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

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Locating information about clinical trials

Doshi *BMJ* 2013. doi: [https://doi.org/10.1136/bmj.f2865](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.”

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?

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.

Problem 2. Non-systematic AEs are a mess and *rarely mentioned* publicly
Neglected, restricted, distorted, and silenced

Even serious AEs are underreported

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 \( \geq 5\% \) 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)

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

<table>
<thead>
<tr>
<th>Preferred Term (%)</th>
<th>441 mg (n = 207)</th>
<th>882 mg (n = 208)</th>
<th>Placebo (n = 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>58.9</td>
<td>57.2</td>
<td>62.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9.7</td>
<td>12.0</td>
<td>11.6</td>
</tr>
<tr>
<td>Akathisia</td>
<td>11.6</td>
<td>11.5</td>
<td>4.3</td>
</tr>
</tbody>
</table>

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.
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27 System Organ Classes
- 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**

<table>
<thead>
<tr>
<th>Preferred Terms</th>
<th>Gabapentin (n = 84)</th>
<th>Placebo (n = 81)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>20 (23.8)</td>
<td>4 (4.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Somnolence</td>
<td>19 (22.6)</td>
<td>5 (6.2)</td>
<td>.004</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (10.7)</td>
<td>3 (3.7)</td>
<td>.13</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (10.7)</td>
<td>7 (8.6)</td>
<td>.79</td>
</tr>
<tr>
<td>Confusion</td>
<td>7 (8.3)</td>
<td>1 (1.2)</td>
<td>.06</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (8.3)</td>
<td>4 (4.9)</td>
<td>.54</td>
</tr>
</tbody>
</table>

*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?

Multiple Data Sources (MUDS) Team

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