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Research Paper

Pneumothorax as an Adverse Drug Event: An Exploratory Aggregate Analysis of the US FDA AERS Database Including a Confounding by Indication Analysis Inspired by Cornfield's Condition

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Abstract

Introduction: Pneumothorax is either primary or secondary. Secondary pneumothorax is usually due to trauma, including various non-pharmacologic iatrogenic triggers. Although not normally thought of as an adverse drug event (ADE) secondary pneumothorax is associated with numerous drugs, though it is often difficult to determine whether this association is causal in nature, or reflects an epiphenomenon of efficacy or inefficacy, or confounding by indication (CBI). Herein we explore this association in a large health authority drug safety surveillance database.

Methods: A quantitative pharmacovigilance (PhV) methodology known as disproportionality analysis was applied to the United States Food and Drug Administration (US FDA) Adverse Event Reporting System (AERS) database to explore the quantitative reporting dependencies between drugs and the adverse event pneumothorax as well the corresponding reporting dependencies between drugs and reported indications that may be risk factors for pneumothorax themselves in order to explore the potential contribution of CBI.

Results: We found 1. Multiple drugs are associated with pneumothorax; 2. Surfactants and oncology drugs account for most statistically distinctive associations with pneumothorax; 3. Pulmonary surfactants, pentamidine and nitric oxide have the largest statistical reporting associations 4. CBI may play a prominent role in reports of drug-associated pneumothorax.

Conclusions: Disproportionality analysis (DA) can provide insights into the spontaneous reporting dependencies between drugs and pneumothorax. CBI assessment based on DA and Cornfield's inequality presents an additional novel option for the initial exploration of potential safety signals in PhV.

Key words: Pneumothorax, disproportionality analysis

Introduction

Pneumothorax may be primary, in which no obvious trigger is identified, or secondary, which may be induced by trauma or iatrogenic factors. The iatrogenic factors typically cited include subclavian line placement, needle thoracentesis, and pleural biopsy.[1]

Another category of reported iatrogenic factors is drugs, although pneumothorax is probably not typically thought of as an adverse drug event (ADE).

The most commonly cited drugs in the published literature include oncology drugs, although other drugs, such as nitrous oxide, inhaled pentamidine and those associated with pulmonary fibrosis are also represented.[2-17] The prominent association of oncology drugs with pneumothorax is intriguing and challenging to understand, as pneumothorax could theoretically be an epiphenomenon of drug efficacy (i.e. chemotherapy-induced lysis of sub-pleural tumor deposits) or inefficacy in this setting (i.e. progression of subpleural tumor deposits due to lack of efficacy). Confounding by indication (CBI)[18] is therefore an important consideration, given that pneumothorax may reflect the natural history/complications of malignancy.[19-21] There is variation in the use of the term CBI[14] but for our purposes CBI means that the treatment indication is independently associated with the ADE. It is difficult to exclude one of the aforementioned possibilities. Further complicating these associations are the co-occurrence of cancers and pneumothorax as part of a syndromic phenotype, such as the association of renal cell carcinoma and pneumothorax as elements of Birt-Hogg-Dube syndrome.[22,23]

Most of the published literature on pneumothorax consists of case reports. As pharmacovigilance (PhV) specialists we routinely access and analyze rich sources of ADEs such as large spontaneous reporting systems (SRS) maintained by health authorities. We were curious to discover and better understand the representation of pneumothorax as an ADE in these data sets.

Herein we present an analysis of the data of pneumothorax as a reported ADE in a large health authority post-approval drug safety database. The primary objective is to increase scientific understanding of this spontaneous reporting association.[24] A secondary objective is to present an adaptation of an "old" epidemiological concept, Cornfield's inequality,[25] that is novel for the application domain of PhV,[26] to explore the potential role of CBI in the association of pneumothorax for a subset of drugs for which this is an especially apt consideration. This could support real-world PhV because when drug-event combinations of interest are initially identified that could represent a signal of a novel association, an analyst will typically perform a first pass qualitative triage based on scientific judgment that includes consideration of CBI.[27] A CBI analysis of this sort therefore has the potential to provide quantitative decision support for first pass triage in PhV.

