Chapter 19: Adverse Effects
Guidance on searching for adverse effects

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My background

- Senior Research Fellow, Department of Health Sciences, University of York
- Co-convenor of the Cochrane Adverse Effects Methods Group @CAEMG1 https://methods.cochrane.org/adverseeffects/
- Research interests: systematic reviews, literature searching, adverse effects, unpublished data, social media research

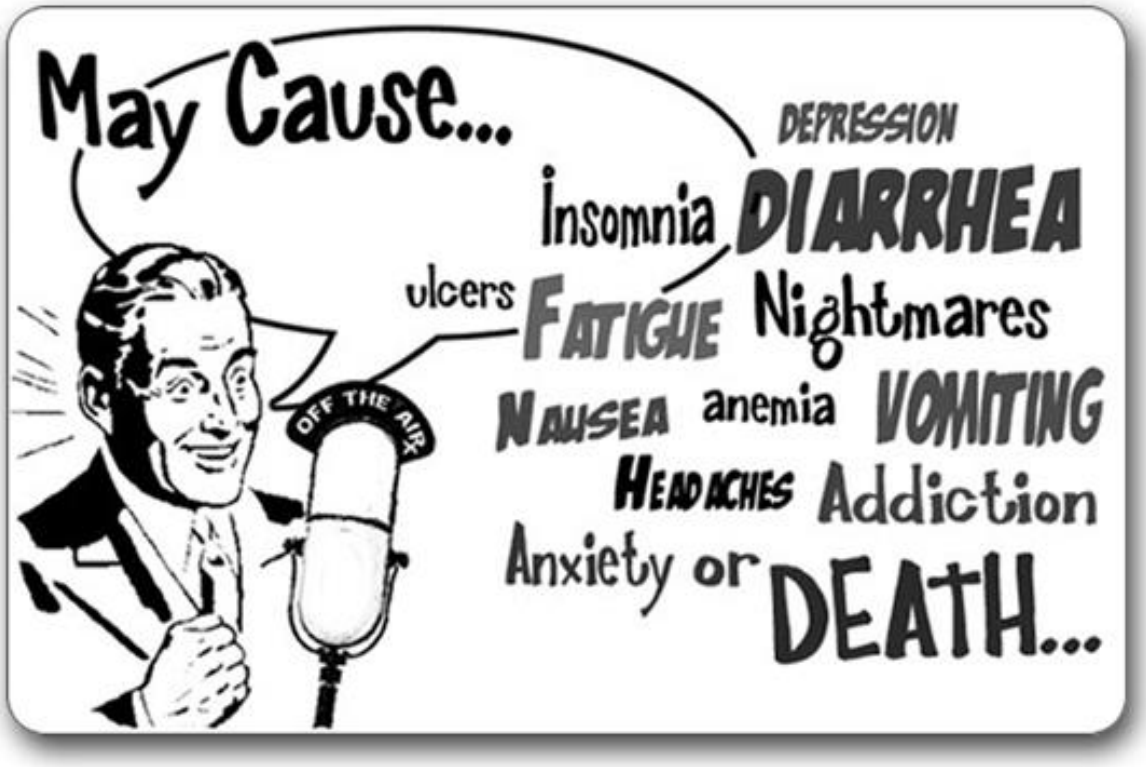
Structure for today's webinar

1. **Importance** of adverse effects
2. **Issues** with searching for adverse effects
3. **Approaches** to searching for adverse effects

