Pharmacovigilance & Pharmacoepidemiology Study Designs

Maribel Salas, MD, DSc, FACP, FISPE

2019

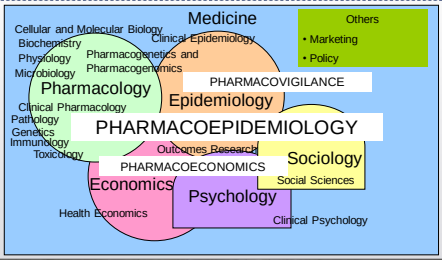
Pharmacepidemiology. Definition

- **Discipline that study the frequency and distribution of health and disease as a result of the use and effects (beneficial and adverse) of drugs in human populations**

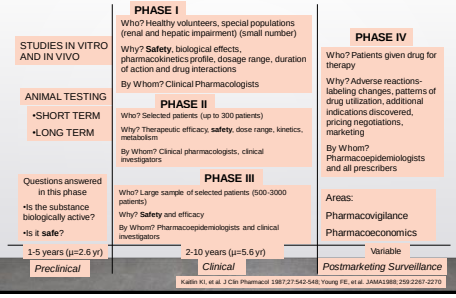
- **Aims:**
  - **Describe**
  - **Explain**
  - **Control**
  - **Predict**

Use and effects of drugs in a defined time, space and population

Pharmacoepidemiology and Other Disciplines



Phases of Drug Development



What Questions Are Answered by Pharmacoepidemiology?

- What is the effect of "X" drug on "X" outcome?
- What are the most common uses/adverse events of "X" drugs?
- How
- Why
- Where
- When

do "X" drugs are used in "Z" population?

Sample Size to Detect ADR

	Statistical Power			
Frequency	95%	90%	80%	63%
1/100	300	231	161	100
1/500	1,500	1,152	805	500
1/1,000	3,000	2,303	1,610	1,000
1/5,000	15,000	11,513	8,048	5,000
1/10,000	30,000	23,026	16,095	10,000
1/50,000	150,000	115,130	80,472	50,000

Hartzema, et al. Pharmacoepidemiology, 1998

Type of Studies. Descriptive Observational Studies

A. *Case Report*

B. *Case Series*

C. Ecologic Studies

D. Cross-sectional Studies

Type of Studies. Analytical Studies

Observational Studies

A. Case-control Studies

B. Cross-sectional Studies

C. Cohort Studies

D. Hybrid Studies

Interventional Studies

A. Controlled clinical trials

B. Randomized, control clinical trials

C. N of trials

D. Simplified clinical trials

E. Community trial

Type of Studies. Analytical Studies

D. ***Hybrid Studies***

1. Nested case-control studies
2. Case-cohort studies
3. Case-crossover studies
4. Case-time studies

Type of Studies. Descriptive Observational Studies

A. **Case Report**

B. ***Case Series***

C. **Ecologic Studies**

D. ***Cross-sectional Studies***

Descriptive Studies

- Describe patterns of disease occurrence with respect to person, place, or time
- Generate etiologic hypotheses
- Types of descriptive studies:
  - Cross-sectional
  - Correlational
  - Case reports, series

Case Report

- Definition
  - Clinical description of a single patient with a specific outcome
- Use
  - Hypothesis generation
- Main limitation
  - Generalizability: patient may be atypical

Example of Case Report

- Acute and Fatal Isoniazid-Induced Hepatotoxicity: A Case Report and Review of the Literature. Wissam K. Kabbara, Aline T. Sarkis, and Paola G. Saroufim. Infectious Diseases, 2016, Article ID 3617408
- A 65-year-old female diagnosed with latent Mycobacterium tuberculosis infection was receiving **oral isoniazid 300 mg daily**.
- She was admitted to the hospital for **epigastric and right sided flank pain of one-week duration**.

Laboratory test	Result	Normal range
Biochemistry		
Total bilirubin	*11.4 mg/dL	<1 mg/dL
Direct bilirubin	*9.9 mg/dL	0–0.2 mg/dL
Indirect bilirubin	*1.5 mg/dL	0-1 mg/dL
γ-GTP	*202 U/L	<40 U/L
ALP	*316 U/L	35–105 U/L
AST (SGOT)	*2099 U/L	<33 U/L
ALT (SGPT)	*1096 U/L	<34 U/L
CRP	*1.54 mg/dL	<0.5 mg/dL
Amylase	*115 U/L	28–100 U/L
Lipase	*97 U/L	13–60 U/L
Total proteins	*5.2 g/dL	6.6–8.7 g/dL
Albumin	*2.9 g/dL	3.5–5.2 g/dL
Hematology		
WBC	*$4.8 \times 10^3/\mu L$	$5.2–12.4 \times 10^3/\mu L$
RBC	$4.5 \times 10^6/\mu L$	$4.2–5.4 \times 10^6/\mu L$
Hb	13.7 g/dL	12–16 g/dL
PLT	$237 \times 10^3/\mu L$	$130–400 \times 10^3/\mu L$
Coagulation		
INR	*1.58	1–1.3