Methodology

1. Databases

The data set analyzed was the United States Food and Drug Administration (US FDA) Adverse Event Reporting System (AERS) database. AERS is a spontaneous reporting system (SRS) database for post-approval safety surveillance that serves as an early warning system for ADEs not detected in pre-approval testing.[24] The AERS database was analyzed from January 1st, 1969 through December 31st, 2010. The data was preprocessed to reduce redundant drug nomenclature and duplicate reports. Suspected adverse drug reactions are coded with hierarchical medical thesaurus known as the Medical Dictionary for Regulatory Activities (MedDRA).[28] The hierarchy maps the verbatim reported term to a Lower level Term (LLT) and then to a Preferred Term (PT) in the hierarchy, that is intended to capture a given medical concept in a standardized manner.[28]

2. Statistical Analysis Methodology

We performed two-dimensional (2-D) disproportionality analysis (DA) limited to suspect drugs. DA calculates the number of reports, proportionate representation, or odds of a given 2-D drug-event combination (DEC), that would be expected based on chance spontaneous reporting and recording of the corresponding drug(s) and event(s) in the database. In combination with the number of reports actually observed, an observed-to-expected ratio of reporting frequencies, ratios or odds is calculated (O/E).[24] There are variations in the specific implementation of DA with SRS data including frequentist and Bayesian formulations. No single method has been proven to be the method-of-choice. Details on DA may be found in the published literature[24,29]

We used a form of DA known as the multi-item gamma-Poisson shrinker (MGPS) (Oracle, Redwood Shores, CA) for this analysis. This algorithm models reporting frequencies as realizations of a Poisson process in which the Poisson parameter is itself considered a random variable whose distribution is a mixture of two gamma distributions. The initial parameters of the gamma mixture are determined using a negative binomial maximum likelihood algorithm to determine the prior probabilities of different possible O/E ratios. Prior probabilities are updated based on the number of reports of the DEC of interest using Baye's rule. In effect this calculates each O/E ratio as a composite of the grand mean O/E of all reported DECs, which is close to one (Hauben M, unpublished data) and that of the combination of interest, with the weighting for each determined by the O and E counts. When one or both of these counts are low the grand mean is heavily weighted but as information is gained, the individual combination's O/E is weighed more heavily and may eventually dominate the calculation.

The O/E metric calculated is the empirical Bayes geometric mean (EBGM) and its associated 90% posterior interval (PI) defined by the lower 5th (EB05) and upper 95th (EB95) percentiles of the EBGM.[24] An EB05>2 was used to define an interestingly large O/E,[30-32] also known as a 'signal of disproportionate reporting (SDR).[33] Calculations were performed at the MedDRA PT level. Basic covariate stratification by age, gender and year of report was performed to mitigate the effects of confounding by these variables and calculate a summary Mantel-Haenszel type O/E ratio.

We also performed the calculation for drug-indication pairs. This was inspired by Cornfield's inequality that in order for an effect with a relative risk (RR) of some magnitude X to be *fully* explainable by a confounding factor, a necessary condition is that factor would have to be X times more common in exposed versus unexposed persons.[25]

For each drug with an SDR for the ADE PT (PT $_{ADE}$) pneumothorax we reviewed the reported drug-indications to identify the most significant confounders for this event based on current clinical knowledge. From the latter indications for each drug, we searched for those that were prominently represented based on the number of reports (and therefore representative indications for that drug) and that were likely to be quantitatively most influential on our calculations based on higher EBGMs. If more than one likely candidate confounding indication was identified all were considered and included in the outputs.

