

The Use of Drug Utilization in Pharmacovigilance

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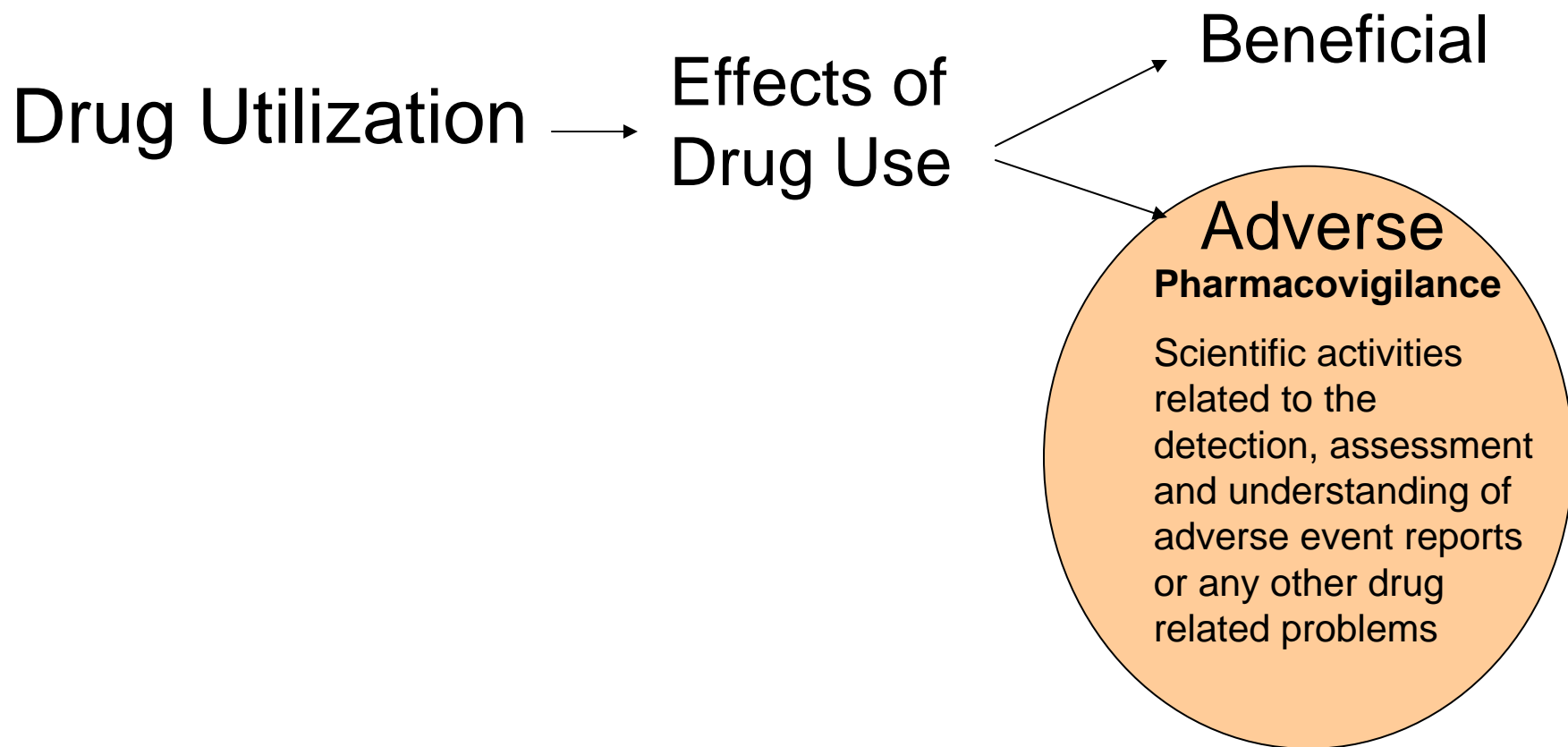
AstraZeneca, LP

Symposium: Drug Utilization

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Drug Utilization and Adverse Events



Drug Utilization Data

- Cost or unit cost
- Number of tablets, capsules, doses, etc
- Number of prescriptions
- Number of patients ingesting drug
- Weight

Drug Utilization

- Assess trends of drug use
 - Among geographic areas (e.g., states, regions, or nations) and/or demographic characteristics of users (e.g., age, gender, race)
- Determine denominators for event rates
- Identify over- and underutilization of certain drugs
- To estimate drug expenditures
- To monitor specific therapeutic categories or effects of regulatory activities
- To plan importation, production & distribution

