Last updated on August 2010

GPRD™ Database Description

Background

- The UK General Practice Research Database (GPRD™) was started up in 1987 as the VAMP Research Data Bank.
- GPRD™ contains longitudinal data from the electronic medical records of patients from a large sample of general practices within the UK.
- The administration of the GPRD™ has undergone several changes since it was initiated by VAMP. In 1993, VAMP was acquired by Reuters Health Information, which in turn donated the research database to the UK Department of Health in 1994, with the stipulation that the database be used for research, on a non-profit basis.
- From 1994 until 1999 the database was operated by the Office for National Statistics.
- In April 1999, Management of the GPRD™ was transferred to the UK Medicines Control Agency, and in April 2003 this agency became part of the newly created Medicines and Health Care products Regulatory Agency.
- The Epidemiology Pharmacology Information Core (EPIC), which grew out of VAMP, was previously a vendor of the GPRD™. Penn's version of the GPRD™ was licensed through EPIC.
- Vision -- a Windows-based software system created by Reuters for managing patient information -- was introduced in 1995 and became the dominant data entry system used by GPs in the GPRD™.

- GPs use their software to create electronic medical records and for the purpose of managing their patients.
- VAMP identified practices meeting specified data entry quality criteria and coded them as “up to standard” The first “up to standard date” was assigned to a practice in 1987, but most practices did not become up to standard until 1990 - 1991.
- Data quality assurance was performed by VAMP until 1994 when the database was donated to the UK Department of Health.
- The UK office of National Statistics was responsible for quality assurance from 1995 - 1999, followed by the Medicines Control Agency.
- GPs receive nominal financial inducements for their participation in this program, and many participate because they believe they are providing a valuable research service and because the computerized system improved their practice.

Population Characteristics

- Initially, there were over 700 practices, representing about 3000 general practitioners (GPs) nationally and representative of general practices in the UK, that provided the entire medical record data (stripped of identifiers) of their patients (about 10 million), and provided also anonymized photocopied referral letters to hospitals and specialists.
- The number of practices declined to 520 in 1995, and declined further to 365 in 2000.
- Further diminishing the overall size of the GPRD™, EPIC has recommended not using data from practices that have not met quality assurance criteria allowing them to receive the “up to standard” designation.
- Additionally, other investigator groups, such as the Boston Collaborative Drug Safety Program, in their licensed copy of the GPRD™, has dropped almost half of all original VAMP practices due to lapses in data entry, unwillingness to provide clinical records, a change in computer systems of the practice, or based on request of the practice that their data be removed.
- In any given year, GPs who are members of the GPRD™ collect data on about 2-3 million patients, yielding about 37 million person-years of follow-up between 1987 and March 2002 (the last year of data collection in the data set at Penn).
- Continuous information has been collected for 6 years or more in most of the practices.
- About 5% of the UK population is included in the GPRD™, which is broadly representative of the general UK population in terms of age, sex, and geographic distributions.
- A portion of patients in GPRD™ overlap with those patients in THIN, although no method is currently validated to make this direct link.

Data Structure

- Full patient histories are available from 1987, with entries made routinely at time of consultation.

- EPIC (http://www.epic-uk.org/GPRD™.htm) licensed to Penn a static version of the GPRD™ (EPICGPRD™) which contains data from a total of 755 practices and has over 9 million patients with the most recent data collected through March 2002.
- The CCEB holds a static version of the GPRD™ (CCEB_GPRD™) which contains data from a total of over 700 practices and has 9 million patients with the most recent data collected through March 2002.
- GPs use the computer software to enter data into different files:
    - **Demographic File** with age, sex, and registration information.
    - **Medical File** includes medical diagnoses that are part of routine care or resulting from hospitalizations, consultations, or emergency care, along with the date and location (e.g., GP's office, hospital, consultant) of the event and an option for adding free text; referrals to hospitals and specialists. The free text is not included in the Penn version of the database but can be obtained from EPIC.
    - **Prescriptions File** includes all prescriptions along with the date of prescription, formulation, strength, quantity, and dosing instructions, indication for treatment for all new prescriptions (cross referenced to medical events on the same date), and events leading to withdrawal of a drug or treatment.
    - **Prevention File** includes vaccinations and prescription contraceptives; miscellaneous information such as smoking, height, weight, immunizations, pregnancy, birth, death, date entering the practice, date leaving the practice, and laboratory results.
    - Significant events prior to the patient's registration with the practice, or prior to the practice commencing with the GPRD™, are retrospectively recorded as well.
- Diagnoses were recorded using OXMIS codes until newer versions of the GP system were made available in 1995 when the Read coding system was introduced. Currently all GPRD™ data are coded in Read codes, which are alphanumeric codes that group and define illnesses using a hierarchical nosologic system. The Read Codes are a very comprehensive coded clinical language developed in the UK and funded by the National Health Service. The codes include terms relating to observations (signs and symptoms), diagnoses, procedures, and laboratory and radiologic tests.
- Prescriptions were originally entered using Prescription Pricing Authority (PPA) codes and are currently entered using Multilex codes issued by First Databank. Drug codes provide detailed information on the drug, dose, and route of administration.
- Patients in the GPRD™ are also issued a number that identifies people residing at the same address or not at the same address but are family members. This data field, in combination with the date of birth of children and the delivery code in the mother's record, can be linked to identify mothers and their children.

Links

http://www.GPRD™.com/_docs/GPRD™PracticePatientPopulations.pdf

❖ GPRD™ Research Considerations

○ Strengths of GPRD™ Database

- The GPRD™ represents a defined population
  - ✓ allows investigators to study all patients with a given disease.
  - ✓ allows investigators to study control patients from the same source population from which those with the disease of interest are derived.
- The GPRD™ is broadly representative of the UK population in general
  - ✓ therefore minimizes selection bias and improves the validity of epidemiologic studies.
  - ✓ therefore findings should generalize to the broader UK population.
- The well-defined population of the GPRD™ allows investigators to study families and to link health events in mothers to outcomes in their children.
- Size of the database
  - ✓ can be used to study rare outcomes using cohort designs for medical conditions with incidence rates of less than 1/10,000 with sufficient statistical power.
- Longitudinal data (since 1987)
- Validated information
  - ✓ The validity of GPRD™ has been extensively studied, demonstrating good agreement between the electronic medical record and capture of information from specialists and the accuracy of information on prescription medications.
- Access to original medical records
  - ✓ Allow investigators to have the opportunity through an intermediate to obtain anonymized copies of the patient's (non-electronic) medical record and a more detailed review of the patient's health history.
  - ✓ This capacity allows researchers to verify information captured on death certificates and letters from specialists.

○ Limitations of GPRD™ Database

- GPRD™ prescription data reflect what was prescribed by the PG.
  - ✓ This is removed from biologic ingestion because it may not have even been dispensed by the pharmacy.
- Incompleteness of data
  - ✓ Although GPRD™ is used by the GP as the patient's medical record, and therefore information generated by the general practitioner is expected to be complete, information from specialists as well as events that occur in the hospital may not be fully captured in the electronic medical record.

- ✓ The database may not contain data on every patient characteristic or disease characteristic that may be required for a study (information on occupation, employment, and socioeconomic status is not available electronically).
- ✓ Communication from specialists, discharge summaries from hospitals, and test results from pathology laboratories are often received in hard copy and must be manually entered into the computer. Since this can be a time consuming process, some practices will only enter information that will affect the care of the patient in the future. Therefore, with test results it is likely that only the abnormal results are entered onto the computer for collection and inclusion into GPRD™.
- ✓ Minor medical events are more likely to be missed than medically significant diagnoses or events.
- ✓ Information on treatments that are restricted by the National Health Service to specialist care (e.g., psoralen plus ultraviolet A therapy, cytotoxic/chemotherapy) may be particularly problematic.
- ✓ Data on non-prescription medications and treatments given in the hospital are not readily available.
- ✓ Data on non significant medical events and exposures to medications that occurred prior to enrollment in the GPRD™ and are no longer active clinical issues may also not be documented in the electronic medical record.
- ✓ Data on important confounding variables (smoking, alcohol use, smoking, body weight and height) are only available for about 70% of patients.

