A Step-by-Step Example of Analysis of OpenFDA Drug Report Data

Last Updated: January 5, 2016

This case illustrates some of the professional pharmacovigilance processes for assessing an apparent association between a drug and a particular adverse event in a collection of drug adverse event reports summarized in a public FDA guidance document.[1] In the past, triggers of increased adverse event reporting to FDA have included news reports, public FDA alerts, and the introduction of new products.[2-5] Among the many other issues with drawing causality conclusions from the reports are limited knowledge of the relative extent of use of the drugs involved, and various other alternative explanations for the apparent association. Aspirin is one of the most common drugs listed in openFDA drug adverse event reports (4.2% of all reports). A natural question is what types of adverse events have been reported for aspirin? Or, this could be rephrased as what types of adverse events were more often reported in the same reports as aspirin, compared to reports that don't mention aspirin? A proportional reporting rate (PRR), a commonly used statistic for this question, of 2 indicates that the proportion of reports for the drug-event combination is twice the proportion of the event in the overall database.[1, 5-6] Using an interactive program designed to look at openFDA drug reports data,[7] we can (relatively) quickly look at the most common events for aspirin. The following steps demonstrate how to proceed through the analytic process.

1. Using an up-to-date browser, go to the URL https://openfda.shinyapps.io/RR_D to open the openFDA RR-Drug application,[7] and click on the "Select Drug and # of Events…" button. (The other related applications may be reached either from inside RR-Drug by clicking on the "Other Apps" tab, or directly at individual URLs.[8-11])

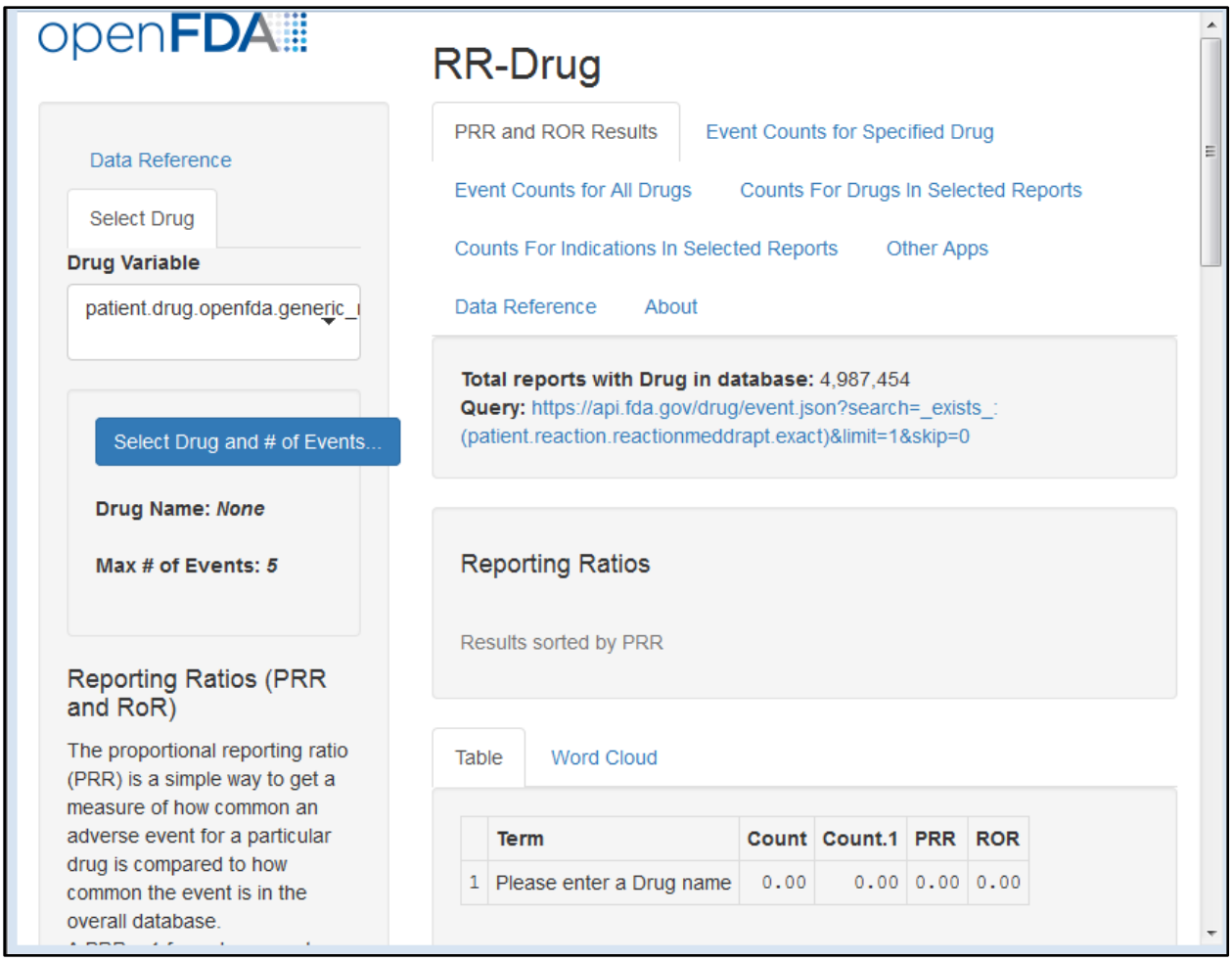


Figure 1. Partial display of the home page of the openFDA RR-Drug application.[1]

2. Enter “aspirin” in the name of drug field, and press the “Update Variables” button.

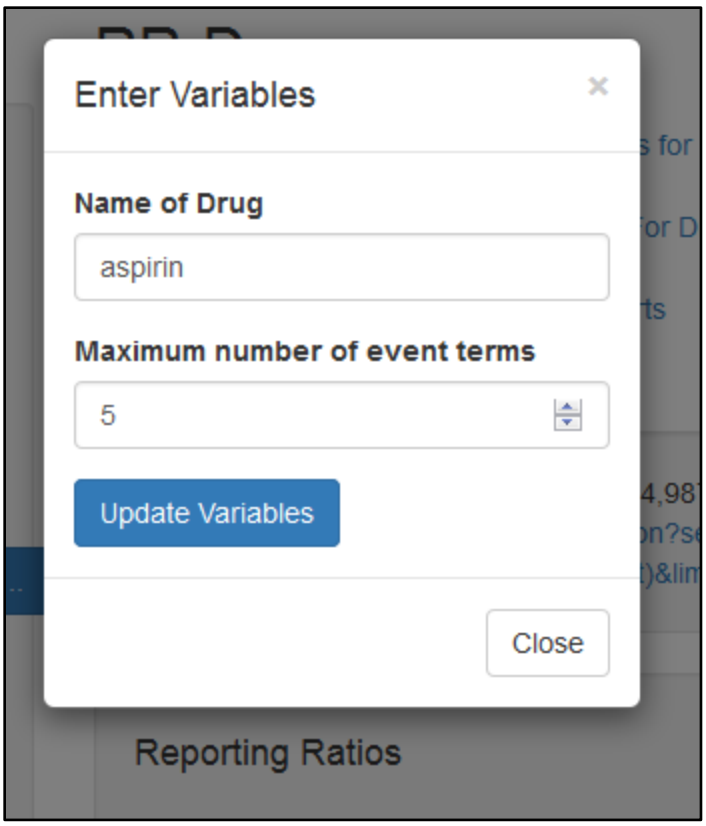


Figure 2. Data entry box for step 2.