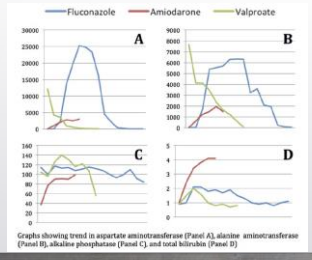
*Abnormal value.

Laboratory results and imaging confirmed **hepatitis**. After ruling out all other possible causes, she was diagnosed with **isoniazid-induced acute hepatitis** (probable association by the Naranjo scale). After discharge, **the patient was readmitted and suffered from severe coagulopathy, metabolic acidosis, acute kidney injury, hepatic encephalopathy, and cardiorespiratory arrest necessitating two rounds of cardiopulmonary resuscitation.** Despite maximal hemodynamic support, the patient did not survive.

Case Series

- **Definition**
  - **Clinical description of patients with a disease**
- **Use**
  - **Characterization of the illness**
- **Main limitation**
  - **No control group: cannot determine which factors are unique to the illness**

Example of Drug-Induced Liver Injury



Graphs showing trend in aspartate aminotransferase (Panel A), alanine aminotransferase (Panel B), alkaline phosphatase (Panel C), and total bilirubin (Panel D)

Trends in Liver Function Tests

Journal of Investigative Medicine, 2018; Volume 6: 1–7

	Case 1	Case 2	Case 3
Implicated drug (route)	Fluconazole (intravenous)	Amiodarone (intravenous)	Valproate (oral)
Age (years)	45	53	27
Sex	Male	Male	Male
Body mass index (kg/m^2)	31.9	39.2	42
Past medical history	Hypertension, diabetes mellitus, dyslipidemia, paraplegia due to gunshot injury, stage 3 decubitus	Hypertension, chronic kidney disease on dialysis, seizures, atrial fibrillation	Chronic obstructive pulmonary disease
Life style habits	Smoker, alcoholic	Former smoker	Alcoholic, smoker
Significant drug history	History of fluconazole-induced asymptomatic altered liver function tests	On phenytoin and phenobarbital	Recently started on valproate
Clinical presentation and diagnosis	Sepsis due to cellulitis	Atrial flutter	Drowsiness due to hyperammonic encephalopathy
Complete blood count at presentation			
Hemoglobin (g/dL)	13.5	6.2	14.8
White blood cell count (per µL)	21 000	2600	5800
Platelet count (per µL)	260 000	133 000	87 000
Basic metabolic panel			
Sodium (mmol/L)	136	135	134
Potassium (mmol/L)	4	4.3	4.0
Chloride (mmol/L)	99	97	101
Bicarbonate (mmol/L)	27	28	21
Blood urea nitrogen (mg/dL)	12	66	20
Creatinine (mg/dL)	1.6	9.2	1.1
Outcome	Recovery	Death	Recovery

Journal of Investigative Medicine, 2018; Volume 6: 1–7

ISPE

Limitations of Spontaneous Reports

- Cannot calculate true incidence of event
- Under-reporting in numerator
  - Recognition of event
  - Know how to report, take effort to report
- Lack of denominator

ISPE

Limitations of Spontaneous Reports

- Report quality
  - Often important data missing
- Bias
  - Reported cases different from unreported
- Lack of comparator group
  - Event rate in unexposed rarely known

ISPE

Analysis of Secular Trends

(Correlational Studies)

- Definition
  - Compares geographical and/or time trends of an illness to trends in risk factors
- Use
  - Rapid, easy support/disproof of hypotheses
- Main limitation
  - Cannot differentiate among those hypotheses consistent with the data

Cross-Sectional Study

- Survey of a sample of a population
- Presence/absence of exposure and disease are assessed at the same time
- Can assess prevalence (disease burden)
  - Setting priorities
  - Allocating resources
  - Plan prevention, education services

Time and Prevalence Measures in Cross-Sectional Studies

- Point prevalence: at single time point
  - Prevalence of antiretroviral use in HIV+
- Period prevalence: over specified time
  - Often used for conditions with short duration
  - Prevalence of steroid use among patients with Crohn's disease during one-year period

Limitations of Cross-Sectional Studies

- Do not capture concept of elapsed time
- No information about transitions from states of health → disease
- Do not distinguish between outcomes that developed recently versus long ago
- Uncertainty as to whether exposure or outcome occurred first

Correlational Studies

- Also referred to as:
  - Ecological studies
  - Analyses of secular trends
- Use aggregated data
- Evaluate correlations, trends over time

Market Withdrawal of Zomepirac as a Case Study

Ross-Degnan D1, Soumerai SB, Fortess EE, Gurwitz JH.