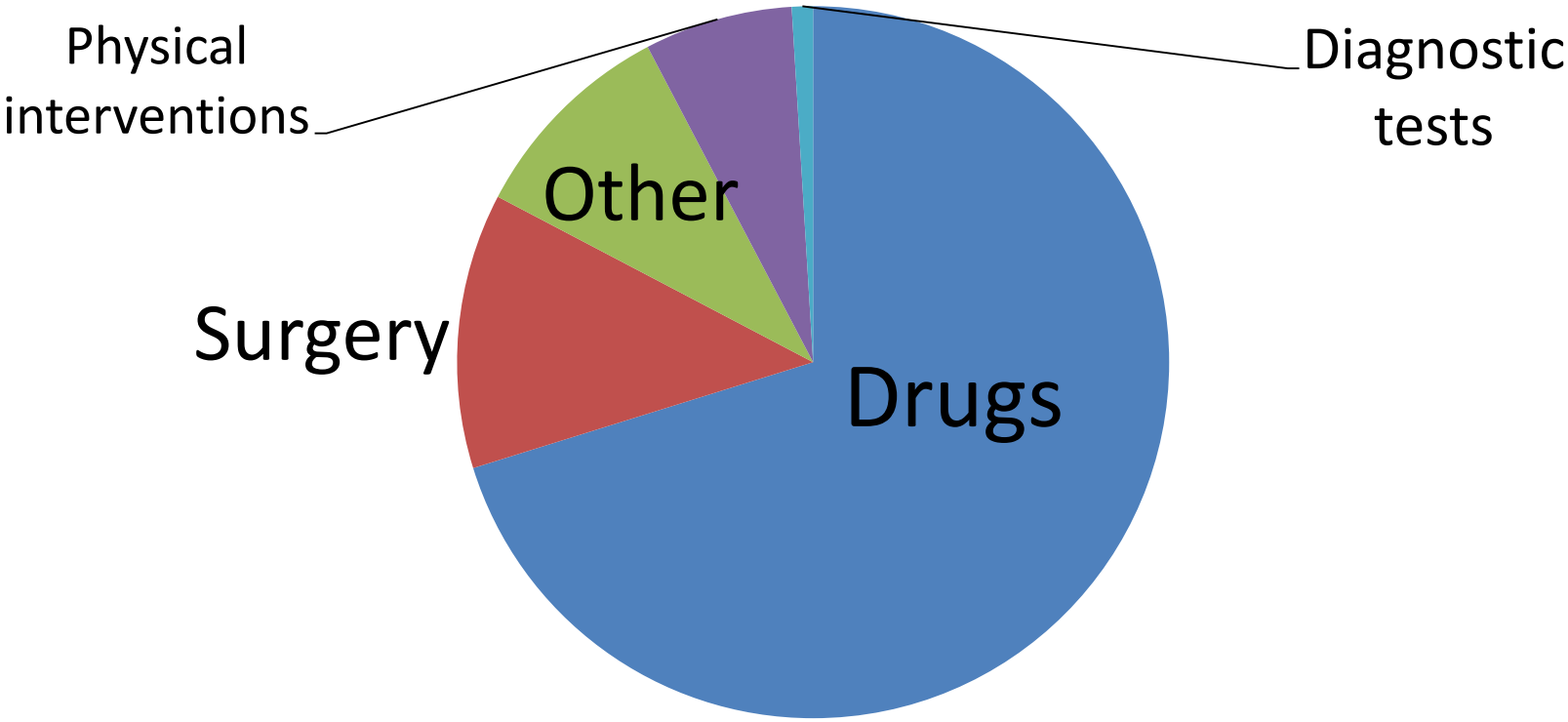
Importance of adverse effects

What is an adverse effect?

An unfavourable or harmful outcome that occurs during or after the use of a drug or other intervention for which there is at least a reasonable possibility of a causal relationship between the intervention and the event.



Types of interventions in systematic reviews of adverse effects



“A Cochrane Review that considers only the favourable outcomes of the interventions that it examines, without also assessing the adverse effects, will lack balance and may make the intervention look more favourable than it should.”

Issues with searching for adverse effects

Special issues for searching for adverse effects

- **Poor reporting** in titles and abstracts and indexing
- **Inconsistent terminology and indexing**
- May wish to identify **all** adverse effects. Hard to predict/plan.
- **Range of study designs**, not just RCTs

Section 19.1.2 and section 19.1.2.3

Approaches to searching for adverse effects

Search method

- **Single search**
  - Retrieves studies evaluating both benefits and harms
  - Not recommended
  - Study designs to evaluate adverse effects may be different to those reporting efficacy.
  - Adverse effects are not necessarily limited to the condition or types of participant.
  - More likely need separate searches

Sources to search

- Performing a search in MEDLINE alone is not recommended.
- **Wide breadth of sources** needed to ensure identification of relevant data.
- **Unpublished sources** particularly important for adverse effects data.
- Examples include **clinical study reports (CSR), trials registers** and **regulatory agency website**s.

Section 19.3.2 and section 19.3.3 and section 19.3.4

Planning a search

P	I	C	O
Population/ Problem	Intervention/ Exposure	Comparison	Outcome
Population characteristics or health issue of interest	Drug, surgery, policy, community program, etc.	No intervention, common practice, control group	Health outcomes of interest

Outcome = adverse effects

Section 19.2.2

Which adverse effects to look for

- **Confirmatory approach**
  - Review authors list one or more adverse effects as outcomes of interest in their review protocol
- **Exploratory approach**
  - Involves extracting any, or all, of the adverse event data found within the included studies.
- **Hybrid approach**
  - Combines elements of both confirmatory and exploratory approaches to capture anticipated and previously unrecognized adverse effects

Example Cochrane Reviews

- **Confirmatory approach**
  - Combined oral contraceptives: venous thrombosis
  - Progestin-only contraceptives: effects on weight
- **Exploratory approach**
  - Adverse side effects of dexamethasone in surgical patients
  - Adverse events in people taking macrolide antibiotics versus placebo for any indication

Searching on outcomes

Specific adverse effects terms (headache, death)

- Textwords (Title/Abstract)
- Indexing terms (MeSH/EMTREE)

Generic adverse effects terms (harms, side effects)

- Textwords (Title/Abstract)
- Indexing terms (MeSH/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.

