Large-scale drug repositioning by safety signals using the OpenVigil 2 pharmacovigilance data analysis tool

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Introduction

Drug discovery is an **expensive** and long-lasting process which is frequently halted due to unforeseen issues. Repositioning of known drugs for new indications is therefore an expedient alternative to traditional drug discovery, i.e. the research on new compounds.
Drug repositioning candidates are found **accidentally by serendipity**, e.g. clinical observation, or **systematically by targeted searches**, e.g. assessing (dis-)similarities in pharmacogenomics, biological pathways and chemical structures (Ashburn TT. Nat Rev Drug Discov. 2004).
Pharmacovigilance, introduced after the thalidomide tragedy, provides early detection of adverse drug reactions by statistical approaches to detect "signals“ of disproportionality, i.e. a deviation between expected and observed frequencies of a drug-event-pair. Advanced computational techniques and growing data foundation move pharmacovigilance into a proactive direction as its statistical methodologies can be used **to identify** inverse and thus desirable safety signals, i.e. **“adverse events” that occur less frequently** than expected (Böhm R et al. PLoS One. 2016). OpenVigil 2 was used to screen for drug repositioning candidates via **disproportionality analyses (DPA)** using **reporting odds ratio (ROR)**.

Results

Screening pharmacovigilance data revealed a multitude of putative **candidate drug-indication-pairs** (e.g. > 500 new putative drugs/medicinal products against nasopharyngitis (figure 1) and > 400 new putative indications for acetylcysteine). The top results are visualized in **figures 2-5**.
Literature research (table below) underpinned most findings by providing either a probable mechanism of action or similar therapeutic observations from clinical trials, case-reports or in vitro experiments.

Drug	Indication	ROR	Affirmative data
paliperidone	nasopharyngitis	0.06	Paliperidone reduces interferone levels and might thus modulate the immune system (Gibney 2013)
levonorgestrel	nasopharyngitis	0.12	
docosanol	nasopharyngitis	0.06	Docosanol has known antiviral properties and is marketed against herpes infections
minoxidil	nasopharyngitis	0.08	
metoclopramide	nasopharyngitis	0.11	Metoclopramide stimulates release of prolactine which in turn stimulates the immune system (Fojtikova 2010).
heparin	nasopharyngitis	0.10	Heparin is known to interfere with the binding and thus entry of various viruses into cells (Feldmann 1999).
drospirenone	nasopharyngitis	0.14	Drospirenone is an antagonists of the mineralocorticoid-receptor which acts proinflammatory (Durango 2015).
ethanol	nasopharyngitis	0.10	
copper	nasopharyngitis	0.09	
medroxyprogesterone	nasopharyngitis	0.21	Medroxyprogesterone reduces IL-6 production (Yamashita 1996) and IL-6 in turn aggravates illness symptoms (Cohen 1999).
asenapine	nasopharyngitis	0.11	Antipsychotics modulate the immune system function (Drzyzga 2006).
nicotine	nasopharyngitis	0.24	Nicotine acts antiinflammatory and immunosuppressive (Kalra 2004).
ethinyl estradiol	nasopharyngitis	0.28	Ethinyl estradiol reduces interferon production (Subramanian 2003).
lactate	headache	0.08	
glucose	headache	0.08	Hypoglycemia is a known predisposing factor for headache (Hufnagl 2002).
docosanol	headache	0.11	In clinical trials, headache was less frequently reported for the docosanol-group (GlaxoSmithKline 2013).
vigabatrin	headache	0.13	Vigabatrin alters glutamate- and GABA-metabolism and is effective for prophyaxis against migraine (Goshe 2002).
copper	headache	0.16	Copper is a co-factor of various enzymes. A comparison of levonorgestrel- and copper-releasing IUDs showed less headache in the copper-group (Andersson 1994).
rosiglitazone	headache	0.19	Rosiglitazone acts against different types of pain (Hasegawa-Moriyama, 2012 & 2013).
cilastatin	headache	0.13	Cilastatin is predicted to bind to glutamate receptors (CHEMBL766).
voriconazole	headache	0.33	Voriconazole is an inhibitor of neuronal CYP46A1 (Shafaati 2010)
vildagliptin	headache	0.19	
Acetylcysteine (NAC)	myalgia	0.32	
Acetylcysteine (NAC)	alopecia	0.34	NAC protects from chemotherapy-induced alopecia (D'Agostini 1998) and was used against trichotillomania (Rodrigues-Barata 2012).
Acetylcysteine (NAC)	blood glucose increased	0.34	No studies found but NAC protects against various sequelae of chronic high blood glucose levels (Diabetes mellitus).
Acetylcysteine (NAC)	insomnia	0.37	NAC reduces insomnia due to drug craving (e.g. Mardikian 2007).
Acetylcysteine (NAC)	feeling abnormal	0.40	
Acetylcysteine (NAC)	nasopharyngitis	0.42	NAC can boost the immune system and thus protect against nasopharyngitis (De Flora 1997).
Acetylcysteine (NAC)	memory impairment	0.45	NAC was shown to prevent or reverse memory impairment in various animal models (e.g. Farr 2003).
Acetylcysteine (NAC)	headache	0.48	
Acetylcysteine (NAC)	arthralgia	0.42	NAC prevents cartilage degeneration (Nakagawa 2010)
aspirin (ASA)	menstruation irregular	0.03	
aspirin (ASA)	amenorrhoea	0.07	
aspirin (ASA)	breast cancer female	0.10	ASA protects against various cancers (Schreinemachers 1994)
aspirin (ASA)	tardive dyskinesia	0.14	
aspirin (ASA)	metrorrhagia	0.14	
aspirin (ASA)	neuroleptic malignant syndr.	0.10	ASA is used as antipyretic in this condition.
aspirin (ASA)	extrapyramidal disorder	0.18	ASA might protect against Parkinson‘s disease (Hernan 2006).
aspirin (ASA)	gynaecomastia	0.18	
aspirin (ASA)	vaginal discharge	0.13	