3. The application will begin to fetch aspirin data from openFDA. After a few seconds, you will see the following display:

Total reports with Drug ASPIRIN in database: 169,838
Query: https://api.fda.gov/drug/event.json?search=_exists_:(patient.reaction.reactionmeddrapt.exact)+AND+patient.drug.openfda.generic_name.exact:(%22ASPIRIN%22)&limit=1&skip=0

Reporting Ratios

Results sorted by PRR

Table | Word Cloud

	M	Preferred Term	Counts for ASPIRIN	Counts for All Reports	PRR	Dynamic PRR	Change Point Analysis	ROR
1	M	FLUSHING	10,071	42,843	7.60	FLUSHING PRR	FLUSHING CPA	6.36
2	M	DYSPNOEA	9,446	140,338	1.78	DYSPNOEA PRR	DYSPNOEA CPA	1.77
3	M	DIZZINESS	8,519	127,907	1.76	DIZZINESS PRR	DIZZINESS CPA	1.75
4	M	FATIGUE	7,461	153,531	1.26	FATIGUE PRR	FATIGUE CPA	1.26
5	M	NAUSEA	9,319	194,645	1.24	NAUSEA PRR	NAUSEA CPA	1.24

Figure 3. Partial display of the results from Step 2, showing the data for Table 1 in the main paper.

4. At the top of the display you can see that there are a total of 169,838 reports that contain aspirin. Below this count is the actual query used to get this value. You can click on the query to see the JSON output in your browser. In general, all blue text is a hyperlink to other information and hovering over the text will display the link. In particular, a number

that is a hyperlink will open an application that displays the individual reports.

5. In the body of the table we can see that "flushing" is the most common event, with 6% (10,071/169,838) of all reports mentioning aspirin also mentioning flushing. The PRR for "FLUSHING" is 7.60, indicating that a report containing aspirin is more than seven times as likely to include flushing as a report that does not contain aspirin.

6. In case you do not know what flushing is, you can click on the "M" next to "FLUSHING", and a new browser window with the Medline Plus definition will open.

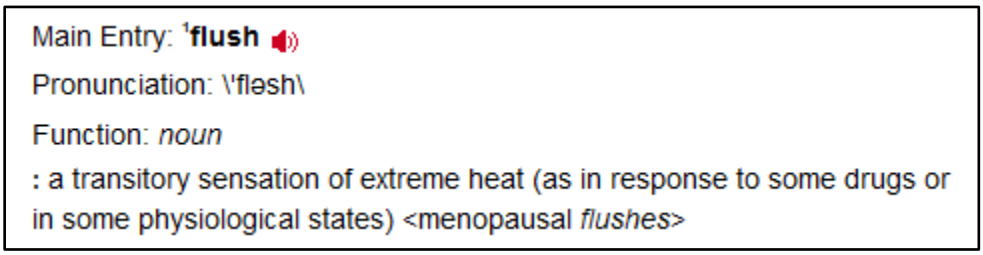
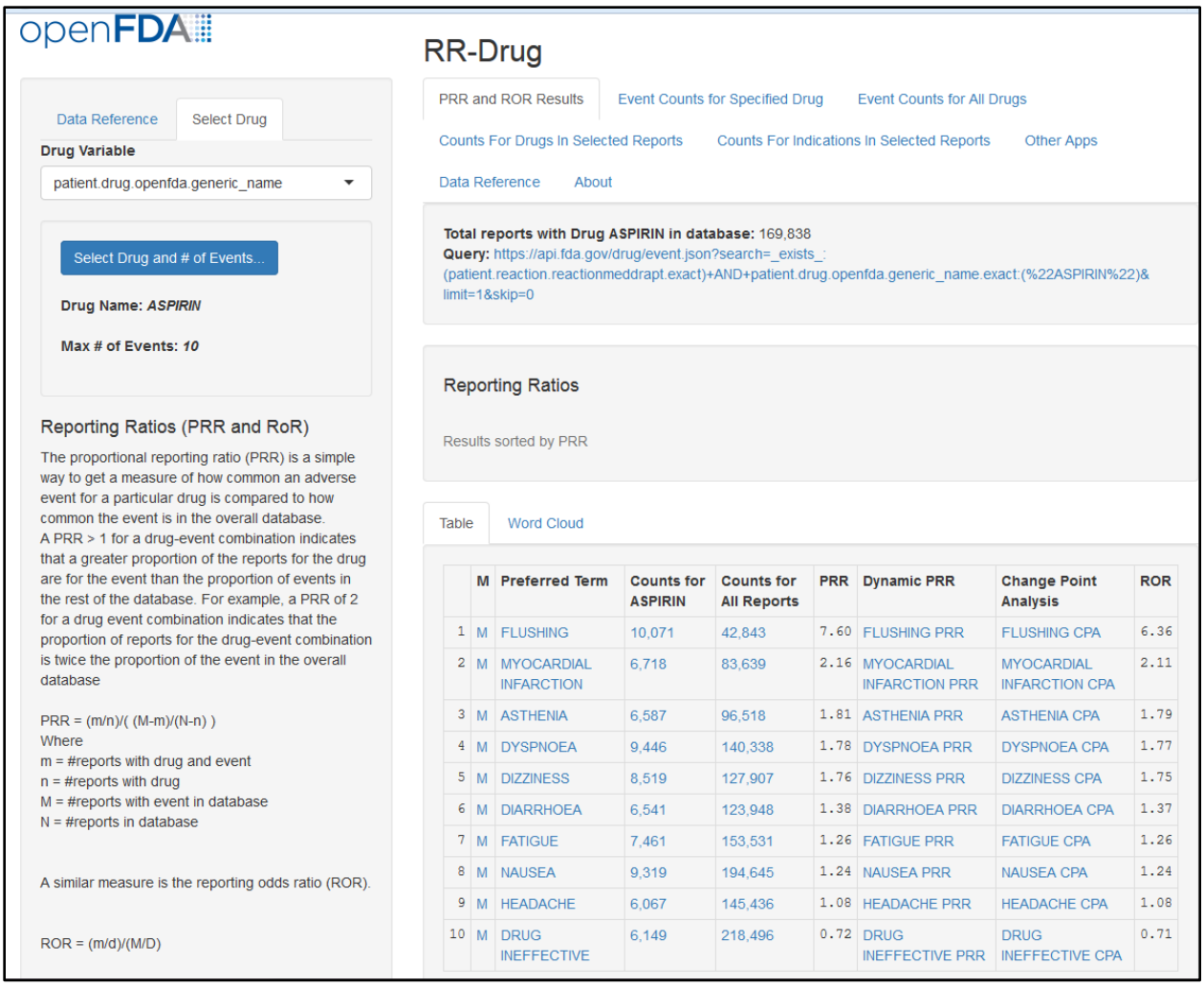


Figure 4. Display box that results from pressing the blue "M" button next to the Preferred Term "FLUSHING".

