Paper AS07

Detriment Index based safety ranking of Opioid drugs

Samadhan Ghubade, Cytel, Pune, India

ABSTRACT

Deaths due to opioid overdose are a serious problem. Aim is to rank common opioid drugs in terms of safety.
This paper discusses a method to rank drugs by fitting exponential growth model to accumulated count of adverse drug reactions. In the exponential model, the coefficient in the exponent (growth rate) is robust and remains the same whether counts are corrected for total exposure or not and hence can be used as an index of safety comparable across drugs with different levels of exposure. Rate of growth is detriment index. Higher value of growth rate implies sharper rise in cumulative count. Individual drugs can be ranked based on growth rate. Smaller the value of growth rate safer is the drug. Data are sourced from VigiBase®, the World Health Organization's (the "WHO") global database for adverse drug reactions ("ADRs"), maintained by the Uppsala Monitoring Centre (the "UMC") [1] and Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) [2].

INTRODUCTION

Deaths due to opioid overdose are a serious problem. Extensive use of opioid painkiller drugs is a fact of life today. Economist (April 6, 2017) states that 'Americans now consume four-fifths of the global supply (of opioid drugs)'. According to American Society of Addiction Medicine, "in 2015, 2 million (Americans) had a substance use disorder involving prescription pain relievers" [3]. Safety aspects of these drugs cannot be overemphasized. According to Centers for Disease Control and Prevention '130 Americans die every day from an opioid overdose' [4]. On October 26, 2017, US President Trump directed the Department of Health and Human Services to declare the opioid crisis a public health emergency, taking long-anticipated action to address a rapidly escalating epidemic of drug use [5]. 70,237 drug overdose deaths occurred in the United States in 2017 [6]. Severity of the opioid crisis has received considerable attention by investigative journalists. To quote the New York Times "'Dopesick' (A recent book on tragedy caused in West Virginia by spread of Oxycontin) Traces the Opioid Crisis, From Beginning to Blow Up" [7]. Even celebrities like Tom Hanks are moved to say "Dopesick is a deep and deeply needed look in to the troubled soul of America" [8].

This paper addresses the question of safety comparison amongst drugs in general and more specifically opioids. A study comparing six opioids in rats found that fentanyl's "side-effect profiling compared to the other opioids was acceptable" [9]. Another study points out that "on individual patient basis, opioids are not all equal" and hence recommendation is "to individualize treatment" [10]. A study comparing five opioid drugs found that codeine looked much riskier than the other four drugs (hydrocodone, oxycodone, propoxyphene, tramadol) with respect to cardiovascular events and all-cause mortality when they were prescribed for pain not related to cancer. These "findings on differential risks of various opioids challenge the conventional notion that the safety profiles of opioids are generally interchangeable". The issue has immediate implications. "If codeine is of middling efficacy for pain and is more risky than other opioids, there would be little reason to use it" [11]. Yet another study found that "The risk of cardiovascular events was similar across opioid groups 30 days after the start of opioid therapy" but diverged after 180 days [12].
It would seem reasonable to suggest that further inquiries about safety comparison of opioids are relevant and potentially useful.

Approach here is to base the comparisons on counts of spontaneous ADR reports. ADR reports are a crucial piece in the drug safety jig saw puzzle. These data in the public domain seem to be underutilized. A general tendency in many countries is to restrict physician's use of opioids to morphine. Randomized studies provide little evidence that, at equi-analgesic doses, commonly used opioids differ markedly in their side effects. In head to head comparisons, most studies have failed to show relevant differences between drugs on a population level [13]. Instead of these conventional approaches, a model based index may be better suited to provide a bird's-eye-view assessment of relative drug safety. What should we expect from such a measure? It should be a single number with the ability to reflect a general trend in ADR report counts. In other words, large value of the measure should go with larger ADR report count and vice versa. Secondly it should be robust and not sensitive to volume of exposure. Lastly, it should facilitate safety comparison among drugs even if its absolute value is of limited significance.

