Evaluating Harms of Interventions - Let's Start at the Very Beginning

Tianjing Li, MD, MHS, PhD
Associate Professor
Department of Ophthalmology
School of Medicine
University of Colorado Anschutz Medical Campus

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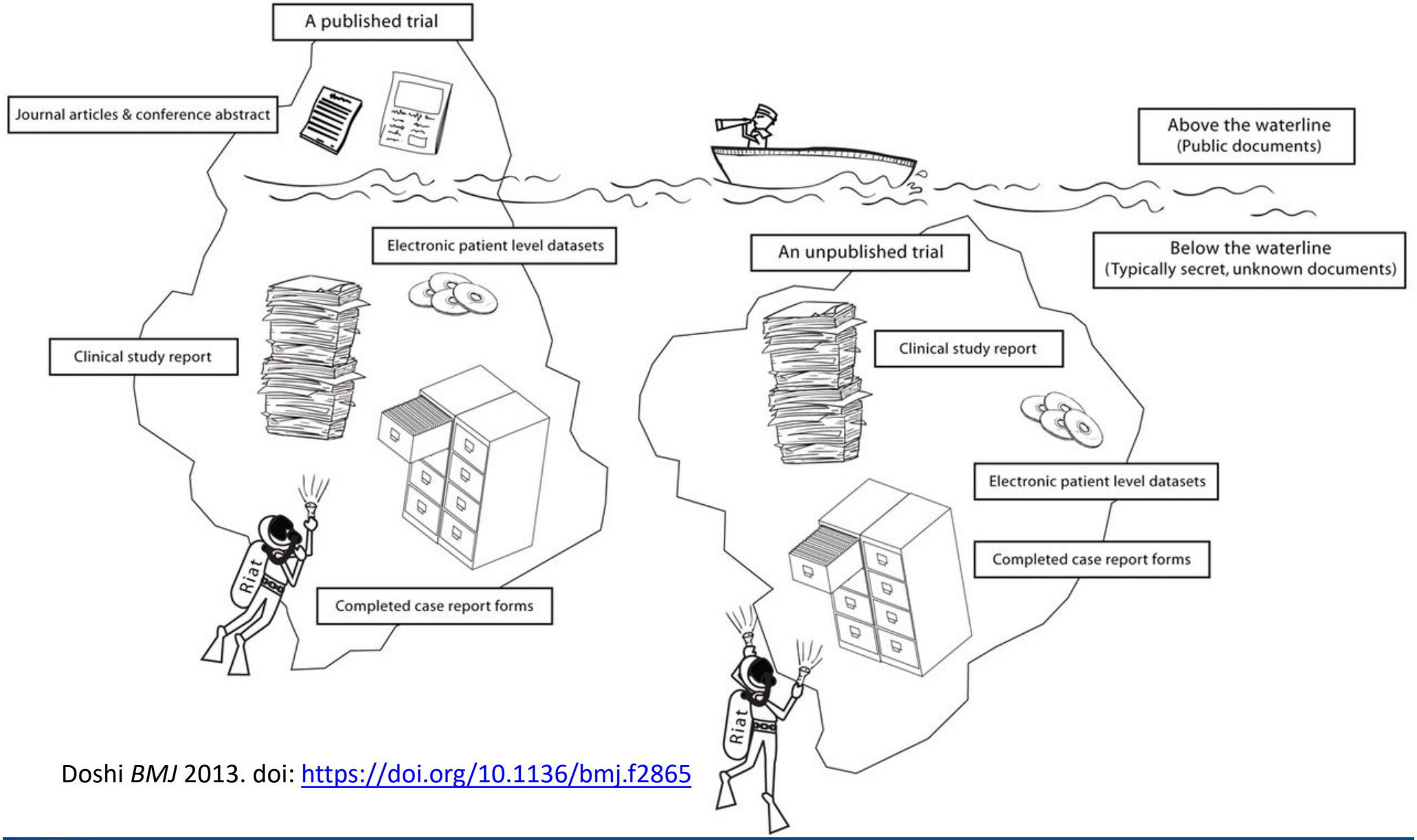
Locating information about clinical trials



