2021 Virtual
Mid-Year Meeting
Event Program Booklet

Use of RWE for regulatory decision-making:
for populations and individuals

April 19-20, 2021

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ISPE 2021 Mid-Year Meeting Planning Committee

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A Note of **Thanks**

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

Helga Gardarsdottir, FISPE
ISPE Mid-Year Committee

M. Elle Saine
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Alvi Rahman
Tania Schink
Satu Johanna Siiskonen
Jessica Young

Monday, 19 April

8:00 AM – 8:15 AM

Welcome and Introduction

Helga Gardarsdottir, FISPE, Chair: 2021 ISPE Mid-Year Planning Committee

Olaf Klungel, FISPE, ISPE President

8:15 AM – 9:25 AM

The Shot Heard Around the World: Development & Distribution of COVID-19 Vaccines

Moderators: Ann McMahon, FISPE, US Food and Drug Administration, Christopher T. Rentsch, London School of Hygiene & Tropical Medicine (LSHTM)

Use of RWE for Development and Lifecycle Management of COVID-19 Vaccines

Kourtney Davis, Janssen R&D

Monitoring of Safety of COVID-19 Vaccines: Challenges and Opportunities

Georgy Genov, European Medicines Agency

COVID-19 Vaccines and Equity in Distribution

Inmaculada Hernandez, University of Pittsburg

9:25 AM – 9:40 AM Break

9:40 AM – 10:40 AM

Oral Presentations – Session 1: Pain and Neuropsychiatric Therapies

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Salvatore Crisafulli

Nationwide Patterns of Hydroxychloroquine Dosing and Monitoring of Retinal Toxicity in Patients with Systemic Lupus Erythematous

Jae-Eun Lee

11:50 AM – 12:00 PM Break

12:00 PM – 1:30 PM

Personal Development

Anton Pottegård, University of Southern Denmark

1:30 PM – 1:40 PM

Closure of Day 1

Helga Gardarsdottir, FISPE, Chair: 2021 ISPE Mid-Year Planning Committee

Tuesday, 20 April

8:00 AM – 8:15 AM	**Welcome and Introduction**
	Helga Gardarsdottir, FISPE, Chair: 2021 ISPE Mid-Year Planning Committee
8:15 AM – 9:35 AM	**Rise of the machines: Big Data Analytics and Machine Learning in Pharmacoepidemiology**
	Moderators: Rolf Groenwold, Leiden University Medical Center, Jeremy Rassen, FISPE, Aetion *Artificial Intelligence in Pharmacoepidemiology* Maurizio Sessa, University of Copenhagen *Counterfactual Prediction for Healthcare Decision-Making* Barbra Dickerman, Harvard T.H. Chan School of Public Health *Use of Machine Learning for Causal Inference Questions* William Crown, Brandeis, Heller School for Social Policy and Management
9:35 AM – 9:50 AM	Break
9:50 AM – 10:20 AM	**Poster Session**
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Breakout room 2	**Spotlight on Pharmacoepidemiology in Cancer and Rheumatic Disease:** Yeon-Hee Baek, Cornelia Kazemali, Lauren McVicker, Niamh McGuckin, Young EunShin, Rosanne Meijboom, Djanilson Santos, Elena Guillen
Breakout room 3	**Capturing The Real World: Design, Reporting & Analysis in Pharmacoepidemiology:** Malahat Khalili, Agne Valinciute-Jankauskiene, Maude Lavallee, Xianghao Kong, Valentina Isgro, Yu-Chia Hsu, Yunjing Zhang, Lexi Rene
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10:25 AM – 11:25 AM

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Sodium-Glucose Co-Transporter 2 Inhibitors and the Risk of Acute Kidney Injury: A Population-Based Cohort Study

Wajd Alkabbani

Effect of Biosimilar Basaglar Entry in the Long-Acting Insulin Market

Emaan Rashidi

Body Weight and Glucolipid Changes Following Anti-TNF-Alpha Treatment in Children with Inflammatory Bowel Disease: A Retrospective Case Series Analysis Combined with Real-World Pharmacovigilance Study

Faizan Mazhar

11:25 AM – 11:40 AM Break

11:40 AM – 12:40 PM

Oral Presentations – Session 4: Pharmacoepidemiology in Contraception, Conception, and Beyond

Risk of Thrombosis Associated with Drug-Drug Interactions Between Oral Hormonal Contraceptives and Verapamil or Diltiazem

Raj Desai

Effective Prevention of Prenatal Exposure to Topiramate in the Presence of Potential Drug-Drug Interactions with Oral Hormonal Contraceptives: Insight from a Real-World Retrospective Cohort Study

Amir Sarayani

Antiepileptic Treatment Pattern During the 1st Trimester of Pregnancy – An Evaluation of the German Embryotox Cohort

Sofia Slimi

Early Life Antibiotic Exposure and Incident Chronic Diseases in Childhood

Matthew Beier

12:40 PM – 12:55 PM

Closure of Meeting

Helga Gardarsdottir, FISPE, Chair: 2021 ISPE Mid-Year Planning Committee

Syd Phillips, FIPSE, Chair: 2021 ICPE Scientific Program Committee

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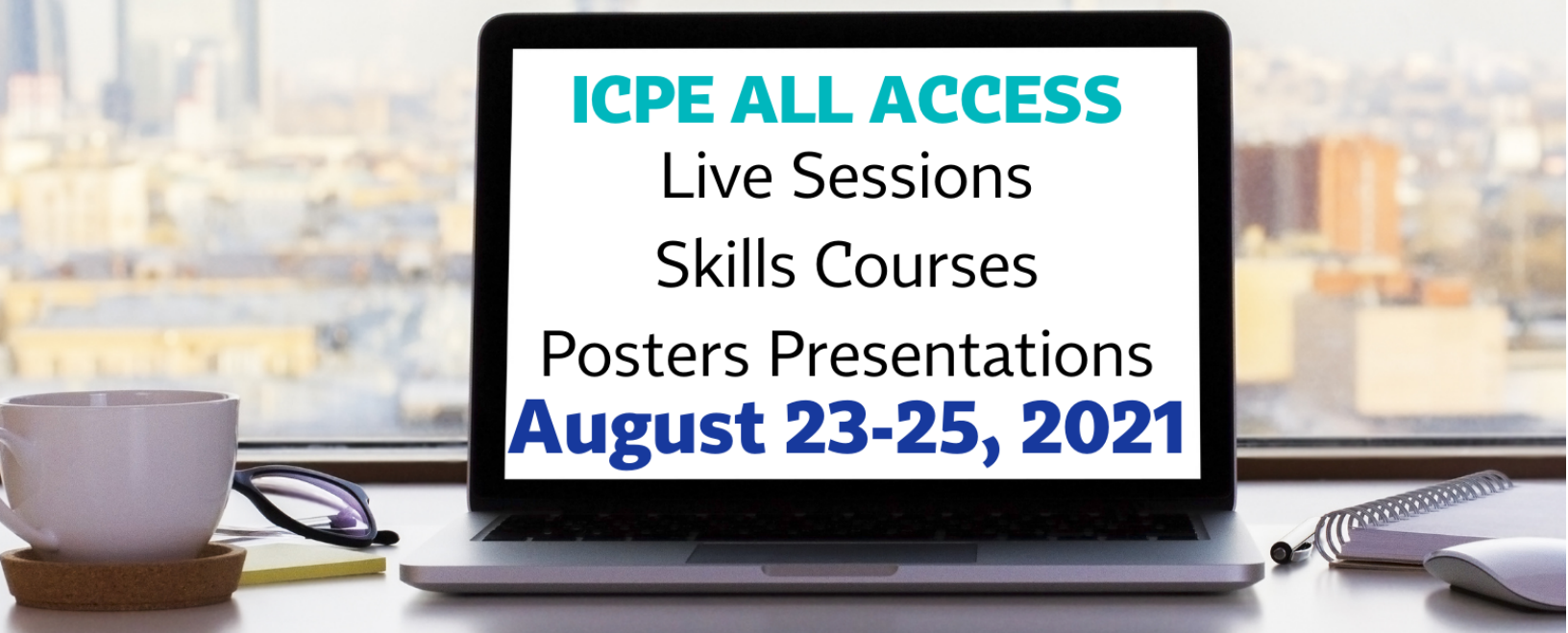

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Oral Presentation Abstracts

Oral Session 1: Pain and Neuropsychiatric Therapies

Monday 19 April | 9:40 AM – 10:40 AM

Abstracts In Presentation Order

Presenting Author Highlighted In **Bold**

Opioid Claim Submission Patterns After the Implementation of the 2019 CMS Edits for Medicare Advantage Beneficiaries in Puerto Rico

Emily Wong[1], Jose Hernandez[1]

[1]*Texas A&M College of Pharmacy*

BACKGROUND: The Opioid Crisis represents an increasing global health challenge. Widespread use of opioids among elderly patients is a concern. On January 1, 2019, the Center for Medicare and Medicaid Services (CMS) recommended its Medicare Part D plans to utilize real-time safety alerts to improve opioid dispensing patterns. The real-time safety alerts are pharmacy claim edits for pharmacists to review at the time of dispensing and decide if the prescription should be dispensed or not. Unfortunately, the Commonwealth of Puerto Rico has often been overlooked in opioid pharmacoepidemiology research.

OBJECTIVES: Assess the impact of the 2019 CMS opioid safety alerts on Medicare Advantage beneficiaries in the Commonwealth of Puerto Rico. This study aims to: (1) to describe the monthly prevalence for each CMS edit during 2019; (2) to describe the age and gender of the beneficiaries with CMS edit; and (3) to describe the proportion of claims that generated edits but ended up being filled (overridden) by the pharmacy.