• Complexity and costs of computer hardware/software needed to work with GPRD™
  - ✓ The size and complexity of the GPRD™ database requires adequate computer hardware and software, as well as experience in data management.
  - ✓ The full GPRD™ dataset received by CCEB from EPIC contains all information in the GPRD™ from 1988 to 2002, approximately 54 gigabytes. It is residing on a Sun Microsystems Enterprise™ server running the Solaris operating system in a Unix environment. The unit requires 170 gigabytes of disk storage.
  - ✓ Within Penn, the data base stored in two different versions. The full data base is housed using Oracle's® relational database. The database tools include Oracle's internet developer's suite of tools, such that clients within our server environment can access the GPRD™ in real time using Oracle Discover®, as well as by using a SAS©-based interface. With these tools it has been possible for clients, using Ethernet-connected PCs, to download data and convert the data into several different database programs including Microsoft Access© and Visual Dbase© and statistical packages such as Stata®, SAS©, and SPSS®. A smaller 10% random sample is housed on a stand alone PC that can be queried using MySQL.

❖ Requirements for Accessing the GPRD™ Database

○ All Users:

- Must complete the **Online Registration and Request for Help Form**. (Link to online form)

- The data access license from EPIC covers aspects of confidentiality. However, for internal use, must sign also the CCEB **Data Use and Approval Agreement.** (Link to online form)

  ✓ Download the Data Use and Approval Agreement Form.
  ✓ Obtain signatures from either Dr. *Brian Strom* (824 Blockley Hall), or Dr. *James Lewis* (720 Blockley Hall), or Dr. *David Margolis* (815 Blockley Hall) at 423 Guardian Drive, Philadelphia, PA 19104-6021.
  ✓ Return the signed form to *Rita Schinnar* (address: CCEB, 807 Blockley Hall, 423 Guardian Drive Fax: 215-573-5315).

- **If using only the pre-collected EPIC GPRD™ data:**

a) Must get scientific review and approval of the protocol from the **Penn IRB**.

  ✓ refer to: http://www.upenn.edu/regulatoryaffairs/human/ApplicationProcedures.html
  ✓ http://www.med.upenn.edu/pennmanual/sp/irb/sr.html
  ✓ http:/www.upenn.edu/regulatoryaffairs/human/FAQs.html

b) Must also get **Scientific Review** and approval of the protocol from **ISAC** - the UK MHRA's Independent Scientific Advisory Committee. However, for EPIC GPRD™ data, the protocol must be sent to EPIC, which in turn will send the protocol to ISAC on behalf of the investigator.

  ✓ For the application form and protocol guidelines refer to:
  ✓ http://www.GPRD™.com/ISAC.
  ✓ To send the application to EPIC refer to: http://www.epic-uk.org/ or the email contact: Mustafa.dungarwalla@epic-uk.org

- **If the study will need to go back to the practices** to obtain any additional data from the practices [Note: This is not recommended for the EPIC GPRD™ – as the last data were collected in 2002 and many patients are not now easy to locate and may have died or moved away]:

a) Follow the same procedure as above but the researcher must also initially contact EPIC to discuss additional arrangements which need to be made through **EPIC. A quote will be prepared by *Anne Costello* at EPIC for the required administration and payments to the General Practitioners.**

   ✓ Refer to: http://www.epic-uk.org/
   ✓ email contact: Anne.Costello@epic-uk.org

b) Following ISAC review, the researcher needs to apply for additional **ethical approva**l via a Multi-centre Research Ethics Committee (MREC) – contact *Mustafa Dungarwalla* at EPIC for more information.

   ✓ email contact: Mustafa.dungarwalla@epic-uk.org

- Must review background readings:

  Strom BL. Overview of Automated Databases in Pharmacoepidemiology. Chapter in Pharmacoepidemiology (Strom BL, Ed). 4th edition. Chichester, England: John Wiley. 2005. pp.219-222.

  Gelfand JM, Margolis DJ, Dattani H. The UK General Practice Research Database. Chapter in Pharmacoepidemiology. (Strom BL, Ed). 4th edition. Chichester, England: John Wiley. 2005. pp.337-346.

❖ Examples of GPRD™ Publications

○ Publications by CCEB Investigators

Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, Bilker WB, Pettitt D. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med.* 2003;349:1628-35.

BACKGROUND: The safety of sulfonamide nonantibiotics is unclear in patients with prior allergic reactions to sulfonamide antibiotics. METHODS: We conducted a retrospective cohort study using the General Practice Research Database in the United Kingdom, examining the risk of allergic reactions within 30 days after the receipt of a sulfonamide nonantibiotic. Patients with evidence of prior hypersensitivity after the receipt of a sulfonamide antibiotic were compared with those without such evidence. Similar analyses were also performed with the use of penicillins instead of sulfonamides, to determine whether any risk was specific to sulfonamide cross-reactivity. RESULTS: Of 969 patients with an allergic reaction after a sulfonamide antibiotic, 96 (9.9 percent) had an allergic reaction after subsequently receiving a sulfonamide nonantibiotic. Of 19,257 who had no allergic reaction after a sulfonamide antibiotic, 315 (1.6 percent) had an allergic reaction after receiving a sulfonamide nonantibiotic (adjusted odds ratio, 2.8; 95 percent confidence interval, 2.1 to 3.7). However, the risk of allergic reactions was even greater after the receipt of a penicillin among patients with a prior hypersensitivity reaction to a sulfonamide antibiotic, as compared with patients

with no such history (adjusted odds ratio, 3.9; 95 percent confidence interval, 3.5 to 4.3). Furthermore, among those with a prior hypersensitivity reaction after the receipt of a sulfonamide antibiotic, the risk of an allergic reaction after the subsequent receipt of a sulfonamide nonantibiotic was lower than the risk of an allergic reaction after the subsequent receipt of a penicillin (adjusted odds ratio, 0.7; 95 percent confidence interval, 0.5 to 0.9). Finally, the risk of an allergic reaction after the receipt of a sulfonamide nonantibiotic was lower among patients with a history of hypersensitivity to sulfonamide antibiotics than among patients with a history of hypersensitivity to penicillins (adjusted odds ratio, 0.6; 95 percent confidence interval, 0.5 to 0.8). CONCLUSIONS: There is an association between hypersensitivity after the receipt of sulfonamide antibiotics and a subsequent allergic reaction after the receipt of a sulfonamide nonantibiotic, but this association appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs.

Apter AJ, Kinman JL, Bilker WB, Herlim M, Margolis DJ, Lautenbach E, Hennessy S, Strom BL. Represcription of penicillin after allergic-like events. *J Allergy Clin Immunol*. 2004;113:764-70.

OBJECTIVE: We sought to determine the frequency of represcription of penicillin to individuals with penicillin allergy and the risk of a second reaction in those who had a previous reaction. METHODS: A retrospective cohort study was conducted within the UK General Practice Research Database. All patients who had received a prescription for penicillin were identified. Within that source population, records of patients who had received at least 2 prescriptions for penicillin at least 60 days apart were selected and examined for allergic-like (hypersensitivity) events on the day of or within 30 days after a prescription. RESULTS: At least one prescription for penicillin was given to 3,375,162 patients. Of 6212 (0.18%) patients who experienced an allergic-like event after the initial prescription, 48.5% were given a second prescription compared with 59.8% of those without an initial allergic-like event (risk ratio, 0.81; 95% CI, 0.79-0.83). Two or more prescriptions for penicillin were given to 2,017,957 patients. Three thousand fourteen (0.15%) patients experienced an allergic-like event after the first prescription, and 57 (1.89%) of those had another event after the second prescription. The unadjusted odds ratio of an allergic-like event after the second prescription for those who experienced an allergic-like event after the first prescription, compared with those who had no initial event was 11.2 (95% CI, 8.6-14.6). Adjusting for confounding had no substantive effect on this result. CONCLUSION: The risk of an allergic-like event after penicillin is markedly increased in those who have had a prior event, although the absolute difference is small (1.72%). Represcription of penicillin to such patients is more frequent than anticipated.

