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A red British telephone box is positioned in the lower-left foreground, angled towards the viewer. The word "TELEPHONE" is printed in large, white, serif capital letters on the side of the box, with a black crown emblem above it. In the background, the Elizabeth Tower (Big Ben) is visible, its golden-yellow stone structure and large clock face clearly seen against a light sky. To the right of the tower, the ornate spires of the Palace of Westminster are partially visible. The overall composition suggests a classic London setting.

ISPE'S 2017 MID-YEAR MEETING

April 2-4, 2017 | Royal College of Physicians
London, United Kingdom

SAVE THE DATE!

33rd ICPE

International Conference on Pharmacoepidemiology
& Therapeutic Risk Management

AUGUST 26-30, 2017
PALAIS DE CONGRÈS DE MONTRÉAL
MONTRÉAL, CANADA

ISPE'S 2017 MID-YEAR MEETING

April 2-4, 2017 | Royal College of Physicians
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**The ISPE Board of Directors expresses its appreciation to the members of the
2017 Mid-Year Meeting Planning Committee for their commitment and dedication
to developing an outstanding educational program.**

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ISPE'S 2017 MID-YEAR MEETING

April 2-4, 2017 | Royal College of Physicians
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THANK YOU

**Thank you to the ISPE Student Council and ISPE members for reviewing the student/
recent graduate abstract submissions:**

Heshu Abdullah-Koolmees
Md. Imteyaz Ahmad
Yasser Albogami
Eirini Apostolidou
Mohammad Bakhriansyah
Sheriza Baksh
Raphaelle Beau
Justine Benevent
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Alex Secora
Sonal Sekhar M
Sarah-Jo Sinnott
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Rene Soria-Saucedo
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Xi Wang
Aaron Winn
Alison Wright
Mellissa Yong
Andrew R. Zullo

ISPE'S 2017 MID-YEAR MEETING

April 1-4, 2017 | Royal College of Physicians
London, United Kingdom

*Embracing the Future:
Ensuring Opportunities Become Reality*

PROGRAM SCHEDULE

Saturday, April 1

9:00am-5:00pm

Council Chamber

ISPE BOARD OF DIRECTORS MEETING ISPE members are encouraged to contact staff if interested in attending the Board meeting

Sunday, April 2

7:00am-6:00pm

Lasdun Hall

REGISTRATION

8:00am-12:00pm

Linacre Room

PRE-CONFERENCE COURSE: Introduction to Pharmacoepidemiology
(Registration Required)

This half-day course will provide participants with a short introduction to the basic principles and concepts of pharmacoepidemiology. The course includes lectures on cohort studies, case-control studies, and bias & confounding

Speakers:

- **Almut Winterstein**, FISPE, University of Florida College of Pharmacy, Cohort Studies
- **Jennifer Lund**, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Case-Control Studies
- **Tobias Gerhard**, FISPE, Ernest Mario School of Pharmacy, Rutgers University, Bias & Confounding

8:30am-12:00pm

Dorchester Library

2017 SCIENTIFIC PROGRAM COMMITTEE MEETING

Sunday, April 2 (continued)

12:00pm-1:30pm

LUNCH ON YOUR OWN

1:30pm-5:30pm

Seligman Theatre

PRE-CONFERENCE COURSE: Advanced Topics in Pharmacoepidemiology
(Registration Required)

Speakers:

- **Tim P Morris**, MRC Clinical Trials Unit at UCL, Using simulation studies to evaluate statistical methods
- **Elizabeth Williamson**, London School of Hygiene and Tropical Medicine, Propensity scores – over-hyped or underused?
- **Irene Petersen**, FISPE and **Tra Pham**, Department of Primary Care & Population Health, UCL, What to do when data are going missing?
- **Henrik Stovring**, Aarhus University and **Anton Pottegaard**, University of Southern Denmark, Using the parametric Waiting Time Distribution to estimate prescription durations

5:30pm-7:00pm

Dorchester Library

WELCOME RECEPTION

Monday, April 3

Scientific Symposium - New Data and Student Presentations

7:30am-5:00pm

REGISTRATION

8:30am-9:30am

Osler Long Room

EXHIBITS/REFRESHMENTS

PROGRAM SCHEDULE

Monday, April 3 (continued)

9:30am-9:40am

Wolfson Theatre

WELCOME AND OPENING SESSION

- **Kiyoshi Kubota**, FISPE, ISPE President
- **Alison Bourke**, FISPE, Co-Chair, ISPE 2017 Mid-Year Planning Committee

9:40am-10:25am

Wolfson Theatre

OVERVIEW – New Sources of Data

- **Will Dixon**, Professor of Digital Epidemiology, Manchester University

10:25-11:10am

Wolfson Theatre

RESEARCH USING WEARABLES/ENVIRONMENTAL DETECTORS

- **Jennifer K Quint**, Clinical Senior Lecturer in Respiratory Epidemiology, Imperial College London

11:10am-11:40am

REFRESHMENT BREAK WITH EXHIBITORS

11:40am-12:20pm

Wolfson Theatre

QUALITY OF LIFE DIRECTLY FROM PATIENTS VIA A PHONE APP

- **Bruce Hellman**, CEO, Umotif

12:20pm-1:00pm

Wolfson Theatre

JOIN THE CONVERSATION WITH YOUR BODY

Continuous Biometric Monitoring

- **William McMillan**, President and Chief Scientific Officer, Profusa

1:00pm-2:00pm

Osler Long Room

NETWORKING LUNCH WITH EXHIBITORS & STUDENT POSTERS

2:00pm - 3:30pm

Wolfson Theatre

STUDENT ABSTRACT ORAL PRESENTATION

- Moderators: Irene Petersen, FISPE & Juan Carlos Bazo-Alvares

The risk of incident osteoarthritis of the hand in new users of statins: a propensity score-matched sequential cohort study

- **Theresa Burkhard**, University of Basel & University Hospital Basel

Monday, April 3 (continued)

Mining twitter for drug-related adverse events using a natural language processing algorithm

- **Eirini Apostolidou**, Aristotle University of Thessaloniki

Risk of acute myocardial infarction associated with non-steroidal anti-inflammatory drugs users: impact of additional confounding control for variables collected from self-reported data

- **Mohammad Bakhriansyah**, Utrecht Institute for Pharmaceutical Sciences & Lambung Mangkurat University

Development of a predictive model for uncontrolled post-operative pain in the inpatient setting using electronic health record data

- **Juan Hincapie-Castillo**, University of Florida

The impact of prescription drug monitoring program characteristics on rates of opioid-related poisonings

- **Nathan Pauly**, University of Kentucky

Indications for long-term extended-release opioid therapy in commercially-insured adults in the US, 2006-2014

- **Jessica Young**, University of North Carolina

2:00pm - 3:30pm

Osler Long Room

STUDENT ABSTRACT "DYNAMIC POSTERS"

- Moderators: Debbie Layton & Sarah-Jo Sinnott

3:30pm - 4:00pm

REFRESHMENT BREAK WITH EXHIBITORS

4:00pm - 5:30pm

Wolfson Theatre

STUDENT ABSTRACT ORAL PRESENTATION

- Moderators: Ian Douglas & Juan Hincapie Castillo

Use of digestive disorders medications by children exposed in utero to atropinic drugs

- **Justine Benevent**, Universite Toulouse III

Androgen deprivation therapy and the risk of dementia in patients with prostate cancer

- **Farzin Khosrow-Khavar**, Jewish General Hospital & McGill University

Development of a predictive model for respiratory syncytial virus (rsV) hospitalizations among infants

- **Yoonyoung Choi**, University of Florida

PROGRAM SCHEDULE

Monday, April 3 (continued)

Androgen deprivation therapy and the risk of anemia in men with prostate cancer

- **Blanaid Hicks**, McGill University & Jewish General Hospital

The effect of dipeptidyl peptidase-4 inhibitors versus sulfonylureas on cognition and physical functioning in frail older nursing home residents

- **Andrew Zullo**, Brown University

Cardiovascular events following treatment initiation with atypical antipsychotic medications in publicly insured U.S. Youth

- **Mehmet Burcu**, University of Maryland-Baltimore

4:00pm - 5:30pm

Osler Long Room

STUDENT ABSTRACT "DYNAMIC POSTERS"

- Moderators: Annalisa Rubino & Amelia Smith

5:30pm

ADJOURNMENT

5:40pm

JOHN SNOW PRESENTATION AND WALK (Optional)

John Snow (15 March 1813 - 16 June 1858) was an English physician and is considered one of the fathers of modern epidemiology, in part because of his work in tracing the source of a cholera outbreak in Soho, London, in 1854. There will be a short presentation at the end of the session before a guided walk (approximately 25 minutes) to the John Snow memorial and public house on Broadwick Street, Soho. Free and open to all, registration not necessary. Option to return in time to join the social event.

7:00pm

SOCIAL EVENT (Registration Required)

Dinner at Mestizo - Restaurant and Tequila Bar

Tuesday, April 4

Scientific Symposium - Use of New Data in Pharmacoepidemiology

7:30am - Noon

REGISTRATION

8:30am-9:30am

Osler Long Room

EXHIBITS/REFRESHMENTS

Tuesday, April 4 (continued)

9:30am - 10:10am

Wolfson Theatre

HOW THE EMA VIEWS NEW DATA SOURCES

- **Enrica Alteri**, Head of Research & Development Support Division, European Medicines Agency

10:10am - 10:50am

Wolfson Theatre

HOW PHARMA VIEWS NEW DATA SOURCES

- **Andrew Roddam**, Vice President & Global Head Epidemiology at GSK

10:50pm - 11:15am

REFRESHMENT BREAK WITH EXHIBITORS

11:15am - 11:45am

Wolfson Theatre

IMPACT OF NEW DATA ON ACCESS

- **Sarah Garner**, Associate Director NICE Science Policy and Research

11:45am - 12:15pm

Wolfson Theatre

WILL PATIENT GENERATED HEALTH DATA SAVE THE NHS OR BE THE FINAL STRAW?