Discussion

A multitude of signals for putative new indications was easily extractable and interesting candidates were identified. Of note, we identified inverse signals for nasopharyngitis and antipsychotics and an inverse signal for “aspirin” and gynecologic events (grouped in MedDRA as “Fertility disorders”). The latter could not be further explained by the available literature. Pharmacovigilance must be used with caution due to missing or incorrectly coded data (e.g. mix-up of “indication” and “event”) and various reporting issues (e.g. under-reporting, biased reporting). Drug dosage and the severity or duration of the adverse events is usually not reported and was thus not analyzed in this study. For most desirable signals detected, convincing affirmative data from other sources or mechanisms of actions could be found in the literature. These confirming literature searches need to be considered biased since the exact methodology was not defined beforehand in a protocol.
Conclusion: OpenVigil 2 (http://openvigil.sf.net) is suitable for hypothesis generation for drug repositioning and thus drug discovery.

Results: Candidates against nasopharyngitis

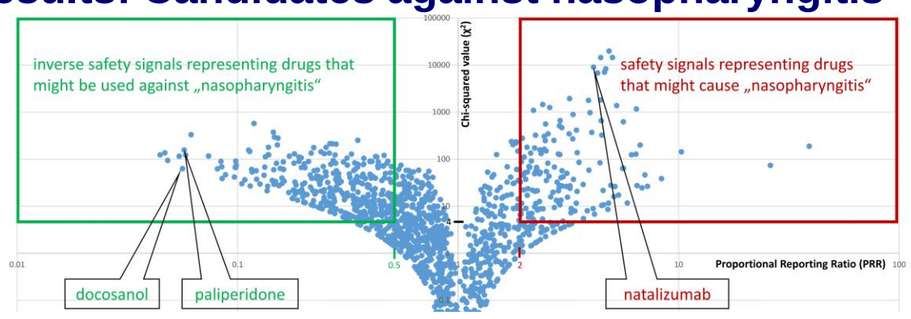

Fig. 1: Full DPA of the event „nasopharyngitis“ arranged by statistical significance (Chi-squared) and clinical relevance (proportional reporting ratio, similar to ROR). PRR values of less than 0.5 denote an occurrence 50% less frequently than expected and Chi-squared>4 significance (green box).