There is a formidable difficulty in using a single number for comparison across a group of drugs. The number may depend on annual volume of drug use or exposure. Generally, ADR counts increase as the drug comes into widespread use. That by itself does not mean that the drug is unsafe. Conversely, a drug that is not popular should not be deemed as safer simply because of lower ADR report counts. Instead, to ensure comparability, counts should be normalized/ scaled down appropriately. As an example, while comparing two drugs, if one drug is twice as much in use as the other drug, we should divide the ADR count of the first, more popular drug, by two and then compare with the counts in the other drug. Unfortunately, there are multiple ways of normalizing values. As one possibility, one may divide the ADR count by sales figures. Number of prescriptions and number of patients taking the drug are two other alternatives. Which of these should be chosen? Will the index and rank of the drug depend on that choice? Such difficulties can be eliminated if the index is unaffected by correction for exposure. Fitting a mathematical model to cumulative ADR counts can lead to development of such a suitable index.

Use of exponential model

We have used the exponential model to rank two groups of drugs; a group of contraceptives and a group of opioids. The purpose behind examining the contraceptives is to check whether applicability of our method to opioids is accidental or whether it is useful more generally.

Contraceptive drugs

There is considerable interest in comparative safety of contraceptives. *Etminan et al* examine the risk of gall bladder problems [14]. *Meador et al* find that in terms of adverse events a contraceptive patch is comparable to a conventional oral contraceptive [15]. Our aim is to compare a group of 7 contraceptives. Out of the lot we display as illustration the exponential model in Figure 1. This demonstrates that our approach works well. Table 1 gives the summary of such exercise for all 7 contraceptives.