Reporting of indications may be inherently different than reporting of events since the former are not necessary to create an ADE report but the latter are a required minimum data element, and because reporting of indications may be more deterministic and less stochastic than events. That is, the drug is nonrandomly selected for specific indications whereas many ADEs are typically the result of multiple random and nonrandom factors. Therefore the range of ADEs reported with a drug is expected to be much wider than the range of reported indications. We therefore introduced an adjustment based on the reduced range of unique indication PTs (PTs $_{IND}$) recorded in the database relative to the range of unique PTs $_{ADE}$, both overall in the database and preferentially for specific drugs. Expressed a little differently the number of unique reported indications in the entire database is less than the number of unique reported ADEs in the entire database and all else being equal, the difference between reported indications and reported ADEs may be larger or smaller for specific drugs depending on the overall safety profile and the number of treatment indications. The idea is to give a "more severe" test, (e.g. part of a best case-worst case scenario) for whether CBI is quantitatively plausible within the set of ADE reports. We calculated the number of unique PTs $_{ADE}$ and PTs $_{IND}$ for the overall database and for the specific subset of drugs with statistically significant reporting relationship. The ratio of these two in the overall database may be viewed as an adjustment for expected indication counts, and that for specific drugs as an adjustment for observed indication counts. Expressed a little differently we isolated the component of observed and expected counts for indication related to the distribution of counts within the reduced range of PTs $_{IND}$ for each drug. The adjusted CBI index (ACBII) was therefore calculated as follows:

Calculate unadjusted CBI index (UCBII)= $(O/E)_{IND}$ / $(O/E)_{ADE}$

Calculate X= (#unique PTs $_{ADE}$/unique PTs $_{IND}$) for overall database

Calculate Y=(#unique PTs $_{ADE}$/unique PTs $_{IND}$) for each drug

$$ACBII = (UCBII) / [(Y)/(X)]$$

Where adjusted $(O/E)_{IND}=(O_{IND}/Y)/(E_{IND}/X)$

The more the ACBIIs metric exceeds one the more it suggest that the restriction of the reported indications to confounding indications is substantial relative to the magnitude of the SDR. We thus are comparing SDRs for drug-ADE pairs and drug-indications pairs, which we denote by SDR_{ADE} and SDR_{IND}.

Results

There were 878 unique reported suspect drugs, (either single drugs or combination products) in 3681 reports recording pneumothorax as an ADE (17% of 5043 total drugs in the database). The 3681 reports of the ADE pneumothorax represents 0.08 % of 4637278 total ADE reports in the database. The number of reports per drug ranged from 1 to a maximum of 115. The majority (821/878 or 93%) of drugs associated with pneumothorax had only a single report compared to 848392/1766279 (48%) of all DECs with only one report.

Fifty-one of the 878 (5.8%) drugs in AERS listing pneumothorax were associated with an SDR (Table1).