- To examine changes in the prescribing of analgesics after the market entry and subsequent withdrawal of zomepirac sodium, a nonsteroidal anti-inflammatory drug (NSAID), following repeated reports of zomepirac-related deaths.
- Natural quasiexperiment used to conduct **time-series analyses** to compare prescribing in two cohorts of primary care physicians from July 1980 through September 1983.
- We identified 260 primary care physicians from the NJ Medicaid Program, and who provided 10 or more prescriptions for zomepirac (zomepirac prescribers) and 308 who provided 10 or more prescriptions for NSAIDs other than zomepirac (other-NSAID prescribers) in Medicaid during the study period. Outcomes: Monthly rates of prescribing for zomepirac and several categories of substitute analgesics among Medicaid patients seen by study physicians.
- Zomepirac accounted for a stable 11.0% of analgesic prescribing among the zomepirac-prescriber cohort; label changes and manufacturer product-risk warnings 11 months before the product's withdrawal from the market had no impact on use. After market entry, zomepirac prescribers reduced use of other NSAIDs and propoxyphene (hydrochloride or napsylate) in comparison with other-NSAID prescribers (-8.1% and -2.8% of total analgesic prescribing, respectively; P < .001). After the product's withdrawal from the market, zomepirac prescribers showed significant increases in relative prescribing of other NSAIDs (+6.8%; P < .001), propoxyphene (+2.1%; P < .05), and analgesics containing barbiturates (+2.7%; P < .001).
- The sudden withdrawal of zomepirac from the market resulted in substitutions not only of other NSAIDs, but also of alternative analgesics that carry risks of habituation and adverse effects.

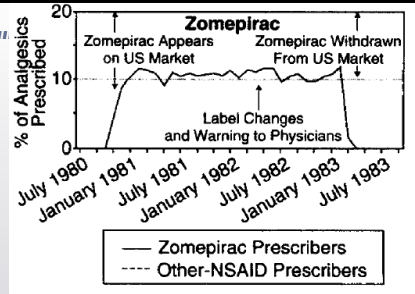
JAMA. 1993 Oct 27;270(16):1937-42.

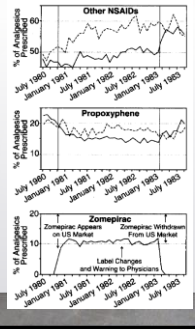
Prescription of Analgesics

Table 1.—Prescriptions for Study Analgesics per 100 Medicaid Recipients in Practice by Provider Specialty, July 1980 Through November 1981

Physician Group	Physicians, No.	Study Analgesics: Zomepirac Sodium	Other NSAIDs*	Analgesic With Opioids†	Analgesic With Barbiturates	All Study Analgesics
General practice	477	5.1	39.2	34.4	8.8	**87.5**
Internal medicine	468	5.5	73.7	55.3	12.9	**147.4**
Family practice	236	3.7	45.3	33.0	8.2	**90.2**
All Primary Care Physicians	**1183**	4.9	49.0	37.1	9.7	**100.7**
Dentistry, oral surgery	140	3.3	4.9	81.8	4.2	**94.2**
Pediatrics	121	0.2	2.7	4.9	0.7	**8.5**
General surgery	122	3.1	36.1	33.3	8.4	**80.9**
Obstetrics, gynecology	106	1.3	9.8	21.7	5.7	**38.5**
Other specialty	287	3.1	29.8	42.8	7.0	**80.7**
All Non–Primary Care Physicians	**776**	1.5	13.1	24.5	4.0	**43.1**

*NSAID indicates nonsteroidal anti-inflammatory drug.
†Analgesic products containing propoxyphene (hydrochloride or napsylate), pentazocine, meperidine hydrochloride, or codeine.





