Pharmacoepidemiological research and the linking of electronic healthcare databases available in the Italian region of Lombardy

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Summary

Objectives. To evaluate the usefulness of linking databases with the purpose of obtaining reliable evidence for pharmacoepidemiological research, we used databases available in the Italian region of Lombardy in an attempt to replicate well-established associations.

Methods. We investigated the effect of: (a) fluoroquinolones on the risk of tendinitis; (b) persistence with hormone replacement therapy (HRT) on the risks of cardiovascular disease, malignant neoplasms, and bone fracture; (c) low persistence with anti-osteoporotic treatment on the risk of bone fracture; (d) initial antihypertensive drug therapy on the risk of treatment discontinuation.

Results. As expected, we observed that: (a) patients treated with fluoroquinolones are at increased risk of developing tendon disorders; (b) women who received HRT for long periods are at decreased risk of developing cardiovascular disease, colorectal cancer and bone fracture, and at increased risk of breast cancer; (c) women showing low persistence with bisphosphonates for treatment of osteoporosis are at increased risk of bone fracture; (d) patients beginning therapy with the newer classes of antihypertensives exhibit better stay-on treatment rates than those starting with diuretics or β-blockers.

Conclusions. Electronic databases may supply reliable evidence for pharmacoepidemiological research, including real-world drug utilisation patterns, detection of adverse drug events, and evaluation of drug effectiveness in actual clinical practice.

KEY WORDS: *claim database, epidemiological studies, reliability.*

Introduction

Pre-market randomised clinical trials (RCTs) of new drugs have well-recognised limits, relating both to sample sizes and patient selection (1). Most adverse effects may become apparent only after a drug's introduction onto the market, when its general use increases both the number and the diversity of patients receiving it. Moreover, efficacy found in RCTs may not be replicated in actual clinical practice. While RCTs often impose strict inclusion and exclusion criteria, patients presenting to physicians for treatment frequently exhibit features that would have them excluded from entry into a trial (2). In addition, patients enrolled in RCTs achieve very high, almost optimal, compliance, whereas in clinical practice, compliance is much lower, often worsening the cost-efficacy profile of a therapy (3).

One of the features of post-market non-experimental studies is the use made of large electronic healthcare databases (EHDs). The usual concerns over drug safety, the rarity of certain outcomes, and the heterogeneity of patients treated in clinical practice, make EHDs essential for pharmacoepidemiological research (4). In the developed world, Europe is playing a leading role in the use of EHDs (5-9). Even though

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the Italian National Health Service (NHS) provides universal coverage of many areas of healthcare, and in spite of the fact that most Italian regions use electronic database systems to manage NHS-reimbursable health services, the use of EHDs in pharmacoepidemiological research is still not widespread.
In recent years, our group has made extensive use of the system of EHDs available within the Italian region of Lombardy, gaining considerable experience of this resource (10-20). One way of evaluating the usefulness of EHDs for the reliable investigation of new hypotheses is to determine whether they are able to reproduce well-established evidence from the medical literature (8). In this paper, with the aim of replicating some well-established evidence, we show the findings of some of our previous epidemiological studies and discuss the strengths and weaknesses of our approach, as well as the challenges it raises.

Methods

Data sources

Lombardy is the largest Italian region, numbering more than 9 million inhabitants according to the 2001 census (16% of the Italian population). This population is entirely covered by the NHS that, since 1997, has managed healthcare delivery through a system of electronically linkable databases containing information on NHS-reimbursable health services. These databases include: (a) the archive of NHS beneficiaries (practically all the resident population), which contains their demographic and administrative data; (b) the hospital discharge database, which contains records of all hospitalisations occurring in the public and private hospitals in the region of Lombardy; and (c) the outpatient prescription drug database, which contains information on the prescriptions of drugs reimbursable by the NHS. Other databases are available but they were not used for this study, either because of the limited contribution they can make to epidemiological studies (e.g. the outpatient services database does not contain diagnostic information) or because they do not cover the entire population (e.g. the registry of causes of death covers only selected health districts of Lombardy).