METHODS: A time-trend analysis was used to evaluate the impact of the CMS concurrent drug utilization review on opioids dispensing among Medicare Advantage beneficiaries during 2019. The impact of five different real-time safety edits on opioid dispensing was evaluated. The five safety alerts are: >7 days' supply for opioids for naïve users, ≥90 morphine milliequivalent (MME) per day per beneficiary, long-acting opioids duplicate therapy, concurrent use of opioids and benzodiazepines, and ≥200 MME per day per beneficiary.

RESULTS: The average monthly prevalence of Medicare Advantage beneficiaries generating opioid safety edits during 2019 was (13,326/128,766) 10.35%. The 13,326 beneficiaries generated a total of 41,443 opioid safety alerts at the point-of-service during the study period. The beneficiaries' average age was 69 (±11) years old, and most were females (56%). The safety alert with the highest average monthly prevalence (1.07%) and with the highest percent decrease (46.77%) during the 12-months study period was >7 days' supply for opioids for naïve users. The ≥90 MME per day safety alert had an average monthly prevalence of 0.05% and was the most effective intervention for the last quarter of the study period, with 100% pharmacy rejections from October to December 2019. The concurrent opioid and benzodiazepine safety alert had an average monthly prevalence of 0.33%, and it was the only edit with a steady increase in the number of overrides at the point-of-service during the study period. The lowest average monthly prevalence for opioid safety alerts was observed for the duplicate therapy of long-acting opioids

(0.01%) and the ≥200 MME per day (0.01%) edits. The last two safety alerts had a consistent prevalence of rejections during the study period.

CONCLUSION: The safety alert for opioid naïve users was the edit with the most significant decrease during the 12-months study period. Therefore, the pharmacists' drug utilization review at the point-of-service minimizes the exposure to long treatment cycles with opioids among opioid naïve users. However, the other four safety alerts were not as useful, as the percent of overrides at the point-of-service were constant or increased during the study period.

Co-Prescription of Opioids with Other Medications and Risk of Opioid Overdose

Nazleen F. Khan[1], Katsiaryna Bykov[2], Robert Glynn[2], Michael Barnett[1], Joshua J. Gagne[1]

[1]Harvard T.H. Chan School of Public Health; 2BWH Division of Pharmacoepidemiology and Pharmacoeconomics

BACKGROUND: Polypharmacy is common among patients taking prescription opioids long-term. Co-dispensing of potentially interacting medications may further increase opioid overdose risk.

OBJECTIVE: To identify non-opioid medications that may increase opioid overdose risk among patients on long-term opioid therapy.

METHODS: Case-crossover-based screening of data from 2003 through 2019. The analysis quantified the odds ratio (OR) for the association between each non-opioid medication and opioid overdose after adjustment for prescription opioid dosage change and benzodiazepine co-dispensing. The false discovery rate (FDR) was used to account for multiple testing. Setting: Electronic claims data from Truven Health MarketScan Database and Optum© Clinformatics® Data Mart. Participants: Individuals with at least 180 days of continuous enrollment and 90 days of prescription opioid use immediately before the first opioid overdose at age 18 years or older. Exposures: Non-opioid medications dispensed in the 90 days immediately before the opioid overdose date. Measurements: Opioid overdose resulting in an emergency room visit or hospitalization.

RESULTS: We identified 24,866 eligible individuals who experienced opioid overdose. Baclofen (OR 1.56, FDR < 0.01), lorazepam (OR 1.53, FDR < 0.01), and gabapentin (OR 1.16, FDR = 0.09), among other non-opioid medications, were associated with opioid overdose.

CONCLUSION: Several non-opioid medications were associated with opioid overdose among patients using prescription opioids long-term. Interventions may focus on prescribing safer alternatives or opioid antagonists when a potential for interaction exists.

The Relationship Between Valproate Versus Lamotrigine/Levetiracetam Use and Prognosis in Patients with Epilepsy and Heart Failure: A Danish Register-Based Study

David Liang[1], Elena Gardella[2], Kristian Kragholm[3], Christoffer Polcwiartek[3], Maurizio Sessa[1]

[1]University of Copenhagen; [2]Danish Epilepsy Centre Filadelfia; [3]Aalborg University Hospital

BACKGROUND: Heart failure and cardiovascular comorbidities are common in patients aged 65 or older with epilepsy. Furthermore, almost 50% of the causes of new-onset epilepsy in individuals aged 65 or older are caused by cardiovascular diseases, and more specifically stroke. The co-existence of epilepsy and heart failure represents a complex clinical scenario as antiseizure medications have cardiac effects. Considering their not negligible cardiovascular effects, it is crucial to understand if the choice of antiseizure medication in patients with epilepsy and concurrent heart failure may influence their

overall prognosis. To date, the evidence on the prognosis of patients having both diseases among those exposed to antiseizure medications is scarce. We aimed to compare the all-cause and heart failure mortality between valproate (VPA) and levetiracetam (LEV)/lamotrigine (LTG) users in older patients with these comorbidities.

METHODS: Registry-based cohort study using Danish administrative registers in the period from January 1996 until July 2018. It included the entire Danish population aged ≥65 with heart failure and epilepsy that during the study period redeemed their first prescription of LTG, LEV, or VPA (i.e., new users design). The operative definitions for the variables codifying exposure, outcome, and potential confounders selected based on clinical expert suggestions and by systematically screening the scientific literature. Other potential confounders in this study were identified using the data-driven approach, described by Schneeweiss et al. in 2009, for constructing the high dimensional propensity score limiting our data sources to redeemed prescriptions in public pharmacies and hospital admissions/ hospitalizations according to Hallas and Pottegård in 2017. Cox regression model was used to compute crude and adjusted hazard ratios for the outcome using an intention-to-treat approach. Average treatment effects (e.g., 1-year absolute risks), risk difference, and the ratio of risks were computed using the G-formula based on a Cox regression model.

RESULTS: 1345 subjects were included in the study population. VPA users (n=696), when compared to LTG/LEV users (n=649), had an increased hazard of heart failure mortality (crude:

Hazard Ratio, HR 3·04; 95% confidence interval, 95%CI 1·45 – 6·49; adjusted: HR 2·39; 95%CI 1·02-5·60) and all-cause mortality (crude: HR 1·77; 95%CI 1·38-2·15; adjusted: HR 1·37; 95%CI 1·01-1·85) in both analyses. The 1-year absolute risks for all-cause mortality were 29% (95%CI 25%-33%) and 22% (95%CI 18%-26%) for VPA and LTG/LEV users. For heart failure mortality, 1-year absolute risks were 5% (95%CI 3%-7%) and 2% (95%CI 1%-4%) for VPA and LTG/LEV users. The average risk ratio, with LTG/LEV as the reference group, was 1·31 (95%CI 1·02-1·71) for all-cause mortality and 2·35 (95%CI 1·11-5·76) for heart failure mortality.

CONCLUSION: In older people with heart failure and epilepsy, treatment with VPA was associated with a higher risk of all-cause and heart failure mortality compared to LTG and LEV.

Risk of Ventricular Arrhythmia and All-Cause Mortality with Citalopram or Escitalopram Versus Paroxetine and Sertraline Among Older Adults in Denmark: A Registry-Based Cohort Study

Sarah K. Werther[1], Mia Aakjær[1], Kathrine Pape[1], Morten Andersen[1]

[1]*Pharmacovigilance Research Centre, Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark.*

BACKGROUND: Selective serotonin reuptake inhibitors (SSRIs) are some of the most prescribed drugs in Denmark. Citalopram and escitalopram are capable of prolongating the QT interval, which can potentially trigger ventricular arrhythmia.

OBJECTIVE: This study sought to examine the comparative risk of an event of ventricular arrhythmia between citalopram or escitalopram and two reference SSRIs.

METHODS: This was a registry-based cohort study consisting of older adults (≥ 65 years old) included during 2002-2016 and conducted on data from the Danish National Registries. It utilized a new-user study design with a wash-out period of 6 months. The exposures were citalopram (ATC code N06AB04) and escitalopram (N06AB10), while paroxetine (N06AB05) and sertraline (N06AB06) constituted the control group. The primary outcome was an incident event of ventricular arrhythmia or cardiac arrest. The secondary outcome was all-cause mortality. Outcomes were identified with ICD-10 diagnostic codes. We used an intention-to-treat approach following patients for a maximum of 90 days from treatment initiation (index date) to the relevant event, censoring or end of study period. Crude and propensity score-adjusted odds ratios (ORs) were estimated with logistic regression. The propensity scores were estimated using information on age, sex, comorbidities and comedications.

RESULTS: There were 148,356 citalopram users, 33,660 escitalopram users, and 30,381 controls included in the study. The mean age of patients was 78.3 years, 78.0 years, 76.5 years for citalopram, escitalopram, and the controls, respectively. The proportion of women was approximately 60 % in all three groups. Among citalopram users, 81 events (0.05%) of ventricular arrhythmia or cardiac arrest were registered. Among escitalopram users, 20 events (0.06 %) and among the controls, 19 events (0.06 %) occurred. Neither citalopram (OR 0.80, 95% confidence interval (CI) 0.48-1.34), nor escitalopram (OR 0.88, 95% CI 0.47-1.67) use was associated with significantly increased risk of an event of ventricular arrhythmia or cardiac arrest compared to the control group. However, both citalopram (OR 1.26, 95% CI 1.19-1.33) and escitalopram (OR 1.31, 95% CI 1.23-1.40) were significantly associated with an increased risk of all-cause mortality.

CONCLUSION: Citalopram and escitalopram use was not significantly associated with an elevated risk of an event of ventricular arrhythmia or cardiac arrest in older adults compared to paroxetine and sertraline. The findings of a significantly increased risk for an outcome of all-cause mortality for both exposures of interest are most likely a result of residual confounding, including unmeasured frailty.