Margolis DJ, Bilker W, Knauss J, Baumgarten M, Strom BL. The incidence and prevalence of pressure ulcers among elderly patients in general medical practice. *Ann Epidemiol*. 2002;12:321-5.

PURPOSE: The objective of this study was to estimate the period prevalence and incidence of pressure ulcer among those 65 years of age and older. METHODS: We used a patient-record database called the General Practice Research Database (GPRD™). Subjects were 65 years of age and older and cases were ascertained based on strict inclusion and exclusion criteria. The accuracy of the ascertainment strategy was estimated using mailed physician-answered questionnaires. Annual period prevalence and age-specific incidence were estimated per 100 person-years with exact 95% confidence intervals (CI). RESULTS: The accuracy of our ascertainment strategy was excellent, with a positive predictive value of 100% (95% CI: 92%,100%) and negative predictive value of 95% (85%, 95%). Over 200,000 person-years of data were analyzed. The annual period prevalence of pressure ulcer among those 65 years of age and older varied from 0.31% to 0.70%. The incidence varied significantly with advancing patient age from 0.18 to 3.36 per 100-person years ($p < 0.001$) but was not

associated with gender (p = 0.95). CONCLUSIONS: Pressure ulcers are seen in the general practice setting. They are most likely to occur in those over 85 years of age. Preventative strategies within the general practice setting should concentrate on the oldest of the elderly.

Margolis DJ, Knauss J, Bilker W. Medical conditions associated with venous leg ulcers. *Br J Dermatol*. 2004;150:267-73.

BACKGROUND: In patients who have a venous leg ulcer, very little is known about the frequency of their concomitant medical conditions. OBJECTIVES: To evaluate the frequency that other medical conditions are associated with a new venous leg ulcer. METHODS: We studied a 10% random sample of elderly patients registered in the General Practice Research Database between 1988 and 1996. We describe the frequency of medical conditions using simple percentages. In order to assess the associations between medical conditions and the onset of a venous leg ulcer, we used logistic regression models. RESULTS: Several medical conditions occur commonly in patients who develop venous leg ulcers, including anaemia, angina, asthma, cellulitis of the lower extremity, depression, diabetes, limb oedema, hypertension, osteoarthritis, pneumonia and urinary tract infection. After statistical adjustment many medical conditions were significantly associated with those who had recent onset of a venous leg ulcer, including asthma, cellulitis of the lower extremity, congestive heart failure, diabetes, deep venous thrombosis, lower limb oedema, osteoarthritis, peripheral vascular arterial disease of the lower extremity, rheumatoid arthritis, history of hip surgery, and history of venous surgery/ligation. Unexpectedly, some illnesses were inversely associated with those that had recent onset of a venous leg ulcer, including angina, cerebral vascular accident, depression, malignancy, myocardial infarction, pneumonia and urinary tract infection. CONCLUSIONS: Physicians caring for individuals with venous leg ulcers need to be aware that it is likely that these individuals may have one of the comorbid illnesses listed above.

Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. *J Invest Dermatol*. 2006;126:2194-201.

Psoriasis is a common, chronic, inflammatory disease. Psoriasis has been hypothesized to be associated with an increased risk of lymphoma due to its pathophysiology, its treatments, or a combination of these factors. We performed a large population-based cohort study of the risk of lymphoma in psoriasis patients using the General Practice Research Database. We identified 153,197 patients with psoriasis and 765,950 corresponding subjects without psoriasis. Psoriasis patients who received a systemic treatment consistent with extensive disease were classified as severe (N=3,994) and those who did not receive systemic therapies were classified as mild (N=149,203). The analyses were adjusted for age, gender, and person-time using a Cox proportional hazards model. For mild and severe psoriasis patients, the respective adjusted relative risks for lymphoma and its subtypes were as follows: all lymphoma 1.34 (1.16, 1.54) and 1.59 (0.88, 2.89); non-Hodgkin's lymphoma 1.15 (0.97, 1.37) and 0.73 (0.28, 1.96); Hodgkin's lymphoma (HL) 1.42 (1.00, 2.02) and 3.18 (1.01, 9.97); cutaneous T-cell lymphoma (TCL) 4.10 (2.70, 6.23) and 10.75 (3.89, 29.76). Psoriasis is associated with an increased risk of lymphoma. The association is strongest for HL and CTCL. The excess risk of lymphoma attributed to psoriasis was 7.9/100,000 psoriasis patients per year. Although patients with psoriasis have an increased relative risk of lymphoma, the absolute risk attributable to psoriasis is low given that lymphoma is a rare disease and the magnitude of association is modest.

Margolis DJ, Knauss J, Bilker W. Hormone replacement therapy and prevention of pressure ulcers and venous leg ulcers. *Lancet*. 2002;359:675-7.

Pressure ulcers and venous leg ulcers are common chronic wounds. Oestrogens in the form of hormone replacement therapy (HRT) might have an effect on wound healing, but this possibility has not been studied in detail. Using a case-cohort study including elderly patients in the UK General Practice Research Database, we showed that patients who received HRT were less likely to develop a venous leg ulcer (age-adjusted relative risk 0.65 [95% CI 0.61-0.69]) or a pressure ulcer (0.68 [0.62-0.76]) than those who did not use HRT. Therefore, we believe that HRT could be beneficial for the prevention of these wounds.

Hennessy S, Bilker WB, Knauss JS, Kimmel SE, Margolis DJ, Morrison MF, Reynolds RF, Glasser DB, Strom BL. Comparative cardiac safety of low-dose thioridazine and low-dose haloperidol. *Br J Clin Pharmacol*. 2004;58:81-7.

AIM: To compare the rate of ventricular arrhythmia, sudden death and unexplained or unattended death among users of thioridazine and haloperidol. METHODS: Observational cohort study of thioridazine and haloperidol users in the UK General Practice Research Database (GPRD™) using data from 1987 through 29 June 2000. Patients were followed for 30 days following each study prescription. The event of interest was a diagnosis of ventricular arrhythmia, sudden death, or unexplained or unattended death. Cox regression was used to calculate rate ratios (RRs) and 95% confidence intervals (CIs), to examine potential confounding factors, and to examine dose-response relationships. RESULTS: Use of thioridazine and haloperidol in the GPRD™ was primarily in older patients, at low dose (median daily dose 31 mg thioridazine, 1.8 mg haloperidol). There was no association between thioridazine use and the rate of ventricular arrhythmia, sudden death, and unexplained or unattended death (adjusted RR 0.9, 95% CI 0.7, 1.1). The rate did not appear to increase with dose for either drug over the range observed. CONCLUSIONS: These results suggest that low-dose thioridazine and haloperidol have similar cardiac safety.

Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiol Drug Saf.* 2005;14:443-51.

BACKGROUND: The General Practice Research Database (GPRD™) is widely used to study incidence rates. This study examines whether incidence rates are overestimated during the first year after registration, how long one needs to wait to obtain accurate incidence rates, and whether the time period of overestimation differs among disease types. METHODS: We measured incidence rates of nine acute, eight chronic, and eight neoplastic outcomes in 3-month intervals through month 36 after enrollment in GPRD™. The incidence rates in months 13-36 were used to estimate baseline incidence rates for each diagnosis. RESULTS: For patients registering with practices that were already UTS, incidence rates were highest in the first 3 months after registration. In eight of nine acute diagnoses, the incidence rate was within 20% of baseline by months 4-6; and in seven of eight cancers, the incidence rate was within 20% of baseline by months 7-9. For chronic conditions, the incidence rate in months 10-12 differed from baseline by more than 20% for five of the eight outcomes, respectively. For patients registering prior to UTS, incidence rates during the first quarter were within 20% of baseline for all acute and cancer diagnoses and six of eight chronic diagnoses. CONCLUSIONS: Reported incidence rates are highest in the first 3 months after registration with an UTS practice and decline to baseline over the first year, more quickly for acute conditions than chronic conditions. For patients who registered prior to UTS, incidence rates are near the baseline level at the start of follow-up.

