Adverse effects 2: Searching for adverse effects

Dr Su Golder, Cochrane Adverse Effects Methods Group

Trusted evidence.
Informed decisions.
Better health.

Today's Objectives

To help searchers select;
- ❖ **Elements of PICOs to use**
- ❖ **Appropriate free-text and indexing terms**
- ❖ **Database and non-database sources**

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Planning your search...

❖ Create your **PICOs (Population, Intervention, Comparators, Outcomes, Study design)** – whereby O (Outcomes) will be your adverse effects

❖ Think **which elements of the PICOs to search on** (depends on lots of factors including the number of hits retrieved)...

Should you search on 'Population'?

❖May be interested in **specific groups**, such as children, elderly or pregnant women

❖May be interested in **all** conditions

  ❖For example, *NSAIDS for headache, arthritis, toothache, chronic back or neck pain and strains and sprains.*

❖Some records may **not** mention the population

  ❖*'Fracture risk with rosiglitazone and pioglitazone compared'* does not mention diabetes.

Should you search on 'Intervention'?

❖Usually essential to search on the intervention

❖Be careful if looking at a class of treatments rather than specific treatment

   ❖For example with selective COX2 inhibitors only rofecoxib and with nonselective COX2 inhibitors only diclofenac associated with increased risk of cardiovascular events

Should you search on 'Comparators'?

❖ Can be too numerous to search

❖ Difficult to search for 'no comparator'

❖ Some study designs do not have a control group

   ❖ For example, case series, case reports, single-arm trials

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Should you search on 'Outcomes'?

❖ May **not know** which adverse effects searching for but can use generic adverse effects terms and create list 'plausible adverse effects'

❖ Adverse effects are often secondary outcomes leading to **poor reporting** in titles, abstracts and indexing

❖ Research on recent records indicates that you may miss between 4% and 8% of studies if you add adverse effects terms to searches

(Golder 2014a, Golder 2012a)

SIDE EFFECTS

Should you search on 'Study design'?

❖ **Range of study designs** may be relevant not just RCTs

❖ Be careful - filters for non-RCTs do not work as well as RCT filters, so you may miss studies
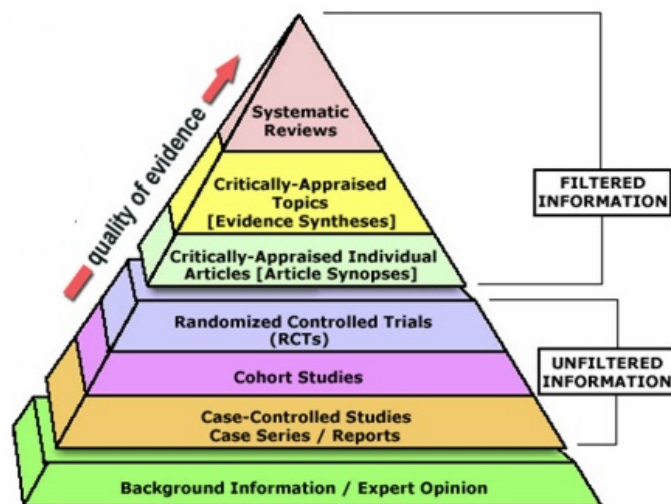
Searching for outcomes (adverse effects) in MEDLINE and Embase

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Which types of adverse effects terms?

Specific named adverse effects terms (e.g. death, fatigue, fracture, insomnia, rash)

Most useful for adverse effects in *hypothesis testing review*.

Can search for expected adverse effects in *hypothesis generating review*. Identified from biological plausibility, textbooks, clinicians, patients, drug labels, social media, pharmacovigilance

Generic adverse effects terms (e.g. side effects, harms, adverse events, complications)

Most useful for unknown adverse effects in *hypothesis generating review.*

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Searching on generic adverse effects terms

❖ Textwords (e.g. title or abstract)

❖ Indexing terms (e.g. MeSH or Emtree)

❖ Subheadings / qualifiers

❖ Search filters / hedges

Example MEDLINE record

Title: Adverse events associated with prolonged antibiotic use.

