effects searching for)

- Relevant adverse effects may come from a range of study designs, not just RCTs

- Many data sources: specialist databases, unpublished data, industry funded data, surveillance data, tertiary sources
Group work

- Two scenarios
- Work out what data you want, and how you are going to find it
- Small groups to discuss (one scenario each)
- Should take 30 minutes
- Followed by open discussion
Group work

**Scenario A:** Review of a specific adverse effect
Long-term use of glitazones and fractures in type 2 diabetes

**Scenario B:** Review of all adverse effects (safety profile review)
Adverse effects of newer drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin) for epilepsy in adults
Points to consider

• Search strategy design
  - PICO (patient group, intervention, comparison, outcome)
  - Restrictions (language, date, study design)

• Where to search
  - Which databases
  - Other sources
Search strategy design

**Scenario A:** Review of a specific adverse effect

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

- **P** (patient group) - ?
- **I** (intervention) - ?
- **C** (comparison) - ?
- **O** (outcome) - ?
**PICO**

- **P** (patient group) - people with type 2 diabetes
- **I** (intervention) - glitazones
- **C** (comparison) - any
- **O** (outcome) - fractures
PICO – Patient Group

• Should we limit to type 2 diabetes?

OR

• Should we include fractures with glitazones in other groups?

• Some titles and abstracts may not mention the patient group (type 2 diabetes)
Example patient group terms

- **Freetext**
  - Diabet*, NIDDM, MODY, non insulin* depend*, noninsulin* depend*, non insulin* depend*, T2DM, type II DM

- **MeSH**
  - exp Diabetes Mellitus, Type 2/

- **EMTREE**
  - non insulin dependent diabetes mellitus/
PICO - Intervention

- Intervention terms may not be included in title and abstract

- Most sensitive search strategy (for breast cancer and oral contraception) in Wieland et al 2005 did not include intervention terms:
Example intervention terms

- **Freetext**
  - rosiglitazone, avandia, avandaryl, avaglim, avandamet, glitazone*, thiazolidinedione*, tzd, ppar gamma agonist*, peroxisome proliferator activated receptor gamma agonist*, pioglitazone*, actos, actoplus, duetact, competact, glustin, nyracta, venvia

- **MeSH**
  - thiazolidinediones/

- **EMTREE**
  - 2,4 thiazolidinedione derivative/, exp glitazone derivative/
PICO - Comparator

• Should we include all possible comparators? (for example, placebo, other drug interventions e.g. glimepiride)

• Would all study designs have a comparator?

• Is it worth trying to include these terms in the search strategy?
PICO - Outcome

- Should we search on the specific named adverse effects terms?
- Should we use generic adverse effects terms?
Example outcome terms

- Freetext
  - Fracture*, bone, bmd

- MeSH
  - exp Fractures, Bone/, bone density/

- EMTREE
  - exp fracture/, bone density/
Restrictions

• Should we limit to specific study designs?
  - RCTs?
  - Observational studies?

• Date or language restrictions?
Example combinations in MEDLINE

A: “glitazones” terms AND “fractures” terms
   - 251 records
   - no need to AND with generic adverse effects terms
   - may risk not retrieving all relevant papers

B: “glitazones” terms AND (“fractures” terms OR “adverse effects” terms)
   - generates thousands of records (over seven thousand in MEDLINE and over thirteen thousand in EMBASE)
Search strategy design

Scenario B: **Review of all adverse effects**
Adverse effects of newer drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin) for epilepsy in adults

- **P** (patient group) - ?
- **I** (intervention) - ?
- **C** (comparison) - ?
- **O** (outcome) - ?
PICO

- **P** (patient group) - adults with epilepsy
- **I** (intervention) - gabapentin, lamotrigine, levetiracetam, carbazepine, tiagabine, topiramate, vigabatrin
- **C** (comparison) - any
- **O** (outcome) - any adverse effects
Example patient group terms

- Freetext
  - epilep*, seizure*, convuls*

- MeSH
  - exp epilepsy/

- EMTREE
  - exp epilepsy/
Example intervention terms

- **Freetext**
  - epitomax, etiracetam, gabapentin, gabitril, gbp, labileno, lamictal, lamotrigine, ltg, keppra, levetiracetam, neurontin, neurotonin, oxcarbazepine, oxocarbazepine, sabril, sabrilex, trileptal, tiagabine, tiabex, topiramate, topamax, topimax, vigabatrin

- **MeSH**
  - vigabatrin/

- **EMTREE**
  - gabapentin/, lamotrigine/, etiracetam/, oxcarbazepine/, tiagabine/, topiramate/, vigabatrin/
Searching with outcome terms

- Adverse effects terms
  - Indexing terms (such as MeSH or EMTREE)
  - Subheadings / qualifiers
  - Textwords
  - Search filters / hedges
Example generic adverse effects
indexing terms

