Determining the Cost of Adverse Drug Reactions from FDA-approved Medications: Implications for Outcomes Research and Formulary Decisions.

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Objective

To estimate the costs associated with post-marketing side effect reports by combining: 1) ADR-specific costs, 2) post-marketing ADR data from FAERS, and 3) drug usage information.

Background

In homogenous pre-approval clinical trials observed Adverse Drug Reactions (ADRs) frequently do not correlate with real-world ADRs in heterogeneous populations.

Therefore, a drug's true safety profile is not known until its marketing phase. FDA maintains a large collection of post-marketing ADR reports known as the Adverse Event Reporting database (FAERS).

Approximately 1,500,000 ADR reports are currently submitted to FDA each year.

Substantial costs are associated with these ADRs.

Healthcare organizations need improved methods to increase patient safety and lower downstream costs associated with ADRs.

Methods

The FAERS database was used to collect ADR data for each drug.

Evaluate Pharma (evaluategroup.com) provided drug usage data.

ICD-9 codes were mapped to serious MedDRA preferred terms (PTs). Individual PTs and patient outcomes were assigned costs based on AHRQ data.

Non-serious terms and disease-related ADRs were ignored.

Either the most costly "primary suspect" ADR or outcome cost was assigned to all eligible case reports for all drugs.

Individual report costs were summed for each drug and then divided by exposure rates to obtain downstream costs per Rx.

AE Information

The AEs listed in the following tables are mostly single MedDRA PTs, but two categories of related PTs were grouped together:

"Cardiac problems": cardiac failure, cardiac failure acute, coronary artery disease, and coronary artery occlusion.

"Cerebral problems": cerebral hemorrhage, cerebral infarction, and cerebrovascular accident.

AE and Drug Labels

We mined the boxed warning, warnings, precautions, and adverse reactions sections of all prescription drug labels for AE terms.

If an AE term is found in one or more of these sections of a given drug's label then it is considered "on-label."

Drug Analyzed in Detail

8 diabetes medications:

- 5 Dipeptidyl Peptidase 4 inhibitors (DPP-4)
- 3 Glucagon-like Peptide-1 (GLP-1) agonists.

DPP-4 downstream costs

Drug Name	Total Costs (2010-2014)	Total Patients (2010-2014)	Downstream Costs Per Rx	N
alogliptin benzoate	$4,507,048	24,772	$16.27	236
linagliptin	$11,165,889	333,448	$4.19	758
sitagliptin phosphate	$62,464,629	2,700,732	$1.93	3,634
saxagliptin hydrochloride	$9,598,866	511,832	$1.56	715
metformin hydrochloride; sitagliptin phosphate	$19,482,002	1,167,632	$1.39	1,102

GLP-1 downstream costs

Drug Name	Total Costs (2010-2014)	Total Patients (2010-2014)	Downstream Costs Per Rx	N
exenatide (Byetta)	$36,098,579	376,408	$7.99	2,498
exenatide (Bydureon)	$9,140,971	195,888	$4.19	677
liraglutide recombinant	$33,675,056	932,008	$3.01	2,934

Top 3 Costliest AEs for DPP-4 drugs

Drug Name	Primary Suspect Cases	Top 3 Costliest AEs				
		AE	N	Total Cost	%	On Label?
metformin hydrochloride; sitagliptin phosphate	2,007	Pancreatic carcinoma	118	$2,213,208	11.36%	NO
		Pancreatitis	157	$1,508,299	7.74%	
		Myocardial infarction	39	$759,369	3.90%	
sitagliptin phosphate	6,669	Pancreatic carcinoma	494	$9,265,464	14.83%	NO
		Pancreatitis	728	$6,993,896	11.20%	
		Pancreatitis acute	134	$1,281,844	2.05%	
alogliptin benzoate	264	Pancreatic carcinoma	10	$187,560	4.16%	NO
		Gastric cancer	7	$169,764	3.77%	NO
		Myocardial infarction	7	$136,297	3.02%	NO
saxagliptin hydrochloride	2,344	Pancreatitis	103	$989,521	10.31%	
		Pancreatic carcinoma	30	$562,680	5.86%	NO
		Pancreatitis acute	28	$267,848	2.79%	
linagliptin	2,131	Pancreatitis	158	$1,517,906	13.59%	
		Pancreatic carcinoma	30	$562,680	5.04%	NO
		Myocardial infarction	19	$369,949	3.31%	NO