7. **Important side note:** Changing the maximum # of events will change the results, for example, Figure 5 shows what happens if the maximum # of events is 10. This happens because the openFDA query searches by count, and the R statistics program calculates the PRR and sorts by PRR within the top # of counts. Note that the counts for flushing, dyspnea, dizziness, fatigue, and nausea are the same in Figures 3 and 5. Myocardial infarction and asthenia had lower counts, but appear higher up in Figure 5 because the PRRs for them are higher than for dyspnea, dizziness, fatigue, and nausea.



	M	Preferred Term	Counts for ASPIRIN	Counts for All Reports	PRR	Dynamic PRR	Change Point Analysis	ROR
1	M	FLUSHING	10,071	42,843	7.60	FLUSHING PRR	FLUSHING CPA	6.36
2	M	MYOCARDIAL INFARCTION	6,718	83,639	2.16	MYOCARDIAL INFARCTION PRR	MYOCARDIAL INFARCTION CPA	2.11
3	M	ASTHENIA	6,587	96,518	1.81	ASTHENIA PRR	ASTHENIA CPA	1.79
4	M	DYSPNOEA	9,446	140,338	1.78	DYSPNOEA PRR	DYSPNOEA CPA	1.77
5	M	DIZZINESS	8,519	127,907	1.76	DIZZINESS PRR	DIZZINESS CPA	1.75
6	M	DIARRHOEA	6,541	123,948	1.38	DIARRHOEA PRR	DIARRHOEA CPA	1.37
7	M	FATIGUE	7,461	153,531	1.26	FATIGUE PRR	FATIGUE CPA	1.26
8	M	NAUSEA	9,319	194,645	1.24	NAUSEA PRR	NAUSEA CPA	1.24
9	M	HEADACHE	6,067	145,436	1.08	HEADACHE PRR	HEADACHE CPA	1.08
10	M	DRUG INEFFECTIVE	6,149	218,496	0.72	DRUG INEFFECTIVE PRR	DRUG INEFFECTIVE CPA	0.71

Figure 5. Partial display of results for sidenote in Step 7, showing the results for the same query in Figure 3, except that the maximum # of events is set to 10.

If one is most interested in finding the top PRRs, a good strategy is to ask for many more events than one anticipates needing. The current maximum is 999, which taxes the computational power of the system. This is on the list of issues to be addressed by future programming and the authors welcome suggested algorithms for improvement.

8. Labeling for aspirin does not include flushing in the list of adverse events. Before concluding that aspirin causes flushing, one must rule out non-causal explanations of the association, including, but

not limited to: 1) the association was a chance occurrence, 2) an extraneous event resulted in the apparent association, 3) the event was related to the underlying condition that prompted the medication use, and 4) other medications are responsible for the relationship.

9. If the flushing signal is a real signal, we would expect it to be stable over time. If we click on the "FLUSHING PRR" link in the table, we can see how the PRR has changed over time.

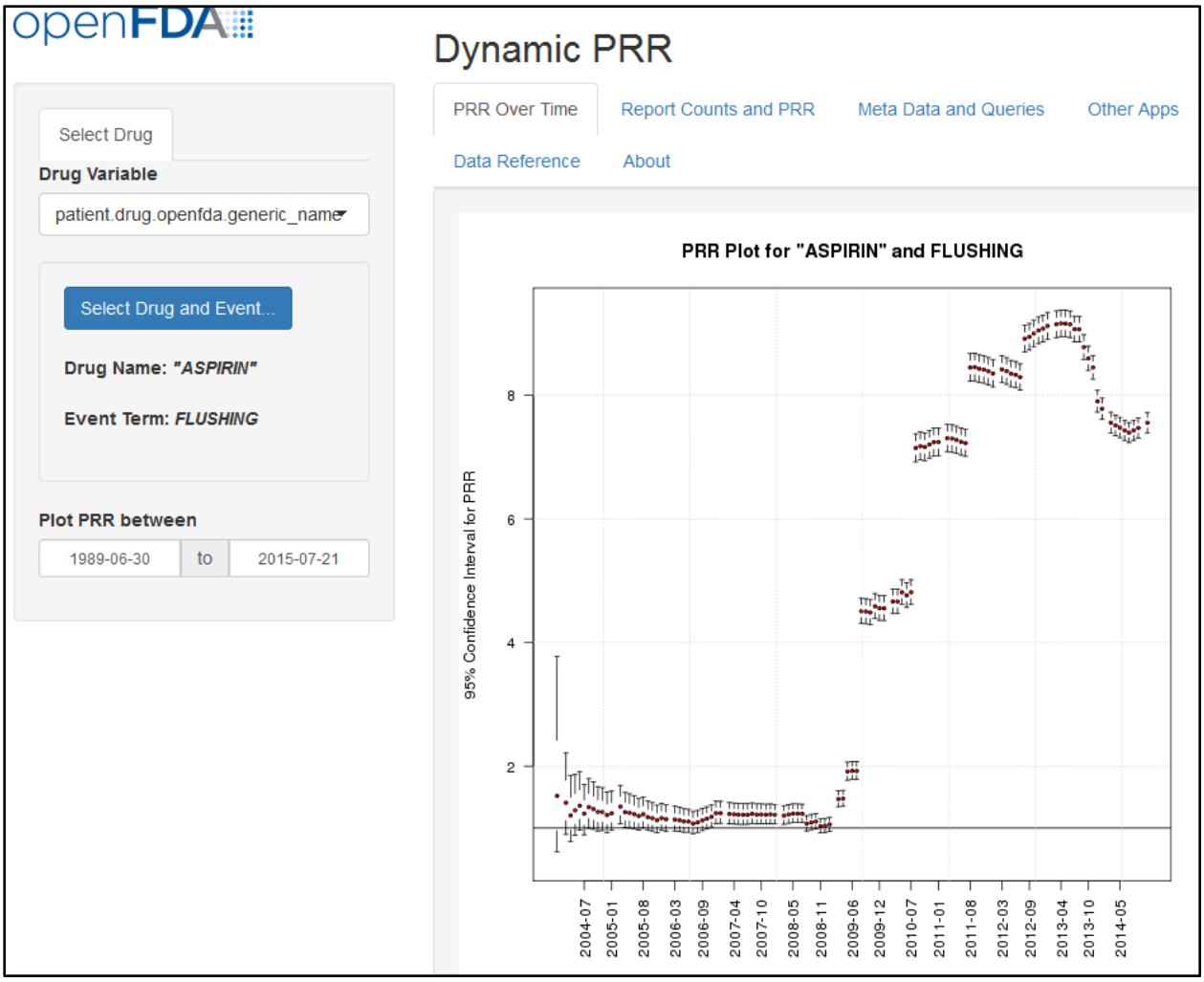
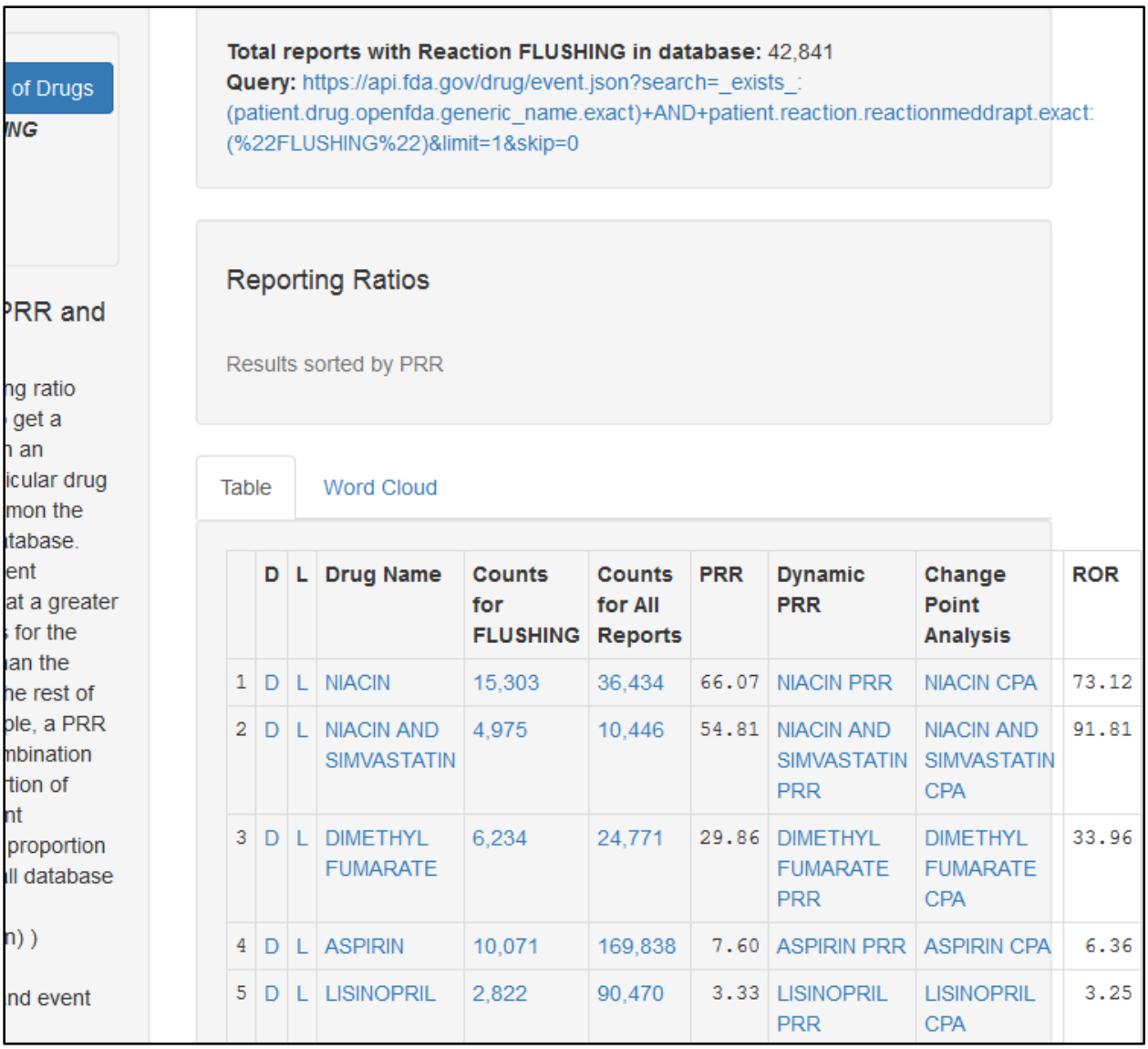


