Using the OpenVigil FDA pharmacovigilance tool to screen for new drug-drug-interactions among neuro- and psychotropic drugs

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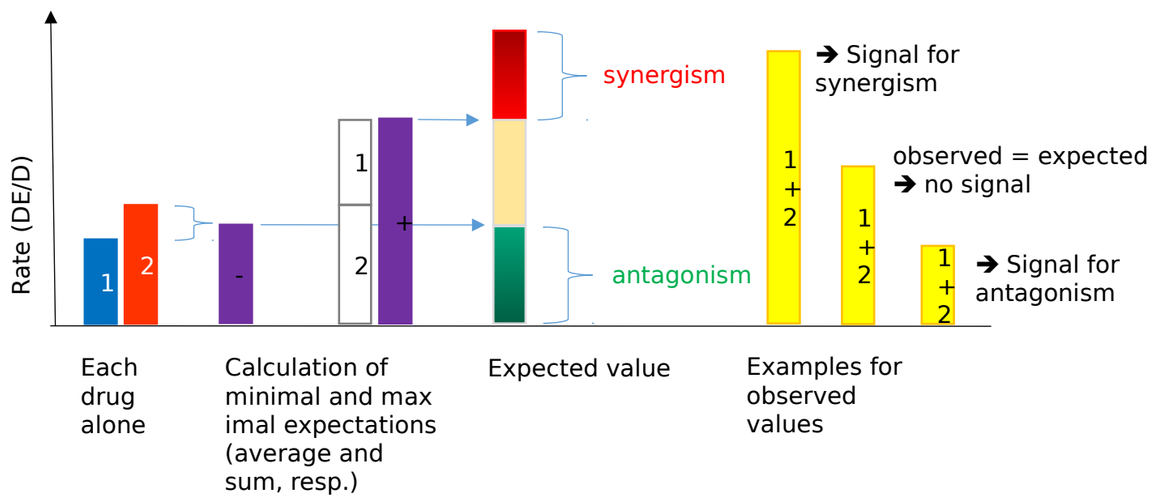
http://openvigil.sf.net

The Problem – „Does anyone have experience with this combination“?

Patients with psychiatric diseases are often prescribed several psychotropic drugs at once. Elderly patients – even if not receiving dedicated psychiatric treatment – are often prescribed drugs to regulate sleep and neuropathic pain which will also act on central nervous targets. Clinical trials are not suited to detect interactions since the trial design aims to show the efficacy of the study drug, not the safety of any combinations. Many interactions are known nowadays thanks to reporting of adverse events from clinical practice. The **ABDA-drug-database contains approx. 1500 monographies on interactions** for approx. 2000 drugs listed in Germany. Mathematically, up to **2 million possible interactions** (for just a simple 2-drug-combination) are possible, even more if taking combinations of 3 or more drugs into account.
Pharmacovigilance data can be used to screen for new signals of yet unknown drug-drug-interactions.

Methods: Observed/Expected Rates

U.S. American pharmacovigilance data from 2004 to date were extracted using OpenVigilFDA 1.0.3pre1. A matrix for the neuro- and psychotropic drugs **citalopram (CIT), lorazepam (LOR), mirtazapine (MIR), pregabalin (PRE) and haloperidol (HAL)** was constructed.



Rates of an drug Y & event X combination (“D_yE_x”) and the total number of reports for a given drug (“D_y”) are calculated as D_yE_x/D_y. From these values, the expected ranges for the combination of the drug ($D_1D_2E_x/D_1D_2$) are derived: The average is used as lower bound, the sum as upper bound. If the real, observed rate is outside these bounds, a signal for an interaction exists.
To correct for total reporting counts, the following formula was used to estimate signals:
$i_x = \text{asinh}((D_1D_2E_x/D_1D_2 - 0.75*(D_1E_x/D_1+D_2E_x/D_2)) / 0.75*(D_1E_x/D_1+D_2E_x/D_2))$
Arbitrary cut-off values for i_x (< 0 and > 3) were chosen to summarize the top interactions for synergism and antagonism. To our best knowledge, there is currently no agreement on clinical significant cut-off values.