Figure 1: Fitting exponential model to Etonogestrel data

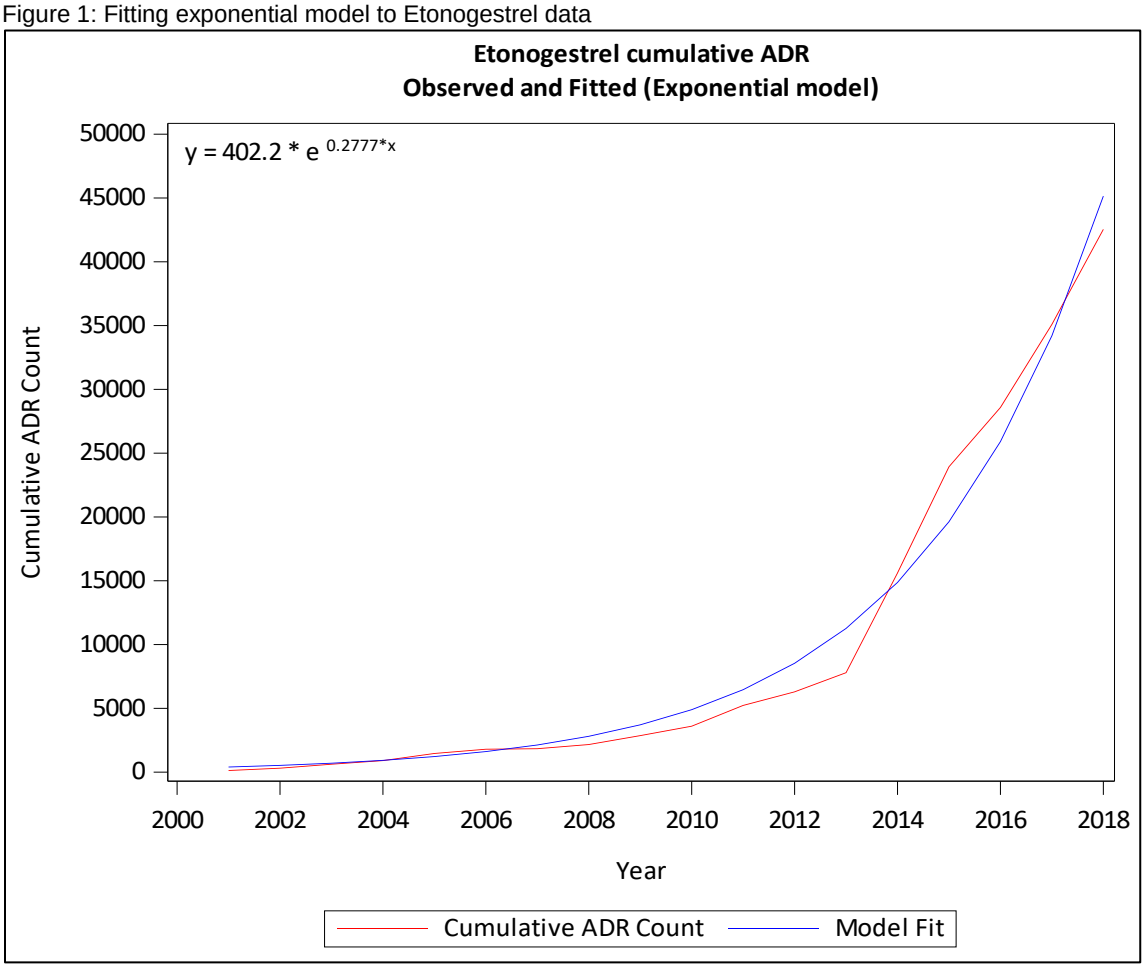

Table 1: Fitting exponential model to cumulative ADR counts of Contraceptives and ranking based on growth rate				
Sr.No.	Drug Name	Equation	Detriment Index (β)	Rank
1	Norethisterone	$y = 162e^{0.0639x}$	0.0639	1
2	Estradiol	$y = 388.6e^{0.0910x}$	0.0910	2
3	Medroxyprogesterone	$y = 500.4e^{0.0943x}$	0.0943	3
4	Levonorgestrel	$y = 171.4e^{0.1597x}$	0.1597	4
5	Desogestrel	$y = 5.7941e^{0.1988x}$	0.1988	5
6	Etonogestrel	$y = 402.2e^{0.2777x}$	0.2777	6
7	Dienogest	$y = 0.8055e^{0.4400x}$	0.4400	7

Going by the detriment index (Table 1) it is seen that Norethisterone is the safest while Dienogest is the least safe.

Opioid drugs

We begin by checking if the exponential model gives a reasonable fit to ADR data on opioids. Following display (Figure 2) shows that the red curve representing cumulative sum of counts for Pethidine is followed closely by the fitted exponential curve. Notice also that the estimated value of β is 0.2913.

