Temporal synchrony between drug dispensings and adverse drug events?

The example of statins & rhabdomyolysis and metamizole or clozapine & agranulocytosis

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Introduction and Background

- Spontaneous reports of adverse events (AE) → detection of unknown adverse drug reactions (ADRs)
- Main issue: Size of population at risk (i.e. exposed to the drug = the denominator) is unknown!
- Can dispensing data help in the detection / validation of safety signals?
Aims and Objectives

- To combine data on spontaneous AE reports and dispensing data
- To develop a new method of signal validation by employing temporal synchrony analysis
- To test the new method for model drugs as a proof of principle

Is the amount of drug dispensed in temporal synchrony with spontaneous AE reports?

Registered: International Clinical Trials Registry Platform DRKS00011398
http://apps.who.int/trialsearch/
Method - Data collection

Drugs and events

- Statins: rhabdomyolysis
- Metamizole and clozapine: agranulocytosis

Data collection

- Aggregated monthly adverse event data: German 'ADR database' of spontaneous reports of the Federal Institute for Drugs and Medical Devices

- Aggregated monthly dispensing data: Pharmacy claims data, extrapolated from > 80% of community pharmacies at the expense of the German Statutory Health Insurance Funds (≈90% of population) from the DAPI database

- 2005 to 2015
Results - Temporal Synchrony - Statins I

Dispensings of statins in outpatient care and number of spontaneous reports of statin-associated rhabdomyolysis from 2005-2015

Values per year
(Incidence rate: 0.14 per 10,000 person-years)

Values per month

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Results - Temporal Synchrony - Statins II

- 1 month

Drug dispensing [DDD]

Synchronous peaks

'peaks' = number of common maxima + minima / number of all maxima + minima

'peaks' = 5 / 13
= 0.38
Results - Statins

Conditions:
Statin mono preparations (simvastatin, lovastatin, rosvastatin, atorvastatin, pravastatin, fluvastatin)

Offset between dispensings and AE: + 1 month

Smoothing by moving average over two months

Monte Carlo randomization → p-value

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No significant synchrony
Results - Metamizole, Clozapine

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No significant synchrony

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Metamizole

Number of reports vs. Mio Defined Daily Doses (DDD)

(Incidence rate: 1.4 per 10,000 person-years)

Clozapine

Number of reports vs. Mio Defined Daily Doses (DDD)

(Incidence rate: 2.1 per 10,000 person-years)
Conclusions

Method appropriate?
- Analysis settings for temporal synchrony analysis need to be adapted
  - Different offset
  - Different granularity of data (other than months)
  - Spreading the dispensed drugs to a calculated therapy duration

Use cases appropriate?
- Selection of other known dose / time-dependent ADRs

Patient data required?
- Factors other than dosage / therapy duration, e.g. genetic variations (e.g. SLCO1B1 or several HLA-genotypes) leading to differences in vulnerability of subpopulations
Thank you very much for your attention!