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Using Taiwan's National Health Insurance Research Databases for Pharmacoepidemiology Research

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ABSTRACT

In order to (1) present the structure of Taiwan's National Health Insurance (NHI) research databases, along with the comparison with automated databases in other countries, (2) estimate the strengths and weaknesses of the NHI research databases, and (3) systematically review pharmacoepidemiology studies using the NHI research databases, we compared the characteristics of existing automated databases to reveal the strengths and weaknesses of the NHI research databases. In addition, the Medline was used as a tool to search pharmacoepidemiology studies using Taiwan's NHI research databases since 1997. The automated NHI research databases are very comparable with large research databases of other countries (US, Canada and UK). As a result, they serve as major resources for up to 11 pharmacoepidemiology studies published since 2002. However, these studies usually focused on the analysis of drug utilization pattern and drug utilization volume. As a result, there is still a huge lack of identification of potential drug safety issues using the NHI research databases. The construction of NHI research databases absolutely provides abundant research resources for scholars not only in medical fields but also in public health-related disciplines. Many studies using the NHI research databases have been published in international journals. Yet, researchers in Taiwan could make even greater progress toward thorough pharmacoepidemiology studies using the NHI research databases.

Key words: National Health Insurance research databases, pharmacoepidemiology

INTRODUCTION

Pharmacoepidemiology is the study of the use and the effects of drugs in large numbers of people. The term- "pharmacoepidemiology"- obviously contains two components: "pharmaco" and "epidemiology"[(1)]. The main scope of pharmacoepidemiology is to explore the therapeutic effects, indications, and adverse drug reactions (ADR) using the techniques of epidemiology. The origin of pharmacoepidemiology, however, was due to the limitations of clinical trials. The current approval process of new drugs in most countries generally includes preclinical testings of pharmacology and toxicology on animals followed by three clinical phases on human subjects to evaluate drug safety and efficacy. Unfortunately, these clinical trials usually conduct on a small number of healthy volunteers or patients with restricted inclusion criteria and over a relative short period of time. Although drug efficacy could be demonstrated in one clinical trial with a standardized 500 to 3,000 patients exposed to a drug, more patients need to be included in the clinical trial in order to detect less common adverse drug reactions. For example, a study including 3,000 patients would allow one to be 95% certain of detecting any adverse drug reaction that occur in at least one exposed patient out of 1000[(2)]. Premarketing clinical trials also tend to provide insufficient information on the drug's efficacy and safety due to their artificial selection of patients. These trials frequently seek subjects who are as homogeneous as possible to reduce unexplained variability. For ethical reasons, subgroups such as the elderly, children, pregnant women, or patients with other diseases are excluded. In addition to limited subjects, restricted study periods restrain the application of premarketing clinical trials into the real-world practice[(3,4)].

The restricted application of clinical trials has triggered the adoption of pharmacoepidemiology studies and pointed out the potential contribution of this discipline. Firstly, pharmacoepidemiology studies could supplement the information available from premarketing studies, such as in patients not studied prior to marketing or in patients with concomitant diseases and medications. Secondly, pharmacoepidemiology studies provide new discoveries of previously undetected beneficial and adverse drug effects. Therefore, using pharmacoepidemiology studies in post-marketing pharmacovigilance to detect drug safety signals, which shall supports more regulation decisions of medicines, has been increasingly recognized[(5-7)]. Other applications of pharmacoepidemiology studies have also been emphasized, which include

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evaluating the safety of vaccines or medical devices and the impact of drugs on patients' quality of life[8-13].

Even though highly recognized as an essential multi-discipline field for today's health care system, pharmacoepidemiology studies used to be relatively expensive and difficult to perform in post-marketing surveillance stage. They need an even larger population than that required by the pre-marketing clinical studies to apply to real-world practice, which makes them highly resources-oriented. Yet, these studies often need to collect information as soon as possible to address acute and serious regulatory, industrial, and public health issues. Besides adequate research subjects and detailed information, a sufficient observational period of time is needed to confirm the association and/or causality between a research drug and its potential drug effects. As a result, the initial development of pharmacoepidemiology studies encountered various barriers.

