Introduction to Drug Utilization Research

Associate Professor Lisa Pont
(University of Technology Sydney, Australia)

This session was developed on behalf of the **ISPE Drug Utilization Special Interest Group** by

- Associate Professor Lisa Pont (University of Technology Sydney, Australia)
- Professor Katja Taxis (University of Groningen, Netherlands)
- Associate Professor Bjorn Wettermark (Karolinska Institute, Sweden)

This session

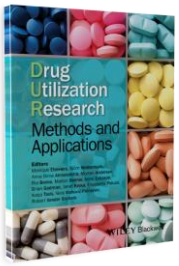
- What is Drug Utilization Research (DUR)?
- How does DUR relate to pharmacoepidemiology?
- DUR Conceptual Framework
- Types of DUR research

Drug Utilization Research

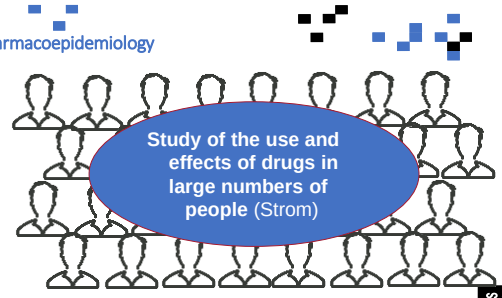
"The marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (WHO 1977)

Current definition

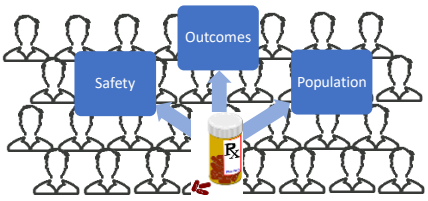
"An eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes." (Wettermark and Vander Stichle, 2008)



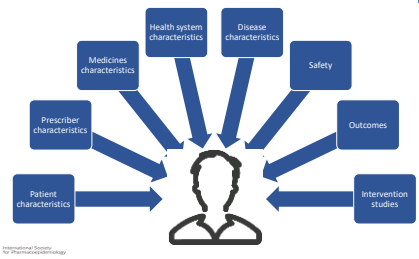
Pharmacoepidemiology



Pharmacoepidemiology



Drug utilization research



Data sources

Primary data

- Patients
- Health care providers
- Prescriptions, dispensing records
- Medical records

Data sources

Secondary data

- Aggregate data
  - sales data
- Individual-level data:
  - electronic health records
  - pharmacy dispensing data
  - reimbursement data
  - patient registries
  - population health survey data

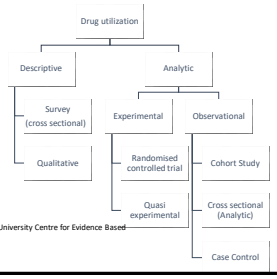
Groupwork: Data sources within Africa

- What data sources do you work with or are aware of?
  - What population do they cover?
  - What information do they include/not include?
  - What is the process for gaining access to them?
  - What is the data quality?
  - What are their strengths and weaknesses?

Taxonomy and terminology

- Classification systems
- Drug
  - World Health Organisation ATC classification
- Disease
  - ICD, SNOWMED
- Measurement units
  - Defined daily dose (DDD)
  - Users
- Usage pattern definitions

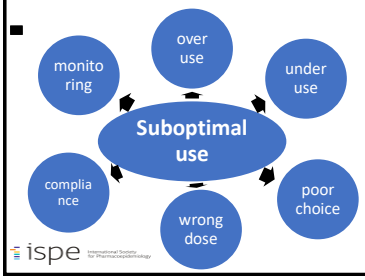
Study designs in drug utilization

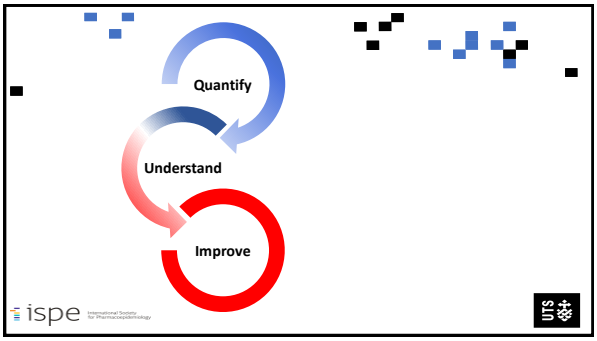


Adapted from Oxford University Centre for Evidence Based Medicine

Conceptual Framework
Drug Utilization Research

Quality and Safety of medicine use





Conceptual Framework

To quantify, understand and improve drug use and health outcomes

Micro level

- Person
  - Patient, prescriber, health care professional

Macro level

- Health System
  - Clinic, hospital, region, country

DUR and the conceptual framework

	Quantify	Understand	Evaluate	Improve
Prescribing				
Dispensing				
Consumption				

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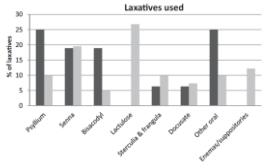
Archives of Gerontology and Geriatrics 56 (2013) 418–424
Contents lists available at ScienceDirect
Archives of Gerontology and Geriatrics
journal homepage: www.elsevier.com/locate/archger

A longitudinal study of constipation and laxative use in a community-dwelling elderly population

Barry L. Werth [a,*], Kylie A. Williams [b], Lisa G. Pont [a]



Quantify

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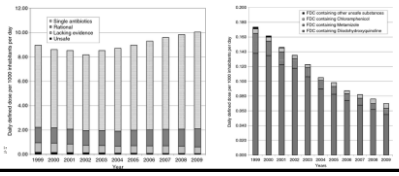
Use of antibacterial fixed-dose combinations in the private sector in eight Latin American Countries between 1999 and 2009

Tropical Medicine & International Health
Volume 18, Issue 6, pages 410–425, 5 FEB 2013 DOI: 10.1111/tmi.12068
http://onlinelibrary.wiley.com/doi/10.1111/tmi.12068/full#tmi12068-fig-0002

