Pharmacovigilance applied to clinical neurology and psychiatry

2. Kiel Neuroscience Day

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Background

Clinical routine often requires the information which drug in the medication list of a patient is most likely evoking an adverse event (AE) or which drug of a drug class to prefer for an individual patient. Data for this usually derive from the pharmkokinetic and -dynamic profile of a drug that is assessed during preclinical development and clinical trials. However, rare adverse events are not detected during clinical trials, and the potential targets as well as the metabolic pathways are only incompletely known. This is why spontaneous reporting was introduced to sample reports of unexpected behavior of drugs. The resulting pharmacovigilance data are not suited either for calculating absolute risks or establishing causal relationships between one (or more) drug(s) and AE. Instead the data can be analyzed to generate hypotheses and test them at bench or bedside.
The pharmacovigilance data analysis tool **OpenVigil FDA** (**openvigil.sf.net**) offers unique analysis options to address the clinical questions mentioned above. We present two analysis modes that can help deciding in the situations mentioned above.

Reverse Disproportionality Analysis

Any new aggreviation of the patient's condition might be due to the pharmacologic treatment. Assuming that, pharmacovigilance data can be used in addition to expert opinions, reviewing the Summaries of Product Characteristics (SoPC, germ. Fachinformationen) or certain databases like SIDER (http://sideeffects.embl.de) which are all influenced by commercial interests and/or intentional overrepresentation of events to avoid legal proceedings.
The first screenshot shows how to compare the occurrence of a certain adverse event with each drug of the current medication using the graphical user interface of OpenVigilFDA.
The second one displays a table with counts of occurrence of the drug-event-combination (DE), the drug total (D), and event total (E). This can be used to calculate ratios and compare risks. This may aid in deciding which drug to discontinue first (visualized in last figure).

Step 2: Enter the new adverse event and the medication list of the patient!

As result, you will get a list (horiz. table) of the frequency of reports for this adverse event and each drug in the input list. This allows you to compare them and select those **most likely being associated with the newly occuring adverse event** (e.g., selection by highest PRR value or highest percentage DE/D).

Adverse event (MedDRA preferred term):	RASH
Current medication list (openFDA substance_name):	
Drug #0	GABAPENTIN
Drug #1	fentanyl
Drug #2	citalopram
Drug #3	mirtazapine
Drug #4	ondansetron
Drug #5	
Drug #6	
Drug #7	
Drug #8	
Drug #9	

***Open Vigil* FDA analysis of the drug in a list being most likely associated with an event 'RASH'**

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Term	Count
Total number of reports with event RASH	97817
Percentage this event of all events	1.96126
All reports (all events/drugs) (total)	4987454

Table of measures of disproportionality for each drug and the specified adverse event:
Interpretation: Large RRR values indicate overproportional reporting of this reaction for this drug. Consider stopping this drug first.

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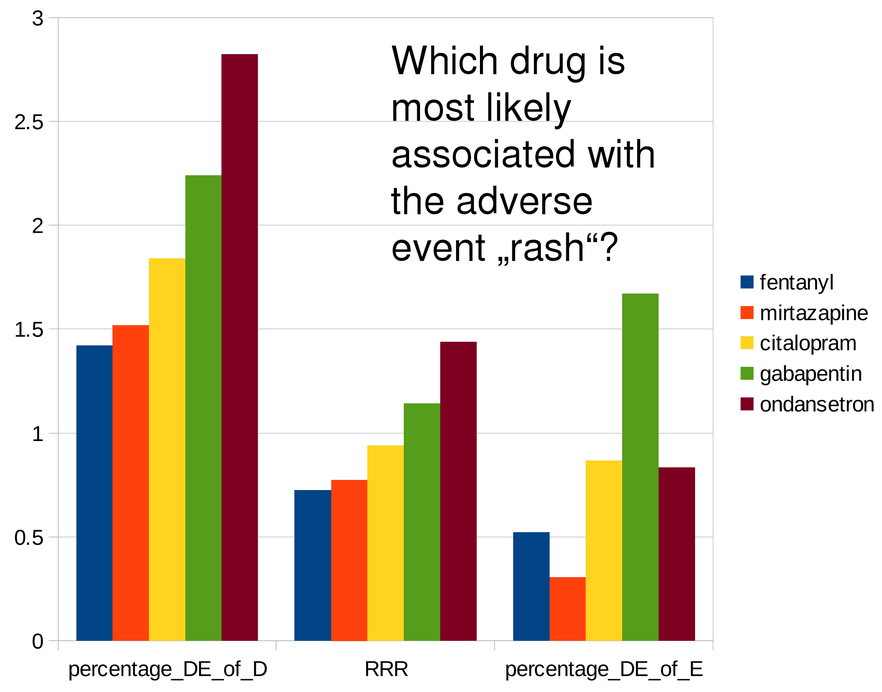
substance_name	DE	D	percentage_DE_of_D	RRR	percentage_DE_of_E
GABAPENTIN	1634	72954	2.23977	1.142	1.67047
fentanyl	511	35980	1.42023	0.72414	0.5224
citalopram	849	46136	1.84021	0.93828	0.86795
mirtazapine	299	19694	1.51823	0.77411	0.30567
ondansetron	817	28936	2.82347	1.43962	0.83523

Query execution time is 8.45 seconds.



