Temporal synchrony between drug dispensings and adverse drug events? The example of statins & rhabdomyolysis and metamizole or clozapine & agranulocytosis

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Background and Objective

- Spontaneous reports of adverse events (AE) have the potential to detect unknown and to estimate the frequency of adverse drug reactions (ADRs), among others.
- Main issue: Size of population at risk (= denominator) is unknown!
- A novel method combining spontaneous AE reports and drug dispensing data by employing temporal synchrony analysis may help to detect signals in pharmacovigilance datasets.
- The method was tested for model drugs as a proof of principle.

Method

Drugs and events

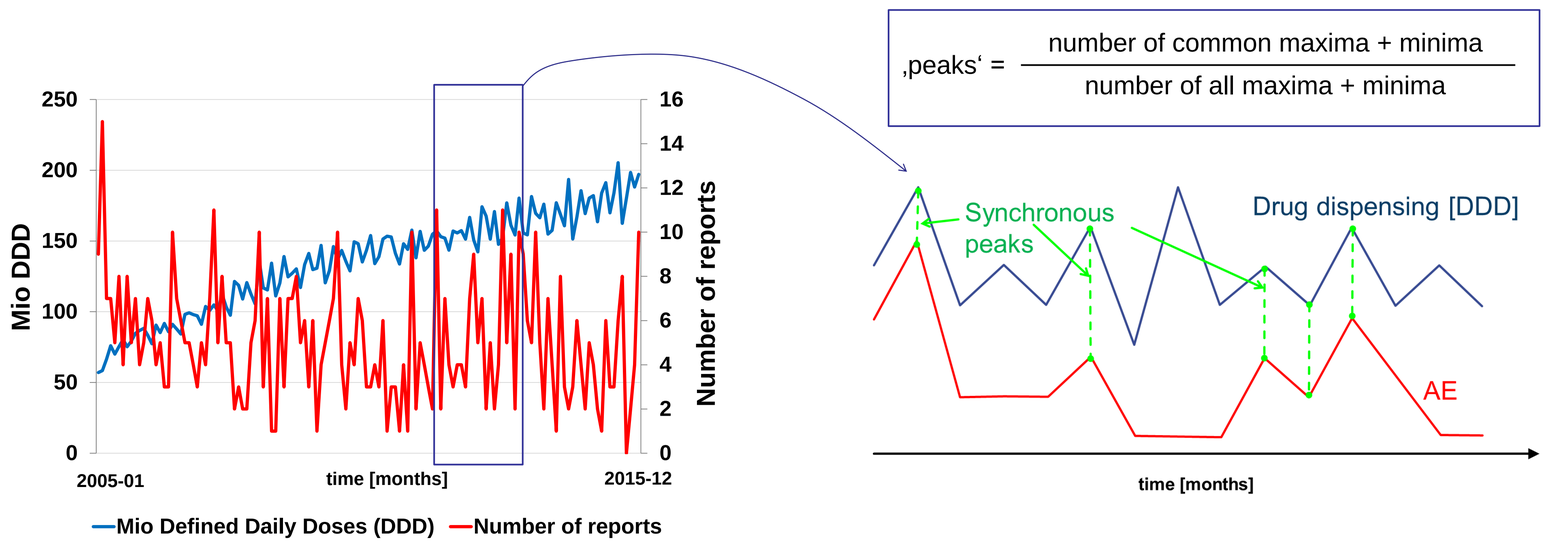
- Statins (mono preparations only; simvastatin, lovastatin, rosuvastatin, atorvastatin, pravastatin, fluvastatin): rhabdomyolysis
- Metamizole and clozapine: agranulocytosis

Data collection

- Aggregated monthly adverse event data: German ‚ADR database' of the Federal Institute for Drugs and Medical Devices
- Aggregated monthly dispensing data as defined daily doses (DDD), extrapolated from pharmacy claims data of the DAPI database from > 80% community pharmacies at the expense of the German Statutory Health Insurance Funds (≈ 90% of the German population)
- Time period: 2005 to 2015

Temporal synchrony analyses (see figures below)

1. Set offset between date of AE reports and dispensings by -1 month
2. Smoothing dispensing and AE curves by moving average (actual and following month)
3. Count synchronous peaks of dispensings and AE, report as ratio to overall peaks (= ‚peaks')
4. Testing for statistical significance by Monte Carlo randomization, statistical significance: $p \leq 0.05$