Oral Session 2: The Shifting Landscape of Pharmacotherapeutics in Population Health

Monday 19 April | 10:50 AM – 11:50 AM

Abstracts In Presentation Order

Presenting Author Highlighted In **Bold**

Geographic Variation in Influenza Vaccination Among US Nursing Home Residents: A National Study

Joe Silva[1], Elliott A. Bosco[1], Melissa Riester[1], Kevin McConeghy[1], Patience Moyo[1], Robertus van Aalst[2,3], Barbara Bardenheier[1], Stefan Gravenstein[1], Rosa Baier[1], Matthew Loiacono[2,4], Ayman Chit[2,4], Andrew Zullo[1,5]

[1]Brown University School of Public Health; [2]Sanofi Pasteur; [3]Department of Health Sciences, University of Groningen, University Medical Center Groningen; [4]Leslie Dan School of Pharmacy, University of Toronto; [5]Center of Innovation in Long-Term Services and Supports, Providence Veterans Affairs Medical Center

OBJECTIVES: Although influenza incidence rates vary widely by location, policymakers lack knowledge on whether the geographic patterns of vaccine use among United States nursing home (NH) residents, especially at the county level and after risk-standardization for differences in NH resident-characteristics between counties. To address this, we estimated risk-standardized vaccination rates among short- and long-stay NH residents by U.S. county and identified potential drivers of geographic variation.

METHODS: We conducted a retrospective cohort study utilizing 100% of 2013-2015 fee-for-service Medicare claims, Minimum Data Set assessments, Certification and Survey Provider Enhanced Reports, and Long-Term Care: Facts on Care in the U.S. (LTCFocUS). We separately evaluated short-stay (< 100 days) and long-stay (≥100 days) residents aged ≥65 years old across the 2013-2014 and 2014-2015 influenza seasons. We estimated county-level risk-standardized vaccination rates (RSVRs) via hierarchical logistic regression adjusting for 32 resident-level covariates. We then used multivariable linear regression models to assess associations between county-level NHs predictors and RSVRs.

RESULTS: The overall study cohort consisted of 2,817,217 residents in 14,658 NHs across 2,798 counties. Short-stay residents had lower RSVRs than long-stay residents (2013-2014: median [IQR], 69.6% [62.8-74.5] vs 84.0% [80.8-86.4]). Counties with the highest vaccination rates were concentrated in the Midwestern, Southern, and Northeast US. Several modifiable facility-level characteristics were associated with increased RSVRs, including higher registered nurse to total nurse ratio and higher total staffing for licensed practical nurses, speech-language pathologists, and social workers. Characteristics associated with lower RSVRs included a higher percentage of residents restrained, with a pressure ulcer, and NH-level hospitalizations per resident-year.

CONCLUSION: Substantial county-level variation in influenza vaccine use exists among short- and long-stay NH residents. Quality improvement interventions to improve vaccination rates can leverage these results to target NHs located in counties with lower risk-standardized vaccine use.

Performance of Elixhauser and Charlson Comorbidity Indices to Predict Mortality Among Adults Hospitalized with COVID-19 in the United States

Kathleen M. Andersen[1], Emaan Rashidi[1], Brian T. Garibaldi[2], G Caleb Alexander[1], Jodi B. Segal[1], Hemalkumar B. Mehta[1]

[1]Johns Hopkins Bloomberg School of Public Health; [2]Johns Hopkins Medicine

BACKGROUND: It is not clear how to best control for comorbidities when examining short-term mortality among individuals with COVID-19. The Charlson and Elixhauser Comorbidity Index were developed to predict 1-year and in-hospital mortality, respectively, and both indices can be operationalized using individual comorbidities or a weighted summary score. We compared the predictive accuracy for these comorbidity scores in predicting in-hospital death among adults hospitalized with COVID-19 from 5 hospitals comprising a health care system in the Mid-Atlantic United States.

METHODS: We used electronic health record data from adults hospitalized for COVID-19 from March 4 - November 6, 2020. We ascertained comorbidities using all available lookback data from January 1, 2018 through COVID-19 hospital admission. We operationalized both comorbidity scores using individual comorbidities – 17 for Charlson and 29 for Elixhauser. We calculated weighted Charlson scores four ways, separately, using weights proposed by Deyo (1992), Schneeweiss (2003), Quan (2011) and Mehta (2016). We calculated the Elixhauser comorbidity score using weights proposed by van Walraven (2009) and Thompson (2015). We used logistic regression to compare the performance of different comorbidity scores in predicting in-hospital death. Nine models were constructed (1 baseline model that included age and sex, 1 for Charlson individual comorbidities, 4 for weighted Charlson scores, 1 for Elixhauser individual comorbidities and 2 for weighted Elixhauser scores). All models included age and sex as covariates. We evaluated the performance of each model using the c-statistic, and compared c-statistics using chi-square statistics, with a p-value < 0.05 considered significant model fit improvement. Secondarily, we compared model fit using Akaike Information Criteria (AIC), where lower values indicate better model fit. We used PROC LOGISTIC in SAS version 9.4.

RESULTS: Of 2,815 COVID-19 hospitalized patients, 12% (n=349) died in the hospital. Each comorbidity score performed significantly better ($p < 0.001$) than age and sex alone (c-statistic 0.775) at predicting COVID-19 related death. Overall, the ranking of the top 4 comorbidity scores were as follows: individual Elixhauser comorbidities (c-statistic 0.822) > Elixhauser-Thompson (c-statistic 0.803) > Elixhauser-van Walraven (c-statistic 0.796) = individual Charlson comorbidities (c-statistic 0.796). Weighted Elixhauser comorbidity scores (c-statistics ranging from 0.796 to 0.803) had significantly better performance than weighted Charlson comorbidity scores (c-statistics ranging from 0.786 to 0.790). Conclusions were similar when using AIC values to assess model fit.

CONCLUSION: The individual comorbidities in the Elixhauser were the most accurate in predicting in-hospital death. If the weighted score needs to be used due to sample size limitations, we found that the Elixhauser-Thompson score was the most accurate in this training set. While statistically significant, the magnitude of predictive accuracy gained by adding covariates to the model for in-hospital mortality were small. Future research should investigate the utility of a customized COVID-19-specific comorbidity score in predicting mortality among adults hospitalized with COVID-19.

Risk of COVID-19 Hospitalization/ Mortality in Patients with Rheumatic Disease Treated with Chloroquine/ Hydroxychloroquine or Other Conventional DMARDs in Italy: A Large-Scale Nested Case-Control Study

Salvatore Crisafulli[1], Stefania Spila Alegiani[2], Paolo Giorgi Rossi[3], Pamela Mancuso[3], Carlo Salvarani[4], Fabiola Atzeni[5], Rosa Gini[6], Ursula Kirchmayer[7], Valeria Belleudi[7], Peter Konstantin Kurotschka[8], Olivia Leoni[9], Monica Ludergnani[9], Eliana Ferroni[10], Susanna Baracco[10], Marco Massari[2], Gianluca Trifirò[11]

[1]University of Messina; [2]Pharmacoepidemiology Unit, National Centre for Drug Research and Evaluation, Istituto Superiore di Sanità; [3]Epidemiology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia; [4]Department of Surgery, Medicine, Dentistry and Morphological Sciences with Interest in Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Italy; [5]Department of Experimental and Internal Medicine, University of Messina; [6]Agenzia Regionale di Sanità della Toscana, Florence, Italy; [7]Department of Epidemiology ASL Roma 1, Lazio Regional Health Service; [8]Department of Medical Science and Public Health, University of Cagliari; [9]Epidemiology Observatory - Department of Health of Lombardy Region; [10]Azienda Zero of the Veneto Region; [11]Department of Diagnostics and Public Health, University of Verona, Verona, Italy

OBJECTIVE: Chloroquine (CLQ)/ hydroxychloroquine (HCQ) are two of the most studied drugs for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. There are very limited data on the effect of treatment of patients affected by rheumatic diseases with HCQ/CLQ and other conventional disease-modifying anti-rheumatic drugs (cDMARDs) on COVID-19. The aim of this study is to investigate the hypothesis that treatment of rheumatic diseases with hydroxychloroquine (HCQ)/chloroquine (CLQ) as compared to other conventional disease-modifying anti-rheumatic drugs (cDMARDs) might decrease the COVID-19-related risk of hospitalization and mortality.

METHODS: This large-scale case-control study nested within a cohort of cDMARD users was conducted in the Lombardy, Veneto, Tuscany and Lazio regions and Reggio Emilia (Emilia Romagna) Local Health Unit, covering a total of 25.1 million inhabitants. Claims databases were linked to loco-regional COVID-19 surveillance registries from the same catchment area through unique fully-anonymized patient identifiers. Risk of COVID-19-related outcomes was estimated as odds ratios (ORs) along with 95% confidence intervals (CIs), using a multivariate conditional logistic regression analysis, by comparing HCQ/CLQ vs methotrexate (primary comparator) and other cDMARDs (secondary comparator). In addition, the same risk for HCQ/CLQ, methotrexate and other cDMARDs separately vs non-use of these drugs as well as for presence of rheumatic diseases vs. absence in a non-nested population was investigated.

RESULTS: From the cohort of cDMARD users, 1275 cases who were hospitalized due to COVID-19 were identified and matched to 12,734 controls. When compared to recent use of methotrexate, no statistically significant association between recent HCQ/CLQ monotherapy with COVID-19 hospitalization (OR 0.83 [95% CI, 0.69 to 1.00]) or mortality (OR 1.19 [95% CI, 0.85 to 1.67]) was observed. A statistically significant lower risk was found when comparing recent use of HCQ/CLQ to treatment with other cDMARDs and glucocorticoids concomitantly. In the sensitivity analysis in the non-nested population, HCQ/CLQ was not associated with COVID-19 hospitalization as compared with non-use, whereas a mild statistically significant increased risk for recent use of both methotrexate as monotherapy (OR 1.19 [95% CI, 1.05 to 1.34]) or other cDMARDs (OR 1.21 [95% CI, 1.08 to 1.36]) vs non-use was found. Finally, the presence of rheumatoid arthritis or systemic lupus erythematosus was not associated with COVID-19 hospitalization (OR 0.98 [95% CI, 0.89 to 1.07]) or mortality (OR 0.88 [95% CI, 0.74 to 1.05]).