AE-profiles of drugs of same drug class

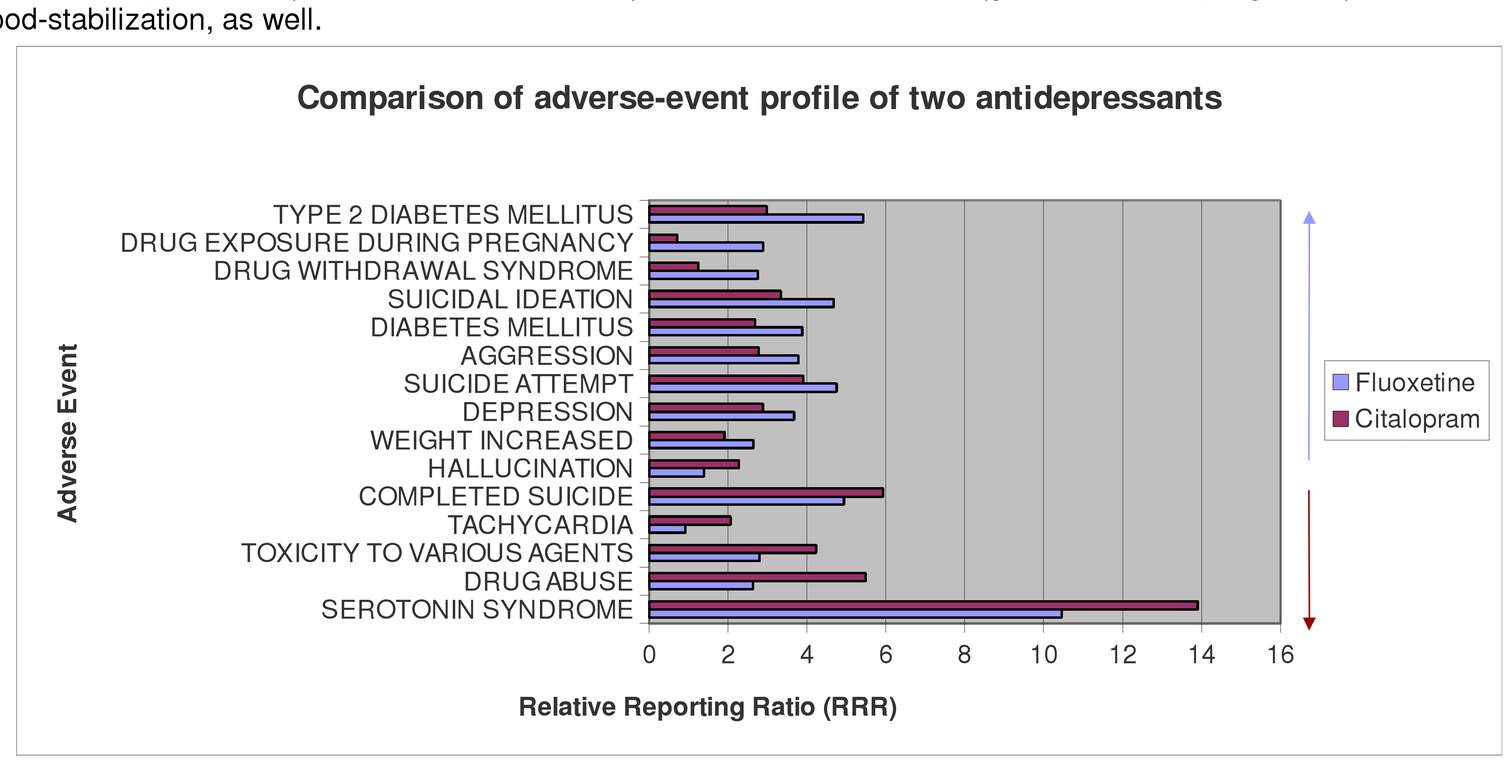
OpenVigilFDA can aid in answering a different question: Which one of two drugs of the same or similar drug class should be preferred, either because of a general lower risk of severe adverse events or the absence or lower risk of certain adverse events which are unacceptable for an individual patient?
Two analyses were carried out (cf. screenshots below) to compare two antidepressants (fluoxetine and citalopram) and two anticonvulsants (gabapentin and pregabalin), the latters being incresingly used for other indications like pain and mood-stabilization, as well.