Private-sector sales data, based on information from manufacturers, retail wholesalers and, for some countries, pharmacies, IMS Health



Quantify

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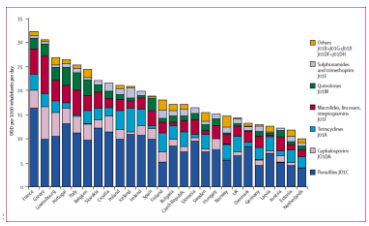
Outpatient antibiotic use in Europe and association with resistance: a cross-national database study

Herman Goossens, Marius Ferech, Robert Vander Stichele, Monique Elseviers, for the ESAC Project Group*



Quantify

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Goossens et al. Lancet 2005

Antimicrobial prescribing in South Africa using a large pharmacy database: A drug utilisation study Ilse Truter

Ilse Truter

To cite this article: Ilse Truter (2015) Antimicrobial prescribing in South Africa using a large pharmacy database: A drug utilisation study Ilse Truter, Southern African Journal of Infectious Diseases, 30:2, 52-56, DOI: 10.1080/23120053.2015.1054181

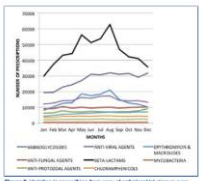

Figure 2: Variation in prescribing frequency of antimicrobial classes over 12 months

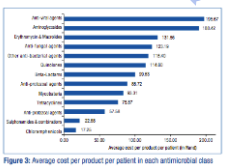

Figure 3: Average cost per product per patient in each antimicrobial class

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DUR and the conceptual framework

	Quantify	Understand	Evaluate	Improve
Prescribing				
Dispensing				
Consumption				

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British Journal of Clinical Pharmacology

Measuring anticholinergic drug exposure in older community-dwelling Australian men: a comparison of four different measures

Lisa G. Pont,[1,2] Johannes T. H. Nielen,[3,4,5] Andrew J. McLachlan,[5,6] Danijela Gnjidic,[6,7] Lewis Chan,[8] Robert G. Cumming[1,9] & Katja Taxis[3]

Agreement between anticholinergic drug exposure scales (Cohen's κ, 95% confidence interval) in the classification of anticholinergic exposure

	Anticholinergic Risk Scale (ARS)	Anticholinergic Drug Scale (ADS)	AnticholinergicCognitive Burden Scale (ACB)
Anticholinergic Risk Scale (ARS)			
Anticholinergic Drug Scale (ADS)	0.263 (0.226, 0.300)		
Anticholinergic Cognitive Burden Scale (ACB)	0.247 (0.208, 0.286)	0.628 (0.593, 0.664)	
Drug Burden Index -Anticholinergic (DBI-ACH)	0.237 (0.192, 0.282)	0.119 (0.084, 0.154)	0.091 (0.054, 0.128)

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British Journal of Clinical Pharmacology

Measuring anticholinergic drug exposure in older community-dwelling Australian me... of four...

Figure 1

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International Journal of Clinical Pharmacology and Therapeutics, Vol. 48 – No. 1/2010 (68-75)

Antihypertensive drug utilization and conformity to guidelines in a sub-Saharan African hypertensive population

T.O. Olanrewaju[1], A. Aderibigbe[1], O.A. Busari[2] and E.O. Sanya[3]

[1]Division of Nephrology, Department of Medicine, University of Ilorin Teaching Hospital, Ilorin, [2]Department of Medicine, Federal Medical Center, Ido-Ekiti, and [3]Division of Neurology, Department of Medicine, University of Ilorin Teaching Hospital, Ilorin, Nigeria

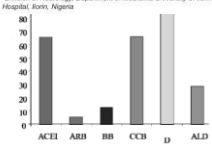


Figure 2. Frequency of classes of antihypertensive agents. ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers; D = diuretics; ALD = α-methyldopa.

Table 3. Number of antihypertensive drugs prescribed per patient.

Drug (n)	Frequency	Percentage (%)
0	17	2.2
1	72	9.1
2	292	37.1
3	282	35.8
4	123	15.6

Tropical Medicine and International Health doi:10.1111/j.1365-3156.2008.02186.x
VOLUME 14 NO 1 PP 93–100 JANUARY 2009

Pharmacy customers' knowledge of side effects of purchased medicines in Mexico

Veronika J. Wirtz[1], Katja Taxis[2] and Anahi Dreser[1]

1 Center for Health Systems Research, National Institute of Public Health, Cuernavaca, Morelos, Mexico
2 Department of Pharmacy, Section of Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands

ORIGINAL ARTICLE

Causes of intravenous medication errors: an ethnographic study

K Taxis, N Barber

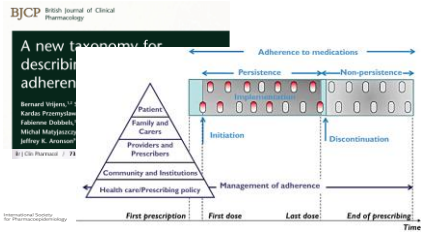
See editorial commentary, pp 326–7
Qual Saf Health Care 2003;12:343–348

Examples of DUR and the conceptual framework

	Quantify	Understand	Evaluate	Improve
Prescribing				
Dispensing				
Consumption		Patient compliance/adherence/persistence studies		

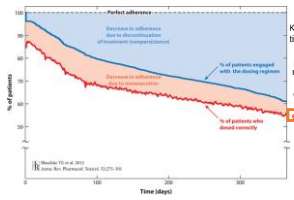
A new taxonomy for describing and defining adherence to medications

A new taxonomy for describing and defining adherence to medications



Brief Review

Measuring, Analyzing, and Managing Drug Adherence in Resistant Hypertension



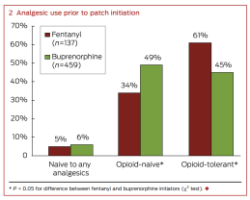
Kaplan–Meier plots of the time course of adherence parameters of 36 907 patients prescribed oral medications for one of a variety of medical conditions in 95 studies during the first year of Electronic compilation of the patients' dosing histories.