CONCLUSION: Prior exposure to HCQ/CLQ in rheumatic patients was not associated with a protective effect against COVID-19-related hospitalization and mortality. On the contrary, an increased risk in patients receiving other cDMARDs was observed when compared to non-use, especially in those patients concomitantly treated with glucocorticoids. This is likely attributable to a synergistic immunosuppressive effect, leading to increased risk of severe SARS-CoV-2 infection.

Nationwide Patterns of Hydroxychloroquine Dosing and Monitoring of Retinal Toxicity in Patients with Systemic Lupus Erythematous

Jae-Eun Lee[1], Seung-Hun You[1], Sun-Young Jung[1]

[1]*Department of Global Innovative Drugs, Graduate School of Chung-Ang University*

BACKGROUND: Hydroxychloroquine (HCQ) is commonly used in systemic lupus erythematous (SLE), however rare but severe retinal toxicity associated its long-term use have been reported. To minimize the risk of HCQ retinopathy, the American Academy of Ophthalmology (AAO)

revised practice guidelines twice, limiting the recommended dose to < 6.5 mg/kg IBW in 2011 and < 5.0 mg/kg ABW in 2016. In addition, AAO guidelines recommend regular ophthalmolgic screening at baseline and annually after 5 years of HCQ use with modern screening methods such as automated visual field assessment or spectral-domain optical coherence tomography.

OBJECTIVE: To identify the temporal trends in HCQ prescriptions and screening of retinopathy in patients with SLE according to update of clinical guidelines, and to describe the prevalence of visual impairment in patients who were prescribed HCQ.

METHODS: We used data of patients with diagnosis of SLE (ICD10, M32) between 2004 and 2019 from the National Health Insurance Service in Korea. To measure HCQ dosing patterns, we used 2 formulas based on ideal or actual body weight and we identified daily dose trends before and after the point of AAO guideline changes. We also evaluated the implementation rate of retinal screening according to update of the AAO guidelines. In addition, we identified patients who were diagnosed with visual impairment (ICD10, H53 or H54) between 2007 and 2019 after using HCQ, and assessed patterns of HCQ dosing, duration, and retinal screening before diagnosis of visual impairment.

RESULTS:Among 249,897 patients with SLE, 183,541 (73.4%) were prescribed HCQ during the study period. Median daily dose of HCQ was decreased from 5.97mg /kg ABW in 2004 to 4.04mg /kg ABW in 2019. The implementation rate of modern retinal screening modalities was increased significantly from 4.34% in 2004 to 26.33% in 2019. Among patients with SLE using HCQ, 4,293 (2.3%) patients were diagnosed with visual impairment; their median daily dose before diagnosed the visual impairment was 4.97 mg/kg ABW.

CONCLUSION: From 2004 to 2019, prescribing dose continued to decline, falling below the recommended dose in the guidelines (< 5.0mg/kg ABW/day). In addition, the screening implementation rate increased steadily and especially in recommended screening modalities during the same period. The prevalence of vision impairment was similar to previously reported prevalence of HCQ retinal toxicity (1.6% to 6.3%), and further research assessing risk factors of HCQ retinopathy is needed.

Oral Session 3: Metabolic Syndromes and Pharmacoepidemiology: From Oral Antidiabetics to Biologics

Tuesday 20 April | 10:25 AM – 11:25 AM

Abstracts In Presentation Order

Presenting Author Highlighted In **Bold**

Sodium-Glucose Co-Transporter 2 Inhibitors and the Risk of Acute Kidney Injury: A Population-Based Cohort Study.

Wajd Alkabbani[1], Arsene Zongo[2], Dean Eurich[3], Baiju Shah[4], Jasjeet K Minhas-Sandhu[1,3], Wasem Alsabbagh[1], John-Michael Gamble[1]

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BACKGROUND: Sodium-Glucose Co-Transporter 2 Inhibitors (Sglt2-I) Are The Newest Class Of Medications For The Management Of Type-2 Diabetes With Favourable Cardio- And Reno-Protective Effects. However, Several Case Reports Raised A Concern That Their Use May Increase The Risk Of Acute Kidney Injury (Aki), Which Has Led To Safety Warnings By The Food And Drug Administration (Fda) And Health Canada.

OBJECTIVE: In This Study, We Assessed The Association Between Sglt2-I Exposure And The Risk Of Aki.

METHODS: We Conducted A Population-Based Cohort Study Using Alberta's Administrative Healthcare Data And The United Kingdom's Clinical Practice Research Datalink (Cprd). Among New Users Of Metformin Monotherapy, Multiple New-User Cohorts Of A Second Antidiabetic Agent Were Defined Based On New Use Of An Sglt2-I Or Active Antihyperglycemic Comparator Between 2013-2018. The Primary Exposure Contrast Of Interest Was Sglt2-I Versus Dipeptidyl Peptidase-4 Inhibitor (Dpp4-I). The Outcome Was hospitalization due to AKI, identified by validated algorithms based on International Classification of Diseases version 10 codes. The independent association between SGLT2-i use and the risk of developing AKI was estimated using a Cox proportional hazards regression model in a high dimensional propensity scores (hd-ps) 1:1 matched cohort. Aggregate data from each database were combined by random effects meta-analysis.

RESULTS: In the primary new-user cohort, there were a total of 29,400 patients (20,564 AB, 8836 CPRD), comprised of 9,608 SGLT2-i users (7,709 AB, 1,899 CPRD), and 19,792 DPP4-i users (12,855 AB, 6,937 CPRD). Crude AKI hospitalization incidence rates in the AB cohort were 5.56 (95% CI: 4.08 – 7.42) for SGLT2-i and 10.21 (95% CI: 8.69 – 11.92) for DPP4-i users per 1,000 person-years. Crude incidence hospitalization rates in the CPRD cohort were 9.01 (95% CI: 5.79 – 13.42) for SGLT2-i and 20.86 (95% CI: 18.24 – 23.75) for DPP4-i users per 1,000 person-years. Hd-ps matching resulted in 7,470 and 1,632 well-balanced pairs from the AB and CPRD cohorts. SGLT2-i exposure was not associated with increased risk of AKI (pooled HR 0.84, 95% CI 0.56 – 1.27). Similar findings were observed within new-user cohorts comparing SGLT2-i users to other antihyperglycemic agents, including sulfonylureas (pooled HR 0.72, 95% CI 0.44 – 1.17), glucagon-like peptide-1 receptor agonists (pooled HR 1.11, 95% CI 0.45 – 2.76), and insulin (pooled HR 0.51, 95% CI 0.34 – 0.76).

CONCLUSION: In agreement with evidence from clinical trials and other observational studies, SGLT2-i use does not appear to increase the risk of developing AKI.

Effect of Biosimilar Basaglar Entry in the Long-Acting Insulin Market

Emaan Rashidi[1]

[1]*Johns Hopkins Bloomberg School of Public Health*

BACKGROUND: High prices for long-acting insulins are an important barrier to treatment for individuals living with diabetes. Biosimilar insulins, like Basaglar, could be lower price alternatives to original biologic insulin products and have been proposed as (1) a cost-saving tool for payers and patients, (2) a way to expand patient access to care, and (3) a method to increase competition on the biologics market. Rebates for the more expensive biologic products may lower net prices paid by insurers but patients who use the biosimilar may have higher out-of-pocket expenses. Previous studies evaluating insulin biosimilar market entry have been restricted to Medicare and Medicaid patients. Considering the differing payment structures and incentives between public and private insurance, this study aimed to understand the effect of biosimilar insulin market entry for commercially insured patients.

METHODS: This study used the IBM MarketScan Commercial Claims and Encounters database to assess changes in quarterly utilization, insurer payments and patient out-of-pockets costs for long-acting insulins: insulin glargine (Lantus Solostar, Toujeo, and Basaglar), insulin determir

(Levemir), insulin degludec (Tresiba) between January 2014 and December 2018. Analyses were restricted to outpatient pharmacy claims. Prices were standardized to cost per unit of insulin(U-100) and adjusted for seasonality. We implemented an interrupted time series analysis to evaluate market changes after Basaglar entry on December 15, 2016.

RESULTS: We analyzed a total of 5,218,907 claims of all five drugs between 2014-2018: Immediately after its 2016 entry, Basaglar gained 4.5% (n=10,496 claims) of the long-acting insulin market share; Lantus had 48.0% (n=112,830), Levemir 23.9% (n=112,830), Tresiba 13.1%(n=112,830), and Toujeo 10.5%(n=24,753). In the first quarter of 2017, Basaglar cost an average of $573.85 per U-100 for insurers and $88.19 per U-100 for patients. Meanwhile, Lantus cost an average of $586.80 per U-100 for insurers and $70.22 per U-100 for patients. By the fourth quarter of 2018, Basaglar had overtaken Toujeo in market share at 13.2% of all long-acting insulin claims, but remained below Levemir (20.0%), Tresiba (23.5%), and Lantus (34.3%); Basaglar cost an average of $445.65 per U-100 for insurers and $51.39 per U-100 in patient out-of-pocket costs. Meanwhile, Lantus cost an average of $613.80 per U-100 for insurers and $45.24 per U-100 in out-of-pocket costs for patients. Across all long-acting insulins, majority of patients (>50%) held Preferred Provider Organization(PPO) insurance. The largest burden for patients' out-of-pocket costs across all products were the copayment.