Changes in Analgesic Preference Following Release of Zomepirac and Its Market Withdrawal Among Prescribers of Zomepirac and Prescribers of Other NSAIDs*

	Study Analgesic Category, Proportional Share of Use (SE)†				
	Zomepirac Sodium	Other NSAIDs	Propoxyphene‡	Other Opioids	Barbiturates
Use at beginning of study period (June 1980)	0.000	0.475 (0.0061)	0.215 (0.0042)	0.206 (0.0040)	0.109 (0.003)
Monthly trend in use (July 1980-September 1983)	<0.001§	0.002§ (0.0003)	<0.001	−0.002§ (0.0002)	<0.001
Changes in average monthly use among prescribers of other NSAIDs					
While zomepirac on market	<0.001	0.058§ (0.0087)	−0.027§ (0.0061)	−0.013¶§ (0.0058)	−0.018§ (0.0045)
Following withdrawal	<0.001	−0.023¶§ (0.0010)	0.008 (0.0069)	0.033§ (0.0066)	−0.018¶ (0.0051)
Difference between prescribers of zomepirac and prescribers of other NSAIDs					
While zomepirac on market	0.110§ (0.001)	−0.081§ (0.0047)	−0.026§ (0.0033)	−0.002 (0.0031)	0.001 (0.0024)
Following withdrawal	−0.110§ (0.003)	0.066§ (0.0118)	0.021¶§ (0.0082)	−0.005 (0.0078)	0.027§ (0.0081)

*NSAID indicates nonsteroidal anti-inflammatory drug.
†Based on time-series regression models.
‡Propoxyphene hydrochloride or propoxyphene napsylate.
§Rounding reported for proportions <0.001.
¶P<.001.
‖P<.05.
#P<.01.

Features of Correlational Studies

- **Measured with correlation coefficient**
- **Popular for initial hypothesis generation**
- **Relatively inexpensive**
- **Can rapidly perform with existing data**

Limitations of Correlational Studies

- **Lack of patient-level data**
  - **Unable to link exposure and outcome in individual patient**
- **Inability to control for confounding factors**
- **Small attributable risks difficult to detect**
- **Represent average levels of exposures rather than actual levels**

Some Uses of Drug Utilization in Pharmacovigilance

- Estimation of drug exposure:
  - Overall population
  - By subpopulations
  - By demographic characteristics & other determinants
- As denominator for calculating rates of reported ADRs (reporting rates)
- Assessing effectiveness of risk minimization measures

Type of Studies. Analytical Studies

Observational Studies

A. Case-control Studies

B. Cross-sectional Studies

C. Cohort Studies

D. Hybrid Studies

Interventional Studies

A. Controlled clinical trials

B. Randomized, control clinical trials

C. N of trials

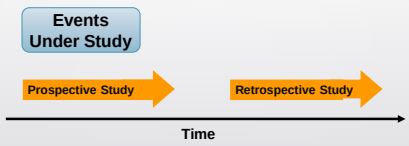
D. Simplified clinical trials

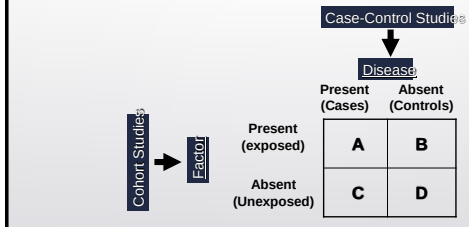
E. Community trial

Study Design

- **Options in directionality**
  - **Case-control study**
  - **Cohort study (follow-up)**
    - **Experimental study (clinical trial)**
- **Options in timing**
  - **Retrospective**
  - **Prospective**
  - **Cross-sectional (exposure, outcome measured at same time)**

Retrospective vs. Prospective Studies

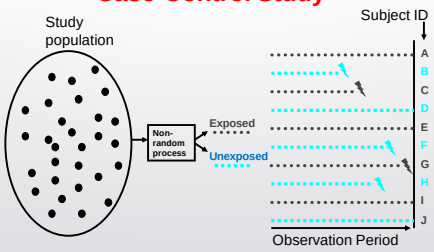




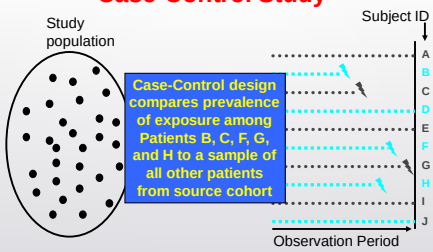
Case-Control Study

- **Definition**
  - **Compares diseased to non-diseased patients, looking for differences in risk factors**
- **Use**
  - **Study risk factors for disease (esp. rare)**
- **Main limitation**
  - **Biases must be avoided (e.g., historically obtained data must be complete, accurate)**