Doshi *BMJ* 2013. doi: https://doi.org/10.1136/bmj.f2865

Sources of clinical trial information

Public sources

- Journal article
- Trial registration (e.g., ClinicalTrials.gov)
- Information from regulators (e.g., FDA approval packages)
- Short reports (e.g., conference abstracts)

Non-public (hidden) sources

- Clinical study report (CSR)
- Individual participant data (IPD)
- Other data (e.g., grant proposal, IRB submission, case report forms, memos and emails)

MUDS design

Two case studies:

- Gabapentin for neuropathic pain
- Quetiapine for bipolar depression

Goals: comparing data sources

- Study characteristics
  - (1) Participants and interventions
  - (2) Methods (risk of bias)
- Outcomes and results
  - (3) Outcomes and results reported across sources
  - (4) Impact of differences on meta-analyses
  - **(5) Adverse events reported across sources**

Results for gabapentin trials

21 trials, 81 unique sources

Public sources (n=69 sources)

- 26 articles
- 20 conference abstracts
- 5 registry entries
- 2 FDA reports
- 16 “other” reports

Non-public sources (n=12 sources)

- 6 CSRs
- 6 IPD (without codebooks)

What is an adverse event (AE)?

"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment."

ICH Harmonised Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. 1994.

Collecting AEs in trials

BENEFITS & SYSTEMATIC AEs

- Measured systematically for all participants
- Active ascertainment
- Predefined for formal recording and statistical analysis

Have you had any pain in the past 30 days?

NON SYSTEMATIC AEs

- Usually spontaneous reporting by participants or their doctors
- Passive ascertainment
- Selected based on ??

Have you noticed any symptoms in the past 30 days?

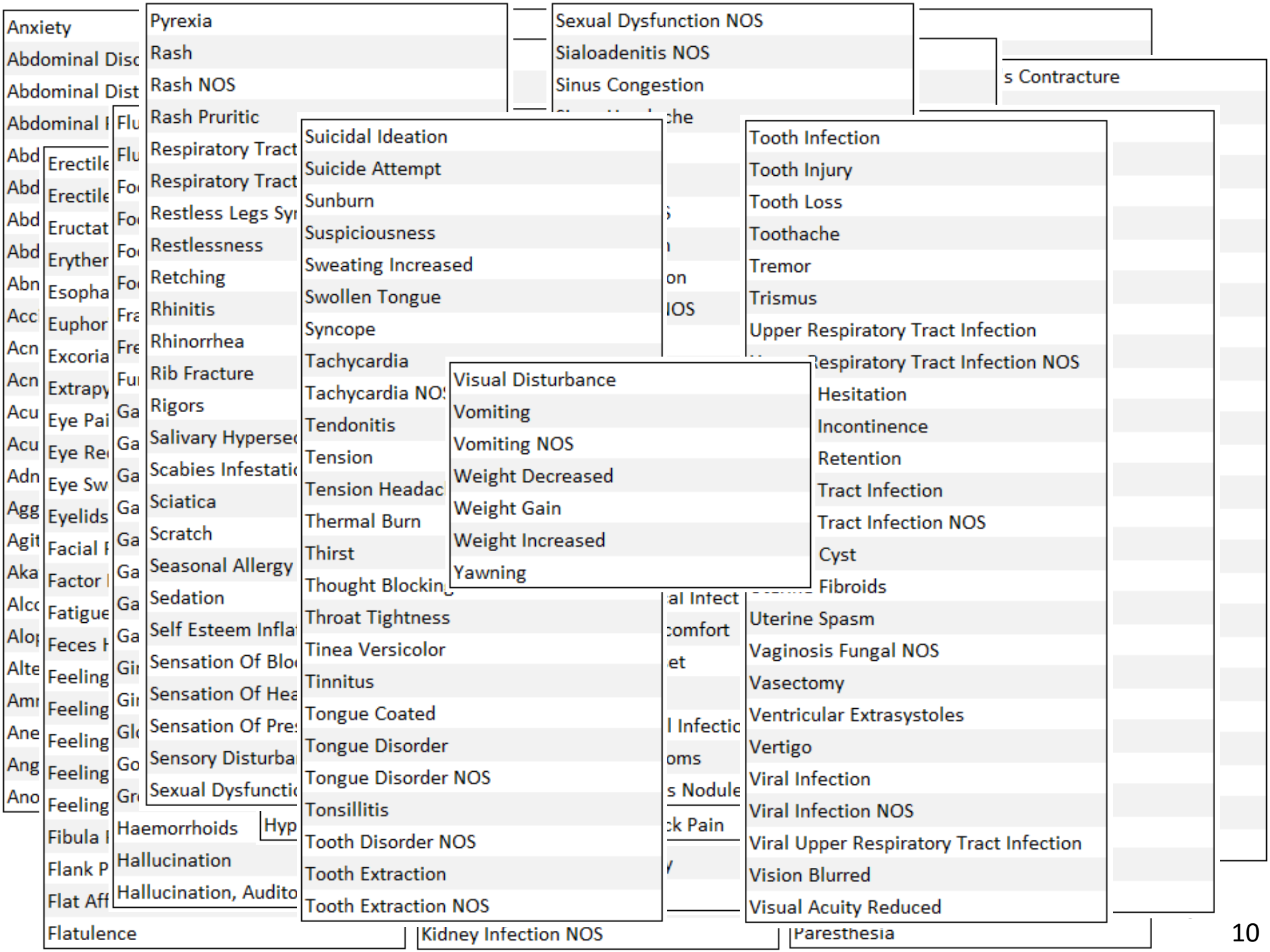
Mayo-Wilson & Fusco *JCE* 2019. doi: 10.1016/j.jclinepi.2019.04.022.
Mayo-Wilson & Fusco *JCE* 2019. doi: 10.1016/j.jclinepi.2019.04.020.