Yang YX, Hennessy S, Lewis JD. Type 2 diabetes mellitus and the risk of colorectal cancer. *Clin Gastroenterol Hepatol*. 2005;3:587-94.

BACKGROUND & AIMS: Type 2 diabetes mellitus might increase the risk of colorectal cancer on the basis of chronic hyperinsulinemia and hyperglycemia. However, epidemiologic evidence for this association is inconclusive. We conducted a population-based study to clarify this association. METHODS: We conducted a case-control study in the United Kingdom General Practice Research Database. Cases included all patients with incident colorectal cancer diagnoses (n = 10,447). Up to 10 control subjects were selected for each case, matching on year of birth, enrollment date, and duration of database follow-up. The exposure of interest was type 2 diabetes mellitus. Odds ratios (ORs) were calculated by using conditional logistic regression. RESULTS: A prior diagnosis of type 2 diabetes mellitus was associated with a modestly increased risk of colorectal cancer (OR, 1.42; 95% confidence interval [CI], 1.25-1.62). The association between type 2 diabetes mellitus and colorectal cancer was observed in both men (OR, 1.36; 95% CI, 1.16-1.61) and women (OR, 1.38; 95% CI, 1.14-1.67). The risk increase was observed in both colon (OR, 1.45; 95% CI, 1.25-1.70) and rectal (OR, 1.34; 95% CI, 1.08-1.68) cancers. CONCLUSIONS: Type 2 diabetes mellitus is associated with an increased risk of colorectal cancer. The risk increase is present in both sexes, as well as in both colonic and rectal cancers.

Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology*. 2004;127:1044-50.

BACKGROUND & AIMS: Endogenous hyperinsulinemia in the context of type 2 diabetes mellitus is potentially associated with an increased risk of colorectal cancer. We aimed to determine whether insulin therapy might increase the risk of colorectal cancer among type 2 diabetes mellitus patients. METHODS: We conducted a retrospective cohort study among all patients with a diagnosis of type 2 diabetes mellitus in the General Practice Research Database from the United Kingdom. We excluded patients with <3 years of colorectal cancer-free database follow-up after the diabetes diagnosis as well as those insulin users who developed colorectal cancer after <1 year of insulin therapy. The remaining insulin users and the noninsulin-using type 2 diabetic patients were followed for the occurrence of colorectal cancer. Hazard ratios (HR) were determined in Cox proportional hazard analysis. A nested case-control study was conducted to perform multivariable analysis and to determine a duration-response effect. RESULTS: The incidence of colorectal cancer in insulin users (n = 3160) was 197 per 100,000 person-years, compared with 124 per 100,000 person-years in type 2 diabetes mellitus patients not receiving insulin (n = 21,758). The age- and sex-adjusted HR of colorectal cancer associated with > or =1 year of insulin use was 2.1 (95% CI: 1.2-3.4, P = 0.005). The positive association strengthened after adjusting for potential confounders. The multivariable odds ratio associated with each incremental year of insulin therapy was 1.21 (95% CI: 1.03-1.42, P = 0.02). CONCLUSIONS: Chronic insulin therapy significantly increases the risk of colorectal cancer among type 2 diabetes mellitus patients.

Lewis JD., Bilker WB., Brensinger C., Deren JJ., Vaughn DJ., Strom BL.: Inflammatory bowel disease is not associated with an increased risk of lymphoma. *Gastroenterology* 2001;121: 1080-7.

BACKGROUND & AIMS: Previous studies of the risk of lymphoma in inflammatory bowel disease patients have provided conflicting results. This study examines the risk of Hodgkin's and non-Hodgkin's lymphoma among patients with inflammatory bowel

disease. METHODS: The authors performed a retrospective cohort study using the General Practice Research Database. Inflammatory bowel disease patients were matched to randomly selected controls on age, sex, and primary care practice. Lymphoma rates were also compared with published age- and sex-specific rates. RESULTS: The study included 6605 patients with Crohn's disease, 10,391 with ulcerative colitis, and 60,506 controls followed for an average of 3.7, 3.9, and 4.4 years, respectively. The incidence of lymphoma was not increased in patients with inflammatory bowel disease (relative risk = 1.20; 95% CI, 0.67-2.06). In subgroup analyses, an increased risk was not observed among patients with Crohn's disease (relative risk = 1.39; 95% CI, 0.50-3.40) or ulcerative colitis (relative risk = 1.11; 95% CI, 0.51-2.19). Compared with inflammatory bowel disease patients not treated with azathioprine or 6-MP, the relative risk of lymphoma among the 1465 inflammatory bowel disease patients treated with these medications (average, 106 mg/day for 2.0 years) was 1.27 (95% CI 0.03-8.20). CONCLUSIONS: Patients with inflammatory bowel disease do not have an increased risk of lymphoma as compared with the general population. Although we cannot completely rule out a modest increased risk of lymphoma with azathioprine or 6-MP therapy, an increased risk was not observed in this cohort.

Lewis JD, Brensinger C, Bilker WB, Strom BL. Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. *Pharmacoepidemiol Drug Saf.* 2002;11:211-8.

PURPOSE: The objective of this study was to evaluate the validity and completeness of the General Practice Research Database (GPRD™) as a tool for research into inflammatory bowel disease epidemiology. METHODS: Patients diagnosed with inflammatory bowel disease were identified from GPRD™. Mailed surveys were sent to the general practitioner caring for a stratified random sample of 170 of these patients and collected information on the diagnosis of inflammatory bowel disease and the most recent surgery and hospitalization. RESULTS: Usable surveys were returned for 157 patients (92%). The inflammatory bowel disease diagnosis was highly probable or probable in 144 (92%, 95% CI 86 to 96%). Among the 53 patients with a potentially incident inflammatory bowel disease diagnosis, 33 (62%) had the first recorded diagnosis in GPRD™ within 30 days of the date reported in the survey (median difference -8 days; interquartile range 0 to -81 days). Of 12 surgeries and 25 hospitalizations reported in the survey, 11 (92%) and 19 (76%) were identified in GPRD™, respectively. CONCLUSIONS: The diagnosis of inflammatory bowel disease in GPRD™ appears reliable for most patients. Important medical events such as hospitalizations and surgery are recorded at a high rate, although algorithms to identify these events are complex.

Lewis JD, Brensinger C. Agreement between GPRD™ smoking data, a survey of general practitioners, and a population-based survey. *Pharmacoepidemiology Drug Safety*. 2004;13:437-441

BACKGROUND: Cigarette smoking is a common habit that is associated with many diseases. Smoking is often an important confounding variable in pharmacoepidemiological studies. The General Practice Research Database (GPRD™) is widely used in pharmacoepidemiological research. In this study, we compare data recorded in the GPRD™ with the smoking history obtained from direct query of general practitioners (GPs) and from a population-based survey. METHODS: We completed a mailed survey of GPs caring for a random sample of 150 patients with inflammatory bowel disease. The survey asked the GP to categorize the patients smoking status on a specified date. These results were then compared to the data recorded in the GPRD™. Smoking status of 225,308 randomly selected GPRD™ patients without inflammatory bowel disease was compared to the results of a population-based household survey. RESULTS: Completed

surveys with usable data were received from GPs on 136 of the 150 patients (91%). The sensitivity and positive predictive value of the database for current smoking were 78% (95% CI: 52-94) and 70% (95% CI: 46-88) respectively. The sensitivity and positive predictive value of former smoking were 53% (95% CI: 28-77) and 60% (95% CI: 32-84) respectively. Current and former smoking rates in the GPRD™ were 79% and 29% respectively of expected rates according to the population-based survey. CONCLUSIONS: Current smoking is more completely recorded in the GPRD™ than former smoking. These data need to be considered when planning GPRD™ studies where smoking is an important exposure variable.