Examples of DUR and the conceptual framework

	Quantify	Understand	Evaluate	Improve
Prescribing				
Dispensing				
Consumption				

Research

Safety of opioid patch initiation in Australian residential aged care



International Journal of Clinical Pharmacy (2018) 40:428–435
https://doi.org/10.1007/s11096-017-0583-7

RESEARCH ARTICLE

Antihypertensive-related adverse drug reactions among older hospitalized adults

Tariq M. Alhawassi[1,2] · Ines Krass[2] · Lisa G. Pont[2]

Received: 2 May 2017 / Accepted: 20 December 2017 / Published online: 1 February 2018

1 in 10 experienced older persons experienced an ADR either leading to or during their hospital admission that was potentially related to their antihypertensive medication

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frontiers in Pharmacology

Changes in Prescribing Symptomatic and Preventive Medications in the Last Year of Life in Older Nursing Home Residents

Helene G. van der Meer*, Katia Tavis and Lisa G. Pont

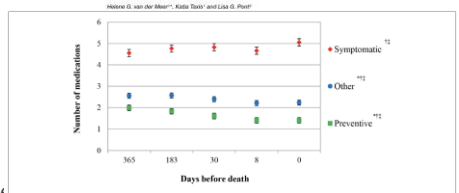

FIGURE 2 | Number of symptomatic, preventive, and other medication in the last year of life. Estimated marginal means (EMMs), adjusted for number of bed days in facility*, age*, and number of medication at 365 days before death*.

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Examples of DUR and the conceptual framework

	Quantify	Understand	Evaluate	Improve
Prescribing			Prescribing quality indicators	
Dispensing				
Consumption				

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Examples of DUR and the conceptual framework

	Quantify	Understand	Evaluate	Improve
Prescribing				Intervention studies
Dispensing				
Consumption				

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Research

Effect of humour therapy on psychotropic medication use in nursing homes

IMAGE: VALDA & JOANNA IN PLAY UP SESSION (LYNNE MALCOLM)

IMAGE: VALDA ENJOYING A SING ALONG (LYNNE MALCOLM)

IMAGE: AILEEN & HER FAMILY DURING A PLAY UP SESSION (LYNNE MALCOLM)

IMAGE: AILEEN WITH HER FAMILY (LYNNE MALCOLM)

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DOI: 10.1111/ajag.12319

Research

Effect of humour therapy on psychotropic medication use in nursing homes

Australasian Journal on Ageing, Vol 35 No 4 December 2016, E7–E12

Jerome BY Leow
Faculty of Medicine, University of New South Wales, New South Wales, Australia

Lisa Pont
Sydney Nursing School, The University of Sydney, New South Wales, Australia

Lee-Fay Low
Faculty of Health Sciences, The University of Sydney, Sydney, New South Wales, Australia

Table 1: Prevalence (%) of psychotropic medication use in Australian nursing homes before Play Up program and after Play Up program

	Any psychotropic	Antipsychotics	Benzodiazepines	Antidepressants
Pre-Play Up (n = 361)	169 (46.8%)	94 (26.0%)	63 (17.5%)	65 (18.0%)
Post-Play Up (n = 361)	151 (41.8%)	82 (22.7%)	52 (14.4%)	61 (16.9%)
Change (%)	−5.69	−3.30	−3.1	−1.1
P value	0.002*	0.024*	0.001*	0.289

*Indicates significant decrease (*P* < 0.05) in prevalence from pre- to post-Play Up period.

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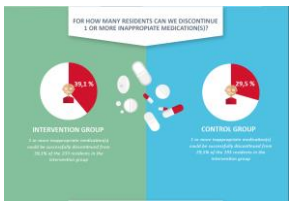
Discontinuation of inappropriate medication in nursing home residents (DimNHR study)



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Wouters et al, 2014; Wouters et al, Ann Int Med, in press

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Reducing the anticholinergic and sedative load in older patients on polypharmacy by pharmacist-led medication review: A randomized controlled trial

Helene G. van der Meer*1, Hans Wouters*1, Lisa G. Pont*2, Katja Taxis*1

BMJ Open

Table 2 Primary outcome - Proportion of patients having a decrease in DBI ≥ 0.5				
	Proportion with decrease of DBI ≥ 0.5 (%, n)		Odds ratio (95% CI) *	p-value
	Intervention	Control		
Intention to treat (n=157)	17.3% (13)	15.9% (13)	1.04 [0.47-2.64]	0.927
Per protocol analysis (n=145)	18.5% (12)	16.3% (13)	1.09 [0.45-2.63]	0.857

* Binary logistic regression, adjusted for age, gender, number of medication at baseline, level of DBI at baseline

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Examples of DUR and the conceptual framework

	Quantify	Understand	Evaluate	Improve
Prescribing				
Dispensing			Risk management	
Consumption				

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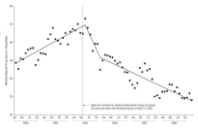
The risk management cycle, Guideline on Good Pharmacovigilance Practices (Module V) of EMA.



Joinpoint Regression Program analysis for atypical antipsychotics use among elderly patients with dementia. The data points represent patients 65 years and older with dementia (smoothed 6-month averages); the solid line, fitted joinpoint time series. IMS data.

Donsey et al. Impact of FDA Black Box Advisory on Antipsychotic Medication Use. Arch Intern Med. 2010 January 11; 170(1): 96–103

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Examples of DUR and the conceptual framework

	Quantify	Understand	Evaluate	Improve
Prescribing				
Dispensing				
Consumption				Patient education

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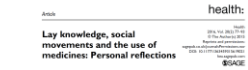
Amplifying the voice of ME/CFS and Fibromyalgia patients in a noisy world

British Journal of General Practice, June 2015; 319



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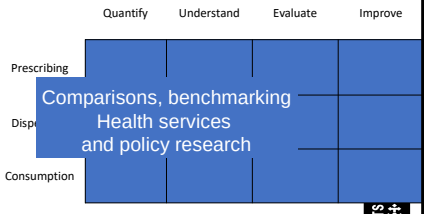
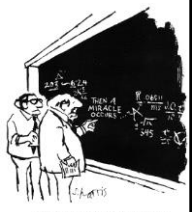
Examples of DUR and the conceptual framework



Challenges in Drug Utilization Research



"I think you should be more explicit here in step two."