The resulting tables can be visualized in a spreadsheet software to compare the most extreme differences in their adverse event-profile (e.g., relative reporting ratio (RRR) or percentage of the occurences of drug-event compared to drug total (DE/D)).

Interpretation:

The risk of an aggravation of the depressive episode with suicide attempts appears higher for fluoxetine as compared to citalopram. On the other hand, drug abuse and serotonin syndrome seem more frequent with citalopram.

Gabapentin is predominantly associated with neuro-psychiatric adverse events like neuropathy, suicide, depression, while pregabalin is overproportionally reported for the adverse event weight increased.



Step 2: Enter two drugnames for comparison and interaction-check!

As result, you will get a list (horiz. table) of the frequency of reports for a certain adverse event and for either one of the drugs and their combination. This allows you to compare similar drugs (e.g., same drugclass) for marked **differences in their adverse-event-profile** or to detect possible synergistic or antagonistic effects, i.e., **drug-drug-interactions**, on these adverse events.

Drug 1	GABAPENTIN
Drug 2	PREGABALIN

***Open Vigil* FDA analysis of drug interactions and the adverse event profile of two drugs 'GABAPENTIN' and 'PREGABALIN'**

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number of reports [results.term]	value [results.value]
GABAPENTIN alone *(with second drug)*	68364 *(72954)*
PREGABALIN alone *(with first drug)*	72745 *(77335)*
All reports for both drugs simultanously	4590
Total current number of reports in database	4987454

Table of adverse event list for both drugs containing 80 entries:
Interpretation: Large delta-values indicate differences between each of the both drugs (safety comparison) or the drugs used without each other and their combination (DDI-search).

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event	only_GABAPENTIN	only_PREGABALIN	both_drugs	GABAPENTIN_rrr	PREGABALIN_rrr	delta_rrr12	both_rrr	delta_both_rrr	event_total	GABAPENTIN_percent	PREGABALIN_percent	delta_1_vs_2	both_percent	delta_both
DRUG INEFFECTIVE	5783	6113	1078	1.69866	1.68745	0.01121	4.71613	-3.02307	248370	8.45913	8.40333	0.0558	23.48584	-15.05461
PAIN	4298	6767	735	2.15544	3.18926	-1.03382	5.48999	-2.81764	145473	6.28693	9.30236	-3.01542	16.01307	-8.21843
NAUSEA	4239	3022	350	1.43255	0.95977	0.47278	1.76169	-0.56553	215876	6.20063	4.15424	2.04639	7.62527	-2.44784
FATIGUE	3513	2771	321	1.53615	1.13872	0.39743	2.09063	-0.7532	166838	5.13867	3.8092	1.32947	6.99346	-2.51953
DIZZINESS	3262	4998	483	1.67347	2.40965	-0.73618	3.69059	-1.64903	142206	4.77152	6.87058	-2.09906	10.52288	-4.70183
HEADACHE	3235	2604	264	1.45511	1.10075	0.35436	1.76865	-0.49072	162192	4.73202	3.57963	1.1524	5.75163	-1.59581
FALL	2967	2548	278	2.32863	1.87935	0.44928	3.2497	-1.14571	92954	4.34	3.50265	0.83736	6.05664	-2.13532
DEPRESSION	2955	1771	286	2.53636	1.42855	1.10781	3.65623	-1.67377	84996	4.32245	2.43453	1.88792	6.23094	-2.85245

***Open Vigil* FDA analysis of drug interactions and the adverse event profile of two drugs 'FLUOXETINE ' and 'CITALOPRAM '**

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number of reports [results.term]	value [results.value]
FLUOXETINE alone *(with second drug)*	41107 *(42174)*
CITALOPRAM alone *(with first drug)*	45069 *(46136)*
All reports for both drugs simultanously	1067
Total current number of reports in database	4987454

Table of adverse event list for both drugs containing 89 entries:
Interpretation: Large delta-values indicate differences between each of the both drugs (safety comparison) or the drugs used without each other and their combination (DDI-search).

