JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Introduction to Drug Utilization Research

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Outline

- Role of drug utilization research
- Choosing a design
- Descriptive designs
- Analytical designs
- Interventional designs

Role of Drug Utilization Research

Benefits of Medication

Used well, medications are some of the most useful, safe, and cost-effective treatments in health care

Image source: Wellness Corporate Solutions. (2015, January 10). *Prescription bottle—pills* [Photograph]. Flickr. https://www.flickr.com/photos/130100316@N04/16161111248. CC BY-SA 2.0

The Problem Is That …

- They are prescribed when they shouldn't be
- They are not prescribed when needed
- Patients don't take them even when prescribed
- Risks are often discovered after large populations have been exposed
- Prescribers often make poor decisions with respect to safety, effectiveness, and costs
- The effect of policy changes are not assessed

We're Talking About Big Numbers Here!

- Half of antibiotics are overused and unnecessary
- As many as one in five new medicines are never filled
- Adherence to medicines for chronic conditions such as hypertension, diabetes, and depression is low
- Each year in the US, adverse drug events—most preventable—account for:
  - More than 3.5 million physician visits
  - 1 million emergency department (ED) visits
  - 125,000 hospitalizations

Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the US, 2005 vs. 2011

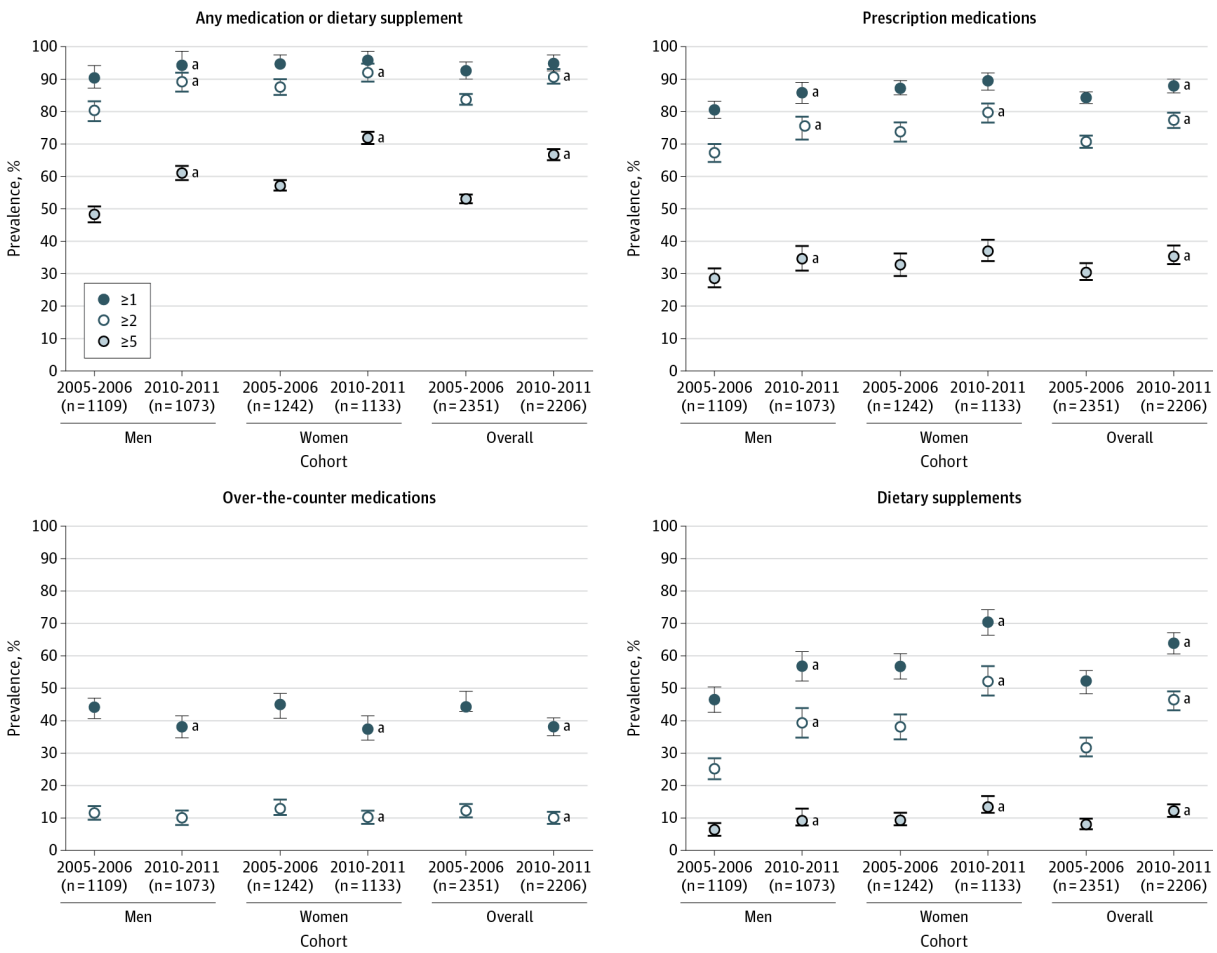


Image source: Qato, D. M., Wilder, J., Schumm, L. P., Gillet, V., & Alexander, G. C. (2016). *Figure: Weighted prevalence estimates of prescription and over-the-counter medication and dietary supplement use among older adults in the United States* [Box-and-whisker charts]. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Internal Medicine*, *176*(4), 473–482. https://doi.org/10.1001/jamainternmed.2015.8581.

What Is Drug Utilization Research?—1

"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."

Source: Hartzema, A. G., Tilson H. H., and Chan, K. A. (2008). *Pharmacoepidemiology and therapeutic risk management*. Harvey Whitney Books.

What Is Drug Utilization Research?—2

"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."

Source: Hartzema, A. G., Tilson H. H., and Chan, K. A. (2008). *Pharmacoepidemiology and therapeutic risk management*. Harvey Whitney Books.