Figure 6. Display of the PRR plot for ASPIRIN and FLUSHING.

The PRR has not been constant over time. Before 2009 there was little or no statistical

association between aspirin and flushing, with the PRR values only slightly above 1, and the 95% confidence intervals often including 1. After 2008 we see the PRR rapidly increase to 4, and then increase further to between 7 and 9. The confidence intervals for post 2008 data all exclude 1, so these are unlikely to be a chance association. No further insights were gained from using change point analysis[10, 12] to detect points in time at which statistical properties of the time series change. What could cause this behavior? Two possibilities are a change in the way aspirin is used, or a change in the drugs that are used with aspirin. Our analysis will focus on the types of drugs used with aspirin.

10. In order to get a sense of which drugs are commonly associated with flushing, we look at the PRRs for most common drugs with the event FLUSHING. We can get to an analysis of the event "FLUSHING" by clicking on the "FLUSHING" link in the "Preferred Term" column from Step 3. In this analysis we see that NIACIN, NIACIN AND SIMVASTATIN, DIMETYL FUMARATE, ASPIRIN, and LISINOPRIL are the drugs most commonly associated with FLUSHING. All of these drugs have PRRs > 3.



Total reports with Reaction FLUSHING in database: 42,841
Query: https://api.fda.gov/drug/event.json?search=_exists_:(patient.drug.openfda.generic_name.exact)+AND+patient.reaction.reactionmeddrapt.exact:(%22FLUSHING%22)&limit=1&skip=0

Reporting Ratios

Results sorted by PRR

Table | Word Cloud

	D	L	Drug Name	Counts for FLUSHING	Counts for All Reports	PRR	Dynamic PRR	Change Point Analysis	ROR
1	D	L	NIACIN	15,303	36,434	66.07	NIACIN PRR	NIACIN CPA	73.12
2	D	L	NIACIN AND SIMVASTATIN	4,975	10,446	54.81	NIACIN AND SIMVASTATIN PRR	NIACIN AND SIMVASTATIN CPA	91.81
3	D	L	DIMETHYL FUMARATE	6,234	24,771	29.86	DIMETHYL FUMARATE PRR	DIMETHYL FUMARATE CPA	33.96
4	D	L	ASPIRIN	10,071	169,838	7.60	ASPIRIN PRR	ASPIRIN CPA	6.36
5	D	L	LISINOPRIL	2,822	90,470	3.33	LISINOPRIL PRR	LISINOPRIL CPA	3.25

Figure 7. Partial display of results from step 10.

11. Going back to the display in step 3, if we look at the “Counts for Drugs In Selected Reports” tab, we see that both niacin and lisinopril are commonly given with aspirin. In contrast, “dimethyl fumarate” is not one of the 100 most commonly used drugs.