Examples of Drug Utilization in Pharmacovigilance

Use of drugs for wrong indications

Use of “toxic” drugs when other less “toxic” drugs are available

Use of concomitant medications

Use of over/under doses

Drug Utilization Databases Definition †

- Large computerized databases that allow the linkage of drug utilization data to diagnoses

	GHC	HPHC	HPRF	HFHS	Fallon	KPNC	KPNW	KPSC	KPCO	KPH	KPG
Automated medical record	2003	1969	1997	1988	2005	2004	1997	2004	1997	2001	2004
Administrative data											
Membership	1980	1969	1990	1980	1987	1970	1982	1971	1992	1998	1995
Outside claims	1979	1990	1990	1991	1987	1991	1986	1991	1993	1995	1995
Patient scheduling	1984	—	1990	1988	1987	1987	1985	1993	1992	1992	1995
Deaths	1972	1979	—	1990	—	—	1979	1988	1988	1992	1995
Cost	1998	1989	1990	1990	1988	—	1998	1996	1997	1997	1995
Automated clinical data											
Outpatient visits	1992	1969	1990	1988	1987	1994	1987	1993	1992	1995	1995
Hospitalizations	1979	1990	1990	1989	1987	1979	1965	1981	1991	1988	1995
Emergency room	1992	—	1990	1988	1987	1988	1985	1993	1994	—	1995
Pharmacy	1977	1988	1990	1992	1987	1993	1986	1992	1993	1992	1995
Laboratory	1988	1969	1994	1995	1990	1994	1993	1991	1994	1988	1995
Long-term care	1992	1990	1990	1995	—	—	1986	1995	1994	—	1995
Home health care	1992	1990	1990	1995	—	—	1987	1995	1994	—	1995
Radiology	1986	1969 text	1990 text	1988 partial	1996	1992	1989	2001	1992	1991	1995
Pathology	—	1969 text	1990 text	1988 partial	1996	1972 partial	1970	—	1994	1995	1995
Cancer registry	1974	1982	—	1972	—	1973	1960	1988	1987	1973	2004

Drug Name	Drug Code	Drug Estimate	Drug Rate per 10,000 Residents	Generic Name	Generic Code	Rx Status	DEA Status	Comp Status
BICILLIN L-A			00009	PENICILLIN G BENZATHINE	70046	1	6	1
IPOL			00012	POLIO VACCINE	54575	1	6	1
MYCOPHENOLATE MOFETIL			00013	MYCOPHENOLATE MOFETIL	59836	1	6	1
PSOR-A-SET			00014	SALICYLIC ACID	55160	2	6	1
A.A.S.			00015	ASPIRIN	50410	1	6	1
SANGCYA			00016	CYCLOSPORINE	51493	1	6	1
CYSTAGON			00018	CYSTEAMINE BITARTRATE	70104	1	6	1
HAWTHORN			00019	HAWTHORN	70105	2	6	1
PREVNAR			00022	PNEUMOCOCCAL 7-VALENT CONJUGATE VAC	70107	1	6	1
PROLEX DM			00024	COMBINATION PRODUCT	51380	1	6	2
A.D.C. VITAMIN DROPS			00025	COMBINATION PRODUCT	51380	2	6	2
SYNAGIS			00027	PALIVIZUMAB	70108	1	6	1
DOSTINEX			00029	CABERGOLINE	70110	1	6	1
DURACLON			00031	CLONIDINE	51275	1	6	1
EXCEDRIN MIGRAINE			00032	COMBINATION PRODUCT	51380	2	6	2
HYGAMTIN			00033	TOPOTECAN HCL	59703	1	6	1
INTERLEUKIN-2			00034	ALDESLEUKIN	70111	1	6	1
A.P.C. BUFFERED			00035	COMBINATION PRODUCT	51380	2	6	2
D-50-W			00043	COMBINATION PRODUCT	51380	1	6	2
PANLOR DC			00044	COMBINATION PRODUCT	51380	1	3	2
A.P.C. NO. 2			00045	COMBINATION PRODUCT	51380	1	3	2
DONNATAL ELIXIR			00047	COMBINATION PRODUCT	51380	1	6	2

WHO Expert Committee. Report 615, WHO, 1977

Characteristics of an “Ideal” Drug Utilization Database

- Large sample size
- Long follow-up period
- Linkable information by unique identifier
- Variety of data that include inpatient and outpatient care, emergency care, mental health care, all laboratory and radiological tests, all prescribed and over-the counter medications, and alternative therapies

Characteristics of an “Ideal” Drug Utilization Database

- Population relatively stable and diversified
- Study drug prescribed in sufficient quantity
- Records updated on a regular basis
- Reliable and verifiable records
- Validated data