Challenges in drug utilization research

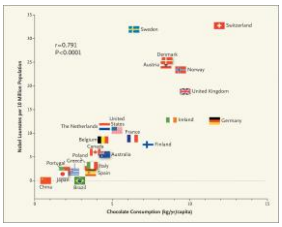
Descriptive quantitative studies

- poor data validity
- limited generalizability

Analytical studies

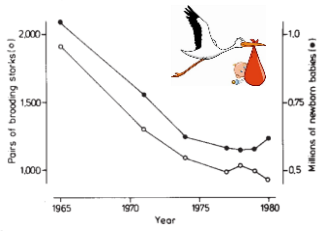
- lack of power
- bias
- confounding

Messerli FH. N Engl J Med 2012;367:1562-1564.



Correlation between Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Association between storks and newborn babies in Western Germany 1965-1980



Sies H. Nature 332;495

Final thoughts

- **Drug utilization research**
- explores practice based issues
- using varied methodologies and data sources
- putting the prescriber, supplier and consumer at the centre of the research
- to inform and improve health practice, policy and patient outcomes.

Resources

Drug Utilization Research Methods and Applications

Monique Elseviers, Björn Wettermark, Anna Birna Almarsdóttir , Morten Andersen, Ria Benko, Marion Bennie, Irene Eriksson, Brian Godman, Janet Krska, Elisabetta Poluzzi, Katja Taxis, Vera Vlahovic-Palcevski, Robert Vander Stichele

Drug Utilization Research (DUR) is an eclectic scientific discipline, integrating descriptive and analytical methods for the quantification, understanding and evaluation of the processes of prescribing, dispensing and consumption of medicines and for the testing of interventions to enhance the quality of these processes. The discipline is closely related and linked mainly to the broader field of pharmacoepidemiology, but also to health outcomes research, pharmacovigilance and health economics.

May 2016 | 9781118949788 | 536 pages | Hardback
£99.99 • €145.00 • $159.95
www.wiley.com/buy/9781118949788

MURIA
(Africa)

EURO-DURG
(Europe)

MURA
(Australia)

Asia-DURG
(Asia)

DUR/HSR SIG
ISPE
(International)

LA DURG
(Latin America)

SESSION 2

- Study designs in DUR
- Considerations when choosing a study design
- Bias and confounding in DUR

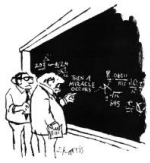
- Drug utilization studies can be conducted using a wide variety of study designs.
- All methodologies have their advantages and limitations,
- Researchers must select the most appropriate method for the questions they want to investigate.

Considerations when choosing a study design

Choice of method influenced by:

- Research question
- Ethical principles
- Type of data available
- Budget
- knowledge and skills of those undertaking the research
- Risk of systematic and non systematic error

Problems with DUR studies



"I think you should be more explicit here in step two."

Groupwork: study design

- What study designs have you worked with?
  - What were there strengths?
  - What challenges did you face?

Study designs used in DUR

Qualitative study

Quantitative study

Interrupted time series

Cohort study

Case-control study

Validation study

Ecological study

Cross-sectional study

Quantitative designs

- Quantification of data (measure, count, summarize…)
- Hypotheses testing
- Causal relationship between measurable variables
- Results with some degree of confidence

Qualitative designs

- Looking for the quality of events
- Exploration of social phenomena
- Gaining insight in the context
- Giving emphasis to the meanings, experiences, and views of participants

Example: patient compliance

- Quantitative

Quantification, relations, significance

- What is the frequency of non-compliance?
- Relationship between age and non-compliance?

- Qualitative

Exploration, meaning, understanding

- What are the barriers to complaince
- What are the thoughts among GPs on non-compliance in patients with chronic treatment?

Aims of qualitative research

- before quantitative work – to explore unfamiliar topics, concepts and variables
- To understand the context of quantitative findings or relating some aspects of behaviours to the wider context
- for in-depth studies of particular topics

Do patients' expectations influence their use of medications?

Qualitative study

Lisa Dolovich Pharm.D. MSc Kalpana Nair MSc MSc Connie Sellors Lynne Lohfeld PhD
Annie Lee MSc(c) Mitchell Levine MD MSc FRCPC FACP

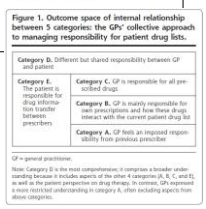
Good grief! Eight pills for supper, wonderful! [sarcastic tone] But then I look at it the other way and I say, "Well, without those 8 pills, I can't go for a walk, I can't do the shopping." You're grateful in many ways that the medications are there. (A011-155)

The birth control pill makes it so that I can sort of function in society. Without it, it gets to a point where the frequency of changing a feminine hygiene product would interfere with class or work. So, again, it's something that sort of keeps me a member of society. (B111-81)

Dolovich et al. Can Fam Physician 2008

Whose Job Is It Anyway? Swedish General Practitioners' Perception of Their Responsibility for the Patient's Drug List

Figure 1. Outcome space of internal relationship between 5 categories: the GPs' collective approach to managing responsibility for patient drug lists.



Bastholm Rahmner et al. Ann Fam Med 2010

Qualitative study methods in DUR

Observation
In depth interviews
Focus groups

Qualitative analysis in DUR

- Thoughts and opinions collected verbatim
- Thematic analysis
- May use pre-defined themes or determine themes from the data

Quantitative study designs

Descriptive

- How are drugs used?
- What do do drug utilization patterns look like?

