2010

Drug Safety Issues Focusing on Liver and Pancreas Toxicity

Thamir M. Alshammari
University of Rhode Island

DRUG SAFETY ISSUES

FOCUSING ON LIVER AND PANCREAS TOXICITY

BY

THAMIR M. ALSHAMMARI

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2010

DOCTOR OF PHILOSOPHY DISSERTATION

OF

THAMIR M. ALSHAMMARI

APPROVED:

Dissertation committee:

Major Professor _____

_____

_____

_____

_____

DEAN OF THE GRADUATE SCHOOL

UNIVERSITY OF RHODE ISLAND

2010

Abstract

Background: Medications benefit people with diseases and medical conditions, improving many patients' lives and in some cases significantly increasing their quality of life. Despite these great benefits, medications can lead to serious adverse effects. Adverse drug reactions (ADRs) are the 4th leading cause of death, greater than major killers including pulmonary diseases, diabetes and automobile death. Not all medication groups have the same incidence in inducing diseases. Anti-infective agents - including antibacterial agents- are the most likely to induce diseases followed by cardiovascular agents and antineoplastic agents.

Objectives: Drug safety is a very important issue in patient therapy. Since antibacterial agents in general and fluoroquinolones specifically are among the most prescribed medications, it is very important to quantify their risks in causing serious adverse reactions such as hepatotoxicity and pancreatitis. In terms of drug safety and preventing ADRs, costs are a very important factor because many conditions like hypoglycemia can be prevented, leading to significant decreases in cost and improvement in quality of life. Since there is a dearth of research that has examined these areas, epidemiological studies are needed. The objectives of the three proposed manuscripts of this dissertation were to a) estimate the risk of hepatotoxicity associated with fluoroquinolones use; b) examine antibacterial agents use and the risk of acute pancreatitis development; c) review the healthcare databases in United States and European countries that are commonly utilized in conducting epidemiological research.

Methods: Two matched case control studies were used to examine the risk of hepatotoxicity and acute pancreatitis development with using fluoroquinolones and antibacterial agents, respectively. The Veterans' Affairs (VA) medical database was used to perform the two studies. Odds ratios (OR) and their 95% confidence intervals (CI) were derived from crude and adjusted conditional logistic regression models. In the third paper, a literature search was performed using Publisher Medline (Pubmed), Embase® and the Iowa Drug Information Services (IDIS) to perform a review of four medical databases including the Nationwide Inpatient Sample database, the Veterans' Affairs medical database, the Health Improvement Network database and the Norwegian medical database.

Results: In the first study, fluoroquinolones use was associated with increased risk of hepatotoxicity. However, only ciprofloxacin was statistically significantly associated with development of hepatotoxicity while levofloxacin and moxifloxacin were not associated with hepatotoxicity development. In the second study, use of antibacterial agents was associated with increased risk of acute pancreatitis.

Conclusion: The findings from both studies show that antibacterial agents are associated with increased risk of hepatotoxicity and acute pancreatitis. Knowing the safety of medication is very important for the clinical practice especially for antibacterial agents since they are commonly used and clinicians are considering these agents very safe. However, further research is needed to confirm these findings and to understand the biological mechanism behind their toxicity.

Acknowledgements

I believe my PhD studies at The University of Rhode Island (URI), College of Pharmacy are a gift from God. It was a great experience for me, not only in the knowledge that I have obtained, but also the level of life experience that I have gained from my advisors during my stay here at URI.

There are many people who have had an impact on my personality and my education and I will start with my father and my mother. Although my father passed away while I was just 10 years old, he had a great effect on me and encouraged me to pursue my education up to the PhD level, which was his dream. Also, I would like to thank my mother who was behind everything that I have achieved in my life until now. She always has supported me and is being patient in not seeing me for more than two years while I have completed my studies in the US. Also, I would like to thank my brothers and my sisters for all their support.

After I arrived here in the United States, I never felt that I was away from my family because I felt as though I was part of another great family, which includes my professors and fellow graduate students.

First, I would like to thank Prof.Paul Larrat for his encouragement and help during my studying at URI. Thanks to him for believing in me and taking the time to guide and keep me on the track. He has been very supportive and always made it easy for me with his kind words of encouragement and the humble heart that he has. Thanks a lot for his advice, efforts, time and everything that he has done for me. He truly has had a great influence on my personality and my success.

I would like to thank Dr.Kerry LaPlante for helping me to master a great database. I remembered first time I met her, she was so kind and very motivated to help me. Although she was so busy, she gave me her attention and advice every time I contacted her. She was very supportive and always encouraged me to do more because she believes in me. I was so lucky to work on the VA database and without her help this dissertation would not have been possible.

Also I will not forget what I have learned from Dr.Brian Quilliam. I would like to thank Dr.Quilliam for everything that I've learned from him during my classes and my research. I was lucky to work on projects with him during my classes. Although he was so busy during the time of my research, he gave me from his time. His way of explaining the epidemiological and statistical methods helped me to understand and love epidemiology.

I would like to thank Prof.Robert Laforge for being in my committee. His help, advice and comments on my statistical methods helped me a lot during my analysis. He was so motivated to help me as one of his student in his class to understand the statistical method that is related to my projects.

I would like to thank Dr.Stephen Kogut. I can't express my feelings towards him. Dr.Kogut dealt with me as his brother. I had the honor of meeting his great family and I was so happy to have this chance. As a professor, Dr.Kogut supported me during the first semester here at URI. His office was always opened for me. He gave me from his time no matter how busy he was. I was lucky to take many classes with

him. Also, I was lucky to do a project with him and with Dr.Quilliam and I learned a great lot during that experience.

I would like also to thank Dr.Marc Hutchison for serving as my dissertation chair and having time for me although he has a very busy schedule.

Finally, I would like to thank my fellow graduate students; Jason, Aisling, Kristen, Chuck and Mark. They were so helpful and are real friends inside or outside the school. I hope we continue to stay in contact because you are part of my family. Also, I would like to thank Suzanne for her help and support during my work in Dr.LaPlante's lab.

Preface

All three Chapters in this dissertation were prepared following the manuscript format for each journal.

Chapter I: Estimating the Risk of Hepatotoxicity Associated with Fluoroquinolone Use: A Case-Control Study Using the National Veterans Affairs Database. The Journal of the American Medical Association (JAMA) format

Chapter II: Antibacterial use and risk of acute pancreatitis: A Case-Control Study Using the National Veterans Affairs Database. Clinical Infectious Diseases (CID) format

Chapter III: Review the healthcare databases in United States and European countries that are commonly utilized in conducting epidemiologic research. Pharmacoepidemiology and Drug Safety (PDS) format.

Table of Contents

List of Tables

Chapter I

Chapter II

Chapter III

CHAPTER I

Estimating the Risk of Hepatotoxicity Associated with Fluoroquinolone Use: A Case-Control Study Using the National Veterans Affairs Database

This manuscript will be submitted to the Journal of the American Medical Association (JAMA)

Abstract

Context: Health care agencies across the world are closely monitoring reports of hepatotoxicity linked with fluoroquinolone use. Medications and herbal remedies currently account for fifty percent of acute liver failure in the United States and liver toxicity is one of the most common reasons for drug removal by the FDA. The incidence of hepatotoxicity due to fluoroquinolone use is currently unknown.

Objective: To assess the risk of hepatotoxicity in patients using fluoroquinolones compared to patients who did not use fluoroquinolones among patients admitted to Veterans Affairs facilities nationally.

Design, setting and patient: Matched case control design was used to evaluate a national cohort of patients admitted to all Veterans Affair facilities between January 1st, 2002 and December 31st, 2008. Patients diagnosed with hepatotoxicity as primary diagnosis served as cases and patients diagnosed with myocardial infarction served as the control group. Conditional logistic regression was utilized to compute odds ratios and the 95% confidence interval (CI). Multivariable models were built to adjust and control for the potential clinical conditions or covariates that might influence hepatotoxicity risk. A stepwise forward entry method (non-computer generated) was used to build the final model.

Main Outcome Measure: The risk of hepatotoxicity associated with fluoroquinolone use.

Results: A total 7,862 patients in the hepatotoxicity-case group and 45,512 patients in control group were entered in the final analysis. The mean age of the cases was 58

years and the majority of the patients were males (96%) and were white (59%), followed by black race (18%) and hispanic (4%). After adjusting for potential confounders, fluoroquinolone use was significantly associated with increased risk of developing hepatotoxicity, odds ratio (OR) was 1.196 (95% Confidence Interval [CI], 1.039-1.375). Further, ciprofloxacin was significantly associated with risk of hepatotoxicity, OR, 1.294 (95% CI 1.051-1.58).

Conclusion: The use of fluoroquinolones was associated with increased risk of hepatotoxicity among a national cohort of veterans.

Background

Hepatotoxicity, defined as an injury to the liver cells is commonly associated with a decrease in liver function. [1] The liver's metabolism and connection with the gastro-intestinal tract increases susceptibility to injury from drugs and other ingested substances. Hepatotoxicity can range from a mild reaction, which can be resolved by discontinuation of the causative agents to a serious fatal reaction.[2] Medications, herbs, chemicals and infectious pathogens are the most common causes of hepatotoxicity.[3-7] Although the incidence of drug induced- hepatotoxicity is considered rare –1 in 10,000 to 1 in 100,000- it is usually clinically significant. [8]

Fifty percent of acute liver failure cases are caused by medications and 5% of all hospital admissions are caused by drug-related hepatotoxicity.[9] Currently, hepatotoxicity is the leading cause of acute liver failure in the United States (US). Acute Liver Failure (ALF) due to medications is usually a fatal reaction and only 20% of patients will respond to therapy and survive.[2] Liver damage due to drugs has different features: hepatocellular, cholestatic or a mixture of both.[10-12] There is no specific treatment for drug-induced hepatotoxicity in most cases; supportive care and withdrawal of causative agent are the only treatment options available. More than 900 drugs can cause hepatotoxicity.[13]As a cost of liver toxicity, the average cost of treating a patient with acute liver failure using 2001 and 2006 data is estimated at is $146,972 to $252,113. [14,15]

Fluoroquinolones are antimicrobial agents that possess a broad spectrum of activity against gram-negative and gram-positive organisms. These drugs are widely

used to treat nosocomial and community acquired infections.[16] Fluoroquinolones are one of the most prescribed medications. [17]

Antimicrobial agents, including fluoroquinolones are the most common cause of non-acetaminophen induced hepatotoxicity. [18] Antimicrobial induced hepatotoxicity usually is an idiosyncratic reaction, dose independent and unrelated to intended pharmacological effect. [18,19] In the past decade, liver toxicity has been one of the most common reasons for drug removal from the U.S. market by the FDA such as troglitazone (Rezulin®). [18]

In the United Kingdom (UK), the Medicines and Healthcare products Regulatory Agency (MHRA) restricted the indication of moxifloxacin for use only when other antibiotics failed to treat acute bacterial sinusitis, acute exacerbation of chronic bronchitis or community acquired pneumonia due to the risk of hepatotoxicity associated with moxifloxacin. [20]

Increases in the reports of hepatotoxicity associated with the usage of fluoroquinolones are a crucial issue in clinical practice, since fluoroquinolones are commonly prescribed because of their broad spectrum of coverage. At the same time liver toxicity is a serious issue and 50% of cases are related to medication and not related to any underlying diseases. However, in the case reports, the association between fluoroquinolones and hepatotoxicity is unclear.[21-24] A well designed epidemiological study is necessary to assess the possible increased risk of hepatotoxicity associated with fluoroquinolones usage. Therefore, the purpose of this

study was to conduct a real-world safety study to assess the association between fluoroquinolones use and risk of hepatotoxicity.

Methods

Data source

In United States, the Veterans Affairs (VA) medical database is considered from the largest medical database with information for more than 7.9 million veterans. [25-27] These data include detailed information on all medical and pharmacy information for each patient. All patient data are stored in electronic form. [28,29] Additionally, Veteran Health Administration (VHA) runs and operates over164 hospital and 800 clinics with more than 180,000 medical personnel. All data are maintained on three levels: the local level, the VA Integrated Services Networks (VISN) level, and the national level.[30] Every patient treated in any VA hospital or other VA facilities has his/her information collected and stored in the National Patient Care Database (NPCD), the source data for the VHA medical SAS datasets. Similar to many other medical databases, VHA uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to code all diseases, procedures, and surgeries in the VA datasets. In addition, the Current Procedure Terminology (CPT) code system is used to code some procedures in the medical SAS outpatient datasets. [31] The Diseases coding in the VA database has been validated and determined to be of high quality. [30,32]

Study design

A matched case-control study was utilized using a national cohort of patients in the VA databases (hospital and pharmacy data) which contain preexisting data to examine the association between fluoroquinolone use and development of

hepatotoxicity. Scrambled Social Security numbers were used to guarantee the privacy of the patients. The study was approved by the Institutional Review Board (IRB) of the VA research committee and the research office at the University of Rhode Island.

Cases and controls

Our patient cohorts were taken from the national VA database in Austin (Austin Automation Center; AAC) between January 1st, 2002 and December 31st, 2008. All patients from the study population diagnosed with hepatotoxicity as primary diagnosis were defined as our case patients. Only the first diagnosis for hepatotoxicity was considered in the instance of patients who have multiple episodes during the study period. Hepatotoxicity term included "hepatotoxicity, acute necrosis of the liver, liver toxicity and toxic hepatitis". Hepatotoxicity cases were identified using ICD-9-CM codes: hepatic necrosis (570) and toxic hepatitis (573.3). [6,33-35] For each case patient we randomly selected up to six controls from the population of patients who were diagnosed as primary diagnosis with myocardial infarction (ICD-9-CM 410.00-410.92). We have chosen myocardial infarction because it has the same hepatotoxicity characteristics which are acute and serious outcome. For both cases and controls, patients with secondary diagnoses for infectious diseases are allowed to be included in our study. Controls were match to cases based on month of admission.

We excluded individuals who meet one of the following criteria: liver cirrhosis, liver cancer, any type of viral hepatitis, alcoholic hepatotoxicity, acetaminophen induce-hepatotoxicity, human immunodeficiency virus/acquired immunocompromised deficiency diseases HIV/AIDS, liver abscess and Wilson's

disease. Also, we excluded patients who were hospitalized during the 180 days prior to the admission date.

Exposure definition

Definition of drug exposure was as patient received a prescription for ciprofloxacin, levofloxacin, or moxifloxacin six months prior to the admission date. Medications were identified using drug description variables along with intermediate product number (IPNUM) variable. Only outpatients' medications were included in the study and most of fluoroquinolones used were oral medications.

Covariates

Covariates that were controlled in the logistic regression model include age, gender, race, alcohol status (ICD-9 codes (305.0, 303.0, V11.3, V79.1), alcohol dependency treatment (BEDSECN=725) and alcohol-related DRGs (DRG=433)), smoking status, illicit drug use, comorbidities (history of diabetes, renal diseases , hypotension, heart failure, gall bladder disease), medications' prescription data for our cases and controls included: tetracyclines, macrolides, amoxicillin, amoxicillin/clavulanic acid, isoniazid , rifampicin, pyrazinamide, ethambutol, antifungal medications, thiazolidinediones, metformin, Proton Pump Inhibitors (PPIs) and phenytoin. These medications were selected because they are known to cause hepatotoxicity. [1]

Data Analyses

The primary analysis of the study was to examine the association between the development of hepatotoxicity and exposure to fluoroquinolone use. Demographic and clinical categorical data was analyzed using X^2 test or Fisher's exact test while continuous variables were analyzed using a student's *t*-test or Mann Whitney test. Conditional logistic regression was used to compute odds ratio and their 95% confidence interval (CI). Bivariate analyses were initially used for the selection of potential clinical covariates for inclusion in the multivariable model. Based on the findings of the bivariate analyses, a multivariable model was built to control for the potentially confounding variables. Covariates with differences of 10% between the cases and controls were included in the multivariable model. A forward entry method (non-computer generated) was used to build the final model, at each step, a covariate was added, and if the estimated coefficient (ß) of fluoroquinolone exposure changes by > 10%, this covariate was kept in the final model. Potential effect modifiers were examined by adding specific interaction terms to the conditional logistic regression models. At each step, an interaction term was added to the model and the interaction will be significant if the estimated coefficient (ß) of fluoroquinolone exposure changes by > 10%. Presence of collinearity was assessed by Variation Inflation Factor (VIF) using value of 2.5 as cut off. [36] All the confounders or covariates were assessed at baseline. Subgroup analysis was conducted to study the association between each drug (ciprofloxacin, levofloxacin and moxifloxacin) and their risk of hepatotoxicity.

All statistical tests were conducted with a two-tailed alpha of 0.05 using SAS® version 9.1.3 (SAS® Institute, Inc, Cary, NC).

Results

There were 21,404 case patients identified with hepatotoxicity. We excluded patients with liver cancer (n=1,033), patients with liver cirrhosis and hepatotoxicity due to alcohol (n=9,543), patients with HIV/AIDS and Wilson's disease (n=349), patients with viral hepatitis (n=1,302), patients with liver abcess (n=48), patients with acetaminophen induced hepatotoxicity (n=183) and any patient admitted in the last 6 months prior to the admission date (n=1,084). 7,862 patients were included in the final analysis as case group. The majority of our study population was male (96%) and the mean age was 58 years for cases and 64 for controls. Approximately, 60% of cases were of white race followed by 17% black. In comparison to the cases, in the control group, 64% of patients were white and 11% black (Table I.1);. In both cases and controls, approximately 20% of race is missing which is acceptable if we consider the fact that most of administrative databases did not include race. The cases tend to use alcohol and illicit drug more than controls while control tend to smoke tobacco more than cases.

Patients in control group had a higher prevalence of diabetes mellitus (33%) in comparison to patients in case group (22%) while prevalence of renal disease was more in cases (13%) than controls (6%). Other comorbidities were almost the same between the cases and controls.

Medication consumptions were similar between the patients in case group compared to the patients in control group with few exceptions. The percentage of patients using hypoglycemic agents "thiazolidinedione and metformin" was more in

controls (3%, 10%, respectively) compared to cases (1.5, 4.5%, respectively). On the other hand, phenytoin was used more in cases (0.80%) compared to controls (0.5%). The other medication groups such as tetracyclines, macrolides, amoxicillin/ amoxicillin+ clavulnate, anti-tuberculosis medications and antifungal were almost similar between cases and controls.

Odds ratios (OR) and the 95% confidence intervals (CI) were computed from the crude and the adjusted conditional logistic regression models. There was a statistically significant association between fluoroquinolones use and developing hepatotoxicity after adjusting for all potential confounders, the adjusted OR was 1.196 (95% CI: 1.039-1.375) (Table I.2). Secondary analysis was done to estimate the risk of hepatotoxicity with drugs of interests (ciprofloxacin, levofloxacin and moxifloxacin) compared to non users. Ciprofloxacin was statistically significant associated with hepatotoxicity OR 1.294 (95% CI 1.051-1.586) (Table I.3). Further, levofloxacin and moxifloxacin were associated with hepatotoxicity as indicated by an OR of 1.164 (95% CI 0.941-1.439) and OR of 0.98 (95% CI 0.67-1.416) respectively, but these associations were not statistically significant. There was no collinearity between the variables in our model.

Discussion

To our knowledge, this is the first study to examine the association between fluoroquinolone antibiotic use and the risk of developing hepatotoxicity. This study utilized an extremely large database. [11] Our population was mainly white and male as expected since most of the patients were veterans. Patients with hepatotoxicity in our study were younger than the controls. This is consistent with many case reports and studies that assess the association between hepatotoxicity and medications. [2,23,37,38] Hepatotoxicity can develop at any age. [2] Based on the results of our study, we found that patients with hepatotoxicity are 1.196 times more likely to have been exposed to fluoroquinolones than control group. Our results indicate that fluoroquinolones use is associated with risk of developing hepatotoxicity. Furthermore, the results showed that ciprofloxacin is significantly associated with risk of developing hepatotoxicity while levofloxacin and moxifloxacin were not statistically significant associated with hepatotoxicity.