Gupta G, Gelfand JM, Lewis JD. Increased risk of demyelinating diseases in patients with inflammatory bowel disease. *Gastroenterology*. 2005;129:819-26.

BACKGROUND & AIMS: Reports of multiple sclerosis (MS), demyelination, and optic neuritis (ON) associated with anti-tumor necrosis factor alpha therapy resulted in warnings on prescribing instructions for infliximab, etanercept, and adalimumab. However, the underlying relationship between IBD and these neurologic conditions has not been established. METHODS: We performed a retrospective cohort study and a retrospective cross-sectional study using 1988 to 1997 data from the General Practice Research Database. A total of 7988 Crohn's disease and 12,185 ulcerative colitis patients were matched for age, sex, and primary care practice to 80,666 randomly selected controls. In the cohort study, incident cases of MS, demyelination, and/or ON (MS/D/ON) had to occur at least 1 year after registration with the physician and after the diagnosis of IBD. In the cross-sectional study, the diagnosis of MS/D/ON could either precede or follow the IBD diagnosis. RESULTS: In the cohort study, the incidence of MS/D/ON was higher in patients with Crohn's disease and ulcerative colitis compared with their matched controls, reaching statistical significance for ulcerative colitis (ulcerative colitis incidence rate ratio [IRR], 2.63; 95% confidence interval, 1.29-5.15; Crohn's disease IRR, 2.12; 95% confidence interval, .94-4.50). In the cross-sectional study, MS/D/ON was more prevalent in patients with Crohn's disease and ulcerative colitis compared with their matched controls (Crohn's disease odds ratio, 1.54; 95% confidence interval, 1.03-2.32; ulcerative colitis odds ratio, 1.75; 95% confidence interval, 1.28-2.39). CONCLUSIONS: Demyelinating diseases occur more commonly among patients with IBD than among non-IBD patients. Future studies should clarify whether treatment with tumor necrosis factor alpha blockers results in further increased incidence of MS/D/ON among IBD patients.

Lewis JD, Aberra FN, Lichtenstein GR, Bilker WB, Brensinger C, Strom BL. Seasonal variation in flares of inflammatory bowel disease. *Gastroenterology* 2004;126:665-73.

BACKGROUND & AIMS: Previous research has yielded conflicting data as to whether the natural history of inflammatory bowel disease follows a seasonal pattern. The purpose of this study was to determine whether relapse of inflammatory bowel disease follows a seasonal pattern either across a cohort of patients or within individual patients. METHODS: We used 1988 to 1997 data from the General Practice Research Database to conduct a retrospective cohort study of 1587 patients with Crohn's disease (mean age at start of follow-up, 41 +/- 17 years) and 2773 patients with ulcerative colitis (mean age at start of follow-up, 48 +/- 16 years). Flares of disease were identified by receipt of a new prescription for either corticosteroids or 5-ASA medications following an interval of at least 4 months without prescriptions for either class of medication. Logistic regression was used to adjust the association of season of the year and flare of disease for potential confounding variables. RESULTS: There was no association between season of the year and flare of Crohn's disease (P = 0.66). Season of the year was only weakly associated with flares of ulcerative colitis (P = 0.02). Compared with winter, spring had very slightly

higher rates of flares (OR = 1.13, 95% CI: 1.05-1.23). We did not observe seasonal patterns within individual patients experiencing multiple flares (P > 0.05 for Crohn's disease and ulcerative colitis). CONCLUSIONS: Although we observed a slight increase in exacerbations of ulcerative colitis in the spring, in general, these data do not support an association between season of the year and flares.

Aberra FN, Brensinger CM, Bilker WB, Lichtenstein GR, Lewis JD. Antibiotic use and the risk for flares of Inflammatory Bowel Disease. *Clinical Gastroenterology and Hepatology*. 2005; 3:459-65.

BACKGROUND & AIMS: Intestinal microbial flora participate in the pathogenesis of inflammatory bowel disease. Because antibiotic therapy alters intestinal microbial flora, we hypothesized that use of antibiotics might decrease the risk of flare. METHODS: We conducted a case-crossover study by using the General Practice Research Database from 1989-1997. Flares of disease were identified by receipt of a new prescription for either corticosteroids or mesalamine medications after an interval of at least 4 months without prescriptions for either class of medication. The primary exposure was receipt of any antibiotics in the 60 days preceding the index date. RESULTS: Among 1205 patients with Crohn's disease, exposure to antibiotics was associated with a reduced risk of flare (adjusted odds ratio [OR], 0.78; 95% confidence interval [CI], 0.64-0.96; P = .019). The effect was strongest with more recent exposure (test for trend, P < .05). Among 2230 patients with ulcerative colitis, use of any antibiotics within 60 days was not associated with flare of disease (adjusted OR, 0.96; 95% CI, 0.82-1.12; P = .581), although a potentially protective effect was observed in those patients with very recent exposure (exposure within 15 days: OR, 0.66; 95% CI, 0.51-0.85). CONCLUSIONS: Antibiotic use within 60 days was associated with a lower risk of flare of Crohn's disease, but not ulcerative colitis. The strength of the protective effect of antibiotics in Crohn's disease wanes over time.

Srinivasan R., Yang YX, Rubin SC, Morgan MA, Lewis JD. Women with a Prior Diagnosis of Breast Cancer Are Not at an Increased Risk for Subsequent Colorectal Cancer. *American Journal of Gastroenterology*. 2005:100:2759-64.

BACKGROUND: Earlier studies regarding the risk of colorectal cancer in women with a prior diagnosis of breast cancer yielded conflicting results. METHODS: A retrospective cohort study was performed using the General Practitioner Research Database of the United Kingdom. Women with a prior diagnosis of breast cancer were compared with female control patients without a prior history of breast cancer. The primary outcome was an incident diagnosis of colorectal cancer. Poisson regression analysis was utilized to assess the effects of potential confounder variables. RESULTS: The study included 17,415 breast cancer patients and 69,660 matched control patients with follow-up time in person years of 52,914 and 331,480, respectively. The relative rate of colorectal cancer among breast cancer patients was 0.80 (95% CI 0.56-1.15). The relative rate of colorectal cancer among women exposed and unexposed to tamoxifen were 0.73 (95% CI 0.49-1.08) and 1.81 (95% CI 0.85-3.85), respectively. CONCLUSION: Women with a prior diagnosis of breast cancer are not at an increased risk of colorectal cancer; these women can follow average risk screening guidelines for colorectal cancer.

Burnham JM, Shults J, Weinstein R, Lewis JD, Leonard MB. Childhood-onset arthritis is associated with an elevated risk of fracture: a population-based study using the General Practice Research Database. *Annals of Rheumatic Diseases*. 2006;65:1074-9.

BACKGROUND: Childhood onset arthritis is associated with low bone mass and strength. OBJECTIVE: To determine whether childhood onset arthritis is associated with greater fracture risk. METHODS: In a retrospective cohort study all subjects with onset of arthritis between 1 and 19 years of age in the United Kingdom General Practice Research Database were identified. As controls, all sex and age matched subjects from a practice that included a subject with arthritis were included. Incidence rate ratios (IRRs) for first fracture were generated using Mantel-Haenszel methods and Poisson regression. RESULTS: 1939 subjects with arthritis (51% female) and 207 072 controls (53% female) were identified. The median age at arthritis diagnosis was 10.9 years. A total of 129 (6.7%) first fractures were noted in subjects with arthritis compared with 6910 (3.3%) in controls over a median follow up of 3.90 and 3.95 years in the subjects with arthritis and controls, respectively. The IRR (95% confidence interval) for first fracture among subjects with arthritis, compared with controls, according to the age at the start of follow up were 1.49 (0.91 to 2.31) for age <10 years, 3.13 (2.21 to 4.33) at 10-15 years, 1.75 (1.18 to 2.51) at 15-20 years, 1.40 (0.91 to 2.08) at 20-45 years, and 3.97 (2.23 to 6.59) at >45 years. CONCLUSIONS: Childhood onset arthritis is associated with a clinically significant increased risk of fracture in children, adolescents and, possibly, adults. Studies are urgently needed to characterise the determinants of structural bone abnormalities in childhood arthritis and devise prevention and treatment strategies.

