A Drug Safety Rating System Based on Post-Marketing Costs associated with Adverse Events and Patient Outcomes

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Objective

To develop a drug safety statistic that estimates downstream medical costs associated with serious adverse events (AEs) and patient outcomes associated with 706 US FDA approved drugs.

Background

multiple limitations are associated with relatively homogeneous pre-approval clinical trials, including:
inadequate data disclosures, slow reaction times from regulatory bodies, and deep rooted bias against disclosing and publishing negative results. Accordingly, there is an acute need for the development of analytics that reflect drug safety in heterogeneous, real world, populations.

Methods

~5 million AE case reports from 1997-2014 were imported from FDA's Adverse Event Reporting System (FAERS).

All "primary suspect" case reports for each drug were collected from FAERS.

Serious AEs and outcomes were MedDRA coded and tallied for each case report.

Medical costs associated with AEs and poor patient outcomes were derived from Agency for Healthcare Research and Quality (AHRQ) survey data and their corresponding ICD-9 codes were mapped to MedDRA terms. Non-serious AEs and outcomes were not included.

For each case report, either the highest AE cost or, if no eligible AE was listed, the highest outcome cost was used.

All costed cases were aggregated for each drug and divided by the number of patients exposed to obtain a downstream estimated direct medical cost burden per exposure. Each drug was assigned a corresponding 1-100 point total.

Results

706 drugs showed an exponential distribution of downstream costs and therefore the data were transformed using the natural log to approximate a normal distribution. The minimum score was 8.29 and the maximum was 99.25, with a mean of 44.32.

Drugs with the highest individual scores tended to be kinase inhibitors, thalidomide analogs, and endothelin receptor antagonists.

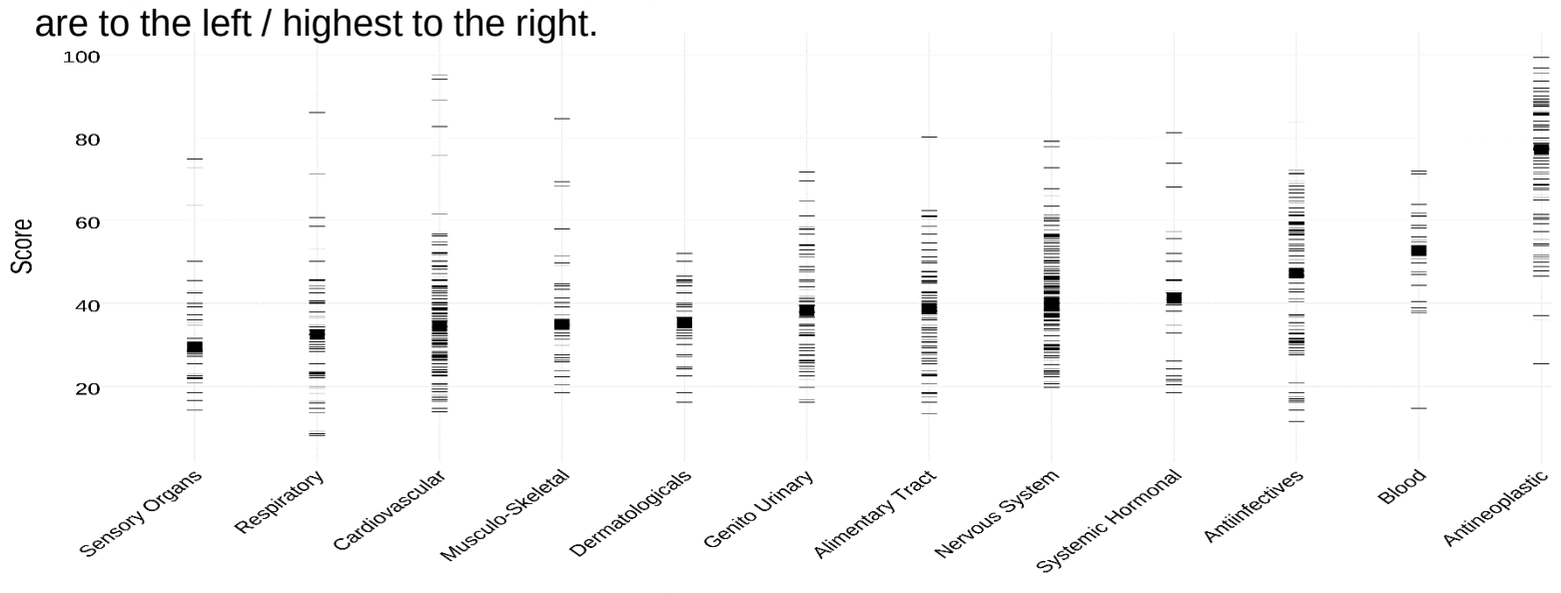
Compound	Score	EPC	N
pomalidomide	99.25	Thalidomide Analog	2,755
lenalidomide	96.72	Thalidomide Analog	23,591
ruxolitinib	95.58	Kinase Inhibitor	2,230
bosentan	94.97	Endothelin Receptor Antagonist	17,346
ambrisentan	93.97	Endothelin Receptor Antagonist	14,542
pazopanib	93.66	Kinase Inhibitor	2,790
everolimus	91.94	Kinase Inhibitor	4,881
ibrutinib	91.88	Kinase Inhibitor	911
deferasirox	91.11	Iron Chelator	6,945
regorafenib	91.06	Kinase Inhibitor	856