- **Indra Joshi**, Clinical Director, HealthTechWomen UK

12:15pm - 12:45pm

Wolfson Theatre

DISCUSSION - Bringing New Data Together with Traditional Thoroughness

- Moderators: Corinne S de Vries, FISPE & Montse Soriano Gabarro
- **Enrica Alteri**, Head of Research & Development support Division, European Medicines Agency
- **Andrew Roddam**, Vice President & Global Head Epidemiology, GSK
- **Sarah Garner**, Associate Director NICE Science Policy and Research
- **Indra Joshi**, Clinical Director, Health Tech Women UK

12:45pm-1:00pm

Wolfson Theatre

FINAL COMMENTS

- **Kiyoshi Kubota**, FISPE, ISPE President
- **Alison Bourke**, FISPE, Co-Chair, ISPE 2017 Mid-Year Planning Committee

1:00pm-2:00pm

Osler Long Room

LUNCH & NETWORKING

2:30pm

ADJOURNMENT

ISPE'S 2017 MID-YEAR MEETING

April 1-4, 2017 | Royal College of Physicians
London, United Kingdom

*Embracing the Future:
Ensuring Opportunities Become Reality*

ISPE ORGANIZATIONAL MEMBERS

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- Center for Drug Safety & Pharmaceutical Health Services Research Graduate Program, University of Maryland School of Pharmacy
- Center for Pharmacoepidemiology Research and Training (CPeRT), Pereleman School of Medicine at the University of Pennsylvania
- Department of Pharmaceutical Outcomes & Policy, College of Pharmacy, University of Florida
- Drug Safety Research Unit, Associated Department, School of Pharmacy, Portsmouth University
- Harvard School of Public Health
- London School of Hygiene and Tropical Medicine
- McGill Pharmacoepidemiology Research Unit, McGill University
- Pharmacoepidemiology Program, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill
- Rutgers, The State University of New Jersey
- University of Massachusetts Medical School- Clinical and Population Health Research

ORAL PRESENTATION ABSTRACTS

Monday, April 3

2:00 – 3:30 PM (*Presentations in order*)

Presenting Author Highlighted in Bold

THE RISK OF INCIDENT OSTEOARTHRITIS OF THE HAND IN NEW USERS OF STATINS: A PROPENSITY SCORE-MATCHED SEQUENTIAL COHORT STUDY

Theresa Burkard^{1,2}, Marlene Bloechliger^{1,2}, Noel Frey^{1,2}, Thomas Huegle³, Bradley Layton⁴, Susan S. Jick⁵, Christoph R. Meier^{1,5}, Julia Spoendlin^{1,2}

¹ Basel Pharmacoepidemiology Unit, University of Basel, Basel, Switzerland

² Hospital Pharmacy, University Hospital Basel, Basel, Switzerland

³ Orthopaedics Clinic, University Hospital Basel, Basel, Switzerland

⁴ Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, USA

⁵ Boston Collaborative Drug Surveillance Program, Boston University, Lexington, USA

Background: Preclinical evidence suggests a potential protective effect of statins on the risk of hand osteoarthritis (HOA), presumably via anti-inflammatory mechanisms. Since evidence from large observational studies remains scarce, we aimed to investigate the association between new statin use and incident HOA.

Methods: We performed a propensity score-matched cohort study using data from the UK-based Clinical Practice Research Datalink. Statin users had ≥ 1 statin prescription between 1996 and 2015 and were matched 1:1 on their propensity score to non-users within 10 sequential 2-year cohort entry blocks. Patients were aged 45–84 years and had a ≥ 3 years statin-free active history prior to cohort entry. After a 180-day run-in period (allowing statin users to reach maintenance dose and excluding all patients with a followup ≤ 180 days), patients were followed in an “as treated” approach until a recorded diagnosis of HOA or until censoring (change in exposure status, maximum follow-up 5.5 years). We applied Cox proportional hazard regression to calculate hazard ratios (HR) with 95% confidence intervals (CI) overall and in subgroups of age, sex, daily statin dose, and treatment duration.

Results: Among 280522 statin users and the same number of non-users, we observed an overall HR of 0.98 (95% CI 0.91–1.04) which remained unchanged in subgroups of age and sex. HRs slightly decreased with increasing treatment duration (HR 0.90, 95% CI 0.810.99, 4–5.5 years of follow-up) and with increasing daily statin dose (HR 0.65, 95% CI 0.44–0.97, >40 mg simvastatin equivalents per day).

Conclusions: The results of this large observational cohort study do not suggest an overall protective effect of statins on the risk of HOA. However, a slight protective effect in association with long-term use or with use of high daily statin doses is possible, and will have to be followed up in future research.

MINING TWITTER FOR DRUG-RELATED ADVERSE EVENTS USING A NATURAL LANGUAGE PROCESSING ALGORITHM

Dimitrios Spachos¹, **Eirini Apostolidou**², Georgios Papazisis², Dimitrios Kouvelas², Panagiotis Bamidis¹

¹ Department of Medical Physics, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

² Department of Clinical Pharmacology, Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: Existing post-marketing adverse event (AE) surveillance systems suffer from under-reporting and data processing lags. Twitter, a social media service with increasing adoption, can be a valuable source of adverse event related information. In this study, we present a machine learning algorithm for automatically collecting tweets containing AE incidents.

Method: Using the Twitter API we searched for tweets containing a drug's name. A natural language processing (NLP) algorithm was used to distinguish messages to potential AE incidents. We chose up to 15 tweets to create a training set for use on a Naive Bayes (NB) classifier. This system periodically collects new messages. Each one gets a value between 0 and 1 using the NB classifier. This number represents the probability of the tweet to refer to an AE. Finally, messages having values over a threshold create a set of AE incidents.

Results: We collected 37K original tweets about Xanax (no re-tweets) in English language during a 2-month time frame. We found 320 potential AE incidents, and our algorithm marked 42 of them as real AE incidents for a threshold of 0.75. The accuracy for our training set was 0.66.

Conclusion: This study proposes an innovative way to use well-known techniques, such as NLP and NB classification, to build a fast and cost-effective real time system for collecting AE incidents from social media platforms, such as Twitter. Future work includes research for more drugs in larger datasets as well as improvements on the NB classifier.

RISK OF ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS USERS: IMPACT OF ADDITIONAL CONFOUNDING CONTROL FOR VARIABLES COLLECTED FROM SELF-REPORTED DATA

Mohammad Bakriansyah^{1,2}, Patrick C Souverein¹, Anthonius de Boer¹, Olaf H Klungel¹

¹ Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands

² Faculty of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesia

Background: Several observational studies have employed electronic health databases to study the association between non-steroidal anti-inflammatory drugs (NSAIDs) and myocardial infarction. Because some important potential confounders might not be routinely collected in such data sources, patients' reports could be utilized additionally. This study evaluated the impact of using additional information from patients' reports when assessing the association between use of NSAIDs and the risk of acute myocardial infarction (AMI).

Methods: A case-control study was conducted among adult patients with hypertension and/or hypercholesterolemia in the Utrecht Cardiovascular Pharmacogenetics study. Information was collected from the Dutch PHARMO Database Network (Pharmacy and hospitalization records) and patients' questionnaires (for body mass index, alcohol use, smoking, physical activity, and familial history of cardiovascular diseases). For each case, up to 13 controls were matched based on age and gender at the date cases were

hospitalized (index date). Conditional logistic regression analysis was applied to estimate odd ratios (ORs) and 95% confidence intervals (95% CI).

Results: We identified 970 AMI cases and 2,974 controls during 1985-2005. Of all cases, 140 patients (14.4%) were exposed to conventional NSAIDs and 9 patients (1.0%) were exposed to selective COX-2 inhibitors at the index date. Compared to nonuse, neither conventional NSAIDs [(Adj. OR 0.98, 95% CI: 0.91-1.06) nor selective COX-2 inhibitors (Adj. OR 1.00, 95% CI: 0.74-1.36) were associated with an increased risk of AMI after adjustment for confounders routinely collected in pharmacy records. Additional adjustment for confounders collected from patients' reports did not change the risk estimates [(Adj. OR 0.97, 95% CI: 0.90-1.05) and (Adj. OR 1.01, 95% CI: 0.75-1.35)], respectively.

Conclusion: This study showed that additional potential confounders collected from patients' reports did not significantly change the risk estimates.

DEVELOPMENT OF A PREDICTIVE MODEL FOR UNCONTROLLED POST-OPERATIVE PAIN IN THE INPATIENT SETTING USING ELECTRONIC HEALTH RECORD DATA

Juan Hincapie-Castillo¹, Benjamin Staley², Carl Henriksen¹, Gigi Lipori², Almut G. Winterstein¹

¹ University of Florida, Gainesville, FL, USA

² UF Health Hospital, Gainesville, FL, USA

Background: More than 80 percent of patients that undergo surgery experience acute post-operative pain, with over half reporting moderate, severe, or extreme pain. Less than half of surgical patients report adequate post-operative pain relief while hospitalized. Focus on the prevention of uncontrolled pain is imperative as it has detrimental effects on quality of life, functional recovery, and it is associated with transition to chronic pain for some patients. This study aimed to construct a dynamic predictive risk model for uncontrolled post-operative pain in hospitalized patients for purposes of real-time use in inpatient electronic health records (EHR).

Methods: We established a retrospective cohort from the two largest University of Florida affiliated hospitals including all admissions aged ≥ 18 years

between 1/2012 – 10/2013. We operationalized 45 risk factors for automated EHR retrieval, and upon univariate analyses, retained 32 for model inclusion. Uncontrolled post-operative pain was defined for post-surgical days having at least two pain scores ≥ 7 (on a 0 to 10 scale) and recorded greater than 4 hours apart. For each of the first 5 post-surgical hospital days we predicted uncontrolled pain at the following hospital day using logistic regression.

Results: A total of 13,484 uncontrolled pain events occurred in 67,717 patient-hospital post-surgical days. C-statistics varied between 0.80 and 0.87 depending on the hospital day. More than 80 and 30 percent of uncontrolled pain events were in the upper 50th and 90th percentile of the risk scores, respectively. Strongly predictive risk factors ($p < 0.01$) included uncontrolled and moderate-severe pain during modeling day, use of nerve blocks during surgery, severe pre-operative pain, history of chronic pain, and diagnosis of anxiety.

Conclusion: Risk models achieved good predictive validity. All risk factors were operationalized from discrete EHR fields and allow for full automation for real-time prediction of high-risk patients.

THE IMPACT OF PRESCRIPTION DRUG MONITORING PROGRAM CHARACTERISTICS ON RATES OF OPIOID-RELATED POISONINGS

Nathan Pauly¹, Svetla Slavova¹, Patricia Freeman¹, Jeffery Talbert¹

¹ University of Kentucky, Lexington, KY, USA

Background: Prescription drug monitoring programs (PDMPs) are state-level interventions that track the dispensing of controlled substances and may assist in identifying drug diversion, abuse, or aberrant prescribing practices. Prior studies assessing the impact of PDMPs on opioid-related poisonings (ORPs) have failed to consider the wide heterogeneity of program features. The objective of this study is to examine the impact of specific PDMP characteristics on the rate of ORPs.

Methods: This retrospective study utilized nationally representative private and Medicare claims data over the years 2004-2014. The main outcome of interest was the incidence rate of ORPs in each state in each month over the 11 year study period. Covariates of interest included age, sex, use

of Schedule II opioids, diagnoses associated with opioid use, and PDMP characteristics related to program administration, data access, and reporting. Data on PDMP characteristics were gathered from the Prescription Drug Abuse Policy System. Covariates assessed at the individual level were aggregated into state-level rates and measures. A generalized estimating equation Poisson regression model was used to assess the impact of PDMP characteristics on rates of ORPs while controlling for other covariates of interest.