Analytical

- What is the effect of drug therapy?
- What has caused the drug use?
- What are characteristics of patients, doctors for particular drug

Interventional

- What is the effectiveness of different interventions to change drug utilization

Descriptive studies

- Studies identifying patterns or trends in drug utilization without having any comparison (control) group that may allow for inferences to be drawn about causal associations.
- Good descriptive reporting answers five basic W: who, what, why, when, where and a sixth: so what?
- Two major types
  - Cross sectional studies
  - Longitudinal studies
    repeated cross sectional studies
    cohort followed over time

Cross sectional studies

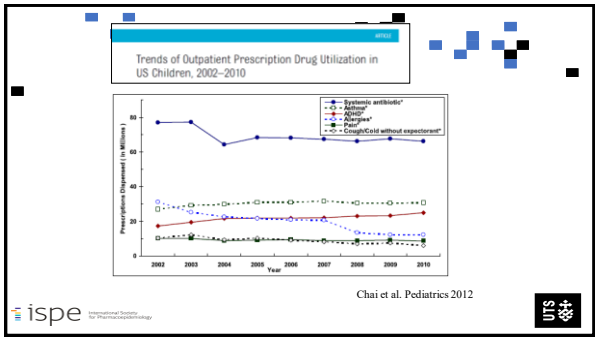
- we measure the frequency of a particular exposure and / or outcome(s) in a defined population *at a particular point in time*.

Strengths of cross sectional studies

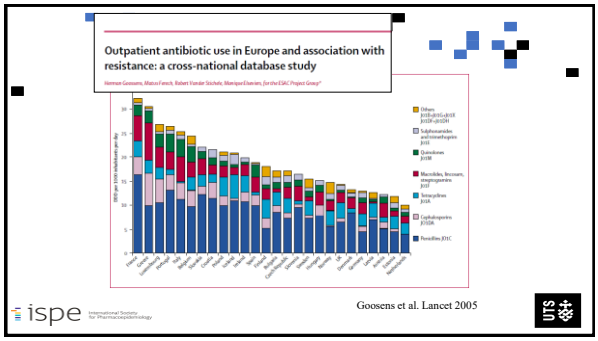
- relatively easy and economical
- provide important information on the distribution and burden of exposures and outcomes.
- valuable for health-service planning.

Weaknesses of cross sectional studies

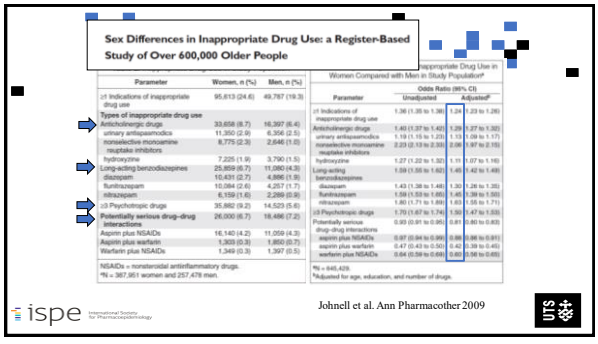
- Cross-sectional studies measure prevalent rather than incident cases.
- limited value for investigating aetiological relationships.
- It can be difficult to establish the time-sequence of events in a cross-sectional study. (reverse causality)



Chai et al. Pediatrics 2012



Goosens et al. Lancet 2005



Johnell et al. Ann Pharmacother 2009

Analytic studies

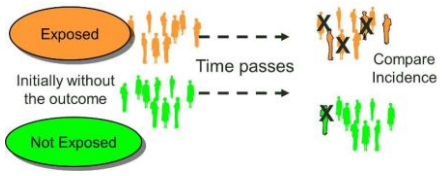
- Studies designed to reach causal inferences about hypothesized relationships.
- Require a design that will permit an evaluation of the causal effect association between exposure and outcome
- Different types
  - (Ecological studies)
  - Cohort studies
  - Case-control studies
  - Case cross-over studies

Cohort studies

- Select a study population or cohort of people who **do not initially have the outcome of interest**.
- We then classify the members of the cohort according to whether they have been **exposed** to the potential risk factor or not.
- We then follow the entire cohort over time
- At study end, compare the incidence of the **outcome(s)** in the exposed individuals with the incidence in those not exposed.

ispe

Cohort studies



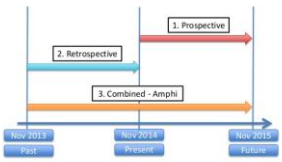
ispe

Cohort studies

- Prospective
  - Identify group without the outcome,
  - determine exposure status
  - and then follow them forward in time
- Retrospective cohort
  - Go back in time (eg using administrative data)
  - Identify group without outcome
  - Determine exposure status
  - Follow them forward in time

ispe

Types of cohort study



ispe

Diabetologia (2009) 52:1745–1754
DOI 10.1007/s00125-009-1444-2

ARTICLE

Insulin glargine use and short-term incidence of malignancies—a population-based follow-up study in Sweden

J. M. Jonasson · R. Ljung · M. Talbäck · B. Haglund · S. Gudbjörnsdóttir · G. Steineck

Cohort study-Strengths

- Less recall bias-**exposure is measured at the start of the study**, before the outcome occurs
- Can determine **causality**-the time sequence of events should be clear in a cohort study, minimising the possibility of reverse causality
- Can study **multiple outcomes**
- Suitable for rare exposures using appropriately selected populations.