Figure 2: Fitting exponential model to Pethidine data

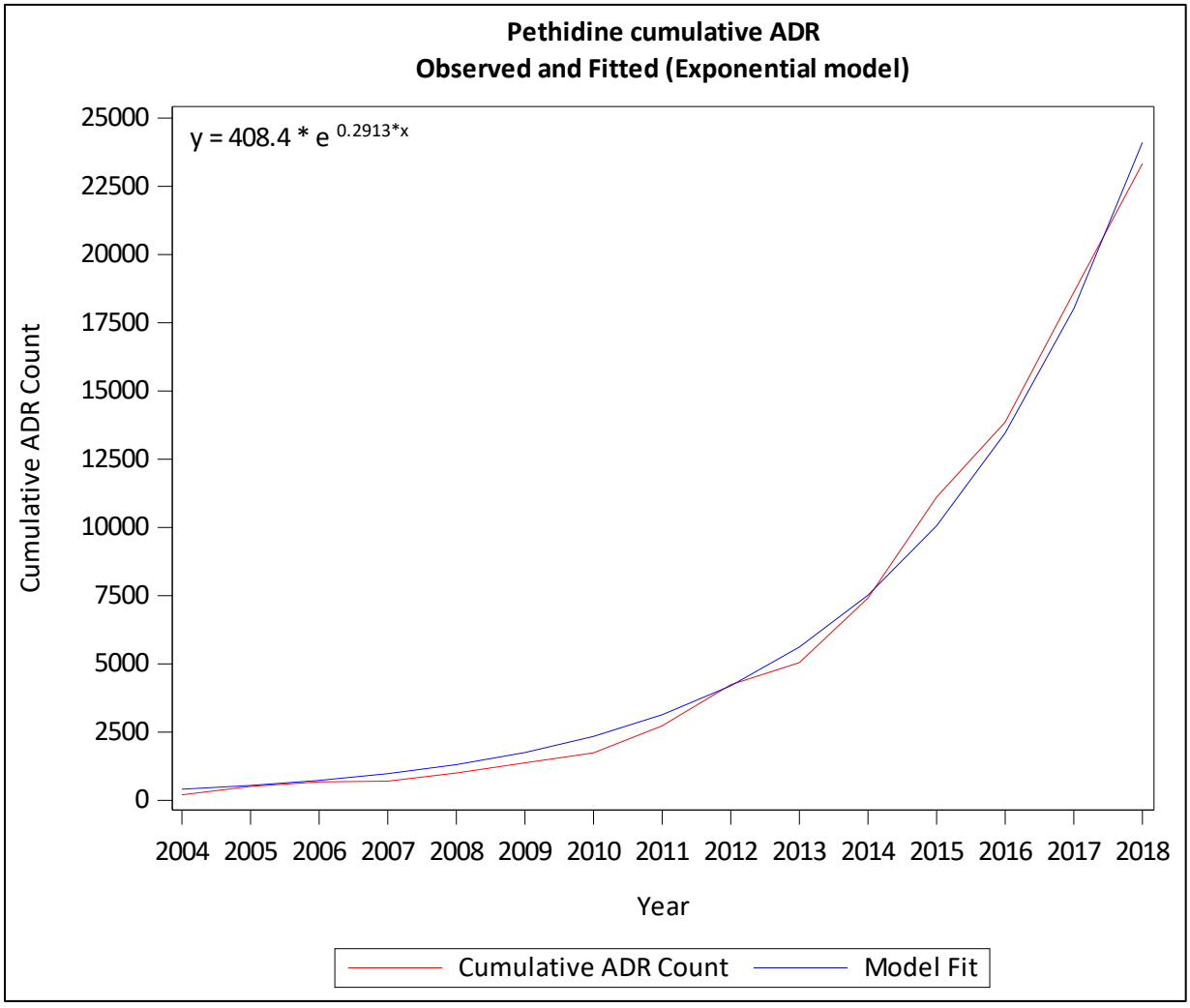

Figure 2 depicts that the fitted exponential curve (highlighted in blue) is close to cumulative ADR count (highlighted in red).

In using SAS 9.4 exponential model fitting can be done with the help of two SAS procedures: `proc reg and proc nlin,` first to get initial estimates by linearization and second to get optimal estimates by non-linear regression. Further, a figure showing data on actual and estimated cumulative counts can be done using `proc sgplot.` (Please see SAS dummy code given below)

```
*Raw data contains yearly count of adverse drug reactions and cumulative sum;
data Drug;
       set raw;
       log_cusum=log(cusum);
run;

*Linear Regression Fitting to estimate alpha and beta estimates;
ods graphics off;
proc reg data=Drug;
      model log_cusum=Year / r clm cli;
       output out=regout pred=p_reg;
run;
quit;

ods graphics off;
*Non-Linear Regression- Exponential model fitting;
proc nlin data=Drug;
      parms alpha=5.6522 beta=0.3227;
      model cusum=alpha*exp(beta*year);
       output out=nlinout pred=p;
run;

*Figure- Exponential model to Pethidine data;
title1 height=1.3 font= 'Calibri' "Pethidine cumulative ADR";
title2 height=1.3 font= 'Calibri' "Observed and Fitted (Exponential model)";

proc sgplot data=nlinout;
       series y=cusum x=Year / lineattrs= (color=red thickness=3 PATTERN=solid)
       LegendLabel="Cumulative ADR Count";
       series y=p x=Year / lineattrs= (color=blue thickness=3 PATTERN=solid)
       LegendLabel="Model Fit";
       xaxis values= (2004 to 2018 by 1) label= "Year";
       yaxis values= (0 to 25000 by 2500) label= "Cumulative ADR Count";
       inset "y = 408.4 * e (*ESC*) {sup '0.2913*x'}”/ position=topleft;
run;
ods rtf close;
```

The results of this computation are displayed above in Figure 2. Similar procedure has been used for individual group of data sets.

Analogous results of fitting exponential model to data on cumulative ADR counts (Yearly count from 2004 to 2018) for several other opioids are given in Table 2. They are ranked based on the value of the growth rate.

