Data Quality and Methodological Transparency in Pharmacovigilance

Ruwen Böhm, Christian Eggeling, Tsvetelin Polomski, Daniela Heidebrecht, Leocadie von Hehn, Thomas Herdegen, Hans-Joachim Klein

ruwen.boehm@pharmakologie.uni-kiel.de

Institut für Experimentelle und Klinische Pharmakologie
UKSH, Campus Kiel

Wissen schafft Gesundheit

2015-03-11
Outline

• Why Pharmacovigilance?
• Cave-ats
• Conclusions
Pharmacovigilance to answer questions from clinics

• Can orlistat cause flue???

  ➔ Böhm R., Herdegen Th. [Risk of infection and liver damage by orlistat. Dtsch Apoth Ztg 2009, 149(32), S. 3623]

• Is there a particular risk for hypoglycemia for certain sulfunylurea or glinide drugs?


• Is there a particular risk for Torsade de pointes after i.v. application of haloperidol?

  ➔ Poster #129 “Cardiototoxicity of intravenous haloperidol – an update”
More clinical applications: Poster #229

The heatmap indicates the severity of the outcome (red = mostly dead, violet = mostly other than dead or life-threatening)

- PROPORTIONAL REPORTING RATIO (PRR)
- CHI-SQUARE VALUE

Drugs:
- cisapride
- nilotinib
- citalopram
- clozapin
- nirolipid (subgroup of cisapride)
- nilotinib
- doxelode
- amiodarone
- methadone
- oxifloxacin
- citalopram
- mirtazapin
- atomoxetine
- moxifloxacin

Other points: ciprofloxacin, risperidone, olanzapine, quetiapine, furosemide, fluoxetine, venlafaxine, omeprazole, sertraline, lorazepam, clonazepam, escitalopram

The heatmap indicates the severity of the outcome (red = mostly dead, violet = mostly other than dead or life-threatening)

- which drug causes an adverse event?
- detection of drug-drug-interactions
Mining a new „big data“ source
(primarily U.S. FDA AERS pharmacovigilance data 1997-2015)

Figure 1.
PhV DMA research evolution described by volume of publications per year indexed in PubMed. 2011 volume is effectively larger due to delayed indexing.

Harpaz 2012
Non-clinical applications of pharmacovigilance

- Hospital administration:
  Purchase decisions for the pharmacy dept.
- Lawyers:
  Arguments for legal proceedings
- Investors, e.g., stock market:
  Bullish Vs. Bearish
- Webmasters:
  Traffic and thus ad revenue generation
Outline

- Why Pharmacovigilance?
- Cave-ats
- Conclusions
Mistakes in Pharmacovigilance

OpenVigil Cave-at document

All examples are based on FDA LAERS and FAERS from 2003-10-4 to 2012-12-31 (OpenVigil 1) or FDA LAERS data from 2003-10-4 to 2012-06-30 (OpenVigil 2), extracted prior to 2014-09-15. Figures may change during further development of software and data import filter.
Outline

• Why Pharmacovigilance?
• Cave-ats
  – Parsing drugnames
  – Handling multiplicates
  – Human and software errors
• Conclusions
COUMADIN (WARFARIN SODIUM)
COUMADIN (WARFARIN SODIUM)
WARFARIN
WARFARIN POTASSIUM
COUMADIN (WARFARIN SODIUM) (5 MILLIGRAM)
(WARFARIN SODIUM)
WARFARIN (WARFARIN /00014801/)

WARFARIN UNKNOWN
BRODIFACOUM (SUPERWARFARIN)
UNSPECIFIED BLOOD THINNING TABLETS
ANTIVITAMIN K ANTICOAGULANT
BLINDED: WARFARIN SODIUM
RIVAROXABAN 20MG OD OR WARFARIN OD (1, 2.5 OR 5MG)
Public drugname mappers

RxNorm

Enter a drugname:   Search RxNorm!

RIVAROXABAN 20MG OD OR WARFARIN OD (1, 2.5 OR 5MG)
→ rivaroxaban (100% score)

WARFARIN (BLINDED)
→ warfarin (100% score)

COUMADIN (WARFARIN SODIUM)
→ coumadin (100% score)
Spelling corrections

- Flomax® (tamsulosin) vs Volmax® (salbutamol)
- iodine vs Lodine® (etodolac)
- amrinone (USAN inamrinone) vs amiodarone
How does OpenVigil 2 handle drugnames?

- Only dosages and very few other (known) elements are discarded from the drugname
  → keywords like “blind” etc. are retained
- Only exact matches of the remaining elements; all matches must be non-contradictory
  → unknown elements let the mapping fail
- Restrictive spelling correction (validated internal list)

→ loss of 28% of records of low data quality

- manual drug mapping interface in OpenVigil 2
Outline

• Why Pharmacovigilance?
• Cave-ats
  – Parsing drugnames
  – Handling multiplicates
  – Human and software errors
• Conclusions
52 reports containing these drugs and adverse events in the FDA AERS data from 2008 → very strong signal for a putative ADR