Gatifloxacin was not included in the study because it is no longer actively marketed after the 2006. Gatifloxacin had a "Black Box" warning regarding increased dysglycemias in diabetic patients before the company stopped manufacturing the drug.[39]

These observed associations between fluoroquinolones are biological plausible. Ciprofloxacin and moxifloxacin are partially metabolized by the liver while levofloxacin is largely execreted unchanged by the kidneys. [40-42] Liver enzymes elevation occurred in 2-3% of patients with fluoroquinolones. Alanine

aminotransferase, aspartate aminotransferase, and alkaline phosphatase are the most reported elevated enzymes with fluoroquinolones use. [43,44] In humans, the intrahepatic concentrations of fluoroquinolones have been found to be eight times as their concentration in the serum. [45] Increasing the concentration of fluoroquinolones in the liver might lead to hepatic injury. However, the liver toxicity usually occurred when the concentration is 20 times intrahepatically compared to serum concentration. [45] Therefore, this may be the reason why ciprofloxacin is associated with hepatotoxicity and levofloxacin was not. However, moxifloxacin was not associated with hepatotoxicity while it is metabolized by liver; this may be because of the small number of patients using moxifloxacin. A possible explanation is that, until, 2006, ciprofloxacin and gatifloxacin were the fluoroquinolones of choice within the VA facilities. Ciprofloxacin was the least expensive drug since it was available as generic. [46,47] Although, there was a new restriction in using moxifloxacin in UK, a recent European review assessed the risk of moxifloxacin safety compared to other fluoroquinolones. Researchers conclude that hepatotoxicity with moxifloxacin was not different than other fluoroquinolones. [48] In addition to the metabolism effect mechanism, some literature suggested that fluoroquinolones hepatotoxicity is a idiosyncratic drug reaction "immune-mediated" manifested by eosinophilia. [49] This mechanism could be the suggested mechanism in the case of medication that is mainly eliminated by renal routes such as levofloxacin.

Although, there is no study to assess the association between fluoroquinolones use and risk of hepatotoxicity, SB Meropol et al, compared the incidence rate of hepatotoxicity with using three different medications which are ciprofloxacin ,

amoxicillin and doxycycline. [50] They compared the incidence of hepatotoxicity with these medications in three different databases. Overall, the incidence rate of hepatotoxicity was more with ciprofloxacin compared to amoxicillin and doxycyline (20.6, 1.4, 0 per 100,000 person day, respectively). The results of this study were consistent with our study results. Many case reports questioned the risk of hepatotoxicity with fluoroquinolone drugs including, ciprofloxacin, moxifloxacin, and levofloxacin. [23,24,38,51] Contreras et al, describe a 32 year old male who was diagnosed with septic arthritis in his ankle. He started ciprofloxacin (500 mg q12h) and subsequently, the patient developed jaundice, his liver enzymes goes up (AST:1,782 U/L (normally < 35) and ALT:2,144 U/L (normally < 40). The patient was suspected to have ciprofloxacin induce liver failure and admitted to intensive care unit (ICU). The patient started to improve and his liver enzymes return to the normal after 6 weeks of discontinuing ciprofloxacin. [52] Schwalm and Lee describe a 73 year old male who developed acute hepatitis after using levofloxacin 250 mg orally per day. He was started on levofloxacin for cellulitis and shortly after initiation of levofloxacin, his liver enzymes increased (AST: 1392 U/L and ALT: 857 U/L). Levofloxacin was stopped and within 1 week, the enzymes returned to near normal levels [53].The time of hepatotoxicity in these reports varied between 5 and 35 days.

Our results indicate that Veterans of Asian race were not at greater risk of developing hepatotoxicity compared to black and Hispanic veterans. This result is consistent with the fact that Asian patients tend to have faster metabolism compared to other races. [54] While, the Native American patients have the highest risk compared to other races, this is may be due to different reasons such; Native Americans are using

many herbs as treatment and as nutritional supplement and these herbs could have an effect on the liver. [55]

Patients with myocardial infarction were chosen as the control group because they are believed to have many similar characteristics to those with hepatotoxicity, including acute onset and serious outcome. In a case control study, having an appropriate control group is challenging.[56] Other controls such as those with renal diseases cannot be used because there is an association between fluoroquinolones medication use and the development of renal diseases.[57,58] Additionally, patients with injury are not a suitable group because those patients usually have severe comorbidities and may be older. [59] One quarter of veterans who served at Iraq and Afghanistan are reported to have head and neck injury type, just one type of the many possible injuries.[60-62]

In our study, we controlled for covariates (social behavior, health conditions and medications) that might influence hepatotoxicity. Further, we controlled for the possible interactions (2-way and 3-way) to minimize the role of effect modifiers.

Observational studies, especially those that assess the effects of medications, should evaluate the potential of confounding by indication, when seriously ill patients being more likely to receive fluoroquinolone medications and more likely to develop the outcome. To assess this, first we excluded any patient who has been admitted in the hospital to avoid including any very ill patient. Additionally, we were able to exclude many major risk factor for hepatotoxicity such as viral hepatitis and liver

abscess and finally we controlled for most of relevant comorbidities in our regression model.

The recognized association between fluoroquinolones and hepatotoxicity is not new. Trovafloxacin was the first drug from fluoroquinolone medications that associated with hepatotoxicity.[63] Trovafloxacin is available with special restrictions for use only in patients with life-threatening or limb infections because of serious liver toxicity including hepatitis, liver failure that resulted in liver transplantation and death. [64,65] In 1999, trovfloxacin was removed from European market because of liver toxicity. [66]

Our study has several strengths; we utilized a large database with sufficient power to assess the association between fluoroquinolones use and risk of developing hepatotoxicity. Moreover, this database allowed us to include patients that may not be in other databases, such as those of Native American race and users of illicit drugs. We were able to control for many major potential confounders such as liver cancer, liver cirrhosis and other risk factors.

However, our study has several limitations. Since we are using an administrative database, there is potentially a problem with coding and missing data, especially for behavioral variables such as alcohol abuse and tobacco smoking. In the VA database, there are specific variables for alcohol abuse and tobacco use but these variables usually are missing at least in the case of our study. Instead, we used ICD-9-CM codes to detect patients who are smoking tobacco, who have history of smoking and patients who are abuse alcohol. We believe that there may be a an underestimation

of the prevalence of these behaviors. Additionally, illicit drug use is determined by patients (self identified), not by using analytical test to test these substances in the blood. Using this method could underestimate illicit drug use and we speculate that not all patients will identify if they use illicit drugs or not. The validity of the ICD-9-CM code as an indicator for hepatotoxicity is not known. In general, the validity of different ICD-9 codes varies. [67,68] However, it is unlikely that hepatotoxicity is ignored as a diagnosis. Another limitation of using administrative database is that we can't determine whether patients receiving fluoroquinolones actually took their medications and adhered to their medication regimen. . The majority of our population in the study are veterans males, therefore we may not generalize our results to women and non-veteran patients.

Finally, as with other observational studies, residual confounding cannot be completely excluded.

Conclusion

In conclusion, it was found in a large national cohort study that fluoroquinolones use is significantly associated with the risk of developing hepatotoxicity compared to non-use. Furthermore, ciprofloxacin was statistically significant associated with the risk of hepatotoxicity compared to non-users. At present, it is believed that clinicians should be aware of this potential issue when they prescribe fluoroquinolones in patients who are at risk of developing hepatotoxicity. Thus, further research is needed to confirm these findings and to better understand the underlying mechanism.

Table I.1: Demographic and clinical characteristics' among patients with hepatotoxicity (cases) and patients with myocardial infarction (controls) in Veterans Affairs database between Jan 2002- Dec 2008.

	Cases N=7,862 (%)	Controls N=45,512 (%)	P value
Age, mean (SD)	58.4 (12.7)	63.8 (11.0)	<0.01
Sex (%male)	96.30%	98.00%	<0.01
Race			
White	4,621 (58.9%)	29,227 (64.2%)	
Black	1,401 (17.8%)	4,990 (10.9%)	
Asian	37 (0.47%)	227 (0.49%)	<0.01
Hispanic	329 (4.2%)	1,264 (2.9%)	
Native American	52 (0.7%)	122 (0.3%)	
Unknown	1,422 (18%)	9,685 (21.3%)	
Alcohol abuse*	493 (6.3%)	280 (0.6%)	
Smoking*			
Never	6,946 (88.4%)	38,562 (84.7%)	
Current	805 (10.2%)	5,504 (12.9%)	<0.01
Past	112 (1.4%)	1,453 (3.2%)	
Illicit drug use	144 (1.8%)	160 (0.35%)	<0.01
Comorbidities			
Diabetes Mellitus	1,787 (22.7%)	15,104 (33%)	<0.01
Hypotension	219 (2.8%)	1,137 (2.5%)	0.13
Gall bladder disease	292 (3.7%)	407 (0.9%)	<0.01
Renal Diseases	1,024 (13%)	2,743 (6%)	<0.01
Heart failure	871 (11.1%)	5,207 (11.4%)	0.35
Prescription medications§			
Tetracyclines	81 (1%)	535 (1.2%)	0.26
Macrolides	212 (2.7%)	1,231 (2.7%)	1.00
Amoxicillin±calvulante	169 (2.15%)	1,082 (2.4%)	0.21
Anti-TB	10 (0.13%)	32 (0.07%)	0.09
Antifungal	25 (0.32%)	87 (0.2%)	0.02
Thiazolidinediones	125 (1.5%)	1,418 (3%)	<0.01
Metformin	359 (4.5%)	4,566 (10%)	<0.01
Statins	717 (9.2%)	10,469 (23%)	<0.01
Proton pump inhibitors	858 (10.9%)	6,493 (14.3%)	<0.01
Phenytoin	60 (0.8%)	217 (0.48%)	0.01

*Based on ICD-9-CM §Medications known to cause hepatotoxicity

Table I.2: The result of multivariable model showing the risk of hepatotoxicity associated with fluoroquinolones (the crude and adjusted odd ratios of study outcomes).

Variable	Crude Odds Ratio (95%CI)	Adjusted Odds Ratio (95%CI)*
Fluroquinolones	1.125 (0.98-1.287)	1.196 (1.039-1.375)
Age	0.958 (0.956-0.961)	0.954 (0.951-0.957)
Gender¥	1.934 (1.688-2.216)	1.509 (1.299-1.753)
Race§		
Black	1.534 (1.430-1.646)	1.473 (1.369-1.570)
Hispanic	1.673 (1.469-1.904)	1.686 (1.471-1.932)
Asian	1.100 (0.767-1.577)	1.225 (0.845-1.775)
Native American	2.140 (1.514-3.025)	2.320 (1.605-3.355)
Unknown	0.948 (0.886-1.016)	0.947 (0.885-1.014)
Alcohol abuse	8.363 (7.168-9.757)	7.770 (6.629-9.108)
Smoking $		
Current smoker	0.642 (0.590-0.698)	0.637 (0.585-0.693)
Ex smoker	0.451 (0.370-0.550)	0.511 (0.414-0.629)
Diabetes mellitus	0.627 (0.592-0.664)	0.674 (0.632-0.719)
Renal diseases	2.992 (2.759-3.246)	3.151 (2.894-3.431)
Gall bladder diseases	4.740 (4.040-5.562)	4.709 (3.994-5.553)
Metformin	0.622 (0.550-0.704)	0.644 (0.569-0.728)
Statin	0.372 (0.343-0.404)	0.420 (0.385-0.460)
Antifungal	1.539 (0.970-2.444)	1.666 (1.033-2.687)
PPI	0.779 (0.721-0.843)	0.845 (0.779-0.917)

*Adjusted for all potential confounders in the table

¥ The reference group is male gender

§ The reference group is white race

$ Compared to people who never smoke using ICD-9-CM

Table I.3: Risk estimates for hepatotoxicity among users of different fluoroquinolones.

Drug	Cases (n=7,862)	Control (n=45,512)	Adjusted Odds Ratio (95%CI)
Ciprofloxacin*	124	651	1.29 (1.05-1.58)
Levofloxacin§	112	696	1.16 (0.94-1.44)
Moxifloxacin†	36	256	0.98 (0.67-1.41)

*Multivariable model adjusted for age, gender, race, smoking, alcohol abuse, diabetes mellitus, renal diseases, metformin use and proton pump inhibitors (PPIs) use.

§Multivariable model adjusted for age, gender, race, alcohol abuse, diabetes mellitus, renal disease, gall bladder diseases metformin use and PPIs use.

† Multivariable model adjusted for age, gender, race, alcohol abuse, diabetes mellitus, renal diseases and proton pump inhibitors (PPIs) use

REFERENCES

1 Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006; 354:731-739

2 Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002; 137:947-954

3 Favreau JT, Ryu ML, Braunstein G, et al. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. Ann Intern Med 2002; 136:590-595

4 Garibaldi RA, Drusin RE, Ferebee SH, et al. Isoniazid-associated hepatitis. Report of an outbreak. Am Rev Respir Dis 1972; 106:357-365

5 Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA 1999; 281:1014-1018

6 Heaton PC, Fenwick SR, Brewer DE. Association between tetracycline or doxycycline and hepatotoxicity: a population based case-control study. J Clin Pharm Ther 2007; 32:483-487

7 Strasser SI, Myerson D, Spurgeon CL, et al. Hepatitis C virus infection and bone marrow transplantation: a cohort study with 10-year follow-up. Hepatology 1999; 29:1893-1899

8 Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis 2002; 22:145-155

9 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279:1200-1205

10 Rivkin AM. Hepatocellular enzyme elevations in a patient receiving ceftriaxone. Am J Health Syst Pharm 2005; 62:2006-2010

11 Romero-Gomez M, Suarez Garcia E, Fernandez MC. Norfloxacin-induced acute cholestatic hepatitis in a patient with alcoholic liver cirrhosis. Am J Gastroenterol 1999; 94:2324-2325

12 May LD, Lefkowitch JH, Kram MT, et al. Mixed hepatocellular-cholestatic liver injury after pioglitazone therapy. Ann Intern Med 2002; 136:449-452

13 Friedman SEG, James H.; McQuaid, Kenneth R. Current diagnosis & treatment in gastroenterology. New York: Lang Medical Books/McGraw-Hill, 2003

14 van Agthoven M, Metselaar HJ, Tilanus HW, et al. A comparison of the costs and effects of liver transplantation for acute and for chronic liver failure. Transpl Int 2001; 14:87-94

15 Sagmeister M, Müllhaupt B. Is living donor liver transplantation cost-effective? J Hepatol. 2005; 43:27-32

16 Walker RC. The fluoroquinolones. Mayo Clin Proc 1999; 74:1030-1037

17 Verispan VONA, Full year 2007.

18 Chang CY, Schiano TD. Review article: drug hepatotoxicity. Aliment Pharmacol Ther 2007; 25:1135-1151

19 Onur O, Guneysel O, Denizbasi A, et al. Acute hepatitis attack after exposure to telithromycin. Clin Ther 2007; 29:1725-1729

20 Moxifloxacin: restricted use. Drug Safety Update. The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and the Commission on Human Medicines 2008; 2:1-10

21 Lopez-Navidad A, Domingo P, Cadafalch J, et al. Norfloxacin-induced hepatotoxicity. J Hepatol 1990; 11:277-278

22 Blum A. Ofloxacin-induced acute severe hepatitis. South Med J 1991; 84:1158

23 Villeneuve JP, Davies C, Cote J. Suspected ciprofloxacin-induced hepatotoxicity. Ann Pharmacother 1995; 29:257-259

24 Soto S, Lopez-Roses L, Avila S, et al. Moxifloxacin-induced acute liver injury. Am J Gastroenterol 2002; 97:1853-1854

25 Kaufman D, Murphy J, Erby L, et al. Veterans' attitudes regarding a database for genomic research. Genet Med 2009

26 Sonnenberg A, Richardson PA, Abraham NS. Hospitalizations for Inflammatory Bowel Disease Among US Military Veterans 1975-2006. Dig Dis Sci 2009

27 Pugh MJ, Fincke BG, Bierman AS, et al. Potentially inappropriate prescribing in elderly veterans: are we using the wrong drug, wrong dose, or wrong duration? J Am Geriatr Soc 2005; 53:1282-1289

28 U.S. Department of Veterans Affairs. VA Information Resource Center. Clinical National Data Extracts (NDEs). http://www.virec.research.va.gov/References/RUG/RUG-DSS00-04.pdf 2008

29 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Decision Support System (DSS). Pharmacy (PHA) Datasets http://www.virec.research.va.gov/References/RUG/RUG-DSSPHAfreq02-03.pdf 2008

30 Kramer JR, Davila JA, Miller ED, et al. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Aliment Pharmacol Ther 2008; 27:274-282

31 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Medical SAS Datasets. http://www.virec.research.va.gov/DataSourcesName/Medical-SAS-Datasets/SAS.htm 2008

32 Schneeweiss S, Robicsek A, Scranton R, et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol 2007; 60:397-409

33 Traversa G, Bianchi C, Da Cas R, et al. Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ 2003; 327:18-22

34 The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Centers of Disease Control and Prevention (CDC). http://www.cdc.gov/nchs/icd/icd9cm.htm.

