On shapes of ADR report accumulation data for banned drugs

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Adverse drug reactions (ADRs) are a matter of great concern in drug research. This study focuses on drugs which have been banned or withdrawn, due to serious problem of adverse reactions. Our attempt is to develop insights through plotting of data on cumulative counts of ADR reports. These data have been sourced from www.vigiaccess.org. Our expectation is that once a drug is banned/withdrawn, its count of ADR reports should fall precipitously and remain there. Instead a variety of shapes is encountered. These include linear, exponential and sigmoidal. We suggest that these curves can be useful in comparing safety of drugs.

Keywords: Adverse drug reactions, curve fitting, side effects, withdrawn drugs.

VIRTUALLY every allopathic drug has the potential to cause some side effects. Drug regulators weigh the benefits of a drug against its adverse side effects before approving it. Typically, this approval is based on evidence gathered during clinical trials (CTs) on the drug. However, once the drug is approved and marketed, adverse reactions not observed during clinical trials can crop up. This is because CTs have limitations of time, number of subjects, their ethnic/age/health composition, etc. In view of this, pharmaceutical companies are expected to monitor, on a continuing basis, the adverse effects experienced by users of their drugs.

Adverse drug reactions (ADRs) are unpleasant events which are suspected to have been caused by a drug or medicine. Such ADRs in the real world are reported simultaneously to health authorities (HA) and the market authorization holders (MAH). These ADRs are then archived by the MAH and HAs. The two major databases of such reports are the US FDA's adverse event reporting system (FAERS) and the WHO's 'Vigibase'. The count of such ADRs in these databases is in millions.

This kind of a monitoring activity is sometimes called pharmacovigilance. It is often based on voluntary reporting of ADRs by doctors, patients, pharmacists, etc. One popular public domain source of the counts of such reports is The Uppsala Monitoring Centre of WHO. Their website www.vigiaccess.org readily provides annual ADR report count data for many drugs. Questions and answers on FAERS on their website (https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects) provide useful introduction to the phenomenon of ADRs.

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As is to be expected, ADR data are subjected to extensive analysis. Fikadu *et al.*[1] compared ADRs for cardio metabolic drugs from sub-Saharan Africa (SSA) with reports from the rest of the world. Ampadu *et al.*[2] provided an overview of the growth of pharmacovigilence activity in Africa. Vivekanandan *et al.*[3] discussed the problem of underreporting of ADRs in India. Some studies followed the Weber pattern. This pattern suggested that spontaneous reporting of adverse events was mainly in the first two years after a drug entered the market with noticeable decline soon after. Eventually, with improved efforts, this pattern seems to have disappeared[4]. Another purpose of ADR analysis from public databases is safety signal detection. Here the attempt is to judge, as early as possible, whether a certain adverse event can be regarded as 'caused' by the drug. Disproportionality analysis can help in identifying safety signals. Here data are put in the 2×2 contingency table format. First row refers to drug under study and second row has other drugs combined. First column has cases that report the specific adverse event of interest (say myocardial infarction or in layman's terms, heart attack) while the second column has other reports. If the drug exhibits a disproportionately high frequency of adverse event of interest compared to other drugs, then it is provisionally implicated as 'cause' of that event. This can be done with suitably disaggregated data to focus on a specific subgroup such as senior citizens[5]. Two other problems investigated are drug–drug interaction and drug-related syndrome. If an event occurs more often than expected when two drugs are taken concomitantly, then it suggests a possibility of interaction between those two drugs. If event types seem to cluster, then we may have a drug-related syndrome.

A limitation of these approaches is that only one adverse event or a small group of them is studied at a time. This does not generate an overall assessment of

Table 1. Fitting exponential model to ADR accumulation data for anesthetic drugs

Drug	Equation: $y = a*\exp(rt)$	R-square	Rate (r)	Rank
Isoflurane	$y = 1E\text{-}89e^{0.105x}$	$R^2 = 0.95$	0.1050	1
Desflurane	$y = 1E\text{-}145e^{0.1689x}$	$R^2 = 0.97$	0.1689	2
Propofol	$y = 7E\text{-}174e^{0.2025x}$	$R^2 = 0.99$	0.2025	3
Sevoflurane	$y = 7E\text{-}186e^{0.2155x}$	$R^2 = 0.99$	0.2155	4
Ketamine	$y = 1E\text{-}207e^{0.2402x}$	$R^2 = 0.98$	0.2402	5

safety aspect of the drug under study. Also, no general statement about comparison of two or more drugs emerges[6]. Such an objective requires an altogether different approach. The present study is a step in that direction.