Gupta G, Lautenbach E, Lewis JD. Incidence and Risk Factors for Herpes Zoster among Patients with Inflammatory Bowel Disease. *Clinical Gastroenterology and Hepatology*. In press.

Background & Aims: An increased risk of herpes zoster in patients with inflammatory bowel disease (IBD) is hypothesized based on altered immune function, especially among patients receiving immunosuppressive medications. Methods: We performed a retrospective cohort study and a retrospective nested case-control study using 1988-1997 data from the General Practice Research Database. In the cohort study, 7823 Crohn's disease (CD) and 11,930 ulcerative colitis (UC) patients were matched on age, sex, and primary care practice to 79,563 randomly selected controls without CD or UC. In the nested case-control study, 185 CD patients with zoster and 266 UC patients with zoster were matched on sex and year of birth to 1787 IBD patients without zoster. Results: In the cohort study, the incidence of zoster was higher in patients with CD and UC compared with their matched controls (UC incidence rate ratio, 1.21; 95% confidence interval [CI], 1.05-1.40; CD incidence rate ratio, 1.61; 95% CI, 1.35-1.92). In the nested case-control study, receipt of a prescription for corticosteroids (adjusted odds ratio, 1.5; 95% CI, 1.1-2.2) or azathioprine/6-mercaptopurine (adjusted odds ratio, 3.1; 95% CI, 1.7-5.6) were both associated with zoster. Conclusions: Patients with IBD, especially those on immunosuppressive medications, are at higher risk for herpes zoster compared with the general population. Future studies should clarify the relative risk associated with anti-tumor necrosis factor alpha therapies and determine the use of the new zoster vaccine for patients with IBD.

Srinivasan R, Yang YX, Rubin SC, Morgan MA, Lewis JD. Risk of colorectal cancer in women with a prior diagnosis of gynecological malignancy. *J Clin Gastroenterol* 2006. In press.

Yang YX, Lewis JD, Epstein S, Metz DC. Chronic proton pump inhibitor therapy and hip fracture risk. *JAMA*. In press.

○ Selected Publications by Other Investigators

de Vries F, de Vries C, Cooper C, Leufkens B, van Staa TP. Reanalysis of two studies with contrasting results on the association between statin use and fracture risk: the General Practice Research Database. *Int J Epidemiol*. 2006;35:1301-8.

BACKGROUND: Two recent case-control studies by Meier et al. and van Staa et al. used the UK General Practice Research Database (GPRD™) to examine the association between the use of statins and the risk of fractures, with different results. The objective of the present study was to examine methodological explanations for the discrepant results. METHODS: We created two datasets, which mimicked the previous study designs: a 'selected population' (SP) case-control dataset, with fracture cases matched to controls nested within a selected cohort (Meier et al.), and an 'entire population' (EP) case-control dataset, with both cases and controls sampled from the total GPRD™ population (van Staa et al.). Cases and controls were matched by gender, age (year of birth or 5 year age bands), and general practice. RESULTS: The study included 131 855 fracture cases. The crude odds ratio (OR) for hip fracture in statin users was 0.37 (95% CI 0.27-0.52) in the SP and 0.54 (95% CI 0.39-0.74) in the EP dataset. This difference was reduced when matching by year of birth, rather than by 5 year age bands: crude ORs were 0.58 (95% CI 0.43-0.79) and 0.61 (95% CI 0.44-0.88), respectively. In the SP dataset, 37% of the cases could be matched by year of birth, while this was achieved for 99% in the 'EP' dataset. The exposure time-window, the selection of confounders, and exclusion of high-risk patients also influenced results. CONCLUSION: Residual confounding by a matching variable and different definitions of the exposure time window explained differences in results. In case-control studies of drug use and fracture risk, broad matching criteria for age should be avoided and the selection of the time-window for exposure should be carefully considered.

Jick H, Kaye JA, Russmann S, Jick SS. Nonsteroidal antiinflammatory drugs and acute myocardial infarction in patients with no major risk factors. *Pharmacotherapy*. 2006;26:1379-87.

STUDY OBJECTIVE: To assess the risk of long-term use of five nonsteroidal antiinflammatory drugs (NSAIDs)--rofecoxib, celecoxib, ibuprofen, naproxen, and diclofenac--in relation to acute myocardial infarction. DESIGN: Five separate nested case-control studies, one for each NSAID, designed to minimize important biases present in other observational studies. Setting. University-affiliated research program. Data Source. The United Kingdom General Practice Research Database (GPRD™**).** MEASUREMENTS AND MAIN RESULTS: We identified all people in the GPRD™ aged 30-79 years who had a first recorded prescription for rofecoxib, celecoxib, ibuprofen, naproxen, or diclofenac after January 1, 1999. Cases of newly diagnosed, first-time acute myocardial infarction were then identified from the study population, along with matched control subjects. Relative risk estimates for acute myocardial infarction in patients with no recorded major clinical risk factors for acute myocardial infarction were determined for each NSAID according to receipt of 2-4, 5-9, 10-19, or 20 or more prescriptions compared with receipt of only 1 prescription. Results were adjusted for relevant variables possibly related to the risk for acute myocardial infarction. No material elevation of risk according to the number of prescriptions received for ibuprofen or naproxen was noted. However, a substantial increased risk similar to that found in clinical trials was noted in patients who received 10 or more prescriptions for rofecoxib, celecoxib, or diclofenac. CONCLUSION: Extensive use of rofecoxib, celecoxib, and diclofenac increases the risk of acute myocardial infarction, but similar use of ibuprofen and naproxen does not.

Filion KB, Chris Delaney JA, Brophy JM, Ernst P, Suissa S. The impact of over-the-counter simvastatin on the number of statin prescriptions in the United Kingdom: a view from the General Practice Research Database. *Pharmacoepidemiol Drug Saf.* 2006 Sep 5; [Epub ahead of print]

PURPOSE: The United Kingdom (UK) government changed the prescription policy of statins, making low-dose simvastatin (10 mg) available as an over-the-counter (OTC) drug in August 2004. We assessed the impact of this policy change on statin prescribing. METHODS: We examined all statin prescriptions in **the General Practice Research Database (GPRD™)**, a well-validated database of approximately 3.5 million patients, from the first quarter of 2001 to the second quarter of 2005. RESULTS: From 2001, the number of statin prescriptions written for GPRD™ patients was increasing by approximately 437 prescriptions per 100,000 people per quarter until the time of the policy change. Over the four quarters post-policy implementation, however, this trend changed abruptly ($p < 0.0001$) with a decrease of 281 prescriptions per 100,000 people per quarter. This decrease was not restricted to prescriptions of 10 mg statins but was also observed for statin prescriptions of >/=20 mg. Several other cardiovascular medications displayed a similar trend as that observed in the number of statin prescriptions. This trend was not observed among non-cardiovascular control medications. CONCLUSIONS: Our study suggests that the policy allowing the OTC sale of 10 mg simvastatin has had a significant impact on statin prescriptions by general practitioners. However, this new policy may also be leading to less aggressive statin therapy. An alternative explanation for the observed decrease in statin prescriptions may be related to the unknown factors responsible for the overall decrease observed with other cardiovascular prescription drugs.

Brankin E, Walker M, Lynch N, Aspray T, Lis Y, Cowell W. The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from three databases. *Curr Med Res Opin*. 2006;22:1249-56.