Cohort study-weaknesses

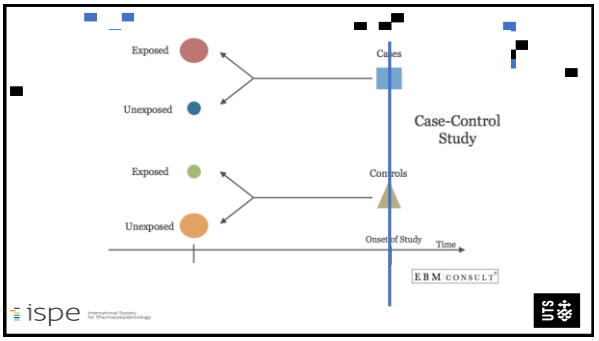
- prospective cohorts are **slow** and **potentially expensive**
- they are **inefficient for rare diseases**
- Retrospective cohort studies depend upon pre-existing records of exposure being available and reliable
- exposure status may change during study
- **differential loss to follow-up** may introduce bias
- in long term cohort studies may be hard to ensure that diagnostic criteria remain consistent

Bias in cohort studies

- Selection bias in **cohort** studies may arise if the comparison groups (exposed and unexposed) are not truly comparable. This could arise because of
- poor choice of the unexposed group, or
- differences in follow-up between the comparison groups

Case control studies

- start by identifying individuals with the **outcome** of interest (cases)
- Then compare them to individuals without this outcome (controls)
- Exposure defined retrospectively after outcome status determine
- Allow calculation of odds ratio



bmj.com

Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study

Jesper Hallas, Michael Dall, Alin Andries, Birthe Segaard Andersen, Claus Aalykke, Jane Møller Hansen, Morten Andersen and Annmarie Touborg Lassen

BMJ 2006;333;726-; originally published online 19 Sep 2006; doi:10.1136/bmj.38947.697556.AE

Table 2 Crude and adjusted odds ratios for association between use of antithrombotic drug and serious upper gastrointestinal bleeding

	Cases (exposed/ unexposed)	Controls (exposed/ unexposed)	Crude odds ratios (95% CI)	Adjusted odds ratios (95% CI)*
Single drug regimens, current use				
Aspirin alone	196/1063	4123/50 498	2.4 (2.0 to 2.8)	1.8 (1.5 to 2.1)
Clopidogrel alone	12/1063	203/50 498	3.1 (1.7 to 5.6)	1.1 (0.6 to 2.1)
VKA alone	56/1063	1227/50 498	2.2 (1.7 to 3.0)	1.8 (1.3 to 2.4)
Dipyridamole alone	36/1063	739/50 498	2.4 (1.7 to 3.4)	1.9 (1.3 to 2.8)
Two drug regimens, current use				
Aspirin and clopidogrel	13/1063	49/50 498	12.6 (6.8 to 24)	7.4 (3.5 to 15)
Aspirin and VKA	16/1063	114/50 498	6.4 (3.7 to 11)	5.3 (2.9 to 9.5)
Dipyridamole and aspirin	441/1063	737/50 498	3.1 (2.2 to 4.2)	2.3 (1.7 to 3.3)
Past use				
Aspirin	106/886	3990/44 968	1.5 (1.2 to 1.8)	0.9 (0.7 to 1.2)
Clopidogrel	4/990	111/48 947	1.8 (0.7 to 5.1)	0.8 (0.3 to 2.2)
Dipyridamole	2/992	152/48 906	0.8 (0.2 to 2.9)	0.4 (0.1 to 1.6)
VKA	48/946	1028/47 930	2.4 (1.8 to 3.3)	1.8 (1.3 to 2.4)

VKA=vitamin K antagonist.
*Adjusted for previous discharge diagnosis of peptic ulcer, peptic ulcer bleeding, chronic obstructive lung disease, ischaemic heart disease, alcohol related diagnosis or drug use, or liver cirrhosis or renal failure; for past *Helicobacter pylori* eradication; and for concurrent use of non-steroidal anti-inflammatory drugs, antiulcer drugs, nitrate vasodilators, selective serotonin reuptake inhibitors, or systemic corticosteroids.

Case control strengths

- can be carried out rapidly and relatively cheaply (compared to cohort studies)
- are useful for studying rare diseases
- can be used to study diseases with long periods of time between the exposure and outcome
- can study multiple exposures for a single outcome

Case control weaknesses

- are prone to selection bias
  - Especially for controls
- are prone to information bias
  - exposure status is determined after the outcome has occurred
- cannot establish the sequence of events: the exposure may be a consequence rather than a cause of the outcome (*reverse causality*)
- are not suitable for studying rare exposures
- cannot usually be used to estimate disease incidence or prevalence

Bias in Case control studies

- In **case-control** studies, bias arises if
- cases selected for the study are not representative of all eligible cases, or
- controls are not representative of the population which produced the cases.

Cohort vs case-control

- Cohort studies

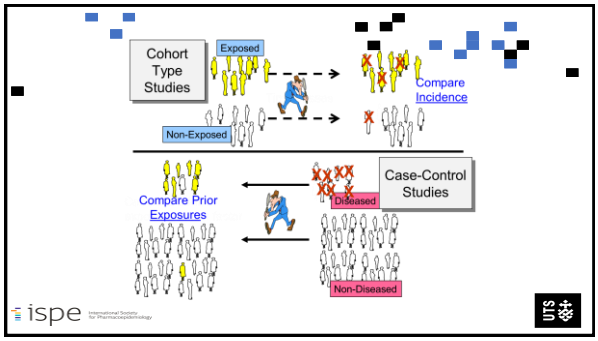
Pros
- Can calculate absolute risk
- Establish time-relation
- Multiple outcomes

Cons
- Loss of follow up
- Large studies need for rare diseases

- Case-control studies

Pros
- Rare outcomes (if you don´t have the data)
- Multiple exposures

Cons
- Difficult to find a control
- risk for recall-bias



Study designs to evaluate the effect of interventions

Quasi experimental designs

- Uncontrolled before and after study
- Controlled before and after study
- Time series analysis

Experimental designs

- Randomized controlled trial
- Cluster randomized trial

Controlled before and after study

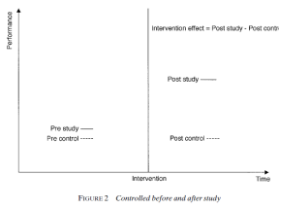
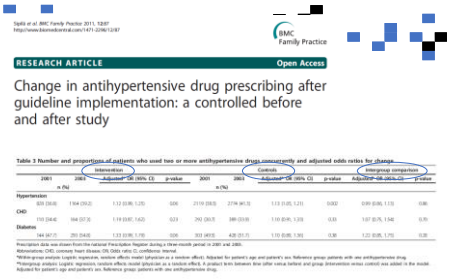