35 The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). ICD9Data. http://www.icd9data.com/

36 Allison PD. Logistic regression using the SAS system-theory and application. Cary, NC: SAS institute, Inc;. 1999

37 Fischer MA, Winkelmayer WC, Rubin RH, et al. The hepatotoxicity of antifungal medications in bone marrow transplant recipients. Clin Infect Dis 2005; 41:301-307

38 Coban S, Ceydilek B, Ekiz F, et al. Levofloxacin-induced acute fulminant hepatic failure in a patient with chronic hepatitis B infection. Ann Pharmacother 2005; 39:1737-1740

39 FDA Alert. Gatifloxacin (marketed as Tequin) Information. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107821.htm 2006

40 Oliphant CM, Green GM. Quinolones: a comprehensive review. Am Fam Physician 2002; 65:455-464

41 Zhanel GG, Noreddin AM. Pharmacokinetics and pharmacodynamics of the new fluoroquinolones: focus on respiratory infections. Curr Opin Pharmacol 2001; 1:459-463

42 Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174:935-952

43 Fish DN. Fluoroquinolone Adverse Effects and Drug Interactions. Pharmacotherapy 2001; 21 (2):253S-272S

44 Wolfson JS, Hooper DC. Overview of fluoroquinolone safety. Am J Med 1991; 91:153S-161S

45 Hooper D, Rubinstein E. Quinolone Antimicrobial Agents. 3rd edition (August 2003) ed: ASM Press, 2003

46 VISN 20 Formulary Restrictions. http://www.visn20.med.va.gov/wwwrx/restrfile.html?restr=RestrictedtoHIVprescribers. . November, 2006

47 Fluoroquinolones Criteria for Use. **http://www.pbm.va.gov**. March 2006

48 Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. Drug Saf 2009; 32:359-378

49 Coleman CI, Spencer JV, Chung JO, et al. Possible gatifloxacin-induced fulminant hepatic failure. Ann Pharmacother 2002; 36:1162-1167

50 Meropol SB, Chan KA, Chen Z, et al. Adverse events associated with prolonged antibiotic use. Pharmacoepidemiol Drug Saf 2008; 17:523-532

51 Thakur BS, Jain AK, Sirkar S, et al. Ciprofloxacin-induced cholestatic jaundice. Indian J Gastroenterol 2007; 26:51-52

52 Contreras MA, Luna R, Mulero J, et al. Severe ciprofloxacin-induced acute hepatitis. Eur J Clin Microbiol Infect Dis 2001; 20:434-435

53 Schwalm JD, Lee CH. Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient. Cmaj 2003; 168:847-848

54 Wood AJ. Ethnic differences in drug disposition and response. Ther Drug Monit 1998; 20:525-526

55 Yeh GY, Eisenberg DM, Kaptchuk TJ, et al. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care 2003; 26:1277-1294

56 Rothman KJ, Greenland S, Timothy L. Modern Epidemiology. 3rd Edition ed: Lippincott, Williams, & Wilkins, 2008

57 Lomaestro BM. Fluoroquinolone-induced renal failure. Drug Saf 2000; 22:479-485

58 Montagnac R, Briat C, Schillinger F, et al. [Fluoroquinolone induced acute renal failure. General review about a case report with crystalluria due to ciprofloxacin]. Nephrol Ther 2005; 1:44-51

59 Bell NS, Amoroso PJ, Wegman DH, et al. Proposed explanations for excess injury among veterans of the Persian Gulf War and a call for greater attention from policymakers and researchers. Inj Prev 2001; 7:4-9

60 Hoge CW, McGurk D, Thomas JL, et al. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. N Engl J Med 2008; 358:453-463

61 Okie S. Traumatic brain injury in the war zone. N Engl J Med 2005; 352:2043-2047

62 Xydakis MS, Fravell MD, Nasser KE, et al. Analysis of battlefield head and neck injuries in Iraq and Afghanistan. Otolaryngol Head Neck Surg 2005; 133:497-504

63 Moellering R. Hepatotoxicity of antimicrobials: The trovafloxacin story.

The 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; Toronto, Ontario, Canada; ; September 1720, 2000. Abstract 1880

64 Chen HJ, Bloch KJ, Maclean JA. Acute eosinophilic hepatitis from trovafloxacin. N Engl J Med 2000; 342:359-360

65 Mandell L, Tillotson G. Safety of fluoroquinolones: An update. Can J Infect Dis 2002; 13:54-61

66 Aagaard L, Soendergaard B, Stenver DI, et al. Knowledge creation about ADRs--turning the perspective from the rear mirror to the projector? Br J Clin Pharmacol 2008; 65:364-376

67 O'Malley KJ, Cook KF, Price MD, et al. Measuring diagnoses: ICD code accuracy. Health Serv Res 2005; 40:1620-1639

68 Kashner TM. Agreement between administrative files and written medical records: a case of the Department of Veterans Affairs. Med Care 1998; 36:1324-1336

CHAPTER II

Antibacterial use and risk of acute pancreatitis: A Case-Control Study Using the National Veterans Affairs Database

This manuscript will be submitted to the Clinical Infectious Diseases (CID) journal

Abstract

Background: Acute pancreatitis is most commonly seen among persons who have gall bladder diseases or abuse alcohol. Medications, including antibacterial agents have also been reported to cause acute pancreatitis. This requires the Food and Drug Administration to focus on the risk of acute pancreatitis with these medication classes. Although there are many case reports discussing the risk of acute pancreatitis with antibacterial agents, no epidemiological studies have assessed this risk in the United States.

Methods: A matched case control study was conducted among a national sample of patients admitted to all Veterans Affairs facilities between January 1, 2002 and June 1, 2009 to estimate the risk of acute pancreatitis after use of antibacterial agents. A patient case was defined as patient diagnosed with acute pancreatitis and the control was defined as a patient diagnosed with myocardial infarction. Conditional logistic regression was used to compute odds ratios and the 95% confidence interval (CI). Multivariable models were built to adjust and control for the potential clinical conditions or covariates that might influence acute pancreatitis risk. A stepwise forward entry method (non-computer generated) was used to develop the final model.

Results: A total of 10,202 patients with acute pancreatitis and 48,111 patients with myocardial infarction were identified and entered into the analysis. The mean age for cases was 55.6 and the mean age for controls was 64.4, and the majority of the study sample were males (96.5%). After adjusting for all potential confounders, antibacterial

agents use was significantly associated with increased risk of developing acute pancreatitis,. The adjusted odds ratio (AOR) was 1.29 (95% CI 1.18 -1.41).

Conclusion: Among a national cohort of veterans, acute pancreatitis development was associated with antibacterial agent use.

Background and Clinical Significance

Acute pancreatitis is an inflammatory disease that affects the pancreas. It usually affects the pancreatic tissues and in some cases, the inflammation involves the surrounding tissues.[1] The amount of inflammation will vary in severity from mild to severe, to life threatening. Most cases are mild, resolve within days and may only require a short hospital stay. Severe cases may require hospitalized for days and sometimes for months due to organ dysfunction. In addition to variety in severity, acute pancreatitis can occur as a single attack or it can also be recurrent. Acute pancreatitis is associated with 15-35% mortality rate and the incidence of acute pancreatitis has increased worldwide.[2,3] In the United States, it is estimated that about 210,000 patients are admitted to the hospital annually for the disease.[2] One study estimated that an average thirty-nine day hospital stay for acute pancreatitis costs approximately $100,000 .[4]

There are several causes of acute pancreatitis. Gallbladder disease and chronic alcohol consumption are the major causes of acute pancreatitis. Also, hyperlipidemia (hypertriglyceridemia, ≥ 1000 mg/dl), inter-abdominal surgical procedures, trauma from endoscopic retrograde cholangiopancreatography (ERCP), ischemia, chronic hypercalcemia, abdominal trauma, infections, autoimmune, hereditary causes, pancreatic tumor, and medications may increase one's risk for developing acute pancreatitis.[5-14] . In addition, 25% of the pancreatitis cases occur with unknown etiology.[15] Acute pancreatitis has no specific treatment and requires only supportive care to prevent complications.[16-18] Acute pancreatitis is a serious disease due to the

difficulty in diagnosis, limited therapeutic approaches, and poor prognosis with severe cases.

Medication use is one of the main causes of acute pancreatitis with an incidence of 0.1-2%.[19] However, this number may not be accurate because pancreatitis is often misdiagnosed, undiagnosed, and underreported[19]. Most medications associated with acute pancreatitis are based on case reports and few epidemiological studies. Over forty drugs are known to cause acute pancreatitis, they include; angiotensin converting enzyme inhibitors, estrogen, diuretics, exenatide, and antipsychotic are some example of drugs that can induce acute pancreatitis.[15,20-23] Some antimicrobial agents have been associated with acute pancreatitis such as erythromycin, tetracyclines, metronidazole, ertapenem, isoniazide, rifampin and ampicillin.[24-28] Most of the medication risk observed are based on case reports, and there are no known mechanisms to describe how these medications cause acute pancreatitis. Direct toxic or hypersensitivity reaction and pancreatic duct constriction are some suggested mechanisms.

The concern over medication, specifically antibacterial agents, causing acute pancreatitis is important because of the popularity of these agents. Antibacterial agents are used in clinical practice in both community and hospital settings. There is therefore a need to understand and determine these potential medical problems risks of acute pancreatitis associated with antibacterial medications.[23,29]

There are currently a series of epidemiological studies that are assessing the risk of acute pancreatitis with different groups of medication (e.g. statins, ACEIs,

diuretics). These studies predict the risk will continue to increase.[15,23,30] There are few studies that assessed the risk of acute pancreatitis, particularly with antibacterial agents. One study assessed diseases and medications as risk factors of acute pancreatitis.[7] another study investigated the risk of acute pancreatitis with use of metronidazole.[31] The aim of the study is to assess and evaluate the risk of acute pancreatitis with use of antibacterial drugs among a national cohort of patients admitted to Veterans Affairs (VA) facilities.

Methods

Study patients. All patients in VA facilities who were diagnosed with acute pancreatitis in the period between January 1, 2002 and June 1, 2009 were selected in this retrospective case-control design. Acute pancreatitis cases were identified using codes from the International Statistical Classification of Diseases and Related Health Problems, 9th revision (ICD-9-CM). The ICD-9-CM code for acute pancreatitis is 577.00. The study was approved by the Institutional Review Board (IRB) at the Providence VA and the research office at the University of Rhode Island.

Data sources. The Veterans Health Administration (VHA) administrative database was utilized to perform this study. There is data for more than 7.9 million veterans maintained and stored in the Veterans Affairs (VA) medical database, making it one from the largest medical database in the United States. [32-34]. Additionally The VA healthcare system includes more than 180,000 medical personnel operating over 164 hospitals, 800 clinics, and 135 nursing homes as of 2001. Patients' data in the VA database is retained on three levels: the local level, the VA Integrated Services Networks (VISN) level, and the national level. [35] The VA database contains all medical and pharmacy information for each individual in electronic form.[36,37] All diseases, procedures, and surgeries in the VA database datasets are coded using the ICD-9-CM , although some procedures in Medical SAS outpatient datasets are coded using Current Procedure Terminology (CPT). [38] Many studies have validated the disease coding in the VA database. [35,39] All data required for the study were available except for weight and height. Weight and height figures were obtained from corporate

data warehouse (CDW), the national repository containing data from many clinical and administrative systems within the VHA.

Case definition and selection of control subjects. Our case patients were defined as patients who were diagnosed with acute pancreatitis as their primary diagnosis using ICD-9-CM codes. Only the first diagnosis for acute pancreatitis was included in patients who had multiple episodes during the study period. For each case patient, six controls were randomly selected from the population of patients who were diagnosed with myocardial infarction (ICD-9-CM 410.00-410.92) as their primary diagnosis and who do not have acute pancreatitis. Controls were matched to cases based upon month of admission. We selected myocardial infarction as the control group because these patients present with both acute symptoms and serious outcomes, similar to acute pancreatitis. For both cases and controls, any patient with infectious disease as secondary diagnosis was allowed to be included in the study. The date of admission was defined as the index date.

Patients with peptic ulcer, hemorrhagic ulcer, gastritis, patients who had ERCP, abdominal trauma, any type of cancer (including pancreatic cancer), human immunodeficiency virus/acquired immunodeficiency syndrome "HIV/AIDS", chronic pancreatitis, bacteremia, alcohol related diseases, gall bladder diseases, and esophagitis were excluded from the study. Also, patients who were hospitalized during the 180 days prior to the admission date were excluded.

Potential covariates. The covariates that were included in the logistic regression model included age, gender, race, alcohol use (the database indicator entries for alcohol dependency treatment (BEDSECN=725), alcohol-related DRGs (DRG=433), ICD-9 codes (305.0, 303.0, V11.3, V79.1)), co-morbidities, diabetes, alcohol related diseases (liver and mental), and inflammatory bowel disease (IBD).[40] All prescription medication data for cases and controls, including drugs that are associated with acute pancreatitis such as hydrochlorothiazide, prednisone, valproic acid, non-steroidal anti-inflammatory drugs (NSAIDs), and azathiopurine were also controlled in the logistic regression model.[24,40-45]

Exposure definition. Drug exposure was defined as having received a prescription of any antimicrobial drug within ninety days prior to the index date. Antimicrobial medications included the following groups: penicillins, cephalosporins, macrolides, fluoroquinolones, tetracyclines, clindamycin, metronidazole, nitrofurantoin, isoniazide, rifampin, pyrazinamide, ethambutol and trimethoprime/sulfamethoxazole (Table II.1). Drug description variables and the intermediate product number (IPNUM) variable were used to identified patient Medications. Only outpatient oral medications were included in the study.

Statistical Analyses. The main analysis of the current study was to investigate the association between the risk of acute pancreatitis and exposure to antibacterial medications. A chi-square test or Fisher exact tests were used to analyze the categorical data while a student's t-test or Mann Whitney test were used to analyze the Continuous variables for both demographic and clinical data. Odds ratio and their 95% confidence interval (CI) were derived from the conditional logistic regression.

Initially, the potential clinical covariates that would be entered the multivariable model were selected based on bivariate analyses. Covariates with differences of 10% between the cases and controls were included in the multivariable model. Then, the final model was built using stepwise forward entry method (non-computer generated). At each time, a covariate was added, and if the estimated coefficient (ß) of antimicrobial exposure changed by more than 10%, this covariate was kept in the final model. Furthermore, two-way and three-way interactions were assessed. At each step, an interaction term was added to the model, and if the estimated coefficient (ß) of antimicrobial exposure changed by more than 10%, the interaction term was kept in the model. Multicollinearity was assessed using variance inflation factor (VIF). A cutoff of 2.5 for VIF was used to indicate the presence of multicollinearity. All statistical tests were conducted with a two-tailed alpha of 0.05. All analyses were conducted using SAS® version 9.1.3 (SAS® Institute, Inc, Cary, NC).

Results

Between January 1, 2002 and June 1, 2009, a total of 23,899 patients were identified with a primary diagnosis of acute pancreatitis. Inclusion and exclusion criterion for the study were applied to these patients. Among these cases, patients with of any type of cancer, including pancreatic cancer, (n=899), chronic pancreatitis (n= 2,861), HIV or AIDS (n=369), bacteremia (n=578), ERCP (n=295), abdominal injury (n=9), alcohol related diseases (n=1,842), gall bladder or biliary diseases (n=3,528), peptic/hemorrhagic ulcer or gastritis (n=376) and esophagitis (n=2,222) were excluded. In addition, patients who were admitted to the hospital for any medical conditions in the previous 180 days prior to the index date (n=718) were excluded from the study. After application of the exclusion criteria, 10,202 patients were eligible for the analyses.

The Distribution of demographic and clinical characteristics of the cases (patients with acute pancreatitis) and the controls (patients with acute myocardial infarction) can be found in Table II.2. Patients in the case group were younger (mean age 55.6) than the patients in the control group (mean age 64.4). The majority of our population was male. In general, our sample's racial breakdown was mainly white non-Hispanic (58%), followed by black (18.5%). The control group had a higher percentage of white non-Hispanic (63.9%) compared to the case group (52.3%). The case group had a higher percentage of black patients (24.3%) compared to the control group (12.6%). Also, there were more native Americans in the case group (0.50%) compared to the control group (0.30%). There was no difference among Asian and Hispanic races.

The case group differed from the control group in alcohol abuse, hypertriglyceridemia, hypercalcemia, and IBD, while there was no difference in other covariates such as diabetes mellitus and use of comparable prescription medications (Table II.2).

Fluoroquinolones antibiotics were the most used antibiotics among case group patients and control group patients (2.8% and 2.9 respectively), followed by penicillin (2.7% and 2.3%, respectively). Nitrofurantoin (0.03 and 0.08, respectively) and anti-tuberculoses medication (0.04 and 0.05, respectively) were the lowest utilized antibiotics by the study population. Use of sulfamethoxazole/trimethoprim was equal among case group patients and control group patients (0.9%).

Odds ratios (OR) and the 95% confidence intervals (CI) were computed from the adjusted conditional logistic regression model (Table II.3 & Table II.4). After controlling for all of the potential confounders in the multivariable model, there was a statistically significant association between antibacterial use and developing acute pancreatitis. The adjusted odds ratio (AOR) was 1.29 (95% CI 1.18 -1.41), suggesting that patients with acute pancreatitis are 1.29 times more likely to have been exposed to antibacterial agents than control group.

Discussion

The current study utilized a matched case control study design using the national Veterans' Affairs database to investigate the association between the use of antibacterial drugs and acute pancreatitis development. To current knowledge, this is the first epidemiological study to assess this association for all oral antibacterial agents as one group in the United States.

There is a known risk with metronidazole use and the risk of acute pancreatitis. Previous investigations found an association with metronidazole use within thirty days prior to index date (AOR was 3.0, 95% CI 1.4–6.6). [31] Furthermore, they found that patients who used metronidazole with proton pump inhibitors to treat peptic ulcers due to helicobacter pylori and/or using amoxicillin, macrolides, or tetracycline within thirty days prior to index date were at risk of developing acute pancreatitis (AOR was 8.3, 95% CI 2.6–26.4). [31] However, it is important to note that the increased risk in patients with peptic ulcers could be due other confounding factors.

Investigators in Sweden used a population case control study to investigate disease and medication risk factors for acute pancreatitis. The risk of using systemic antibacterial agents was evaluated in addition to several other medication classes. After adjusting all the potential confounders, the AOR was 1.9, 95% CI 1.1-3.2, indicating that systemic antibacterial agents were associated with acute pancreatitis development.[7]

Numerous case reports have linked acute pancreatitis with several antibacterial agents. Penicillins, fluoroquinolones, macrolides, tetracyclines, metronidazole, and

sulfamethoxazole-trimethoprim are some of the antibacterial agents that have case reports associating them with acute pancreatitis. [28,46-56] The majority of these case reports found that patients with acute pancreatitis induced by antibacterial agents were middle aged. This data is consistent with our results. In this study, the patients with acute pancreatitis were younger than the control group. Newer antibacterial agents also have generated case reports of acute pancreatitis. [27,57]

Another report described a case of acute pancreatitis that resulted from using tigecycline, a compound related to tetracyclines.[57] The patient was a thirty five year old male, who had undergone surgery to remove tissue that was infected with *Enterobacter cloacae*. He was initially given tigecycline, imipenem and amikacin. After thirteen days of treatment, he developed upper abdominal pain, and his lipase level was elevated. He was subsequently diagnosed with acute pancreatitis. Tigecycline and amikacin were stopped; the patient's lipase level then started to decrease and he was no longer experiencing any abdominal pain. After five months, his lab tests returned to baseline.

The incidence of drug induced acute pancreatitis is between 0.1-2%.[19] Although the exact mechanism of antibacterial induced acute pancreatitis is still not known, several mechanisms were suggested for different antibacterial groups. The mechanisms for tetracyclines to be associated with acute pancreatitis were suggested as: (1) accumulation of toxic metabolite, (2) hypertriglycerdemia induced by tetracyclines, and (3) increased concentration of tetracyclines in the biliary duct. It is theorized that the formation and accumulation of a toxic tetracycline metabolite is responsible for causing acute pancreatitis, although no metabolite has been identified

yet. [58] Furthermore, tetracyclines inhibit protein synthesis, which could lead to a build up of defective protein within the hepatocyte and inhibit triglyceride release to the liver. This process leads to increased triglyceride levels causing acute pancreatitis. [59] The other possible mechanism is that the high concentration of tetracyclines in the bile is the major reason for tetracyclines induced acute pancreatitis. [57] Minocycline concentration in bile was found to be ten times the concurrent serum concentration.[59] Also, the concentration of doxycycline and tetracycline in the bile reached up to eight times and 10 times the serum concentration, respectively. [60] Further, tigecycline biliary elimination rate is 500 times the plasma rate, which could be a major reason for acute pancreatitis.[59]

An rational for acute pancreatitis and macrolides use has been postulated. It is suggested that macrolides cause acute pancreatitis through their prokinetic property. They stimulate contraction of gastrointestinal tract, resulting in spasms and increased pressure of the sphincter of Oddi and bile reflux. [7,49,61-63] Some medications diffuse directly to the pancreas, leading to acute pancreatitis by direct toxic effect through the release of free radicals like in the case of metronidazole. [19,28,64,65] Immune mediated reaction, hypersensitivity reaction, and toxic effect are suggested mechanisms of drug induced acute pancreatitis in several antibiotics such as sulfonamides, anti tuberculosis medications, and nitrofurantoin. [7,19,66,67] Generally, middle-aged patients are at greater risk of developing acute pancreatitis than elderly patients and black patients at greater risk than white patients, which are both consistent with this study's results. [68]

Antibacterial agents are considered an integral part in the therapeutic plan for acute pancreatitis to prevent the complications of acute pancreatitis such as

bacteremia.[1] However, using antibacterial agents in acute pancreatitis still remains controversial. [69] Using antibacterial agents in patients with acute pancreatitis is based upon results from a randomized clinical trial that found administration of imipenem reduced infectious complications. [70] However, a recent randomized clinical trial that compared ciprofloxacin plus metronidazole to placebo and found there is no difference in outcomes between the two groups.[71] Therefore, routine use of prophylactic antibiotics in acute pancreatitis is not recommended until the patient develops an infection. This study's results also support these recommendations since it was found that antibacterial agents were associated with acute pancreatitis. Thus, unnecessarily giving the patient with acute pancreatitis prophylactic antibacterial agents to prevent infections should be avoided since these medications were associated with acute pancreatitis development.