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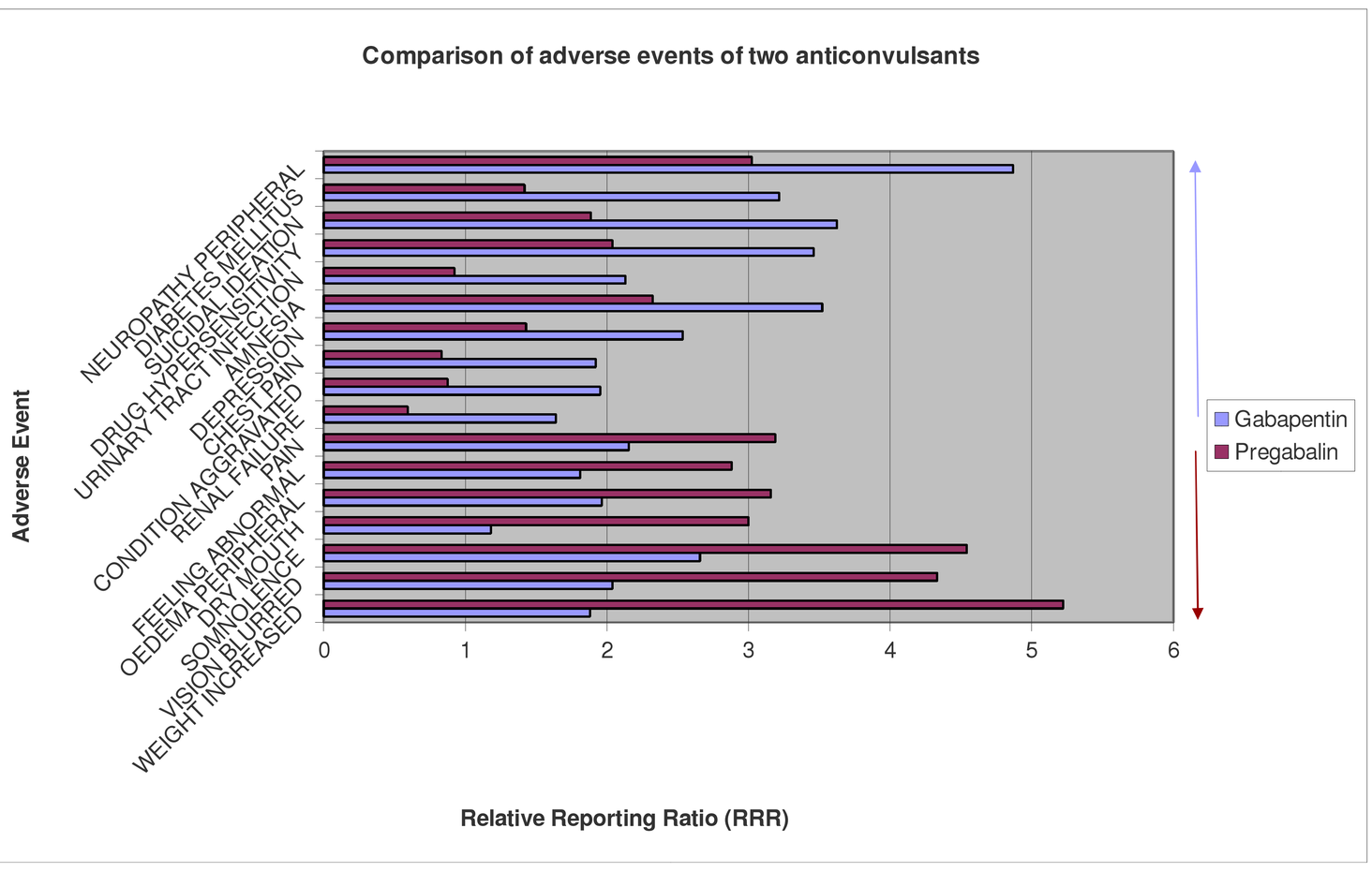
event	only_FLUOXETINE	only_CITALOPRAM	both_drugs	FLUOXETINE_rrr	CITALOPRAM_rrr	delta_rrr12	both_rrr	delta_both_rrr	event_total	FLUOXETINE_percent	CITALOPRAM_percent	delta_1_vs_2	both_percent	delta_both
DEPRESSION	2576	2218	131	3.67714	2.88778	0.78936	7.20423	-3.92177	84996	6.26657	4.92134	1.34523	12.27741	-6.68346
NAUSEA	2558	2595	75	1.43767	1.33025	0.10742	1.62395	-0.23999	215876	6.22278	5.75784	0.46495	7.02905	-1.03874
DRUG INEFFECTIVE	2248	1749	63	1.09815	0.77928	0.31887	1.18565	-0.24694	248370	5.46865	3.88072	1.58794	5.9044	-1.22972
ANXIETY	2061	2029	121	2.85559	2.56412	0.29147	6.45884	-3.74899	87568	5.01374	4.50199	0.51176	11.34021	-6.58234
FATIGUE	2023	2231	71	1.47117	1.47981	-0.00864	1.9892	-0.51371	166838	4.9213	4.95019	-0.02888	6.65417	-1.71843
HEADACHE	1936	1937	71	1.44824	1.3216	0.12664	2.04618	-0.66126	162192	4.70966	4.29785	0.41181	6.65417	-2.15041



All data refer to numbers of unique reports extracted with OpenVigil FDA v1.0rc4 from the FDA AERS data 2004Q1 to current.