The different pieces of information on NHS beneficiaries recorded in the different databases can be linked, for each individual, using one, or more than one, personal identification codes (fiscal code and/or regional health code). In our studies, procedures for protecting personal data were implemented in order to safeguard the individuals' privacy and to prevent the disclosure of individual data relating, for example, to hospitalisations and drug use. In practice, each identification code was automatically converted into a unique and anonymous code and the reverse process was prevented by deletion of the conversion table.
All data for the studies we herein describe were derived from record linkage between the above-mentioned databases.

Issues investigated

Fluoroquinolones and tendinitis. In order to assess the independent effect of the use of fluoroquinolone agents on non-traumatic tendinitis, as well as its joint action with concurrent exposure to corticosteroids, a case-control study was conducted (14). Cases were selected from the hospital discharge database among patients aged 18 years or over, who were hospitalised during 2002-2003 for non-traumatic tendinitis. Up to five controls for each case were randomly selected from the regional archive of residents after matching for gender, age, and date of hospitalisation of the index case (index date). Data regarding the dispensing of fluoroquinolones, corticosteroids, and other medicaments to cases and controls during the one year prior to the index date were collected from the prescription drug database. The odds ratio of tendinitis as a whole, as well as of rupture of the Achilles tendon, associated with use of fluoroquinolones during selected time-windows was estimated. The joint effect of fluoroquinolones and corticosteroids on the risk of tendinitis was also evaluated.
Hormone replacement therapy and selected outcomes. In order to assess the effects of persistence with hormone replacement therapy (HRT), three studies investigating the association between use of HRT and the risks of hospitalisation for cardiovascular disease (CVD) (16), malignant neoplasms (17), and bone fracture (18) were performed. All the

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women aged 45 or over who received at least one HRT prescription during 1998-2000 were followed up to identify those who experienced at least one hospitalisation for the considered outcomes. The hazard ratios for CVD and cancer associated with a time-dependent indicator of persistence with HRT during follow up were estimated. Women belonging to the cohort who experienced bone fracture during follow up constituted the cases of the nested case-control study. Up to six controls were randomly selected for each case from the cohort after matching for age and date of cohort entry. The odds ratio of fracture associated with use of HRT during selected time-windows was estimated.

Hospitalisations recorded in the hospital discharge database were evaluated against cases traced through two population-based registers covering selected areas within Lombardy, namely the infarction and cerebrovascular accidents register of the Brianza area, and the cancer register of the province of Varese, respectively covering a target population of almost 915,000 and 820,000 people. Because the registers adopt standardised criteria for data collection and classification derived from the WHO MONICA project (21) and the International Network of Cancer Registers (22), they were deemed "gold standard" for these specific hospital discharge diagnoses.

Persistence with osteoporosis therapy and risk of fractures. In order to investigate the implications of low persistence with anti-osteoporotic treatment on the short-term risk of bone fracture, a cohort study was conducted (unpublished data). All the women aged 45 years or over who, during 2003, received for the first time at least one prescription for bisphosphonates entered the study and were followed up until December 2004. The pattern of osteoporosis medication (calcitonine, bisphosphonates and raloxifene) was reconstructed for each included woman using the prescription drug database. Hospitalisations for bone fractures during the follow up were also recorded. The hazard ratio for fracture associated with a time-dependent indicator of persistence with anti-osteoporotic drug therapies during follow up, was estimated.

Discontinuation of antihypertensive drug therapy. In order to assess rates and determinants of discontinuation of initial antihypertensive drug therapy, a cohort of patients aged 40 to 80 years, who received their first antihypertensive drug prescription (monotherapy) during 1999-2002, was recruited (20). Discontinuation was defined by the absence of any antihypertensive prescription in the 90 days following the end of the most recent prescription. The hazard ratio for the first discontinuation episode associated with the class of antihypertensive prescribed as the initial monotherapy was estimated.

For all hypotheses tested, two-tailed p-values less than 0.05 were considered significant.