Life Cycle of Product and Knowledge

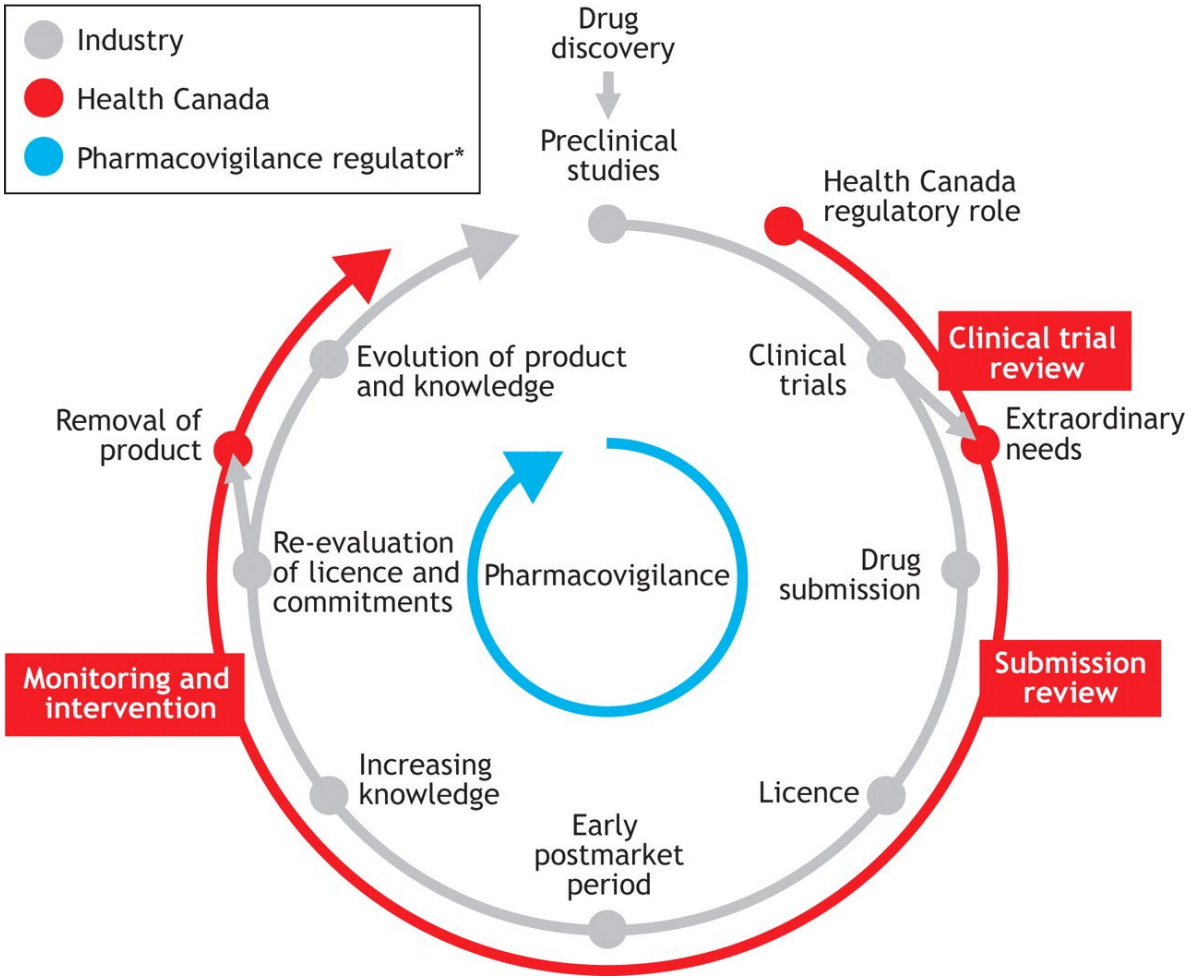
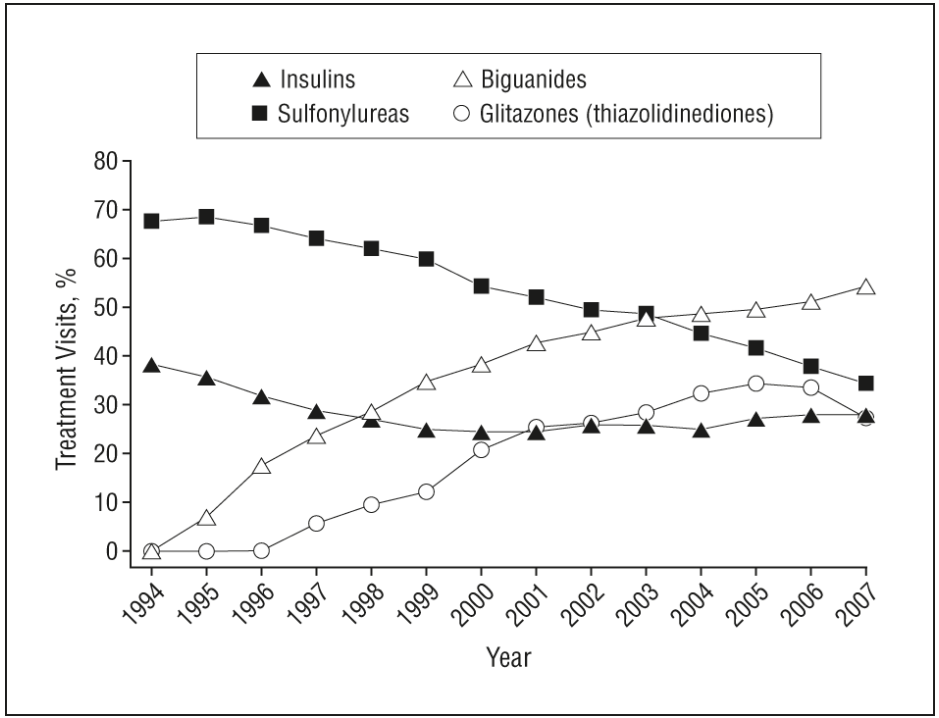


Image source: Yeates, N., Lee, D. K., & Maher, M. (2007). *Figure 1: The "life cycle" of a drug* [Diagram]. Health Canada's progressive licensing framework. *Canadian Medical Association Journal, 176*(13), 1845–1847. https://doi.org/10.1503/cmaj.070597. All rights reserved.

Example of Drug Life Cycle: National Trends in Treatment of Type 2 Diabetes Mellitus, 1994–2007



- Drug life cycle has implications for:
  - Academic research
  - Clinical care
  - Regulatory policy
  - Public health

Image source: Alexander, G. C., Sehgal, N. L., Moloney, R. M., & Stafford, R. S. (2008). *Figure 1: National trends in the use of different therapeutic drug classes to treat diabetes, 1997–2004* [Chart]. National trends in treatment of type 2 diabetes mellitus, 1994-2007. *Archives of Internal Medicine*, *168*(19), 2088–2094. https://doi.org/10.1001/archinte.168.19.2088. All rights reserved.

Drivers of the Life Cycle

- Innovation
  - Chemical and clinical innovation
- Changes in clinical care
  - Trends in disease prevalence, incidence, diagnosis, comorbidities
- Scientific insights
  - New safety and effectiveness evidence
- Regulatory changes
  - Supplemental new drug applications
- Payers
  - Incentive-based formularies
- Market forces
  - Marketing and promotion
- Other drivers
  - Social and cultural changes

An Example of Drug Utilization Research

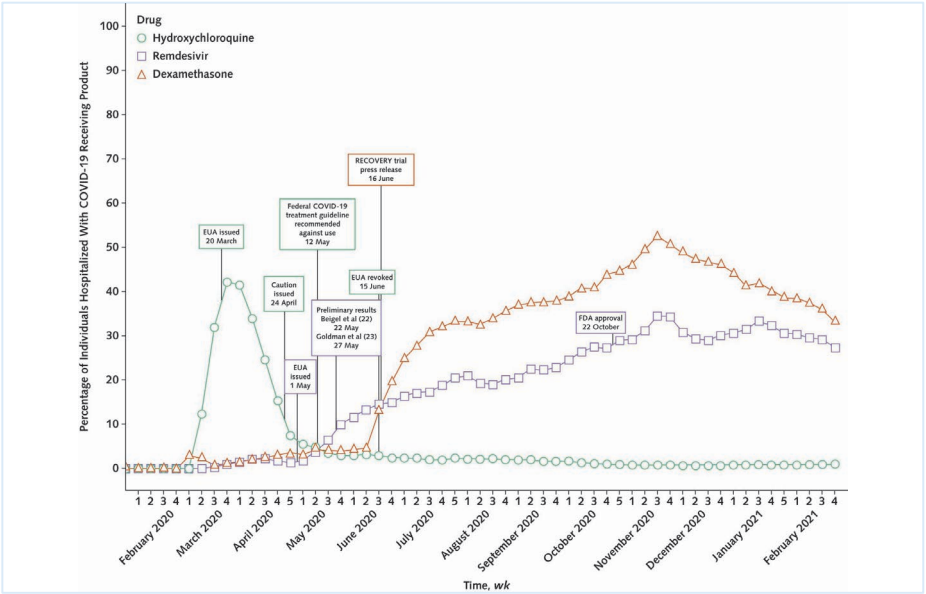
Treatment of COVID-19 in the US—1

- During the first year, more than 33 million infections and 600,000 US deaths from COVID-19
- Intense scientific scrutiny of safety and effectiveness of three main therapies: hydroxychloroquine, remdesivir, and dexamethasone
- Very limited information was available at the time regarding their utilization
- We used National COVID Cohort Collaborative (N3C), a large, multicenter, longitudinal cohort of individuals with confirmed or suspected COVID in the US, to characterize use of these products
- We also examined hydroxychloroquine deadoption, and variation in treatments across health systems