Results: Rates of ORPs per 100,000 beneficiaries ranged from 0 to 24.8 (median 0.94) over the 6,732 state-month pairs. State-months that had PDMPs with data access had significantly higher mean ORP rates than those without PDMPs (1.21 vs. 0.93, $p < 0.001$). Rates of ORPs also varied significantly based on the presence of specific PDMP features. Several PDMP characteristics were observed to have a significant impact on rates of ORPs

Conclusion: PDMPs offer a valuable tool to reduce opioid-related morbidity and mortality. Results of this study may be used to improve the efficacy of existing PDMPs and to guide best practices for future programs.

INDICATIONS FOR LONG-TERM EXTENDED-RELEASE OPIOID THERAPY IN COMMERCIALLY-INSURED ADULTS IN THE US, 2006-2014

Jessica Young¹, Michele Jonsson-Funk¹, Nabarun Dasgupta¹

¹ University of North Carolina, Chapel Hill, NC, USA

Background: The use of extended-release (ER) opioids in the US has expanded beyond cancer pain in the last decade. However, few utilization studies have focused on long-term users of ER opioids, a patient population of high interest in understanding the opioid crisis.

Methods: Using Truven's MarketScan Commercial Claims and Medicare Supplemental data (2006-2014), we identified incident long-term use of ER opioids (≥ 90 days) and examined pain diagnoses in the 182-day baseline period prior to initiation of therapy. We calculated the proportion of patients with cancer and other non-cancer chronic pain, by active ingredient.

Results: We identified 1,309,286 patients initiating ER opioids, of which 343,403 (26%) were long-term users. Long-term users had a mean age of 54 years; 43% were male. The median length of use was 199 days, with a median of 7 prescriptions with median 30 days' supply. The most common opioid prescribed was oxycodone (28% of initiators), followed by fentanyl (24%), and morphine (21%). Length of treatment was longest for oxycodone (median=220 days), and shortest for hydrocodone (median=152 days). Among long-term ER opioid initiators, 16% of patients had a diagnosis of cancer in the 182-day baseline period, 88% had a non-cancer chronic pain diagnosis, and 10% had no pain-related diagnosis. Most long-term users (65%) had ≥ 2 types of pain-related diagnosis, and 83% of those with cancer also had ≥ 1 diagnosis for non-cancer related pain. The most common non-cancer pain diagnoses were back pain (65%), arthritis (48%), and joint pain (28%).

Conclusions: In a national sample of adults with employee-sponsored insurance, only 16% of patients on long-term opioid therapy had a cancer diagnosis, and back pain was the most common diagnosis preceding initiation of opioid therapy. Amid increasing concerns regarding long-term opioid therapy, our findings provide real world evidence regarding the conditions for which long-term opioid therapy are prescribed.

Monday, April 3

3:50 – 5:20 PM (*Presentations in order*)
Presenting Author Highlighted in Bold

USE OF DIGESTIVE DISORDERS MEDICATIONS BY CHILDREN EXPOSED IN UTERO TO ATROPINIC DRUGS

Justine Benevent¹, Caroline Hurault-Delarue¹, Mélanie Araujo¹, Jean-Louis Montastruc¹, Isabelle Lacroix¹, Christine Damase-Michel¹

¹ Pharmacologie Médicale et Clinique, UMR 1027, Centre Hospitalier Universitaire de Toulouse, Faculté de Médecine, Université Toulouse III, Midi-Pyrénées, France

Background: Several drugs, such as psychotropics or antihistamines, exhibit atropinic properties. Exposure on late gestation to atropinic drugs sometimes results in neonatal digestive disorders, acting on muscarinic receptors of gastro-intestinal

tract. However, long-term digestive effects of in utero exposure have never been studied before. This study aimed at assessing the risk of digestive disorders in early childhood after in utero exposure to atropinic drugs. Secondary analysis was conducted to evaluate the potential effect of the exposure intensity.

Methods: We performed a cohort study in POMME (Prescription Médicaments Mères Enfants), a database including prescribed and dispensed reimbursed drugs to children in utero and during the first 3 years of life (N=8,372). According to Duran's list, we assigned an atropinic score (0=null, 1=low, 3=strong) to each prescribed drug. Atropinic burden (AB) consisted in the sum of the atropinic scores of drugs prescribed during antenatal life. Dispensations of digestive disorders medications were applied as proxy for constipation, diarrhea, vomiting, gastroesophageal reflux disease or gastrointestinal pain. The association between the number of digestive disorders' occurrences and in utero exposure to atropinic drugs was estimated by a Poisson regression incorporating corrections for overdispersion.

Results: More than 30% (N=2,652) of the children were exposed in utero to atropinic drugs. They had significantly more digestive disorders (5.0 versus 4.0) than unexposed children (RR_a = 1.11 [1.06; 1.16]), especially diarrhea and gastroesophageal reflux. The strength of the association increased with both AB and the number of dates of atropinic drugs dispensations.

Conclusion: Our results suggest an association between fetal exposure to atropinic drugs and occurrence of digestive disorders in childhood. Muscarinic receptor blockade during antenatal life might disturb the development of the cholinergic system, leading to long term digestive effects. Further studies are needed to improve knowledge about the risks of using too many atropinic drugs during pregnancy.

ANDROGEN DEPRIVATION THERAPY AND THE RISK OF DEMENTIA IN PATIENTS WITH PROSTATE CANCER

Farzin Khosrow-Khavar^{1,2}, Soham Rej^{3,4}, Hui Yin¹, Armen Aprikian^{5,6}, Laurent Azoulay^{1,2}

¹ Center for Clinical Epidemiology, Jewish General Hospital, Montreal, Quebec, Canada

² Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

³ Division of Geriatric Psychiatry, University of Toronto, Toronto, Ontario, Canada

⁴ Department of Psychiatry, Jewish General Hospital, Montreal, Quebec, Canada

⁵ Gerald Bronfman Department of Oncology, Montreal, Quebec, Canada

⁶ McGill University Health Center, Montreal, Quebec, Canada

Background: Recent observational studies have associated the use of androgen deprivation therapy (ADT) with an increased risk of dementia and Alzheimer's disease. However, these studies had methodological limitations. The objective of this study was to determine whether the use of ADT is associated with an increased risk of dementia, including Alzheimer's disease, in patients with prostate cancer.

Methods: Using the United Kingdom Clinical Practice Research Datalink, we assembled a cohort of 30,903 men newly-diagnosed with non-metastatic prostate cancer between April 1, 1988 and April 30, 2015, and followed until April 30, 2016. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of dementia associated with use of ADT compared with non-use. ADT exposure was lagged by one year to account for delays associated with the diagnosis of dementia, and to minimize reverse causality. Secondary analyses assessed the risk with cumulative duration of use and by ADT type.

Results: During a mean (standard deviation) follow-up of 4.3 (3.6) years, 799 patients were newly-diagnosed with dementia (incidence rate: 6.0 (95% CI: 5.6-6.4) per 1000 person-years). Compared with non-use, ADT use was not associated with an increased risk of dementia (incidence rates 7.4 vs 4.4 per 1000 person-years, respectively; adjusted HR: 1.02, 95% CI: 0.87-1.19). In secondary analyses, cumulative duration of use (p -value for heterogeneity=0.78) and no single type of ADT was associated with an increased risk of dementia. Consistent results were observed in sensitivity analyses: varying the length of the exposure lag period, stratification on disease risk score, marginal structural models for possible time-dependent confounding, and competing risks due to death from any cause.

Conclusion: In this population-based study, the use of ADT was not associated with an increased risk of dementia. Additional studies in different settings are needed to confirm these findings.

DEVELOPMENT OF A PREDICTIVE MODEL FOR RESPIRATORY SYNCYTIAL VIRUS (RSV) HOSPITALIZATIONS AMONG INFANTS

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Background: Most children have at least one RSV infection before they reach two years of age. Passive immunization is available, but high cost necessitates careful selection of high-risk patients. Current selection criteria consider limited risk factors and no holistic risk score that integrates relevant risk factors is available.

Objective: To develop a predictive model for RSV hospitalizations among infants aged 0-2 years.

Methods: We conducted a retrospective cohort study using Florida and Texas Medicaid claims records linked to birth certificates from children aged 0-24 months and their mothers between 1999-2010. We operationalized risk factors during the RSV season, which were identified from literature review and expert opinion. We tested correlation between risk factors and linearity of continuous variables using penalized splines. The association of risk factors with RSV hospitalizations was quantified among a random sample of 75% of the entire study population, using a Cox regression model.

Results: Approximately 2.8 million infants and 1.1 millions mothers were included for the analysis. During a mean follow up of 78

days during a 4-months RSV season, 28,974 RSV hospitalizations occurred. Significant predictors included chronological age ≥3 months (HR 8.73, 95% CI 8.41-9.06), gestational age 29 to <32 weeks (1.83, 1.64-2.00), low Apgar score (1.16, 1.10-1.21), presence of siblings <5 years of age (1.45, 1.42-1.48), Downs syndrome (3.16, 2.78-3.60), airway anomaly (2.01, 1.87-2.15), cancer or transplant (3.15, 2.97-3.34), chronic lung disease (1.80, 1.56-2.08), cyanotic heart disease (1.58, 1.44-1.75), maternal smoking during pregnancy (1.21, 1.17-1.26) breastfeeding at birth (0.82, 0.79-0.84) and use of palivizumab (0.46, 0.41-0.51). Patients in the highest 20th percentile of the predicted probability attributed to 42% of all RSV hospitalizations.

Conclusion: Our prediction model successfully identified significant risk factors and highlighted the potential value of a clinical risk score.

ANDROGEN DEPRIVATION THERAPY AND THE RISK OF ANEMIA IN MEN WITH PROSTATE CANCER

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Background: The use of androgen deprivation therapy in prostate cancer may be associated with an increased risk of anemia, but to date evidence remains limited. This study aimed to determine if androgen deprivation therapy is associated with an increased risk of anemia in patients newly-diagnosed with non-metastatic prostate cancer.

Methods: This was a population-based cohort study using the United Kingdom Clinical Practice Research Datalink linked to the Hospital Episode Statistics repository. The cohort consisted of 10,364 men newly-diagnosed with non-metastatic prostate cancer between April 1, 1998 and September 30, 2015. Time-dependent Cox proportional hazards models were used to estimate

adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for anemia (defined as a hemoglobin value of <130 g/l) associated with current and past use of androgen deprivation therapy, compared with non-use.

Results: There were 3,651 incident anemia events during 31,574 person-years of follow-up (rate: 11.6/100 person-years). Current androgen deprivation therapy use was associated with a nearly 3-fold increased hazard of anemia, compared with non-use (23.5 vs 5.9 per 100 person years, respectively; HR: 2.90, 95% CI: 2.67, 3.16). The HR was elevated in the first 6 months of use (HR: 2.20, 95% CI: 1.95, 2.48) and continued to be elevated with longer durations of use. Past androgen deprivation therapy use was associated with a lower estimate (HR: 1.27, 95% CI: 1.12, 1.43), which returned closer to the null ≥25 months after treatment discontinuation (HR: 0.95, 95% CI: 0.79, 1.15). Overall, these findings remained consistent across several sensitivity analyses, including high dimensional propensity score and marginal structural model analyses.