Source: Pharmacoepidemiology & Drug Safety. 17(5):523-32, 2008 May.

MeSH Subject Headings:
Adolescent
Adult
Adverse Drug Reaction Reporting Systems
Aged
Amoxicillin / ad [Administration & Dosage]
Amoxicillin / ae [Adverse Effects]
Anthrax / pc [Prevention & Control]
*Anti-Bacterial Agents / ae [Adverse Effects]

Textword

Indexing term

Subheading

Free text terms

☐ **Examples**

adrs, adverse drug effect*, adverse drug reaction*, adverse effect*, adverse event*, adverse outcome*, adverse reaction*, complication*, harm, harmful, harms, risk, safe, safely, safety, side effect*, tolerability, toxicity, treatment emergent, undesirable effect*, undesirable event*, unexpected effect*, unexpected event*

☐ **Warning**

False hits; *'relative risk', 'self-harm', 'patient safety', 'adverse effects were not considered'*

Generic MeSH terms

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Hazards
risk assessment/

Surgery
intraoperative complications/
postoperative complications/
postoperative pain/

Device
equipment contamination/
equipment failure/
equipment safety
medical device recalls/
safety-based medical device withdrawals/

Drugs
abnormalities, drug induced/
adverse drug reaction reporting systems/
drug recalls
drug hypersensitivity/
drug monitoring/
drug related side effects and adverse reactions/
poisoning/
safety-based drug withdrawals/
substance-related disorders/

Drug/device
product surveillance postmarketing/

Many of these terms can be exploded to include narrower indexing terms

Generic Emtree terms

Drug
adverse drug reaction/
drug safety/
drug monitoring/
drug hypersensitivity/
drug surveillance program/
intoxication/
side effect/
postmarketing surveillance/
drug recall/
product recall/

Surgery
postoperative complication/
periperative complication/
surgical risk

Non-drug
complication/

Device
medical device complication/
device recall/
adverse device effect/

Many of these terms can be exploded to include narrower indexing terms

Subheadings

MEDLINE

/adverse effects (ae)

/chemically induced (ci)

/complications (co)

/contraindications (ct)

/poisoning (po)

/toxicity (to)

Embase

/adverse device effect (am)

/adverse drug reaction (ae)

/complication (co)

/drug toxicity (to)

/side effect (si)

How to use subheadings (1)

Free floating subheadings

Subheadings attached to **any** indexing term

Examples for OVID MEDLINE

ae.fs. (adverse effects) (or exploded ae.xs. to include toxicity and poisoning)

ci.fs. (chemically induced), co.fs. (complications), ct.fs. (contraindications), de.fs. (drug effects), po.fs. (poisoning), to.fs. (toxicity)

Examples for OVID Embase

ae.fs. (adverse drug reaction), am.fs. (adverse device effect), co.fs. (complication), si.fs. (side effect), to.fs. (drug toxicity)

How to use subheadings (2)

MEDLINE
Attached to intervention
'Aspirin/ae'
Aspirin is the MeSH term and *adverse effects* is the subheading

Embase

'Acetylsalicylic-acid/ae'
Acetylsalicylic-acid is the EMTREE term and *adverse-drug-reaction* is the subheading

Attached to adverse effect
'headache/ci'
Headache is the MeSH term and *chemically induced* is the subheading

'headache/si'
Headache is the EMTREE term and *side effect* is the subheading

Evaluated search strategies in MEDLINE

Badgett 1999

((ae **OR** co **OR** po **OR** de).fs. **OR** case report/) **AND** human/

Golder 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 2012b)

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Quiz Time

Which search term retrieved the highest number of relevant records in MEDLINE?