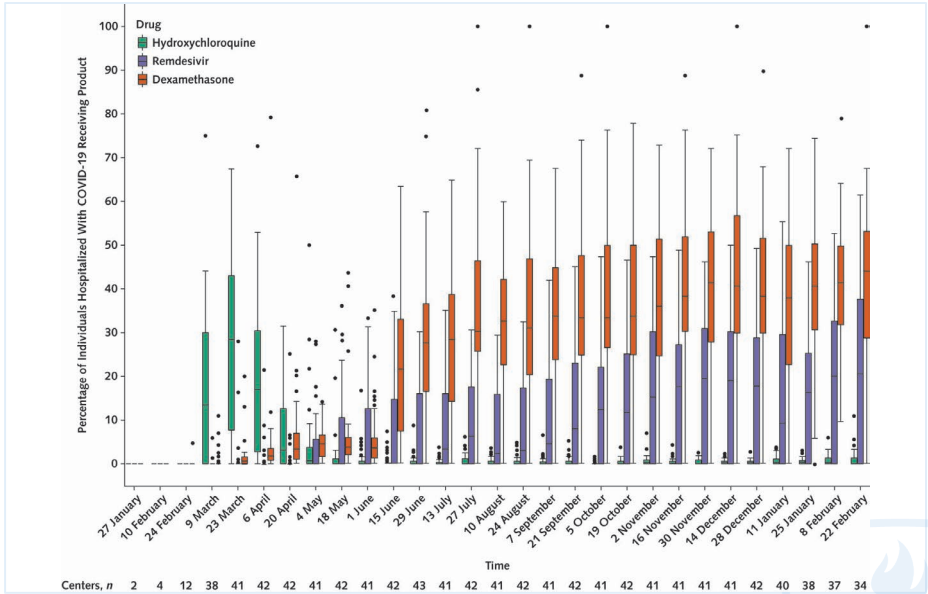
Source: Mehta, H. B., An, H., Andersen, K. M., Mansour, O., Madhira, V., Rashidi, E. S., Bates, B., Setoguchi, S., Joseph, C., Kocis, P. T., Moffitt, R., Bennett, T. D., Chute, C. G., Garibaldi, B. T., Alexander, G. C., & National COVID Cohort Collaborative (N3C). (2021). Use of hydroxychloroquine, remdesivir, and dexamethasone among adults hospitalized with COVID-19 in the United States: A retrospective cohort study. *Annals of Internal Medicine*, *174*(10), 1395–1403. https://doi.org/10.7326/M21-0857.

Treatment of COVID-19 in the US—2

Overall utilization



Center-level variation



Images source: Mehta, H. B., An, H., Andersen, K. M., et al. (2021). (left) *Figure 1: Use of hydroxychloroquine, remdesivir, and dexamethasone among individuals hospitalized with COVID-19, 1 February 2020 to 28 February 2021 (n = 137 870)* [Chart] and (right) *Figure 2: Variation in hydroxychloroquine, remdesivir, and dexamethasone use across health centers over time, 1 February 2020 to 28 February 2021 (n = 137 870)* [Chart]. Use of hydroxychloroquine, remdesivir, and dexamethasone among adults hospitalized with COVID-19 in the United States: A retrospective cohort study. *Annals of Internal Medicine*, *174*(10), 1395–1403. https://doi.org/10.7326/M21-0857. All rights reserved.

Conduct of This Work Required Many Different Skills

- Clinical knowledge and familiarity with COVID practice guidelines
- Knowledge to inform cohort derivation (e.g., time windows constituting “positive” test and “COVID” hospitalization, management of individuals with multiple COVID episodes)
- Understanding of drugs of interest (e.g., management of other glucocorticoids, consideration of potentially interacting drugs)
- Database management, programming, statistical analyses
- Interpretation and dissemination

Utilization Research Addresses Critical Stakeholder Questions

Clinical care

- What products are used to treat a given disease?
- How does such use comport with best practice?
- How does this vary over time, patients, providers, and health systems?
- Where are gaps in care largest, and how can they best be addressed?

Health policy

- How does pharmaceutical policy impact drug utilization?
- Where are new policies—at a local, state, or federal level—needed to address specific concerns?

Regulation

- What effect do regulatory interventions have on drug utilization?
- How does this vary based on the type, timing, and intensity of the intervention?

Coverage and reimbursement

- What is the association between coverage and reimbursement and drug utilization?
- How can coverage and reimbursement policies be designed and refined, so as to optimize pharmaceutical value?

Scientific research

- How can efforts to measure and improve pharmaceutical utilization be improved?
- How can the value of new data sources to measure utilization best be captured?

Choosing a Design

Choosing a Design for Drug Utilization Research

- From question to data—or from data to question
- The right design depends upon the scientific question
- There is no perfect design—nor perfect study
- You don't need p-values to be important
- Analytic challenges are similar to other areas of epidemiology
- Dynamic scientific, clinical, regulatory, and payment environment
  - Good questions keep on arising!

Descriptive vs. Analytical vs. Interventional Designs

Descriptive	Analytical	Interventional
▶ Cross-sectional	▶ Ecological	▶ Controlled before-after
▶ Longitudinal	▶ Cohort	▶ Time series
	▶ Case-control	▶ Randomized controlled trials (RCTs)

Descriptive Designs

Descriptive Designs in Drug Utilization Studies

- Information collected without changing or manipulating environment
- The who, what, when, where of epidemiology
- “First scientific toe in the water in new areas of inquiry” (Grimes & Schulz, 2002)
- In studies of drug utilization, descriptive analyses can be incredibly powerful, and they may also prompt analytic studies
  - Analysis of antipsychotic use among elderly preceding quasiexperimental study examining effect of quality improvement intervention on prescribing
  - Analysis of GLP-1 inhibitor use preceding analytic study examining comparative efficacy of different products

Source: Grimes, D. A., & Schulz, K. F. (2002). Descriptive studies: What they can and cannot do. *Lancet*, *359*(9301), 145–149. https://doi.org/10.1016/S0140-6736(02)07373-7

Cross-Sectional Analyses

Cross-sectional analyses

- Carried out at one time point
- Can be used to estimate prevalence of drug utilization, or association between exposures (e.g., marketing) and outcome (utilization)
- Cannot establish causation, only association
- Data sources include claims databases, electronic health records, surveys

Serial cross-sectional analyses

- Commonly used, may be mistaken as longitudinal by casual observer

Correlation Between Prescribing Quality and Pharmaceutical Costs in English Primary Care: National Cross-Sectional Analysis