Problem 1. Systematic AEs are underreported like benefits

- **Hidden:** most systematic AEs and associated results were not in the public domain.
- **Inconsistent:** trials of the same intervention for the same health problem did not collect and report the same systematic AEs.
- **Distorted:** by changing the outcome definition, a drug could be harmful or harmless.

Mayo-Wilson & Fusco *JCE* 2019. doi: 10.1016/j.jclinepi.2019.04.022.

Problem 2. Non-systematic AEs are a mess and *rarely mentioned* publicly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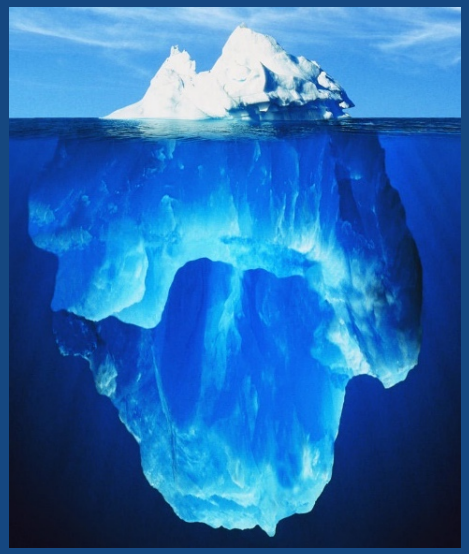
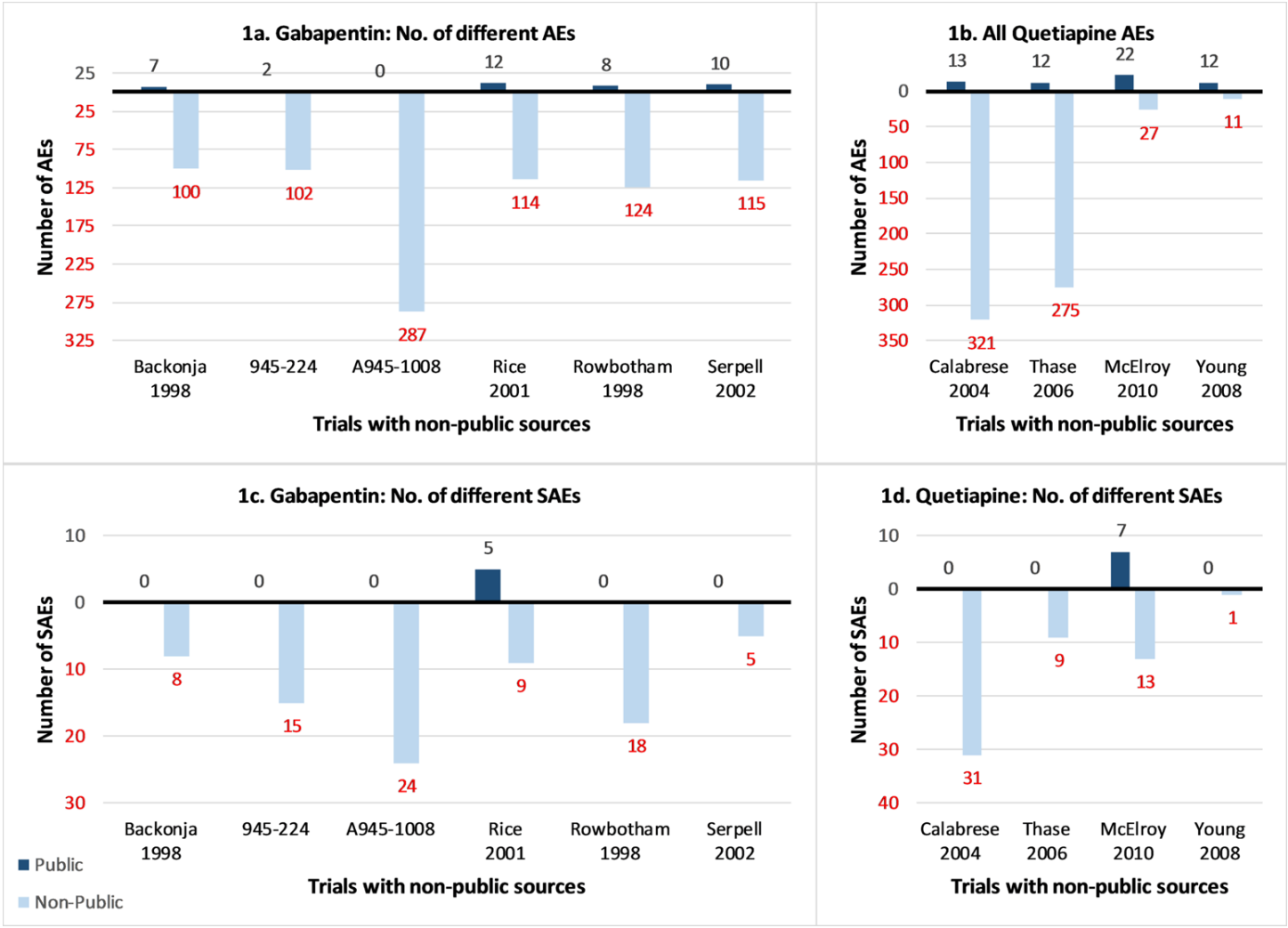


Even serious AEs are underreported

Neglected, restricted, distorted, and silenced



Mayo-Wilson & Fusco *JCE* 2019. doi: 10.1016/j.jclinepi.2019.04.020.

Problem 3. AEs are reported based on selection criteria

Reporting thresholds may be different across sources – even for the same trial

(1) Snapshot

Table 3. Adverse Reactions that Occurred in 2% or more of ARISTADA-Treated Patients and at Greater Incidence than in the Placebo-Treated Patients

(2) Prescribing information ("drug label")

ADVERSE REACTIONS

Most commonly observed adverse reaction with ARISTADA (incidence ≥5% and at least twice that for placebo) was akathisia (6.1).

(3) Trial registration (NCT01469039)

Frequency Threshold

Threshold above which other adverse events are reported	5%

(4) Journal article (Meltzer *et al.*, 2016)

Treatment-emergent adverse events occurring in ≥2% of patients in the aripiprazole lauroxil treatment groups are reported in Table 2. The most common TEAEs occurring in >5% of patients in the aripiprazole lauroxil groups were insomnia, akathisia, headache, and anxiety. Akathisia was the only TEAE with an incidence of ≥5% in each aripiprazole lauroxil group that was at least twice the rate of placebo (11.6%, 11.5%, and 4.3%). The majority (>75%) of all akathisia episodes occurred before the second injection,

Table 2. Treatment-Emergent Adverse Events (TEAEs) Occurring in ≥2% of Aripiprazole Lauroxil–Treated Patients, Safety Population