However, there is not an ideal database and its limitations include:

- Regional differences in data collected
- Lack of validation
- Potential confounding by indication and self-selection
- Incomplete information of exposure, outcome or confounding factors

Types of Databases and Examples

- Non-diagnosis linked
 - Medicaid Management Information Systems



Provider → Payor → Data user

- Saskatchewan Health Plan
 - Spain's Drug Data Bank
 - Swedish National Corporation of Pharmacies
- Diagnosis-linked
 - Kaiser Permanente Medical Plan
 - United Kingdom's General Practice Research Database
 - The Netherlands' Integrated Primary Care Information Database

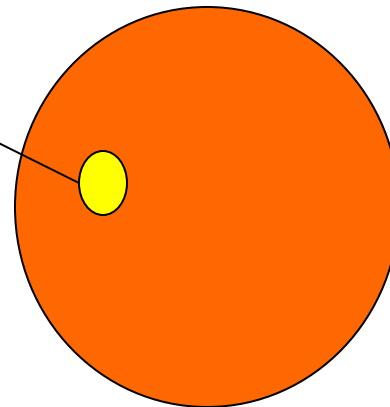
Denominator in Spontaneous Reporting

New users with adverse drug reaction

Incidence Rate= -----

All patients potentially at risk

Patients that are
capable of presenting
with the AE



- Have indeed been treated with the drug
- Have been treated in conditions that allow the expression of the adverse event (e.g. indication, duration of exposure, dose)
- Be physically capable of presenting with the given effect

Issues in the estimation of denominators

- The **number of incident cases** and the characteristics of **exposure in the whole population** of treated patients are **unknown**
- Denominator might be estimated from drug sales and/or prescription data
- However, not all drugs sold or prescribed are **always consumed**. As a consequence, the number of exposed patients estimated from crude sale figures is likely to produce a denominator that is too large, which results in a lower “incidence rate” than the real one

Drug Utilization Measures

- Defined Daily Dose (DDD)
- Prescribed Daily Dose (PDD)
- Minimum Marketed Dose (MMD)
- Medication Possession Rate (MPR)
- Drug expenditures

Issues

- Not all drugs sold or prescribed are consumed
- Noncompliance varies by therapeutic class. True exposed patients may be lower than the estimated from drug sales
- There is variation in exposure (indication, dose and duration of treatment)

Continuation

- For adverse events that are dose-dependent, additional adjustment (exclusion/stratification by dosage) might be necessary
- There is a potential for confounding by indication
- The length of treatment and latency period to observe an adverse event needs to be considered

Databases in Developing Countries

- International Network for Rational Use of Drugs and WHO
 - Recommendations on minimum sample size
 - Sampling methods
 - Data collection techniques
 - Drug use indicators (e.g. average number of drugs per encounter, % drugs prescribed by generic name, % of drugs actually dispensed, availability of key drugs)