Several indicators were used to find patients with alcohol use among the cases and controls. These indicators included ICD-9 codes, alcohol dependency treatment indicators, and alcohol-related DRGs. This variable in the model was determined using the previous indicators. The Department of Veterans Affairs (VA) requires an annual alcohol screening for any VA patient.[72] In 2000, the screening rate was 85%, which is considering a high rate.[73] To continue this screening program of VA patients, the Veterans Health Administration (VHA) implemented an evidence-based alcohol screening program. A study done in 2006 found that the screening rate of alcohol misuse was 93%.[74] Additionally, the Computerized Patient Record System (CPRS) at the VA has a reminder for the clinician to perform an AUDIT- consumption (AUDIT-C) questionnaire for alcohol misuse.[74] These programs were established for the

purpose of screening as well as providing counseling to patients with alcohol misuse. Based on these programs, it was determined that virtually all VA patients werescreened for alcohol use.

In any observational study, the potential of confounding by indication should be evaluated. Confounding by indication is when patients with severe diseases and comorbidities were more likely to received antibacterial agents than those with moderate diseases. In this study, patients with major risk factors (e.g. patients with gall bladder diseases and alcohol related disease) and those who had been admitted in the hospital during the last six months prior to the index date were excluded from the study. Additionally, the remaining variables were controlled in the regression model.

This study has several strengths. The use of a very large database provides data for a large sample size. This allowed all exclusion and inclusion criteria that have been identified to be applied. Additionally, many potential confounders such as hypertriglycerdemia, alcohol abuse, and other confounders were controlled.

While this study has several strengths, it also has potential limitations. As with all administrative databases, the pharmacy data describes the dispensed antibacterial agents, but it is not known if the patients were actually administered their medications. Also, the validity of acute pancreatitis diagnosis in the VA databases was not evaluated and assessed in an epidemiological study. The diagnosis of acute pancreatitis may be underestimated and not classified in mild cases.[75] additionally, incideince of drug induced acute pancreatitis is not accurate because it is often misdiagnosed, undiagnosed and underreporting.[19] Furthermore, as with most of

administrative databases, missing data and missing codes are always potential problems. In this study, initial plans included incorporating BMI in the analysis. Weight and height were used to calculate BMI, but up to 48% of the height and weight values were missing. Therefore, it was decided not to include BMI in this study. Additionally, the majority of the population in the study are male veterans, therefore the results may not be generalized to women and non-veteran patients. Finally, as with other observational studies, residual confounding cannot be completely excluded.

Conclusion

In conclusion, it was found that antibacterial medications were significantly associated with increased risk of acute pancreatitis among a large national sample of veterans. In addition, further studies are required to confirm this conclusion and to understand the underlying mechanism of this association. Further research is also required to investigate the role of individual antibacterial agent is in the development of acute pancreatitis.

Table II.1: List of antibacterial agents including in this study.

Antibacterial group	Drug name
Penicillin	- Penicillin VK
	- Amoxicillin
	- Amoxicillin/clavulnate
	- Cloxacillin
Cephalosporin	- Cephalexin
	- Cephradine
	- Cefaclor
	- Cefuroxime
	- Cefprozil
	- Cefixime
Macrolide	- Erythromycin
	- Azithromycin
	- Erythromycin
Fluoroquinolone	- Ciprofloxacin
	- Levofloxacin
	- Moxifloxacin
Tetracycline	- Tetracycline
	- Oxytetracycline
	- Doxycycline
	- Minocycline
Lincosamides	- Clindamycin
Anti-tuberculosis	- Isoniazide
	- Rifampin
	- Pyrazinamide
	- Ethambutol
Nitroimidazole	- Metronidazole
Miscellaneous	- Trimethorpim/Sulfamethoxazole
	- Nitrofurantoin

Table II.2: Demographic and clinical characteristics among patients with acute pancreatitis (cases) and patients with myocardial infarction (controls) in the Veterans Affair database (Jan 2002-June 2009).

	Cases (N=10,202)	Controls (N=48,111)	P
Age, mean (SD)	55.6 (12.3)	64.4 (11.7)	<0.01
Gender (male%)	95.4%	97.9%	<0.01
Race			
White	5,336 (52.3%)	30,723 (63.9%)	
Black	2,479 (24.3%)	6,052 (12.6%)	
Asian	50 (0.49%)	218 (0.45%)	<0.01
Hispanic	335 (3.3%)	1,645 (3.4%)	
Native American	51 (0.50%)	149 (0.30%)	
Unknown	1,951 (19%)	9,351 (19.3%)	
Alcohol abuse*	3,502 (34.3%)	2,247 (4.7%)	<0.01
Comorbidities			
Diabetes Mellitus	3,545 (34.8%)	17,656 (36.7%)	<0.01
Hypertriglyceridemia	970 (9.5%)	1,033 (2.2%)	<0.01
Hypercalcemia	99 (0.97%)	112 (0.23%)	<0.01
Inflammatory Bowel Diseases (IBD)	97 (0.95%)	137 (0.28%)	<0.01
Prescription Medications§			
Prednisone	161 (1.6%)	952 (1.9%)	0.01
Valproic acid	18 (0.18%)	46 (0.10%)	0.03
Azathioprine	13 (0.13%)	38 (0.08%)	0.13
SSRI	791 (7.8%)	3,044 (6.3%)	<0.01
NSAID's	781 (7.66%)	3,693 (7.68%)	0.94
Hydrochlorothiazide	783 (7.67%)	3,649 (7.58%)	0.75
Antifungal	19 (0.19%)	48 (0.10%)	0.02

*Based on ICD-9-CM, alcohol-related DRGs and alcohol dependency indicator

§Medications known to cause acute pancreatitis

Tables II.3: The results of multivariable model showing the risk of acute pancreatitis associated with antibacterial agents used.

Variable	Crude Odds Ratio (95%CI)	Adjusted OR (95% CI)*
Antibacterial agents	1.18 (1.09-1.29)	1.29 (1.18-1.41)
Age	0.94 (0.93-0.94)	0.96 (0.95-0.97)
Gender$	2.14 (1.87-2.47)	2.10 (1.83-2.41)
Race§		
Black	1.83 (1.71-1.95)	1.58 (1.47-1.70)
Hispanic	1.17 (1.02-1.35)	1.16 (0.99-1.35)
Asian	1.48 (1.04-2.12)	1.62 (1.13-2.33)
Native American	1.55 (1.08-2.24)	1.33 (0.89-1.98)
Unknown	1.18 (1.11-1.27)	1.18 (1.11-1.27)
Alcohol abuse	7.32 (6.83-7.86)	7.10 (6.61-7.61)
SSRI	1.18 (1.08-1.30)	1.30 (1.18-1.44)

* Adjusted for all potential confounders in the table

$ The reference group is male gender

§ The reference group is white race

Tables II.4 Estimate of the risk of acute pancreatitis among users of antibacterial agents in a population of veterans.

	Cases (n=10,202) (%)	Controls (n=48,111) (%)	Adjusted OR (95%CI)*
Antibacterial agents	1007 (9.87%)	4485 (9.32%)	1.29 (1.18- 1.41)

* Adjusted for all potential confounders in the table II.3

REFERENCES

1 Carroll JK, Herrick B, Gipson T, et al. Acute pancreatitis: diagnosis, prognosis, and treatment. Am Fam Physician 2007; 75:1513-1520

2 Russo MW, Wei JT, Thiny MT, et al. Digestive and liver diseases statistics, 2004. Gastroenterology 2004; 126:1448-1453

3 Dervenis C, Johnson CD, Bassi C, et al. Diagnosis, objective assessment of severity, and management of acute pancreatitis. Santorini consensus conference. Int J Pancreatol 1999; 25:195-210

4 Soran A, Chelluri L, Lee KK, et al. Outcome and quality of life of patients with acute pancreatitis requiring intensive care. J Surg Res 2000; 91:89-94

5 Megarbane B, Montambault S, Chary I, et al. Acute pancreatitis caused by severe Legionella pneumophila infection. Infection 2000; 28:329-331

6 Lloret Linares C, Pelletier AL, Czernichow S, et al. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. Pancreas 2008; 37:13-12

7 Blomgren KB, Sundstrom A, Steineck G, et al. A Swedish case-control network for studies of drug-induced morbidity--acute pancreatitis. Eur J Clin Pharmacol 2002; 58:275-283

8 Burkey SH, Valentine RJ, Jackson MR, et al. Acute pancreatitis after abdominal vascular surgery. J Am Coll Surg 2000; 191:373-380

9 Lin Y, Tamakoshi A, Hayakawa T, et al. Associations of alcohol drinking and nutrient intake with chronic pancreatitis: findings from a case-control study in Japan. Am J Gastroenterol 2001; 96:2622-2627

10 Freeman ML, DiSario JA, Nelson DB, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc 2001; 54:425-434

11 Carnaille B, Oudar C, Pattou F, et al. Pancreatitis and primary hyperparathyroidism: forty cases. Aust N Z J Surg 1998; 68:117-119

12 Uchida K, Okazaki K, Konishi Y, et al. Clinical analysis of autoimmune-related pancreatitis. Am J Gastroenterol 2000; 95:2788-2794

13 Gallagher P, Chadwick P, Jones DM, et al. Acute pancreatitis associated with campylobacter infection. Br J Surg 1981; 68:383

14 Lin A, Feller ER. Pancreatic carcinoma as a cause of unexplained pancreatitis: report of ten cases. Ann Intern Med 1990; 113:166-167

15 Eland IA, Sundstrom A, Velo GP, et al. Antihypertensive medication and the risk of acute pancreatitis: the European case-control study on drug-induced acute pancreatitis (EDIP). Scand J Gastroenterol 2006; 41:1484-1490

16 Cappell MS. Acute pancreatitis: etiology, clinical presentation, diagnosis, and therapy. Med Clin North Am 2008; 92:889-923, ix-x

17 Despins LA, Kivlahan C, Cox KR. Acute pancreatitis: diagnosis and treatment of a potentially fatal condition. Am J Nurs 2005; 105:54-57

18 Gurusamy KS, Farouk M, Tweedie JH. UK guidelines for management of acute pancreatitis: is it time to change? Gut 2005; 54:1344-1345

19 Balani AR, Grendell JH. Drug-induced pancreatitis : incidence, management and prevention. Drug Saf 2008; 31:823-837

20 Ahmad SR, Swann J. Exenatide and rare adverse events. N Engl J Med 2008; 358:1970-1971; discussion 1971-1972

21 Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. Diabetes Care 2006; 29:471

22 Singh S, Nautiyal A, Dolan JG. Recurrent acute pancreatitis possibly induced by atorvastatin and rosuvastatin. Is statin induced pancreatitis a class effect? Jop 2004; 5:502-504

23 Gasse C, Jacobsen J, Pedersen L, et al. Risk of hospitalization for acute pancreatitis associated with conventional and atypical antipsychotics: a population-based case-control study. Pharmacotherapy 2008; 28:27-34

24 Badalov N, Baradarian R, Iswara K, et al. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007; 5:648-661; quiz 644

25 Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: an update. J Clin Gastroenterol 2005; 39:709-716

26 Eltookhy A, NL P. Drug-induced pancreatitis. CPJ/RPC 2006; 139:58-60

27 Martinez-Granados F, Navarro JN, Estrada JL, et al. Ertapenem-induced acute pancreatitis in a surgical elderly patient. Pharm World Sci 2008; 30:278-280

28 Sura ME, Heinrich KA, Suseno M. Metronidazole-associated pancreatitis. Ann Pharmacother 2000; 34:1152-1155

29 Koller EA, Cross JT, Doraiswamy PM, et al. Pancreatitis associated with atypical antipsychotics: from the Food and Drug Administration's MedWatch surveillance system and published reports. Pharmacotherapy 2003; 23:1123-1130

30 Thisted H, Jacobsen J, Munk EM, et al. Statins and the risk of acute pancreatitis: a population-based case-control study. Aliment Pharmacol Ther 2006; 23:185-190

31 Norgaard M, Ratanajamit C, Jacobsen J, et al. Metronidazole and risk of acute pancreatitis: a population-based case-control study. Aliment Pharmacol Ther 2005; 21:415-420

32 Kaufman D, Murphy J, Erby L, et al. Veterans' attitudes regarding a database for genomic research. Genet Med 2009

33 Sonnenberg A, Richardson PA, Abraham NS. Hospitalizations for Inflammatory Bowel Disease Among US Military Veterans 1975-2006. Dig Dis Sci 2009

34 Pugh MJ, Fincke BG, Bierman AS, et al. Potentially inappropriate prescribing in elderly veterans: are we using the wrong drug, wrong dose, or wrong duration? J Am Geriatr Soc 2005; 53:1282-1289

35 Kramer JR, Davila JA, Miller ED, et al. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Aliment Pharmacol Ther 2008; 27:274-282

36 U.S. Department of Veterans Affairs. VA Information Resource Center. Clinical National Data Extracts (NDEs). http://www.virec.research.va.gov/References/RUG/RUG-DSS00-04.pdf 2008

37 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Decision Support System (DSS). Pharmacy (PHA) Datasets

http://www.virec.research.va.gov/References/RUG/RUG-DSSPHAfreq02-03.pdf 2008

38 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Medical SAS Datasets. http://www.virec.research.va.gov/DataSourcesName/Medical-SAS-Datasets/SAS.htm 2008

39 Schneeweiss S, Robicsek A, Scranton R, et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol 2007; 60:397-409

40 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Medical SAS Datasets -Inpatient Datasets 2006

41 Kaurich T. Drug-induced acute pancreatitis. Proc (Bayl Univ Med Cent) 2008; 21:77-81

42 Rion RJ. Recurrent pancreatitis after treatment with hydrochlorothiazide. J Am Board Fam Pract 1994; 7:74-76

43 Floyd A, Pedersen L, Nielsen GL, et al. Risk of acute pancreatitis in users of azathioprine: a population-based case-control study. Am J Gastroenterol 2003; 98:1305-1308

44 Evans RJ, Miranda RN, Jordan J, et al. Fatal acute pancreatitis caused by valproic acid. Am J Forensic Med Pathol 1995; 16:62-65

45 Fernandez J, Sala M, Panes J, et al. Acute pancreatitis after long-term 5-aminosalicylic acid therapy. Am J Gastroenterol 1997; 92:2302-2303

46 Sammett D, Greben C, Sayeed-Shah U. Acute pancreatitis caused by penicillin. Dig Dis Sci 1998; 43:1778-1783

47 Torosis J, Vender R. Tetracycline-induced pancreatitis. J Clin Gastroenterol 1987; 9:580-581

48 Nicolau DP, Mengedoht DE, Kline JJ. Tetracycline-induced pancreatitis. Am J Gastroenterol 1991; 86:1669-1671

49 Fang CC, Wang HP, Lin JT. Erythromycin-induced acute pancreatitis. J Toxicol Clin Toxicol 1996; 34:93-95

50 Alberti-Flor JJ, Hernandez ME, Ferrer JP, et al. Fulminant liver failure and pancreatitis associated with the use of sulfamethoxazole-trimethoprim. Am J Gastroenterol 1989; 84:1577-1579

51 Bartels RH, van der Spek JA, Oosten HR. Acute pancreatitis due to sulfamethoxazole-trimethoprim. South Med J 1992; 85:1006-1007

52 Brett AS, Shaw SV. Simultaneous pancreatitis and hepatitis associated with trimethoprim-sulfamethoxazole. Am J Gastroenterol 1999; 94:267-268

53 Mann S, Thillainayagam A. Is ciprofloxacin a new cause of acute pancreatitis? J Clin Gastroenterol 2000; 31:336

54 Mennecier D, Thiolet C, Bredin C, et al. [Acute pancreatitis after treatment by levofloxacin and methylprednisolone]. Gastroenterol Clin Biol 2001; 25:921-922

55 Dominguez Jimenez JL, Bernal Blanco E, Marin Moreno MA, et al. [Acute pancreatitis associated with levofloxacin]. Gastroenterol Hepatol 2009; 32:323-324

56 Cheung O, Chopra K, Yu T, et al. Gatifloxacin-induced hepatotoxicity and acute pancreatitis. Ann Intern Med 2004; 140:73-74

57 Gilson M, Moachon L, Jeanne L, et al. Acute pancreatitis related to tigecycline: case report and review of the literature. Scand J Infect Dis 2008; 40:681-683

58 Steinberg WM. Acute drug and toxin induced pancreatitis. Hosp Pract (Off Ed) 1985; 20:95-102

59 Hung WY, Kogelman L, Volpe G, et al. Tigecycline-induced acute pancreatitis: case report and literature review. Int J Antimicrob Agents 2009; 34:486-489

60 Zhanel GG, Homenuik K, Nichol K, et al. The glycylcyclines: a comparative review with the tetracyclines. Drugs 2004; 64:63-88

61 Schouwenberg BJ, Deinum J. Acute pancreatitis after a course of clarithromycin. Neth J Med 2003; 61:266-267

62 Gonzalez Carro P, Perez Roldan F, Legaz Huidobro ML, et al. Acute pancreatitis and modified-release clarithromycin. Ann Pharmacother 2004; 38:508-509

63 Fiorucci S, Bosso R, Morelli A. Erythromycin stimulates gallbladder emptying and motilin release by atropine-sensitive pathways. Dig Dis Sci 1992; 37:1678-1684

64 Wallace JR, Cushing RD, Bawdon RE, et al. Assessment of antimicrobial penetrance into the pancreatic juice in humans. Surg Gynecol Obstet 1986; 162:313-316

65 Sanford KA, Mayle JE, Dean HA, et al. Metronidazole-associated pancreatitis. Ann Intern Med 1988; 109:756-757

66 Jin CF, Sable R. Isoniazid-induced acute hepatitis and acute pancreatitis in a patient during chemoprophylaxis. J Clin Gastroenterol 2002; 35:100-101

67 Rabassa AA, Trey G, Shukla U, et al. Isoniazid-induced acute pancreatitis. Ann Intern Med 1994; 121:433-434

68 Fagenholz PJ, Fernandez-del Castillo C, Harris NS, et al. National study of United States emergency department visits for acute pancreatitis, 1993-2003. BMC Emerg Med 2007; 7:1

69 Whitcomb DC. Clinical practice. Acute pancreatitis. N Engl J Med 2006; 354:2142-2150

70 Pederzoli P, Bassi C, Vesentini S, et al. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 1993; 176:480-483

71 Isenmann R, Runzi M, Kron M, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004; 126:997-1004

72 Desai MM, Rosenheck RA, Craig TJ. Screening for alcohol use disorders among medical outpatients: the influence of individual and facility characteristics. Am J Psychiatry 2005; 162:1521-1526

73 Barry KL, Blow FC, Willenbring ML, et al. *Implementation of a Screening and Brief Alcohol Intervention Program: National Survey and Feasibility Study.* Ann Arbor, Mich: Dept of Veterans Affairs, Veterans Health

Administration, Health Services Research and Development; November 30, 2001.

74 Bradley KA, Williams EC, Achtmeyer CE, et al. Implementation of evidence-based alcohol screening in the Veterans Health Administration. Am J Manag Care 2006; 12:597-606

75 Yadav D, Eigenbrodt ML, Briggs MJ, et al. Pancreatitis: prevalence and risk factors among male veterans in a detoxification program. Pancreas 2007; 34:390-398

CHAPTER III

Review the healthcare databases in United States and European countries that are commonly utilized in conducting epidemiologic research

This manuscript will be submitted to the Pharmacoepidemiology and Drug Safety (PDS) journal

Abstract

Medical databases play a major role in conducting pharmacoepidemiological studies. They are used to perform descriptive and observational studies. Having an ideal database is challenging and not easy to find, especially in countries lacking a universal healthcare system. Countries with a social healthcare system have the ideal environment to have an ideal medical database. There are many medical databases in the U.S as well as Europe and other countries worldwide. Each database has its own structure with unique variables included in that database. Also, each database has its own strengths and limitations, giving each one the ability to answer different research questions. In this review, four databases will be investigated. Two databases from the U.S., the NIS-HCUP database and the VA database, and two databases from Europe, the THIN database and the Norwegian databases are included in this review. In addition to providing detailed information on each database, the purpose of this review is to explain the differences between the U.S databases and Europe databases and the benefit of having a social healthcare system in the competence and validity of these databases.