Table 2: Fitting exponential model to cumulative ADR counts of Opioids and ranking based on growth rate

Sr.No.	Drug Name	Equation	Detriment Index (β)	Rank
1	METHADONE	$y = 1931.2e^{0.1559x}$	0.1559	1
2	AMITRIPTYLINE	$y = 1442.4e^{0.1871x}$	0.1871	2
3	OXYCODONE	$y = 4565.6e^{0.2058x}$	0.2058	3
4	TRAMADOL	$y = 3346.3e^{0.2442x}$	0.2442	4
5	FENTANYL	$y = 4551.9e^{0.2467x}$	0.2467	5
6	CODEINE	$y = 383.4e^{0.2473x}$	0.2473	6
7	MORPHINE	$y = 2094.3e^{0.2542x}$	0.2542	7
8	VICODIN	$y = 637.6e^{0.2828x}$	0.2828	8
9	PETHIDINE	$y = 408.4e^{0.2913x}$	0.2913	9
10	HYDROMORPHONE	$y = 10.3263e^{0.5809x}$	0.5809	10
11	PERCOCET	$y = 0.4867e^{0.7902x}$	0.7902	11
12	HYDROCODONE	$y = 0.0041e^{1.1288x}$	1.1288	12

The above table (Table 2) suggests that METHADONE is the safest while HYDROCODONE is the least safe. Clearly, for opioids, the ranking procedure based on exponential model goes through without glitch. However, this analysis has a drawback. In case of opioids the stark reality is a growing number of deaths due to overdose. Any approach that combines deaths with other adverse events may be frowned upon by clinicians. Hence, we need to examine (instead of all ADR counts) counts of deaths (Yearly count from 2004 to 2018). Such data are available in the FAERS data base [2].

Table 3: Fitting exponential model to cumulative counts of deaths of Opioids and ranking based on growth rate

Sr.No.	Drug Name	Equation	Detriment Index (β)	Rank
1	VICODIN	$y = 941.3e^{0.1209x}$	0.1209	1
2	PETHIDINE	$y = 126.8e^{0.1213x}$	0.1213	2
3	PERCOCET	$y = 641.9e^{0.1419x}$	0.1419	3
4	AMITRIPTYLINE	$y = 1204.7e^{0.1488x}$	0.1488	4
5	MORPHINE	$y = 3718.9e^{0.1509x}$	0.1509	5
6	CODEINE	$y = 1518.1e^{0.1536x}$	0.1536	6
7	HYDROCODONE	$y = 2331.4e^{0.1690x}$	0.1690	7
8	FENTANYL	$y = 2272.9e^{0.1702x}$	0.1702	8
9	METHADONE	$y = 1287.2e^{0.1752x}$	0.1752	9
10	OXYCODONE	$y = 2479.7e^{0.1784x}$	0.1784	10
11	TRAMADOL	$y = 1276.4e^{0.1851x}$	0.1851	11
12	HYDROMORPHONE	$y = 358.1e^{0.1903x}$	0.1903	12

This table (Table 3) implies that VICODIN is the safest while HYDROMORPHONE is the least safe. One may argue that in addition to deaths, count of life-threatening adverse events should also be taken in to consideration.

This is done and results are given in table 4.

Table 4: Fitting exponential model to cumulative counts (death + life threatening) of Opioids and ranking based on growth rate				
Sr.No.	Drug Name	Equation	Detriment Index (β)	Rank
1	VICODIN	$y = 1296.6e^{0.1194x}$	0.1194	1
2	PETHIDINE	$y = 182.8e^{0.1200x}$	0.1200	2
3	PERCOCET	$y = 934.9e^{0.1380x}$	0.1380	3
4	MORPHINE	$y = 5000.2e^{0.1473x}$	0.1473	4
5	AMITRIPTYLINE	$y = 1703.9e^{0.1476x}$	0.1476	5
6	CODEINE	$y = 2244.2e^{0.1493x}$	0.1493	6
7	FENTANYL	$y = 3359.9e^{0.1640x}$	0.1640	7
8	HYDROCODONE	$y = 2607.9e^{0.1686x}$	0.1686	8
9	METHADONE	$y = 1495.4e^{0.1735x}$	0.1735	9
10	OXYCODONE	$y = 2974.7e^{0.1768x}$	0.1768	10
11	TRAMADOL	$y = 1992.8e^{0.1772x}$	0.1772	11
12	HYDROMORPHONE	$y = 490.6e^{0.1861x}$	0.1861	12