Table 1. Drug-PT_{ADE} (Pneumothorax) Pairs Associated with an SDR_{ADE}

Generic Name	PT_{ADE}	N	EB05	EBGM	EB95
Colfosceril	Pneumothorax	9	84.1	152.2	258.4
Poractant Alfa	Pneumothorax	9	34.3	62.0	105.3
Beractant	Pneumothorax	11	35.3	60.1	97.1
Nitric Oxide	Pneumothorax	19	9.77	16.4	24.4
Pentamidine	Pneumothorax	11	5.58	14.3	27.4
Alglucosidase Alfa	Pneumothorax	18	5.3	9.06	15.8
Carmustine	Pneumothorax	15	4.75	8.52	16.2
Dacarbazine	Pneumothorax	13	4.18	7.57	15.3
Bleomycin	Pneumothorax	22	4.46	6.52	9.59
Gefitinib	Pneumothorax	32	4.75	6.45	8.7
Docetaxel	Pneumothorax	86	5.25	6.3	7.51
Bevacizumab	Pneumothorax	104	4.76	5.6	6.57
Vinblastine	Pneumothorax	13	3.29	5.35	8.58
Epoprostenol	Pneumothorax	13	3.06	4.94	7.74
Actinomycin-D	Pneumothorax	10	2.83	4.92	8.39
Carboplatin	Pneumothorax	80	4.05	4.89	5.85
Dornase Alfa	Pneumothorax	6	2.16	4.56	10.9
Gemcitabine	Pneumothorax	70	3.69	4.51	5.46
Leflunomide	Pneumothorax	31	3.27	4.42	5.88
Etoposide	Pneumothorax	52	3.47	4.38	5.47
Paclitaxel	Pneumothorax	81	3.57	4.3	5.14
Ifosfamide	Pneumothorax	18	2.78	4.14	6
Vinorelbine	Pneumothorax	21	2.82	4.08	5.75
Everolimus	Pneumothorax	22	2.75	3.94	5.51
Pamidronic Acid	Pneumothorax	23	2.76	3.92	5.44
Erlotinib	Pneumothorax	24	2.75	3.88	5.35
Doxorubicin	Pneumothorax	61	3.04	3.76	4.62
Mycophenolic Acid Slow Release	Pneumothorax	8	2.04	3.72	6.39
Vincristine	Pneumothorax	55	2.85	3.58	4.44
Ambrisentan	Pneumothorax	19	2.42	3.57	5.11
Methylprednisolone	Pneumothorax	40	2.57	3.35	4.31
Hydrocortisone	Pneumothorax	13	2.09	3.34	5.12
Prednisolone	Pneumothorax	45	2.5	3.2	4.06
Amiodarone	Pneumothorax	40	2.46	3.2	4.12
Methotrexate	Pneumothorax	75	2.64	3.2	3.85
Trastuzumab	Pneumothorax	16	2.09	3.18	4.69
Melphalan	Pneumothorax	17	2.11	3.18	4.64
Dexamethasone	Pneumothorax	40	2.44	3.18	4.09
Midazolam	Pneumothorax	18	2.14	3.18	4.59
Bosentan	Pneumothorax	28	2.3	3.16	4.26
Cisplatin	Pneumothorax	59	2.5	3.11	3.83
Pemetrexed	Pneumothorax	19	2.09	3.08	4.41
Heparin	Pneumothorax	47	2.37	3.03	3.82
Azathioprine	Pneumothorax	21	2.07	2.99	4.2
Sunitinib	Pneumothorax	34	2.24	2.99	3.92
Botulinum Toxin Type A	Pneumothorax	23	2.06	2.93	4.07
Tacrolimus	Pneumothorax	41	2.24	2.91	3.73
Propofol	Pneumothorax	21	2	2.89	4.07
Cyclophosphamide	Pneumothorax	62	2.29	2.83	3.47
Palivizumab	Pneumothorax	27	2.04	2.82	3.82
Oxaliplatin	Pneumothorax	30	2.03	2.76	3.68

The statistical reporting dependencies or SDRs (e.g. O/E reporting that exceeds chance expectation), expressed in the EBGM, ranged from 2.76 to a maximum of 152.2. Six non-oncology drugs accounted for the strongest statistical reporting associations. Pulmonary surfactants accounted for three of these (152.2 for colfoceril, 62.0 for poractant alpha, and 60.1 for beractant), followed by nitric oxide (16.4), pentamidine (14.3) and alglucosidase alpha (9.06). The highest values involving pulmonary surfactants illustrate the potential for CBI through various reporting mechanisms in SRS databases, as these compounds have been documented to actually decrease the incidence of pneumothorax in clinical trials.[34] Twenty-six oncology drugs were associated with an SDR_{ADE}. The EBGMs for these drugs ranged from 2.76 for oxaliplatin to 8.52 for carmustine.

The CBI analysis (Table 2) is notable for a wide range of UCBIIs with all drug-specific values >1, and two drugs, carmustine and docetaxel, with an ACBII consistently <1. Among the six strongest drug-ADE associations described above, there are potentially confounding indications with significant statistical associations (SDR_{IND}) with each drug that are large relative to the magnitude of the SDR_{ADE} as reflected in large UCBIIs and/or ACBIIs greater than one for beractant, nitric oxide, pentamidine, and poractant alpha. The most obvious of these, as discussed qualitatively above, is neonatal respiratory distress syndrome for the pulmonary surfactants beractant and proractant alpha (the precise indications were not recorded in colfosceril reports), which, as stated above, have been shown in clinical trials to decrease the risk of pneumothorax in this condition.[34] Pentamidine was notable for a very high ACBII (13.79) consistent with clinicopathological correlates of pneumocystis tissue invasion, inflammation, and necrosis.[17] Similarly nitric oxide is used to treat pulmonary hypertension in neonates with pneumothorax and in both of the latter clinical scenarios maximal ventilation may be employed which may cause air leaks.