Introduction

Computerized healthcare database or medical databases contain a variety of information that can be used for descriptive and observational studies. These medical databases provide sufficient information to answer research questions related to health, including diseases, drug therapies, and beneficial and adverse effects to drug therapies.[1] The strengths and weaknesses of each database vary and are limited to the data collected and the quality of the input.

Healthcare databases are divided into medical record databases and administrative databases. Various healthcare databases are available in United States (U.S.) as well as in other countries.[2] The Veterans Affairs (VA) database, Group Health Cooperative of Puget Sound, Medicaid, and Kaiser Permanente Medical Care Programs are some examples of healthcare databases in the U.S. In Europe, there is generally a universal healthcare system, and large collective databases making for are an ideal database to study where complete healthcare information is needed.

The ideal healthcare database would include inpatient care, outpatient care, emergency care, mental health care, laboratory tests, radiological tests, prescribed and over the counter (OTC) medications, and alternative therapies.[2,3] In addition to medical information, the availability of economic data (direct and indirect medical costs) increases the capability of the database, especially when pharmacoepidemiologic and pharmacoeconomic studies are being performed.

With a wide variety of healthcare databases available to the researcher, many research questions can be answered by comparing the research question to the different components of the various databases.

We conducted a comprehensive review of four different globally available databases. We will describe each database, identify the advantages and disadvantages, and the type of research questions that can be answered using the database. Included in this review are two databases from the United States (The Nationwide Inpatient Sample-Healthcare Cost and Utilization Project (NIS-HCUP), and the Veterans' Affairs (VA) Medical Database), the Health Improvement Network (THIN) from the United Kingdom, and the Norwegian medical databases. A lack of publically available resources on the Canadian and Japanese medical databases limited our attempt to critique them in this review.

The Nationwide Inpatient Sample-Healthcare Cost and Utilization Project (NIS-HCUP)

The largest all-payer inpatient care database in the United States is said to be the Nationwide Inpatient Sample (NIS) medical database. It was created under the Healthcare Cost and Utilization Project (HCUP), which is a large family of healthcare databases.[4,5] The Kids' Inpatient Database , the State Inpatient Databases, the State Ambulatory Surgery Databases and the State Emergency Department Databases are also members in HCUP databases. The HCUP is federally supported and sponsored by the Agency for Healthcare Research and Quality (AHRQ).[6] The NIS database released its first dataset in 1988, which at that time, included information from eight states. State participation increased considerably and in 2007, AHRQ collected data from 1,044 hospitals in forty states.[4] This Nationwide Inpatient Sample represents about a 20% stratified sample of all patients admitted to community hospitals in the U.S annually and in 2007, 90% of all hospital discharges in the United States were included in the sampling frame of NIS. To establish a sample that represents the hospitalization in United States, the hospitals selected in NIS were stratified based on five characteristics: U.S. geographic region, bed size, teaching status, rural or urban location, and ownership.[5,7,8] Community hospitals are defined by the American Hospital Association (AHA) as all public, non-federal, short-term hospitals where the average length of stay is less than 30 days. These hospitals have identifiers that connect to the AHA annual survey database and county identifiers that permit linkages to the Area Resource File. [5] This database has been used by many researchers to identify and analyze different national healthcare trends, including, healthcare

utilization, charges, quality, access, and outcomes.[9-11] Since 1988 all datasets are publicly available to conduct research projects and to analyze information regarding different types of diseases and medical conditions as well as other aspects of health. One of the main advantages of NIS is the ability to run an analysis of trends over time.[4] In 1988, the estimated number of discharges was slightly over 35 million observations in comparison to 39 million discharges in 2005. This database continues to grow. NIS contains a significant amount of data, including information that cannot be studied in other medical databases, specifically, it contains information on rare diseases such as autoimmune hepatitis; uncommon treatments such as organ transplantation; and special groups of patients, such as the uninsured patients.[4,12]

Essential elements of NIS

The information included in NIS consists of patient hospitalization admission and discharge information. NIS has more than 100 clinical and nonclinical data components for each hospital admission. These elements include primary and secondary diagnoses, primary and secondary procedures, admission source, discharge destination, payment source, and hospital characteristics (hospital size and teaching status) (Tables III.1). [4,8] Descriptive data regarding patient demographics, include age, gender, race, and the median income for each area (via zip code) is also included.

In addition, other elements have been added, such as all patient refined diagnosis related groups (APR-DRGs), all payer Severity-Adjusted Diagnosis related groups (APS-DRGs), disease staging, and AHRQ co-morbidity indicators.[4] The typical discharge abstract includes all clinical and resource use information, which are

all protected to safeguard the privacy of the individual patient, physician, and hospital. The confidentiality of individuals' information is achieved by using two procedures: (1) no patient identifiers are included in the discharge abstracts or other parts of the database, and (2) researchers or users of the database agree, through data use agreement, to use the data for research and statistical purposes without any attempt to identify individuals. [4,6,13] Nevertheless, NIS excludes any data elements that could directly or indirectly lead to the identification of individuals. The identity of some institutions can be released when the data resources of these institutions are available to the public or there is an agreement to release the information. [4,13,14]

Using NIS

Like most U.S medical databases, all diagnoses in NIS database are recorded using administrative data. The NIS uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and up to 15 diagnoses are recoded.[8,15] To enable researchers to perform a study that spans multiple years, NIS created NIS- trends supplemental files (NIS-Trends). It is recommended to include only years after 1993 to perform study with trend analysis.[12] Since NIS is a uniform, multiple-year and multi-state database, it could be used to explore different topics such as quality of care, medical treatment effectiveness, or healthcare cost (Table III.2). Furthermore, it is useful for answering research questions related to patient outcomes, cost of hospital care provided to specific populations, cost of treating different types of diseases, and other salient healthcare questions (Table III.3). [4,16]

The diversity of the NIS database and the extensive data available attracts many profit and non-profit organizations' researchers to utilize this data source. State and federal government agencies, healthcare consultants, hospitals, and healthcare systems are the main users of NIS (Table III.4).[4]

Access to NIS database

NIS datasets can be accessed through the HCUP central distributer (http://www.hcup-us.ahrq.gov/nisoverview.jsp). New data are released each year. This can be downloaded to a desktop computer with CD-ROM reader, and can be run using statistical software packages such as Statistical Analysis System (SAS)®, Statistical Package for the Social Sciences (SPSS)® and Stata®. To obtain the datasets, a NIS Data Use Agreement must be signed to guarantee the privacy and security of individual information. In addition, a dataset charge is assessed, which is considerable inexpensive in comparison to the real value of the datasets. The dataset for year 2006 may cost $200, which includes a set of two CD-ROMs and accompanying documentation. HCUP supports NIS's users with "HCUP User Support" to answer questions through a toll free number and via email.[4]

Advantages and limitation of the NIS database

NIS is the largest all-payer inpatient database in the United States[5,6] It is unique because it has data documentation containing many variables for a large number of patients. It started in 1988, making it a useful database to perform analysis of trends over time. It also covers thirty eight states, and it samples 90% of all hospital discharges in the United States, allowing for appropriate representative of the US

population. Other reasons that make NIS a valuable database include its ability to study rare diseases due to the large number of documented patients and to perform studies in different areas such as healthcare cost, epidemiology of diseases, access to care, quality of care, and health outcomes with the information regarding different sources of insurance (e.g. Medicaid, Medicare, private insurance companies) and uninsured patients. On the other hand, NIS has some limitations. One major limitation is the lack of pharmacy data therefore, performing studies related to medications is not possible.[17] In addition, data outside the hospital system (i.e. outpatient physician office) is not available. NIS database does not include data on alcoholism and drugs abuse and the data on race and ethnicity is incomplete in some states (Table III.5).[5]

Veterans Affairs Medical Database

The Veteran Health Administration (VHA) is a part of the United States Department of Veterans Affairs (VA). VHA services began in 1777 when the first federal hospital was built in Pittsburgh. [18] The hospital originally offered surgical services to military personnel. [19] Between 1916 and 1945, the VA hospitals broadened their medical expertise and the number of hospitals increased. [19 20 21] After 1980, the VA expanded into a powerful health system in the United States by opening and operating numerous hospitals, outpatient clinics, medical centers, and long-term health care facilities across the country. Currently, the VA operates 163 medical centers, 909 ambulatory care and community-based outpatient clinics, 232 Veterans Centers, 137 nursing homes, 108 comprehensive home-care programs, and 47 residential rehabilitation treatment programs, providing high quality medical, surgical, and rehabilitative care. [22,23]

The Veterans Affairs (VA) medical database is considered from the largest medical databases in the United States. [24-26] It contains information for more than seven million veterans and their dependents.[22,27] The large number of patients in the VA medical database makes it a very unique database that can address many research questions.

VA structure and information center

The VA database maintains patients' data on three tiers: the local level, the VA Integrated Service Networks (VISN) level, and the national level. The local level refers to the patient data in the Veterans Health Information Systems and Technology Architecture (VistA) system, which is usually one medical facility. The second level is VISN level, whereby VHA structured and grouped medical facilities across the country are divided into 21 VISNs. VISNs are classified based on their geographical area. The VISN database contains data from multiple VistA giving it more data than the local level but less data than the national level. For the purpose of research in a specific health or medical field, the appropriate choice would be the national level database. The national level is a combination all local facilities stored in a central location. National data is maintained by The National Data Systems (NDS) Division of Information Assurance, VHA Office of Information. [28] Housed in Austin, Texas, the Austin Information Technology Center (AITC) is the central location for the national level database, and the VA's centralized computer-processing center. [28,29]

The VA Information Resource Center (VIReC) is responsible for assisting researchers on how to use the database and giving full information about the datasets in AITC. In addition, VIReC provides detailed information in different areas such as requesting access to the datasets, programming tips, and how to connect to the Austin mainframe to run analyses. [14,30] All medical variables are described in detail and determined in which file these variables are available. [14]

Data structure

There are different data sources within the VA database that can be utilized by researchers to conduct their studies (Table III.6). [31,32] Each separate data source has different types of information that helps to conduct several types of studies (medical and non-medical). This review will focus on VA Decision Support System (DSS) (production data and National Data Extracts) and the VHA Medical SAS® Datasets because they are the most utilized datasets. [31]

The VHA Medical SAS Datasets

The VHA Medical SAS® Datasets include all of the healthcare utilization information for veterans who have been treated in VA hospitals or other treatment facilities. These datasets include information on non-veterans such as VA employees and research participants. [33] These data are extracted from national patient care database (NPCD) and provided in SAS® format for each fiscal year (Oct 1 – Sep 30). All VHA Medical SAS® Datasets are stored on an IBM mainframe computer at the Austin Information Technology Center and maintained by the VHA Office of Information at the same center. Patient information transmitted from the local VistA to the Austin Automation Center (AAC), where it is converted to SAS format.

The VHA Medical SAS® datasets include two major datasets: Medical SAS® Inpatient Datasets and Medical SAS® Outpatient Datasets. [33,34]

Medical SAS® Inpatient Datasets

The Medical SAS® Inpatient Datasets have four main categories for inpatient admissions: acute care, extended care, observation care, and non-VA care. Within each type of care, there are four datasets: main, bed section, procedure, and surgery. All the categories have these four datasets (main section, bed section, procedure section and surgery section) except observation care, which has only main, bed section and procedure. The definitions of these datasets are illustrated in Table III.7. [14,33]

The main section dataset includes most of the important inpatient variables, such as demographic data, socioeconomic data, and clinical data. It includes one principal diagnosis, or the condition causing the patient admission to the hospital and up to twelve secondary diagnoses. Other variables included in the datasets are date of admission and date of discharge (time, date, month and year), date of death, drug related group (DRG), race , ethnicity, source of admission, and VISN number. Bed section dataset refers to the patient care that is provided by treating specialty during the inpatient stay and does not refer to a physical location of care, it has variables related to the bed section, such as admission and discharge date and DRG for bed section. It also has one primary diagnosis or the main reason for the full stay in bed section, and up to four secondary diagnoses. It has very unique variables not contained in other datasets, including a drug abuse indicator and a suicide indicator. The procedure dataset contains data for each procedure performed during the inpatient stay. It includes up to five procedure codes for the diagnosis, admission, and discharge dates and other procedure variables. The surgery datasets contain up to five surgery codes for the diagnoses, date of admission and discharge, and other variables related to

surgery. A Scrambled Social Security Number (SCRSSN) is used as an Identification Number (ID) for each patient to protect patient privacy. All of these datasets can be combined using SCRSSN. [35]

Medical SAS® Outpatient Datasets

The Medical SAS® Outpatient Datasets include patient information that is available in the VHA's ambulatory care. This data is collected and stored at the Austin Information Technology Center (AITC). This data is transferred from each local VistA and organized "electronically" at AITC. This data is updated by AITC every two weeks. Medical SAS® Outpatient Datasets include three datasets; visit dataset, event dataset, and inpatient encounter datasets. The visit dataset was created in 1980 and contains information about each day's outpatient care encounter. It contains all patient's demographic data and clinic stop codes (up to fifteen codes) for a day's care. Any patient who has been seen in any of the VA outpatient clinics has a record. The event dataset was created in 1997 and contains information for each ambulatory clinic stop by a patient during a day's outpatient care. The event dataset is larger than the visit dataset in the number of variables and has no limited number of clinic stops. It has information regarding patients' demographic data and procedures and surgery performed in an outpatient setting. There is one primary diagnosis and nine secondary diagnoses. The inpatient encounters dataset includes information about each outpatient encounter during an inpatient stay. It is similar to the event dataset, although it does have more variables. It is the only dataset among outpatient datasets that contains the admission date and discharge date. [30,36]

Coding system

All diseases, procedures, and surgeries in the Medical SAS® Inpatient Datasets are coded using ICD-9-CM. The ICD-9-CM is also used to code diseases and surgeries in Medical SAS® Outpatient Dataset while Current Procedure Terminology (CPT) is used to code procedures. Smoking and substance abuse are very important issues in any dataset; there are different sources of coding for these variables, using ICD-9-CM in Medical inpatient dataset "in main and bed section" to find the patients who are smoker or substance abuser. In addition there is a substance abuse indicator in bed section. In medical outpatient datasets, these variables can be captured using ICD-9-CM in Visit dataset while clinic stop coded can be used in both Event and Inpatient Encounter datasets.[35-37]

VHA Decision Support System (DSS)

The VHA Decision Support System (DSS) is a national system using specific software to integrate clinical and financial data for both inpatient and outpatient care. This software transports the patient data from three main resources: VistA, NPCD, and Patient Treatment File (PTF). VHA DSS was created in 1994 and completed in 1999. It has three levels of aggregation: VHA DSS Production databases, VHA DSS Report summary, and VHA DSS National Data Extracts (NDE). [38]

VHA DSS Production Databases

DSS production database contains data regarding costs; clinical information, such as resource utilization and patient outcomes; and workload captured over different levels (e.g. encounter, day and laboratory results). The software also has tools to help the researcher or the team staffs to perform a variety of analyses. The researcher can study a pattern of care for inpatient stay, following a cohort of patients with a specific outcome over time; study a specific topic related to laboratory results; or a multitude of similar research questions.[37,38]

VHA DSS Report summary

DSS report summaries are provided by the VISN Supported Service Center (VSSC). These reports are made using National DSS SAS Datasets and can be accessed and downloaded through the VA intranet website. Hundreds of reports are available in the VA intranet, such as average patient cost, costs by DRGs, and other reports.[37]

VHA DSS National Data Extracts (NDE)

VHA DSS NDE has been created by co-working between the DSS Program Office and the VHA VSSC selected database fields. These NDE datasets are created in SAS format and each dataset is released in January for the fiscal year that ends on September 30th. DSS SAS NDE are stored and housed in AAC (Table III.8). [37,38]

In this review, Pharmacy National Data Extracts, Laboratory National Data Extracts, and Laboratory Result National Data Extracts will be discussed in detail.

The Radiology National Data Extracts are very similar to the datasets that are included in the review; it has the same sources, structure, and some similar variables.

Pharmacy National Data Extracts

Pharmacy datasets are often the largest component of the database, forcing them to be separated based on VISN. In 2002 and 2003, the pharmacy datasets were divided based on group of VISNs (e.g. VISN 1 – 5 Inpatient, VISN 6 – 10 inpatient, VISN 11-16, VISN 17-22 and the same arrangement for outpatient files), but starting in 2004, these datasets were divided based on each individual VISN combining both inpatient and outpatient (e.g. VISN 1, VISN 2 consecutively through VISN 23). These datasets include records of every prescription filled by a VA outpatient pharmacy or by the Consolidated Mail Outpatient Pharmacy (CMOP), each inpatient unit dose order, and every IV solution that is dispensed from a pharmacy. Ward stock medications, Bar Code Medication Administration (BCMA) packages, and controlled substances are not included in these datasets. [37,39]

Different sources, including the VistA Pharmacy Prescription File, the Unit Dose Extract File, and the IV Extract File, are used to collect the medication data. DSS files are the source for all information pertaining to costs. Patient demographics are collected from patient's file, and encounter information is collected by VistA Patient Care Encounter file (PCE). [37]

In addition to pharmacy data, both the direct cost (e.g. drug cost) and the indirect cost (e.g. the indirect costs of medical center) are included in the dataset. Other datasets inside NDE, including the Outpatient Extract, Inpatient Discharge

Extract, and Inpatient Treating Specialty Extract, have some pharmacy cost information. This additional information is one of the major strengths of these datasets as it is not available in many non-VA databases.[40,41]

In the dataset, there is one section for inpatient encounter records and another section for outpatient encounter records. The inpatient encounter records contain all inpatient pharmacy prescription starting from admission until discharge. The outpatient encounter records contain all outpatient pharmacy prescriptions. In these datasets, there are more than thirty seven variables that include demographic, medication, and cost data. Most of these variables use a code unique for pharmacy datasets, such as VA_Class, Intermediate Product Number (IPNUM) , INOUT. IPNUM variable refers to the DSS product number that is assigned to each drug. IPNUM can be used to identify a patient's medications and the drug description variable (DRUGDESC). These variables are updated every time for easy use (Table III.9). [37,42]

These datasets are very useful to conduct many researches because they have all of the important medication information, including the name of the drug. National Drug Code (NDC), formulary indicator (formulary Vs non-formulary), fill date (service date), quantity dispensed, all cost types, patient SCRSSN, age, gender, provider identification number , and provider treating specialty.[37,43]

The DSS Pharmacy NDEs are a major source for researchers to conduct research requiring information on medications. They are not the only datasets that include medication information, but they are the largest.