Example:

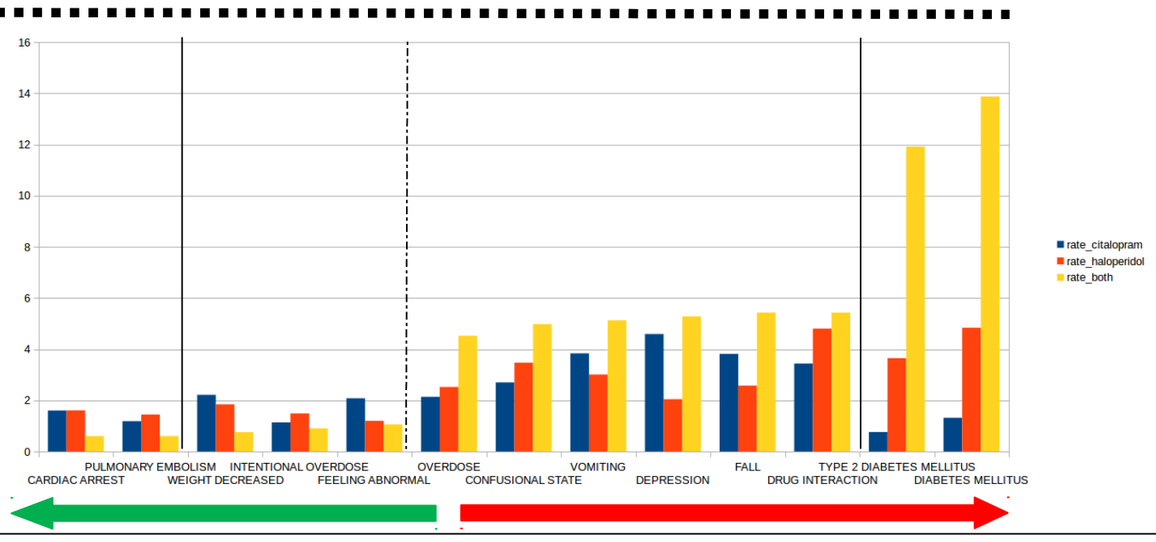
Analyzing citalopram and haloperidol concurrently delivers the dataset shown below (shortened). Only events with extreme interaction values were considered.

antagonism

event	i
CARDIAC ARREST	-0.1461591
PULMONARY EMBOLISM	-0.1461591
WEIGHT DECREASED	0.00414999
INTENTIONAL OVERDOSE	0.15436621
FEELING ABNORMAL	0.30123355

synergism

event	i
OVERDOSE	2.03861805
CONFUSIONAL STATE	2.14843419
VOMITING	2.18258123
DEPRESSION	2.21562592
FALL	2.24763969
DRUG INTERACTION	2.24763969
TYPE 2 DIABETES MELLITUS	3.10797873
DIABETES MELLITUS	3.26921436



Results

	CIT	LOR	MIR	PRE	HAL
CIT					
LOR	No findings				
MIR	- CHILLS - BLOOD PRESSURE INCREASED	No findings			
PRE	+ PAIN	+ PAIN	- PALPI-TATIONS		
HAL	+ TYPE 2 DIABETES MELLITUS + DIABETES MELLITUS - CARDIAC ARREST - PULMONARY EMBOLISM	No findings	+ TYPE 2 DIABETES MELLITUS + DIABETES MELLITUS - ECG QT PROLONGED - COMA	+ DRUG INTERACTION - FEELING ABNORMAL	

Interpretation

Data quality. Due to incomplete data cleaning of the FDA, many reports remain inaccessible to OpenVigilFDA. Some signals are not detected.
The finding „drug interaction“ for haloperidol and pregabalin appears to be an artifact caused by multiple reports for the same 22 year old female patient with the additional drugs quetiapine and procyclidine.

Confounding. Result are confounded by the underlying illness and the subsequently resulting treatment, including pharmacologic co-medication. E.g., „type 2 diabetes mellitus“ with haloperidol+citalopram might be the result of previous therapies with atypical antipsychotics and/or antihistaminergic antidepressants. Both groups attribute to weight gain and metabolic disorders.
The available data do not allow to mine for drug-advere events resulting from medication changes over time.
Cofounding by underlying illness might be corrected for by employing background corrections (e.g., using indication to filter a certain therapeutic area).

Signal strength (clinical and statistical significance). Further indicators for the strength of any signal is whether the disproportionality finding disappears (e.g., cardiac arrest is associated with either citalopram or haloperidol alone but not with the combination) or whether it is further boosted (e.g., the diabetes findings for haloperidol + citalopram and haloperidol + mirtazapine.

Conclusions. After applying all the additional considerations mentioned above only five signals for the 10 drug-drug-pairs remain: Metabolic/diabetic disorders for the combination haloperidol with antidepressants and for a decreased risk of cardiac arrest for haloperidol + citalopram. Both groups of signals appear to be caused by previous treatment or additional vigilance when prescribing QT-prolonging drugs, respectively.