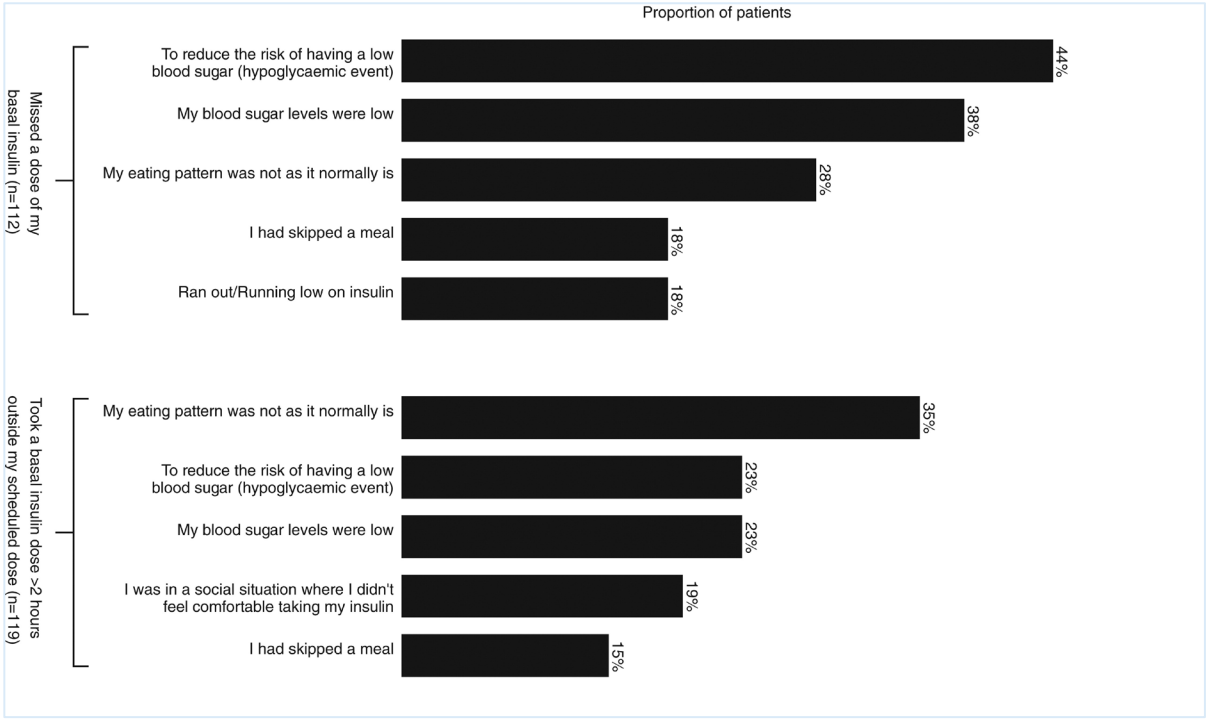
Table 3. Associations between achievement of prescribing quality indicator and related pharmaceutical spend, in eight prescribing areas and all areas combined

Prescribing area		Correlation (multiple regression)[a]		Correlation (bivariate)
ACE/ARB	R^2	0.033	Pearson's *r*	0.141
	Beta	0.003	*P*-value	<0.001
	P-value	<0.001	*n*	7600
Antiplatelet treatment	R^2	0.020	Pearson's *r*	0.058
	Beta	0.014	*P*-value	<0.001
	P-value	<0.001	*n*	7811
Beta blockers	R^2	0.042	Pearson's *r*	0.149
	Beta	0.047	*P*-value	<0.001
	P-value	<0.001	*n*	7962
Diabetes	R^2	0.098	Pearson's *r*	0.000
	Beta	0.005	*P*-value	0.998
	P-value	0.007	*n*	7960
Hypertension	R^2	0.044	Pearson's *r*	−0.058
	Beta	−0.021	*P*-value	<0.001
	P-value	<0.001	*n*	5415
Influenza vaccination	R^2	0.108	Pearson's *r*	0.167
	Beta	0.001	*P*-value	<0.001
	P-value	<0.001	*n*	7946
Lipid lowering	R^2	0.076	Pearson's *r*	0.092
	Beta	0.009	*P*-value	<0.001
	P-value	<0.001	*n*	7962
Smoking cessation	R^2	0.027	Pearson's *r*	−0.027
	Beta	−0.012	*P*-value	0.018
	P-value	0.018	*n*	7790
Combined score, equal weights	R^2	0.080	Pearson's *r*	−0.012
	Beta	0.003	*P*-value	0.399
	P-value	0.093	*n*	5176
Sensitivity analysis, combined score with health gain weights	R^2	0.061	Pearson's *r*	−0.022
	Beta	−0.008	*P*-value	0.110
	P-value	0.788	*n*	7497

[a]Beta = non standardised beta coefficient on cost; coefficients on other covariates are available from the authors. ACE = angiotensin converting enzyme. ARB = angiotensin receptor blocker.

- There was no association between overall prescribing quality indicator achievement and associated pharmaceutical costs (Pearson's *r* = -0.012, P = 0.399; multiple regression beta coefficient on cost = 0.003, P = 0.093)
- Sensitivity analysis gave similar nonsignificant results, with overall quality score weighted by health gain as the dependent variable (Pearson's *r* = -0.022, P = 0.110; multiple regression beta coefficient on cost = -0.008, P = 0.788)

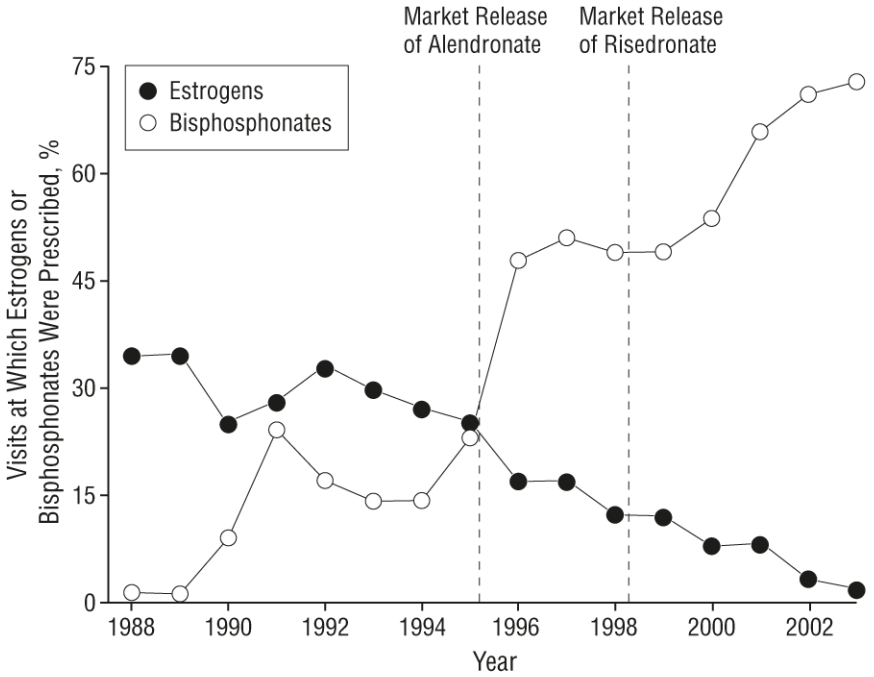
Adherence Patterns in Patients With Type 2 Diabetes on Basal Insulin Analogues: Missed, Mistimed, and Reduced Doses



- The most common reasons reported for intentional dosing irregularities, including missed, mistimed, and reduced doses

Image source: Adapted from Brod, M., Rana, A., & Barnett, A. H. (2012). *Figure 2: The five most common reasons for intentional dosing irregularities* [Chart]. Adherence patterns in patients with type 2 diabetes on basal insulin analogues: Missed, mistimed and reduced doses. *Current Medical Research and Opinion*, *28*(12), 1933–1946. https://doi.org/10.1185/03007995.2012.743458. (Third chart cropped from image).