For the oncology drugs, various carcinomas, sarcomas and lymphomas were potentially confounding indications associated with strong statistical associations with the drug. Carmustine and docetaxel have the largest and fifth largest EBGM among oncology drugs and were the two oncology drugs associated with an ACBII <1 for the single identified confounding indication for each drug. Of note carmustine is the drug with the most established association with pneumothorax based on the occurrence of upper lobe fibrobullous disease.[3] Docetaxel is the one drug for which we were able to identify a case report involving multiple positive rechallenges with each multidrug chemotherapy course.[6] However bleomycin, another oncology agent with an established reputation for pulmonary toxicity that could provide a mechanistic context for pneumothorax, had the second largest EBGM and was associated with one of the highest ACBII.

Table 2. Analysis of Spontaneous Reporting Pneumothorax

	PT_{ADE}: Pneumothorax			Confounding Indication*				PTs_{ADE}/PTs_{IND}		$(O/E)_{IND}/(O/E)_{ADE}$	
Drug	**N**	**EB_{05}**	**EBGM**	**PT_{IND}**	**N**	**EB_{05}**	**EBGM**	**Crude Counts**	**Ratio**	**UCBII**	**ACBII**
Actinomycin-D	10	2.83	4.92	Nephroblastoma	56	243.3	304.9	829/85	9.75	61.97	11.06
				Rhabdomyosarcoma	148	124.3	142.6			28.98	5.17
Alglucosidase alpha	18.3	5.03	9.06	NA	NA	NA	NA	NA	NA	NA	NA
Ambrisentan	19	2.42	3.57	NA	NA	NA	NA	NA	NA	NA	NA
Azathioprine	21	2.07	2.99	NA	NA	NA	NA	NA	NA	NA	NA
Beractant	11	35.3	60.1	Neonatal resp distress synd	8	297.3	560.3	115/11	10.45	9.32	1.55
Bevacizumab	104	4.76	5.6	Colorectal cancer metastatic	1319	64.8	67.8	3083/467	6.60	12.11	3.19
				Non-small cell lung cancer	1193	17	17.8			3.18	0.84
Bleomycin	22	4.46	6.523	Hodgkin's disease	511	345.1	371.3	1386/180	7.70	56.93	12.86
				Testis cancer	150	344.3	394.6			60.50	13.67
Carboplatin	80	4.05	4.89	Non-small cell lung cancer	2278	43.6	45.2	3143/539	5.83	9.24	2.76
				Lung neoplasm malignant	690	30.5	32.4			6.63	1.98
Carmustine	15	4.75	8.52	Non-Hodgkin's lymphoma	55	29.5	37	1052/119	8.84	4.34	0.85