Harpaz 2010, Harpaz 2012
## 52 Reports → 2 Cases

<table>
<thead>
<tr>
<th>ISR</th>
<th>CASENO</th>
<th>AGE</th>
<th>GNDR_COD</th>
<th>ISR</th>
<th>CASENO</th>
<th>AGE</th>
<th>GNDR_COD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5720314</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5870223</td>
<td>6606588</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>5725407</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5872822</td>
<td>6606588</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>5730698</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5875821</td>
<td>6606588</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>5733756</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5878262</td>
<td>6606588</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>5739400</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5887085</td>
<td>6606588</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>5745564</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5895043</td>
<td>6606588</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>5748300</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5907868</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5754359</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5908455</td>
<td>6779317</td>
<td>31</td>
<td>M</td>
</tr>
<tr>
<td>5761683</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5913038</td>
<td>6779317</td>
<td>31</td>
<td>M</td>
</tr>
<tr>
<td>5775505</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5915428</td>
<td>6779317</td>
<td>32</td>
<td>M</td>
</tr>
<tr>
<td>5779565</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5915614</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5792486</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5922981</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5798936</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5923020</td>
<td>6779317</td>
<td>31</td>
<td>M</td>
</tr>
<tr>
<td>5804940</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5924321</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5817165</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5929880</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5817165</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5929979</td>
<td>6779317</td>
<td>31</td>
<td>M</td>
</tr>
<tr>
<td>5823641</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5939203</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5827849</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5945356</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5831253</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5950910</td>
<td>6779317</td>
<td>31</td>
<td>M</td>
</tr>
<tr>
<td>5832879</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5952525</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5839127</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5955691</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5846900</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5967498</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5848843</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5969314</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
<tr>
<td>5853362</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5969706</td>
<td>6779317</td>
<td>31</td>
<td>M</td>
</tr>
<tr>
<td>5856680</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5971373</td>
<td>6779317</td>
<td>31</td>
<td>M</td>
</tr>
<tr>
<td>5860082</td>
<td>6606588</td>
<td>F</td>
<td></td>
<td>5974110</td>
<td>6606588</td>
<td>51</td>
<td>F</td>
</tr>
</tbody>
</table>

Harpaz 2010
How does OpenVigil 2 handle multiplicates

- Detection of multiplicates on report basis
- Output of FDA case_id for statistical analysis
Outline

• Why Pharmacovigilance?
• Cave-ats
  – Parsing drugnames
  – Handling multiplicates
  – Human and software errors
• Conclusions
Signal distortion by human and software errors

Table 2. Signal scores for warfarin-, aspirin- and clopidogrel-associated haematemesis.

<table>
<thead>
<tr>
<th>Statins</th>
<th>N</th>
<th>PRR (kai2)</th>
<th>ROR (95% two-sided CI)</th>
<th>IC (95% two-sided CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>268</td>
<td>1.991 (131.982)</td>
<td>2.006 (1.778, 2.234)*</td>
<td>0.985 (0.811, 1.158)*</td>
</tr>
<tr>
<td>Aspirin</td>
<td>332</td>
<td>6.469 (1525.210)*</td>
<td>6.566 (5.889, 7.244)*</td>
<td>2.661 (2.504, 2.818)*</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>235</td>
<td>2.254 (163.238)*</td>
<td>2.270 (1.995, 2.544)*</td>
<td>1.160 (0.975, 1.346)*</td>
</tr>
</tbody>
</table>

N: the number of co-occurrences; PRR: the proportional reporting ratio; ROR: the reporting odds ratio; IC: the information comp

OpenVigil 2 can find 162 reports (out of 140 unique cases) and calculates – based on the counting of reports – a PRR of 3.109 and a ROR of 3.122.

Sakaeda 2013
Re-calculation of Sakaeda 2013 – data source

<table>
<thead>
<tr>
<th>Data files and filtering</th>
<th>all reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>all files and 2003-12-31 &gt; FDA_DT &lt; 2010-01-01</td>
<td>2234986</td>
</tr>
<tr>
<td>all reports in these quarterly files</td>
<td>2234929</td>
</tr>
<tr>
<td>only these quarterly files and 2003-12-31 &gt; date &lt; 2010-01-01</td>
<td></td>
</tr>
<tr>
<td>FDA_DT</td>
<td>2234923</td>
</tr>
<tr>
<td>EVENT_DT</td>
<td>1655915</td>
</tr>
<tr>
<td>MFR_DT</td>
<td>2180288</td>
</tr>
<tr>
<td>FDA_DT minus data files</td>
<td>1805798</td>
</tr>
<tr>
<td>DEMO04Q1 till DEMO05Q2</td>
<td></td>
</tr>
<tr>
<td>Sakaeda 2013</td>
<td>2231029</td>
</tr>
<tr>
<td>raw line count (minus headers)</td>
<td>2234931</td>
</tr>
</tbody>
</table>

cf. OpenVigil tutorials
Re-calculation of Sakaeda 2013 – filtered reports

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>OpenVigil 1 GUI without DEMO data prior to 2005Q3</td>
<td>268, maybe more</td>
</tr>
<tr>
<td>OpenVigil 1 SQL without DEMO data prior to 2005Q3</td>
<td>256 reports, maybe more or less (for 212 individuals)</td>
</tr>
<tr>
<td>OpenVigil 1 SQL (full LAERS data)</td>
<td>413 (for 316 individuals according to CASENO, some less because of multiplicates)</td>
</tr>
<tr>
<td>OpenVigil 2 GUI</td>
<td>162 (for 140 individuals according to CASE)</td>
</tr>
<tr>
<td>Sakaeda 2013</td>
<td>268</td>
</tr>
</tbody>
</table>
Regulatory bodies

The U.S. (FDA) and Germany (BfArM) use a commercial software package:

„.. Source code for gps/mgps has never been made available..”

“…Oracle is not aware of any other implementation of MGPS that has been verified by running the same database through the two different programs….”

(William DuMouchel, PhD. Chief Statistical Scientist, Oracle Health Sciences, pers. comm. 2014)
Figure 1: Trial profile
... good pharmacovigilance practice!
Outline

• Why Pharmacovigilance?
• Cave-ats
• Conclusions
Conclusions

• Publications should include comprehensive **material and methods** section which allows reproduction of the result section

• Where appropriate, datasets or algorithms should be included in the **supplementary material**

• This way, the scientific community can comment on the results (**no „black box“!**) and help to improve the analysis method