National Trends in Osteoporosis Visits and Treatment, 1988–2003



- Values depict percentage of bisphosphonate and estrogen use among patients with reported osteoporosis seen by office-based physicians in the US
- Data are from the National Disease and Therapeutic Index, IMS Health

Longitudinal Analyses

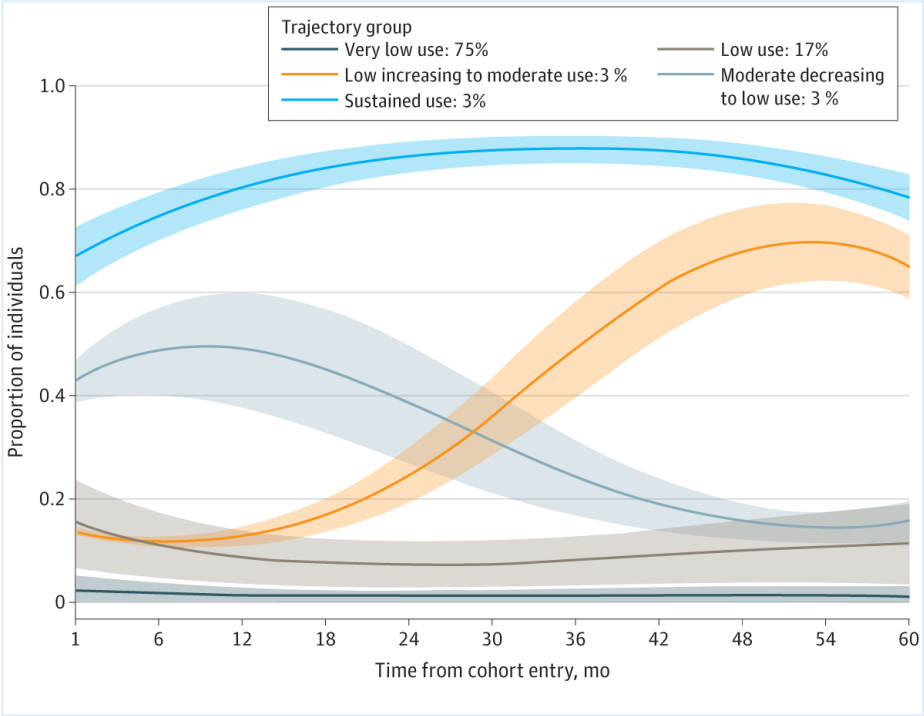
- Tracks the same subjects over a period of time
  - Cohort and panel
  - Retrospective or prospective
- Can establish sequence of events
- Data sources include claims databases, electronic health records, surveys
- Pros and cons

Prescription Coverage, Use, and Spending Before and After Part D Implementation: A National Longitudinal Panel Study

Table 1: Prescription coverage transitions from 2003 to 2006

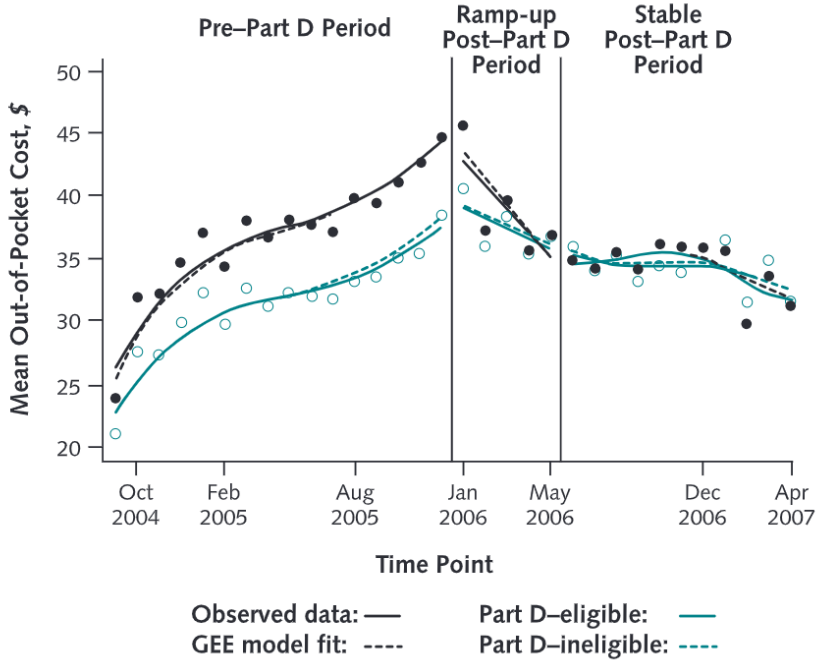
Source of Rx Coverage in 2003 (Column sums to 100%)	Total		Source of Rx Coverage in 2006 (Rows sum to 100%)						
			Part D			Employer (n=2576)	VA (n=296)	Other (n=760)	None (n=770)
			Total (n=5171)	PDP (n=3635)	MAPD (n=1536)				
Total (n=9573)	100.0%	→	47.5%	33.0%	14.5%	31.8%	4.3%	8.9%	7.5%
None (n=2538)	25.7%	→	63.1%	49.6%	13.5%	6.7%	3.2%	9.6%	17.4%
Medicaid (n=1172)	5.2%	→	94.2%	78.4%	15.8%	2.6%	0.5%	2.7%	0.0%
HMO (n=917)	8.8%	→	78.2%	5.5%	72.7%	4.4%	4.1%	8.8%	4.5%
Medigap/Other Private (n=1641)	19.8%	→	50.2%	46.3%	3.9%	24.3%	2.4%	15.5%	7.6%
Employer (n=2753)	34.4%	→	21.6%[a]	13.7%	7.9%	69.5%	0.9%	5.2%	2.8%
VA (n=309)	3.9%	→	22.0%	18.0%	4.0%	20.2%	56.2%	0.6%	1.0%
State (n=214)	2.1%	→	55.2%	52.9%	2.3%	2.3%	6.3%	30.0%	6.2%
Other Public (n=29)	0.1%	→	74.2%	60.5%	13.7%	12.9%	4.0%	7.2%	1.7%

Five-Year Trajectories of Prescription Opioid Use



- Population-based study used linked Australian state and national datasets
- Solid lines represent mean monthly proportion of cohort using opioids in each trajectory group
- Shaded areas indicate 95% confidence intervals

Effect of the Medicare Part D Prescription Benefit on Drug Utilization and Expenditures



- Trends in average monthly out-of-pocket expenditures for the Part D–eligible and Part D–ineligible groups
- Generalized estimating equations used to estimate changes in expenditures and utilization among beneficiaries
- Control group was included to control for secular trends unrelated to the Part D benefit

Image source: Adapted from Yin, W., Basu, A., Zhang, J. X., Rabbani, A., Meltzer, D. O., & Alexander, G. C. (2008). *Figure 1: Trends in out-of-pocket prescription expenditures* [Line chart]. The effect of the Medicare Part D prescription benefit on drug utilization and expenditures. *Annals of Internal Medicine*, *148*(3), 169–177. https://doi.org/10.7326/0003-4819-148-3-200802050-00200. (Bottom chart cropped from image). All rights reserved.