BACKGROUND: Bisphosphonates are currently among the most effective therapies for the treatment of osteoporosis and provide one of the mainstays of treatment in the UK. However studies in several countries have all reported sub-optimal compliance and persistence with treatment. OBJECTIVE: To examine the impact of dosing frequency on compliance and persistence with bisphosphonates in the UK. METHODS: Three UK General Practitioner sourced databases, the General Practice Research Database (GPRD™), IMS Disease Analyzer (MEDIPLUS) and the Doctors Independent Network Database (DIN-LINK) were used to identify bisphosphonate naive postmenopausal women. In each of the three retrospective analyses women were grouped into weekly or daily cohorts and followed for 12 months from an initial prescription. Compliance was measured as a Medication Possession Ratio (MPR), defined as the proportion of days for which patients had prescription coverage. Persistence was measured as the number of continuous days of treatment from the initial prescription to the end of the last prescription issued in the follow-up period. RESULTS: GPRD™, MEDIPLUS and DIN-LINK provided access to 7567, 5962 and 1801 women, respectively. All three analyses consistently demonstrated that those on weekly regimens had a higher MPR than those on daily regimens (GPRD™ 76.2%, CI(95%,) 75.4-77.0 vs. 63.5%, CI(95%) 61.2-65.8, MEDIPLUS 70.3%, CI(95%) 69.3-71.2 vs. 56.3%, CI(95%) 53.8-58.9, DIN-LINK 59.5%, CI(95%) 59.4-59.6 vs. 46.3%, CI(95%) 45.9-46.7) ($p < 0.0001$) and persisted longer with treatment (GPRD™ 249, CI(95%) 246-253 vs. 208, CI(95%) 199-217, MEDIPLUS 228, CI(95%) 224-231 vs. 186, CI(95%,) 176-196, DIN-LINK 235, CI(95%) 234-236 vs. 189, CI(95%) 187-191) days respectively), ($p < 0.0001$). CONCLUSIONS: Although this study only provided an indirect measure of medication usage, it demonstrated that a less frequent dosing regimen significantly improved levels of both compliance and

persistence; however, even on weekly regimens bisphosphonate usage remains sub-optimal thereby reducing the clinical benefits.

Handoko KB, Souverein PC, van Staa TP, Meyboom RH, Leufkens HG, Egberts TC, van den Bemt PM. Risk of aplastic anemia in patients using antiepileptic drugs. *Epilepsia.* 2006;47:1232-6

PURPOSE: To assess the association between exposure to antiepileptic drugs (AEDs) and the occurrence of aplastic anemia. METHODS: A retrospective case-control study was conducted using data from the U.K. General Practitioners Research Database (GPRD™). Cases were defined as patients diagnosed with aplastic anemia. For each case, up to three control patients were matched on age, sex, and medical practice. Cases and controls were compared with respect to AED use. The effects of duration of AED use were assessed. Characteristics of individual cases with AED use were reviewed. RESULTS: The study population comprised 173 cases and 497 controls. AED use was more prevalent among cases (9.2%) than among controls (0.8%). After adjustment for confounders, the use of AEDs was significantly associated with aplastic anemia (adjusted odds ratio (OR), 9.5; 95% confidence interval (CI), 3.0-39.7). The most frequently used AEDs were carbamazepine (CBZ), valproic acid (VPA), and phenytoin. The 16 exposed cases were heterogeneous with respect to patient and exposure characteristics: the age of these patients varied from 1 to 92 years, and the duration of AED use varied from 17 days to 6.8 years. CONCLUSIONS: This study indicates that use of AEDs, in particular CBZ and VPA, is associated with a ninefold increased risk of aplastic anemia. Physicians should be alert to the possibility of AED-associated aplastic anemia.

Smith S, Smith GE, Heatlie H, Bashford JN, Ashcroft DM, Verlander NQ, Duckworth GJ, Mason B, Smyth B, Maxwell S. Reducing variation in antibacterial prescribing rates for 'cough/cold' and sore throat between 1993 and 2001: regional analyses using the general practice research database. *Public Health*. 2006;120:752-9.
OBJECTIVE: To use the General Practice Research Database (GPRD™) to explore the regional variation in prescribing for single diagnostic episodes of 'cough/cold' and sore throat and how this changed between 1993 and 2001. METHODS: Data from the GPRD™ was used to conduct a longitudinal survey of morbidity and antibiotic prescribing data. RESULTS: Nationally there has been a substantial reduction in diagnosed episodes per 1000 patient years at risk for both diagnoses: from 104.6 (104.0-105.2) to 86.5 (86.0-86.9) for cough/cold (-17.3%) and from 102.8 (102.2-103.4) to 69.2 (68.8-69.6) for sore throat (-32.6%). In addition to the changes in diagnostic rate there have been reductions in diagnosis-related prescribing: from 41.8% to 34.8% of cough/cold episodes (-7.0%) and from 77.3% to 60.8% of sore throat episodes (-16.4%). These aggregated data conceal wide regional variations. For cough/cold the change in prescribing rate during the study varied from -16.0% to +5.3% and for sore throat from -28.3% to -7.3%. CONCLUSIONS: In addition to a substantial reduction in diagnosis of cough/cold and sore throat, there has been a reduction in diagnosis-related prescribing episodes in almost all regions. Although there continues to be regional variation in diagnosis-related prescribing this has reduced substantially over the 9-year study period.

Hardy JR, Leaderer BP, Holford TR, Hall GC, Bracken MB. Safety of medications prescribed before and during early pregnancy in a cohort of 81,975 mothers from the UK General Practice Research Database. *Pharmacoepidemiol Drug Saf*. 2006;15:555-64.

PURPOSE: To demonstrate a linkage methodology for mother and baby automated medical records, and describe frequency, type, and pregnancy risk level of medications

prescribed during pregnancy in a GPRD™ cohort, 1991-1999. METHODS: We linked records using a two-stage algorithm and selected pairs with > or = 7 months prenatal records and > or = 2 records in baby's first year of life. Periods of interest were: 90 days prior to a woman's earliest identified pregnancy record (Period I), and this record plus 70 days (Period II, approximate early pregnancy). Medications were classified using the British National Formulary and US Food and Drug Administration Pregnancy Risk Categories. RESULTS: We achieved over 80% record linkage and defined a cohort of 81,975. Sixty-five per cent of mothers had > or = 1 prescription during both periods combined. Most frequent medications in Period I were anti-bacterial, contraceptive, topical steroid, and bronchodilator. In Period II, they were folic acid, anti-bacterial, antacid, and gynecological anti-infective. In Period I, 4% were FDA category A (considered safest), 34% B, and 49% C and D combined. By Period II, prescription of category A medications increased (folic acid, iron) while other categories declined. Category X medications, with potential teratogenic risk that outweighs maternal benefit, were prescribed to 5714 (7%) women in Period I, and 501 (0.6%) women in Period II (46% progesterone). CONCLUSIONS: One in every 164 women received a category X prescription in early pregnancy. The visit when pregnancy is first medically recognized represents an opportunity to review prescribed medications in light of contraindication and/or fetal risk

Andersohn F, Schade R, Suissa S, Garbe E. Cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs and the risk of ischemic stroke: a nested case-control study. *Stroke*. 2006;37:1725-30. Epub 2006 May 25

BACKGROUND AND PURPOSE: Several randomized trials and a large number of epidemiological studies have provided evidence of an increased risk of acute myocardial infarction associated with the use of cyclooxygenase (COX)-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs). Few data are available concerning the risk of ischemic stroke associated with COX-2 inhibitors. METHODS: We performed a nested case-control study in a cohort of 469,674 patients registered within the UK General Practice Research Database (GPRD™), who had at least 1 prescription of an NSAID between June 1, 2000 and October 31, 2004. A total of 3094 cases with ischemic stroke were identified and 11 859 controls were matched on age, sex, year of cohort entry and general practice. Odds ratios (ORs) of ischemic stroke associated with the use of COX-2 selective NSAIDs were calculated by conditional logistic regression. RESULTS: Current use of rofecoxib (OR=1.71; 95% CI, 1.33 to 2.18), etoricoxib (OR=2.38; 95% CI, 1.10 to 5.13), but not of celecoxib (OR=1.07; 95% CI, 0.79 to 1.44) was associated with a significantly increased risk of ischemic stroke. For rofecoxib and etoricoxib, ORs tended to increase with higher daily dose and longer duration of use and were also elevated in patients without major stroke risk factors. CONCLUSIONS: Our study suggests that COX-2 selective NSAIDs differ in their potential to cause ischemic cerebrovascular events. An increased risk of ischemic stroke may be influenced by additional pharmacological properties of individual COX-2 inhibitors.