A: 'adverse effects (ae) ' as a floating subheading

B: 'adverse adj3 event*' in title or abstract

C: 'safety' in title or abstract

(Sample of 27 systematic reviews, Golder 2012a)

Most sensitive search terms in MEDLINE (drugs)

1	Adverse effects (ae)	Floating subheading	51%
2	Adverse adj3 event*	Title or abstract	32%
3	Safety	Title or abstract	31%
4	Adverse adj2 events	Title or abstract	29%
5	Risk	Title or abstract	27%
6	Drug effects (de)	Floating subheading	27%
7	Complications (co)	Floating subheading	18%
8	Exp risk/	MeSH	12%
9	Tolerability	Title or abstract	10%
10	Side effect*	Title or abstract	10%
11	Pharmacology (pd)	Floating subheading	10%
12	Adverse adj3 effects	Title or abstract	8%
13	Risk factors/	MeSH	8%
14	Safe	Title or abstract	7%

Most sensitive search terms in Embase (drugs)

1	Adverse drug reaction(ae)	Floating subheading	83%
2	Side effect(si)	Floating subheading	83%
3	exp drug safety/	Emtree indexing term	38%
4	Adverse adj3 event*	Title or abstract	32%
5	Safety	Title or abstract	28%
6	Adverse adj2 events	Title or abstract	28%
7	Risk	Title or abstract	27%
8	**Exp adverse drug reaction/**	**Emtree indexing term**	**19%**
9	**Tolerability**	**Title or abstract**	**11%**
10	**Complications(co)**	**Floating subheading**	**11%**
11	**Side effect***	**Title or abstract**	**10%**
12	**Adverse adj3 effect***	**Title or abstract**	**9%**
13	**Safe**	**Title or abstract**	**8%**
14	**Adverse adj2 effects**	**Title or abstract**	**7%**

What about non-drug interventions?

❖Top terms for medical device interventions found to differ from top terms for drug interventions

(Golder 2014a, Farrah 2016)

Most sensitive search terms in MEDLINE (device)

1	Adverse effects (ae)	Floating subheading	47%
2	Complication*	Title or abstract	35%
3	Postoperative complications/	MeSH indexing term	27%
4	Safety	Title or abstract	20%
5	Safely	Title or abstract	20%
6	**Safe**	Title or abstract	12%
7	**Risk**	**Title or abstract**	**12%**
8	**Adverse events**	**Title or abstract**	**12%**
9	Complications (co)	**Floating subheading**	8%
10	Chemically induced (ci)	**Floating subheading**	8%
11	**Adverse effects**	**Title or abstract**	**6%**
12	**Risk factors/**	**MeSH indexing term**	**6%**

Most sensitive search terms in Embase (device)

1	Complication (co)	Floating subheading	49%
2	Complication*	Title or abstract	35%
3	Adverse drug reaction (ae)	Floating subheading	22%
4	Postoperative complication/	Emtree indexing term	20%
5	Safety	Title or abstract	18%
6	Side effect (si)	Floating subheading	16%
7	Adverse reaction titles	Embase section heading	16%
8	**Adverse adj2 events**	**Title or abstract**	**15%**
9	**Risk**	**Title or abstract**	**15%**
10	**Safe**	**Title or abstract**	**13%**
11	**Adverse events**	**Title or abstract**	**13%**
12	Drug safety/	Emtree indexing term	5%

Sources

Resources for your search

❖ Bibliographic databases (e.g. BIOSIS Previews)

❖ 'Grey' literature (e.g. theses, reports, internet, conferences)

❖ Trial registries/ Industry registries (e.g. ClinicalTrials.gov)

❖ Regulatory data (e.g. US FDA, MHRA, EMA etc.)