FIGURE 2 *Controlled before and after study*

Grimshaw et al. Fam Pract 2000



RESEARCH ARTICLE Open Access

Change in antihypertensive drug prescribing after guideline implementation: a controlled before and after study

Sipilä et al. BMC Fam Pract 2011

Time series analyses

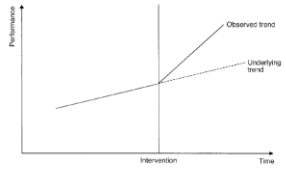
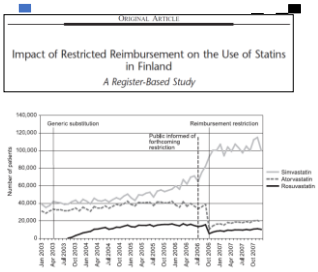


FIGURE 1 *Time series analysis*

Grimshaw et al. Fam Pract 2000



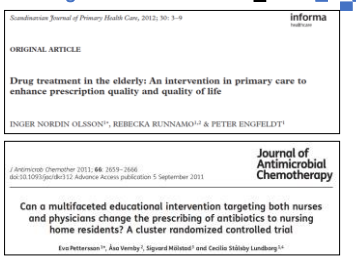
ORIGINAL ARTICLE

Impact of Restricted Reimbursement on the Use of Statins in Finland

A Register-Based Study

Martikainen et al. Med Care 2010

RCT – the golden standard



Scandinavian Journal of Primary Health Care, 2012; 30: 3–9

informa healthcare

ORIGINAL ARTICLE

Drug treatment in the elderly: An intervention in primary care to enhance prescription quality and quality of life

INGER NORDIN OLSSON[1*], REBECKA RUNNAMO[1,2] & PETER ENGFELDT[1]

J Antimicrob Chemother 2011; **66**: 2659–2666
doi:10.1093/jac/dkr312 Advance Access publication 5 September 2011

Journal of Antimicrobial Chemotherapy

Can a multifaceted educational intervention targeting both nurses and physicians change the prescribing of antibiotics to nursing home residents? A cluster randomized controlled trial

Eva Pettersson[1*], Åsa Vernby[2], Sigvard Mölstad[3] and Cecilia Ståhlby Lundborg[1,4]

Intervention studies in DUR

- Start with population without outcome
- Allocate subjects (individuals or clusters) to different treatment groups
- Can evaluate differences between groups to determine the effects of a treatment
- Can be used to evaluate health service interventions

Strengths of intervention studies

- Minimize bias and confounding
- if properly randomised the intervention and control groups will be similar in all respects except the intervention.
- if the participants are "blind" to the treatment allocation, reporting bias is minimised;
- if the investigators are "blind" to the allocation, observer bias is minimised
- powerful evidence of a causal relationship between the intervention and the outcome
- multiple outcomes can be examined
- the incidence rate of the outcome can be measured

Weaknesses of intervention studies

- they are often expensive to conduct:
- May require a large study team, perhaps at several sites, and may require a long follow-up period.
- Some intervention studies impossible to conduct for ethical reasons

Validation studies

- Generate evidence that the utilization patterns observed are a good presentation of the "true" drug consumption
- Could either validate the drug exposure as recorded in a database or a survey *or* use drug utilization data to validate other clinical information
- May be conducted through linkage between data on drug exposure collected from different sources
- Requires a decision on which method that should be considered as the truth or "the gold standard".

Sensitivity

the ability of the method under investigation to correctly classify an individual as using the drug

Problem with…

- OTC, hospital use
- Internet pharmacies
- Purchases abroad
- "Borrowing" from relatives, neighbours

Specificity

the ability of a method to correctly classify

an individual as drug-free

Problem with…

- Poor compliance

Concordance between parental-reported use and dispensed asthma drugs

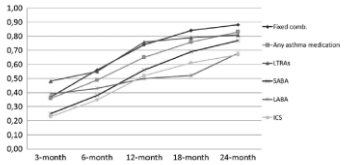


Figure 1. The sensitivity for the drug groups comparing the different time windows in the drug register with the use as reported in the questionnaire ($n = 3316$)

Dahlén et al . PDS 2103

Error in DUR studies

- There are three main types of error in DUR studies:
- Random error i.e. error resulting from the effect of chance
- Bias
- Confounding

- These are all affected by study design

Random error in DUR

- **Random error** is also known as variability, random variation, or 'noise in the system'
- Random error occurs because the estimates we produce are based on samples, and samples may not accurately reflect what is really going on in the population at large.
- In DUR the estimates we observe might be inaccurate just based on who happened to end up in our sample

Random error in DUR

- Random error (variability, imprecision) can be overcome by increasing the sample size.

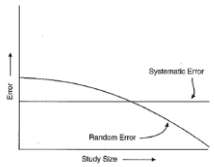


Figure 3–1. Relation of systematic error and random error to study size.

Reliable
Precise
Lack of Random Error

Reliable and Valid

Valid
Lack of Systematic Error

Bias

- Bias refers to any systematic error in the design or conduct of an epidemiological study that results in an incorrect estimate of the association between exposure and outcome (risk of disease).
- When bias occurs the associations are not 'there' at all, they only exist within your study.

Bias in DUR

- in descriptive studies
  - **study population are not representative** of the population we want to describe.
- in analytical studies
  - **comparison groups are not comparable**.