Top 3 Costliest AEs for GLP-1 drugs

Drug Name	Primary Suspect Cases	Top 3 Costliest AEs				
		AE	N	Total Cost	%	On Label?
exenatide (Bydureon)	4,616	Pancreatitis	122	$1,172,054	12.82%	
		Pancreatic carcinoma	15	$281,340	3.08%	NO
		Myocardial infarction	13	$253,123	2.77%	NO
exenatide (Byetta)	5,725	Pancreatic carcinoma	397	$7,446,132	20.63%	NO
		Pancreatitis	522	$5,014,854	13.89%	
		Pancreatitis acute	156	$1,492,296	4.13%	
liraglutide recombinant	13,888	Pancreatitis	746	$7,166,822	21.28%	
		Pancreatic carcinoma	195	$3,657,420	10.86%	NO
		Pancreatitis acute	237	$2,267,142	6.73%	

To provide more insights on non-label AEs that are being reported more than expect, the Reporting Odds Ratio (ROR) was calculated for "primary suspect" cases for one drug from each group. RORs above 2.0 are highlighted in red. DME = Designated Medical Event (by FDA).

exenatide (Byetta)

Adverse Event	ROR (CI)	Cases	RxSignal	On Label?	DME?
Accidental overdose	1.71 (1.03 - 2.83)	15	Watchlist	NO	
Adenocarcinoma pancreas	**76.75** (53.49 - 110.13)	34	Active	NO	
Angina unstable	0.65 (0.16 - 2.59)	2			
Cardiac problems *	0.91 (0.68 - 1.21)	47		NO	
Cerebral problems *	0.45 (0.33 - 0.60)	45		NO	
Cholelithiasis	**8.11** (6.90 - 9.53)	153	Active	NO	
Colon cancer	**2.16** (1.19 - 3.90)	11	Active	NO	
Drug-induced liver injury	0.54 (0.13 - 2.15)	2		NO	
Hepatic steatosis	**4.76** (3.32 - 6.83)	30	Active	NO	
Hepatitis	0.95 (0.51 - 1.76)	10		NO	
Hyperkalaemia	0.46 (0.19 - 1.10)	5		NO	
Interstitial lung disease	0.00	0		NO	
Liver disorder	0.97 (0.57 - 1.63)	14		NO	
Nephrolithiasis	**3.17** (2.34 - 4.28)	43	Active	NO	
Pancreatic carcinoma	**97.69** (88.04 - 108.38)	448	Active	NO	
Renal failure	**7.02** (6.25 - 7.88)	308			✓
Renal failure acute	**4.61** (4.01 - 5.28)	213			✓
Renal impairment	**2.36** (1.81 - 3.09)	54			✓
Thyroid cancer	**64.61** (54.27 - 76.92)	145	Active	NO	
Vision blurred	0.44 (0.28 - 0.68)	20		NO	
Visual acuity reduced	1.54 (1.07 - 2.22)	29	Watchlist	NO	

alogliptin

Adverse Event	ROR (CI)	Cases	RxSignal	On Label?	DME?
Accidental overdose	0.00	0		NO	
Adenocarcinoma pancreas	0.00	0		NO	
Angina unstable	**14.16** (3.52 - 56.97)	2		NO	
Cardiac problems *	**3.44** (1.70 - 6.93)	8	Active	NO	
Cerebral problems *	**4.14** (2.56 - 6.67)	18	Active	NO	
Cholelithiasis	1.11 (0.16 - 7.90)	1		NO	
Colon cancer	**17.21** (6.41 - 46.24)	4		NO	
Drug-induced liver injury	**11.78** (2.93 - 47.39)	2			
Hepatic steatosis	**10.33** (3.31 - 32.25)	3		NO	
Hepatitis	0.00	0		NO	
Hyperkalaemia	1.99 (0.28 - 14.21)	1		NO	
Interstitial lung disease	**15.01** (7.72 - 29.20)	9	Active	NO	
Liver disorder	**6.07** (2.26 - 16.30)	4		NO	
Nephrolithiasis	**3.18** (0.79 - 12.79)	2		NO	
Pancreatic carcinoma	**42.82** (23.39 - 78.39)	11	Active	NO	
Renal failure	0.00	0		NO	✓
Renal failure acute	1.36 (0.44 - 4.25)	3		NO	✓
Renal impairment	**2.85** (0.91 - 8.89)	3		NO	✓
Thyroid cancer	0.00	0		NO	
Vision blurred	0.00	0		NO	
Visual acuity reduced	0.00	0		NO	

Conclusions

ADRs are responsible for a huge cost burden for the healthcare industry, but techniques to analyze specific costs are lacking.

The drug safety statistic detailed here assigns AHRQ-derived cost data to post-market case reports submitted to FDA in order to calculate downstream costs associated with side effects and poor patient outcomes.

By quantifying the post-approval phase of a drug into downstream medical costs, the system can serve as a needed window into the patient population that matters most, the real world.