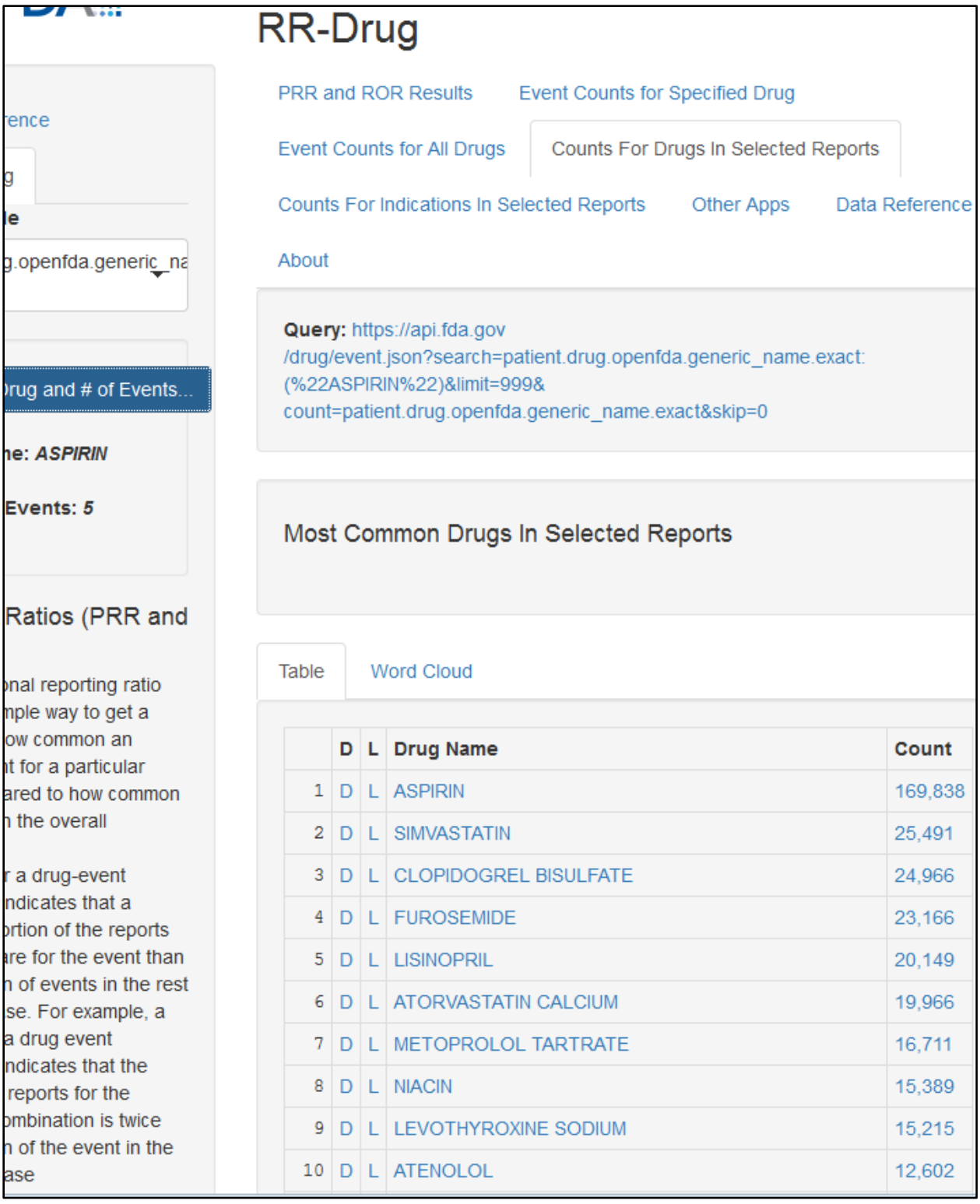


Figure 8. Partial display of results for step 11.

Using openFDA drug labeling, we found that the drugs in Figure 8 that list “flushing” are “niacin,” “niacin and simvastatin,” and “lisinopril.” The combination of niacin with simvastatin was first approved as Simcor, 19 February 2008, just before the rise in reports noted in Figure 6. Niacin was reported to reduce the risk of myocardial infarction and stroke in 1975, and to reduce atherosclerosis beginning in 1987.[13] Consensus guidelines for niacin therapy were published in 2012 and 2013.[14-15] Lisinopril was approved in 1988.[16]

12. We then test whether these three drugs explain all of the apparent association between aspirin and flushing. We can analyze the aspirin reports that don’t contain niacin by clicking on the “Select Drug and # of Events…” button and enter “ASPIRIN NOT(NIACIN)”, waiting a few seconds, and then clicking the tab “PRR and ROR Results”. You can see flushing is no longer one of the five most related events. If you rerun the analysis with “Max # of Events” set to 100 you will find that flushing is not in the first 100 most related events once we remove niacin. This indicates that the flushing effect was largely or entirely due to niacin.

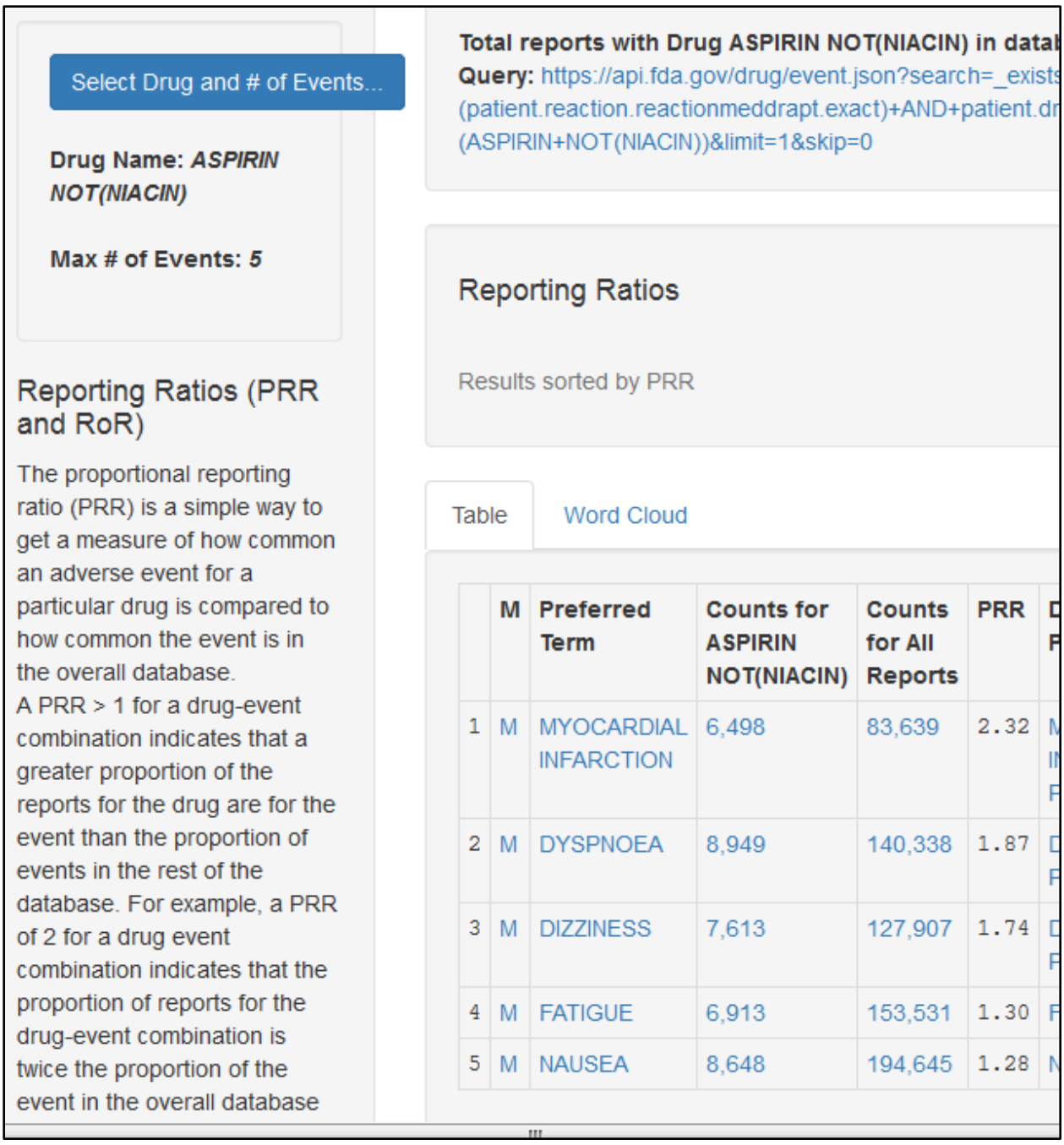


Figure 9. Partial display of results for step 12.