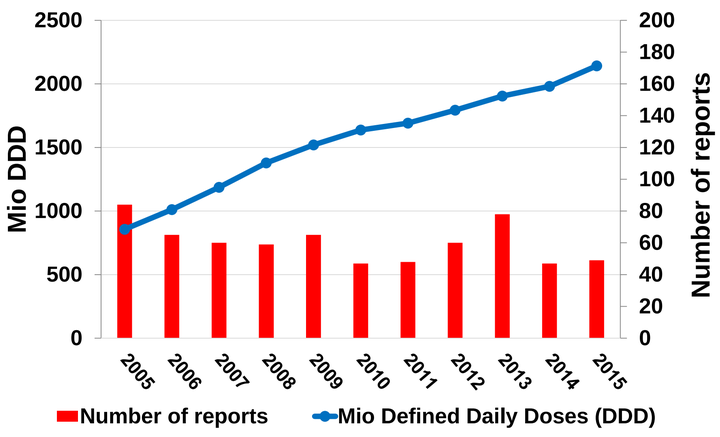


Results

Statins

‚peaks'	p-value
0.31	0.64

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

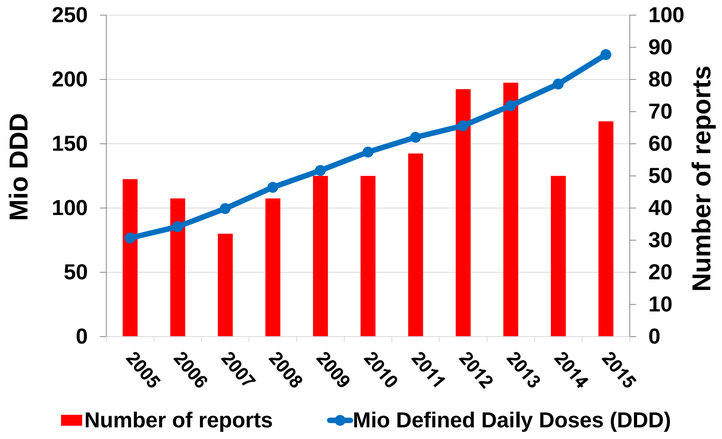


Incidence rate: 0.14 per 10,000 person-years

Metamizole

‚peaks'	p-value
0.36	0.28

Dispensings of **metamizole** in outpatient care and number of spontaneous reports of metamizole-associated **agranulocytosis** from 2005-2015

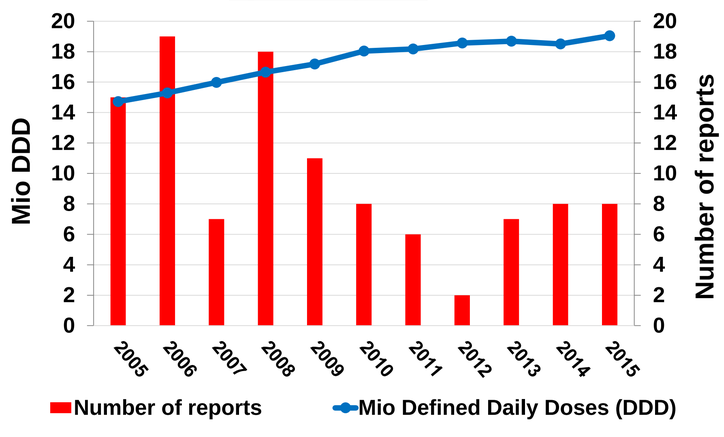


Incidence rate: 1.4 per 10,000 person-years

Clozapine

‚peaks'	p-value
0.19	0.99

Dispensings of **clozapine** in outpatient care and number of spontaneous reports of clozapine-associated **agranulocytosis** from 2005-2015



Incidence rate: 2.1 per 10,000 person-years

- No significant temporal synchrony detected for all three drugs with the method and the chosen parameters.

Discussion and Conclusions

- No temporal synchrony between dispensing data and AE reports could be found for statins and rhabdomyolysis and for metamizole or clozapine and agranulocytosis using the parameter settings applied.
- It remains to be investigated whether adaptation of the method (e. g. varying time offset between dispensings and AE, different granularity for time scale) or selection of other known dose- / time-dependent ADRs would lead to different results.
- Limitations such as underreporting of AE, unknown and variable time lag between drug dispensing, time of ingestion, development of AE, and reporting the AE and the influence of patient-related factors e. g. genetic variations, could be a general issue for temporal synchrony analyses.

References:

Study registered at International Clinical Trials Registry Platform: DRKS00011398, http://apps.who.int/trialsearch/

Conflict of interest:

None declared.

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