Conclusions: The results of this large population-based study provide evidence that the use of androgen deprivation therapy is associated with clinically-significant anemia in patients with prostate cancer. Importantly, this association was reversed upon androgen deprivation therapy discontinuation.

THE EFFECT OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS VERSUS SULFONYLUREAS ON COGNITION AND PHYSICAL FUNCTIONING IN FRAIL OLDER NURSING HOME RESIDENTS

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Background: Little evidence exists about the comparative effectiveness of dipeptidyl peptidase-4 inhibitors (DPP4Is) and sulfonylureas (SUs) in frail older nursing home (NH) residents with diabetes, especially for outcomes of central importance like

cognitive and physical functioning. We evaluated the risk of functional decline in U.S. NH residents aged 65 and older who were newly prescribed DPP4Is versus SUs.

Methods: We conducted a retrospective, new user cohort study of residents in 2007-2010 using national data from the Minimum Data Set (MDS) and Medicare Parts A, B, and D (N=6,978). Follow-up began at the initial dispensing of a DPP4I or SU and continued until each study outcome (evaluated separately), insurance disenrollment, death, 1-year follow-up, or study end, whichever occurred first. Outcomes were a 1-point increase in MDS Cognitive Performance Scale score, 3-point increase in MDS Activities of Daily Living Scale score, and hospitalization/emergency department (ED) visit for altered mental status. Cox models were used to determine hazard ratios (HR) with 95% CIs of each outcome in the propensity score-matched cohort. We used Fine and Gray regressions, nonparametric propensity score estimation, and multiple imputation in sensitivity analyses.

Results: The study cohort included 892 DPP4I initiators matched to 892 SU initiators. DPP4I users were less likely than SU users to experience a hospitalization/ED visit for altered mental status (HR=0.72, 95%CI 0.48-1.08), but had a similar risk of decline in cognitive (HR=1.06, 95%CI 0.68-1.66) and physical functioning (HR=1.07, 95%CI 0.76-1.51). Results from the sensitivity analyses were similar to the primary analysis, though estimates in the nonparametric propensity score-matched cohort were further from the null (altered mental status, HR=0.65, 95%CI 0.42-1.02).

Conclusions: Use of DPP4Is versus SUs may result in a lower risk of altered mental status hospitalization/ED visit, but had little impact on cognitive and physical functioning.

CARDIOVASCULAR EVENTS FOLLOWING TREATMENT INITIATION WITH ATYPICAL ANTIPSYCHOTIC MEDICATIONS IN PUBLICLY INSURED U.S. YOUTH

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Background: The increased use of atypical antipsychotics (AAPs) in publicly-insured U.S. youth has been profound. However, little is known about AAP-treatment emergent risk of cardiovascular events in youth. The main objective of this study was to assess the risk of incident cardiovascular events that led to hospitalizations or emergency department visits following AAP use in youth.

Methods: We conducted a retrospective cohort study of youth (5-20 years) who initiated AAP treatment using computerized Medicaid claims data. AAP use was operationalized in a time-dependent manner according to current vs. former use, average daily dose (in risperidone dose equivalents), and duration of use. In a secondary analysis, concomitant use of stimulants or serotonin reuptake inhibitors (SSRI/SNRIs) with AAPs was also assessed. Cardiovascular events were derived from hospitalizations or emergency department visits. To account for confounding, we used the disease risk score methodology in discrete time failure models.

Results: There were 74,700 youth who initiated AAP treatment (average follow-up=24.8 months). Compared to former users, there was an increased risk of cardiovascular events for current AAP users (Relative Risk [RR]=1.55, 95% CI=1.09-2.21). In current AAP users, the risk of cardiovascular events increased with increasing average daily dose, exhibiting a RR of 2.04 (95% CI=1.11-3.77) for >3.75 mg/day compared to ≤1.25 mg/day. The risk of cardiovascular events was more common in the early phase of AAP treatment. Also, in AAP-treated youth, concomitant use of SSRI/SNRIs was associated with an increased risk of cardiovascular events (RR=1.61, 95% CI=1.01-2.57). By contrast, concomitant stimulant use was not significantly associated with an increased risk of cardiovascular events.

Conclusion: In publicly-insured U.S. youth, current AAP use was associated with an increased risk of incident cardiovascular events, which intensified with increasing dose and with concomitant SSRI/SNRI use. The findings support baseline assessment of cardiovascular health status prior to AAP treatment initiation.

DYNAMIC POSTER PRESENTERS

ATYPICAL ANALGESIC USE AS A SCREENING TOOL FOR TOTAL HIP ARTHROPLASTY IMPLANT SURVIVAL: A POPULATION-BASED COHORT STUDY

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Background: The need for effective screening tools to monitor implant performance and identify poorly performing implants early has been highlighted by recent failings of metal-on-metal devices. We investigate whether atypical analgesic (Tricyclic Antidepressants, Gabapentin and Pregabalin) utilisation in the first year following total hip arthroplasty (THA) and total knee arthroplasty (TKA) surgery is associated with long-term implant survival.

Methods: A retrospective observational cohort study was conducted. Data was used from the Catalan Joint Registry (RACAT) linked to primary care records and pharmacy invoice data in the SIDIAP Database (www.sidiap.org). All participants registered in both SIDIAP and RACat undergoing primary THA or TKA between 2005 and July 2012 were eligible (n=40,854). Patients under the age of 45 whose indication for surgery was not Osteoarthritis and used atypical analgesia prior to surgery were not included. Fine & Gray models were used to investigate the association between atypical analgesic use and implant survival adjusting for age, gender, body mass index, alcohol drinking, smoking, Charlson comorbidity Index and socio-economic status.

Results: Atypical analgesic use following THA surgery was significantly associated with revision rate. Adjusted sub-hazard ratio (SHR) was 2.04 [95%CI 1.41-2.95, p <0.001]. A significant association was also found with atypical analgesic use following TKA surgery and subsequent revision rate. Adjusted SHR was 1.56 [95%CI 1.26-1.94, p <0.001].

Conclusion: This study demonstrates an association between atypical analgesic use within the first post-operative year following THA or TKA surgery and subsequent revision rates. Atypical analgesic prescriptions can, through linkage to arthroplasty registries, potentially be used as an early surrogate to identify patients and implants at high risk of device failure.

BURDEN OF SIDE EFFECTS OF PRESCRIPTION MEDICATIONS ON DEPRESSION AMONG ADULTS IN THE U.S.

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Background: Medications are widely, and increasingly, used among the U.S. adult population and many have depression, including suicide, side effects. While depression is a growing public health problem, there is limited information on the association between medication side effects and depression.

Objectives: To examine whether the use of multiple medications with depression side effects, including suicide, is associated with depression among US adults.

Methods: We used a nationally-representative sample from the National Health and Nutrition Examination Survey (NHANES) of 20,805 adults aged 18 years or older between 2005-2006 and 2011-2012. We conducted multivariable logistic regression to examine the association between the use of multiple medications with depression side effects and depression. Depression was defined as a PHQ-9 score ≥10. Micromedex was used to identify medications with known depression, including suicide, adverse effects.

Results: In 2011-2012, 41.4% of US adults used at least one medication with a depression side effect, which is a significant increase from 35.8% in 2005-2006 (p<0.001). The use of medications with suicide effects also increased from 17.8 to 20.4% during this time period (p=0.02). The number of medications used with depression side effects was associated with increased prevalence

of depression; among adults using at least one prescription medication, those using 1-2 or 3 or more medications with depression side effects were more likely to report depression (OR 2.6 and 8.0, respectively), when compared to adults not using such medications ($p<0.001$). These patterns persist in analyses excluding users of psychotropic medications.

Conclusions: Prescription medications with depression side effects are frequently, and increasingly, being used and their use is associated with a substantial increase in depression in U.S. adults. Efforts to reduce the risk of depression, and ultimately improve mental health, should incorporate an evaluation of depression and suicidal risks associated with the use of multiple medications.

TRENDS OF NEONATAL ABSTINENCE SYNDROME EPIDEMIC RELATED TO OPIOIDS UTILIZATION AND OTHER RISK FACTORS DURING LATE PREGNANCY

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Background: Neonatal Abstinence Syndrome (NAS) has increased dramatically in the past decade. Our objective was to examine the temporal trends of (1) maternal opioid use in late pregnancy, (2) NAS incidence stratified by late maternal opioid use and (3) maternal risk factors among NAS deliveries.

Methods: We identified women with a live birth who were enrolled 90 days before and 30 days after delivery in Florida Medicaid Analytic Extract billing records linked to birth certificates from 1999 to 2010. Annual prevalence of opioid use during pregnancy was defined as the proportion of deliveries with pharmacy opioid dispensing per calendar year. Annual incidence of NAS, defined as ICD-9-CM 779.5 in children's or mothers' in- or outpatient encounters, was stratified by prescription opioids exposure in the last 90-day of pregnancy. To identify contributors to the increase in NAS incidence, we examined the variation in annual prevalence of opioid dispensing, smoking, antidepressant use, and substance use disorder among NAS and non-NAS deliveries.

Results: There were 42,292 (9.4%) deliveries exposed to at least one prescription opioid in late pregnancy, which remained stable from 2000 to 2010 ($P>0.05$). Among opioid exposed deliveries, NAS incidence increased from 1.6 to 25.2 per 1,000 live-births during the study period. While the prevalence of maternal opioid use, tobacco use, and antidepressant use remained stable among NAS deliveries, the prevalence of substance use disorder diagnoses increased substantially from 38.9% in 1999 to 67.9% in 2006 ($P<0.05$).

Conclusions: The incidence of NAS increased dramatically while the prevalence of major risk factors, including maternal opioid use, remained stable. The intensity of maternal opioid use and the increase in substance use disorder may be responsible for the sharp increase in NAS incidence.

HYBRID APPROACH TO THE EVALUATION OF THE EFFECTIVENESS OF ADDITIONAL RISK MINIMISATION MEASURES CORRELATING PROCESS AND OUTCOME INDICATORS AT THE INDIVIDUAL-PATIENT LEVEL

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Background: The GVP Module XVI recommends the evaluation of additional risk minimisation measures with process indicators and outcomes. Outcomes are difficult to assess and most evaluations study only process indicators. We illustrate how a novel hybrid design can be used to study and relate outcomes and process indicators at the individual-patient level. Patient Alert Cards (PACs) for intravenous and subcutaneous abatacept (Orencia®) formulations have been in place since 2007 and are used to inform patients of the need to provide an adequate history of specific infections and that they should be screened for these infections, and to inform patients about allergic reactions. The study aims to evaluate the effectiveness of the abatacept PACs for patients with rheumatoid arthritis in a sample of EU countries.