Facing the emerging importance and the difficulties in conducting pharmacoepidemiology studies, the development and use of automated databases have experienced considerable growth over the past two decades. Large electronic databases constructed by regulatory organizations or research institutes could often meet the need for post-marketing surveillance studies, such as prescription-event monitoring (PEM) system in the UK, pharmacy-based surveillance databases in the US, or pharmacovigilance database in Taiwan. Claims data from a person's use of the health care system, such as health maintenance organization (HMO) and Medicaid database in the US are other data sources. General practice research database (GPRD) of UK or Ontario and Saskatchewan province databases of Canada, although originally designed for administrative purposes, could also provide abundant information and large samples for pharmacoepidemiology studies[14]. These computerized databases have several valuable advantages in conducting pharmacoepidemiology studies. Among all potential advantages, the capacity of providing adequate sample size is uniquely essential. In addition, the variability of participants recorded in these databases could reflect the real-world use of medications, especially for the subsets of the population usually omitted in the pre-marketing clinical trials. Therefore, these databases could be population-based. There is also no opportunity for recall bias since the automated databases do not rely on patient recall or interviewers to obtain their data.

Taiwan's National Health Insurance (NHI) research databases, therefore, pose the opportunities to conduct pharmacoepidemiology studies as compared with automated databases in other countries[15-18]. Although researches using NHI research databases were abundant[19], they seldom focused on pharmacoepidemiology issues so far. As a result, the objectives of our article were to explore the potential applications of Taiwan's NHI research databases for pharmacoepidemiology studies, to present the structure of the NHI research databases, to compare it with automated databases in other countries, to analyze the strengths and weaknesses of the NHI research databases, and finally to systematically review pharmacoepidemiology studies using the NHI research databases. Our ultimate goal of this article is to promote the applications of NHI research databases for future studies in pharmacoepidemiology.

NATIONAL HEALTH INSURANCE RESEARCH DATABASES IN TAIWAN

The NHI program in Taiwan, with approximately 23 millions insured, covers over 99% of Taiwan's population. Therefore, this mandatory health insurance program could reach to all geographic regions in Taiwan, even to the distant regions or the off-shore islands such as the Pescadores and Kinmen. The enrollees of this program are predominantly employer-based but also include disadvantaged individuals, such as people with low income or disability.

To respond rapidly and effectively to current and emerging health issues, the Bureau of National Health Insurance (BNHI) cooperates with the National Health Research Institute (NHRI) to establish NHI research databases.

Firstly, registration datasets and claim datasets are maintained in the NHRI as following components (Table 1):

I. *Registry for Beneficiaries*

Registry for beneficiaries (ID) allows follow-up and identification of insured subscribers. Data elements include date of birth, gender, and unit/type of enrollment. A unique identification code is assigned to each insured and retained even if a member dis-enrolls or later re-enrolls. Precautions are taken to safeguard the confidentiality of individually identifiable information.

II. *Registry for Contracted Medical Facilities and Medical Personnel*

Registry for contracted medical facilities (HOSB) and registry for medical personnel (PER) are two separate files containing data on the NHI's practicing health care facilities and professionals. The type (academic medical center, metropolitan hospital, community hospital, or primary care clinic) and location of the health care facilities as well as the demographic information of the health care professionals are specified. A unique identification code is assigned to each institution and professional. Precautions are taken to protect the identities of healthcare professionals.

III. *Outpatient Visits*

There are two subsets of databases providing the

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Table 1. Data elements included in the National Health Insurance research database

Database	Content	Comment
Registry for beneficiaries	Members' identifiers, date of birth, gender, unit of enrollment, type of enrollment and enrollment date/status, geographic location	Allows follow-up and identification of insured subscribers.
Registry for contracted medical facilities and medical personnel	***Medical facilities*** Medical facilities' identifiers, owner of medical facility, type of contract, date of contract, level of medical facility (academic medical center, metropolitan hospital, local community hospital, primary clinic), geographic location ***Medical personnel*** Medical personnel' identifier, date of birth, gender, work facility, work status, date of licensing, category of medical personnel	Allows identifying the source of treatment (ex. identifying treating physician) to provide further evaluation on quality of care.
Outpatient visit	Encounter form-based data set with date, time of visit; patient demographics (identifier, gender, date of birth); medical facility visited, department visited, prescribing physician, dispensing pharmacist; 3 ICD-9-CM codes, case type, primary procedure (ex. drug or diagnostic procedure), other procedures, type of copayment, billed and paid amounts	Important resources for disease prevalence and comorbidity measurement.
Inpatient visit	Encounter form-based data set with date of hospitalization, end date of hospitalization, 1 primary ICD-9-CM code, 4 secondary 3 ICD-9-CM codes, 1 primary operational code, 4 secondary operational codes, primary treating physician, type of copayment, billed and paid amounts	Major source of medical outcomes. Most diagnoses are highly accurate which can also serve as case-mix adjustment.
Service costs	Service costs for each patient encounter and service	Costs for every aspect of services can be calculated.
Pharmacy database	Pharmacy identifier, prescribing date, dosage, prescription duration in days, prescribing physician, dispensing pharmacist and cost of prescription drugs	Details for prescription drugs use dispensing in contracted pharmacies.