Nightingale AL, Farmer RD, de Vries CS. Systemic lupus erythematosus prevalence in the U.K.: methodological issues when using the General Practice Research Database to estimate frequency of chronic relapsing-remitting disease. *Pharmacoepidemiol Drug Saf*. 2006 May 15; [Epub ahead of print]

PURPOSE: The purpose of this study was to calculate the prevalence of systemic lupus erythematosus (SLE) between 1992 and 1998 using the General Practice Research Database (GPRD™) METHODS: We identified all individuals who had contributed at least 3 years of data to the GPRD™ and who had a diagnosis of SLE with supporting evidence of their diagnosis. We calculated the annual age- and sex-specific prevalence of SLE.

Additionally, we stratified the prevalence by years of data contributed to the GRPD. RESULTS: In males the point estimate of the prevalence of SLE increased from 7.5/100 000 (CI(95) 6.3, 8.8) to 10.1/100 000 (CI(95) 7.8, 12.2) but this rise was not statistically significant. However, prevalence appeared to increase significantly amongst females from 42.6/100 000 (CI(95) 39.6, 45.6) in 1992 to 70.8/100 000 (CI(95) 65.1, 76.6) in 1998. This increase was mainly amongst women aged 50-79 and in those contributing more than 5 years of data and could not be explained by increasing incidence of SLE or decreasing mortality during the study period. CONCLUSIONS: We found an increasing prevalence of SLE that could not be explained by increasing incidence or decreasing mortality. This is almost certainly an artefact caused by the increased likelihood of detecting or confirming cases of chronic relapsing-remitting diseases with increasing time contributed to the GPRD™.

Burke TA, Sturkenboom MC, Lu SE, Wentworth CE, Lin Y, Rhoads GG. Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. *J Hypertens*. 2006;24:1193-200

OBJECTIVES: To evaluate antihypertensive drug discontinuation among newly diagnosed hypertensive patients. METHODS: This was a population-based cohort study using the UK General Practice Research Database (GPRD™). Patients newly diagnosed with hypertension between 1991 and 2001 and subsequently treated with antihypertensive drugs were included. Overall antihypertensive drug discontinuation was evaluated from a patient's first-ever antihypertensive prescription. Class-specific discontinuations were evaluated from a patient's first-ever prescriptions of angiotensin-converting enzyme (ACE) inhibitors (ACE-I), alpha antagonists, angiotensin-2 antagonists (AIIA), beta blockers, calcium-channel blockers (CCB), miscellaneous, potassium-sparing diuretics, and thiazides. Discontinuation occurred when no antihypertensive prescription was issued within 90 days following the most recent prescription expiration. RESULTS: The study population comprised 109 454 patients, with 223 228 antihypertensive drug-class episodes contributing to the class-specific analysis. Overall antihypertensive drug discontinuation was 20.3% [95% confidence interval (CI): 20.0, 20.5%] at 6 months and 28.5% (95% CI: 28.2, 28.7%) at 1 year, with a median time to discontinuation of 3.07 years. The median time to antihypertensive class discontinuation was longest for AIIAs (2.90 years) followed by ACE-I (2.24), CCB (1.86), beta blockers (1.50), thiazides (1.50), alpha antagonists (1.35), potassium-sparing diuretics (0.40), and miscellaneous (0.39). One-year discontinuation ranged from 29.4% (95% CI: 28.0, 30.7) for AIIAs to 64.1% (95% CI: 62.1, 66.3) for potassium-sparing diuretics. Forty-four percent who discontinue their first-ever antihypertensive drug class failed to switch to a different drug class within 90 days of discontinuation. CONCLUSION: It is important that general practitioners (GPs) monitor patients closely in the first year following antihypertensive drug initiation, due to the high early risk of discontinuation, and the low percentage of patients who switch to a different antihypertensive drug class after a drug-class discontinuation. AIIA, followed by ACE-I and CCB, had the lowest risk of discontinuation among antihypertensive drug classes.

Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. *Diabetologia.* 2006;49:660-6. Epub 2006 Jan 24

AIMS/HYPOTHESIS: We compiled up to date estimates of the absolute and relative risk of all-cause mortality in patients with type 1 diabetes in the UK. MATERIALS AND METHODS: We selected patients with type 1 diabetes (n=7,713), and for each of these diabetic subjects five age- and sex-matched control subjects without diabetes

(n=38,518) from the General Practice Research Database (GPRD™). Baseline was 1 January 1992; subjects were followed until 1999. The GPRD™ is a large primary-care database containing morbidity and mortality data of a large sample representative of the UK population. Deaths occurring in the follow-up period were identified. RESULTS: The study comprised 208,178 person-years of follow-up. The prevalence of type 1 diabetes was 2.15/1,000 subjects in 1992 (mean age 33 years, SD 15). Annual mortality rates were 8.0 per 1,000 person-years (95% CI 7.2-8.9) in type 1 diabetic subjects compared with 2.4 per 1,000 person-years (95% CI 2.2-2.6) in those without diabetes (hazard ratio [HR]=3.7, 95% CI 3.2-4.3). The increased mortality rates in patients with type 1 diabetes were apparent across all age-bands. The HR was higher in women (HR=4.5, 95% CI 3.5-5.6 compared with non-diabetic women) than men (HR=3.3, 95% CI 2.7-4.0), such that the sex difference ($p<0.0001$) in mortality in the non-diabetic population was abolished ($p=0.3$) in the type 1 diabetic patients. The predominant cause of death in patients with type 1 diabetes was cardiovascular disease.
CONCLUSIONS/INTERPRETATION: Despite advances in care, UK mortality rates in the past decade continue to be much greater in patients with type 1 diabetes than in those without

Hogler W, Wehl G, van Staa T, Meister B, Klein-Franke A, Kropshofer G. Incidence of skeletal complications during treatment of childhood acute lymphoblastic leukemia: Comparison of fracture risk with the General Practice Research Database. *Pediatr Blood Cancer.* 2007;48:21-7.

BACKGROUND: Skeletal complications during or after treatment of acute lymphoblastic leukemia (ALL) have been frequently reported and can cause substantial morbidity, yet their incidence is not well established. The present study assessed the incidence of fractures, osteonecrosis (ON), and bone pain during ALL treatment and compared the fracture incidence with age- and sex-specific reference data from the UK General Practice Research Database (GPRD™).
PROCEDURE: Medical records of 122 ALL patients diagnosed at our institution from 1992 to 2004 were reviewed for information on fractures, ON, bone pain, and their anatomical location, risk group, phase of antileukemic therapy, and time since diagnosis. Evaluation of skeletal complications was followed up until July 2005 or the patient's death. Thirteen children were excluded as they were transferred to other institutions shortly after diagnosis. RESULTS: Skeletal complications occurred at a 5-year incidence of 32.7%. The 5-year incidence of fractures, ON, and isolated bone pain was 13.5%, 12.1%, and 12.3%, respectively. The relative rate of fractures adjusted for age and sex was 2.03 (95% confidence interval 1.15-3.57) compared to the GPRD™, with greatest rates in children <5 years. Thirty ON occurred in 10 patients with a 15 times greater incidence in children >10 years than in those <5 years. Nearly all skeletal complications occurred during maintenance therapy at a median of 14.92 months (range 0.0-53.8) after diagnosis and in weight-bearing bones. CONCLUSIONS: The doubled fracture rate and the high incidence of skeletal complications during the first years after diagnosis suggest the developing skeleton is very vulnerable in this period. Adolescents develop more ON whereas younger children may be more prone to fractures. Serious "immediate effects" of chemotherapy on bone appear of great concern and should entail preventative studies in this group of patients.