Analytical Designs

Descriptive vs. Analytical vs. Interventional Designs

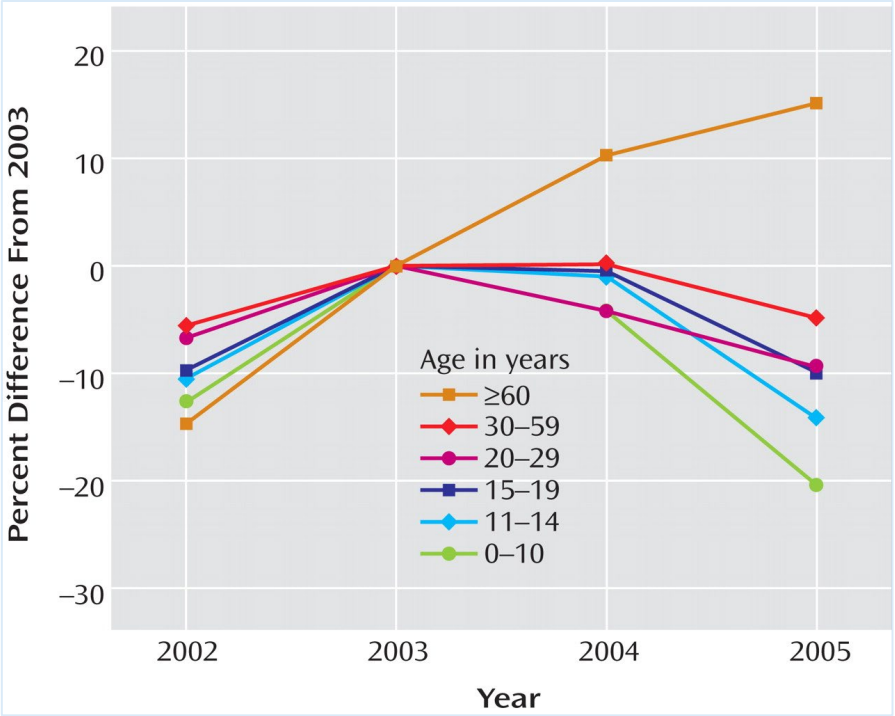
Descriptive	Analytical	Interventional
▶ Cross-sectional	▶ Ecological	▶ Controlled before-after
▶ Longitudinal	▶ Cohort	▶ Time series
	▶ Case-control	▶ Randomized controlled trials (RCTs)

Analytical Designs in Drug Utilization Studies

- Focus on “why”
- Three main types
  1. Ecological
  2. Cohort
  3. Case-control
- More likely to use longitudinal data, but ecological studies can be done with serial cross-sectional data as well

- Not as common as descriptive designs in drug utilization research; however, they represent the bread and butter of safety and effectiveness studies
- There are some examples of drug utilization studies using these alternative designs (ecological, cohort, or case-control), such as adherence studies that follow an incident cohort of patients
- Many quasi-experimental studies begin with a cohort of patients, in which case there is an interest in the effect of an intervention (or exposure) on drug utilization (or outcome)

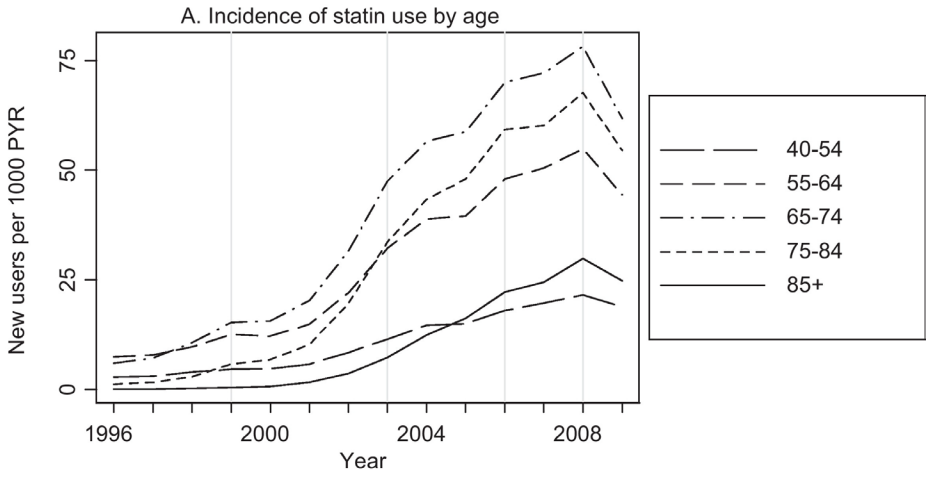
Ecological Study: Early Evidence on the Effects of Regulators' Suicidality Warnings on Selective Serotonin Reuptake Inhibitor (SSRI) Prescriptions and Suicide in Children and Adolescents

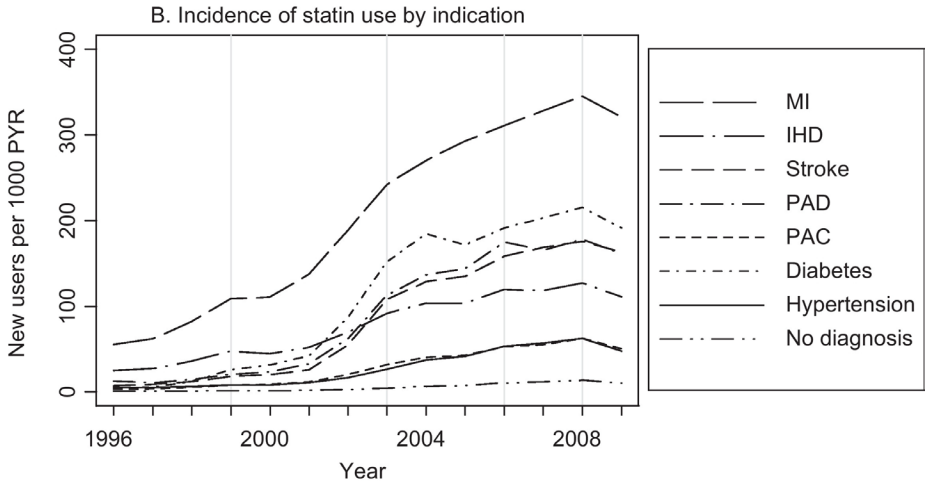


- SSRI prescription rates in the US, 2002–2005
- Stratified by age group and expressed as a percentage of the 2003 rate
- SSRI prescriptions for youths decreased by approximately 22% in both the US and the Netherlands after warnings were issued
- Decreases were associated with increases in suicide rates in children and adolescents

Image source: Gibbons, R. D., Brown, C. H., Hur, K., Marcus, S. M., Bhaumik, D. K., Erkens, J. A., Herings, R. M., & Mann, J. J. (2007). *Figure 1: SSRI prescription rates in the United States, 2002–2005, stratified by age group and expressed as a percentage of the 2003 rate* [Chart]. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *American Journal of Psychiatry*, *164*(9), 1356–1363. https://doi.org/10.1176/appi.ajp.2007.07030454.

Cohort Study: Statin Utilization According to Indication and Age: A Danish Cohort Study on Changing Prescribing and Purchasing Behaviour





- Incidence rate of statin use between 1996 and 2010, by age (A) and indication (B)
- The vertical grey lines mark the driver periods

Case-Control Study: A Controlled Study of Physicians Who Requested Additions to a Hospital Drug Formulary

Table 2.—Physician Interactions in the Past Year With Drug Companies in General, According to Self-reports by Physicians Who Submitted Formulary Requests (Cases) and by Those Who Did Not (Controls)

Type of Interaction*	No. (%) of Cases (Physicians Submitting Requests) (n=36)†	No. (%) of Controls (Physicians Not Submitting Requests) (n=69)†	P
Shared meals worth > $10			
Never	17 (47)	42 (61)	.01
Rarely	11 (31)	24 (35)	
Occasionally	3 (8)	2 (3)	
Often	5 (14)	1 (1)	
Accepted money for travel or lodging to attend educational symposia			
Never	27 (75)	63 (91)	.06
Rarely	7 (19)	5 (7)	
Occasionally	2 (6)	0 (0)	
Often	0 (0)	1 (1)	
Accepted money to speak at educational symposia			
Never	17 (47)	55 (80)	<.001
Rarely	5 (14)	9 (13)	
Occasionally	5 (14)	4 (6)	
Often	9 (25)	1 (1)	
Accepted money to perform research			
No	14 (39)	49 (71)	.002
Yes	22 (61)	20 (29)	

*Types of interactions are defined in the text. "Rarely" was defined as one to two times in the past year, "occasionally" as three to five times in the past year, and "often" as more than five times in the past year. One column does not total 100% due to rounding.