Methods: This study consists of 3 related sub-studies: a cross-sectional survey of rheumatologists/nurses (i.e. HCPs) and a cross-sectional survey of patients to describe receipt/distribution, awareness, utilisation, utility, knowledge, and behaviour (relating to infections and allergic reactions), and a retrospective chart review to collect clinical and safety outcomes (relating to infections only). The study will describe survey results individually and correlate, in the same patients, responses to the survey with outcomes related to risks targeted by the PACs e.g. infection leading to hospitalisation, results of any test to screen for tuberculosis and viral hepatitis prior to administration of abatacept. Four hundred patients allow for the detection of a moderate decrease in the risk of infection-related hospitalisations (odds ratio <0.23) from adherence (80% correct response) compared to being non-adherent with the PAC. Patient and HCP data are collected electronically, although patients may also complete the questionnaire on paper.

Results: The protocol was approved by the PRAC and the study is ongoing. Details of the design will be described during the presentation. Qualitative methods were used to review and linguistically validate the questionnaires in the five participating countries.

Conclusion: The appropriateness and usefulness of this novel hybrid design to correlate process indicators and outcomes at the individual-patient level will be fully appreciated when results become available, and provide another potential model for future evaluation studies of this type.

THE EFFECT OF POOR ADHERENCE ON THE RELATIONSHIP BETWEEN ANTI-HYPERTENSIVE MEDICATION AND FALLS: A PROSPECTIVE COHORT STUDY OF OLDER ADULTS

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Introduction: There is on-going debate as to whether anti-hypertensive medication are associated with an increased falls risk in older

adults. Patients initiating anti-hypertensive treatment have been observed to have an increased risk of falling; however studies of prevalent users of anti-hypertensive medication have reported conflicting findings. One factor that has not been measured in published studies of prevalent anti-hypertensive users is adherence. Non-adherent patients may be repeatedly exposed to an increased fall risk similar to initial anti-hypertensive dosing. The objective was to investigate the longitudinal association between poor adherence to anti-hypertensive medication and falls in older adults (>65 years).

Methods: Community dwelling older adults (N=1592) were recruited from 106 community pharmacies across the Republic of Ireland between March and May 2014, completing a baseline structured telephone interview and were followed-up at 12 months, completing a second structured telephone interview. Adherence was estimated as the number of 5 days gaps in medication supply from linked dispensing records for the 12 month period prior to the baseline interview and falls were ascertained for the 12 month period prior to the follow-up interview.

Results: Adjusting for relevant covariates including age, gender, medical history and medication use, increasing occasions of 5 day gaps in adherence to anti-hypertensive medication was associated with an increased risk of falls (aRR 1.11, 95% CI 1.03-1.19, p=0.005), injurious falls (aRR 1.19, 95% CI 1.06-1.33, p=0.003) and a greater number of falls (aIRR 1.15, 95% CI 1.04-1.27, p=0.006) during the subsequent 12 months.

Conclusion: In older adults, non-adherence to anti-hypertensive medication may be a precipitating factor in the relationship between long-term anti-hypertensive medication use and falls. In reconciling the risk-benefit of continuing anti-hypertensive therapy in older patients at risk of falling, clinicians should be aware of this potential mechanism, which may relate to fluctuations in blood pressure secondary to non-adherence.

IMPLEMENTING NEAR-REAL TIME VACCINE SAFETY SURVEILLANCE USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD) - IS THERE ENOUGH POWER?

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Background: Near real-time vaccine safety surveillance (NRTVSS) using electronic health records has been used to detect timely vaccine safety signals. These methods have not been fully implemented in the UK. Our work aims at assessing the feasibility of implementing a NRTVSS using the Clinical Practice Research Datalink (CPRD), in terms of power and timeliness.

Methods: We selected seasonal influenza vaccine and Guillain-Barre Syndrome (GBS) as a case-study and performed power and expected time to signal calculations for 2013-2014/2014-2015 seasons. Power depends on the incidence of GBS, vaccine uptake, vaccine risk window, study period, relative risk to detect (RR), and statistical method used. GBS is rare meaning the most appropriate method is the continuous Poisson-based maximized sequential probability ratio test (PMaxSPRT), which compares observed-to-expected. Calculations were performed for detecting RRs=1.5-10. The remaining factors affecting power were included through their impact on the expected number of events. For each study season we obtained an average GBS age-sex-adjusted rate from the 5 previous seasons (2008-2013 and 2009-2014) and then used this rate to calculate the expected number of events, considering only vaccinated individuals and a risk window of 42 days. Delays in recording outcomes and receiving data influence the feasibility of NRTVSS, we thus performed calculations based on the absence/presence of these delays. R-package Sequential was used.

Results: For the season 2013/14 power to detect a signal is >80% for RR \geq 4 for all delays scenarios. Season 2014/15 presents similar results except for scenario considering both sources of delays where power>80% for RR \geq 5. Signals were expected by early January.

Conclusion: CPRD seems to have enough power to detect a safety signal for GBS and seasonal

influenza for increases in RR \geq 4. CPRD data can be used to implement NRTVSS as a way to exclude big increases in the risk of rare outcomes after seasonal influenza vaccine.

VALIDATION OF THE RECORDING OF ASTHMA DIAGNOSIS IN UK ELECTRONIC HEALTH RECORDS (CLINICAL PRACTICE RESEARCH DATALINK)

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Aim & Objectives: The aim of this study is to validate strategies to identify asthma patients in UK electronic primary care records by determining the positive predictive value (PPV) of 8 unique pre-defined algorithms within CPRD.

Methods: The PPV is calculated as the number of true positives over the number of positive calls. The positive calls can be found in the database, while the true positives were determined using questionnaires sent to GPs of 880 randomly selected possible asthma patients identified using 8 pre-defined algorithms. The questionnaires were reviewed by two independent experts to construct a gold standard. The algorithms consist of a combination of one or more of the following: definite or possible asthma Read codes, evidence of reversibility testing and recording of two or more prescriptions of inhaled maintenance asthma therapy, and core asthma symptoms.

Results: 463 questionnaires were returned at the time of abstract submission. Of these, 457 were deemed usable and reviewed by 2 experts. The mean PPV across all of the algorithms was 72% using the study chest physician's opinion, 71% according to the study team's GP and 71% in the judgement of the patient's own GP. The PPV's of the particular algorithms are calculated separately. In this preliminary stage of analysis, it appears that a record of definite asthma codes gives a high PPV (81%-85%). Additional conditions of reversibility testing, repeated inhaled asthma therapy do not improve the PPV. The best PPV (86%-88%) was reached by the combination of possible asthma

codes with evidence of reversibility testing and more than one prescription of inhaled maintenance asthma therapy. Algorithms based on asthma symptoms instead of asthma codes showed lower PPVs (all less than 60%).

Conclusion: At this preliminary stage, using only definite asthma codes appears the most efficient approach.

RISK FACTORS ASSOCIATED WITH SEVERE HYponatremia AMONG HOSPITALIZED PATIENTS. THE CONSTRUCTION OF A PREDICTIVE MODEL USING ELECTRONIC MEDICAL RECORDS

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Background: Hyponatremia is the electrolyte abnormality with the highest prevalence in hospitalized individuals. Even mild hyponatremia is associated with increased mortality and morbidity. Yet, in-hospital risk factors have not been fully identified. Using Electronic Health Records (EHR), we aim to develop and validate a 5-day predictive model to assist to an earlier identification of high-risk hyponatremia patients during a hospital encounter.

Methods: Analysis was based on 75,036 patients hospitalized in two tertiary hospitals in Florida. Hyponatremia was defined as one abnormal serum sodium value ($[Na^+] < 130 \text{ mmol/L}$). A total of 90 clinical indicators extracted from EHR in the first 5 days of admission were evaluated. Models were constructed using multivariable logistic regression and evaluated by the c-statistic and ROC curves for discrimination, Akaike Information Criterion for goodness of fit, and internally validated using bootstrapping sampling.

Results: The development and validation sample included 252,165 patient-days. A hyponatremia event was reported in 2,101 days (8.3 hyponatremia events/1,000 patient-hospital days). The strongest risk factors included medication prescriptions (diuretics, mild and high sodium-decreasing medications); clinical diagnosis (ascites, hypopituitarism, cirrhosis, stroke); previous clinical conditions (history of chronic hypertension, history of COPD), older age, and previous post prostate or

uterus surgery. Protectors were being admitted from a nursing home, enteral feeding, administration of cancer drugs 30 days before modelling day, a surgery episode, and "1 unit decrease of creatinine clearance". The validated area under the curve (AUC) was 0.886 (0.884-0.899).

Conclusion: A combination of 27 past and current medical conditions, types of medications, clinical measurements, and laboratory variables was 89% accurate in predicting severe hyponatremia in hospitalized patients. The routinely use of EHR can enhance prescribers' ability to discriminate high risk patients earlier and prevent severe hyponatremia more effectively.

PATIENT REPORTING OF ADVERSE DRUG REACTIONS: HOW READY ARE WE? AN INTERNATIONAL SURVEY OF NATIONAL COMPETENT AUTHORITIES¹

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Background: Patient reporting of Adverse Drug reactions (ADRs) to spontaneous reporting systems can make a valuable contribution to pharmacovigilance. However, the implementation and promotion of patient reporting systems (PRS) differ worldwide. The objective of the study was to describe attitudes towards PRS, and progress towards implementing such systems among national competent authorities listed on the WHO Programme for International Drug Monitoring.

Methods: A web-based questionnaire was constructed based on qualitative interviews, and distributed through the SurveyMonkey® platform to all countries listed on WHO Programme for International Drug Monitoring (n=178) during November/December of 2015. Data were analyzed using descriptive statistics and chi-square (χ^2) tests.

Results: Questionnaires were received from 141 countries (79,2%). A system for both healthcare professionals and patients was present in 58 countries (41,1%). Official PRS to report ADRs directly is implemented in 44 countries (31,2%)

and in a pilot stage in 5 countries (3,5%). Patients are not allowed to report in 34 countries (24,1%). Lack of resources/budget (56,5%) or lack of information/education for patients (56,5%) were the main reasons for not implementing an official PRS. Respondents acknowledge that general public can contribute to pharmacovigilance with information that Healthcare professionals cannot (81,0%). However, they also claim that promoting and handling patient reports will require extra resources. To be able to further PRS, respondents say that they need more training courses/conferences (72%) and information on how to promote patient reporting among the general public (71%).

Conclusions: Most of the countries accept ADRs reports from patients by an official reporting system designed for patients or through the existing systems for professionals. The main reason for not having PRS is due to financial restraints and lack of information/education of patients. Attitudes towards PRS are positive but some countries fear that they will not be able to handle an increase in reports.

FACING UNMEASURED CONFOUNDING: INSTRUCTIONS MANUAL FOR PROPENSITY SCORE CALIBRATION

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Background: Confounding is a well-recognized source of bias which may arise mainly in non-interventional studies, due to lack of randomization and to patient features being determinants of the exposure and, simultaneously, of the outcome of interest. If data on one or more confounders have not been collected, statistical methods for adjustment need to be generalized to work in the unmeasured framework, addressing either marginal or conditional estimation. Propensity Score Calibration (PSC) is one of the candidate methods based on data from an external study, but the operating characteristics in various settings have not been assessed leading to a lack of practical recommendations.