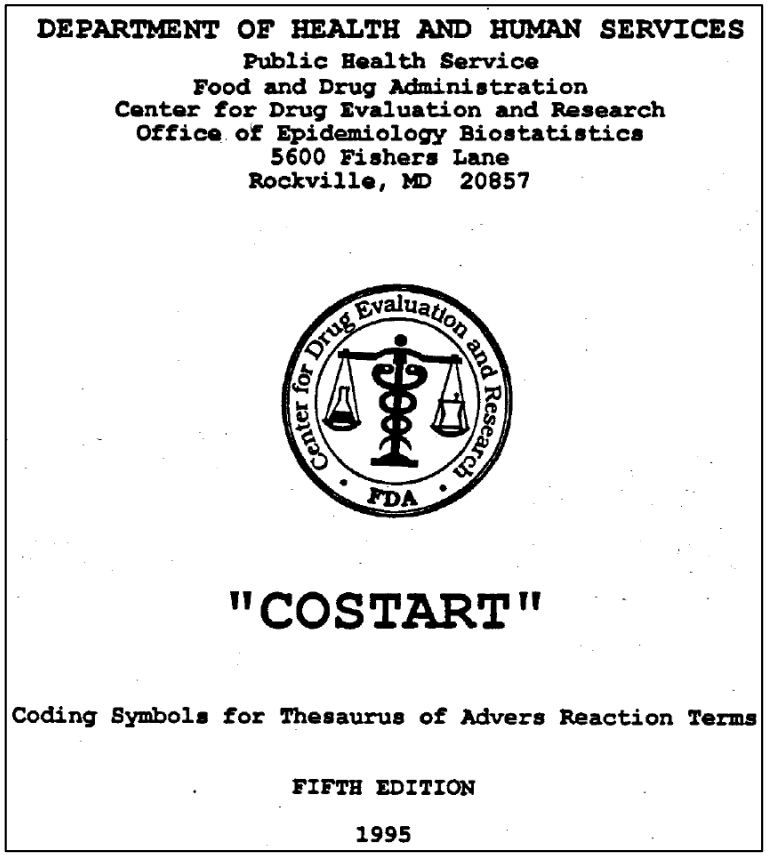
	Aripiprazole Lauroxil		
Preferred Term (%)	441 mg (n=207)	882 mg (n=208)	Placebo (n=207)
Any TEAE	58.9	57.2	62.3
Insomnia	9.7	12.0	11.6
Akathisia	11.6	11.5	4.3

Slide courtesy of Evan Mayo-Wilson of the MUDS study

Problem 4. Implications of grouping AEs

Non-systematic

AEs can be organized and "grouped" for analysis



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Epidemiology Biostatistics
5600 Fishers Lane
Rockville, MD 20857

"COSTART"

Coding Symbols for Thesaurus of Advers Reaction Terms

FIFTH EDITION

1995

WBB PtC Contact FAQs Downloads

MedDRA Medical Dictionary for Regulatory Activities

Search the site

Welcome to MedDRA

In the late 1990s, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed MedDRA, a rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans... (more)

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MedDRA Training

14 November 2018 London, United Kingdom Face-to-Face Training - Coding with MedDRA class

15 November 2018 London, United Kingdom Face-to-Face Training - MedDRA: Safety Data Analysis and SMQs

20 November 2018 Lyon, France Face-to-Face Training - Coding with MedDRA

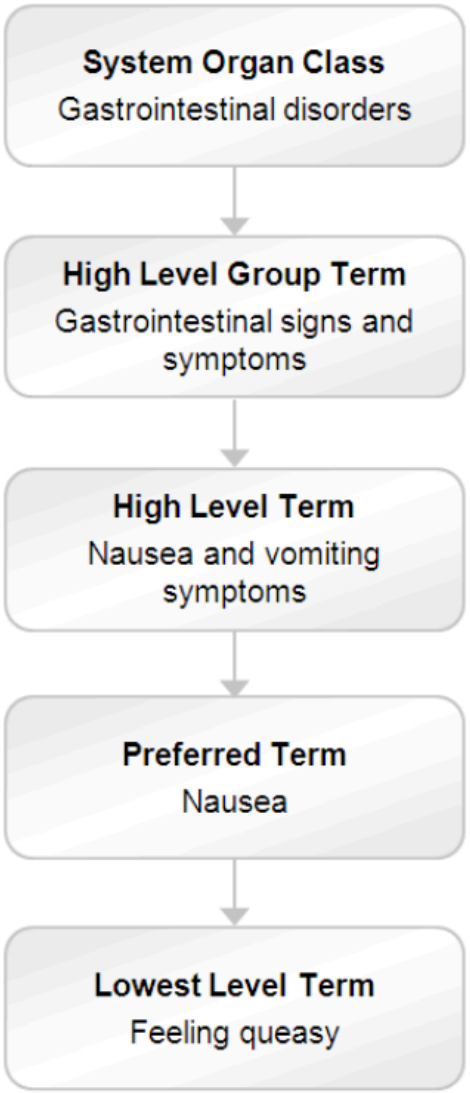
21 November 2018 Lyon, France Face-to-Face Training - MedDRA: Safety Data Analysis and SMQs