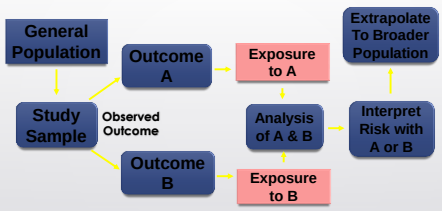
Case-Control Study



Case-Control Study



Case-Control Study



Advantages of Conventional Case-Control Studies

- Relatively efficient for rare medical outcomes & medical outcomes with long induction time (latency)
- Relatively small number of subjects
- Relatively low cost
- Multiple drugs can be assessed
- Can be used to study UDEs when RCT is not ethical

Disadvantages of Conventional Case-Control Studies

- Selection bias due to study design issues (sources of cases & controls) & nonparticipation
- Potentially uninformative if use of drug is rare
- Records on past drug use may be unavailable or inaccurate
- Self-reported drug use subject to recall bias
- Do not provide data on incidence rate of UDE
- Confounding problematic (especially in "opportunistic" studies)

Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease

LUISA IBÁÑEZ, MÀRIUS MORLANS, XAVIER VIDAL, MARÍA JOSÉ MARTÍNEZ, and JOAN-RAMON LAPORTE

Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease.

Background. Studies on the association between the long-term use of aspirin and other analgesic and nonsteroidal anti-inflammatory drugs (NSAIDs) and end-stage renal disease (ESRD) have given conflicting results. In order to examine this association, a case-control study with incident cases of ESRD was carried out.

Methods. The cases were all patients entering the local dialysis program because of ESRD in the study area between June 1, 1995 and November 30, 1997. They were classified according to the underlying disease, which had presumably led them to ESRD. Controls were patients admitted to the same hospitals from where the cases arose, also matched by age and sex. Odds ratios were calculated using a conditional logistic model, including potential confounding factors, both for the whole study population and for the various underlying diseases.

Results. Five hundred and eighty-three cases and 1190 controls were included in the analysis. Long-term use of any analgesic was associated with an overall odds ratio of 1.22 (95% CI, 0.89–1.66). For specific groups of drugs, the risks were 1.56 (1.05–2.30) for aspirin, 1.03 (0.60–1.76) for pyrazolones, 0.80 (0.39–1.63) for paracetamol, and 0.94 (0.57–1.56) for nonaspirin NSAIDs. The risk of ESRD associated with aspirin was related to the cumulated dose and duration of use, and it was particularly high among the subset of patients with vascular nephropathy as underlying disease [2.35 (1.17–4.72)].

Conclusion. Our data indicate that long-term use of nonaspirin analgesic drugs and NSAIDs is not associated with an increased risk of ESRD. However, the chronic use of aspirin may increase the risk of ESRD.

Kidney International 2005;67:2393-2398

Table 1. Risk of ESRD associated with the use of analgesics and NSAIDs, according to the duration of use and the cumulated dose[a]

	Number of cases ($N = 520$)	Number of controls ($N = 982$)	Odds ratio	95% CI
Non users	398/520	816/982	1.0	(Reference class)
Users	122/520	166/982	1.22	0.89–1.66
Age of case				
<65 male	33/190	45/367	1.00	0.56–1.79
<65 female	13/92	17/173	1.61	0.68–3.82
≥65 male	45/162	54/302	1.73	0.95–3.15
≥65 female	31/76	50/140	1.12	0.62–2.02
Male	78/352	99/669	1.20	0.80–1.80
Female	44/168	67/313	1.18	0.71–1.94
All <65	46/282	62/540	1.18	0.74–1.90
All ≥65	76/238	104/442	1.40	0.92–2.12
Duration				
≤1 year	39/517	64/975	0.96	0.61–1.54
>1–5 years	33/517	46/975	1.30	0.75–2.25
>5 years	47/517	54/975	1.41	0.87–2.27
Cumulated dose (DDDs)				
≤100	37/506	64/946	0.85	0.52–1.39
>100–500	29/506	45/946	1.05	0.60–1.86
>500	42/506	42/946	1.69	0.99–2.88

[a]Based on 520 cases and 982 controls. For 3 and 14 cases and 7 and 36 controls, respectively, information on the duration of use or the cumulated dose was lacking.