Methods: PSC aims at correcting the error-prone exposure-covariates association by defining a gold-standard PS model in a validation database, where all the confounders are available. The extended practice of PS and the frequent accessibility of permanent multi-disease datasets support PSC as primary choice of investigation. We used extensive Monte Carlo simulations covering a variety of situations in order to estimate marginal hazard ratios (HRs) matching treatment cohorts on the predicted gold-standard PS.

Results: In a setting designed to be ordinarily met in oncology drug development, where the method assumptions are fulfilled and a true HR of 0.80 is generated (crude HR 1.12; 95%CI: 0.99-1.29), PSC proves to reduce bias (HR 0.90; 95%CI: 0.58-1.18) compared with standard PS matching (HR 0.96; 95%CI: 0.84-1.10). Varying the parameter values over a wide range generally resulted in similar patterns.

Conclusions: The use of PSC to improve the estimation of treatment effects on survival responses is supported by simulation results. Nonetheless, it is shown that transportability, sizes of databases, correlations and strength of covariates effects on treatment and outcome may affect final results and they should be considered to guide the validation study choice, the matching algorithm and the definition of the Cox model.

PRE-DIAGNOSTIC STATIN USE, LYMPH NODE NEGATIVITY, AND MORTALITY IN WOMEN WITH STAGE I-III BREAST CANCER

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Background: Statins, or 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGCR) inhibitors, are prescribed for cardiovascular disease prevention. A window-of-opportunity trial has shown that statin treatment can increase breast tumour expression of HMGCR. Additionally, studies have shown that tumour expression of HMGCR is associated with lymph node negativity at diagnosis. Therefore, we examined the association between pre-diagnostic statin use, lymph node involvement at diagnosis, breast cancer-specific and all-cause mortality.

Methods: Women with stage I-III breast cancer were identified from the National Cancer Registry of Ireland (N=6314). Pre-diagnostic statin users were identified from linked prescription claims data (N=2082). Relative risks (RR) were estimated for associations between pre-diagnosis statin use and lymph node status at diagnosis. Hazard ratios (HR) were estimated for associations between pre-diagnostic statin use and breast cancer specific, and all-cause mortality.

Results: Pre-diagnostic statin use was not associated with lymph node negativity at diagnosis (RR 1.00 95% CI 0.98, 1.03). In survival analyses, pre-diagnostic statin use was associated with reduced all cause (HR 0.78 95% CI 0.69, 0.89) and cancer-specific mortality (HR 0.81 95% CI 0.68, 0.96). This reduction in cancer-specific mortality was greater in statin users with ER+ tumours (HR 0.69 95% CI 0.55, 0.85)

Conclusions: While pre-diagnostic statin use is not associated with lymph node status in this study, patients with pre-diagnostic statin exposure had a statistically significant 19% reduction in breast cancer-specific mortality, even after adjusting for major prognostic factors. In such observational studies, it is important to consider residual confounding; such healthy user bias. However, there is increasing evidence to support a biological anti-cancer role of statin drugs.

EFFECTIVENESS OF PENTOXIFYLLINE AMONG CHRONIC KIDNEY DISEASE PATIENTS WITH PROTEINURIA.

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Background: Proteinuria is an important target to slow down the progression of chronic kidney

disease (CKD). Some studies have demonstrated the pentoxifylline (PTX) may reduce proteinuria in CKD patients; however, its renoprotective effect in proteinuria CKD remains controversial.

Objectives: The objective of this study is to assess the renoprotective effects of the add-on PTX among proteinuric CKD patients under regular treatment.

Methods: We conducted a cohort study using the electronic medical records (EMRs) from an integrated CKD care program of a tertiary teaching hospital from January 2009 through December 2015 in Central Taiwan. Patients who developed proteinuria (PCR > 200 mg/g or ACR > 30 mg/g) and received angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) after the enrollment were included in this study and classified according to add-on PTX or not. We excluded patients who were <20 or >90 years of age, or have treated by ACE inhibitors, ARBs or PTX before the index date, which was defined as the first day of prescription after the diagnosis of proteinuria. The outcome was defined as dialysis and analyzed by using Cox's proportional hazards model with competing risk analysis for death

Results: During the study period, we analyzed 405 patients prescribed ACE inhibitors/ARBs, and 814 patients prescribed ACE inhibitors/ARBs plus PTX. The mean age at index date was 66.9 years. Compared to ACE inhibitors/ARBs only group, patients in the add-on PTX group had greater concomitant use of anti-diabetes medication, statin, alpha blockers and beta blockers. The adjusted HR (95% CI) of dialysis events for add-on PTX compared with ACE inhibitors /ARBs only were 1.14 (0.76, 1.69).

Conclusion: The renoprotective effect of PTX was not observed in this study. More prospective evidence are required to recommend the widespread use of PTX in CKD.

THE IMPACT OF CLASSIFICATION AS A CONTROLLED SUBSTANCE ON TRAMADOL UTILISATION IN THE UNITED KINGDOM

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Background: In the past decade, at the same time as a two-fold increase of annual tramadol utilisation, there has been a marked increase in tramadol-related deaths in the United Kingdom (UK). In June 2014, tramadol was classified as a Controlled Substance due to the safety concerns and potential risk of misuse. However, the effectiveness of this policy intervention still remains uncertain. Therefore, this study aimed to evaluate the impact of classification on tramadol utilisation.

Methods: This cross-sectional study used two data sources; aggregated-level national statistics and dispensing data from official UK government sources and prescriptions to individual patients from Clinical Practice Research Datalink (CPRD) between October 2010 and September 2015. Monthly tramadol utilisation was measured in Defined Daily Doses per 1000 inhabitants using both aggregated and CPRD data sources. In CPRD, tramadol utilisation was further stratified into existing and new (patients receiving their first tramadol prescription) tramadol users in each calendar month. Interrupted time series analysis was used to evaluate the impact of tramadol classification.

Results: Before the classification, the trend of tramadol utilisation measured in CPRD significantly increased in existing users ($\beta_1: 0.59$, $p<0.001$) but decreased in new users ($\beta_1: -0.07$, $p<0.001$). After tramadol classification, the level ($\beta_2: -12.9$, $p=0.017$) and trend ($\beta_3: -1.6$, $p=0.002$) of the aggregated monthly tramadol utilisation decreased significantly. However, although monthly tramadol utilisation in CPRD significantly decreased in both existing ($\beta_2: -13.8$, $p=0.041$) and new ($\beta_2: -2.6$, $p<0.001$) users after the classification, there was no significant change in the trend of tramadol utilisation for both existing and new users.

Conclusion: The implementation of tramadol classification decreased the monthly tramadol utilisation but did not change the increasing trend of tramadol utilisation in existing tramadol users. Further studies are needed to evaluate the impact of tramadol classification on individual utilisation pattern.

IMPROVING INCIDENT COLORECTAL CANCER (CRC) IDENTIFICATION IN CLAIMS USING A MULTISTAGE MACHINE LEARNING APPROACH.

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Background: Pharmacoepidemiologic studies on cancer outcomes using administrative claims data require reliable cancer identification through claims-based algorithms because pathologic confirmation is usually unavailable. Algorithms developed in a 1997-2000 Pennsylvania Medicare population had a markedly lower positive predictive value (PPV) in a 2006-2009 North Carolina (NC) Medicare population. Goals: Improve claims-based differentiation between true positive (TP) and false positive (FP) CRC, thereby increasing algorithm specificity and PPV.

Methods: We identified all individuals age ≥ 65 ($N=4268$) with ≥ 2 ICD-9 CRC diagnosis codes within 60 days in a cohort of NC Medicare beneficiaries continuously enrolled in Parts A/B for ≥ 13 months (July06-Dec09). TP cases ($N=2370$) were identified via linkage to the NC Central Cancer Registry. We identified all diagnoses and procedures recorded within +/- 90 days of the first CRC diagnosis that were statistically associated ($\alpha<0.025$) with FP ($N=1898$) versus TP status, accounting for multiple ($N=6237$) comparisons. We aggregated codes by concept similarity (e.g. all colonoscopy codes) into variables. We randomly split the data into training and validation datasets ($N=2134$) and used classification and regression trees (CART) to develop algorithms predicting TP status.

Results: Qualitatively, diagnosis and procedure codes associated with FP status appeared to indicate prevalent cases (e.g., history of CRC (ICD-9=V10.05-6) and non-specific ("Neoplasm of colon or rectum, NOS") diagnoses), whereas TP status reflected incident case characteristics (e.g., specific CRC diagnosis, colonoscopy, or pathologist tissue exam). Excluding outcomes with codes associated with FP, we were able to reclassify 64% of FP as non-cases. In the validation dataset, sensitivity declined from 89.6% (CI=88.4-90.7%) to 82.0% (CI=79.9-84.1%) but specificity

increased from 98.7% (CI=98.6-98.8%) to 99.5% (CI=99.5-99.6%) and PPV increased from 56% (CI=54-57%) to 76% (CI=73.4-77.8%) in the validation dataset.

Conclusions: We were able to substantially improve the PPV for identification of incident CRC using machine learning. The timing of potentially prevalent CRC in new-user studies should be examined.

CONCOMITANT USE OF OPIOID AND BENZODIAZEPINES AND THE RISK OF OPIOID OVERDOSE REQUIRING HOSPITALIZATIONS: A RETROSPECTIVE COHORT STUDY

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Background: Although opioids and benzodiazepines are now the leading cause of prescription drug poisoning and overdose deaths in the United States, their concomitant use is increasing. We aimed to compare the risk of an opioid overdose requiring hospitalization in patients concomitantly using opioids and benzodiazepines to patients using only opioids.

Methods: We identified a cohort of opioid initiators with a non-cancer pain diagnosis in a commercial claims database from 2008-14. Exposure was classified into periods of concomitant and opioid only use. For each concomitant user, we matched four control periods of opioids-only use on time since opioid initiation using an incidence density sampling approach. We estimated a propensity score on the matched sample using 86 baseline characteristics including patterns of prior opioid use. The outcome was defined as hospitalization with principal diagnosis of an opioid overdose. Using a Cox proportional hazard model with stabilized inverse probability of treatment weighting (IPTW), we calculated the hazard ratio (HR) of an opioid overdose associated with concomitant use compared to opioid only use, modelled as a time-varying covariate.

Results: We created a matched cohort of 1,114,456 opioid initiators (mean [SD] age 48[11], 64% female). The unadjusted hazard ratio (HR) for

an opioid overdose was 3.08 (95% CI, 2.28-4.16). After IPTW adjustment, the HR decreased to 2.36 (95% CI, 1.86-3.03), corresponding to an absolute excess risk of 12.83 (95% CI 8.18, 19.16) overdose hospitalizations per 10,000 patient years.

Conclusions: Compared to opioid use alone, concomitant use of opioids and benzodiazepines was associated with a significantly higher risk of opioid overdose requiring hospitalization; however the absolute risk difference was small. Further research should evaluate the mechanism of this association.