This study analyses ADR report counts of drugs that have either been banned by regulators or withdrawn from market by the manufacturer for the simple reason that these drugs have poor safety records. This group is relatively small and detection of any patterns in ADR report count should be easier. The tally of this group of drugs exceeds forty. Of these, we examined 25 drugs with a reasonably large ADR report count. The notion of banning/withdrawal is not as clear-cut as it may seem. A drug may be banned in one country but not in another. It may be reintroduced later. A drug may be in the market in multiple versions and only some may be withdrawn. Such ambiguities create difficulty in the curve fitting method applied in our study. However, there is some merit in persisting with efforts in virgin areas in spite of such problems.

We have analysed cumulative counts instead of available annual counts. This is because generally cumulative sums have a smoother behaviour than individual counts. Also, our main interest is broader patterns rather than anomaly, if any, in a given year. We have plotted data with year (time) on the x-axis and cumulative count of adverse events on the y-axis. Regarding the pattern, it is generally expected that when a drug is banned/withdrawn, the annual count of ADR reports on that drug should fall precipitously and stay there. In other words, initially before withdrawal the graph should rise and after withdrawal it should reach a plateau. This is called saturating shape. About half the cases examined broadly followed the expected saturating pattern. (In an ideal situation use of a drug should stop completely right after withdrawal or banning. Occurrence of ADRs should stop very soon. But sometimes there is the phenomenon of stimulated reports. These reports arise partly because of increased awareness and partly because there is an active search inspired by possibility of seeking compensation from producers of the drug.) However, surprisingly, many drugs fail to follow this pattern. Instead we see one of the three patterns, viz. linear, exponential and sigmoidal. Implications of these patterns need to be looked into. Frequent variations from the expected saturating pattern is a surprising feature.

In addition to the set of 25 drugs, there were over 17 drugs with smaller ADR count. In this set majority of them followed the saturating pattern.

Saturating growth

Our example of a typical case following saturating curve is the drug 'troglitazone' by Daiichi Sankyo prescribed for Type II Diabetes Melitus. It was marketed in 1998 and withdrawn in 2000. Figure 1 shows the observed accumulation curve and a saturating hyperbola fitted to the data. A good fit is noticed with R^2 value of 0.99.

The saturating fit suggests that the count of ADR reports after withdrawal has declined and reached negligible levels. This shows that the withdrawal is effective. There are nearly 13 drugs which fall in the same saturating pattern. A list of these drugs is given in appendix.

Linear growth

There are at least seven drugs which fall in the linear pattern (see appendix). As pointed out in the earlier section, the objective is to locate drugs which do not follow the expected saturating pattern. One drug deviating from that pattern is 'flunitrazepam' by Roche for insomnia. It was approved in 1974 and by 2016 it was withdrawn in most of the countries. Figure 2 gives a linear model which shows a good fit with R^2 value of 0.98.

The linear fit suggests that the yearly count of ADR reports has roughly stabilized at about 70 per year. Our interpretation is that there is a constant probability of adverse reaction per use and a steady volume of consumption, together leading to a steady number of ADR reports. Also, the withdrawal may be only partial and its use may have been continued in some countries. Lastly this drug has been reported to be addictive and involved in date rape.

Exponential growth

Our next example is the drug 'co-proxamol' (propoxyphene) for severe acute or chronic pain. It is in the market since 1926 and partly withdrawn in 2005. Figure 3 gives an exponential model which shows a good fit with R^2 value of 0.85.

The exponential fit suggests that the count of ADR reports has exploded and has reached a value of over 2000 by 2016. Therefore the explanation given in the earlier

case does not work here. This is a recreational drug. Its consumption appears to have expanded systematically. It has been reported to be addictive and involved in date rape.

Sigmoidal growth

The next example is drug vioxx by Merck approved in 1999 and withdrawn in 2004. For the next eight years or so, the ADR count continued to increase. Only after 7 or 8 years did it show the tendency to reach a plateau. Here the fit is better as shown by R^2 value of 0.98 (Figure 4). However, the explosive growth in ADR count after withdrawal of the drug is puzzling.