Conclusion

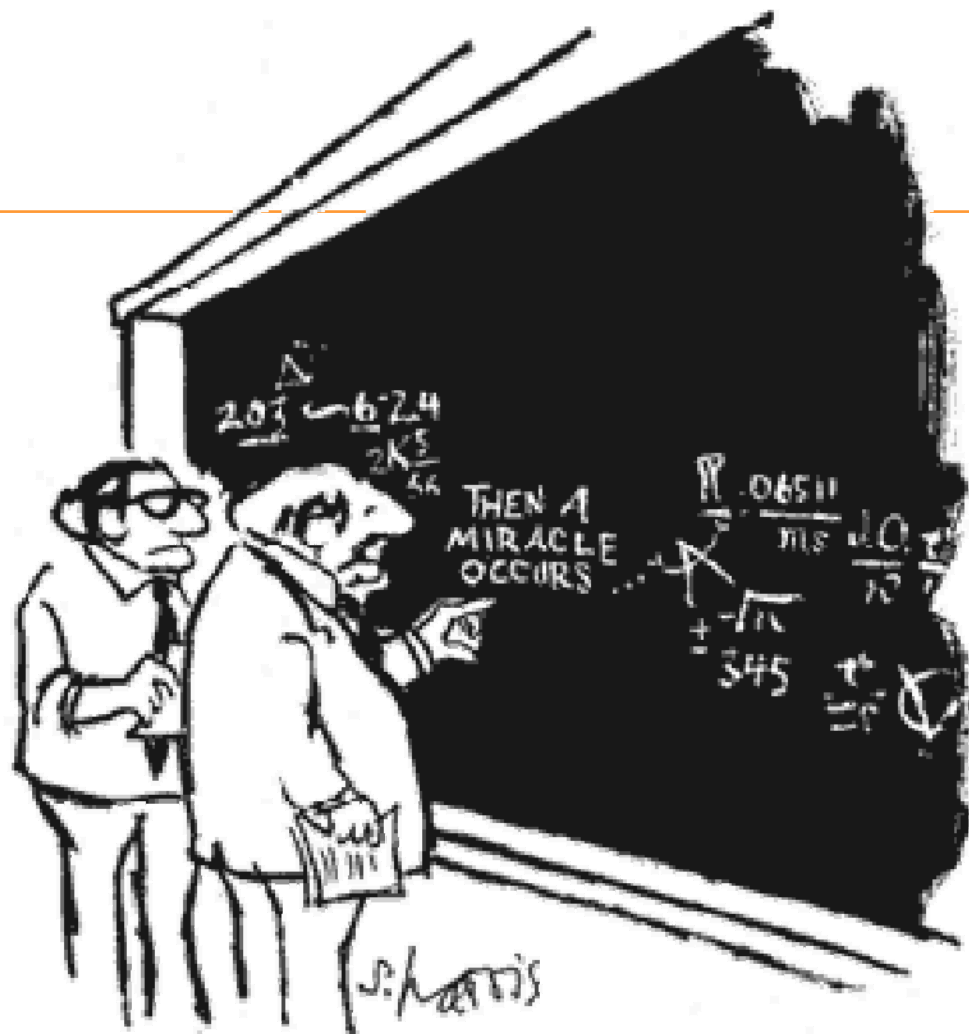
- Drug utilization databases are useful to provide proxy denominators to calculate event rates
- There is not an ideal drug utilization database and efforts should be done to improve the quality of data collected
- New technology is being developed to improve the linkage process, volume of data and data analysis capacity of the electronic system

Conclusion

- New users of drug utilization databases need to be familiar with collected information, data collection process and issues of a specific database
- Those who are planning to use/build a new DU database should consult with experienced DU researchers



"Fiction! I don't do fiction.
I only do non-fiction."



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

Estimation of Rates using Defined Daily Dose (DDD)

- Rates (DDDs / population / time)

- Numerator

$$\frac{\text{Quantity of drug} \times \text{Strength of drug}}{\text{DDD of drug}}$$

- Denominator

- Total population or users

- e.g. elderly U.S. population or users of temazepam

Defined Daily Dose

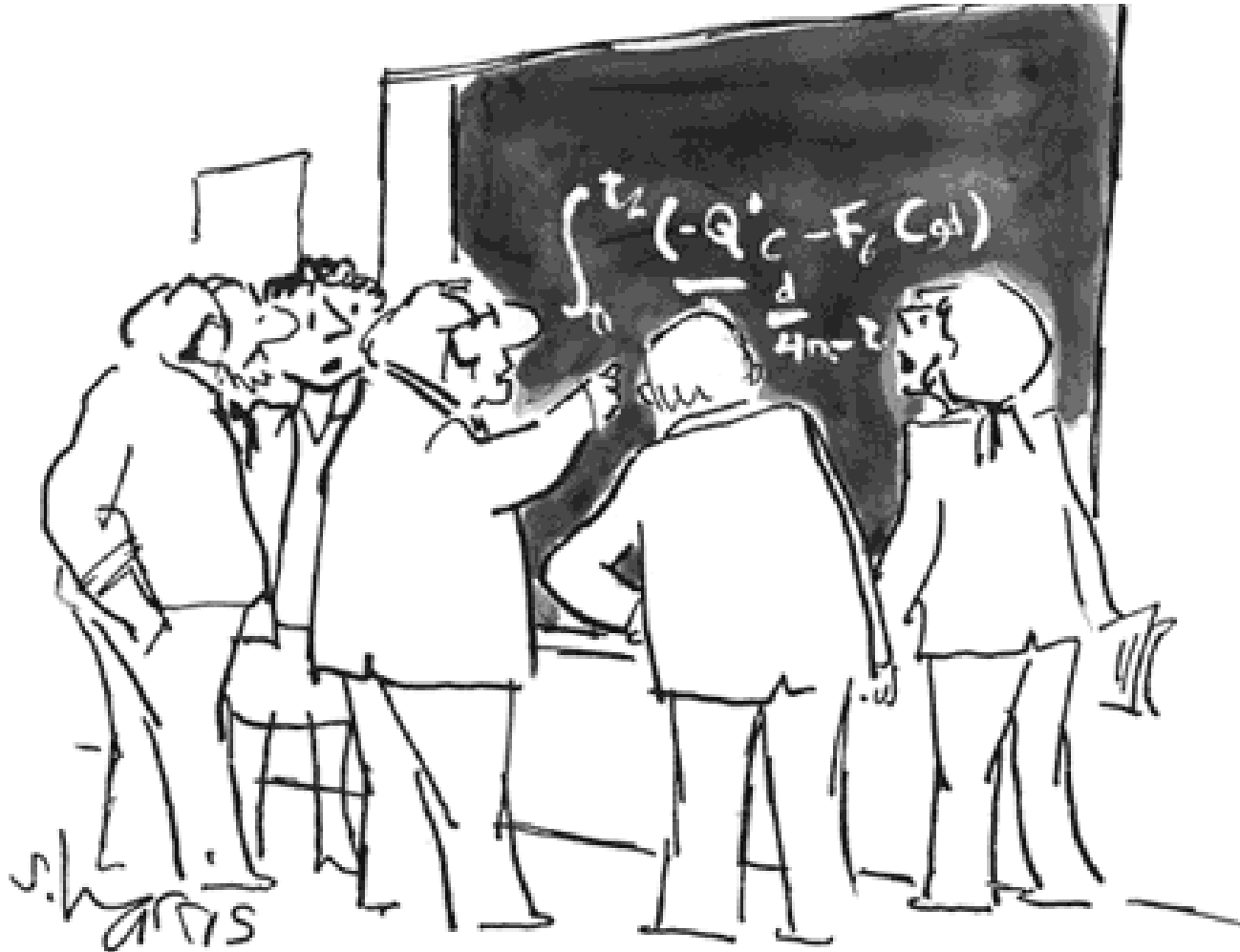
- Example
 - Zopiclone
 - Benzodiazepine-related drug
 - Main indication: short-term treatment for insomnia
 - DDD: 7.5mg
 - Sample prescription:
 - Strength: 3.75mg
 - Quantity: 100 pills
 - 1.5 million prescriptions/year