Based on this table (Table 4), VICODIN is the safest while HYDROMORPHONE is the least safe. It is reassuring to see that inclusion of life-threatening events does not radically change the safety ranking based on deaths only. This ranking may be of use to clinicians and practitioners.

CONCLUSION

It is indeed possible to rank opioid drugs by fitting exponential model to cumulative counts of deaths.

This ranking does not radically change even if we include counts of LIFE-THREATENING events together with deaths.

The method used does not depend upon popularity or total exposure of an opioid.

REFERENCES

[1] www.vigiacess.org

[2] https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html

[3] http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf

[4] https://www.cdc.gov/drugoverdose/images/resources/graphics/opioidoverdose/3B.png

[5] https://www.independent.co.uk/news/world/americas/us-politics/opioid-crisis-trump-public-health-emergency-latest-announcement-a8022131.html

[6] https://www.cdc.gov/drugoverdose/data/statedeaths.html

[7] https://www.nytimes.com/2018/07/25/books/review-dopesick-beth-macy-opioid-crisis.html

[8] Beth Macy, Dopesick : dealers, doctors, and the drug company that addicted America, New York, NY : Little, Brown and Company, [2018]

[9] Meert TF, Vermeirsch HA, Pharmacol Biochem Behav, A preclinical comparison between different opioids: antinociceptive versus adverse effects, 2005 Feb;80(2):309-26. Epub 2005 Jan 7

[10] Asbjørn M Drewes, Rasmus D Jensen, Lecia M Nielsen, Joanne Droney, Lona L Christrup, Lars Arendt-Nielsen, Julia Riley, and Albert Dahan, Differences between opioids: pharmacological, experimental, clinical and economical perspectives, Br J Clin Pharmacol. 2013 Jan; 75(1): 60–78. Published online 2012 May 3.

[11] https://www.health.harvard.edu/blog/the-safety-of-painkillers-20101220915

[12] Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J, Schneeweiss S,The comparative safety of opioids for nonmalignant pain in older adults, Arch Intern Med. 2010 Dec 13;170(22):1979-86. doi: 10.1001/archinternmed.2010.450.

[13] Asbjørn M Drewes, Rasmus D Jensen, Lecia M Nielsen, Joanne Droney, Lona L Christrup, Lars Arendt-Nielsen, Julia Riley, and Albert Dahan, Differences between opioids: pharmacological, experimental, clinical and economical perspectives, Br J Clin Pharmacol. 2013 Jan; 75(1): 60–78. Published online 2012 May 3. doi: 10.1111/j.1365-2125.2012.04317.x

[14] Etminan M, Delaney JA, Bressler B, Brophy JM, Oral contraceptives and the risk of gallbladder disease: a comparative safety study, CMAJ. 2011 May 17;183(8):899-904. doi: 10.1503/cmaj.110161. Epub 2011 Apr 18.

[15] Sibai BM, Odlind V, Meador ML, Shangold GA, Fisher AC, Creasy GW, A comparative and pooled analysis of the safety and tolerability of the contraceptive patch (Ortho Evra/Evra), Fertil Steril. 2002 Feb;77(2 Suppl 2):S19-26.

ACKNOWLEDGMENTS

Thanks to all reviewers and our colleagues who provided their valuable time and feedback. Thanks to Munshi Imran for help in extracting relevant data from FDA website.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Author Name: Samadhan Ghubade
Company: Cytel Statistical Software & Services Pvt Ltd
Address: SN 150, Lohia Jain IT Park, 6th Floor, A wing, Paud Road, Kothrud
City / Postcode: Pune, 411038
Work Phone: +91-20 - 67090198
Fax: +91-20-67090120
Email: samadhan.ghubade@cytel.com
Web: www.cytel.com