information of outpatient visits, which are the *Ambulatory care expenditures by visits (CD)* and the *Details of ambulatory care orders (OO).* The outpatient visit database is an encounter form-based data set with date of each visit, ICD-9-CM diagnosis codes, type of providers, health professionals, and service costs. Outpatient visit database is a key source for comorbidity measurement.

IV. *Inpatient Visit*

There are also two subsets of databases providing the information of outpatient visits, which are the *Inpatient expenditures by admission (DD)* and the *Details of inpatient care orders (DO).* The inpatient visit database is also an encounter form-based data set with date of each admission, ICD-9-CM diagnosis codes, procedure codes, type of providers, health professionals, and service costs.

V. *Pharmacy Database*

The pharmacy databases (GD and GO) include all relevant information of prescription drugs dispensed by contracted pharmacies in NHI in Taiwan. Pharmacy identifier, prescribing date, dosage, prescription duration in days, prescribing physician, dispensing pharmacist and cost of prescription drugs are all included in the pharmacy database.

In addition to the administrative-oriented registration datasets and claim datasets, the NHRI also provides research-oriented databases, including sampling databases, longitudinal cohort databases, and databases for specific topics. The sampling databases are representative databases from the entire database using systematic sampling method, with 5% of inpatient visits and 0.2% of outpatient visits to the entire database, respectively. The longitudinal cohort databases are used for researches when long-term follow-up is needed. For example, researches investigating the clinical outcomes of chronic diseases (e.g. diabetes mellitus) will need longitudinal cohort databases to meet their objectives. Currently, the NHRI provides a 9-year (1996-2004) longitudinal cohort database including a total of 200,000 beneficiaries randomly selected in 1996. Except for sampling databases and longitudinal cohort databases, databases for specific topics are also created to fulfill research needs of significant health issues. Twelve databases for specific topics, including diabetes, cancer, psychology, case payment, and others, are currently available.

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THE STRENGTHS AND WEAKNESSES OF THE NHI RESEARCH DATABASES IN TAIWAN

I. *Strengths*

The NHI research databases have several important advantages:

1. Large sample size: The NHI covers over 99% of Taiwan's 23-million population and the NHI databases are very representative of the general population. Therefore, the databases could be used to calculate population-based rate, such as prevalence or incidence of specific disease among the whole population.

2. Relatively inexpensive: Given the existing administrative databases and the available sample size, studies using the NHI research databases do not incur considerable cost for data collection, other than for those populations whose supplement information should be obtained from medical charts or interviews.

3. Abundant information on medical service utilization: The NHI research databases use a population-based data collection process. A variety of outpatient and inpatient medical records are included in the NHI research databases. Therefore, subgroup populations usually excluded in other clinical trials, such as the elderly, children, and pregnant women are all covered in the NHI research databases.

4. Capturing detailed prescription drug use: The records for each reimbursed outpatient or inpatient prescription are maintained in the NHI research databases. With each claim specifying drug name, date of prescription issued, dosage of medication dispensed, prescription duration in days, and actual quantity dispensed, specific treatment can be identified using the drug files to meet the need of pharmacoepidemiology studies. However, it is of significant concern that the majority of primary clinics in the NHI system are allowed to use fixed daily cost for prescription drugs. Claims data of primary clinics do not include details of prescription drugs use under this unique payment system only for primary clinics as those from other medical settings.