❖ Handsearching (e.g. conference proceedings, journals)

❖ Citation tracking (e.g. Google Scholar, Web of Science)

❖ Contacting experts (e.g. authors)

❖ Contacting Industry (e.g. drug/manufacturers)

❖ Reference lists

Case study with a drug intervention

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

(Golder 2012c)

Quiz Time

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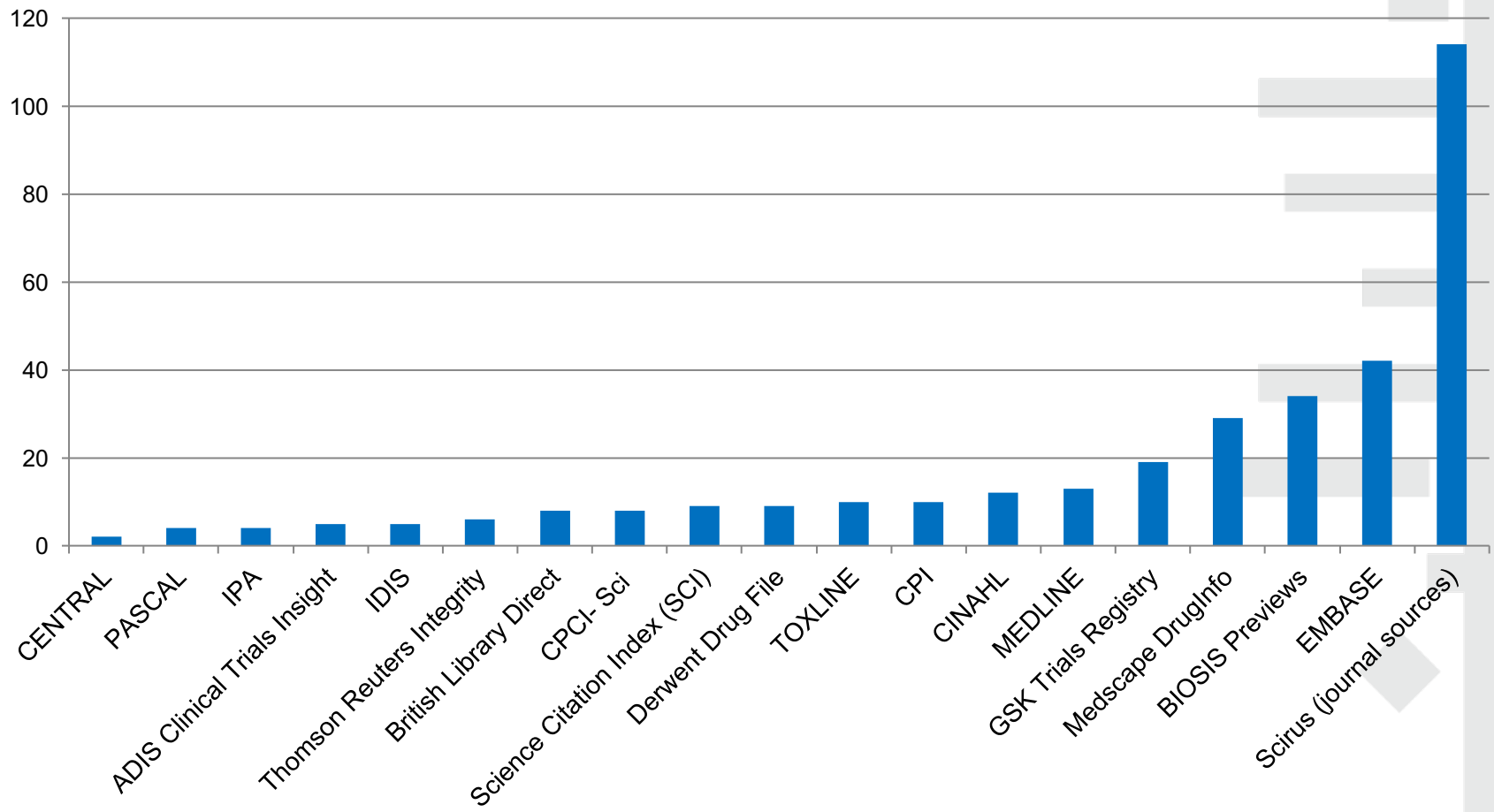
A: MEDLINE