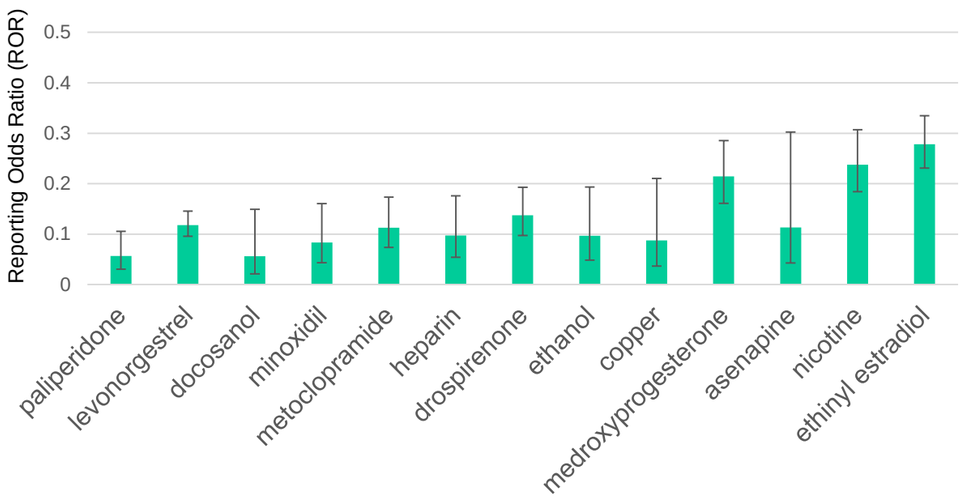

Fig. 2: Leading inverse safety signals of a DPA of the event „nasopharyngitis“ sorted by upper bound of the 95% confidence interval of the ROR (error bars)

Results: Candidate drugs against headache

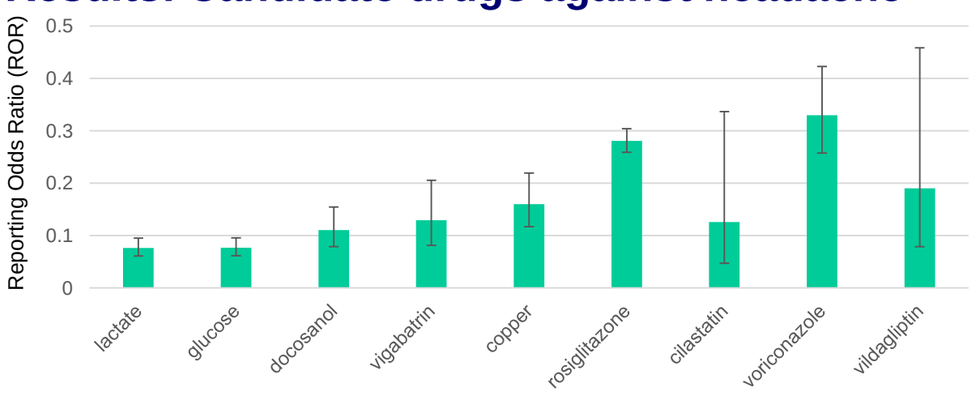

Fig. 3: Leading inverse safety signals of a DPA of the event „headache“ sorted by upper bound of the 95% confidence interval of the ROR (error bars).