5. Performing database linkages within the NHI research databases: Registry for these linkages between separate databases could make the NHI research databases an important data source for identifying patients with a disease and for measuring and adjusting for levels of comorbidity.

6. Performing database linkages with other databases: Other databases can be linked to the NHI research databases to enhance their utility. For example, the NHI research databases can be linked to mortality data upon special request. Although precautions need to be taken regarding the validity of diagnoses of causes of death, the linkage of the NHI research databases to mortality data could meet the need for studies of fatal adverse events and other outcome assessments (e.g. mortality rate[17]). In addition, linkage of the NHI research databases to the National Health Interview Survey (NHIS) database could provide advanced information on the insured demographics, such as socioeconomic status. Linkage to additional datasets such as cancer registry and rare disease registry could also provide valuable information. Precautions are invariably taken to safeguard the confidentiality of individually identifiable information when making linkage with other databases.

7. Constructing longitudinal histories for cohort study design: Information on the diagnosis, treatment, and occurrence of adverse clinical events, as coded with identical number for each insured on claims, can be tracked across time since 1996.

II. *Weaknesses*

1. The NHI research databases only record the medical utilizations covered by the BNHI. As a result, drugs not covered by the BNHI, such as over-the-counter (OTC) drugs, are not included for studies.

2. The construction and maintenance of NHI research databases by BNHI is primarily for administrative purposes. Therefore, research is a secondary use of the NHI research databases, and these databases may not be well suited to some types of studies.

3. The claims lag or the length of time required to obtain all claims for a given time frame is another limitation. Though the lead time between the collection of claims data and the payment to health care providers has been kept at two months, the time lag for NHI research database released to public and academic access could be as long as 12 to 24 months.

4. The NHI research databases do not contain information on some potentially important confounding variables in pharmacoepidemiology studies, such as smoking, alcohol use, exercise, diet, education, family history, and non-prescription drug use. Pharmacoepidemiology studies concerning these factors should consider alternative methods to obtain such information, for instance, by linking the NHI research databases to other datasets such as NHIS. Medical charts or census data could also be optimal choices.

5. Diagnoses in NHI research databases are coded using the ICD-9-CM coding scheme since 2000. ICD-9-CM code, though the most popular coding system in claims databases, has several limitations. The ICD-9-CM code do not always precisely fit the clinical condition of interest. For example, it is difficult to distinguish disease severity (e.g. New York Heart Association (NYHA) Classification for Heart Failure) using ICD-9-CM codes. Also, some outcomes are poorly defined by the ICD-9-CM coding system, such as Stevens-Johnson syndrome. In addition, there is a limit of maximum three ICD-9-CM coding available in the NHI research databases. Therefore, other information is often needed to define the disease of interest or to identify complications and comorbidities. Besides, precautions need to

be taken regarding the diagnosis codes before 2000 in the NHI research databases since the "A-code" system was used during that period (1997-1999). Changes in diagnostic coding system may bias the investigation of long-term disease trends in epidemiologic studies due to potential misclassification of patient populations.

6. Automated laboratory data are not available in the NHI research databases, which become a barrier for some kinds of pharmacoepidemiology studies. It is not easy to identify disease severity (lipid profile in hyperlipidemia), adverse drug events (e.g. ALT (alanine aminotranferease) and AST (aspartate aminotransferase) in hepatotoxicity), and treatment outcomes (e.g. HbA1c in diabetes mellitus) without laboratory tests information.

To sum up, the NHI research databases provide a large population-based and valuable source for pharmacoepidemiology studies as compared with databases of other countries (Table 2). Complete data including enrollment data, hospitalization data, inpatient drug exposure data, and outpatient diagnosis data are maintained by the NHI research databases. Therefore, this database is also suitable for cohort studies and case-control studies. Although certain disadvantages should be taken into account or minimized through study design, the NHI research databases could still serve as a powerful tool for future pharmacoepidemiology studies, the following reviews will present specific applications of the utilization of Taiwan's NHI research databases to address pharmacoepidemiologic research questions.