CONCLUSION: Following Basaglar market entry there was a rapid decrease in Lantus Solostar claims but a consistent number of Levemir claims between 2014 and 2018. Due to distortions in the market and possible prevalence of rebates, net prices for Lantus are lower than for Basaglar. The existence of coupons and patient assistance programs may also distort prices in favor of the most expensive products. The evidence shows that patients are not reaping the full benefits of a lower price long-acting insulin and end up paying higher out-of-pocket costs for biosimilars. We discuss policy options to tackle this market failure.

Body Weight and Glucolipid Changes Following Anti-Tnf-Alpha Treatment in Children with Inflammatory Bowel Disease: A Retrospective Case Series Analysis Combined with Real-World Pharmacovigilance Study

Faizan Mazhar[1], Vera Battini[1], Albaraa Mohammed N. Marran[1], Sonia Radice[1], Emilio Clementi[1], Carla Carnovale[1]

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BACKGROUND: Anti-Tumour necrosis factor (TNF)-α therapy are effective in inducing sustained remission in inflammatory bowel diseases (IBD). Prior studies have inconsistently suggested that TNF-α inhibitors therapy may be associated with excess weight gain in children.

OBJECTIVES: To determine the frequency of weight gain in children with IBD on maintenance anti-TNF-α therapy and evaluate the impact on glycolipid profile and serum trough levels. To better characterize adverse events related to 'real-life' use of anti-TNF-α inhibitors in children, we also analyse the safety signals of anti-TNF-α inhibitor-associated adverse events related to body-changes in a large international pharmacovigilance database.

METHODS: Paediatric patients with IBD, treated with anti-TNF-α inhibitors for at least 24 months were retrospectively reviewed. Anthropometric data (expressed as z scores of weight and BMI) and glycolipid measures were collected at the time of anti-TNF initiation, 12 and 24 months. Excess

weight gain was assessed by CDC cut-points. A nested case/non-case analysis was performed using the Food and Drug Administration Adverse Event Reporting System (FAERS) database, focusing on events related to body-changes reported in connection with the use of anti-TNF-α inhibitors. The risk was expressed as a measure of disproportionality using the reporting odds ratio while adjusting potential confounders. We also applied the Weibull proportional hazards models to time-to-event data in FAERS for anti-TNF-α inhibitors to examine the expression patterns of event.

RESULTS: Sixteen patients were included with a median age of 9.5 years and a median duration of treatment of 26 months. At baseline, mean weight was -2.88 (SD 1.7), while mean BMIz was -0.14 (1.3). Compared to baseline, there was a significant increase in body weight z score after 2 years (mean gain 2.06 ±0.38 $p < 0.0001$). Changes in body weight between the first and second year of treatment were statistically significant (1.99 ± 0.36; $p< 0.001$). Variations in BMIz was not statistically significant at any time point. At 1-year, there was a significant increase in total cholesterol and low-density lipid. At 1-year follow-up, the difference in the mean BMIz of patients with subtherapeutic trough levels (Δ -0.83 ± 1.13) and patients with therapeutic trough levels was statistically significant (Δ 1.36 ± 0.55; $p< 0.05$). Disproportionate reporting of body-change events in FAERS was found for anti-TNF-α in general (pooled aROR: 1.10 (1.04; 1.15). Sensitivity analysis showed stronger disproportionality for paediatrics [pooled aROR: 3.14 (2.47; 3.18)] than in adults [pooled aROR: 1.02 (0.97; 1.08)]. Among paediatrics, the strongest association with body-change was observed for etanercept [aROR:5.20 (3.77; 7.21)]. Indication subset analysis among paediatric did not reach the signal threshold for IBD. Time-to-onset analysis revealed that anti-TNF-α treatment-associated weight changes in IBD had a wear-out failure-type profile.

CONCLUSION: Anti-TNF-α agents could cause an excess weight gain in paediatric IBD. Given the potential of anti-TNF-α treatment to induce excess weight gain and dysmetabolism, continuous attention for this side effect with appropriate counselling regarding lifestyle modifications is warranted.

Oral Session 4: Pharmacoepidemiology in Contraception, Conception, and Beyond

Tuesday 20 April | 11:40 AM – 12:40 PM

Abstracts In Presentation Order

Presenting Author Highlighted In **Bold**

Risk of Thrombosis Associated with Drug-Drug Interactions Between Oral Hormonal Contraceptives and Verapamil or Diltiazem

Raj A. Desai[1], Thuy N. Thai[1], Phoung N. Pham[1], Stephan Schmidt[1], Almut Winterstein[1], Joshua Brown[1]

[1]*University of Florida*

BACKGROUND: Cytochrome P450 3A4 (CYP3A4) is a key enzyme in the metabolism of hormonal contraceptive agents (HCAs). Both, verapamil and diltiazem are CYP3A4 inhibitors, reducing enzyme activity. Thus, concomitant use of HCAs and verapamil or diltiazem (V/D) could result in increased risk of adverse effect of HCAs, especially thrombosis. However, the clinical significance of this drug-drug interaction remains unknown.

OBJECTIVE: To investigate the risk of thrombosis associated with concomitant use of oral HCAs and verapamil or diltiazem (HCA-V/D) compared to concomitant use of oral HCAs and sumatriptan (HCA-sumatriptan).

METHODS: We conducted a retrospective cohort study using IBM MarketScan® Commercial claims data from 2005 to 2018. We included women aged 12-48 years with a history of oral HCAs use and newly initiating V/D or sumatriptan for migraine prophylaxis. The first day of overlapping use was defined as the index date. Patients were required to have at least 12-months of continuous medical and pharmacy enrollment prior to the index date during which risk factors for thrombosis were assessed. The primary outcome was incident thrombosis defined as the first inpatient or emergency department encounter with a principal diagnosis of stroke, acute myocardial infraction, pulmonary embolism, deep vein thrombosis, or arterial thrombosis. Follow-up ended at the first occurrence of the outcome, discontinuation of concomitant use, switching to the comparator drug, surgery, pregnancy, hospitalization, health plan disenrollment, reaching 6 months follow-up, or end of study period. Baseline thrombosis risk was balanced via stabilized inverse probability of treatment weighting (SIPTW) based on propensity scores. Additionally, to control for changing baseline hazards of thrombosis with HCAs, we also adjusted for the time since the first HCAs use during baseline to index. A weighted Cox proportional hazard regression model was used to estimate adjusted hazard ratio (HR) and 95% confidence intervals (95% CI).

RESULTS: A total of 13,865 patients in the HCA-V/D group and 126,254 patients in the HCA-sumatriptan group had crude thrombosis incidence rates of 0.94 and 0.58 per 100 person-years, respectively. After SIPTW, concomitant HCA-V/D use did not significantly increase the risk of thrombosis compared to concomitant HCA-sumatriptan use (aHR 1.60; 95% CI: 0.77, 3.34).

CONCLUSION: Though potent CYP3A4 inhibitors, we did not find a significantly increased risk of thrombosis among HCA-V/D users in this active comparator design though the low event rates limited power. Future study with larger sample size is needed to confirm our findings.

Effective Prevention of Prenatal Exposure to Topiramate in the Presence of Potential Drug-Drug Interactions with Oral Hormonal Contraceptives: Insight from a Real-World Retrospective Cohort Study

Amir Sarayani[1], Joshua Brown[1], Stephan Schmidt[1], Almut Winterstein[1]

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BACKGROUND: Prevention of prenatal exposure to teratogenic drugs among women of childbearing potential depends on effective contraceptive measures. However, some teratogenic drugs like topiramate induce CYP3A4 and could undermine the efficacy of hormonal contraceptives. The impact of this potential drug-drug interaction on contraception failure in the real world is unknown.

OBJECTIVE: To evaluate the contraception failure rate among patients with migraine who concomitantly used topiramate and oral hormonal contraceptives.

METHODS: In a retrospective cohort study with an active comparator design, we used a national U.S. commercial insurance claims database (2005-2018) to identify female patients aged 12-48 with migraine whose maintenance treatment was either topiramate (a weak/moderate CYP3A4 inducer) or an active comparator drug (propranolol, metoprolol, amitriptyline, venlafaxine, verapamil). The index date was defined as the first day of concomitancy for a migraine maintenance treatment and progestin-only/combined oral contraceptives (< 50 mcg estrogen). We measured concomitancy episodes using the days' supply information on dispensing

records allowing for a 14-days gap and cohort re-entry if inclusion/exclusion criteria were met. A six-month look-back period with continuous insurance enrolment before each concomitancy episode was required to ascertain patients' clinical history. We excluded patients diagnosed with infertility, hormonal dysfunctions, hirsutism, and concomitant use episode less than 14 days. Contraception failure was operationalized as pregnancy conception identified in our database based on an algorithm that utilizes diagnosis and procedure codes for pregnancy endpoints and prenatal screening tests. We assessed the risk for conception from the index date until diagnosis for infertility, hormonal dysfunctions, hirsutism, or end of the concomitancy episode. We constructed a treatment propensity score model to account for confounding and estimated the average treatment effect among topiramate users with a weighted generalized estimating equation model to account for cohort re-entry. Sensitivity analysis on conception date and concomitancy gap were conducted. We also constructed a high-dimensional propensity score model and applied a matching strategy to achieve a more robust confounding adjustment.

RESULTS: We identified 63,669 concomitancy episodes for topiramate and 59,040 for the comparator drugs. Demographic and clinical features were reasonably balanced before propensity score weighting except for a higher prevalence of hypertension and anxiety diagnosis in the comparator group. After weighting, the pseudo-population achieved adequate balance for all covariates. We identified 159 contraception failures (11,898 person-years) in the topiramate

cohort and 145 failures in the comparator cohort (11,060 person-years). The adjusted failure rate was 1.3 (1.1, 1.6) per 100 person-years in the topiramate cohort and 1.3 (1.1, 1.6) per 100 person-years in the comparator cohort. The adjusted risk ratio was 1.00 (95% compatibility interval: 0.80, 1.26). The study findings were robust in sensitivity analyses on the conception date, concomitancy gap, and using a high-dimensional propensity score approach (1.04; 0.82, 1.33).