Ibanez et al. 2005

Table 4. Risk of ESRD associated to aspirin according to the duration of use and cumulated dose

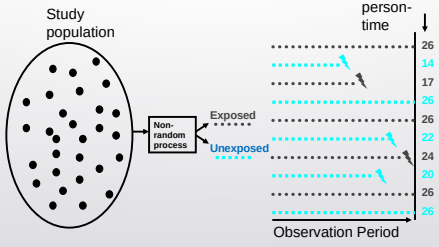
	Number of exposed cases	Number of exposed controls	Odds ratio	95% CI
Duration				
≤1 year	19	23	1.24	0.60–2.57
>1–5 years	21	33	1.37	0.72–2.61
>5 years	37	36	2.07	1.16–3.70
Cumulated dose, DDDs				
≤100	25	35	1.15	0.62–2.14
>100–500	24	27	1.75	0.87–3.49
>500	24	26	2.09	1.05–4.17

Ibanez et al. 2005

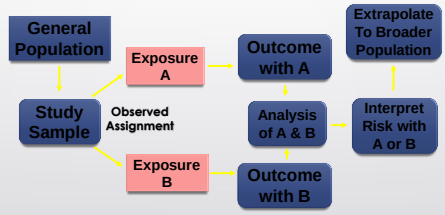
Cohort Study

- **Definition**
  - **Compares patients with risk factor/exposure to others without for differences in outcome**
- **Use**
  - **Study any number of outcomes from singly risk factor/exposure**
- **Main limitation**
  - **Prolonged, costly**

Cohort Study



Cohort Study



Cohort Studies: Key Points

- Selects patients based on exposure
- Can study many outcomes
- Can be retrospective or prospective
- Enables calculation of:
  - Incidence, incidence rate
  - Prevalence
  - Attributable risk

Incidence

$$\text{Incidence} = \frac{\text{No. of } \textit{new cases} \text{ of disease over a period of time}}{\text{No. of people } \textit{at risk} \text{ of developing the disease during that time}}$$

- May want to calculate person-time of follow-up
- Account for different entry, dropout rates → varying duration of follow-up

Cohort Studies. Calculation of Relative Risk

	Cohort Size	# Developing Disease
Exposed	A+B	A
Unexposed	C+D	C

$$\text{Risk of Disease Among Exposed} = \frac{A}{(A+B)}$$

$$\text{Risk of Disease Among Unexposed} = \frac{C}{(C+D)}$$

$$\text{Relative Risk (Risk Ratio)} = \frac{\left(\frac{A}{A+B}\right)}{\left(\frac{C}{C+D}\right)}$$

Relative Risk

$$\text{Relative Risk (RR)} = \frac{\text{Incidence of Outcome in Exposed}}{\text{Incidence of Outcome in Unexposed}}$$

- RR > 1.0 → Exposure assoc. with outcome
- RR = 1.0 → No relation for exposure, outcome
- RR < 1.0 → Exposure may be protective

Cohort Study Design

Advantages	Disadvantages
• Calculate incidence	• Large sample size needed for rare dz
• Study many outcomes	• Long follow-up required
• Outcome unknown at study start	• Loss to follow-up
• Intuitive	• Changes over time in criteria, methods
	• Costly

Advantages of Cohort Studies

- Can establish temporal relationships: drug use preceded onset of medical outcome (especially when time of onset of outcome is clear)
- Relatively efficient for rarely used drugs
- Multiple outcomes can be assessed
- Minimal potential selection bias
- High quality data (accurate & objective measurement, sometimes blind) can be developed in prospective cohort studies
- Can maximize efficiency by targeting study to subjects with high background rate of medical outcome due to underlying medical conditions
- Can be used to study UDEs when RCT is not ethical

Disadvantages of Cohort Studies

- Require large numbers of subjects unless medical outcome is common
- Potentially uninformative for rare medical outcomes
- Long observation period required for outcomes that develop only long after the start of drug use
- Relatively intense observation & medical evaluation of cohort may limit generalizability
- Bias due to losses to follow-up ("dropouts")
- High cost (but less than large RCT)
- Confounding problematic in studies using automated databases

Diabetes mellitus and antipsychotic treatment in the United Kingdom ☆

Christopher Carlson, Kenneth Hornbuckle, Frank DeLisle, Ludmila Kryzhanovskaya, Alan Breier, Patrizia Cavazzoni *

Eli Lilly and Company, Indianapolis, IN, USA

Received 10 June 2005; received in revised form 26 October 2005; accepted 4 November 2005