Results

Fluoroquinolones and tendinitis

During the study period, 22,194 cases of tendinitis and 104,906 controls complied with the inclusion criteria and entered the study. Most of the cases were women (63.5%), and their mean age was 55.9 years (matching variables). Compared with the controls, the cases had a higher prevalence of exposure to fluoroquinolones (3.8% vs 2.8%; $p<0.001$) and corticosteroids (2.0% vs 1.4%; $p<0.001$) dispensed at any time in the 90-day period preceding the index date. Conversely, cases and controls did not differ significantly in the use of other antibacterials (10.1% vs 9.7%). Use of fluoroquinolones in the 15-day period before or on the index date increased the risk of tendinitis as a whole (OR = 1.7, 95% CI = 1.4, 2.0) and, even more so, of rupture of the Achilles tendon (OR = 4.1, 95% CI = 1.8, 9.6).

Table 1 shows the independent and combined effects of fluoroquinolones and corticosteroids on the risk of each outcome. There is evidence that recent exposure to both fluoroquinolones and corticosteroids acted as independent risk factors for tendinitis. No significant departure from the multiplicative structure of interaction between the considered factors was observed for tendinitis as a whole. Conversely, significant departures from the multiplicative structure of interaction were observed for rupture of the Achilles tendon ($p<0.05$). In fact, the effects of recent exposure to fluoroquinolones were much higher in people who had recently used corticosteroids compared to those who had not used corticosteroids.

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Table 1. Independent and combined effects of fluoroquinolones and corticosteroids on the risk of tendinitis.

Fluoroquinolones†	Corticosteroids†	Cases	Controls	Odds ratio (95% CI)‡
		Tendinitis as a whole		
Non use	Non use	21,384	102,423	1.0 (reference)
Recent use	Non use	366	1048	1.7 (1.5 to 1.9)
Non use	Recent use	420	1,371	1.5 (1.3 to 1.7)
Recent use	Recent use	24	64	1.8 (1.1 to 2.9)
		Rupture of the Achilles tendon		
Non use	Non use	796	4,023	1.0 (reference)
Recent use	Non use	13	21	3.0 (1.5 to 6.0)
Non use	Recent use	22	46	2.1 (1.2 to 3.6)
Recent use	Recent use	9	1	43.2 (5.5 to 341.1)

† Exposure to fluoroquinolones and corticosteroids categorised as recent use (exposure in the period of 30 days before or on the index date), and non use (exposure in the period of more than 30 days or not exposure in the period of one year before the index date)
‡ Adjusted for use of other antibacterials and other drugs in the 30-day period before the index date.

Hormone replacement therapy and selected outcomes

During 1998-2000, about 75,000 women who received for the first time at least one prescription of drugs commonly used for HRT complied with the inclusion criteria and entered the study. At entry, these women had a mean age of 57 years (SD = 7 years). During follow up, they generated 828 hospitalisations for diseases of the circulatory system (including 473 for ischaemic heart disease and 298 for cerebrovascular disease), 3,687 hospitalisations for malignant neoplasms (including 383 for colorectal cancer, 1,296 for breast cancer), and 1,321 hospitalisations for bone fracture.

The positive predictive values obtained through comparison of the hospital discharge database with population-based registers were 88% for ischaemic heart disease, 84% for cerebrovascular disease, 96% for colorectal cancer, 94% for pancreatic cancer, 85% for malignant neoplasm of the skin, 91% for breast cancer, 100% for endometrial cancer, and 90% for renal cancer.

Table 2 gives the relationship between persistence with HRT and risk of hospitalisation for the considered outcomes. As persistence with HRT increased, significant trends towards decreasing risks of cardiovascular diseases as a whole, cerebrovascular disease, colorectal cancer and bone fracture, were observed. Conversely, the risk of breast cancer increased with increasing HRT persistence. There was no evidence that persistence with HRT is related to the risks of the other investigated neoplasms including cancers of oral cavity and pharynx, stomach, liver, pancreas, skin melanoma, other neoplasm of skin, lung, uterine cervix, ovary, bladder, kidney, brain, thyroid, non-Hodgkin's lymphoma, and multiple myeloma.