B: Embase

C: Science Citation Index (SCI)

D: Other

(Golder 2012c)

Included references retrieved in glitazone review (n=58)

(Golder 2012c)

Number needed to read (NNR)

(Golder 2012c)

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Quiz time

What percentage of papers would we have missed in the glitazone review if we had searched MEDLINE, EMBASE, CENTRAL and reference checking?
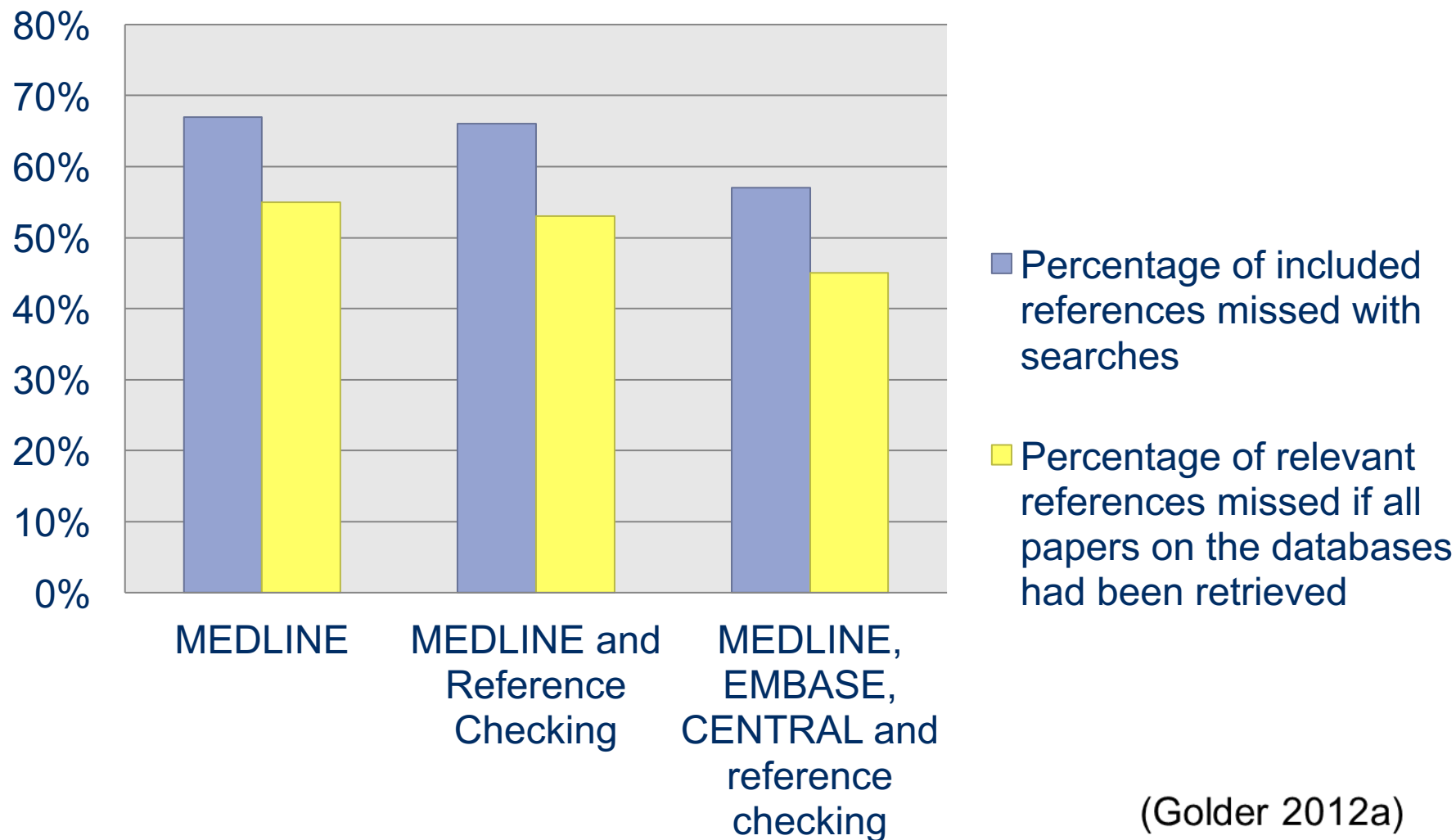
    A: 25%