	PT ADE: Pneumothorax			Confounding Indication*				PTs ADE/PTs IND		(O/E)IND/ (O/E)ADE	
Drug	**N**	**EB05**	**EBGM**	**PT IND**	**N**	**EB05**	**EBGM**	**Crude Counts**	**Ratio**	**UCBII**	**ACBII**
Cisplatin	59	2.5	3.11	Sm cell lung cancer stage unspec	414	52.5	56.9	3320/623	5.33	18.30	5.97
				Oesophageal carcinoma	335	44.1	48.3			15.53	5.07
				Non-small cell lung cancer	1484	23.9	24.9			8.01	2.61
Colfosceril	9	84.1	152.2	NA**	NA	NA	NA	NA	NA	NA	NA
Cyclophosphamide	62	2.29	2.83	Breast cancer	2667	21.9	22.6	4259/915	4.65	7.99	2.99
Dacarbazine	13	4.18	7.57	Metastatic malignant melanoma	87	328.1	392.8	804/91	8.84	51.89	10.22
				Malignant melanoma	158	191.5	218.7			28.89	5.69
Docetaxel	86	5.25	6.3	Non-small cell lung cancer	868	18.6	19.7	3116/436	7.15	3.13	0.76
Doxorubicin	61	3.04	3.76	Breast cancer	1597	15.5	16.2	3574/638	5.60	4.31	1.34
Erlotinib	24	2.75	3.88	Lung neoplasm malignant	687	70.4	75	2050/236	8.69	19.33	3.87
				Non-small cell lung cancer	1328	53.9	56.4			14.54	2.91
Etoposide	52	3.47	4.38	Sm cell lung cancer stage unspec	476	137.1	147.9	2865/540	5.31	33.77	11.07
Gefitinib	32	4.75	6.45	Lung adenocarcinoma	453	190.9	206.3	1587/252	6.30	31.98	8.84
				Non-small cell lung cancer	1056	46.4	48.8			7.57	2.09
Gemcitabine	70	3.69	4.51	Non-small cell lung cancer	1621	30.3	31.5	3159/498	6.34	6.98	1.92
Ifosfamide	18	2.78	4.14	Sarcoma	135	220.8	255	1609/331	4.86	61.59	22.05
Oxaliplatin	30	2.03	2.76	Colon cancer	1426	75.9	79.3	2450/312	7.85	28.73	6.37
				Colorectal cancer	1047	44.8	47.1			17.07	3.78
Melphalan	17	2.11	3.18	NA	NA	NA	NA	NA	NA	NA	NA
Methotrexate	75	2.64	3.2	NA	NA	NA	NA	NA	NA	NA	NA
Nitric Oxide	19	9.8	16.4	Pulmonary Hypertension	49	85.8	109.2	237/62	3.82	6.67	3.04
Paclitaxel	81	3.57	4.3	Non-small cell lung cancer	1598	27.8	29	3343/473	7.07	6.74	1.66
				Lung neoplasm malignant	692	27.6	29.4			6.84	1.68
Pemetrexed	19	2.09	3.08	NA	NA	NA	NA	1748/192	9.1	NA	NA
Pentamidine	11	5.6	14.3	Pneumocystis jiroveci pneumonia	23	522.9	748.3	587/89	6.60	52.26	13.79
Poractant Alfa	9	34.3	62	Neonatal resp distress synd	26	779.1	1090.4	132/15	8.80	17.59	3.48
Sunitinib	34	2.24	2.99	Metastatic renal cell carcinoma	2170	64.6	66.9	2251/337	6.68	22.37	5.83
				Renal cell carcinoma	2546	50.5	52.2			17.46	4.55
Trastuzumab	16	2.09	3.18	Breast cancer metastatic	778	56.8	60.3	2107/159	13.25	18.96	2.49
				Breast cancer	2177	35.9	37.2			11.70	1.54
Vinblastine	13	3.29	5.35	Hodgkin's disease	385	495.6	539.3	1190/133	8.95	100.80	19.60
Vincristine	55	2.85	3.58	Non-Hodgkin's lymphoma	1009	55.9	58.8	3593/602	5.97	16.42	4.79
Vinorelbine	21	2.82	4.08	Non-small cell lung cancer	677	47.2	50.3	1786/172	10.38	12.33	2.07

The overall ratio of PT_{ADE}/PT_{IND} in the database= 15005/8646=1.73

*"NA"-no obvious confounding indications identified in any reports

**Specific indications not reported

Discussion

We found a significant number of ADE reports of pneumothorax in a large health authority SRS database though it was rare as a proportion of all reports. Most drugs with SDRs were oncology drugs of various mechanisms of action but the strongest statistical associations involved a small number of non-oncology drugs, namely pulmonary surfactants and pentamidine, that our analysis supports as CBI. The results are consistent with pulmonary surfactants' reported reduction in the incidence of pneumothorax in neonatal respiratory distress syndrome, and clinical-pathological correlates indicating that pneumothorax in the setting of pneumocystis pneumonia may reflect peripheral microbial inflammation, invasion and tissue necrosis corresponding to gradients in aerosol particle deposition.[14-17] Of note ACBIIs for the surfactant preparations for which indication was reported were all greater than one and for pentamidine was 13.79. The two oncology drugs with a consistent finding of an ACBII <1 seem to have the most persuasive association with pneumothorax from independent datasets. Therefore this approach to CBI analysis showed preliminary hints of utility for initial exploratory analysis to provide quantitative support for initial understanding and triage of SDRs in PhV. The absence of obvious confounding indications does not necessarily rule out CBI as a causal or contributory factor. In some instances the absence of an obvious recorded indication was due to the fact that the indication was not reported in any reports (i.e. colfosceril). In other instances the reported indication could have been a confounding factor, though not as well established as in the classic examples of various oncology drugs. For instance the reported indication for alglucosidase alpha was glycogen storage disease type II, which involves serious pulmonary disease that could at least theoretically be associated with pneumothorax via natural history or iatrogenic disease.[35]