Persistence with osteoporosis therapy and risk of fractures

During 2003, 12,872 women who received for the first time at least one prescription of bisphosphonates complied with the inclusion criteria and entered the study. At the time of dispensing the index prescription their mean age was 72 years (SD = 10 years). During follow up the cohort members were observed for 237,286 months (on average, 18 months per patient), accumulating 104,553 months in treatment with osteoporosis therapy, and 384 cases of bone fracture were recorded. The median of the persistence indicator was 196 days (interquartile range: 56-409 days). As shown by Table 3, a significant trend towards increasing risk of fracture as persistence decreased was observed ($p<0.001$). Age, history of fractures and concurrent use of corticosteroids also significantly affected the risk.

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Table 2. Dose-response relationship between cumulative exposure to hormone replacement therapy and the risk of cardiovascular diseases, malignant neoplasms, and bone fracture.

	Persistence with HRT (months with drug available)					Trend test†
	≤ 6	7-12	13-24	25-36	> 36	(p-value)
All cardiovascular diseases	1.00 (reference)	0.94 (0.79, 1.11)	0.82 (0.67, 1.00)	0.70 (0.53, 0.94)	0.65 (0.45, 0.92)	0.0034
Ischaemic heart disease	1.00 (reference)	1.00 (0.80, 1.26)	0.85 (0.65, 1.11)	0.83 (0.58, 1.20)	0.61 (0.37, 0.99)	0.1690
Cerebrovascular disease	1.00 (reference)	0.82 (0.61, 1.10)	0.74 (0.53, 1.06)	0.57 (0.34, 0.94)	0.53 (0.30, 0.94)	0.0030
	Persistence with HRT (months with drug available)					
	≤ 6	7-12	13-24	> 24		
All malignant neoplasms	1.00 (reference)	0.94 (0.86, 1.02)	0.98 (0.88, 1.08)	1.07 (0.96, 1.19)		0.5350
Colorectal cancer	1.00 (reference)	0.87 (0.67, 1.12)	0.81 (0.59, 1.11)	0.78 (0.68, 0.92)		0.0441
Breast cancer	1.00 (reference)	1.03 (0.89, 1.19)	1.19 (1.01, 1.40)	1.34 (1.13, 1.58)		0.0004
	Persistence with HRT (months with drug available)					
	≤ 2 months	2-6 months	6-20 months	> 20 months		
Bone fracture	1.00 (reference)	1.04 (0.88 to 1.23)	0.96 (0.80 to 1.15)	0.80 (0.65 to 0.99)		0.0432

† Testing the null hypothesis that the hazard ratios do not vary linearly along the categories of months with drug available.
Estimates are expressed as age-adjusted hazard ratios for cardiovascular disease and malignant neoplasms. The estimates concerning bone fracture are expressed as odds ratio adjusted for signs suggestive of thyroid disease, diabetes, chronic renal failure, connective tissue disease, and osteoporosis recorded during follow up, cumulative duration of corticosteroid use during follow up, and history of bone fractures prior to the index prescription.

Discontinuation of antihypertensive drug therapy

The study cohort comprised the 445,356 patients for whom the initial treatment consisted of a single antihypertensive drug. Most of the included patients were women (53.2%) and their mean age was 60.5 years (SD = 10.2 years). The majority of the patients were initially treated with ACE inhibitors, diuretics, β-blockers, and calcium channel blockers. During the follow up the cohort generated 209,229 first discontinuation events (incidence rate 2.7 per 100 person-months). The cumulative incidence of discontinuation was 33% at six months, 41% at one year, and 50% at five years after starting treatment.

Table 4 shows the relationship between the class of drug prescribed as the initial monotherapy and the risk of discontinuation after one year of therapy. Taking patients who started the treatment with an ACE inhibitor as reference, the discontinuation rate was lower in patients who started with an angiotensin receptor antagonist and higher in patients who started with all other drug classes, the maximum discontinuation rate occurring with the initial use of diuretics and β-blockers.