Other pharmacy resources

In addition to the DSS Pharmacy National Data Extract, other important resources include VISTA system, DSS National Pharmacy Extract "Planned" datasets, and the Pharmacy Benefits Management (PBM) group. [41,44]

Laboratory National Data Extracts and Laboratory Results National Data Extracts

Laboratory National Data Extracts and laboratory results National Data Extracts were created in 2002 and 2000, respectively. As in Pharmacy NDEs, these datasets have been divided based on groups of VISNs until 2003. After 2003, these datasets were produced for each individual VISN (e.g. VISN1…VISN23).[37] Laboratory NDEs include all laboratory workload data and the cost of these laboratory tests. The laboratory tests and laboratory results are entered at the individual level for both inpatient and outpatient encounters. [43]

The major source of these extracts is the DSS. DSS records all patient entries in the VistA lab package, which are then transported to laboratory and laboratory result datasets. Each year, DSS posts more tests in the datasets, and by the 2008 fiscal year, these datasets included seventy one of the most commonly ordered tests. The result of these seventy one laboratory tests are extracted from the laboratory result NDEs. [37,43] VistA system is not the only source for laboratory and laboratory results datasets. Other sources are used to collect demographic, clinical, and economic information. These resources are patient file (#2) , the referral patient file (#67), VistA

patient movement file (#405), VistA patient care encounter file, and DSS processes (Table III.10). [43]

Both datasets have very useful variables that can be used to obtain data related to laboratory tests and laboratory results, including date of admission, date of discharge, time collection of the specimen, date of service, and other variables. Each dataset has its own unique variables, for instance cost data is only found in laboratory datasets. These cost variables include ACT_COST "actual total cost," LAB_VD "laboratory variable direct costs," LAB_FD "laboratory fixed direct costs," and LAB_FI "laboratory fixed indirect costs." Another unique variable is TESTNAME, which is used to determine the name of the test. On the other hand, Laboratory results datasets have DSSLARNO, which is the test number in the laboratory results dataset, and HILO_IND, which is to indicate the abnormality of test results. These two variables are only in laboratory results datasets. Both datasets have the SCRSSN variable for each individual patient to help combine these and other datasets. [37,43,45,46]

The datasets include both inpatient and outpatient laboratory tests and their results. All inpatient laboratory tests and the results are placed in each inpatient encounter record by DSS. The encounter starts from the date of admission until the discharge date. Outpatient laboratory tests and laboratory results that are done in the same day are appointed to a single outpatient encounter regardless of how many tests are performed. Laboratory tests results are presented in a non-numeric field, such as positive or negative, but DSS software does not read non-numeric values. Therefore, these non-numeric values need to be translated into a numeric field to be recognized by DSS software. This step is performed by the DSS Laboratory Results VistA

extract. These translation values (i.e. 0, 1, 2, 3….etc) are placed in the DSS and on the NDE "laboratory results extracts" (Table III.11).

In 2000, DSS started posting the laboratory results. Laboratory test results started with forty tests in 2000 and new tests have been added in each subsequent year. There were nine, one, six and three tests added in 2001, 2002, 2003 and 2004 respectively. In 2008, there were seventy one of the most common tests chosen to be in these datasets (Table III.12).

Access to VA database

To access the VA database, different procedures are required depending on the type of the dataset(s) needed. To access VHA Medical SAS Datasets and VHA Decision Support System (DSS), a Time Share Option (TSO) user account is required. Also, permission is required to utilize the required datasets. A specific form (VA Form 9957) is required to identify and access the required dataset(s). These datasets are housed and maintained by the Austin Information Technology Center (AITC).

Advantages and Limitations

Veterans Affairs medical databases are a unique and comprehensive databases (Table III.13). However, the VA databases have some limitations, such as the validity of ICD-9 for some diseases. For example, based on a study done in 2009, the ICD-9 for gout disease is not accurate.[47] Another study found that using ICD-9 to identify viral hepatitis (type B) is not accurate in the VA database. [48] Nevertheless, many diseases have an accurate ICD-9, such as opportunistic infections and serious bacterial infections, chronic liver diseases, viral hepatitis (type C), HIV, and many other

diseases.[48,49] Not all demographic data such as height and weight is available directly by using medical SAS® databases or DSS databases. The Corporate Data Warehouse (CDW), another medical database, should be used to access these variables. CDW requires researchers to submit certain documents if they require access.

The Health Improvement Network (THIN) database

In the United Kingdom (UK), there are more than fourteen databases containing clinical and demographical data for patients in the UK.[50] Most of European countries, such as the UK, Germany, the Netherlands, and Norway, have a national healthcare system. Having a national healthcare system is beneficial for a comprehensive and ideal healthcare database. In the UK, the National Health Service (NHS) is a government agency that is responsible for health services. One of largest health agencies in European countries, the World Health Organization (WHO) also considers it to be one of the best agencies. It has over 1.3 million employees, including doctors, nurses, and technicians. The entire population is required to be registered with one General Practitioner (GP). Information is transferred if patients switch to a different GP. To facilitate this information sharing, the UK started to compile several databases back in the late 1980s. The General Practice Research Database (GPRD) was formed from the old electronic databases in 1987 by Value Added Medical Products (VAMP) Health. [50,51] The GPRD contains patients' demographic, medical, prescription, and laboratory data. [52] The Health Improvement Network (THIN) database was created in November 2002 and includes patients' data from 1985 until today. [50,52] THIN is a result of collaboration between the two large companies; EPIC and Cegedim. EPIC is a non-profit company that has expertise in providing primary care patient data and facilitates access to electronic research data. In addition to providing a data source for research, THIN was created with the aim to improve the quality and completeness of recording of clinical data in GP practices. It was created by Dr. Alan Dean, who is also the creator of GPRD. His experience in

accessing the primary care research data has played a major role in the development of the THIN database. Cegedim is a European company and parent company of In Practice Systems (INPS), which is responsible for developing and providing the vision practice software.[53,54] This software is the same software that is used by GPRD.[55] and is used by over 95% of the primary care practice and health boards in the UK. [54] Although the THIN database is a new database, it is considered a good alternative resource for medical research since it has informative, valuable, and has complete data for each patient. Considering how new this database is, it has a very high possibility of becoming one of the premier healthcare databases in the UK.

THIN Data

In UK, the general practitioner is considered as gate keeper for the patients as they are required to visit their GP if they need medical assistance. There are only a few exceptions to this rule. When the patient visits the GP, the GP will assess the patient's case and decide to either issue a prescription, refer the patient to a specialist, refer them for tests, refer to an emergency room, arrange for hospital admission, or offer advice. A patient does not need to go to the GP first if he/she is receiving services from an emergency room, a dentist, an optician, or a family planning and sexual health clinic. [56,57] At each practice site, the GP has all the information for the patient using INPS's vision software "general practice management software package." THIN collects a patient's data from participating GP practices without any disruptions to the GP's work. Then, THIN sends all the data on monthly basis to EPIC, and EPIC, in turn, sends the datasets to the interested researchers to conduct their research. [58]All patient data collected by THIN and sent to EPIC are collected

using de-identified information making a patient's identity no longer available in the THIN database. [55] All data collection procedures are approved by the an ethics committee (Southeast Multi-Centre Research Ethics Committee ; MREC). Additionally, all studies that are going to be conducted using the THIN database need to be approved by MREC. In the near future, the approval process will be changed, whereby the scientific protocol review committee (SPRC) will replace MREC. Unless these studies need to collect additional data or need validation, MREC's approval is still required. [53] In April, 2009, the THIN database had data from over 7 million patients (approximately 3 million active patients) from over 386 practices. Some of these practices are also found in GPRD, creating an overlap between GPRD and THIN in some practices. However, the THIN database contains data from practices that have never been in GPRD. [55,59]

THIN database contains demographic, medical, and prescription data at the patient level. THIN provides a longitudinal record for each patient organized at the practice level. Furthermore, the data is arranged in four files, or datasets, and two linked files per practice. The main files contain different patient, medical, therapeutic, and additional health data (AHD) files, and the two linked files are postcode variable indicators (PVI) file and dosage records file. These files were created in 2002 and they contain data for some patients as far back as 1985. [53,58] The patient file contains complete demographic data, including the patient unique identifier, age, year of birth, gender, death date, registration date with the practice, and date of leaving if the patient leaves a specific practice. The medical file contains all health and disease conditions and symptoms recorded at the GP office as well as the patient unique identifier. These

files include the event date, diagnosis, diagnostic data (e.g. X-ray, CT scan, MRI and others), episode type, location of consultation, medical history, and referral data (Table III.14). [53,58,59] If the patient is transferred to secondary care, all the data from their secondary care is sent back to the GP and entered into the system.[58] This data consists of very detailed information including type of specialty; hospital admission; hospital discharge, diagnosis, and medication; outpatient consultation diagnosis; investigation; and treatment outcome. [52,58]

All health conditions and diseases in THIN databases are coded using the READ clinical classification version 2. [60] READ codes are alphanumeric codes that define diseases using a hierarchical nosologic system (Table III.15). [61-65] The code terms used in READ are related to the observations (signs and symptoms), diagnoses, procedures, and laboratory and radiologic tests. [53] The therapy file includes information about prescription data. After the GP enters the prescription data, one copy is sent to the pharmacy and one printed copy is given to the patient to take it to the pharmacy. [58] Using this procedure creates a medication record for each patient that includes all medication prescribed for the patient since his or her first day of registration at the GP office. Medication information in the THIN database includes patient unique identifier, product code, British National Code (BNF), date of prescription, formulation of the drug, dose strength of the drug, indication for treatment, duration of prescription in days, route of administration, prescriber identifier, and prescription type (acute or refill). [52,59] Drugs are coded using First Databank's Multilex® coding system and the BNF coding system (Table III.16). [58,66,67] There are three codes for BNF (BNF code1, BNF code2, BNF code3) each

representing different groups of medications. Therefore, some medications that may have more than one BNF code. For example, aspirin can be classified as a non-steroidal anti-inflammatory drug (NSAID) and an anti-platelet. [68] The above procedure ensures most medications are well recorded in the THIN database with only a few exceptions. Controlled substances, immunizations, and drugs administered during home visits are not issued from the computer but are entered into the system at a later time. Therefore, there is a chance of under-recording these groups of medications. Over the counter (OTC) medications may also be included in the THIN database if the OTC drug has been prescribed by the GP. [58,68,69]

Medication that is prescribed outside the GP office by hospital physicians and specialist physicians usually is not recorded in the system, excluding it from the THIN database. However, if the patient continues to take the medication that he/she started taking in the hospital, the drug will be recorded in the database because the patient will follow up with the GP. [58] Some of the medications data from outpatient specialty care may also be found in the GP summary. [58]

The additional health data (AHD) file contains supplemental information such as patient unique identifier, GP consultations, details from other healthcare interventions, patient's height and weight, allergies, vaccinations and immunization, contraceptive prescriptions, pregnancy, birth details, death details, laboratory tests and results, and life style information including smoking and alcohol intake. [53,59] Recently, the pathology laboratory has been electronically linked to many practices making it easier to record patient tests results and store them in their records.

Some of the data in AHD can be found in other files. For example, data on smoking and alcohol use can be found in medical records, and contraception data can be found in therapy files and in medical files. [68]

In addition to these main files, EPIC creates Postcode Variable Indicators (PVI). PVI files provide unidentified postcodes which link the area based on socioeconomic, ethnicity, and environmental characteristics to help researchers who are planning to conduct a study using THIN to understand the differences between the areas to avoid any potential bias or confounders that could affect the study. Under the PVI file, there are information related to the degree of deprivation, ethnicity, and the degree of pollution (with particulate matter 10 (PM10), sulfur dioxide (SO2) and nitrogen dioxide (NO2). Each one of these three variables is matched to the UK postcode. The ethnicity is categorized into white, black, mixed, Asian, and other.[53,58,59]

Additional information about any patient may be obtained through the Additional Information Service (AIS), which includes information such as death certificate, unidentified questionnaires filled out by the patient or by the GP, and a specific intervention (e.g. specific diagnostic test to confirm a specific diagnosis). [59]

Validation of THIN database

Although the THIN database, created in 2002, is considered a new database, many studies have been conducted using this database.[70-73] Validity of the information in the database needs to be investigated, especially the diagnosis of the diseases. A study in 2006 investigated the validity of THIN database through conducting different

case control studies to study the association between disease and drug use (e.g. peptic ulcer medication and Non-Steroidal Anti-inflammatory Drugs (NSAIDs) use) and between diseases (hypertension and stroke). The results of the four studies were consistent with the information in the literature. Additionally, in their results, they found that the results were identical between the GPRD practices and non-GPRD practice. In their conclusion, they stated that the results of the different studies support the validity of data within the THIN database. [55] Another study, assessed the quality of the THIN database by assessing the quality of the practices that participated in THIN. Two hundred thirty six practice sites agreed to participate. They concluded that all of these practices demonstrated a high level of completeness of recording the clinical information in many of the practices. [74] Recently, many studies have been done to validate the THIN database and it found that the data in THIN database are valid and accurate . [55,75] In addition to these studies, researchers can request EPIC to validate the information of their study using the THIN database. [68]

THIN database files structure

THIN provides the entirety of each file in the American Standard Code for Information Interchange (ASCII) format, a standardized fixed width text format, making it "user friendly" for researchers. THIN database users can load and import the files into different database and statistical software such as Oracle®, Statistical Package for the Social Sciences (SPSS®), Structured Query Language (SQL), Statistical Analysis Software (SAS®), and Microsoft Access® [53]. All of these files have a patient unique identifier (patid) allowing all of the files to be linked together using patid. In addition, all files are sorted by patid and by date.

Access

EPIC is responsible for providing access to the THIN database.[53,59] They facilitate access to the data in several ways. First, they provide raw datasets to the researching organization to perform their own research. They also perform some statistical analysis based on the submitted protocol. Furthermore, they help obtain additional information from the GP and coordinate with AIS Company. EPIC provides the dataset on hard-drives, tapes, and compact discs (CDs).[53,76] Researchers from the UK as well as other countries worldwide can access THIN database to conduct their research. Any researcher wanting to use the THIN database to conduct a study needs to get an ethical approval for their protocol from the UK MERC.

Advantages and limitations of THIN database

The THIN database has many advantages for both the health system in the UK and for research studies (Table III.17). It helps to improve the quality of clinical data recording and, subsequently, will improve the quality of healthcare in the UK. THIN offers many training sessions for the users (GP and researchers) to become familiar with the database. [77] THIN is a computerized database, allowing for the compilation of complete and updated data for each patient. Therefore, any investigator can obtain new and additional patient information for a study. It is a population-based database, so selection bias will be minimized making epidemiological study more valid. [58] In addition, recall and interviewer biases are not a problem since all information that has been collected is not based on patient recall. Additionally, in conducting epidemiological study, the cases and controls are derived from the same type of

population. Therefore, all the criteria inside the database were applied to all patients (including cases and controls). Another advantage of the THIN database is that it contains longitudinal data allowing studies with long follow up to be conducted easily.

Another advantage of THIN database is the size of database. It has a large number of patients enabling many health conditions, including rare conditions, to be studied. The THIN database has been validated through many studies, and these studies have found the information inside THIN database to be valid and complete. [55,75] This is one of the important issues for any database. However, additional studies are still needed to validate different disease states.

Finally, researchers have the ability to access the original medical records pertaining to the topic being studied. The researcher can request a copy of a patient's medical record (non-electronic). There will not be any identification for the patient on the medical record, but this service can help the researcher in many aspects such as validating the information and getting detailed information about the patient. [68]

However, there are some disadvantages to using the THIN database. As a UK population database, THIN database has several limitations: first, it can only be generalized to UK population, not other populations. Secondly, the data in the THIN database may not be complete enough given the fact that there are a lot of communications between the GPs and specialists and hospitals that may not be found in the database. Some conditions and symptoms may not be found in the THIN database such as headache and cold symptoms, especially if the GP did not prescribe any medication for the patient. In addition, information about OTC medications are

not available in the databases except if they were prescribed by the GP. Also, medications that were prescribed by specialists may not be found in the database. Psychiatry medications may also not be found if the patients were treated by community mental health teams. As with many databases, obtaining complete race and ethnicity information is still a problem with the THIN database. ethnicity information is available but incomplete.[78] Finally, the THIN database is very costly, and the researcher must pay extra for additional services (i.e. accessing non electronic medical records).

The Norwegian Medical Database

Norway, a Scandinavian country in Europe, has a population of 4.8 million as of 2009. [79] The population has increased by 1. 5 million since 1950. [80] This increase in the growth rate was caused by a rising birth rate, prolonged life expectancy, and an increased number of immigrants to Norway. Norway is considered to be among the highest ranked nation in the number of immigrants. Norway has many strengths in its educational and economic systems. [81] More than 57% of the population aged 16 and more had completed their secondary school, placing Norway among the most educated countries worldwide. [81,82]

The healthcare system in Norway is structured on three levels: the national level, the regional level, and the local level. The national level is responsible for establishing and providing necessary legislation, determining the national health policy, and funding the health services. [81,83] The regional and local levels are responsible for providing the health care services through a network of hospitals, primary care clinics, psychiatric clinics, pharmacies, outpatient clinics, dental clinics, ambulance services, and other health services. [81] Overall, the regional authority is responsible for specialist healthcare while the local level is responsible for primary health care. The Ministry of Health and Care Services is responsible at the national level. Norway has an excellent environment to have a good healthcare system. Its national health system grants each citizen the right to health services access regardless of their geographic location or economic and social status. [81] This allows each patient to go to the primary care or hospital when he/she is sick. Access to healthcare creates

data about most people's health status that can be used to build a comprehensive database for most of the population in Norway.

The Royal Norwegian Ministry of Health and Care Services (Helse-og omsorgs departementet) is the superior agency that is responsible for providing the healthcare services to the Norway population. There are several agencies that are under the ministry of health umbrella that have an important role in the healthcare system and medical database development in Norway, such as the Norwegian Institute of Public Health, Norwegian Board of Health Supervision, Norwegian Medicines Agency and Norwegian Directorate of Health. [81,84]

Patient pathway

Patients who seek medical advice or therapy must visit the general practitioner (GP) first. Approximately, 99% of the population is registered with one general practitioner. The ministry of health gives the freedom to the patient to choose a GP among from a list in their local area. [81,85] The GP is usually located at the municipality's level and acts as a gatekeeper to further medical care. The GP will take one of the following actions: diagnose the patient and give the suitable treatment or make a referral if the patient needs to be seen by a specialist physician. The specialist physicians are located at the specialized healthcare centers or institutes. The specialized healthcare centers include hospitals and specialized medical services such as laboratory services, radiology services, and special care for alcoholics and or persons with drug addiction. Furthermore, it includes somatic and psychiatry

institutes. [81,84,86] Each regional healthcare authority is responsible for running these centers to deliver high quality specialized healthcare to each patient in the region. [81]

Registries and databases

As mentioned previously, Norway has a good healthcare system to build good registries and databases. In Norway, there are different types of databases that focus on different areas at different levels (i.e. hospital level and population level). The two types of electronic databases at the hospital level are the local electronic level and the national electronic level. At the local electronic level, there is an electronic database in the hospital that includes all patients' information during the hospitalization. This information includes the patient identification number, admission and discharge dates, codes for one primary diagnosis and secondary diagnoses, and codes for surgical procedures performed at the hospital. [87] The national electronic database, "The Norwegian Patient Register," includes patients' information from all hospitals in Norway. The Norwegian Patient Register includes an anonymous patient number, which contains the number for each year and number for the hospital. It also includes one primary diagnosis and two secondary diagnoses. [87,88] More than 90% of the primary care physicians and hospitals already use the electronic health record system (EHR). This method of electronic documentation has many benefits including building the electronic database and reducing the risk of losing important clinical documents. [89]

Other types of specific databases or registries are The Cause of Death Register, The Cancer Registry of Norway, The Medical Birth Registry of Norway, The Norwegian Surveillance System for Communicable Diseases (MSIS), The

Tuberculosis Registry, The Childhood Vaccination Register (SYSVAK) and The Norwegian Prescription Database. [90] Furthermore, there are more specialized registries like the National Injury Register (NIR) and Database over Occupational Injuries and Occupational Diseases (Table III.18). [91] These databases and registries are run by different institutes such as The Norwegian Institute of Public Health, Institute of Epidemiological Cancer Research Statistics of Norway, and The Association of Norwegian Insurance Companies. [90,91] Additionally, there are other discontinued databases that have available data and can still be accessed. [91]

Previous databases were used to establish a new monitoring system that combined many health indicators that make it a comprehensive database (Table III.19). [92] Since the official registries and databases in Norway have the patient unique personal identification number, it became a very useful tool to link these registries together to make this monitoring health system. Additionally, this method assists linking the health information with other information such as education and socioeconomic data. It is called Norhealth, or the Norwegian Health Information System, and it is used to monitor health related conditions over time. Having a system like Norhealth helps to produce a very good health monitoring system and high quality research using the variety health indicators from different types of registries. Norhealth includes basic elements such as population and socioeconomic factors, risk and protective factors, morbidities and diseases, births and abortions, health services and treatment, mortality, determinants of health (lifestyle, biological measurement, vaccination), and social inequalities in health. As of 2008, there are fifty health indicators with over seventy health indicators slated in the future. [92]

The Norwegian Prescription Database (NorPD) "Reseptregisteret"

In Norway, their drug database has different transition levels. In 2000, the Royal Ministry of Health and Care Services decide to established a national prescription registry. The Department of Pharmacoepidemiology was established in 2002 under Division of Epidemiology at NIPH. [93] The Department of Pharmacoepidemiology is responsible for drug consumption in Norway, developing and maintaining the anatomical therapeutic chemical (ATC) classification system, defining daily doses (DDDs) for international use and to run NorPD. Additionally, the World Health Organization (WHO) Collaborating Centre is located at the Department of Pharmacoepidemiology. [94]

In October 2003, the final regulation on the Norwegian prescription database was released to achieve many objectives. The regulation obligates pharmacies in Norway to submit all prescription data "electronically" to NIPH on a monthly basis. [95] The main objective of NorPD is to collect and process the data on drug utilization for both humans and animals. In addition to this main objective, NorPD has several aims (Table III.20). [93,96] In January 2004, all pharmacies in Norway started to send data on dispensed prescriptions to NIPH. Each year, the Pharmacoepidemiology Department at NIPH receives data for over 34 million prescriptions from over 600 pharmacies in Norway. Since all pharmacies have a computerized system for entering and dispensing the prescribed medications, this helps in transmitting the data to NIPH. From NorPD's establishment until 2007, over 150 million records are available for over 4.2 million patients. [93,97]

In NorPD, there are several variables for every record for each element in the prescription pathway (i.e. patient data, prescriber data, drug data and pharmacy data). Some examples of these variables are the patient identification number, patient age and gender, prescriber specialty, prescriber profession, number of drug packages dispensed, ATC codes and DDDs, date of dispensing, and pharmacy name and license number (Table III.21). NorPD has this data for all dispensed prescriptions and over the counter (OTC) medications prescribed by a physician.