CONCLUSION: Concomitant use of topiramate with oral contraceptives did not result in higher contraception failure rates among patients with migraines. Our findings can inform risk mitigation measures and family planning for female patients of childbearing age who need topiramate treatment. Further studies in other patient populations (e.g., epilepsy) with higher topiramate doses are needed.

Antiepileptic Treatment Pattern During the 1st Trimester of Pregnancy – An Evaluation of the German Embryotox Cohort

Sofia Slimi[1], Maria Hoeltzenbein[1], Anne-Katrin Fietz[1], Marlies Onken[1], Katarina Dathe[1], Christof Schaefer[1]

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BACKGROUND: Due to their teratogenicity, not all antiepileptic drugs (AEDs) are suitable for therapy in pregnancy. Nevertheless, antiepileptic therapy throughout pregnancy is often required. Adjustment of AED regimen to protect the unborn should take place before conception. Concerns about adverse fetal effects may lead to discontinuation or switching of AEDs after recognition of pregnancy. Overestimating the risk of prenatal drug exposure may also cause unnecessary treatment changes which might impair seizure control. Data on AED treatment changes during the 1st trimester of pregnancy are still scarce, so far.

OBJECTIVES: To analyze AED treatment pattern at conception and during the 1st trimester including the proportion of recommended (lamotrigine/levetiracetam) AEDs, non-recommended (valproate/phenobarbital/phenytoin/topiramate) AEDs, and mono- vs. polytherapies. In addition, changes of treatment pattern during the study period 2000 – 2018 will be evaluated.

METHODS: All cases of risk consultation on AEDs at the German Embryotox Pharmacovigilance Institute between 2000 and 2018 were evaluated. Prospectively ascertained pregnancies in women with epilepsy and AED use at conception were identified for analysis of AED treatment pattern.

RESULTS: 2,395 of 3,763 pregnant women with AED treatment at conception had a diagnosis of epilepsy (64%). In women with epilepsy, the proportion of monotherapies (76%) to polytherapies (24%) remained essentially unchanged between 2000 and 2018. Analysis of treatment pattern over time showed an increased use of recommended AEDs and a decrease in the use of non-recommended teratogenic AEDs. However, at the end of the study period (2017-2018), 13% of women still used non-recommended AEDs at conception. Despite limited evidence of safety for the unborn, zonisamide, lacosamide, eslicarbazepine, and brivaracetam as newer AEDs with marketing authorization after 2004 were increasingly used, even shortly after their approval.

Among women with livebirth and complete information on course of AED use 90% (1,361/1,506) did not change AED treatment

during the 1st trimester, 7% discontinued, and 2% switched to other AEDs. Valproate, oxcarbazepine, and topiramate were more likely discontinued or switched than other AEDs. 4% of women on AED monotherapy discontinued anti-seizure medication, 2% switched to other AEDs, and 1% added an AED during the 1st trimester. 16% of women with polytherapy at conception reduced the number of concomitantly used AEDs.

CONCLUSION: This first analysis of treatment pattern in AED exposed pregnancies in Germany confirms a trend also observed in other countries towards less teratogenic and newer AEDs. However, it remains questionable whether women on non-recommended AEDs, particularly valproate and topiramate, are refractory to AEDs of lower risk or if common guidelines and risk minimization measures released from health authorities are disregarded. AED treatment should be optimized before pregnancy. This concerns all women at risk of getting pregnant, not only those planning pregnancy. There are still too many pregnancies exposed to AEDs with a teratogenic potential or insufficient evidence of safety. Healthcare professionals and patients should be advised that these AEDs are only acceptable, in women of childbearing age, when drugs of choice do not adequately control seizures. This work was funded by the German Federal Institute for Drugs and Medical Devices (BfArM).

Early Life Antibiotic Exposure and Incident Chronic Diseases in Childhood

Matthew A. Beier[1], Soko Setoguchi[2], Tobias Gerhard[3], Jason Roy[4], Avinash Gabbeta[1], Brian L. Strom[5], Martin J. Blaser[6], Daniel B. Horton[3]

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BACKGROUND: Antibiotic exposure leads to disruption of gut microbiota and has been implicated in the rise of allergic, immunologic, and behavioral illnesses. Many prior studies have been limited by concerns for residual confounding. This study aimed to investigate the association between early-life antibiotic exposure and a broad range of chronic pediatric diseases, adjusting for important confounders.

METHODS: A retrospective cohort study was conducted within the population-representative UK primary care database CPRD GOLD. We included children within the Mother-Baby Link (MBL) enrolled within 3 months after birth, had prenatal data, and at least 27 months of follow-up. Subjects were excluded for diagnosis of immunodeficiency or relevant outcome before age 2. The primary exposure was any antibiotic prescription before age 2. We also evaluated for dose-response based on number of childhood antibiotic courses. Three outcome categories (allergic/atopic, autoimmune, and neuropsychiatric) included 17 conditions based on Read Codes; forearm fracture was examined as a negative control outcome. Follow-up began at 27 months, allowing for a 3-month lag period, and ended with the outcome of interest or censoring (transfer out of practice, end of data collection,

death, age 12). Multivariable Cox regression analysis was used to adjust for childhood covariates (gestational age at birth, delivery mode, sex, sibling order, infection type and number before age 2), and maternal covariates (age, smoking, Group B Streptococcus infection, history of relevant illness, gestational antibiotic use). Adjusted hazard ratios are presented with 95% confidence intervals.

RESULTS: We identified 1,096,385 eligible children within CPRD MBL born in 1987-2018; 62.8% were antibiotic-exposed during the first 2 years of life. Allergic conditions showed the strongest dose-dependent association with childhood antibiotic prescriptions, including asthma (1-2 doses: 1.01 [0.99, 1.03]; 3-4 doses: 1.19 [1.17, 1.21], 5+ doses: 1.45 [1.42, 1.49]) and food allergy (1-2 doses: 1.13 [1.07, 1.20]; 3-4 doses: 1.27 [1.18, 1.37]; 5+ doses: 1.54 [1.43, 1.66]). Associations were mixed for autoimmune outcomes, with no positive association for type 1 diabetes (any dose: 0.82 [0.74, 0.91]) with any childhood exposure. However, an apparent dose-response was seen for celiac disease (1-2 doses: 0.93 [0.82, 1.05]; 3-4 doses: 1.13 [0.98, 1.32]; 5+ doses: 1.29 [1.09, 1.52]). Neuropsychiatric conditions most strongly had a positive, dose-dependent association for ADHD (1-2 doses: 1.02 [0.96, 1.08]; 3-4 doses: 1.06 [0.99, 1.14]; 5+ doses: 1.12 [1.04, 1.22]). Antibiotic exposure was not significantly associated with forearm fracture (any dose: 1.01 [0.98, 1.04]), suggesting little residual bias from unmeasured confounding.

CONCLUSION: This study demonstrates positive, dose-dependent associations between early-childhood antibiotic exposure and subsequent chronic illness in a broad range of diseases, with the strongest associations for allergic conditions. Further analyses will examine timing and type of antibiotic exposure and incorporate sibling-matched analyses to control for unmeasured genetic and environmental confounding.

Poster Presentation Abstracts

Breakout Room 1: From Prescribing to Adherence: Drug Utilization Around the World

Tuesday 20 April | 9:50 AM – 10:20 PM

Abstracts In Presentation Order

Presenting Author Highlighted In **Bold**

Referral, Diagnostic and Treatment Delays of Tuberculosis Patients Associated with Community Pharmacies-Referral Network in Pakistan

Waseem Ullah[1], Hadi Almansour[2], Razia Fatima[3], Bandana Saini[2], Gul Majid Khan[1]

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BACKGROUND: Globally, a major issue in controlling and eradicating Tuberculosis (TB) is the delay in diagnosis and treatment initiation among patients suffering from this infectious disease. Delay in health-seeking for TB care contributes to poor treatment outcomes for patients when eventually diagnosed. Pakistan which is a lower-middle-income high TB burden country and where incidence, prevalence, and high transmission of TB are crucial, limited studies are available on patient and health system delay for seeking and initiating TB treatment. This study aims to assess the delay in referral, diagnosis, and treatment initiation among notified TB patients counseled at Pakistani community pharmacies.

METHODS: The study utilized an innovative Public-Private Mix (PPM) Health Partnership between private pharmacies, private general partitioner (GP), and public (national) TB control program that was implemented in three Pakistani districts. The pharmacies willing to refer the presumptive TB patients instead of providing anti-TB medications and GPs' willingness to notify diagnosed TB patients to national TB database and initiating anti-TB medication therapy according to national TB management guidelines comprised the inclusion criteria. The time period between comprehensive training of pharmacy staff and first presumptive referred from the trained pharmacy was categorized as 'referral delay'. While the time-period between referral provision to a patient and patient registration at the GP clinic as notified TB case was termed as 'diagnostic delay'. The 'treatment delay' was defined as the time-period between TB patient notification by GP and anti-TB treatment initiation at the GP clinic.

RESULTS: Out of 500 pharmacies trained in PPM partnership, 427 (85%) pharmacies were active in providing referrals to GP clinics. The highest number (25%) of active pharmacies started referring TB presumptives within a range of 1-30 days, followed by a referral delay of 31-60 days, which was the case for 18% of pharmacies. The median referral delay in PPM partnership was found to be 46 days. Among the 547 TB cases notified through the community pharmacies-referral network, their diagnostic delay ranged from a shortest of < 1day (i.e., on the same day of the referral provision) and a longest of 29-32 days. While the median diagnostic delay for diagnosed TB patients was found to be 4 days, After diagnosis, TB treatment delay in PPM model ranged from a shortest of < 1day (i.e., on the same day of the patient diagnosis) and a longest of >2 days. The median treatment delay was found to be just 1 day.