    B: 8%

    C: 57%

    D: 0%

(Golder 2012c)

Relevant references missed in glitazone review

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- Percentage of included references missed with searches
- Percentage of relevant references missed if all papers on the databases had been retrieved

Categories: MEDLINE; MEDLINE and Reference Checking; MEDLINE, EMBASE, CENTRAL and reference checking

(Golder 2012a)

Unique records in glitazone review

![Cochrane logo]

(Golder 2012c)
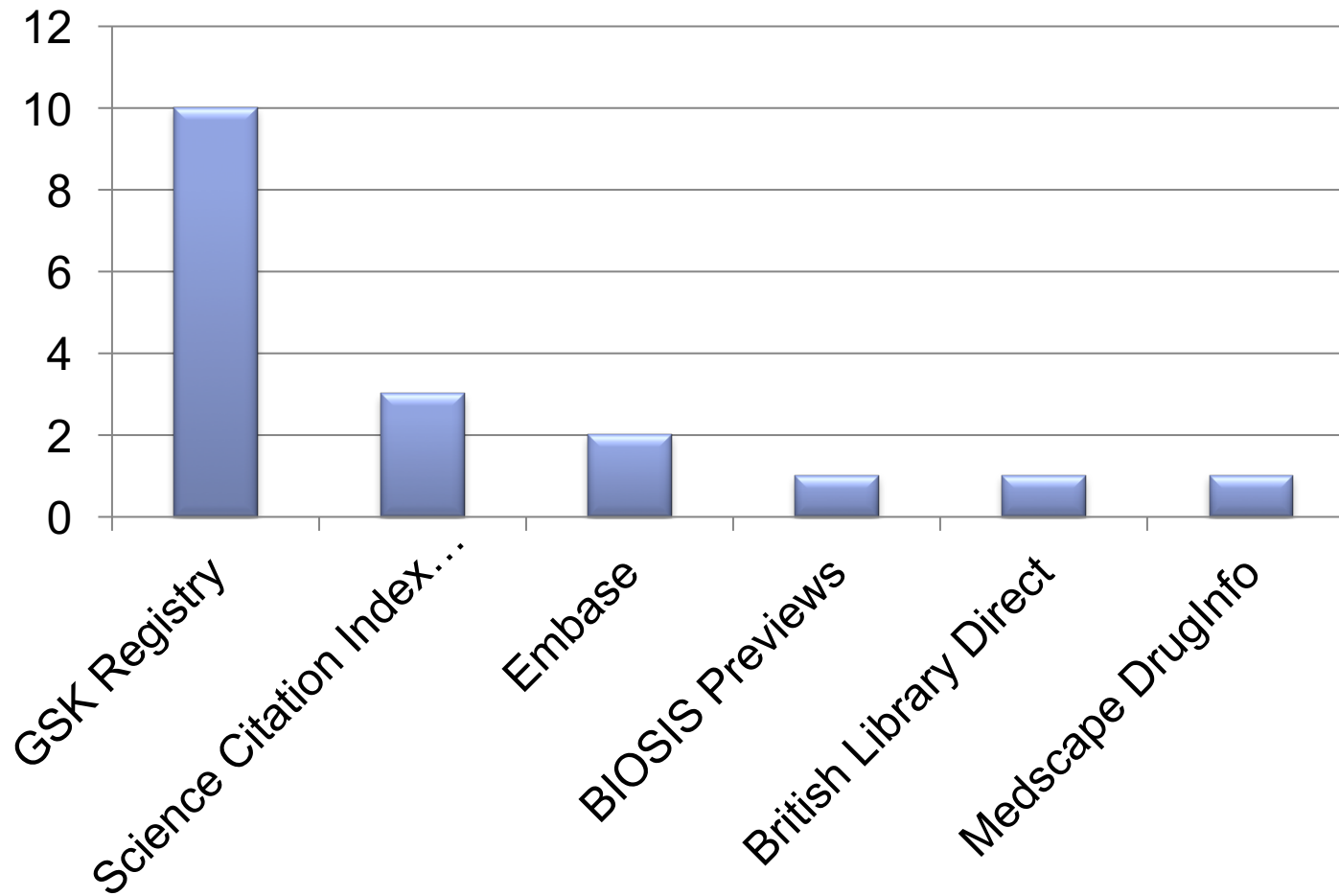
Minimum combination of sources in glitazone review