Types of bias

- Selection bias
- Information bias

Selection bias

- Selection bias refers to error due to **systematic differences in characteristics** between **those who take part in a study** and **those who do not**
- the people who are selected to participate in a study are not representative of the reference population
- the comparison groups are not comparable
- Some study designs are more prone to selection bias than others

Types of selection bias

- (non) Response bias
- Self-selection bias
- Sampling bias.
- Loss to follow up bias
- Observer selection.
- Healthy worker bias
- Hospital patient bias (Berkson's bias)

Selection bias

Example

Suppose we carried out a postal survey to determine vaccination rates. People who have not vaccinated their children may be less likely to participate than those who have vaccinated their children and thus the true vaccination rate of the reference population would be underestimated.

- This would be *selection bias* because people who have vaccinated their children would be over re-presented

Information bias

- Any error in the measurement of exposure or outcome that results in systematic differences in the accuracy of information collected between comparison groups.
- Information bias can be divided into two main types:
  - reporting bias
  - observer bias

Information bias

- Differential bias
  - All study participants have the same probability of bias
    - Spread evenly between study groups
    - may lead to completely wrong conclusions
- Non-differential bias
  - The spread of bias differs between study groups
  - may lead to an underestimation of the hypothesized relationship between exposure and outcome

Types of information bias

- There are two main types of information bias:
  - reporting bias
  - observer bias

Reporting bias

- **Reporting bias** arises:
- when study participants with a specific health outcome report previous **exposures** with a different degree of accuracy to those without the outcome
- when study participants who have experienced a specific exposure report **subsequent health events** with a different degree of accuracy to those who have not experienced the exposure.

Reporting bias

Example

Mothers of children born with an abnormality may have thought more about their medication use during pregnancy than mothers of children without and abnormality

This is **recall bias**

Observer bias

- When the accuracy of outcome data recorded by the investigator differs systematically between individuals in different exposure groups

Observer bias

Study nurses may be more likely to diagnose meningitis in children who have not been vaccinated than children who have been vaccinated if they believe that vaccination is protective.

Minimizing bias

- Cannot adjust for bias in analysis
- if you study the wrong people, or collect data from them in the wrong way , no amount of analysis will be able to correct it.
- Choose a study design that minimizes bias for your question
- Identify potential sources of bias at the stage of study design

Minimizing selection bias

- Ensure study participants are representative of the target population
- Response rates are as high as possible.

Minimizing information bias

- **Avoiding information bias**
- blinding
- collecting data on exposure as near as possible to the time of exposure and before outcome known
- standardising questionnaires, measurement tools and processes and training interviewers
- good questionnaire design

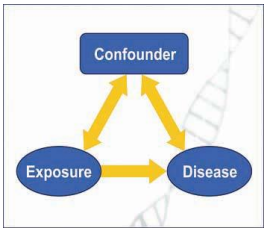
Confounding

- Confounding is the situation where an observed association between an exposure and an outcome is entirely or partially due to another exposure
- Systematic error

Confounding

- May be positive or negative
- Positive confounders
- Increase the size of the observed association
- Negative confounders
- Decrease the size of the observed association

onfounder



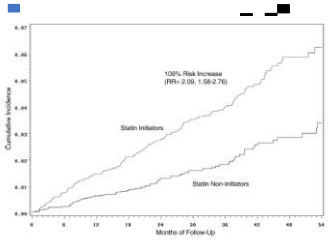


Figure 5. Follow-up for myocardial infarction (MI) among unmatched cohorts

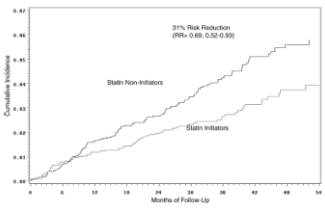
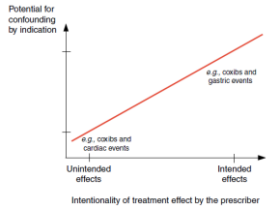


Figure 6. Follow-up for MI among matched cohorts

Confounding in DUR

- Common problem in DUR studies
- There is always a reason for drug prescribing
  - Potential for confounding by indication

Confounding by indication



Schneweiss. CPT 2007

Confounding

- Three criteria must be met for potential confounders:
- It must be **associated with the exposure** of interest ***among the source population*** (represented by the controls in a case-control study).
- It must be a **risk factor for the outcome** of interest ***among the non-exposed***.
- It must not be ***on the causal pathway*** between the exposure of interest and the outcome of interest.

Confounding

- No statistical test for confounding
- Identify potential confounders when designing studies:
- think about exposures that are **biologically plausible** as risk factors for the disease in question
- **Search the literature** to find out what exposures have been found to be risk factors in previous studies.

Confounding and analysis

- Calculate crude estimates
- Adjust for potential confoudners
- Mantzel Haenszel OR
- Regression
- If adjusted estimate different to crude estimate then confounding is likely.

Minimizing Confounding

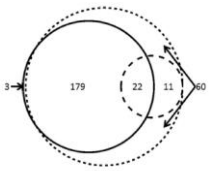
- Study design
- Randomisation
- Restriction
- Matching

- Analysis
- Standardization (age)
- Stratification
- Multivariate analysis

Designing DUR studies

- Refine the **research question**
- Select an appropriate **study design**
- Identify the **target population**
- Identify the **study population**
- **What is your selection process**
  - Purposive (high risk of bias)
  - Random (minimizes bias)
- Define **outcomes and exposures**
- Potential **confounders**
- **Design data collection**

Various ways of defining "use"



Dahlén et al. Eur J Clin Pharmacol 2016

Summary

- Drug utilization studies can be conducted using a wide variety of study designs.
- Researchers must select the most appropriate method for answering the questions they want to investigate.
- Research methods in drug utilization can broadly be categorized as either quantitative or qualitative.

Summary

- Quantitative descriptive studies identify patterns or trends in drug utilization without making inferences about causal associations.
- Quantitative analytical studies are designed to reach causal inferences about hypothesized relationships.
- A variety of study designs can be used to evaluate interventions, including quasi experimental designs (uncontrolled or controlled before-and-after studies and interrupted time series) and experimental designs, such as randomized controlled trials.

ispe International Society for Pharmacoepidemiology

UTS