Discussion

This series of population-based observational studies based on the linking of EHDs from the Italian region of Lombardy gave results that were consistent with the findings reported in the medical literature. In particular, we showed: (a) that patients currently treated with fluoroquinolone antibiotics are at increased risk of developing tendon disorders as a whole and rupture of the Achilles tendon, and that concurrent expo-

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Table 3. Effects, on the risk of fractures, of persistence with osteoporosis therapy and of selected characteristics of the patient cohort.

	Patients†	Fracture events†	Hazard ratio (95% CI)
During follow up#			
Persistence with osteoporosis therapy##			
High	3,220 (25.0%)	25	1.00 (reference)
Intermediate	3,325 (25.8%)	129	1.23 (0.77 to 1.96)
Low	4,687 (36.4%)	159	1.39 (0.88 to 2.19)
Very low	1,640 (12.7%)	71	1.94 (1.19 to 3.14)
Use of corticosteroids			
Yes vs No (reference)	1,511 (11.7%)	73	1.77 (1.30 to 2.40)
Use of hormone replacement therapy			
Yes vs No (reference)	191 (1.5%)	4	0.71 (0.27 to 1.91)
At the time of the index prescription			
Age			
≥ 75 years vs < 75 years (reference)	5,000 (38.8%)	218	1.95 (1.59 to 2.39)
History of fractures§			
Yes vs No (reference)	1,688 (13.1%)	107	2.45 (1.95 to 3.07)
History of corticosteroid use//			
Yes vs No (reference)	2,438 (18.9%)	87	0.99 (0.75 to 1.32)

† Includes patients and fracture events observed at the last available time point.
# From the time of the index prescription until exit from the cohort.
Number of days with drug available for osteoporosis therapy (bisphosphonates, calcitonine and raloxifene), categorised as very low (less than 2 months), low (from 2 to 6 months), intermediate (from 6 months to 1 year), and high (more than 1 year) persistence.
§ From January 2000 until the time of the index prescription.
// Within one year prior to the time of the index prescription.

Table 4. Effect of the class of drug used for initial antihypertensive therapy on the cumulative incidence of discontinuation.

Initial antihypertensive drug class‡	Hazard ratio (95% confidence interval)†
ACE inhibitors	1.00 (reference)
ARBs	0.92 (0.90, 0.94)
CCBs	1.08 (1.06, 1.09)
Diuretics	1.83 (1.81, 1.85)
α-blockers	1.23 (1.20, 1.27)
β-blockers	1.64 (1.62, 1.67)

† Estimates are adjusted for age at entry (continuous), gender, and for concomitant use of digitalis glycosides, organic nitrates, lipid-lowering agents, other cardiovascular drugs, and anti-diabetic drugs
‡ ACE inhibitors=angiotensin-converting enzyme; ARBs=angiotensin II type 1 receptor blocking agents; CCBs=calcium channel blockers.

sure to corticosteroids multiplies the effect of fluoroquinolones on the risk of tendon rupture; (b) that, compared with postmenopausal women treated with HRT for very short periods, women who have received HRT for long periods are at decreased risk of developing CVD, colorectal cancer and bone fracture, and at increased risk of breast cancer; (c) that women showing low persistence with bisphosphonates for the treatment of osteoporosis are at increased risk of bone fracture compared with those who are highly compliant; (d) that hypertensive patients beginning therapy with the newer classes of antihypertensives (i.e. angiotensin receptor antagonists, ACE inhibitors, and calcium channel blockers) exhibit a better stay-on treatment rate with respect to those starting with diuretics or β-blockers.

These findings, taken together, suggest that the EHDs available in the region of Lombardy may supply reliable evidence in relation to several pharma-

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coepidemiological issues, including real-world drug utilisation patterns, detection of adverse drug events, and evaluation of drug effectiveness in actual clinical practice. These databases have at least three appreciable characteristics: (i) they cover an observational setting of the Southern European clinical practice for which less data than Northern European and Northern American settings are available; (ii) they cover a very large population; indeed, to the best of our knowledge, this population is the largest of those covered by European claim databases; this makes it possible to investigate very rare outcomes and, in general, to generate estimates little affected by casual uncertainty; (iii) they cover a well-defined and unselected dynamic population, thereby generating estimates unaffected by selection bias.