U.S. Food and Drug Administration (FDA). Coding Symbols for a Thesaurus of Adverse Reaction Terms 5th Ed. 1995. https://bioportal.bioontology.org/ontologies/COSTART

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Introductory Guide MedDRA Version 17.0. 2014. https://www.meddra.org/sites/default/files/guidance/file/intguide_17_0_english.pdf

Non-systematic

AEs can be organized and "grouped" for analysis



27 System Organ Classes

MedDRA

- Blood and lymphatic system disorders
- Cardiac disorders
- Congenital, familial and genetic disorders
- Ear and labyrinth disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Hepatobiliary disorders
- Immune system disorders
- Infections and infestations
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders

Can we reliably assess harms of interventions without IPD or CSRs? - Junk in, junk out

Table 3.—Most Frequently Reported Adverse Events*

Preferred Terms	Gabapentin (n = 84)	Placebo (n = 81)	*P* Value†
Dizziness	20 (23.8)	4 (4.9)	<.001
Somnolence	19 (22.6)	5 (6.2)	.004
Headache	9 (10.7)	3 (3.7)	.13
Diarrhea	9 (10.7)	7 (8.6)	.79
Confusion	7 (8.3)	1 (1.2)	.06
Nausea	7 (8.3)	4 (4.9)	.54

*Data are number (percentage).
†Data were calculated using the Fisher exact test.

- Collected systematically or non-systematically?
- Grouped or not?
- Reporting threshold?
- Duration? Severity? Serious?
- Definitions consistent across sites within trials and across trials?
- Unit of analysis?

Conclusions

- AEs are under- and selectively-reported.
- Inconsistent outcome definition, poor ascertainment, and suboptimal reporting are problematic for systematic reviews relay exclusively on published, aggregated data.
- IPD and CSRs should be considered when the available published or other aggregated data do not permit a good quality review, especially for understanding harms of intervention.
- Observational data and big data solution?

Li *Trials* 2018. https://doi.org/10.1186/s13063-018-2888-9

Multiple Data Sources (MUDS) Team

Steering Committee
Dickersin, Kay (KD)
Mayo-Wilson, Evan (EMW)
Li, Tianjing (TL)
Fusco, Nicole (NF)
Tolbert, Elizabeth (ET)

Conception & design, funding
Doshi, Peter (PD)
Vedula, Swaroop (SV)
KD, TL

Protocol development, study implementation
Haythornthwaite, Jennifer (JH)
Payne, Jennifer (JP)
Cowley, Terrie (TC)
Singh, Sonal (SS)
EMW, KD, TL, NF, ET, JE

Data acquisition
Rosman, Lori (LR)
Twose, Claire (CT)
Bertizzolo, Lorenzo (LB)
Ehmsen, Jeffery (JE)
Gresham, Gillian (GG)
Heyward, James (JHe)
Lock, Diana (DL)
Suarez-Cuervo, Catalina (CS)
KD, NF, EMW, TL, SV

Analysis and interpretation of data
Hong, Hwanhee (HH)
Canner, Joseph (JC)
Guo, Nan (NG)
Elizabeth Stuart (ES)
NF, EMW, KD, TL

Risk of bias figures
Elise Diard

Systematic Review Data Repository
Lau, Joseph (JL)
Smith, Bryant (BS)
Jap, Jens (JJ)

Ancillary studies
Golozar, Asieh (AG)
Hutfless, Susie (SH)
EMW, KD, TC

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