REVIEWS OF PHARMACOEPIDEMIOLOGY STUDIES USING THE NHI RESEARCH DATABASES

Pharmacoepidemiology studies have attracted noticeable attention due to the development of large electronic databases. In early days before electronic databases are available, post-marketing surveillance studies (phase IV clinical trials) were difficult to conduct because of the cost of sample and data collection. For example, studies of the size having the ability to detect drug effect with an incidence as low as 1 per 1000, the sample size included should be at least 10,000 exposed persons in a cohort study, or case (diseased) patients for a case-control study[2]. Besides, post-marketing surveillance studies often need to be conducted quickly to identify acute and serious regulatory, commercial, or public health problems. As a result, large electronic databases could provide a cost-effective and efficient data sources to meet all requirements described above.

Over the past two decades, automated databases have been well established in many industrialized countries. The use of these databases as resources for pharmacoepidemiology researches have also been growing. The Kaiser Permanente (KP) Medical Care Program (USA) could serve as a good example. The theoretical framework is very similar to the NHI program in Taiwan. The KP Medical Care Program, with approximately 8.2 million subscribers, is the largest prepaid health care system in the United States. The majority of health care services in the KP Medical Care Program are delivered by providers belonging to a single health care system. All administrative and clinical information such as membership datasets, demographic databases, outpatient visits, hospitalization, pharmacy utilization, and laboratory uses are therefore represented accurately. Using these data, the KP research centers could evaluate the quality of their medical program. More importantly, a large number of pharmacoepidemiology studies within KP were derived from these valuable databases. The KP databases provide a variety of potential for pharmacoepidemiology studies, such as searching the disease-prevention effects of drug (e.g. aspirin use and risk of prostate cancer), evaluating the therapeutic effects of drugs (e.g. oral antidiabetic drug therapy and patients' blood level of hemoglobin (HbA1c)), and identifying potential adverse effects with the use of antidepressants or antihistamines and the occurrence of cancer[20-22]. The study on antidepressants and the occurrence of cancer is also one example of drug safety investigation funded by FDA.

Since the inception of Taiwan's NHI in 1995, the NHI automated and manual databases have served as major resources for many epidemiologic studies. The researches that have been conducted and published using the NHI datasets are listed in Table 3. The target drugs included psychotropic drug[23], anti-asthmatic medications[24], anti-ulcer drug[25], hepatoprotectants[26], antimicrobial agents[27], non-steroidal anti-inflammatory drugs (NSAIDs)[28], sleep-related medications[29], and oral antidiabetic drugs[30]. However, currently available pharmacoepidemiology studies using the NHI research databases usually focused on the analysis of drug utilization pattern and drug utilization volume.

Drug utilization pattern study (e.g. anti-ulcer drug[25]), though simply calculating the total prescribed amount of specific drugs, can also provide important information. In Chen's study[25], cohort data sets of 200,000 people and their ambulatory and inpatient claims from 1997 to 2001 were analyzed. The annual prescribed amount of anti-ulcer drug had grown from 4.9 DDDs (defined daily dose)/1000 inhabitants/day in 1997 to 7.5 in 2001 in the study. H_2-receptor antagonists and the expanding number of users were two major contributors shown in the study. By using the standardized unit of DDDs to present the final result, this study could serve as a good reference for international comparison and health policy implementation.

Other pharmacoepidemiology studies using the NHI research databases revealed the inappropriateness of drug prescription[28,31]. Three inappropriate problems were identified in Hsu's study[28], using a 0.2% sampling of total non-narcotic analgesics as an example, which were overdose, duplication, and drug-drug interaction.

Table 2. Comparisons of automated databases: National Health Insurance databases versus other databases

Database	Country	Years of available data	Population[a] (million)	Nationally representative	Population-base data	Suitable for cohort studies	Suitable for case-control studies	Enrollment	Hospitalization	Inpatient drug exposure data	Outpatient diagnosis data	Suitable for case-control studies
National Health Insurance research databases	Taiwan	1996-present	21.982[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medicaid databases	USA	1992-present	51.00	✗	✓	✓	✓	✓	✓	✗	✓	✓
The HMO Research Network	USA	1942-present	10.81	✗	✓	✓	✓	✓	✓	✓	✓	✓
Kaiser Permanente Medical Care Program	USA	1961-present	8.20	✗	✓	✓	✓	✓	✓	✗	✓	✓
United Health Group	USA	1989-present	50.00	✗	✗	✓	✓	✓	✓	✗	✓	✓
Group Health Cooperative	USA	1947-present	0.56	✗	✓	✓	✓	✓	✓	✓	✗	✓
Health Services Databases in Saskatchewan	Canada	1975-present	1.00	✗	✓	✓	✓	✓	✓	✗	✓	✓
General Practice Research Database	UK	1987-present	2.693[c]	✗	✗	✓	✓	✓	✓	✓	✓	✓
The Tayside Medicines Monitoring Unit	UK	1961-present	0.40	✗	✓	✓	✓	✓	✓	✗	✓	✓