KEYWORDS
Antipsychotics;
Diabetes;
Epidemiology

Abstract
Objective: Treatment-emergent diabetes has been reported during exposure to conventional and atypical antipsychotics. This retrospective cohort study explored the UK General Practice Research Database (GPRD) to determine hazard ratios of diabetes for patients prescribed antipsychotics.
Methods: A Cox proportional hazard regression model using age, gender, and obesity (BMI >30 kg/m²) was used to determine the hazard ratio (HR) of diabetes development in conventional antipsychotic (N=59,089), atypical antipsychotic (N=9053), individual antipsychotic, and general patient population cohorts (N=1,491,548).
Results: Compared with the general GPRD patient population, patients exposed to conventional or atypical antipsychotics had a higher risk of developing diabetes (atypical antipsychotic cohort: HR=2.9, CI=2.8–4.4; and conventional antipsychotic cohort: HR=1.9, CI=1.6–2.3). The risk of developing diabetes during thioridazine, risperidone, or olanzapine treatment was significantly higher compared with the general GPRD patient population.
Conclusion: Consistent with other epidemiology studies, this study supports an increased risk of developing diabetes during treatment with antipsychotics.

Table 5 Hazard ratio of diabetes in patients while taking antipsychotics

Cohort	Hazard ratio			
	Number of patients[a]		Ratio	95% CI
	Total	New cases		
Conventional antipsychotics				
All conventional antipsychotics[b]	26,992	105	1.9	1.6–2.3
Thioridazine only	7312	24	1.7	1.1–2.5
Fluopenthixol only	4419	8	1.7	0.8–3.3
Trifluoperazine only	2294	6	1.8	0.8–4.0
Chlorpromazine only	1594	2	1.4	0.3–5.5
Haloperidol only	1693	3	1.2	0.4–3.8
Atypical antipsychotics				
All atypical antipsychotics[b]	3106	24	2.9	2.0–4.4
Risperidone only	1619	12	2.5	1.4–4.5
Olanzapine only	915	7	3.9	1.9–8.1
General patient population	807,153	19,930	1.0	–

[a] Number of patients with available BMI data used in the Cox proportional hazards analyses.
[b] Includes antipsychotics not listed in this table that were less commonly prescribed in the UK.

Atypical antipsychotic drugs and diabetes mellitus in a large outpatient population: a retrospective cohort study[?]

Truls Østbye MD, PhD[1]*, Lesley H. Curtis PhD[2], Leah E. Masselink BA[3], Steve Hutchison PhD[4], Alan Wright MD[4], Peter E. Dans MD[5], Kevin A. Schulman MD[2] and Ranga R. Krishnan MB, ChB[3]

[1]*Department of Community and Family Medicine, Duke University Medical Center, Durham, NC, USA*
[2]*Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA*
[3]*Center for Clinical and Genetic Economics, Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA*
[4]*AdvancePCS, Scottsdale, AR, USA*
[5]*AdvancePCS Clinical Services, Blue Valley, MD, USA*

SUMMARY

Purpose Previous research has suggested an association between use of atypical antipsychotics and onset of diabetes mellitus. We sought to compare the incidence of new-onset diabetes among patients receiving atypical antipsychotics, traditional antipsychotics or antidepressants.

Methods Retrospective cohort study of outpatients with claims for atypical antipsychotics (n = 10 265) compared to controls with claims for traditional antipsychotics (n = 4607), antidepressants (n = 60 856) or antibiotics (n = 59 878) in the administrative claims database of a large pharmaceutical benefit manager between June 2000 and May 2002. Main outcome measures were adjusted and unadjusted incidence rates of diabetes (new cases per 1000 per year) in a 12-month period, as measured using new prescriptions for antidiabetic drugs after a 6-month lead-in period.

Results Annual unadjusted incidence rates of diabetes (new cases per 1000 per year) were 7.5 for atypical antipsychotics, 11.3 for traditional antipsychotics, 7.8 for antidepressants and 5.1 for antibiotics. In multivariable analyses, age, male sex and Chronic Disease Score were associated with greater odds of diabetes onset. There were no statistically significant differences in outcome between the atypical antipsychotic, traditional antipsychotic and antidepressant groups. Multivariable comparisons among specific agents showed increased odds of diabetes for clozapine, olanzapine, ziprasidone and thioridazine (relative to risperidone), but these comparisons did not reach statistical significance.

Conclusions In a large prescription claims database, outpatients taking atypical antipsychotics did not have higher rates of diabetes onset, compared to subjects taking traditional antipsychotics or antidepressants.