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
**ten key journals

(Golder 2012c)

Availability of relevant references in glitazone review

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

BIOSIS Previews

British Library Direct

Medscape DrugInfo
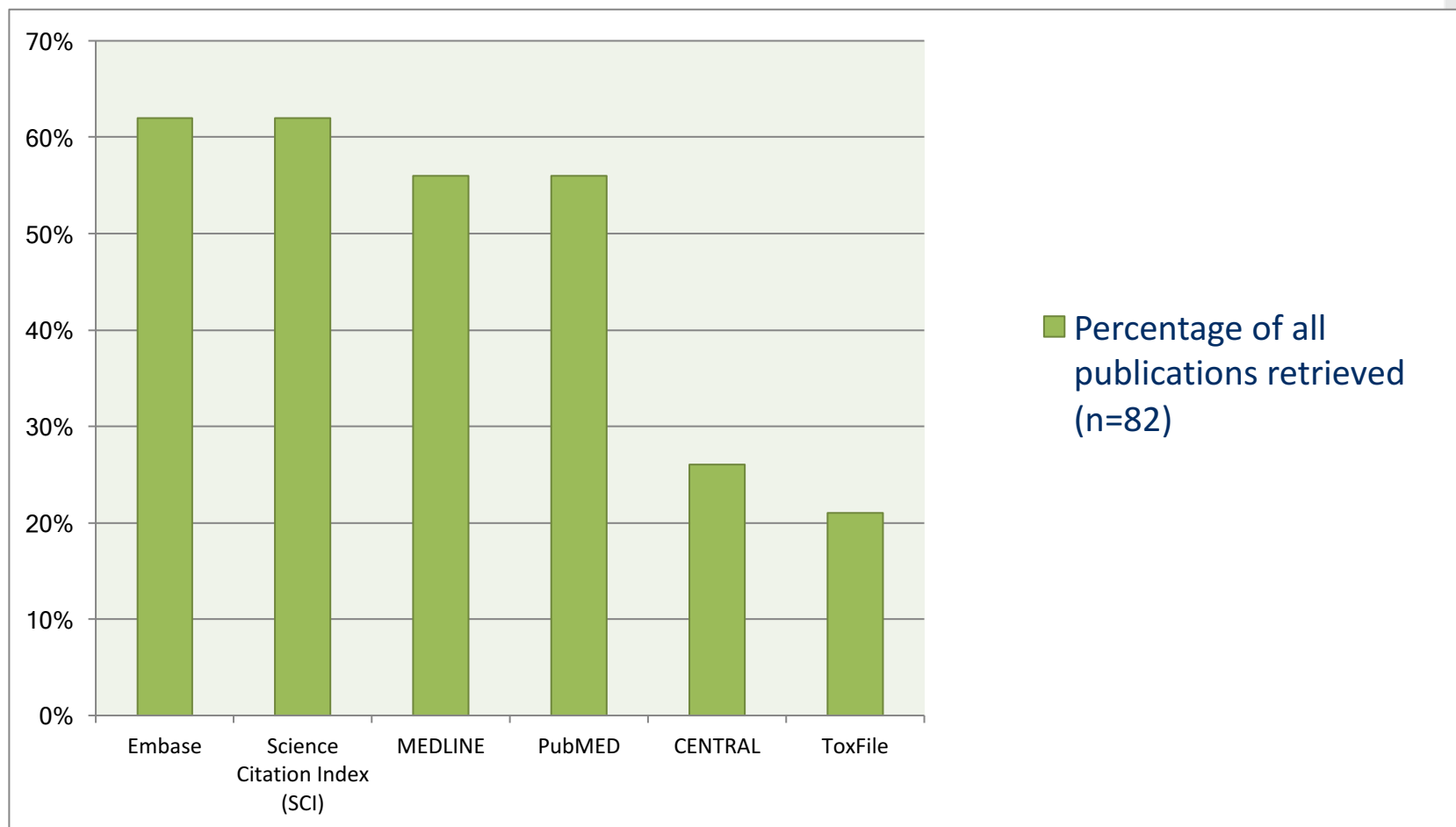
Science Citation Index