We have come across six drugs which fall in the same sigmoidal pattern (see appendix). It is noted that the sigmoidal pattern differs from saturating pattern only in some details. In fact there is saturation in this category as well.

Curve fitting method and safety comparison of drugs

The reported counts of ADRs for banned/withdrawn drugs, when accumulated, are expected to follow the saturation model. It is however, surprising to note that some of these drugs follow the linear, exponential and sigmoidal growth. This could be due to stimulated reporting and/or bulk reporting of previously unreported ADRs. Occasionally, patients may continue with a drug in spite of adverse reports because of gratifying experience (see https://www.drugs.com/comments/alosetron/).

The present curve fitting method can be extended to drugs that are still in use. It will also be relevant to work on disaggregated data and check patterns for key organ classes such as heart, lung, liver and kidneys. If necessary the set of adverse events can be trimmed to include only those clinically considered serious/critical. Key question

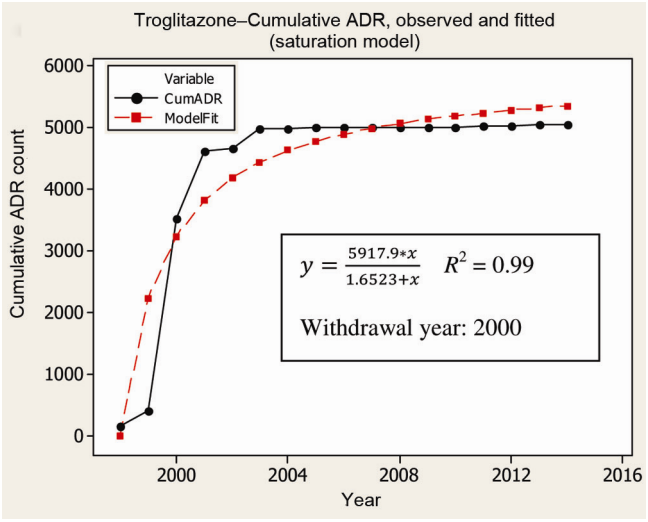

Figure 1. Saturating growth for troglitazone.

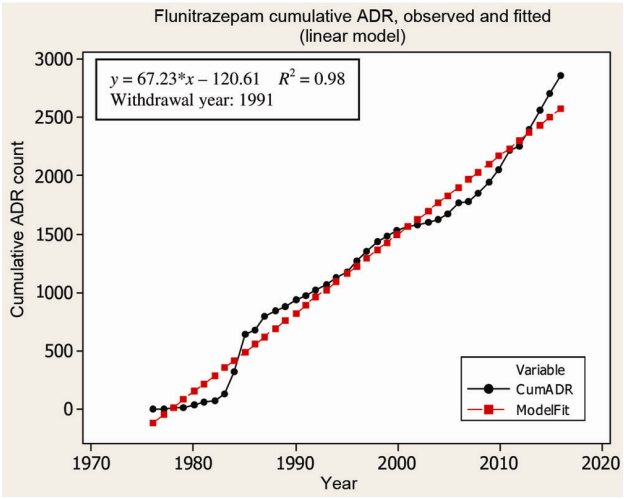

Figure 2. Linear growth for flunitrazepam.

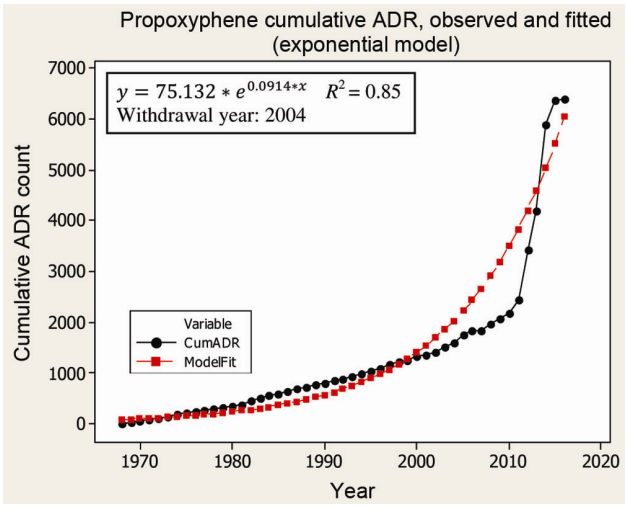

Figure 3. Exponential growth for propoxyphene.