Norwegian databases and pharmacoepidemiological research

In addition to being important in conducting a pharmacoepidemiological research, NorPD is used to produce statistics on medications in Norway such as number of medication users; stratification of users by variables such as age, sex, county, and other variables; turn over in dosage; and any statistics about the variables in NorPD. [96]

NorPD can be used alone and with other databases as well. It can be used alone to conduct research related to medications because all variables regarding medications are available in NorPD. Also, it can be used alone to conduct pharmacoepidemiological research given that some medications can be used as proxy for diseases in cases where there is no data about diagnosis. The main advantage in Norway is that most of the databases contain the patient's personal identification number allowing these databases to be linked together using the patient identification number. [93,98] NorPD can be linked to several other databases. For example, a researcher could study the protective effect of some medications on different type of

cancers by linking NorPD with the Cancer Registry or the negative effect of medications used during pregnancy can be studied by linking the Medical Birth Registry with NorPD. This feature makes the structure of the health system in Norway unique and the epidemiological research very applicable and beneficial. Since the establishment of NorPD, many pharmacoepidemiological studies and reviews have been conducted. Since the first publication in 2004, the number of publications has increased through the years reaching up to twenty five publications in 2007. [99] In the period of 2004-2009, a total of around 50 publications had utilized NorPD. [98] This number is expected to increase due to the increased popularity of the database and the facilities presented by Norwegian Institute of Public Health.

Accessing NorPD

The Norwegian Institute of Public Health facilitates the access of NorPD for researchers who are interested in conducting pharmacoepidemiological research. The researchers can access the data without paying any charges for the data itself. The researcher will only pay if there is any administrative work or file processing that must be done in order to obtain the data. In case where statistics related to the medication pattern used in Norway, NorPD has a website that includes all information related to the database, and from that website, one can create a report related to any variable related to medications (http://www.norpd.no/Prevalens.aspx). [93,100]

NIPH requires detailed information about the researcher, co-researchers, the institute, and the protocol of the study to make sure that the aim of the study is compatible with the NorPD's aims. [98]

Advantages and limitations

The health system in Norway has many factors that make it one of the most unique health systems worldwide. These factors help to establish and maintain distinctive databases and registries. It is well known that having a national "social" health system is considered an important factor to have an ideal health database. [2,3] Norway has several advantages pertaining to the databases. It has several databases that specialized in areas such as cancer, medical birth, death, and communicable and non-communicable disease. Having a specialized database in each area, it is important to have a patient's complete and comprehensive data within these specialized databases. For instance, the data in the cancer registry is almost 100% complete. [101] In addition to having specialized databases, Norway has more than eight databases that cover most health areas in addition to medication data. Since most individuals are registered within one primary care clinic, most patients have their health information in these databases. Therefore, any study done using these databases will be considered externally valid (i.e. can be generalized to the Norwegian population) All these databases have the eleven-digit personal identification numbers (person nummer) that makes it easy to link all these databases together simply by using this number. Therefore, it is possible to conduct different epidemiological researches in different areas. In addition, performing a system of monitoring allows researchers to follow the trend of the diseases in Norway, and post-marketing surveillances to detect the signals for adverse drug reactions as well. Furthermore, it is a relatively inexpensive database for researchers to access.

Like other countries' databases, Norwegian databases have some limitations. The validity of the diagnoses in these databases is not clear. One study found that the number of certain diagnoses in these databases are overestimated or underestimated, possibly caused by the transition steps that take place until the data reaches the final destination. Also, the results of any study used in the Norwegian database are generalized to Norwegian population only. Some of these databases have missing information; in case of NorPD, it does not include OTC medications data (except prescribed OTC), the indication for use is not mentioned, and the medications dispensed to the patients in the hospitals and nursing homes are not available in NorPD.

Conclusion

In conclusion, each database has its own strengths and limitations.NIS can answer many research questions related to healthcare utilization and healthcare cost, but it is not the best database to answer questions related to medication exposure since there is no detailed information about medications. The latter research question can be investigated thoroughly and accurately by using the VA databases because these databases contain enough data on patient medications. Many other research questions can also be answered using VA databases because they have ample data on most clinical aspects as well as economic aspects. Pharmacoepidemiologic, pharmacoeconomic, and other behavioral studies can be performed using the VA databases. However, any study conducted using VA database will only be generalized to the VA population. This problem is not a big issue in countries with a social healthcare system such as the UK and Norway. The conclusions of studies that use the THIN database in the UK can be applied to the entire UK population. This is also true of studies that used the Norwegian database. The THIN database shares similar characteristics of the VA database in its ability to answer many research questions related to diseases and medications. Finally, the Norwegian databases are very interesting and well-organized databases. The major strength of these databases is that they can be linked together to produce large amounts of patient information to conduct many studies. Researchers from inside as well as outside Norway should start to utilize these databases. The major difference between U.S databases and European databases is a result of the type of healthcare system in each country. As mentioned before, the social healthcare system is an ideal environment to produce a good

database. This can be found with the THIN database and the Norwegian databases. The VA database also has similar attribute because VA health care system somewhat resembles a government-run, universal healthcare system.

Table III.1: Essential elements available in nationwide inpatient sample

Primary and secondary diagnoses
Primary and secondary procedures
Admission and discharge status
Patients demographic data
Payment resources
Total charge
Length of stay
Hospital characteristics

Table III.2: Areas and topics that can be answered through using nationwide inpatient sample database

Analyses of states and communities
Health care cost inflation
Hospital financial distress
Use and cost of hospital services
Utilization of health services by special populations
Medical practice variation
Medical treatment effectiveness
Quality of care
Impact of health policy change
Access to care
Diffusion of medical technology

Table III.3: Examples of research questions that can be answered by nationwide inpatient sample

Research question examples	Type
What is the cost of treating asthma?	Economic
What is the epidemiology of meningitis?	Epidemiology
What is the mortality rate in patients treated with thrombolysis?	Outcome
Are there racial differences in seeking health care?	Access to care
What is the difference between patients going to teaching hospital and patients going to other hospitals?	Medical practice

Table III.4: Primary users of nationwide inpatient sample data

State and federal government agencies	Pharmaceutical companies
Hospital information system firms	School of pharmacies, public health and business
Healthcare systems	Health services researchers and policy analysts
Health insurance companies	Health professions societies
Hospitals	Managed Care Organizations (MCOs)

Table III.5: Advantages and limitations of the nationwide inpatient sample database

Advantages	Limitations
Sponsored by AHRQ	Does not include reliable pharmacy data
Largest inpatient database	Does not include data outside the hospital system
Inexpensive	Race and ethnicity data is incomplete
Ability to perform analysis of trends over time	Does not include all hospitals
Generalizability	
Ability to study rare diseases	
Includes different types of insurance sources	
Can be used with different type of statistical packages (SAS®,SPSS® and Stata®)	
Contains health information as well as economic information	
Easy to use	
Contains detailed information about the datasets	
Web-based training	

Table III.6: Data sources within Veterans Affairs database

Data source	Description
The National Survey of Veterans	Socioeconomic background. Military background. Health status and healthcare use. Veterans' understanding of and use of VA benefits.
VHA Assistant Deputy Under Secretary for Health (ADUSH) Enrollment Monthly File	National statistics on VHA expenditures, enrollment, and patients.
Beneficiary Identification & Records Locator System (BIRLS)	Death File. Veterans who have applied for VA benefits. Veterans discharged from the military service since March 1973. Recipients of the Medal of Honor Service members with accounts for VA education benefits.
VA Decision Support System (DSS)	Clinical and financial data for inpatient and outpatient care. DDS production database that combine cost data, clinical data and other data. DSS National Data Extracts that include several extracts such as Pharmacy, Laboratory and other types of extracts.
The VA-Medicare Data Merge Initiative	This initiative sponsored by VA to assist the researchers to access Medicare database. Several Medicare data can be accessed such as Medicare Data File Documentation, Medicare Current Beneficiary Survey (MCBS) and United States Renal Data Systems (USRDS).

The VHA Medical SAS Datasets	It's extracted from the National Patient Care Database (NPCD). It is the most utilized medical dataset. They include all inpatient and outpatient care data.
The National Prosthetics Patient Database (NPPD)	It developed by the Prosthetic and Sensory Aids Service Strategic Health Care Group (PSAS). It includes information about orthotic, prosthetic and sensory devices dispensed to veterans nationwide. NPPD available since 2000.
The Pharmacy Benefits Management (PBM)	National database that include all prescription medications that dispensed with VHA system. It comprises all inpatient intravenous and unit dose prescriptions in VA facility and outpatient prescriptions. It includes data about dosing instructions, National Drug Code (NDC), product name, ordering provider, quantity dispensed ,drug product costs, formulary status, and VA drug class In includes controlled prescription information.
Resident Assessment Instrument - Minimum Data Set (RAI-MDS)	RAI-MDS defined by VHA as "a core set of screening, clinical and functional status elements, including common definitions and coding categories, that forms the foundation of the comprehensive assessment for all residents of long-term care facilities". Data available since 2001.

The VA Vital Status files	The file comprises the death dates from all VA resources. It comprises from two files, the master and mini files.

Table III.7: The four major datasets in the Medical SAS Inpatient Datasets and their definition

Dataset	Contained Data
Main section	Data for the patients' inpatient stay. Demographics, primary/secondary diagnoses and other variables (up to 91 variables in 2006).
Bed section	Include the patients' data that are under a specified physician treating specialty during the inpatient stay. It includes Primary/secondary diagnoses and length-of-stay and other variables up to 48 variables in 2006.
Procedure section	One day procedure (up to four procedures) during the inpatient stay; it has up to 25 variables in 2006.
Surgery section	One day surgery (up to 5 surgeries) performed in the main or specialized room during the inpatient stay; it has 28 variables in 2006.

Table III.8. Description of the National Data Extracts datasets

NDE dataset	Narrative	Acronym	Availa-bilty
Discharge	Discharge datasets includes one record for every hospital stay in a specific fiscal year. They were implemented in 1999 and it has several variables such as number of X-rays, discharge DRG, different type of costs and other variables.	DISCH	FY1999-2009
Outpatient	Outpatient datasets include services that are not available in the NPCD. They have more detailed cost data and some clinical data. The files are divided to different group because of the big size.	OutPat	FY1999-2009
Treating Specialty	Treating specialty datasets could have more than one record for each hospital stay. They are divided into different sections based on the month and treating specialty of the provider for each stay. It is associated with the location such as medical care, surgical ward or long-term care unit.	TRT	FY1999-2009
Laboratory results	Laboratory results dataset includes laboratory results for defined number of laboratory tests. It has both inpatient and outpatients encounters.	LAR	FY2000-2009

Laboratory	Laboratory datasets include record for every individual "patient" laboratory tests for both inpatient and outpatient encounter during the extract period.	LAB	FY2002-2009
Radiology	Radiology datasets include data such as type, cost and number of radiological procedures that performed in the Diagnostic Radiology and Nuclear Medicine Departments for every encounter.	RAD	FY2002-2009
Pharmacy	Pharmacy datasets provide data on drugs that used in both inpatient and outpatient. They include prescription, unit dose, and IV pharmacy detail.	PHA	FY2002-2009

Table III.9: Examples of variables in the Pharmacy National Data Extract

Variable	Definition
COMP	Patient has received the medication by mail.
DAY_SUPPLY	Number of the days' supply for each drug (maximum 180 days to avoid errors)
DRUGDESC	Drug description
ACT_COST	Actual total cost

Table III.10: Sources of the laboratory and laboratory results National Data Extracts

Source	Data	Laboratory	Laboratory result
VistA Data File (#63) and the Referral Patient File (#67)	Lab workload	√	√
Patient File (#2) and the Referral Patient File (#67)	Patient's demographic data	√	√
VistA Patient Movement file (#405)	Inpatient information	√	√
VistA Patient Care Encounter file	Encounter information (e.g. date)	√	√
DSS	Cost, product and department information.	√	

Table III.11: Examples of numeric value for non-numeric laboratory test results

Non-numeric value	Numeric value
Negative, Non reactive	0
Positive , Reactive	1
Borderline results	2
Test has been done	5

Table III.12: Examples of Laboratory Tests those are available in Laboratory datasets

Laboratory test (Unit)	Availability year	Result ID number
Potassium (MEq/L)	FY2000	2
Sodium (MEq/L)	FY2000	3
Blood Urea Nitrogen "BUN" (Mg/dl)	FY2000	5
Creatinine Clearance (Ml/min)	FY2000	11
Digoxin (Ng/ml)	FY2000	7
AST "Aspartate Transaminase" (U/L)	FY2000	9
ALT "Transferase Alanine Amino" (U/L)	FY2001	45
Hematocrit (%)	FY2002	50
INR "International Normalized Ratio"	FY2003	52
Creatinine GFR (ML/MIN/1.73M2)	FY2006	66

Table III.13: Advantages and limitations of the VA databases

Advantages	Limitation
Largest database in the US	Majority are male
National database	Contains variables reported by patients such as using illicit drug
Includes most of the information that required to conduct a research (i.e. diseases, medications, laboratory, radiology, all patient demographics..etc)	Smoking status is not well documented
Most of the databases are free to access	
Uses single unique identifier to lin dataset in fiscal year	
Most diseases' definition by ICD-9 have been validated	
Many measures are taken to guarantee the patient privacy	
Help and technical support is very active	

Table III.14: Some variables in the THIN database and their original sources

Variable	Original source*
Patient identifier (Patid)	All files
Age Sex Death date	Patient file
Event date Read medical code Hospital referral Medical history	Medical file
Prescription date Drug code (multilex code) BNF codes Dosage and duration of prescription	Therapy file
Height Weight Vaccination Smoking and alcohol intake Pregnancy and birth details Laboratory tests and their results	Additional Health Data (AHD) file

*Some variables can be found in more than one source.

Table III.15: Examples of READ codes in the THIN database

Read code	Description
D21z	Anemia
G33	Angina pectoris
M03z000	Cellulitis Not otherwise specified (NOS)
F00..	Bacterial meningitis
713..	Breast operations
535..	Standard chest X-ray

Table III.16: Examples of British National Formulary (BNF) drug codes in the THIN database

BNF code	Drug name	Therapeutic group
05.01.01.03a	Amoxicillin	Broad spectrum penicillins
06.02.01.00a	Levothyroxine	Thyroid hormones
02.04.00.00b	Bisoprolol	Beta-Blocker
02.06.01.00a	Glyceryl Trinitrate	Nitrates
07.03.02.01c	Levonorgestrel	Oral progestogen-only contraceptives

Table III.17: Advantages and limitations of the THIN database

Advantages	**Limitations**
Computerized	Generalized to UK population only
Population-based	Not fully completed
Longitudinal	Costly
Large number of patients	
Validated	
Access the original medical record	
Confidentiality	

Table III.18: Examples of databases available in Norway

Database	Description
The Cause of Death Register [90]	- Includes the cause of death data since 1922. - It used to publish statics about the causes of death annually. - It has different information in addition to the underlying cause of death like age, gender, region of the person and if it is suicide or not. - It has information about death due to alcohol narcotics and medications. - It runs by statistics Norway with a cooperation with the Norwegian Institute of Public Health
The Cancer Registry of Norway [90,91]	- The purpose of this registry is to prevent the caner by knowing the reasons that cause cancer and most common cancers, to have a real statistics about the number of cancer cases and the distribution of these cases among Norwegian population and to have a good resource to conduct epidemiological researches related to cancer. - It has all cancer cases since 1953 to date and it has over 500,000 cancer cases. - It has a statistics about the major common cancer types among men and women. - The reporting system to this registry is consider of very complete (near to 100%) - Patients can be linked using their unique personal identification number
The Medical Birth Registry of Norway [90,102]	- The aim of this registry is for conducting surveillances about the newborn babies' health and the pregnancy outcomes and to conduct epidemiological researches related to the babies' health and to pregnancy outcomes. - It is a national registry in Norway and includes all babies born there. - It has all babies' data since 1967 therefore, it considered the world's first

	medical birth registry - Can be linked with other registries in Norway so it a great resource for research in combined with other registries - The registry is responsible by the Norwegian Institute of Public Health and the University of Bergen
The Norwegian Surveillance System for Communicable Diseases (MSIS) [90,103,104]	- MSIS has data about all infectious diseases at national and local level. - It is the official monitoring system for communicable diseases in Norway. - The sources of MSIS are from physicians, hospitals and laboratories. - The information include; disease name, month and year of diagnosis, age group of the patient, county of residence and place of the infection and the mode of transmission in case of HIV, syphilis, gonorrhea and viral hepatitis. - MSIS is responsible by the Norwegian Institute of Public Health
The Tuberculosis (T.B) Registry [90,105,106]	- It is responsible by the Norwegian Institute of Public Health under department of infectious disease epidemiology. - It has all TB cases since 1962 - All counties in Norway are required to have TB control program. - All the cases data should be send to the Tuberculosis Registry - The aim of the registry is to detect early TB cases and treat it and to conduct epidemiological research related to TB disease. - The sources of the registry are physicians, antituberculosis prescriptions and laboratory. - It has important variables such as; patient age, gender, site of the disease and birth place.
The Childhood Vaccination Register (SYSVAK) [90]	- The aim of the registry is to make sure that all children are vaccinated and to conduct researches related to vaccines. - All centers are required to register the child's immunizations to the registry. - It also used to monitor the adverse effect of the immunizations.