13. Now let's look at lisinopril with count=25. In contrast to what we saw with niacin, removing the lisinopril reports only slightly reduces the PRR.

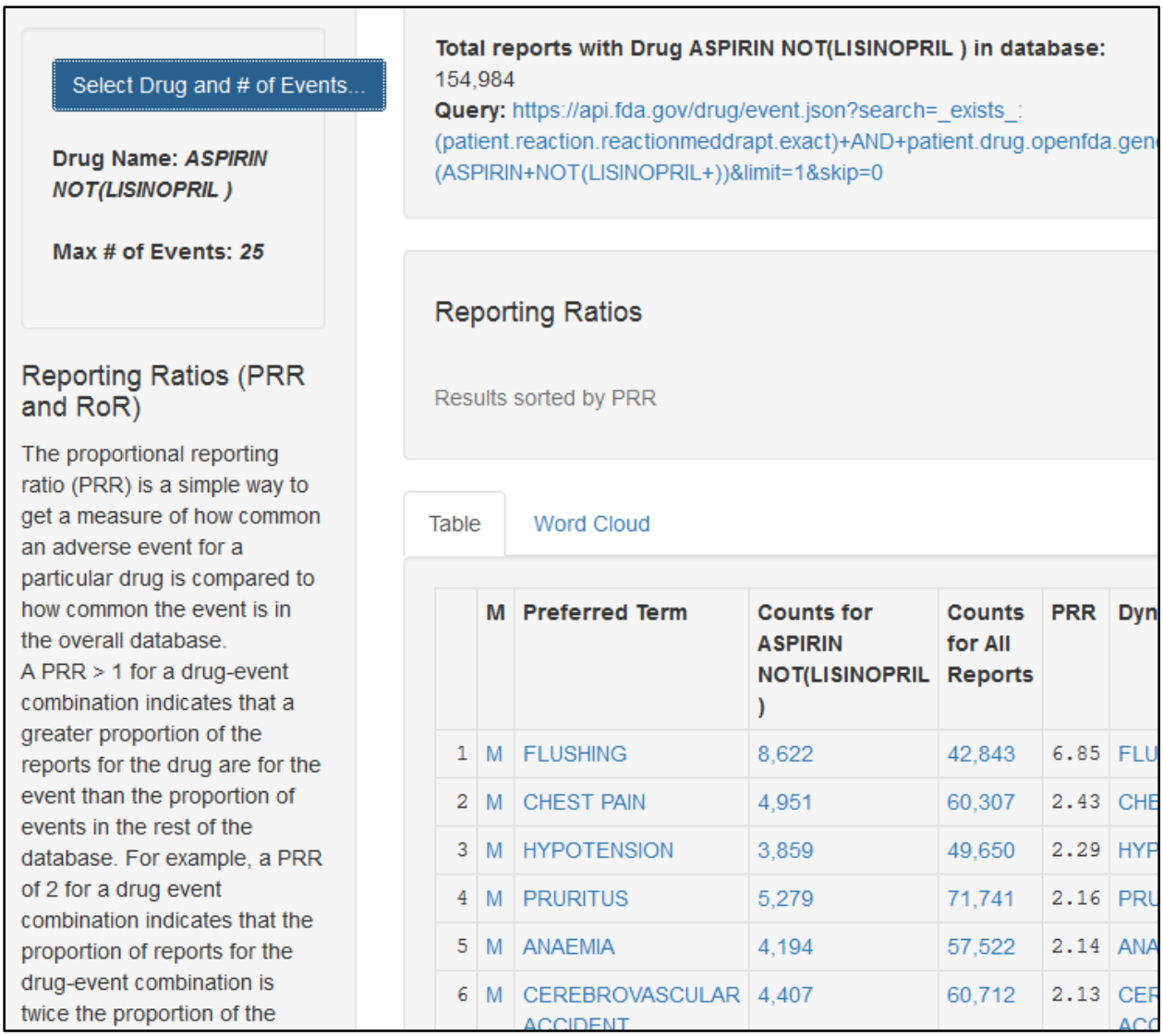


Figure 10. Display associated with step 13.

14. Similarly, if we look at lisinopril reports that don't contain niacin, we don't see "FLUSHING" among the first 25 events.

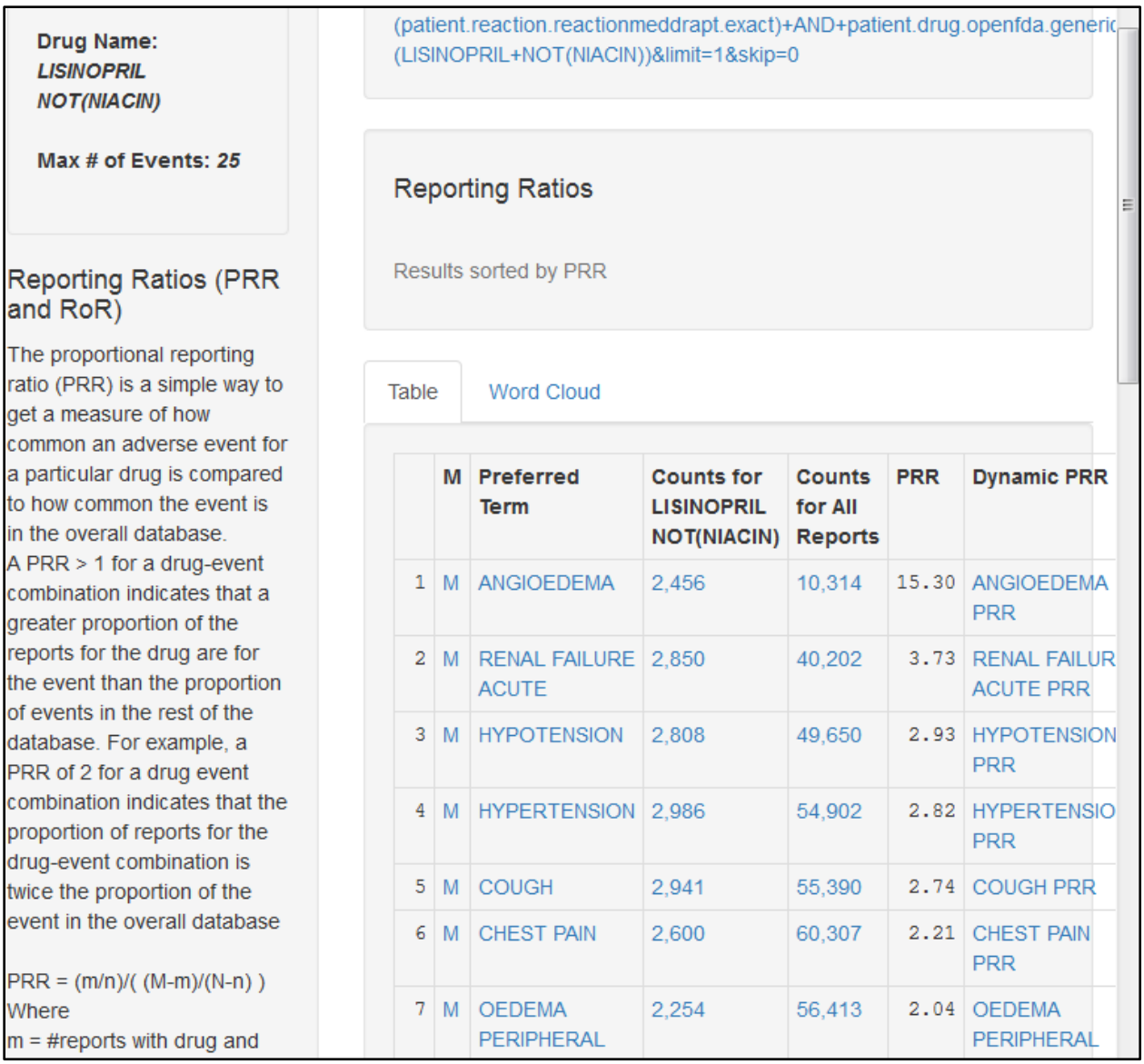


Figure 11. Partial display of results for step 14.