Handsearching

(Golder 2012c)

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Case study with a medical device

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

❖Searched 10 databases plus reference checking, contacting authors, industry and automated current awareness service

❖Used intervention terms; recombinant human bone morphogenetic protein-2 (rhBMP-2) and spinal fusion

❖Multiple textwords and indexing

(Golder 2014b)

Cochrane Included references retrieved in rhBMP-2 review

(Golder 2014b)

Minimum combination of sources in rhBMP-2 review

❖Industry

❖Science Citation Index (SCI)

❖Embase

❖CENTRAL

❖MEDLINE or PubMED

❖Reference checking

❖Contacting authors

❖Automated current awareness service

(Golder 2014b)

![Cochrane logo]

The importance of unpublished data

More unpublished studies

❖ More unpublished studies contain adverse effects data compared to published studies (83% versus 43%)

❖ Even for the same study the unpublished version is more likely to contain adverse effects data than the published version (95% versus 43%)

(Golder 2016b)

More

The importance of unpublished data

More adverse effects reported

❖A median of 64% of adverse effects (in terms of numbers) are missed if systematic reviews rely on published evidence (range 43% to 100%)

❖More types of adverse effects are reported in unpublished than published versions of the same study

(Golder 2016b)

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More

The importance of unpublished data

Searching for unpublished data

❖ 348 reviews of adverse effects from 2014

❖ 136/348 (39%) searched specific source for unpublished data

❖ 65/136 (48%) were **successful** in identifying unpublished data for inclusion

❖ Most successful sources searched were **ClinicalTrials.gov, contacting authors and searching conferences**

(Golder 2016a)

Summary

❖'Adverse effects' terms increasingly prevalent in title, abstract or indexing

❖Subheadings are useful in Embase and MEDLINE

❖Relevant sources will be dependent on search topic

❖Key to searching for adverse effects is to search widely

❖Much data on adverse effects are unpublished

What help is available?

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Guidance

❖ **Cochrane Handbook**

❖ **CRD's Guidance:**
www.york.ac.uk/inst/crd/systematic_reviews_book.htm

❖ **BMC Paper:** Loke YK et al. Systematic reviews of adverse effects: framework for a structured approach. BMC Med Res Methodol 2007;7:32.

❖ **AHRQ Paper:** Chou R et al. Assessing harms when comparing medical interventions. In Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD. 2009

Reporting standards

❖ **CONSORT** Extension for Harms

❖ **PRISMA** Harms Extension

Cochrane Adverse Effects Methods Group

❖ Website (http://aemg.cochrane.org/)

❖ Advisory Team

❖ Method Papers

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

❖ Twitter #CAEMG1

❖ Workshops

❖ Enquiry Database (FAQs)

❖ Ongoing Research

Any questions?

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