ASSOCIATION BETWEEN ORAL CONTRACEPTIVE USE AND ANTERIOR CRUCIATE LIGAMENT INJURY AMONG COMMERCIALLY-INSURED FEMALES IN THE UNITED STATES

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Background: Two previous case-control studies suggested a protective association between low-dose oral contraceptive (OC) use and anterior cruciate ligament (ACL) injury; however, both studies compared "ever" versus "never" users. While an association is biologically plausible due to estrogen receptors in the ACL, concern about confounding casts doubt on previous conclusions. We aim to further investigate this topic using an active comparator new user study design among commercially-insured women in the United States.

Methods: All women aged 13-45 years who initiated low-dose OC or underwent intrauterine device (IUD) insertion between 2000 and 2014 were identified from the Truven Health MarketScan Commercial Claims and Encounters database. New OC users were defined using a 180-day washout period. ACL injury was identified by CPT (29888) or ICD-9 (717.83, 844.2) diagnosis code. Women were followed for ACL injury starting 90 days after OC initiation or IUD insertion until the earliest of the following events: OC discontinuation (defined using days' supply and a 30-day grace period), IUD removal, or end of continuous enrolment. Cox

proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Estimates were standardized to the cohort age distribution using inverse probability of treatment weighting.

Results: There were 2,370,286 women who initiated OCs and 621,798 who underwent IUD insertion. Women in the OC group were younger than women in the IUD group (mean age 26.7 vs. 32.4 years). There were 3,571 (0.15%) ACL injuries during an average 370.6 days of continuous OC use and 1,620 (0.26%) during an average 590.5 days of IUD use (HR=1.49, 95%CI 1.41, 1.58). After weighting, there was a harmful association between initiation of OC versus IUD insertion and ACL injury (adjHR=1.29, 95%CI 1.24, 1.34).

Conclusions: Unmeasured confounding between women who use contraception compared to those who do not may have influenced previous findings.

ASSOCIATION BETWEEN RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEINS AND POST-OPERATIVE OPIOID USE IN LUMBAR FUSION PROCEDURE PATIENTS: A PROPENSITY-SCORE MATCHED ANALYSIS

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Background: Prolonged opioid use is associated with significant morbidity. Recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) is often used during fusion procedures as a replacement for autograft bone. Little is known about the effectiveness of the rhBMPs in reducing the demand for opioids after surgery.

Objective: To investigate the association between rhBMP use and the demand for opioids in the first post-surgical year.

Methods: Using the Multi-Payer Claims Database (MPCD) 2007-2010, patients aged > 20, who received a Degenerative Disc Disease-indicated lumbar fusion procedure and had at least one opioid prescription filled in the three months prior to surgery, were identified. Propensity score matching (1:1) of rhBMP-exposed and unexposed patients was used to mitigate the effects of confounding. Outcomes of interest were opioid independence and decreases in opioid doses as measured in morphine equivalents assessed at 3-6 and 9-12 months post-procedure. Logistic regression and Analysis of Covariance models were used to examine the association between rhBMP-use and post-operative opioid use patterns.

Results: A total of 318 patients were included in the propensity score matched cohort; most were female (61%) and under 65 years old (68%). Few patients achieved opioid independence at either the 3-6 (n=71, 22.3%) or 9-12 months (n=115, 36.2%) post-surgical windows. During the 3-6 months window, patients who received rhBMPs reduced their opioid use rates (Estimated Mean Difference: -28.4 vs. -19.5, p value= 0.69) and achieved opioid independence (21.4% vs. 23.3%, OR=0.92, 95% CI, 0.54-1.56, p value = 0.74) at rates that were statistically comparable to their matched comparators. Similar patterns were observed during the 9-12 months window.

Conclusion: We found no evidence to suggest that rhBMP use during spinal fusion procedures is associated with either the discontinuation or decrease of opioid analgesic therapy. The high prevalence of continued opioid use after surgery warrants further study.

POLYPHARMACY AMONG WEST VIRGINIA MEDICAID BENEFICIARIES: PREVALENCE, UTILIZATION, COST, AND POTENTIAL GEOGRAPHICAL DISPARITIES

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Background: Polypharmacy has not been well studied in the non-elderly population. The proposed study aims to estimate the prevalence of polypharmacy by integrating the definitions used in the literature and establishing a feasible approach for assessing this issue in a non-elderly population using administrative claims data.

Methods: In this cross-sectional study, we analyzed the 2010 West Virginia Medicaid claims data for adults aged 18-64. We defined polypharmacy as simultaneous use of drugs from five or more different drug classes for at least 60 consecutive days in one year. Multilevel logistic regression was used to explore the individual- and county-level factors associated with polypharmacy. The associations of polypharmacy with healthcare utilizations were evaluated using zero-inflated negative binomial models. The impact of polypharmacy on non-drug medical costs was assessed using a generalized linear model. We also applied univariate local indicators of spatial association (LISA) to study spatial patterns of polypharmacy prevalence in WV.

Results: The prevalence of polypharmacy as we defined it was 10.5% in WV. We also identified high-high clusters of polypharmacy in southwestern WV, which indicated that a county with an above-average polypharmacy rate was surrounded by counties with above-average polypharmacy rate. Polypharmacy rates were over 35% in patients with congestive heart failure and chronic kidney disease. Being older, with Medicaid eligibility not due to medical need, having more chronic diseases, and living in a county with a distressed economy were positively associated with polypharmacy. Polypharmacy was associated with more hospitalizations, emergency department visits, and outpatient visits, and with higher non-drug medical costs.

Conclusions: Given the high prevalence of polypharmacy and its significant economic burden, particularly in southwestern WV, targeted programs are warranted to identify high-risk populations and help local communities to develop strategies to improve medication use and reduce polypharmacy burden.

ASSESSING THE EFFECT OF PROPENSITY SCORE TRIMMING ON THE ESTIMATION OF TREATMENT EFFECT IN OBSERVATIONAL COMPARATIVE EFFECTIVENESS RESEARCH.

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Background: Propensity score (PS) matching is often employed to select 'similar' patients from different treatment groups in observational comparative effectiveness research (CER). The use of PS trimming has been suggested to ensure patients within a region of common support are matched.

Objectives: To estimate the effect of PS trimming prior to matching on the relative risk of fracture (i.e. anti-fracture effectiveness) amongst users of two anti-osteoporosis drugs (AOD) used for different indications: 1. Alendronate, the first line therapy for most patients, and 2. SERMs, used only in younger women with less severe osteoporosis.

Methods: The effect of PS trimming on treatment effect estimation was evaluated using the association between AOD use and fracture risk (major osteoporotic fracture). Using the SIDIAP database (anonymized primary care medical records from Catalonia, Spain from 2006-2014), users of Alendronate (reference group) were compared to users of SERMs. After estimation of PS for all patients, PS matching was performed using a) all patients in the two groups, and b) patients whose PS lay between the 25th and 75th percentile of the PS distribution for their group (i.e. PS-trimmed population). The relative risk of fracture (SHR) was estimated using a proportional hazards regression model accounting for competing mortality.

Results: PS were estimated for a total 73194 Alendronate and 11520 SERMs users. After trimming, 37289 Alendronate and 5067 SERMs

users remained. Matching resulted in standardised mean difference between Alendronate and SERMs groups of 0.01 and 0.02 with trimming prior to matching and without, respectively. No difference in treatment effect (relative fracture risk) was observed with trimming prior to matching (0.705 [0.640 0.778]) and without (0.706 [0.659 0.757]).

Conclusion: Despite the support for PS trimming in simulation studies, we have not found evidence of its effect using routinely collected data. More research is needed on use PS trimming for observational CER.

UTILITY OF NUMERIC THRESHOLDS OF POLYPHARMACY TO PREDICT ADVERSE OUTCOMES IN DEMENTIA

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Background: On average a person with dementia suffers from 4-5 long-term conditions, leading to complex medication regimes and increased levels of polypharmacy. One approach to measure polypharmacy is to count the number of drugs prescribed, whereby higher levels polypharmacy have been associated with adverse outcomes in the general population. Aim of this study was to investigate predictors of polypharmacy in people diagnosed with dementia, and if commonly used numeric thresholds were associated with adverse outcomes.

Methods: We assembled a retrospective cohort from a large mental health care database in South London, linked to Hospital Episode Statistics and mortality data. Using regression models we investigated if common definitions of polypharmacy (prescribed ≥ 4 or ≥ 5 medications) or 'excessive' polypharmacy (prescribed ≥ 10 medications) were related to hospitalization and mortality.

Results: 3,839 patients with a first diagnosis with dementia were identified. Factors predicting higher levels of polypharmacy included male gender, non-white ethnicity, psychotic symptoms, physical health problems, psychotic and previous hospitalization due to metabolic illness. Neither being prescribed ≥ 4 medications nor ≥ 5

medications at the time of dementia diagnosis was associated with an increased risk of hospital admissions in the 2 years post diagnosis. Only dementia patients who were subject to excessive polypharmacy had significantly higher risks for hospital episodes due to cancer, metabolic illness, circulatory disease and genito-urinary disease. No associations between numeric polypharmacy and mortality risk were identified.

Conclusions: With the exception of excessive polypharmacy, numeric thresholds of concurrently prescribed medications do not appear to predict hospitalization or mortality risk in dementia patients. The complex interplay of various conditions in this patient group might make polypharmacy a 'necessary evil'. More sophisticated tools, taking into account appropriateness of prescribing and the clinical picture, might be better placed to evaluate prescribing outcomes in dementia and make practice recommendations.

TRENDS IN REPORTED PEDIATRIC ACETAMINOPHEN EXPOSURES IN THE UNITED STATES FROM 2006 – 2014

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Background: Acetaminophen is the leading cause of pediatric acute liver failure in the United States. In 2011, acetaminophen manufacturers reduced the concentration of infants' products to match that of children's products to reduce pediatric overdoses. Additionally, media campaigns have sought to increase awareness of acetaminophen's hepatotoxicity and narrow therapeutic window. Our goal was to evaluate the effects of public health efforts on exposure trends and quantify exposures by demographics and clinical characteristics.

Methods: We used the National Poison Data System to identify cases of single-ingredient acetaminophen exposure in individuals under 19 years of age from January 2006 to December 2014. Exposures were summed by age, year, gender, state, clinical effects, therapies, and outcomes and

stratified by intentionality. Interrupted time series modeling was used to detect trend differences before and after marketing changes.

Results: Of 382,852 total exposures, 340,603 (10%) were unintentional and 39364 (89%) were intentional. From 2012-2014, the period following changes in pediatric products, unintentional exposures (mean [SD] age, 2.9 [2.8], 48% female) demonstrated a decreasing trend (-.54, 95% CI: -0.72, -.35) and declined 4.5%, while intentional exposures (mean [SD] age, 15.4 [2.3], 77% female) demonstrated an increasing trend (.54, 95% CI: .4, .67) and rose 4.5%. Trends in this period were significantly different from 2006-2008 and 2009-2011 periods. The largest decrease in unintentional exposures occurred in 2 year olds (19.5%) and the largest increase in intentional exposures occurred in 14 year olds (85%). Intentional exposures were more likely to result in intensive care unit admission (17% vs <1%, $P < .001$) and require N-acetylcysteine (45% vs 1%, $P < .001$).