†Of the 120 physicians, 36 cases and 69 controls responded to the survey instrument.

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- "Rarely" was defined as one to two times in the past year, "occasionally" as three to five times in the past year, and "often" as more than five times in the past year

Image source: Chren, M. M., & Landefeld, C. S. (1994). Table 2: Physician interactions in the past year with drug companies in general, according to self-reports by physicians who submitted formulary requests (cases) and by those who did not (controls) [Table]. Physicians' behavior and their interactions with drug companies. A controlled study of physicians who requested additions to a hospital drug formulary. *JAMA*, *271*(9), 684–689. https://doi.org/10.1001/jama.1994.03510330062035. All rights reserved.

Interventional Designs

Descriptive vs. Analytical vs. Interventional Designs

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	▶ Case-control	▶ Randomized controlled trials (RCTs)

Interventional Designs: Controlled Before-and-After Study

- An example of a controlled before-and-after study
  - Cates C. (1999). An evidence based approach to reducing antibiotic use in children with acute otitis media: Controlled before and after study. *BMJ*, *318*(7185), 715–716. https://doi.org/10.1136/bmj.318.7185.715

An Evidence-Based Approach to Reducing Antibiotic Use in Children With Acute Otitis Media: Controlled Before and After Study

Monthly totals of prescriptions for all amoxicillin suspensions for 12 months before (1996-7) and after (1997-8) new prescribing policy was introduced

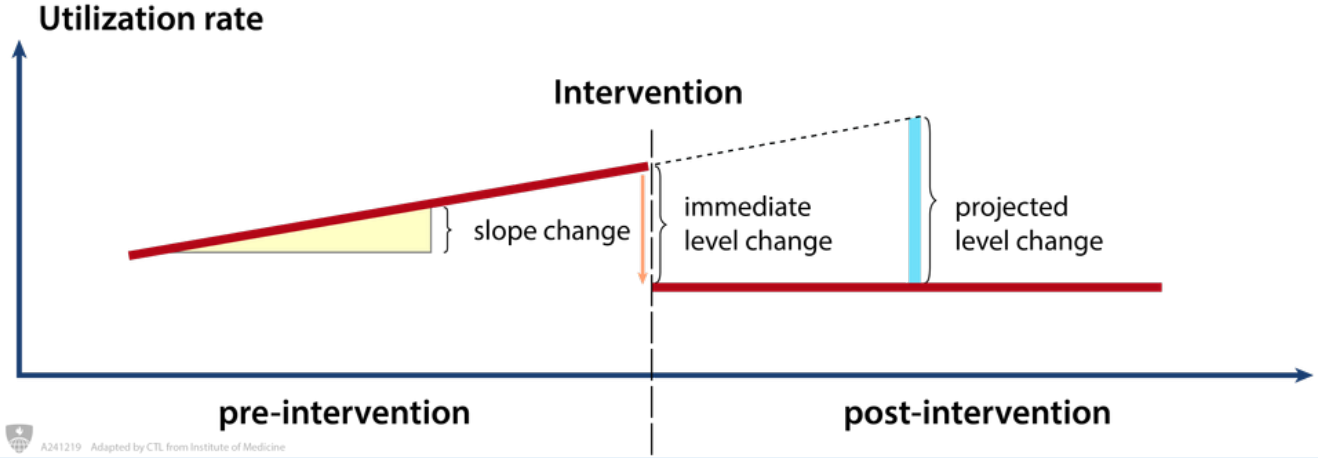
	Practice using new policy		Control practice		Nationally	
Month	Before	After	Before	After	Before	After
July	68	55	68	66	392 367	364 831
August	35	31	35	26	220 606	214 292
September	74	33	56	40	367 901	366 957
October	65	45	72	54	429 828	503 459
November	106	62	150	90	502 174	530 556
December	162	117	169	155	869 621	752 960
January	95	49	85	72	634 195	489 216
February	86	78	83	91	538 509	591 498
March	80	49	86	74	470 010	515528
April	70	44	64	66	392 452	354 032
May	76	39	72	50	442 111	323 566
June	71	37	51	51	345 765	369 194
Median	75	47	72	66	435 970	429 205
% change from previous year (95% CI)*	–32% (–39% to –25%)		–12% (–20% to –4%)			

- The 12 months before July 1997 were used for baseline comparison, and the following 12 months were used to assess impact of policy change
- As there was seasonal and annual prescribing variation, monthly odds of prescriptions in relation to national total were calculated by practice
- Estimates weighted and pooled using the Mantel-Haenszel method

Interventional Designs: Time Series Studies

- Examples of interrupted time series studies
  - Schneeweiss, S., Soumerai, S. B., Glynn, R. J., Maclure, M., Dormuth, C., & Walker, A. M. (2002). Impact of reference-based pricing for angiotensin-converting enzyme inhibitors on drug utilization. *Canadian Medical Association Journal, 166*(6), 737–745. https://www.cmaj.ca/content/166/6/737.long
  - Tamblyn, R., Laprise, R., Hanley, J. A., Abrahamowicz, M., Scott, S., Mayo, N., Hurley, J., Grad, R., Latimer, E., Perreault, R., McLeod, P., Huang, A., Larochelle, P., & Mallet, L. (2001). Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *JAMA*, *285*(4), 421–429. https://doi.org/10.1001/jama.285.4.421
  - Hsu, J. C., Lu, C. Y., Wagner, A. K., Chan, K. A., Lai, M. S., & Ross-Degnan, D. (2014). Impacts of drug reimbursement reductions on utilization and expenditures of oral antidiabetic medications in Taiwan: An interrupted time series study. *Health Policy*, *116*(2-3), 196–205. https://doi.org/10.1016/j.healthpol.2013.11.005

Interrupted Time Series



- **Assumption: the (counterfactual) experience of patients had the policy not been implemented is correctly reflected by the extrapolation of the pre-policy trend**
- Even stronger with comparison series