[a]Data source: 2003.
[b]Data source: Bureau of National Health Insurance. http://www.nhi.gov.tw/index.asp
[c]Data source: General Practice Research Database. http://www.gprd.com/whygprd/activepatientsbyyear.asp

Table 3. Selected recent pharmacoepidemiology studies using National Health Insurance research databases

Reference	Study design	NHI research databases	Target medication	Outcome measurement	Findings
Su *et al.* (2002)	Descriptive pharmacoepidemiology	Outpatient visits – Systematic sampling (2000)	Psychotropic drug	Drug utilization volume (defined daily dose, DDD)	The annual prescribed amount of psychotic drugs was 32.94 DDDs/1000 inhabitants/day in 2001, which was lower than other developed countries.
Chen *et al.* (2003)[a]	Descriptive pharmacoepidemiology	Not specified (Febuary, 1998-July, 1998)	Anti-asthmatic medications	Number of prescriptions	Overall, patients were treated more frequently with oral medications. Monotherapy with oral β-agonists was the most popular regimen, accounting for 13.70% of the total prescriptions studied. Only 6.70% of patients were taking inhaled corticosteroids.
Chen *et al.* (2003)[b]	Descriptive pharmacoepidemiology	Outpatient/ inpatient visits – sampled cohort (1997-2001)	Anti-ulcer drug	Drug utilization volume (DDD)	The annual prescribed amount of anti-ulcer drugs had grown from 4.9 DDDs/1000 inhabitants/day in 1997 to 7.5 in 2001. This increase was largely attributed to H_2-receptor antagonists and the expanding number of users.
Chen *et al.* (2003)[b]	Descriptive pharmacoepidemiology	Outpatient visits – sampled cohort (2000)	Hepatoprotectants	Drug utilization pattern	Among the valid cohort of 46,614 people, 783 (1.7%) were identified as patients with liver disease and receiving hepatoprotectants. Highest prevalence of hepatoprotectant use was 4.9% in the 60-69 year age old group. Silymarin, multivitamins, methionine, ursodeoxycholic acid, and liver hydrolysate accounted for 88.8% of the 3215 prescribed items of hepatoprotectants.
Ho *et al.* (2004)	Descriptive pharmacoepidemiology	Outpatient visits – Systematic sampling (2001)	Antimicrobial agents	Drug utilization volume (DDD)	The majority of antibiotics use was for upper respiratory infection. Among all antibiotics prescribed, aminopenicillin (35.2%) and cephalosporins (19.5%) accounted for a large percentage.
Hsu *et al.* (2004)	Descriptive pharmacoepidemiology	Outpatient visits – Systematic sampling (1997)	Non-steroidal anti-inflammatory Drugs (NSAIDs)	Drug utilization pattern -Overdose -Duplication -Drug-drug interaction	Among the 134,726 non-narcotic analgesic prescriptions, 6.7% of non-narcotic analgesic prescriptions had over-dosage problems, and 14.0% had drug-drug interaction problems. 6.3% of prescriptions with non-steroidal anti-inflammatory drugs (NSAIDs) had duplication regimen problems.
Huang *et al.* (2005)	Descriptive pharmacoepidemiology	Outpatient visits (2001)	Sleep-related medications	Drug utilization pattern	Benzodiazepines and newer non-benzodiazepine hypnotics were still the most frequently used drugs for treating insomnia in the elderly in Taiwan. Elderly patients with concomitant anxiety or depression consumed more hypnotics.
Chiang *et al.* (2006)	Descriptive pharmacoepidemiology	Outpatient visits-Systematic sampling (1997-2003)	Oral antidiabetic drugs (OAD)	Drug utilization pattern	The numbers of OAD prescriptions rose 1.23-fold. The sulfonylurea (SU) class was the most commonly used OAD, but the prescribing rates for this class declined over time. The largest increase in prescribing rates was for acarbose use. The prescribing rates of two new classes of OAD, meglitinide (MG) and thiazolidinedione (TZD) also significantly increased within a short period of time.
Gau *et al.* (2006)	Descriptive pharmacoepidemiology (Cohort study)	Outpatient visits-Systematic sampling (2000) and longitudinal health insurance database (LHID 2000)	Cisapride-erythromycin co-medication	Drug utilization pattern -Drug-drug interaction	The cisapride-erythromycin comedication prevalence rate in 2000 was 4.5%, with higher prevalence in clinics (9.2%) than in other medical institutes (3.7-5.4%).