Textword

MeSH Subject Headings:

Adolescent

Adult

Adverse Drug Reaction Reporting Systems

Indexing term

Aged

Amoxicillin / ad [Administration & Dosage]

Amoxicillin / ae [Adverse Effects]

Subheading

Anthrax / pc [Prevention & Control]

*Anti-Bacterial Agents / ae [Adverse Effects]

Free text adverse effects 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', 'risk of bias', 'self-harm', 'patient safety', 'adverse effects were not considered'*

Generic MeSH terms

- **Hazards**

risk assessment/

- **Surgery**

intraoperative complications/
postoperative complications/
postoperative pain/

- **Device**

equipment contamination/
equipment failure/
equipment failure analysis/
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

How to use subheadings (1)

MEDLINE

Attached to intervention

'Aspirin/ae'

Aspirin is the MeSH term and *adverse effects* is the subheading

Attached to adverse effect

'headache/ci'

Headache is the MeSH term and *chemically induced* is the subheading

Embase

'Acetylsalicylic-acid/ae'

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

'headache/si'

Headache is the EMTREE term and *side effect* is the subheading

How to use subheadings (2)

- **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)

Summary

- Likely require **separate search** for adverse effects and efficacy
- The search process needs to be **reported** for all searches
- Searching on **generic** and/or **specific adverse effects** terms may be necessary depending on the question
- Different search approaches are required for adverse effects of **drugs, medical devices and surgical procedures**

Guidance

- **Cochrane Handbook**

  Peryer G, Golder S, Junqueira D, Vohra S, Loke YK. Chapter 19: Adverse effects. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1 (updated Sept 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

- **Overview Paper**

  Golder S, Peryer G, Loke YK. Overview: comprehensive and carefully constructed strategies are required when conducting searches for adverse effects data. J Clin Epidemiol. 2019 May 28.

- **Search Filters**

  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.

  Golder S, Wright K, Loke YK. The development of search filters for adverse effects of surgical interventions in medline and Embase. Health Info Libr J. 2018 Mar 31. doi: 10.1111/hir.12213

  Golder S, Farrah K, Mierzwinski-Urban M, Wright K, Loke YK. The development of search filters for adverse effects of medical devices in medline and embase. Health Info Libr J. 2019 Jun 11. doi: 10.1111/hir.12260.

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Cochrane Methods
Adverse Effects

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About CAEMG

About CAEMG

- More about us
- Scope of our work

Welcome to the Cochrane Adverse Effects Methods Group (CAEMG)

The Cochrane Adverse Effects Methods Group (AEMG) was formally registered with Cochrane on the 14th June 2007. The Group aims to develop the methods for producing high quality systematic reviews and to advise Cochrane on how the validity and precision of systematic reviews can be improved.

The main purposes of the group are;

- to raise awareness of the adverse effects of interventions, and to promote the inclusion of adverse effects data in Cochrane reviews;
- to provide educational help to reviewers and users of reviews to spread and deepen understanding of the principles involved in assessing adverse effects;
- to provide methodological guidance on specific aspects of evaluating adverse effects;
- to identify areas of methodological uncertainty, and to develop a toolbox for the assessment of adverse effects.

Questions

Further Reading

- Chou R, Fu R, Carson S, Saha S, Helfand M. Methodological shortcomings predicted lower harm estimates in one of two sets of studies of clinical interventions. *Journal of Clinical Epidemiology* 2007; **60**: 18-28.
- Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, Whitlock E, Wilt TJ, Moher D. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. *Journal of Clinical Epidemiology* 2010; **63**: 502-512.
- Golder S, Loke YK. The contribution of different information sources for adverse effects data. *International Journal of Technology Assessment in Health Care* 2012; **28**: 133-137.
- Golder S, Loke YK, Zorzela L. Some improvements are apparent in identifying adverse effects in systematic reviews from 1994 to 2011. *Journal of Clinical Epidemiology* 2013; **66**: 253-260.
- Golder S, Loke YK, Wright K, Norman G. Reporting of adverse events in published and unpublished studies of health care interventions: a systematic review. *PLoS Medicine* 2016; **13**: e1002127.
- Kicinski M, Springate DA, Kontopantelis E. Publication bias in meta-analyses from the Cochrane Database of Systematic Reviews. *Statistics in Medicine* 2015; **34**: 2781-2793.
- Loke YK, Mattishent K. If nothing happens, is everything all right? Distinguishing genuine reassurance from a false sense of security. *CMAJ: Canadian Medical Association Journal* 2015; **187**: 15-16.
- Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. *BMJ* 2014; **349**: g6501.
- Schroll JB, Penninga EI, Gøtzsche PC. Assessment of Adverse Events in Protocols, Clinical Study Reports, and Published Papers of Trials of Orlistat: A Document Analysis. *PLoS Medicine* 2016; **13**: e1002101.
- Smith PG, Morrow RH, Ross DA. *Outcome measures and case definition in: Field Trials of Health Interventions: A Toolbox*. Smith PG, Morrow RH, Ross DA, editors. Oxford (UK): Oxford University Press; 2015.
- Tang E, Ravaud P, Riveros C, Perrodeau E, Dechartres A. Comparison of serious adverse events posted at ClinicalTrials.gov and published in corresponding journal articles. *BMC Medicine* 2015; **13**: 189.
- Viswanathan M, Berkman ND. Development of the RTI item bank on risk of bias and precision of observational studies. *Journal of Clinical Epidemiology* 2012; **65**: 163-178.
- Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, Moher D, Vohra S, PRISMA Harms Group. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016; **352**: i157.

Section 19.7