However, the use of claim databases presents several potential limitations. A major weakness is the uncertain validity of the diagnostic data. We attempted to validate our diagnostic codes through comparison with local population-based registers. The hospital discharge database was found to perform well for coronary heart, cerebrovascular, and malignant diseases in our studies (16, 17). However, these comforting results cannot be generalised to other outcomes for which diagnostic accuracy is less certain. For example, in a case-control study on lipid-lowering drugs and peripheral neuropathy that used the claim databases of one Lombardy health district, the diagnosis of peripheral neuropathy was not supported by objective clinical signs, nor was it the main reason for hospital admission in two fifths of the included patients (10). This suggests that studies using claim databases sometimes need to be supplemented with medical record review and validation.

The absence of information about the extent of exposure misclassification is another source of systematic uncertainty of estimates. We had no information on patient compliance, since redeeming a prescription was used as a proxy for actual use of a drug. Furthermore, data on NHS prescriptions do not allow us to establish the dosage regimens of the dispensed drugs. Instead, the typical adult's daily maintenance dose can be used to calculate the theoretical coverage of each drug prescription.

An important weakness of the approach based on record linkage between databases is the lack of knowledge regarding the magnitude of potential bias due to errors in the personal identification codes (23). Our group has worked extensively with, and acquired considerable experience of, methods for matching data elements (24). Mainly, we drew on the work of Fellegi and Sunter (25) and Jaro (26) to perform probabilistic record linkages. However, we used deterministic record linkage to perform the above-described studies. Ethical and legal problems remain to be solved before probabilistic record linkage can be used.

A main pitfall of using claim databases is the inability to capture and control the effects of most confounders. For example, in claim databases there are no data on lifestyle factors, such as cigarettes smoking, alcohol consumption, physical exercise, menopause data etc., all of which can be very important in the context of certain research questions (4). Socioeconomic status, too, may play a crucial role as a confounder since it affects healthcare utilisation, including access to and maintenance of drug therapies, as well as the onset and the progression of several diseases. However, some surrogate markers for exposure to high-risk behaviours and/or for socioeconomic status may be recovered from other sources. For example, individual income data for women included in the HRT / CVD study were obtained from the local tax register. The inverse relationship between HRT and CVD disappeared when the estimates were adjusted for income (16), making them very close to those of meta-analyses of observational studies reporting estimates adjusted for socioeconomic status (27, 28). The capacity of socioeconomic disparities to affect access to and maintenance of antihypertensive drug therapy was also recently investigated (29).

Factors such as the tendency of certain individuals to have frequent contacts with the health system (e.g. nursing home residence, frequent physician contact and hypochondriacy) and the selective prescription of the drug of interest to patients with specific disease profiles might entail no causal associations (30, 31). Our group has applied some unconventional observational designs specifically developed to tackle some of these specific issues (11-13). Although the lack of data on the disease profile remains the main source of uncertainty when using electronic archives, our exercises suggest that unconventional observational designs, such as those used to analyse case-

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distribution (case-only) studies (32), may help to prevent some flaws. It may be prudent to use several observational designs to investigate a single hypothesis, since each design may be vulnerable to confounding in a different way. This strategy seems to be warranted and economically feasible when using claim databases.

Finally, the EHDs available in the Italian region of Lombardy have provided the setting for extensive methodological work in the field of pharmacoepidemiological research, which has included study design issues in drug epidemiology (11-13, 33), statistical methods for adverse drug events (15), and statistical models for joint assessment of discontinuity and failures of drug therapy (19).

In conclusion, the limitations notwithstanding, this study suggests that the EHDs available in the Italian region of Lombardy may supply reliable evidence relating to several pharmacoepidemiological issues, including real-world drug utilisation patterns, detection of adverse drug events, and evaluation of drug effectiveness in actual clinical practice.

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