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CONCLUSION: TB patients notified through Pakistani PPM Health Partnership might be taking slightly longer times to show consent to be referred but once referred they visited and were timely diagnosed at GP clinics and treatment was initiated well in time. This improved, lower diagnostic and treatment delays in this study may be partly attributed to TB patient's commitment with the pharmacy staff to follow the referral pathway designed as well as the prompt response of GP's and laboratories towards expected referrals from nearby pharmacies leading to timely patient sputum reports, diagnosis, and treatment initiation of patients with active TB infection.

Assessment of Prescribing Practices Using the World Health Organization Prescribing Indicators

Nondumiso B. Ncube[1], Ferdinand C. Mukumbang, Hazel A. Bradley[1], Helen Schneider[1], Richard Laing[1]

[1]*School of Public Health University of the Western Cape*

BACKGROUND: Irrational use of medicines is a long-standing concern in health systems, Minimal work has been done on irrational use of medicines in the context of the growing burden of non-communicable diseases. This study examined medicine use in Eswatini, between March 2017 and March 2019, with a focus on prescribing practices linked to specific diagnoses. It also tested the effects of a short intervention – prescription audit and feedback coupled with small group education – on prescribing practices in health facilities.

METHODS: This was a pre-post intervention study using the World Health Organization/ International Network for the Rational Use of Drugs (WHO/INRUD) prescribing indicators at three time points: baseline, post-intervention and post-follow-up. Baseline results were used to design an unblinded intervention in 32 health facilities, randomly allocated to intervention (16) and control (16) arms. Descriptive statistics, mean difference-of-differences (MD), and multilevel mixed logistics models were performed to analyse data, comparing intervention and control facilities. Analyses of rational medicine use are provided nationally and disaggregated to regional levels, as well as by diagnoses and level of care.

RESULTS: Most WHO/INRUD prescribing indicators, except prescribing of injections, were outside the WHO recommended standards. Although not reaching statistical significance, small changes were documented immediately post-intervention: the average number of medicines per prescriptions increased more in control than intervention facilities (mean difference of differences (MD) = -0.23; p = 0.48); generic prescribing increased in both groups, more in control facilities (MD = -4.38; p = 0.35); antibiotics prescribing decreased slightly in both intervention and control facilities, with a higher decrease in control facilities (MD = 7.06; p = 0.26). A statistically significant increase in the use of antibiotics in control facilities was observed at the end of the follow-up period (MD = -8.31, p = 0.03, 95% CI = -15.74 - -0.89). Improvement in prescribing indicators was observed more in secondary than primary level facilities. Most of these changes, however, were not sustained at the end of the follow-up period. Polypharmacy and high levels of antibiotic prescribing persisted in all regions, with some regional variations (notably in the Shiselweni and Lubombo regions). A previously unreported finding peculiar to this study was that antibiotics were frequently prescribed for chronic non-communicable conditions.

CONCLUSION: This research concludes that irrational use of medicines remains a critical issue in Eswatini. The lack of impact of a simple intervention indicates that irrational use of medicine is a complex problem that is beyond prescribers and supervisors in facilities alone

to resolve. Improving rational medicines use in Eswatini requires mixed interventions and concerted effort from a range of stakeholders and policymakers at different levels.

Investigation of Diclofenac and Paracetamol Prescribing for Adults in Primary Care

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BACKGROUND: The most commonly prescribed analgesic drugs were reported to be diclofenac and paracetamol, respectively. Though being similar with respect to overall indications and efficacy, these drugs exhibit different safety and suitability profiles in terms of rational drug use. We aimed to examine the details of prescriptions containing diclofenac and paracetamol for adult patients in primary care in Istanbul.

METHODS: Among the prescriptions generated by primary care physicians (n=1431) selected by systematic sampling, we analyzed those containing paracetamol and/or diclofenac for adults (>18 age) in Istanbul in 2016. The demographic characteristics of the patients, diagnoses, and details of the drugs in these prescriptions were evaluated and compared in terms of diclofenac vs. paracetamol-containing status.

RESULTS: We identified 280,488 prescriptions containing paracetamol and 337,934 prescriptions containing diclofenac (the number of drugs per prescription was 3.80±2.25 and 3.90±2.32, respectively). The mean ages of the patients in these prescriptions were 52.6 ± 18.8 and 56.3 ± 16.1 years, respectively. Women were more likely to receive prescriptions in both groups (69.8% and 67.9%, respectively). When single-diagnosis prescriptions were examined, we found that among the first fifteen diagnoses in the paracetamol-group, eleven were respiratory tract infections (47.9%) and among the rest, three were pain-related indications (4.6%). In the diclofenac-group, eight of the most common fifteen diagnoses were pain-related indications (28.5%), and among the rest, four (7.8%) were respiratory tract infections. While hypertension was the third most common diagnosis in the paracetamol-group (6.1%), it was the first in the diclofenac-group (8.0%). The most frequently prescribed concomitant drug in the paracetamol-group, "other cold preparations" (4.0%), ranked second in the diclofenac-group (3.3%). The most frequently prescribed concomitant drug in the diclofenac group, thiocolchicoside (3.5%), was not detected to be listed in the first fifteen drugs in the paracetamol group. The percentage of prescriptions containing additional analgesics in the diclofenac-group (18.3%) was significantly higher than that in the paracetamol-group (14.0%, p< 0.0001). The percentage of prescriptions containing proton pump inhibitors in the diclofenac-group (18.4%) was also significantly higher than that in the paracetamol-group (13.8%, p< 0.0001). The percentage of prescriptions containing antihypertensive drugs was significantly higher in the diclofenac group (24.8%) compared to that in the paracetamol-group (22.0%), (p< 0.0001).

CONCLUSION: Our results indicate that nearly half of the prescriptions for paracetamol constitute respiratory tract infection-associated indications, more pronounced compared to diclofenac. These and other findings suggest that pain-dominant indications are likely to be managed with diclofenac. In addition, the fact

that hypertension is at the top of single-diagnosis prescriptions of these analgesic drugs, especially for diclofenac, may imply an irrational practice in establishing a diagnosis-treatment relationship.
Keywords: Primary care, paracetamol, diclofenac, pain, analgesic

Evaluation of Statin Discontinuation Stratified by Primary Versus Secondary Prevention Following Bariatric Surgery: A Retrospective Cohort Study

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BACKGROUND: Bariatric surgery leads to an improvement in hyperlipidemia and subsequent decline in the use of hyperlipidemia-related medications, including statins. In patients with a history of atherosclerotic cardiovascular disease (ASCVD), it is recommended to continue statins; however, it is unknown if there is a differential risk for statin discontinuation in patients with and without a history of ASCVD.

OBJECTIVE: To estimate the rates and factors associated with statin discontinuation following bariatric surgery. Setting: Large US administrative claims database of privately insured beneficiaries, January 2005 through December 2017.

METHODS: We identified patients aged ≥19 years who were statin users at the time of bariatric surgery. Patients were stratified into primary prevention and secondary prevention (patients with a history of ASCVD) groups. Time to statin discontinuation was defined as the first 90-days gap after exhausting the days' supply of the last statin prescription. Factors associated with statin discontinuation were assessed using the Cox proportional hazards regression model.

RESULTS: We identified 19,332 statins users at the time of bariatric surgery, of whom 84% (16,221) used statins for primary prevention. At six months, 62% and 53% of patients in the primary and the secondary prevention treatment groups, respectively, discontinued statin use. Patients in the primary prevention treatment group were 18% more likely to discontinue statin therapy compared to the patients in the secondary prevention treatment group (Hazard Ratio (HR), 1.18; 95% confidence interval (CI), 1.13-1.24) in a multivariable analysis.

CONCLUSION: Our findings suggest that the rate of discontinuation of statin therapy after bariatric surgery was more pronounced in the primary versus secondary prevention treatment group.

Antimicrobial Prescribing Patterns Among Children and Adolescents Receiving Cancer Chemotherapy in the Private Health Sector of South Africa.

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[1]*North-West University, Potchefstroom, South Africa*

BACKGROUND: Treatment modalities used in the management of children with cancer compromise their immunity, predisposing them to several infectious episodes requiring the use of antimicrobial agents. There is however a paucity of information on the antimicrobial prescribing patterns among these patients.

OBJECTIVE: This study aimed at investigating the antimicrobial prescribing patterns among patients aged younger than 19 years diagnosed with, and on treatment for, cancer in a section of the South African private health sector.

METHODS: A cross sectional study design was used in this drug utilisation study. Medicine claims data spanning 1 January 2008 to 31 December 2017 from a nationally representative

Pharmaceutical Benefit Management (PBM) company in South Africa were queried to identify antimicrobial agents prescribed using the Monthly Index of Medical Specialties (MIMS) classification system. Data were analysed descriptively by gender and age (categorised into age groups 0-4, 5-9, 10-14 and 15< 19 years).

RESULTS: A total of 173 participants, 68.8% of which were males were included in this study. The mean age of the study population was 10.0 ±5.4 years. The highest proportion of patients (34.1%) were in the 5-9 years age group compared to the 15.6% of patients in the 0-4 years age group. A total of 458 antimicrobial agents were identified in reimbursed claims of the study population during the study period. Beta lactams (n = 225, 49.1%) of which 61.8% were penicillins, Sulphonamides and combinations (n = 65, 14.2%), and erythromycin and other macrolides (n = 49, 10.7%) were the top three most frequently prescribed, whilst tetracyclines (n = 5, 1.1%) were the least prescribed antimicrobial classes in our study population. Amoxycillin/Clavulanic acid combination were the most frequently prescribed penicillin, whilst trimethoprim/sulphamethoxazole was the most frequently prescribed Sulphonamide.