Conclusion: While public health efforts have coincided with a decrease in accidental exposures, intentional ingestions remain a problem in adolescents. Decreasing acetaminophen accessibility and promoting its hepatotoxicity may further diminish accidental exposures and prevent intentional overdoses.

A SELF-SELECTING PROCEDURE FOR THE OPTIMAL PATIENT TIMELINE DISCRETIZATION OF ADMINISTRATIVE DATA USING LONGITUDINAL CAUSAL INFERENCE METHODS

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In pharmacoepidemiology, administrative databases have become abundantly used to conduct research on drug safety and effectiveness. In longitudinal settings, administrative databases provide information on data that is collected in real-time. In such settings, a potential source of bias is time-dependent confounding, which can be addressed with longitudinal causal inference methods such as Marginal Structural Models (MSM). However, these methods usually rely on

a discretization of the patient timeline that may not reflect the underlying continuous nature of administrative data. Thus bias may result when the discretization is arbitrarily chosen by the researcher, which is common practice.

We develop a new method for the automatic selection of an optimal data timeline discretization for use with Longitudinal Targeted Maximum Likelihood Estimation (LTMLE) of MSMs. We use a simulation study to evaluate the bias-variance tradeoff of such a method. The method is then applied to a context of comparison of alternative asthma treatments during pregnancy on pregnancy duration.

We show how coarsening changes the underlying true population of interest as well as how it creates bias of our parameter of interest and affects its variance. We also demonstrate the performance of our selection procedure in simulated and applied settings.

In conclusion, this research is of utmost importance since it reflects flaws in common practices and addresses this problem by evaluating the impact of discretization and by proposing an automatic optimal discretization selection method that seems to perform appropriately.

AVAILABILITY OF ESSENTIAL MEDICINES FOR DIABETES AND CARDIOVASCULAR DISEASES IN HEALTH FACILITIES OF BANGLADESH: EVIDENCE FROM NATIONALLY REPRESENTATIVE SURVEY

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Background: The burden of diabetes and cardiovascular diseases (CVDs) continues to increase in developing countries including Bangladesh. One of the main factors responsible

for this burden is availability and accessibility of essential medicines. However, there is not much research done on the availability of essential medicines for these diseases in Bangladesh. We aimed to assess the availability and distribution of selected essential medicines for diabetes and CVDs in health facilities of Bangladesh.

Methods: We used data from the nationally representative 2014 Bangladesh Health Facility Survey. The availability of essential medicines within the facility was measured using the methodology proposed by World Health Organization (WHO) and United States Agency for International Development (USAID). Data were collected from 1,548 public, private, and non-governmental (NGO) health facilities throughout Bangladesh. Based on our inclusion criteria (e.g., hospitals \geq 20 beds), information from 275 facilities was used in the analyses.

Results: The results showed that 10% of the facilities that offer diabetes care services had metformin available during the survey and only 7% had glibenclamide. Twelve percent of the facilities had injectable insulin and 8% had injectable glucose solution. Among the facilities that offer CVDs care services, 22% had beta-blockers (BB), 20% had calcium channel blockers (CCB), 12% had aspirin, 6% had thiazide diuretics, and 6% had angiotensin converting enzyme (ACE) inhibitors. Urban facilities were more equipped (23-45%) with essential medicines than the rural facilities (2-5%). Additionally, private hospitals had a higher proportion of essential medicines than small city health complex and NGO facilities.

Conclusion: Overall a few health facilities had adequate essential medicines for treating either diabetes or CVDs. There are vast disparities between rural and urban facilities as well as private and public facilities in availability of these essential medicines. The drug policy should address availability and accessibility of essential medicines in Bangladesh.

REAL-WORLD ADHERENCE WITH DIRECT ORAL ANTICOAGULANTS IN ADULTS WITH VENOUS THROMBOEMBOLISM

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Background: Adherence to anticoagulation (AC) therapy is critical as it has direct impact on clinical outcomes and healthcare utilization. This is especially important in venous thromboembolism (VTE) as the initial months of therapy are crucial in reducing the risk of recurrent VTE. The objective of this study is to evaluate patterns of medication adherence in a real-world setting amongst VTE patients treated with direct oral anticoagulants (DOACs).

Methods: Patients with VTE were identified from the Truven Health MarketScan® Commercial Claims and Encounters database (2009-2013). Patients newly-initiated on a DOAC were followed from their first (index) DOAC prescription date until 180, 270 or 360 days post index date. Patients were categorized as either AC therapy naïve (no prior AC use) or non-AC naïve (prior AC use). Patients initiating a DOAC with a minimum of 6 months of continuous plan enrollment pre and post-index date were included. DOAC adherence patterns were assessed using proportion of days covered (PDC). Additional analyses are underway to evaluate predictors of adherence.

Results: A total of 7,782 VTE patients newly-initiated on DOAC therapy were included. Of those patients, 30.6% (N=2,381) were AC naïve and 69.4% (N=5,401) were non-AC naïve (age: 61.3 ± 16.5 vs. 62.9 ± 15.3 years, $p < 0.001$, respectively; male: 1,180 (49.6%) vs. 2,753 (51.0%), $p = 0.25$, respectively). Patients primarily used rivaroxaban as their index DOAC (N=5634, 72.4%). The mean PDC in AC naïve and non-naïve patients at 180 days, 270 days and 360 days post-index was $68.3\% \pm 33.5$ vs. $74.8\% \pm 31.2$, $p < 0.001$; $56.8\% \pm 34.9$ vs. $69.8\% \pm 33.4$, $p < 0.001$; and $49.2\% \pm 36.7$ vs. $65.7\% \pm 35.3$, $p < 0.001$, respectively.

Conclusion: Medication adherence was low at 6 months post-index, and further decreased at a rate of nearly 20% over an additional 6 months of follow-up. Adherence was lower at each timepoint in AC naïve patients compared to non-AC naïve. Further investigation is warranted to examine reasons for low adherence rates.

ISPE'S 2017 MID-YEAR MEETING

**April 2-4, 2017 | Royal College of Physicians
London, United Kingdom**

MEETING NOTES

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UPCOMING MEETINGS

Save the dates for ISPE's upcoming meetings!
More information can be found on pharmacoepi.org

33rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management

August 26-30, 2017
Palais des congrès de Montréal
Montreal, Canada

ISPE's 10th Asian Conference on Pharmacoepidemiology

October 29-31, 2017
University of Queensland,
Brisbane, Australia

2018 ISPE Mid-Year Meeting

April 21-24
Sheraton Centre Toronto
Toronto, Canada

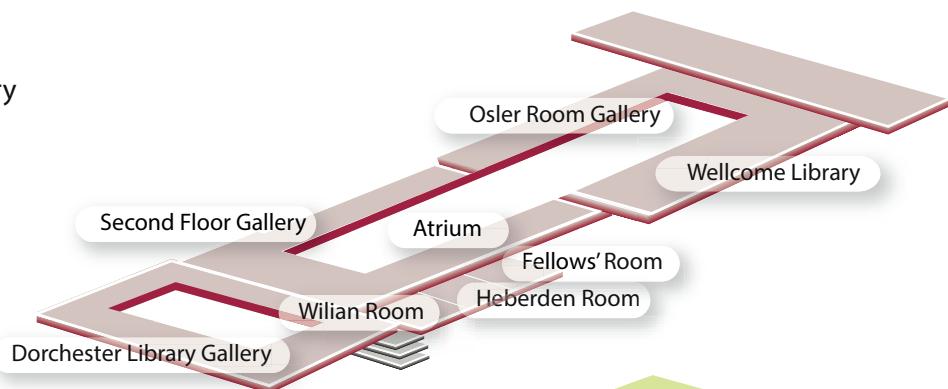
34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management

August, 2018
Prague, Czech Republic

ROYAL COLLEGE OF PHYSICIANS

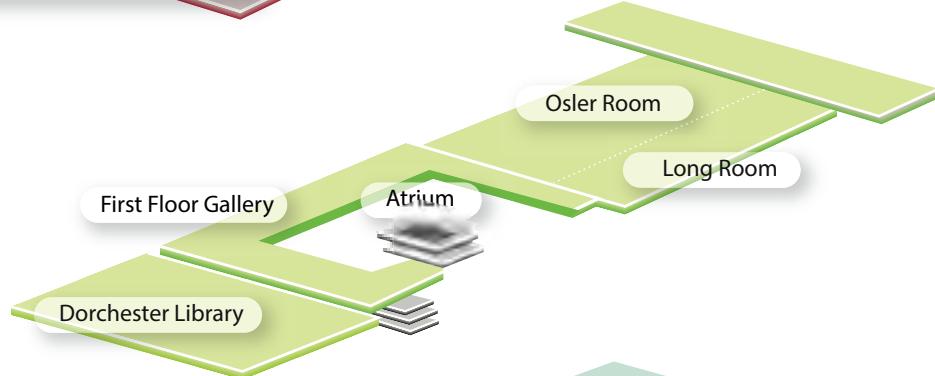
Second Floor

Dorchester Library Gallery
Gallery
Osler Gallery
Wilian Room
Heberden Room



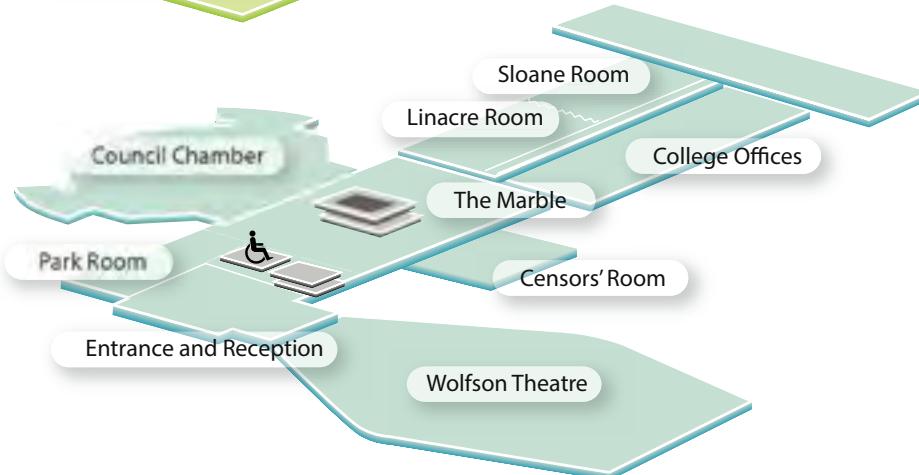
First Floor

Dorchester Library
Gallery
Long Room
Osler Room



Ground Floor

Council Chamber
Censors' Room
Park Room
Linacre Room
Sloane Room
Entrance & Reception
The Marble
Wolfson Theatre



Lower Ground Floor

Amenities
Lower Hall
Platt Room
Seligman Theatre
Silver Room

Amenities
Cloakroom
Lap-top ComPoint
Wi-Fi
Accessible Entrance
Showers
Toilets including accessible facilities