There are significant limitations to our analysis most notably the usual 'warnings, precautions and indications for use' for SRS data which precludes making causal inferences except in unusual circumstances[24] which are amplified by the aforementioned differences in event versus indication reporting. We did not perform a case-level clinical review (case narratives are not included in AERS extracts for public use) and results of any quantitative analysis of SRS data is most meaningful when correlated with case-level clinical information. DA is based on 2x2 contingency tables methods and therefore do not accommodate the complex multivariate drug and event relationships that are characteristic of such data and which may be especially pertinent to the oncology setting where multi-drug treatment protocols are common. For example, the pulmonary toxicity of docetaxel has been reported to be enhanced by co-administered gemcitabine.[36,37] Finally like any observational database, and perhaps especially so for SRS data, there are other reporting artifacts such as unrecorded confounding and effect modification which this approach does not address and which typically remain unresolved in initial signal detection in PhV.

The application of even basic disproportionality analysis has been the subject of heated debate with extreme viewpoints of "unbridled optimism" to "considerable skepticism".[38] In other words some authorities consider such analysis a "garbage in garbage out" exercise of no value and potential harm, while others unrealistically maintain that such quantitative analysis, if performed with certain proprietary software, can neutralize the enormous limitations of spontaneous reports. We take a moderate position between the aforementioned extremes. With our analysis, which went beyond the usual drug-ADE analysis to include a drug-indication analysis, so one must be even more cautious in interpretation.

While the above limitations are substantial and clearly disqualifies this approach for making inferences, it is does not necessarily disqualify its judicious application as an exploratory analysis tool to help refine an initial index of suspicion related to CBI. Quoting an author writing about another exploratory analysis tool[39] "data mining and fishing expeditions are dirty words, but tempered with an awareness of the fallacies they can lead to, and supported by honest documentation, it is not a scientific crime" to use them in this context to search for a possible contribution of CBI to the reporting association between the drug and the event.

An analysis using Cornfields's inequality in this setting has advantages including the fact that it is simply an extension of the same basic calculation used for the drug-ADE pair to drug-indication pairs and thus easily implementable for front-end signal detection in PhV, as well as being transparent and intuitive but there are other alternative approaches including calculating O/E ratios within different levels of a confounding variable and/or calculating an adjusted summary measure as with Mantel-Haenzsel methods (as we did with age, gender and reporting year). Another approach applied to SRS data is to perform the DA on a subset of drugs within a pharmacological/therapeutic class or for specific indication(s).[40-48] Although this has been performed at times there are

limitations to these approaches as well. For example depending on the specific implementation of the DA such an approach can potentially mask[24] credible associations if they exist with multiple drugs within the pharmacological/therapeutic class. Utilizing the generality of the database as a background may provide a better picture of the statistical reporting associations in the universe of drugs, rather than just differences between drugs within a subset of drugs. This may inevitably entail a trade-off between sensitivity and specificity. Finally such an approach allows analysis of only one drug class per analysis.

Finally our adjustment, while based on plausibility considerations, is still essentially somewhat ad hoc, (as are many exploratory analysis in PhV) but it provides a starting point for further discussion and research including a systematic assessment of its operating characteristics, as well as that of other potential adjustment factors. It would also be interesting to perform a systematic study to establish operating characteristics of U/ACBII that could potentially identify optimum thresholds that might obviate the need for correction.

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Competing Interests

Manfred Hauben is a full time employee of, and owns stock and stock options in, Pfizer Inc which manufactures/markets drugs discussed in this article and/or competing drugs from the same pharmacological/therapeutic class as those discussed in this article and owns stock and stock options in other pharmaceutical companies that may manufacture drugs included in this study and/or other drugs within the same pharmacological/therapeutic classes.

Eric Hung is a full time employee of Pfizer Inc and owns stock and stock options in Pfizer Inc.

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