**MEDLINE:**
- adverse drug reaction reporting systems/
- drug toxicity/
- abnormalities, drug induced/
- drug monitoring/
- drug hypersensitivity/
- poisoning/
- substance-related disorders/
- product surveillance
- postmarketing/
- postoperative complications/
- intraoperative complications/

**EMBASE:**
- adverse drug reaction/
- drug toxicity/
- drug safety/
- drug monitoring/
- drug hypersensitivity/
- drug surveillance program/
- intoxication/
- side effect/
- postmarketing surveillance/
- postoperative complication/
- peripерative complication/

Many of these terms can be exploded to include narrower indexing terms.
Example subheadings

**MEDLINE**
/adverse effects
/poisoning
/toxicity
/chemically induced
/contraindications
/complications

**EMBASE**
/side effect
/adverse drug reaction
/drug toxicity
/complication
How to use subheadings (1)

Free floating subheadings

- Subheadings can be searched for attached to any indexing term in MEDLINE and EMBASE
- Examples for OVID MEDLINE:
  - ae.fs (adverse effects)
  - co.fs (complications)
  - po.fs (poisoning)
  - de.fs (drug effects)
How to use subheadings (2)

MEDLINE
Example:
Aspirin/adverse effects
Aspirin is the MeSH term and adverse effects is the subheading

Example:
headache/chemically induced
Headache is the MeSH term and chemically induced is the subheading

EMBASE
Example:
Acetylsalicylic-acid/adverse-drug-reaction
Acetylsalicylic-acid is the EMTREE term and adverse-drug-reaction is the subheading

Example:
headache/side effect
Headache is the EMTREE term and side effect is the subheading
Example free text adverse effects terms

Safe, safety, side effect*, undesirable effect*, treatment emergent, tolerability, toxicity, adverse drug reaction*, adrs, adverse effect*, adverse drug effect*, adverse reaction*, adverse event*, adverse outcome*, complication*, harm, harmful, harms, risk
Problems with free text search

- Wide range of terms for adverse effects - so try to include as many relevant synonyms as possible
  - general (toxicity, side effect, adverse effect, harms)
  - specific (e.g. lethargy, tiredness, malaise)

- Specific terms may not be known in advance

- Free text search cannot find adverse effects not mentioned in the title or abstract (even though they appear in the full report)

- False hits; ‘Relative Risk’, ‘Self-harm’, ‘Patient safety’, ‘adverse effects were not considered’
Evaluated adverse effects search strategies in MEDLINE

- Badgett et al 1999
  - (ae OR co OR po OR de).fs OR case report/ AND human/

- Golder et al 2006
  - (ae OR co OR de).fs OR (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))).ti,ab

- Tested in 27 systematic reviews. Sensitivity ranged from 72% to 100%. (Golder et al 2012)
Adverse effects search filters

• In 2001, 23% of published reports that contained harmful effects data had no adverse effects textwords or indexing terms (Derry et al 2001)

• In 2011 this figure had decreased to 8% (Golder et al 2012)
Where to search?
Number of included references retrieved by databases in glitazone review

- Science Citation Index (SCI)
- BIOSIS Previews
- EMBASE
- MEDLINE
- Scirus
- Derwent Drug File
- PASCAL
- British Library Direct
- Thomson Reuters Integrity
- TOXLINE
- ADIS Clinical Trials Insight

- Missed references
- Relevant references retrieved
Quiz time

• What percentage of papers would have been missed in the glitazone review if the search had been limited to MEDLINE, EMBASE, CENTRAL and reference checking?
  – A: 25%
  – B: 8%
  – C: 57%
Percentage of relevant references missed in glitazone review

- Percentage of included references missed with searches
- Percentage of relevant references missed if all papers on the databases had been retrieved
Minimum combination of sources in glitazone review

Identifies all 58 included references with search strategy for ‘glitazones’ and ‘fractures’

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

*either database
Availability of relevant references

Minimum combination of sources in which the 58 included references were available

BIOSIS Previews
British Library Direct
Medscape DrugInfo
Science Citation Index
Handsearching
Citation Searches

• Case reports or series of suspected new adverse effects may lead you to more detailed studies as researchers unlikely to design safety study without a ‘signal’ (Kuper et al 2006)

• Especially useful if find relatively old studies

• Examples: Google Scholar, MEDLINE, PsycINFO, SciFinder, Scopus, Web of Science
Take home message

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

• Adverse effects search terms or adverse effects search filters can be useful particularly when large numbers of records would otherwise be retrieved.

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

• Searching only MEDLINE may miss over half the relevant references.
Future

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

• Review of 849 systematic reviews suggests **improvements in searches** (Golder et al 2013)
  - More databases searched
  - Fewer reviews restricted to searching only MEDLINE or to date or language restrictions
  - More transparent reporting of searches

• **Better reporting in primary studies**
  - CONSORT Extension for Harms (Ioannidis et al 2004)
  - Only 8% of published reports that contained harmful effects data had no ‘adverse effects’ related textwords or indexing terms (Golder et al 2012)
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
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