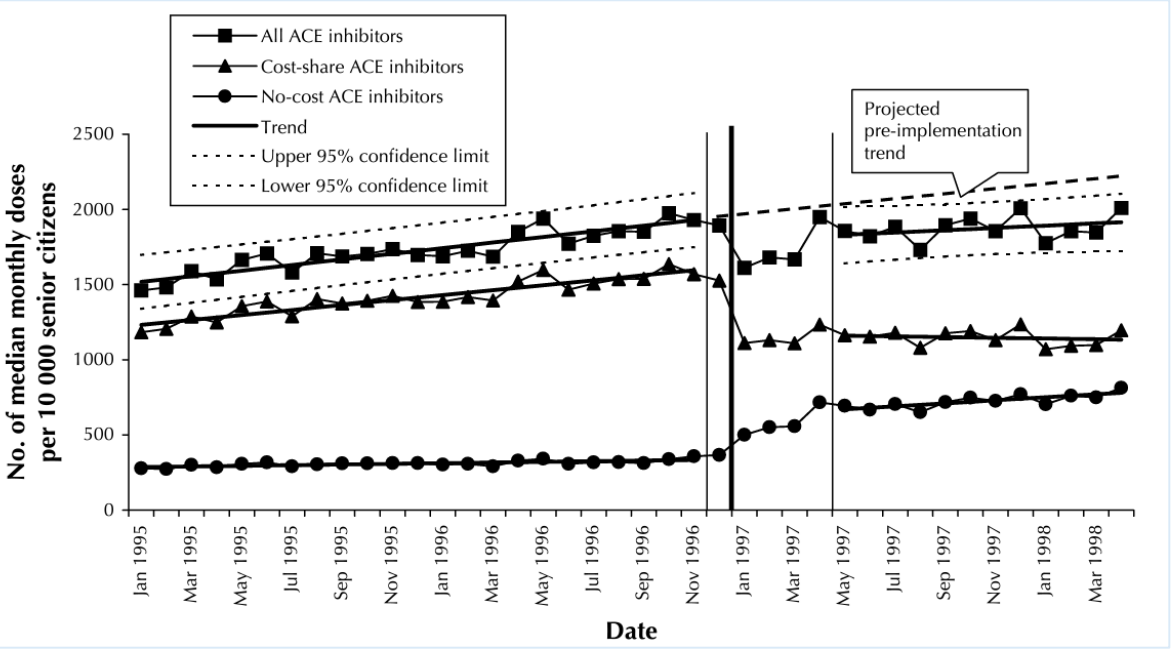
Source: Schneeweiss, S., Soumerai, S. B., Glynn, R. J., Maclure, M., Dormuth, C., & Walker, A. M. (2002). Impact of reference-based pricing for angiotensin-converting enzyme inhibitors on drug utilization. *Canadian Medical Association Journal, 166*(6), 737–745. https://www.cmaj.ca/content/166/6/737.long
Image source: Adapted from Institute of Medicine. (2007). *Figure 1-2: Hypothetical changes in level and slope of a time–series* [Diagram]. *The learning healthcare system: Workshop summary* (p. 52). The National Academies Press. https://doi.org/10.17226/11903

Quality Criteria for Interrupted Time Series Design

1. Intervention occurred independently of other changes over time
2. Intervention was unlikely to affect data collection
3. The primary outcome was assessed blindly or was measured objectively
4. The primary outcome was reliable or was measured objectively
5. The composition of the data set at each time point covered at least 80% of the total number of participants in the study
6. The shape of the intervention effect was prespecified
7. A rationale for the number and spacing of data points was described
8. The study was analyzed appropriately using time series techniques

Source: Ramsay, C. R., Matowe, L., Grilli, R., Grimshaw, J. M., & Thomas, R. E. (2003). Interrupted time series designs in health technology assessment: Lessons from two systematic reviews of behavior change strategies. *International Journal of Technology Assessment in Health Care*, *19*(4), 613–623. https://doi.org/10.1017/s0266462303000576

Impact of Reference-Based Pricing for Angiotensin-Converting Enzyme (ACE) Inhibitors on Drug Utilization



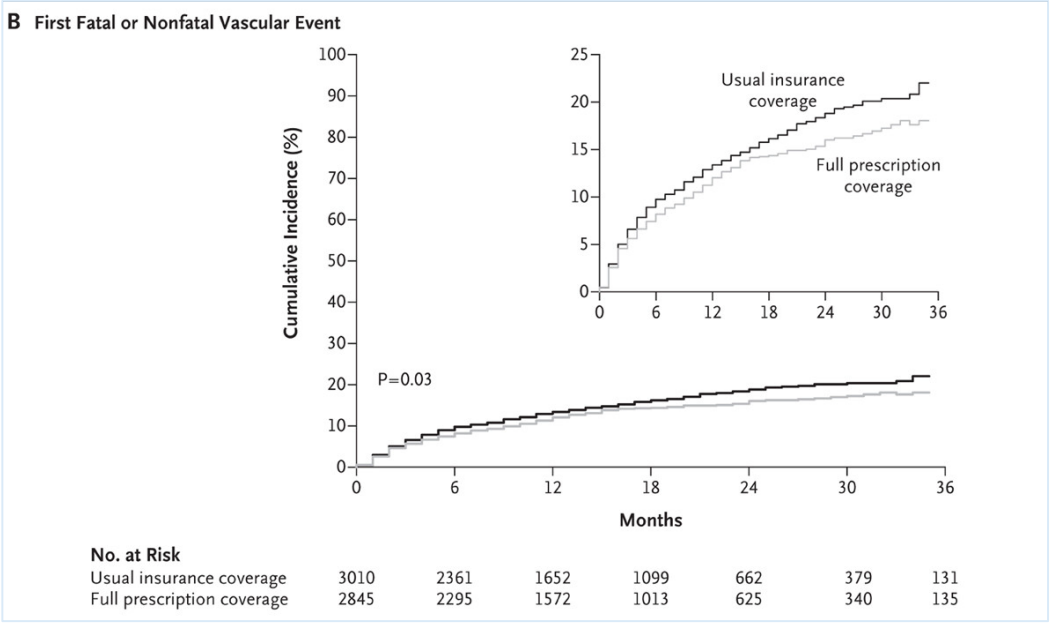
- Changes in utilization of ACE inhibitors in British Columbia residents 65 years or older
- Thick vertical line marks start of reference-based pricing; two thinner flanking lines represent 5-month transition period
- Utilization rates were adjusted for length of individual months

Image source: Schneeweiss, S., Soumerai, S. B., Glynn, R. J., Maclure, M., Dormuth, C., & Walker, A. M. (2002). *Figure 1: Changes in utilization of angiotensin-converting enzyme (ACE) inhibitors in British Columbia senior citizens (residents at least 65 years of age)* [Chart]. Impact of reference-based pricing for angiotensin-converting enzyme inhibitors on drug utilization. *Canadian Medical Association Journal, 166*(6), 737–745. https://www.cmaj.ca/content/166/6/737.long. All rights reserved.

Interventional Designs: Randomized Controlled Trials

- RCTs are very rarely used for drug utilization research but occasionally can be
- Challenge is that much information related to patterns of drug utilization is not amendable to being randomized
- Randomization for drug utilization research has all the benefits and costs as in other settings
- Greatest benefit is the ability to equally distribute unknown or immeasurable differences between treatment and control group
- Often, utilization is not the only outcome of interest, but it may be an outcome of interest

Full Coverage for Preventive Medications After Myocardial Infarction



- Cumulative incidence of first fatal or nonfatal acute myocardial infarction, unstable angina, stroke, or congestive heart failure
- Adherence ranged from 35.9%–49.0% in usual-coverage group and were 4%–6% higher in full-coverage group
- No significant difference in primary outcome, first major vascular event

Image source: Adapted from Choudhry, N. K., Avorn, J., Glynn, R. J., Antman, E. M., Schneeweiss, S., Toscano, M., Reisman, L., Fernandes, J., Spettell, C., Lee, J. L., Levin, R., Brennan, T., Shrank, W. H., & Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial (2011). *Figure 1: Cumulative incidence of outcomes* [Kaplan-Meier curve]. Full coverage for preventive medications after myocardial infarction. *New England Journal of Medicine*, *365*(22), 2088–2097. https://doi.org/10.1056/NEJMsa1107913 (only Panel B shown). All rights reserved.

Other Designs

- Generalized estimating equations
  - Regulatory policy (prescription drug monitoring program)
  - Payment policy (Part D)
  - Clinical policy (blood factor review)

- Survival analysis
  - Time to discontinuation of therapy (statin)
  - Time to dose escalation (opioid)
  - Time to treatment augmentation (antidepressant)

Summary

- There are large gaps in the quality of drug utilization in the US and around the world
- Drug utilization research consists of an eclectic group of descriptive and analytic methods to understand these gaps and to assess the impact of interventions designed to close them
- The drug life cycle is important to understand
  - Drivers of the drug life cycle include key determinants of drug utilization
  - The life cycle has direct implications for academic research, clinical care, health policy, and public health
- There are three key types of drug utilization studies—descriptive, analytical, and interventional—and each design has its merits, strengths, and limitations