Table 3. Continued

Reference	Study design	NHI research databases	Target medication	Outcome measurement	Findings
Huang *et al.* (2006)	Cohort study	Outpatient/inpatient visits (2001-2003)	COX-2 inhibitors (celecoxib and rofecoxib)	Adverse drug events - Cardiovascular events	Patients taking celecoxib had a lower risk of cardiovascular events than those taking meloxicam. Patients taking rofecoxib were not found to be at higher cardiovascular risk than those taking meloxicam. The most significant determinant of cardiovascular risk was a 1-year prior history of such cardiovascular disease.
Huang *et al.* (2006)	Cohort study	Outpatient/inpatient visits (2001-2003)	COX-2 inhibitor (celecoxib) and 4 NSAIDs (Etodolac, Nabumetone, Ibuprofen, Naproxen)	Adverse drug events - Cardiovascular events	No significant difference of cardiovascular risks (AMI, angina, stroke, or TIA) was found between long-term users of nonselective NSAIDs (etodolac, nabumetone, ibuprofen, or naproxen) and celecoxib. The most significant determinant of cardiovascular risks is the patients' 1-year prior history of such diseases recorded in the NHI databases before initiation of medication. Patients with a 1-year prior history of other medical conditions recorded in the NHI databases before initiation of medication also appear to have higher risk of cardiovascular adverse events.

[a]Chen, T. J. *et al.*
[b]Chen, C. Y. *et al.*

A significant inappropriate prescribing pattern was noticed in this study. Among the 134,726 non-narcotic analgesic prescriptions, 6.7% of non-narcotic analgesic prescriptions had overdose problems, 14.0% had drug-drug interaction problems, and 6.3% of prescriptions with non-steroidal anti-inflammatory drugs (NSAIDs) had duplication regimen problems. This approach usually generated important signal related to drug safety and pointed out further improvement in future researches and clinical practices. Studies using similar approach but focusing on specific population, especially the elderly, could provide fruitful evidence for clinical practice and for reimbursement policy modification. For instance, the utilization pattern of benzodiazepines and newer non-benzodiazepine hypnotics in the elderly for insomnia in Taiwan was conducted by Huang[29] and his colleagues using the NHI datasets.

Other studies identifying the adverse drug events of COX-2 inhibitors were conducted by Huang and his colleagues using a three-year national dataset from the NHI[32,33]. The risk of acute myocardial infarction (AMI), angina, stroke and transient ischemic attack (TIA) in long-term users of celecoxib and/or rofecoxib in Taiwan was explored and compared with that of those using meloxicam[32] or other traditional NSAIDs[33]. Result of this study also provide key information since the safety issue on COX-2 inhibitors is still of concern after the automatic withdrawal of rofecoxib in September, 2004. Yet, there is still a substantial gap of identifying potential drug safety issues using the NHI research databases since large automated databases are usually the major resources for identifying and quantifying adverse drug reactions. With the unique national and comprehensive NHI research databases, researchers in pharmacoepidemiology in Taiwan should continue the studies presented above, and also place additional emphasis on under-explored drug safety issues.

COMMENTS

The construction and maintenance of NHI research databases absolutely provides abundant research resources for scholars not only in medical fields but also in public health-related disciplines. The publications using the NHI research databases are therefore various in many international journals. Yet, as presented in the sections above, researchers could make even greater progress toward thorough pharmacoepidemiology studies using the NHI research databases.

Although concern must be taken to ensure that all potential limitations are addressed in appropriate ways, the NHI research databases could still provide a low-cost and a highly accessible platform for potential pharmacoepidemiology studies. Enthusiastic efforts should be advocated to encourage more research activities in this field in Taiwan.

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