Results: Candidate indications for NAC

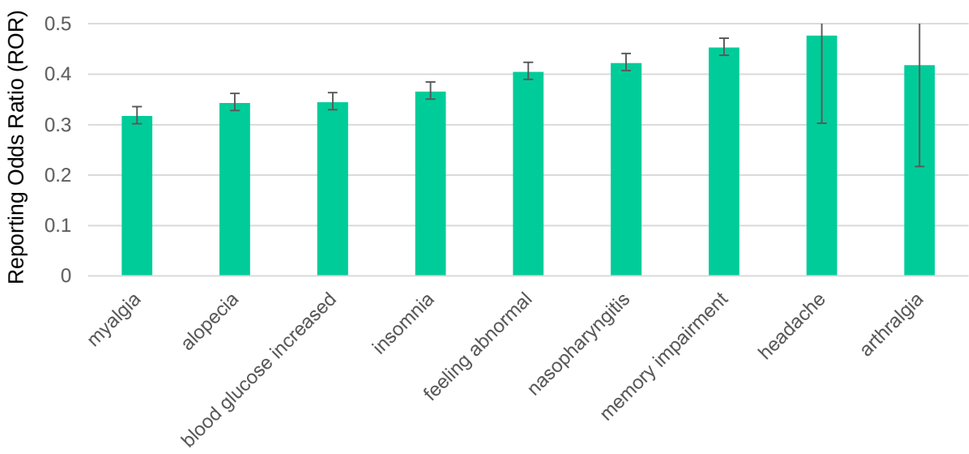

Fig. 4: Leading inverse safety signals of a DPA of the drug „acetylcysteine“ sorted by upper bound of the 95% confidence interval of the ROR (error bars).

Results: Candidate indications for aspirin

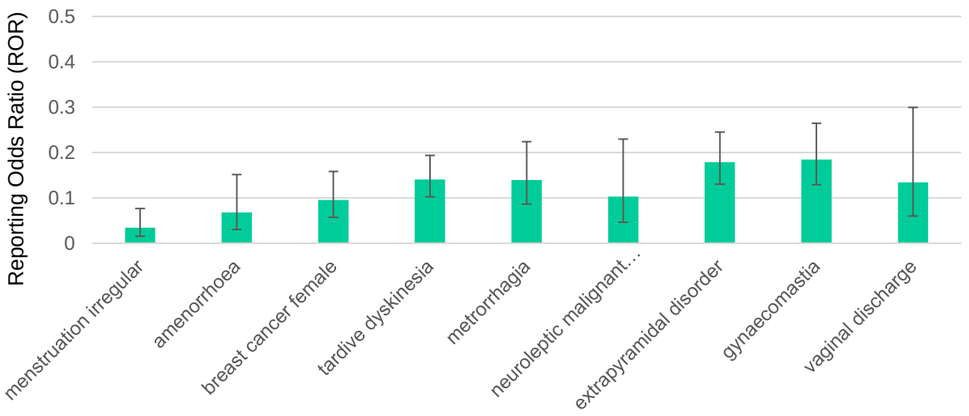

Fig. 5: Leading inverse safety signals of a DPA of the drug „aspirin“ sorted by upper bound of the 95% confidence interval of the ROR (error bars).

Methods

Using OpenVigil 2 (openvigil.sf.net, U.S. American pharmacovigilance data from 2004 to 2018Q3), **disproportionality analyses (DPA)** for the drugs "aspirin" and "acetylcysteine" and DPAs for the adverse events (AE) "nasopharyngitis" and "headache“ based on cases were performed. Results were sorted for ascending disproportionality between expected and observed frequency using **reporting odds ratios (ROR)** values and their upper and lower bounds of the 95%-confidence interval. In addition, disproportionality signals referring to brandnames were resolved to names of active substances and included as well. Only findings with n > 3 were considered. Obviously confounded signals and terms that could not be used in a clinical context such as chemotherapeutics or narcotics were eliminated. At least the first five **inverse safety signals (ROR < 1)** with statistical significance (upper bound of the 95%-confidence interval of the ROR < 1) and putative clinical relevance (ROR < 0.5, denoting approx. 50% less reports as expected by chance) were extracted and subsequently analyzed by literature research in MEDLINE and Google Scholar for affirmative data from controlled clinical trials and putative mechanisms of actions.