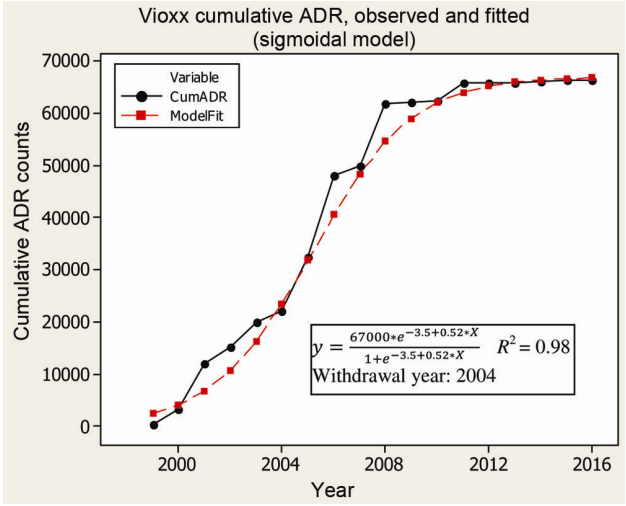

Figure 4. Sigmoidal growth for vioxx.

is whether the set of shapes encountered in banned drug group will suffice to cover the larger group.

One potential use of patterns identified above is in comparison of drugs. If two drugs are similar in their efficacy (they give similar benefits to subjects with targeted ailment), then one with better ADR profile should be preferred. A set of adverse reactions is a complex entity. A drug may have hundreds of different types of adverse reactions. So comparison has to be based on a few summary measures. In case of a drug with linear growth of ADR report counts, slope is one summary in the sense that it is the typical number of ADR reports per year. So, when two drugs have similar efficacy and linear growth of ADR report counts, lower the slope better the drug (or so it may seem). However, this requires caution as the actual counts may differ substantially due to differing popularity/exposure of two drugs. Greater the exposure, greater the ADR count. When the x-axis is common (time), the slope is essentially equal to the annual increment in count. But a drug cannot be judged as unsafe just because the absolute count of ADR is larger. Also, a drug cannot be called safer just because the actual count of ADR is smaller. For example, consider two drugs A and B. A has a sale of 1000 doses and B has 100 doses. If A has 100 ADR reports and B has only 50, which is safer? For A, chance of ADR report is one in ten doses sold. For B it is one in two doses. So A is safer. Hence some modification is required to make the two data sets comparable. It can be in the form of division by annual sale or its proxy. Here, we assume that other factors such as spontaneous reporting rates are similar for two drugs under comparison. In case of exponential or sigmoidal growth, comparison can be based on r, the growth rate. Thus, this method is useful for such comparisons. We apply this idea to one group of drugs namely anaesthetic drugs.

Safety comparison of anaesthetic drugs

While patterns in ADR counts of banned drugs may be of some interest, what is more interesting is the application of this approach to comparison of drugs currently in use. We have considered the case of anaesthetic drugs. There are five drugs in wide use. It is interesting to compare desflurane, isoflurane, ketamine, propofol and sevoflurane. Among these the last one is perhaps the most popular[7]. One recent study has called it an ideal anaesthetic[8]. Hence our aim is to see how it fares with others in terms of ADR count. An exponential model was fitted in all cases. The result is given in Table 1.

In all cases the exponential model was found to give a good fit. Residual plots were also satisfactory. In this model the exponential growth rate is the parameter that determines the shape and shows how fast the ADR count grows. In other words, lower the value of r, safer the drug. This parameter does not depend on extent of usage. If usage is doubled, and all counts double, the growth rate r remains unaffected. Doubling affects only the parameter a. However, in terms of r, the relative performance of the 'ideal' drug sevoflurane is in fact not that good. Three other drugs prove to be safer than it. This surprising result will have to be further investigated by domain experts.

Appendix 1. Banned drugs by shape of ADR accumulation count curve

Drug		
Saturating	Linear	Sigmoidal
Benoxaprofen	Clobutinol	Aprotinin
Bromfenac	Diethylstilbestrol	Dexfenfluramine
Cerivastatin	Dinoprostone	Remoxipride
Cisapride	Drotrecogin alfa	Rimonabant
Efalizumab	Etretinate	Rosiglitazone
Nefazodone	Flunitrazepam	Vioxx
Sibutramine	Phenylbutazone	
Tegaserod		
Temafloxacin		
Terfenadine		
Tolcapone		
Troglitazone		
Trovafloxacin		

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