Within-drug class results differentiate similar drugs. 6 serotonin reuptake inhibitors had a score range of 36 to 53 and 6 proton pump inhibitors ranged from 27 to 47.

Compound	Score	Cost Per Patient	N (Costed Cases)
paroxetine CR	53.16	$ 21.93	215
paroxetine	46.21	$ 8.68	2,803
fluoxetine	40.18	$ 3.89	2,454
sertraline	39.85	$ 3.72	3,273
escitalopram	36.62	$ 2.42	1,745
citalopram	35.91	$ 2.20	2,573

Compound	Score	Cost Per Patient	N (Costed Cases)
esomeprazole	46.56	$ 9.10	9,344
esomeprazole; naproxen	40.28	$ 3.94	150
rabeprazole	36.52	$ 2.39	402
lansoprazole	33.42	$1.58	647
pantoprazole	32.08	$ 1.32	885
omeprazole	26.80	$ 0.65	1,780

When Anatomical Therapeutic Chemical (ATC) classifications were analyzed, antineoplastic drugs were an outlier with ~80% of their individual scores ≥ 60, while blood and anti-infective drugs had ~20-30%
of their scores ≥ 60. ATC groups are plotted vertically with a thick band indicating the median of each group. The lowest average group scores
are to the left / highest to the right.



Conclusions

This system is based on estimated direct medical costs from post-marketing AEs and patient outcomes - and thereby helps fill a large information gap regarding drug safety in real world patient populations.

What is already known about this subject:
• Pre-approval trials cannot predict many AEs observed in real world patients.
• Post-marketing AE reporting has increased dramatically over the past decade with approximately 1,500,000 reports now being submitted to FAERS annually.
• FAERS data are not yet widely used by healthcare Professionals.

What this study adds:
• Post-marketing AE reports can be assigned direct medical costs in order to estimate a drug's downstream financial impact.
• By quantifying reported post-approval AEs into downstream direct medical costs, this system can serve as a needed window into drug safety in real world patient populations.
• AEs and poor patient outcome data were obtained from FAERS and direct medical costs were estimated for 706 approved drugs.

Limitations

A number of limitations must be considered when using and interpreting this system, including reporting rates and potential biases contained in FAERS. The "primary suspect" designation in FAERS is subjective and the influence of other drugs or factors cannot be ruled out from a given case report. While we excluded obvious cases where a disease-related symptom was mistakenly denoted as an AE, we assume that we did not catch all such mistakes. Our cost estimates come from mapping AHRQ HCUP cost survey data to MedDRA terms found in FAERS. While we believe this is appropriate, we could not determine if variations between FAERS patient populations and those used for HCUP surveys could influence the results presented here. Finally, limitations in both the accuracy of MEPS data and patient exposure estimates used herein may cause artificial increases, or decreases, in calculated direct medical costs. We vigorously recommend that patients must have a consultation with their prescribing physician before taking any action that relates to FAERS or the analytic system presented here.

Declaration of Financial/Other Relationship
KBH, MD, RFK, CBE, AD, DC and BMO are employees of Advera Health Analytics, Inc. (AHA) which self-funded this study. NPT is an employee of Columbia University and a consultant to AHA.

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