Table 1. Subject characteristics*

Characteristic	Cohort				
	Overall study population (n = 170 030)	Atypical antipsychotics (n = 10 265)†	Traditional antipsychotics (n = 4607)†	Antidepressants (n = 60 586)†	Antibiotics (n = 59 878)†
Male	64 796 (38.1)	5689 (55.4)	2396 (52.0)	18 217 (30.1)	24 507 (40.9)
Age, mean (SD), year	41.9 (21.5)	42.3 (27.5)	57.0 (21.2)	43.6 (16.5)	37.8 (23.5)
Age group					
0–19 year(s)	31 819 (18.7)	3148 (30.7)	279 (6.1)	4561 (7.5)	18 059 (30.1)
20–29 years	15 172 (8.9)	891 (8.7)	197 (4.3)	7091 (11.7)	3799 (6.3)
30–39 years	27 465 (16.2)	1162 (11.3)	436 (9.9)	12 949 (21.3)	7001 (11.7)
40–49 years	34 812 (20.5)	1229 (12.0)	750 (16.2)	15 750 (26.0)	10 092 (16.9)
50–59 years	26 596 (15.6)	780 (7.6)	803 (17.4)	10 895 (18.0)	9319 (15.6)
60–69 years	14 653 (8.6)	602 (5.9)	651 (14.1)	4820 (8.0)	5975 (10.0)
70–79 years	11 223 (6.6)	974 (9.5)	677 (14.7)	2896 (4.8)	3980 (6.7)
≥80 years	8290 (4.9)	1479 (14.4)	794 (17.2)	1624 (2.7)	1643 (2.7)
Chronic Disease Score					
Mean (SD)	3.1 (3.3)	3.0 (3.1)	3.5 (3.3)	2.7 (3.0)	2.8 (3.1)
0	57 778 (34.0)	3598 (35.1)	1240 (27.0)	22 898 (37.8)	22 065 (36.9)
1	12 284 (7.2)	511 (5.0)	320 (7.0)	5536 (9.2)	3955 (6.6)
2	11 244 (6.6)	590 (5.8)	218 (4.7)	4038 (6.7)	4644 (7.8)
3	29 641 (17.4)	2233 (21.8)	950 (2.6)	9703 (16.0)	10 027 (16.8)
4	12 304 (7.3)	720 (7.0)	391 (8.5)	4455 (7.4)	5970 (6.6)
≥5	46 719 (27.5)	2613 (25.5)	1488 (32.3)	13 936 (23.0)	15 217 (25.4)
Drug exposure groups‡					
Atypical antipsychotics	35 717 (21.0)				
Traditional antipsychotics	10 607 (6.2)				
Antidepressants	92 659 (54.5)				
Antibiotics	76 908 (47.8)				

*Values are expressed as number (percentage) unless otherwise indicated.
†Subjects filled prescriptions for psychotropic drugs from only one drug class.
‡Subjects may be included in more than one drug exposure group.

Table 3. Characteristics associated with diabetes in the 'pure' exposure cohort*

	Model 1 (n = 135 336)†		Model 2 (n = 14 872)†	
	Univariate	Multivariable	Univariate	Multivariable
Atypical antipsychotics				
Clozapine			0.91 (0.13–6.53)	1.13 (0.15–8.37)
Olanzapine			1.11 (0.74–1.67)	1.34 (0.83–2.15)
Quetiapine			0.60 (0.27–1.37)	0.66 (0.28–1.57)
Risperidone			0.60 (0.39–0.90)	1.00
Ziprasidone			1.69 (0.23–12.24)	2.64 (0.35–19.90)
Any	1.13 (0.89–1.43)	0.86 (0.60–1.23)		
Traditional antipsychotics				
Haloperidol			1.35 (0.85–2.15)	1.00 (0.57–1.74)
Thioridazine			1.46 (0.65–3.25)	1.27 (0.54–2.98)
Other			1.55 (1.06–2.25)	1.43 (0.89–2.31)
Any	1.73 (1.30–2.29)	1.00		
Antidepressants	1.34 (1.17–1.53)	1.08 (0.81–1.45)		
Antibiotics	0.69 (0.61–0.79)	0.68 (0.50–0.92)		
Age (per 10 years)	1.40 (1.36–1.46)	1.21 (1.17–1.26)	1.25 (1.16–1.34)	1.16 (1.06–1.26)
Male	1.13 (0.99–1.29)	1.26 (1.10–1.45)	0.68 (0.48–0.97)	0.89 (0.62–1.28)
Chronic Disease Score	1.27 (1.25–1.29)	1.23 (1.21–1.25)	1.23 (1.18–1.28)	1.19 (1.14–1.25)
Likelihood ratio		993.35		98.31
c-statistic		0.78		0.75

*Values are expressed as odds ratio (95% confidence interval) unless otherwise indicated.
†Subjects filled prescriptions for psychotropic drugs from only one drug class during the study period.
‡Subjects filled prescriptions for only one psychotropic drug during the study period.

Questions