Defined Daily Dose

- DDD Rate per 100,000 residents in U.S. aged 35+
 - Per year

$$\frac{\text{Quantity} \times \text{Strength}}{\text{Population}} \div \text{DDD} = \frac{1,500,000 \times 3.75\text{mg}}{150,000,000} \div \frac{7.5\text{mg}}{100,000 \text{ population}} = 500 \text{ DDDs}$$

- Estimated days of treatment per user per year
- Per day
 - 500 DDDs per 100,000 per year / 365 days = 1.5 DDDs per 100,000 per day
 - Estimated number of users per day
- These rates can be more accurate if actual number of users is known



"Let's see now. Wilkes is nine years younger than Gottlieb, and Gottlieb is one-third older than me. Foster's age minus Rivera's age..."

Prescribed Daily Dose

- The average dose prescribed per day
- Calculated from actual data
 - Use the drug utilization data sources such as MEPS or Mail-Order Prescription Audit
- Used only for tablets or capsules due to inconsistency in how injection drugs dose is reported

Prescribed Daily Dose

- Can be calculated as the ratio of two rates
 - Rate 1: The rate of amount of drug dispensed per population-time
 - Rate 2: The rate of days of drug dispensed per population-time
 - The ratio of the rates gives the amount prescribed per person (or user) per day

Prescribed Daily Dose

- From the zopiclone example
 - 1.5 million prescriptions per year
 - 100 tablets per prescription
 - 3.75mg per tablet
 - 90-day supply
- Rate 1:
 - $150,000,000 \text{ tablets} * 3.75\text{mg} / 150 \text{ million population} = 3750 \text{ mg} / 1000 \text{ persons} / \text{year}$
- Rate 2:
 - $135,000,000 \text{ days supplied} / 150 \text{ million} = 0.9 \text{ days supplied} / \text{user}$
- PDD:
 - $3,750\text{mg per } 1000 \text{ per year} / 0.9 \text{ day per user} = 4.17\text{mg/user/day}$

Minimum Marketed Dose

- The minimum dose that produces the desired therapeutic effect
- Usually the minimum dose marketed by the manufacturer, thus the name MMD

Medication Possession Rate

- Calculated as the sum of the days supply for each prescription from first fill to most recent fill, divided by the number of days between the first and most recent fill
- Ranges from 0-1
- Particularly useful if you have in-house pharmacy data
 - e.g., Veteran's Affairs data
- Can also be a measure of compliance

Drug Expenditures

- Drug utilization can also be measured in terms of money spent
- Good for cross-sectional measures of drug utilization
 - Can be difficult to compare utilization across years since currency value changes from year-to-year