	- It is under the department of vaccine and immunity at t the Norwegian Institute of Public Health - It has information about the child such as child name, unique identification personal number, family address, vaccine name and vaccination date and any adverse events.
The National Injury Register (NIR) [90,91]	- It is responsible by the Norwegian Institute of Public Health - It was established in 1985 and it has all injury cases till now. - NIR are using other register as references such as The National Register of Deaths, The National Hospital Discharge Register and The National Injury Sample Register. - The variables in NIR include age, sex, place of residence, type of accident, mechanism of injury, type and severity of injury, product involved, time and event of injury and the medical information on the site. - The aim of NIR is to have information about the number and type of injuries for statistics and prevention purposes and to conduct epidemiological research.
Database over Occupational Injuries and Occupational Diseases [91]	- It was established in 1990. - It is responsible by the Association of Norwegian Insurance Companies. - It includes all Occupational Injuries and Occupational Diseases that reported to the insurance companies. - The variables are unique identification personal number, degree of disability, types of contact, the part of body injured, item caused the injury, the diagnoses "for occupational diseases" and the worker's compensation. - The aim of the registry is to use the information in the database for prevention purposes and for research purposes.

Table III.19: Resources for Norwegian Health Information System ("Norhealth")

Source name
Cause of Death Register
Medical Birth Registry of Norway
Tuberculosis Registry
Norwegian Patient Register
Statistics Norway's Health Interview Survey
Cancer Registry of Norway
Norwegian Prescription Database
Norwegian Surveillance System for Communicable Diseases
Childhood Vaccination Register

Table III.20: Aims of the Norwegian Prescription Database (NorPD)

To explain the pattern of medication utilization and monitor the trends of utilization over time
To function as a base resource for drug related statistics to be used by authorities to assess the quality of drug prescription, controlling and planning
To function as an internal control for prescribers to improve the quality of prescribing practice.
To function as the main resource for medication and pharmacoepidemiological research.

Table III.21: Variables available at Norwegian Prescription Database (NorPD)

Element	Variables
Patient	- Encrypted personal identification number - Gender - Date of birth - Place of residence - Date of death
Prescriber	- Encrypted personal identification number - Gender - Date of birth - Profession - Specialty
Drug	- Drug brand name, strength ,package size and number of package - ATC code and DDD - Category of prescription - Code of reimbursement - Date of Dispensing - Drug cost - Area of application and prescribed dose
Pharmacy	- Pharmacy name - License number - Place of pharmacy (municipality and county)

REFERENCES

1 Neubert A, Sturkenboom MC, Murray ML, et al. Databases for pediatric medicine research in Europe-assessment and critical appraisal. Pharmacoepidemiol Drug Saf 2008; 17:1155-1167

2 Hennessy S. Use of Health Care Database in Pharmacoepidemiology. Basic & Clinical Pharmacology & Toxicology 2006; 98:311-313

3 Strom BL. Pharmacoepidemiology: Wiley InterScience, 2005

4 The Agency for Healthcare Research and Quality. The Nationwide Inpatient Sample. http://www.hcup-us.ahrq.gov/nisoverview.jsp retrieved on 08/2009

5 Cox S, Posner SF, Kourtis AP, et al. Hospitalizations with amphetamine abuse among pregnant women. Obstet Gynecol 2008; 111:341-347

6 The Agency for Healthcare Research and Quality. The Healthcare Cost and Utilization Project (HCUP). http://www.hcup-us.ahrq.gov/overview.jsp retrieved on 11/2008

7 Tsai CJ, Griffin MR, Nuorti JP, et al. Changing epidemiology of pneumococcal meningitis after the introduction of pneumococcal conjugate vaccine in the United States. Clin Infect Dis 2008; 46:1664-1672

8 Grijalva CG, Nuorti JP, Arbogast PG, et al. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. Lancet 2007; 369:1179-1186

9 Kim WR, Gores GJ, Benson JT, et al. Mortality and hospital utilization for hepatocellular carcinoma in the United States. Gastroenterology 2005; 129:486-493

10 Scarborough JE, Pietrobon R, Marroquin CE, et al. Temporal trends in early clinical outcomes and health care resource utilization for liver transplantation in the United States. J Gastrointest Surg 2007; 11:82-88

11 Russell RB, Green NS, Steiner CA, et al. Cost of hospitalization for preterm and low birth weight infants in the United States. Pediatrics 2007; 120:e1-9

12 *The Agency for Healthcare Research and Quality.* Nationwide Inpatient Sample Trends Supplemental (NIS-Trends) Files. http://www.hcup-us.ahrq.gov/db/nation/nis/nistrends.jsp. retrieved on 05/2008

13 Schumacher HC, Bateman BT, Boden-Albala B. Use of Thrombolysis in Acute Ischemic Stroke: Analysis of the Nationwide Inpatient Sample 1999 to 2004. Ann Emerg Med 2007; 50:99-107

14 VIReC. VIReC Research User Guides. http://www.virec.research.va.gov/References/RUG/RUG.htm retrieved on 09/2009

15 Alshekhlee A, Hussain Z, Sultan B, et al. Guillain-Barre syndrome: incidence and mortality rates in US hospitals. Neurology 2008; 70:1608-1613

16 McPhee J, Eslami MH, Arous EJ, et al. Endovascular treatment of ruptured abdominal aortic aneurysms in the United States (2001-2006): a significant survival benefit over open repair is independently associated with increased institutional volume. J Vasc Surg 2009; 49:817-826

17 Chung L, Krishnan E, Chakravarty EF. Hospitalizations and mortality in systemic sclerosis: results from the Nationwide Inpatient Sample. Rheumatology (Oxford) 2007; 46:1808-1813

18 Pittsburgh World Firsts. Carnegie library of Pittsburgh. http://www.carnegielibrary.org/research/Pittsburgh/history//pghsts3.html. retrieved on 01/2009

19 History of The Hospital COPRS United States Navy. Integrated Publishing. http://www.au.af.mil/au/awc/awcgate/medical/navy-hospital-corp-history.pdf. retrieved on 01/2007

20 Veterans Administration Created. History of the Department of Veterans Affairs. http://www1.va.gov/opa/feature/history/history4.asp retrieved on 09/2008

21 Torres DA. Handbook of federal police and investigative agencies Greenwood Publishing Group, 1985, 1985

22 Fact Sheet: Facts About the Department of Veterans Affairs. http://www1.va.gov/opa/fact/vafacts.asp. retrieved on 01/2009

23 History of the Department of Veterans Affairs, Part 10. Department of Veterans Affairs. http://www1.va.gov/opa/feature/history/history10.asp. retrieved on 07/2009

24 Kaufman D, Murphy J, Erby L, et al. Veterans' attitudes regarding a database for genomic research. Genet Med 2009

25 Sonnenberg A, Richardson PA, Abraham NS. Hospitalizations for Inflammatory Bowel Disease Among US Military Veterans 1975-2006. Dig Dis Sci 2009

26 Pugh MJ, Fincke BG, Bierman AS, et al. Potentially inappropriate prescribing in elderly veterans: are we using the wrong drug, wrong dose, or wrong duration? J Am Geriatr Soc 2005; 53:1282-1289

27 U.S. Department of Veterans Affairs. VA Information Resource Center. Introduction to VA Data. The VA Information Resource Center (VIReC). http://www.virec.research.va.gov/Support/Training-NewUsersToolkit/IntroToVAData.htm 2009

28 Introduction to VA database. http://www.virec.research.va.gov/Support/Training-NewUsersToolkit/IntroToVAData.htm. retrieved on 08/29/2008

29 U.S. Department of Veterans Affairs. VA Information Resource Center. Austin Information Technology Center (AITC). http://www.virec.research.va.gov/Support/Training-NewUsersToolkit/UsingDataAAC.htm retrieved on 08/29/2008

30 Maynard C, Chapko MK. Data resources in the Department of Veterans Affairs. Diabetes Care 2004; 27 Suppl 2:B22-26

31 U.S. Department of Veterans Affairs. VA Information Resource Center. Data Sources Within The VA. http://www.virec.research.va.gov/DataSourcesName/DataNames.htm. retrieved on 05/01/2008

32 Sohn MW, Arnold N, Maynard C, et al. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr 2006; 4:2

33 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Medical SAS Datasets. http://www.virec.research.va.gov/DataSourcesName/Medical-SAS-Datasets/SAS.htm retrieved on 09/30/2008

34 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Medical SAS Datasets - Location http://www.virec.research.va.gov/Support/Training-NewUsersToolkit/IntroToVAData.htm. retrieved on 09/30/2008

35 U.S. Department of Veterans Affairs. VA Information Resource Center. http://www.virec.research.va.gov/References/RUG/RUG-Inpatient06.pdf. retrieved on 09/2007

36 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Medical SAS Outpatient Datasets http://www.virec.research.va.gov/References/RUG/RUG-Outpatient06er.pdf. retrieved on 07/2007

37 U.S. Department of Veterans Affairs. VA Information Resource Center. Clinical National Data Extracts (NDEs). http://www.virec.research.va.gov/References/RUG/RUG-DSS00-04.pdf retrieved on 08/2008

38 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Decision Support System (DSS) - Introduction. http://www.virec.research.va.gov/DataSourcesName/DSS/DSSintro.htm retrieved on 09/2008

39 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Decision Support System (DSS). Pharmacy (PHA) Datasets http://www.virec.research.va.gov/References/RUG/RUG-DSSPHAfreq02-03.pdf retrieved on 01/2005

40 Barnett PG. Determination of VA health care costs. Med Care Res Rev 2003; 60:124S-141S

41 Smith MW, Joseph GJ. Pharmacy data in the VA health care system. Med Care Res Rev 2003; 60:92S-123S

42 Phibbs CS, Yu W, Barnett PG. *Research Guide to Decision Support System National Cost Extracts 1998-2004.* Health Economics Resource Center of Health Service R&D Services, Department of Veterans Affairs, Menlo Park, California, . 2005

43 U.S. Department of Veterans Affairs. VA Information Resource Center. DSS NDE Techincal Guide for FY08. . 2008

44 Cunningham F, Sales M, Valentino M. The Pharmacy Benefits Management (PBM) Database: A Primary Resource for Nation-Wide VA Medication Data. Hines, IL: VA Information Resource Center; 2001. VIReC Insights, Vol. 2, No. 2. (PDF). . 2001

45 U.S. Department of Veterans Affairs. VA Information Resource Center.VHA Decision Support System Laboratory (LAB) Datasets. http://www.virec.research.va.gov/References/RUG/RUG-DSSLABfreq02-03.pdf retrieved on 01/2005

46 U.S. Department of Veterans Affairs. VA Information Resource Center. VHA Decision Support System Laboratory Results (LAR) Datasets. http://www.virec.research.va.gov/References/RUG/RUG-DSSLARfreq00-03.pdf. retrieved on 03/2005

47 Malik A, Dinnella JE, Kwoh CK, et al. Poor Validation of Medical Record ICD-9 Diagnoses of Gout in a Veterans Affairs Database. J Rheumatol 2009; 36:1283-1286

48 Kramer JR, Davila JA, Miller ED, et al. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Aliment Pharmacol Ther 2008; 27:274-282

49 Schneeweiss S, Robicsek A, Scranton R, et al. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. J Clin Epidemiol 2007; 60:397-409

50 ISPOR Digest of Internationl databases. International Society for Pharmacoeconomics and Outcomes Research. http://www.ispor.org/DigestOfIntDB/CountryList.aspx retrieved on 11/2008

51 Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. Pharmacotherapy 2003; 23:686-689

52 Neubert A, Sturkenboom MC, Murray ML, et al. Databases for pediatric medicine research in Europe--assessment and critical appraisal. Pharmacoepidemiol Drug Saf 2008; 17:1155-1167

53 The Health Improvement Network (THIN) database. http://www.epic-uk.org/thin.htm retrieved on 12/2008

54 Cegedim Group. http://www.cegedim.com/. retrieved on 01/2009

55 Lewis JD, Schinnar R, Bilker WB, et al. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf 2007; 16:393-401

56 The National *Health* Service (*NHS*). NHS structure. http://www.nhs.uk/NHSEngland/aboutnhs/Pages/NHSstructure.aspx. retrieved on 04/2009

57 Health Services in the UK. http://www.bcattbhi.org.uk/resources/english_leeds.pdf. retrieved on 01/2004

58 Primary care data from The Health Improvement Network (THIN). www.ispor.org/publications/value/...6/7272_appendix_Blak.doc retrieved on 07/2008

59 University College London. Primary Care and Population Health. THIN database. http://www.ucl.ac.uk/pcph/research/thin/db.htm retrieved on 07/2009

60 Myles PR, McKeever TM, Pogson Z, et al. The incidence of pneumonia using data from a computerized general practice database. Epidemiol Infect 2009; 137:709-716

61 Preece J. The Use of Computers in The General Practice, Read codes. Fourth ed: Elsevier Health Sciences, 2000

62 Robinson D, Schulz E, Brown P, et al. Updating the Read Codes: user-interactive maintenance of a dynamic clinical vocabulary. J Am Med Inform Assoc 1997; 4:465-472

63 Buckley BS, Simpson CR, McLernon DJ, et al. Five year prognosis in patients with angina identified in primary care: incident cohort study. BMJ 2009; 339:b3058

64 The Clinical Terms Version 3(The Read Codes). National Health System (NHS). http://www.connectingforhealth.nhs.uk/systemsandservices/data/readcodes/docs/chap1.pdf. retrieved on 03/2000

65 Quick Guide to Read code mapping in ISOFT Synergy. Nottingham University Hospital NHS Trust. http://qmc.nhs.uk/electronicdocs2gp/documents/synergy%20-%20Mapping%20process%20document.doc.

66 Gonzalez EL, Johansson S, Wallander MA, et al. Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Health 2009; 63:332-336

67 Formulary. Basingstoke and North Hampshire NHS Foundation Trust. http://www.formulary.org.uk/index.html retrieved on 06/2008

68 The Institute for the Translational Medicine and Therapeutics (ITMAT). University of Pennsylvania. http://www.itmat.upenn.edu/ctsa/acard/docs/faq_GPRD_THIN.pdf. retrieved on 12/2007

69 Hubbard R, Lewis S, Smith C, et al. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. Tob Control 2005; 14:416-421

70 Raine R, Wong W, Ambler G, et al. Sociodemographic variations in the contribution of secondary drug prevention to stroke survival at middle and older ages: cohort study. BMJ 2009; 338:b1279

71 Myles PR, Hubbard RB, McKeever TM, et al. Risk of community-acquired pneumonia and the use of statins, ace inhibitors and gastric acid suppressants: a population-based case-control study. Pharmacoepidemiol Drug Saf 2009; 18:269-275

72 Smeeth L, Douglas I, Hall AJ, et al. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. Br J Clin Pharmacol 2009; 67:99-109

73 Tata LJ, Lewis SA, McKeever TM, et al. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. Thorax 2008; 63:981-987

74 Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. Inform Prim Care 2004; 12:171-177

75 Lo Re V, 3rd, Haynes K, Forde KA, et al. Validity of The Health Improvement Network (THIN) for epidemiologic studies of hepatitis C virus infection. Pharmacoepidemiol Drug Saf 2009; 18:807-814

76 Data from EPIC - Access to data. http://www.epic-uk.org/access_to_data.htm retrieved on 12/2008

77 The Health Improvement Network (THIN) database website. http://www.thin-uk.com/. retrieved on 01/2009

78 Bulugahapitiya U, Siyambalapitiya S, Sithole J, et al. Age threshold for vascular prophylaxis by aspirin in patients without diabetes. Heart 2008; 94:1429-1432

79 Population Statistics. Statistics Norway. http://www.ssb.no/folkendrkv_en/ retrieved on 07/2009

80 An ageing society. Statistics Norway. http://www.ssb.no/norge_en/norge_2009_en.pdf retrieved on 02/2009

81 Johnsen JR. Health Systems in Transition in Norway. http://www.euro.who.int/Document/E88821.pdf. retrieved on 12/2006

82 Education statistics. Population´s level of education in Norway. Statistics Norway. http://www.ssb.no/utniv_en/ retrieved on 10/2008

83 Noord Pvd, Hagen T, Iversen T. The Norwegian Health Care System Economics Department working papers, N0. 198. Organisation for Economic Co-operation and Development (OECD). http://www.oecd.org/dataoecd/34/49/1864965.pdf retrieved on 06/1998

84 The Royal Norwegian Ministry of Health and Care Services. http://www.regjeringen.no/en/dep/hod.html?id=421. retrieved on 07/2009

85 Heskestad B, Baardsen R, Helseth E, et al. Incidence of hospital referred head injuries in Norway: A population based survey from the Stavanger region. Scand J Trauma Resusc Emerg Med 2009; 17:6

86 The Royal Norwegian Ministry of Health and Care Services. http://www.regjeringen.no/upload/HOD/Vedlegg/HOD-brosjyre_engelsk.pdf retrieved on 05/2007

87 Lofthus CM, Cappelen I, Osnes EK, et al. Local and national electronic databases in Norway demonstrate a varying degree of validity. J Clin Epidemiol 2005; 58:280-285

88 Espehaug B, Furnes O, Havelin LI, et al. Registration completeness in the Norwegian Arthroplasty Register. Acta Orthop 2006; 77:49-56

89 Lium JT, Faxvaag A. Removal of paper-based health records from Norwegian hospitals: effects on clinical workflow. Stud Health Technol Inform 2006; 124:1031-1036

90 Norway's Seven Central Health Registers. The Norwegian Institute of Public Health. http://www.fhi.no/eway/default.aspx?pid=238&trg=MainLeft_5853&MainArea_5811=5853:0:15,2825:1:0:0:::0:0&MainLeft_5853=5825:52966::1:5857:1:::0:0. retrieved on 03/2009

91 HASTE. The European Health and Safety Database. http://www.ttl.fi/Internet/partner/Haste/Norway/ retrieved on 04/2004

92 Trewin C, Strand BH, Groholt EK. Norhealth: Norwegian health information system. Scand J Public Health 2008; 36:685-689

93 Furu K. Establishment of the nationwide Norwegian Prescription Database (NorPD) – new opportunities for research in pharmacoepidemiology in Norway. Norsk Epidemiologi 2008; 18 129-136

94 Department of Pharmacoepidemiology. The Norwegian Institute of Public Health.

http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5903:0:15,4165:1:0:0:::0:0 retrieved on 02/2008

95 Bramness JG, Furu K, Engeland A, et al. Carisoprodol use and abuse in Norway: a pharmacoepidemiological study. Br J Clin Pharmacol 2007; 64:210-218

96 The Norwegian Prescription Database (NorPD). The Norwegian Institute of Public Health. http://www.norpd.no/Viktig.aspx. retrieved on 10/2009

97 Rønning M, Lie Berg C, Furu K, et al. The Norwegian Prescription Database 2004-2007. The Norwegian Institute of Public Health. . 2008

98 Furu K. Norwegian Prescription Database (NorPD). http://www.nhv.se/upload/dokument/forskning/N%C3%A4tverk/NorPEN/1st%20meeting/Norway_Kari_Furu.pdf. retrieved on 03/2009

99 Publications which have used data from the Norwegian Prescription Database (NorPD), May 2008. Norsk Epidemiologi 2008; 18:208-209

100 Extraction of data from the NorPD - Access and Guidelines. The Norwegian Institute of Public Health. http://www.fhi.no/eway/default.aspx?pid=238&trg=Area_5954&MainLeft_5812=5954:0:&Area_5954=5825:67758::0:5955:1:::0:0. retrieved on 02/2008

101 Larsen IK, Smastuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 2009; 45:1218-1231

102 Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. Acta Obstet Gynecol Scand 2000; 79:435-439

103 Sandberg M, Nygard K, Meldal H, et al. Incidence trend and risk factors for campylobacter infections in humans in Norway. BMC Public Health 2006; 6:179

104 Jakopanec I, Borgen K, Aavitsland P. The epidemiology of gonorrhoea in Norway, 1993-2007: past victories, future challenges. BMC Infect Dis 2009; 9:33

105 Dahle UR, Eldholm V, Winje BA, et al. Impact of immigration on the molecular epidemiology of Mycobacterium tuberculosis in a low-incidence country. Am J Respir Crit Care Med 2007; 176:930-935

106 Farah MG, Rygh JH, Steen TW, et al. Patient and health care system delays in the start of tuberculosis treatment in Norway. BMC Infect Dis 2006; 6:33