15. What about dimethyl fumarate? If we look at look at ""dimethyl fumarate not(niacin)" we still see a large (30) PRR for dimethyl fumarate (note that we need to include dimethyl fumarate in quotes. Otherwise openFDA will include all drugs that contain either dimethyl or fumarate).

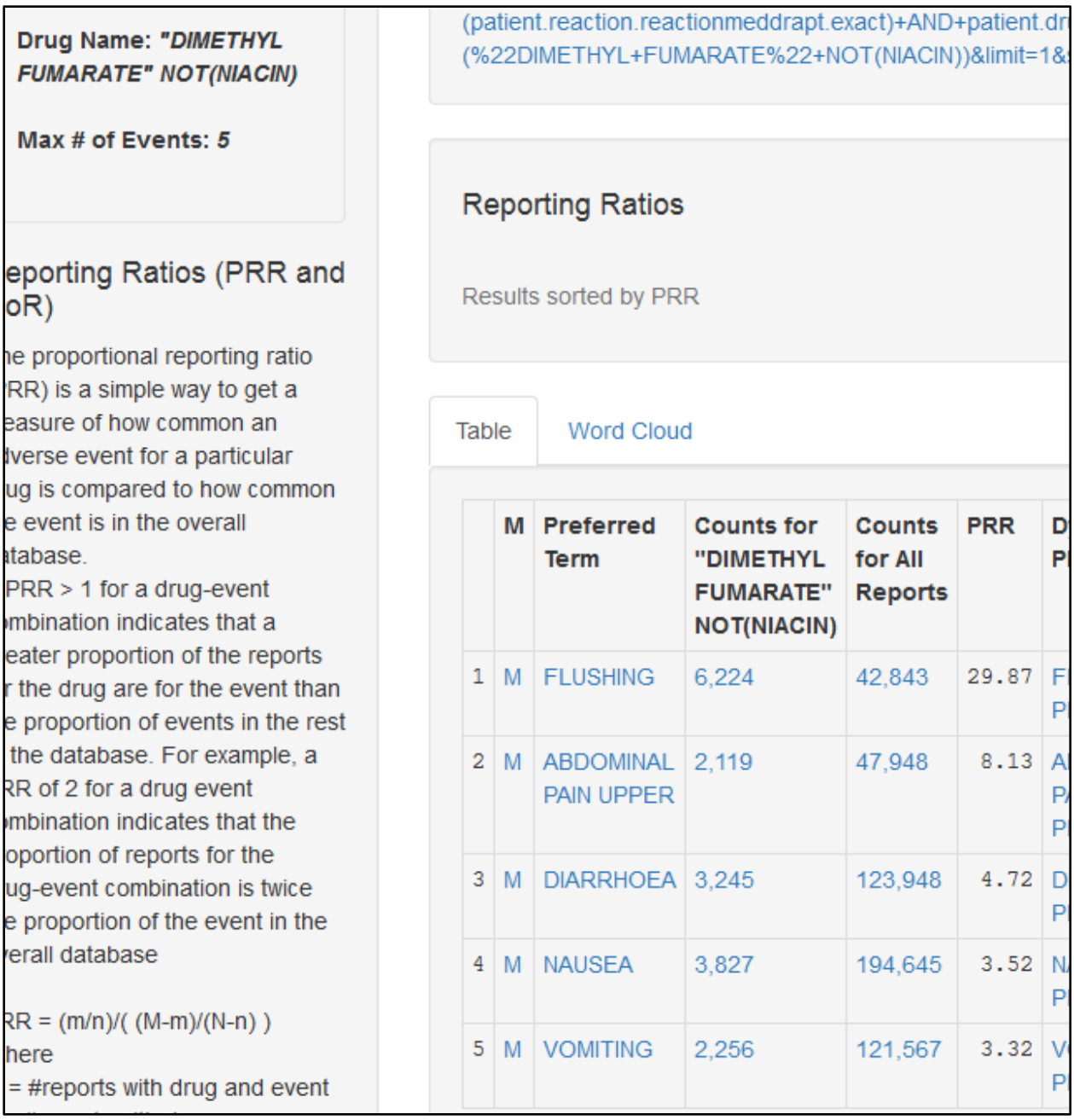


Figure 12. Partial display of results for step 15.

16. If we are interested in seeing which drugs are labeled for flushing, we can look at the PRR analysis for FLUSHING (Figure 7) and click on the link labeled “L” next to the drug name of interest. If we do this for “DIMETYL FUMARATE” we get the following:

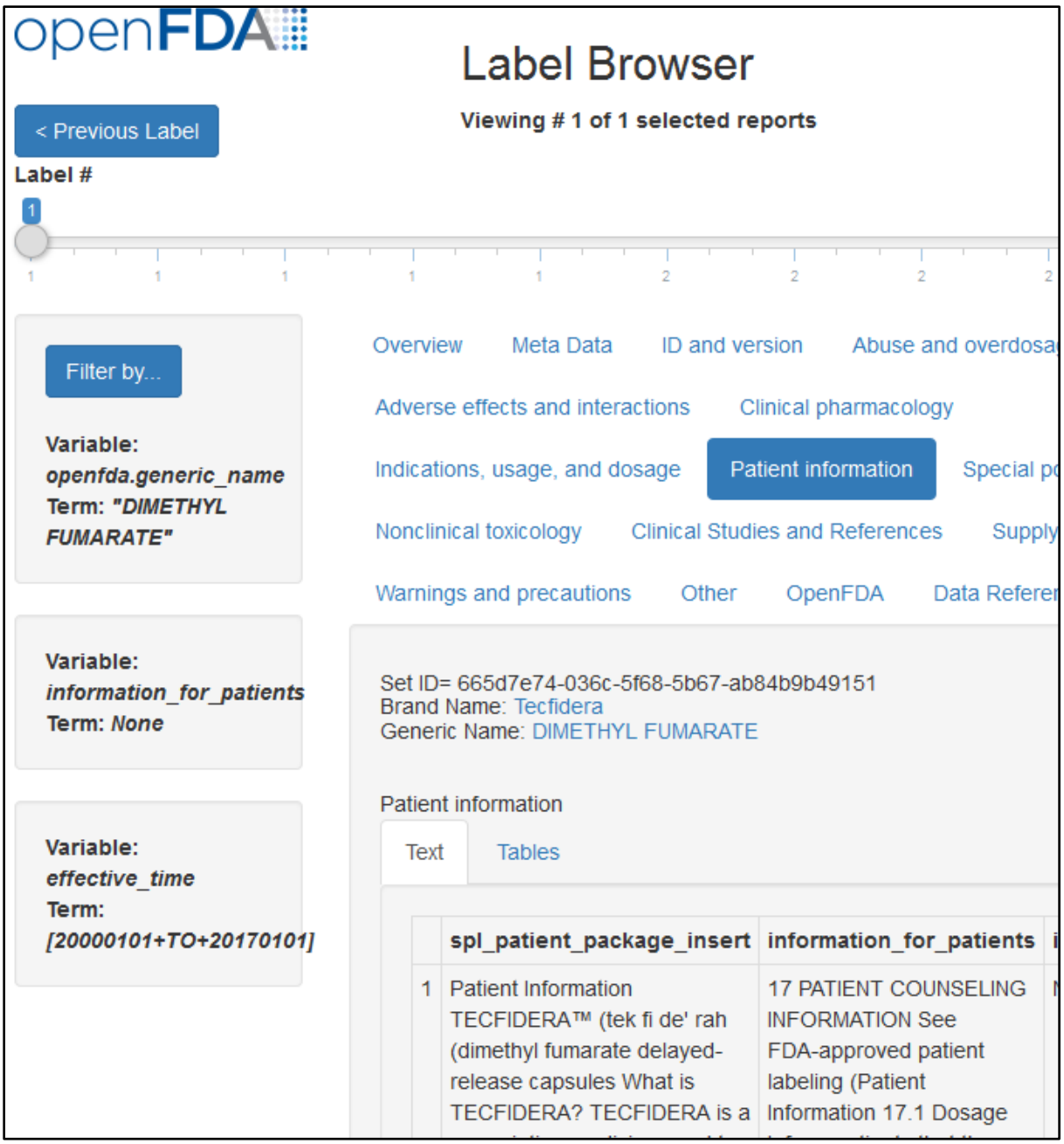


Figure 13 Display for step 16.

If we scroll down the “information_for_patients” field, we see this text:

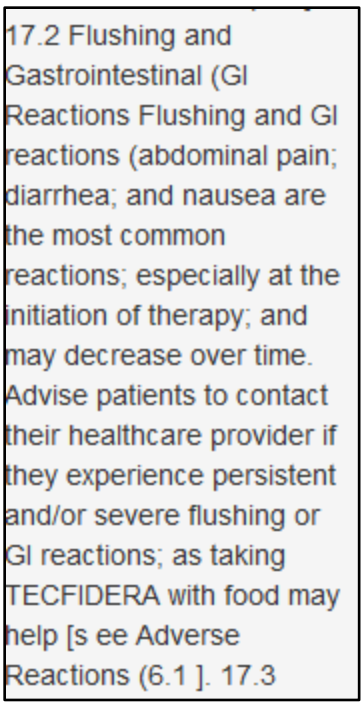


Figure 14. Display of "information for patients" field for "DIMETHYL FUMARATE".

A similar review of the niacin labels will show that flushing is also listed as a reaction for niacin.

17. Looking at the association of flushing and any drug with "niacin" in the generic name shows a very large PRR for flushing, and large PRR for terms that could be associated with flushing, such as "feeling hot", "pruritis", "erythema", and "paraesthesia".

Summary

We have demonstrated that a drug-event association is unlikely to be causal. Research beyond the reporting data is usually essential to fully understand the relationship between drug-event

pairs. For example, Cefali et al. (2007) found that aspirin is a good way to treat flushing. [44] Our case may be a drug (niacin) causing the event (flushing), and an event (flushing) leading to use of the drug (aspirin).

If the association of aspirin and flushing had remained after removing reports that also mentioned niacin and lisinopril, one could have given serious consideration to searching the labeling for drugs that mention synonyms for flushing and then repeating the above analyses with the synonyms and additional drugs.

Apparent associations that survive initial analysis with just the reports, are then often analyzed in light of other data, such as relative sales data, health care claims data, premarketing data, and original clinical studies.

By: Jonathan Levine, PhD, Roselie A. Bright, ScD, Elaine Johanson Taha A. Kass-Hout, MD, and Zhiheng Xu, PhD

References

1. Guidance for Industry. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. *Food and Drug Administration, US Department of Health and Human Services*. March, 2005. http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf. Accessed in February 2015.
2. Tsong Y. Comparing reporting rates of adverse events between drugs with adjustment for year of marketing and secular trends in total reporting. *J Biopharm Stat* 1995; 5:95-114.
3. McAdams M, Staffa J, Dal Pan G. Estimating the extent of reporting to FDA: a case study of statin-associated rhabdomyolysis. *Pharmacoepidemiol Drug Safety*. 2008 Mar,17(3): 229-39.
4. Dasgupta N, Mandl KD, Brownstein JS. Breaking the news or fueling the epidemic? Temporal association between news media report volume and opioid-related mortality. *PLoS One*. 2009;4(11):e7758. doi:10.1371/journal.pone.0007758.
5. Bate A, Evans, S. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol and Drug Saf* 2009 Jun;18(6):427-36. doi: 10.1002/pds.1742.
6. Szarfman A, Tonning JM, Doraiswamy PM. Pharmacovigilance in the 21st century: new systematic tools for an old problem. *Pharmacotherapy* 2004 Sep;24(9):1099-104.
7. Levine J. openFDA RR. https://openfda.shinyapps.io/RR_D . Accessed in July 2015.
8. Levine J. openFDA RR-Event. https://internal.shinyapps.io/openfda/RR_E/ . Accessed in July 2015.
9. Levine J. openFDA Dynamic PRR. https://internal.shinyapps.io/openfda/dynprr/ . Accessed in July 2015.

10. Levine J. openFDA Change Point Analysis. https://openfda.shinyapps.io/ChangePoint . Accessed in July 2015.

11. Levine J. Report Browser. https://openfda.shinyapps.io/reportview . Accessed in July 2015.

12. Kass-Hout TA, Xu Z, McMurray P, et al. Application of change point analysis to daily influenza-like illness (ILI) emergency department visits. *JAMIA*, 2012. Doi:10.1136/amiajnl-2011-000793.

13. Subedi FH, Joshi PH, Jones SR, et al. Current guidelines for high-density lipoprotein cholesterol in therapy and future directions. *Vasc Health Risk Manag*. 2014;10:205-216.

14. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *National Guideline Clearinghouse, Agency for Healthcare Research and Quality*. 2012. Retrieved from www.guideline.gov/content.aspx?id=38432&search=niacin in May 2015.

15. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation*. 2013; doi:10.1161/01.cir.0000437738.63853.7a.

16. Drugs@FDA: FDA Approved Drug Products. Searched for "Zestril". *Food and Drug Administration*. Retrieved from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm in May 2015.

17. Cefali EA, Simmons PD, Stanek EJ, et al. Aspirin reduces cutaneous flushing after administration of an optimized extended-release niacin formulation. *Int J Clin Pharmacol Ther.* 2007 Feb;45(2):78-88.