CONCLUSION: There were variations in the classes of antimicrobials prescribed for the study population, with penicillins being the most frequently prescribed. Concerns have been raised about the emergence and dissemination of antimicrobial-resistant organisms in patients with cancer. With chemotherapy-induced febrile neutropenia commonly observed in children on cancer treatment, and requiring antimicrobial use, more stringent antibiotic stewardship programs should be instituted in childhood and adolescent cancer care to curb antimicrobial resistance.

Patterns of Meropenem Utilization and Resistance at a Kenyan Public Referral Hospital

Dennis K. Makau

BACKGROUND: Meropenem is a second generation carbapenem with a broad spectrum of activity. As such, it is prone to misuse and this raises concern about the emergence of microbial resistance to this agent in Kenya and beyond. Resistance to meropenem is challenging due to the high prevalence of infections, irrational use and inadequate antimicrobial susceptibility testing.

OBJECTIVES: The study aimed to describe patterns of use and resistance to meropenem at Kenyatta National Hospital. The beliefs and attitudes of clinicians with regard to prescribing of meropenem was also assessed.

METHODS: A retrospective review of prescriptions and culture and sensitivity results was conducted for the period January 2016 and December 2017. A cross-sectional study on meropenem prescribing practices by clinicians was also conducted. Clinicians were interviewed with the use of a structured questionnaire. Abstracted data were subjected to descriptive and inferential data analysis was done using SPSS version 13 software.

RESULTS: Meningitis, (45, 27.6%) and severe pneumonia, (41, 25.2%) were the major indications in children while soft tissue infections, (75, 26%) in adults. Meropenem was used empirically in 77% of the patients. Gram-negative bacteria were the main isolates on culture and sensitivity testing (97.6%). Acinetobacter baumannii (90.0%) and Pseudomonas aeruginosa (55.6%) had the highest prevalence of resistant strains. Escherichia coli were the most susceptible, (921, 84.2%). Most clinicians, (29, 74.4%) advocated for cessation of empirical use of meropenem. Clinicians mostly

relied on advice from an Infectious Disease Specialist (22, 56.4%) and senior colleagues (20, 51.3%). The Pharmacists, (5, 12.8%) were the least accessible to provide guidance on meropenem prescribing. Inappropriate selection, (22, 56.4%) and over-prescription, (28, 71.8%) of meropenem were the most prevalent medication use problems.

CONCLUSION: Meropenem was mainly used empirically. Antimicrobial stewardship is needed to promote its use.

The Impact of Age and Sex Concordance Between Patients and Physicians on Medication Adherence: A Population-Based Study

Shenzhen Yao[1], Lisa Lix[2], Gary Teare[3], Charity Evans[1], David Blackburn[1]

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BACKGROUND: Patients who share the same sex or age as their prescriber (i.e., sex or age concordance) report strong satisfaction with care.

OBJECTIVE: To determine the impact of age and sex concordance on optimal adherence to statin medications.

METHODS: A retrospective cohort study. Setting: Population-based health administrative data from Saskatchewan, Canada. Participants: Patients newly initiated on statin medications between January 1, 2012 and December 31, 2017.

Explanatory variables: Sex concordance (i.e., same sex) and age concordance (i.e., age within five years) between patients and prescribers.

RESULTS: Optimal adherence (i.e., proportion of days covered ≥ 80%) measured at one year after the first statin claim.

Statistical analysis: Multivariable logistic regression models using generalized estimating equations.

RESULTS: Among 51,874 new statin users, 20.6% (n=10,710) were age concordant with prescriber. The vast majority of age concordance occurred in patients younger than 66 years (88.6%, 9,486/10,710). Sex concordance was observed in 62.8% (n=32,551) of patients and age-sex combined concordance in 13.2% (n =6,856). Among patients younger than 66 years (n= 36,641), age concordance did not have a significant impact on optimal adherence [adjusted OR (aOR) = 1.02, 95%CI 0.97 to 1.07]. The association between sex concordance (aOR=1.05, 95%CI 1.00 to 1.11), and age-sex combined concordance reached borderline significance (aOR = 1.05, 95%CI 0.99 to 1.12).

CONCLUSION: Age and sex concordance were not statistically significant predictors of optimal statin adherence. However, a weak signal was detected for sex concordance. Future studies should examine this factor in different health care settings.

Medication Nonadherence for Patients with Stage 2 Hypertension: A Community-Setting Survey in Indonesia

Aliza A. Sholawati[1], Riana Rahmawati[1]

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BACKGROUND: Non-adherence to medication has been considered as an important factor of suboptimal hypertension treatment. Stage 2 hypertension significantly contribute to the high-risk cardiovascular score. However, the extent of adherence among these group of patients is rarely reported.

OBJECTIVE: This study aimed to determine the level of adherence to hypertension medication among patients with stage 2 hypertension in a

community health worker-based program for the elderly (i.e. Posyandu lansia) in Indonesia.

METHODS: A cross-sectional study was undertaken in July-October 2019. Respondents were members of Posyandu lansia who have previously diagnosed with stage 2 hypertension. The validated Indonesian Medication Adherence Reported Scale-5 (MARS-5) was applied to assess the patients' adherence. The level of adherence was categorized as: non-adherent (total score < 20 or did not take any medication in the preceding 30 days), partially adherent (20-23), and adherent (24-25).

RESULTS: The total number of respondents was 108; aged 67.2 ± 9 years (ranged 45-90 years old). Thirty respondents did not take any hypertension medications. Only 8.3% respondents were adherent; only 16 respondents (14.8%) answered "never" or "rare" for the statement "I stop my hypertension medications for a while" . The Indonesian MARS-5 used in this study had moderate reliability (the Cronbach's Alpha=0.76, the Intraclass Correlation Coefficient=0.66).

CONCLUSION: This community-based survey showed non-adherence to medication was commonly reported among people with stage 2 hypertension. Given the high risk of cardiovascular event due to uncontrolled hypertension, the strategies to improve adherence to medication in the community setting should be comprehensively formulated.

Breakout Room 2: Spotlight on Pharmacoepidemiology in Cancer and Rheumatic Disease

Tuesday 20 April | 9:50 AM – 10:20 PM

Abstracts In Presentation Order

Presenting Author Highlighted In **Bold**

Survival Outcomes of Patients with Non-Small Cell Lung Cancer Concomitantly Receiving Proton Pump Inhibitors and Immune Checkpoint Inhibitors

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BACKGROUND: Recent evidence suggests that gut microbiota dysbiosis adversely affects the efficacy of immune checkpoint inhibitors. The association between the concomitant use of proton pump inhibitors with immune checkpoint inhibitors and poor prognosis remains controversial.

OBJECTIVE: To investigate the association between concomitant use of proton pump inhibitors and immune checkpoint inhibitors and poor prognosis in patients with non-small cell lung cancer.

METHODS: We conducted a cohort study using a completely enumerated lung cancer cohort from a nationwide healthcare database in South Korea. We identified 2,963 patients treated with immune checkpoint inhibitors as second-line or above therapy for stage ≥ IIIB non-small cell lung cancer. Proton pump inhibitor use was ascertained within 30 days before and on the date of immune checkpoint inhibitor initiation, and non-use

was defined as no prescription of proton pump inhibitors during this period. We assessed the risk of all-cause mortality, using national vital statistics in South Korea, associated with concomitant proton pump inhibitor use using a propensity score-matched Cox proportional hazard model and Kaplan–Meier survival

RESULTS: Among 1,646 patients included after 1:1 propensity score-matching, concomitant proton pump inhibitor use was associated with a 28% increased risk of all-cause mortality compared to non-use (adjusted hazard ratio, 1.28; 95% confidence interval, 1.13-1.46). We observed an increased risk when we restricted the analysis to new users of proton pump inhibitors (adjusted hazard ratio, 1.64; 95% confidence interval, 1.25-2.17). Subgroup analysis showed that proton pump inhibitor use was associated with particularly prominent mortality risk among patients with viral hepatitis (adjusted hazard ratio, 2.72; 95% confidence interval, 1.54-4.78; p for interaction, 0.048).

CONCLUSION: Our study indicates that proton pump inhibitor use is associated with poor prognosis in non-small cell lung cancer patients treated with immune checkpoint inhibitors. The risk-benefit balance of the concomitant use of proton pump inhibitors and immune checkpoint inhibitors warrants careful consideration.

Comparing Clinical Characteristics and Outcomes of Negative, Weakly, and Strongly Positive Estrogen Receptor Breast Tumors by Endocrine Therapy Status: Results from a 15-Year Follow-Up Study

Cornelia Kazemali[1], Caroline Diorio[2], Cynthia Mbuya-Bienge[1], Julie Lapointe[3], Louise Provencher[4], Simon Jacob[5], Julie Lemieux[6], Hermann Nabi[1]

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OBJECTIVE: Currently, adjuvant endocrine therapy (AET) is considered for breast cancer (BC) patients with any positive level of estrogen receptor (ER) expression. However, its benefit for patients with weakly ER positive (1-9%) BC is still a matter of debate. We aim therefore to compare clinical characteristics and outcomes of patients with ER negative, weakly and strongly positive BC tumors by AET status.

METHODS: A total of 5879 non-metastatic BC patients diagnosed between 1995 and 2011 and followed at a tertiary BC center in Quebec City were included. ER expression levels were measured by immunohistochemistry and used to categorize patients as ER negative (< 1%), weakly (1-9%) and strongly (≥10%) ER positive. Cross-comparisons of survival outcomes between these groups according to AET status were performed using Cox regressions models adjusted for age, progesterone receptor, clinicopathological characteristics, body-mass-index, menopause and treatment regimens.

RESULTS: Overall, 18.4%, 1.3% and 81.3% of patients had ER negative, weakly, and strongly ER positive tumor, respectively. As expected, the

15-year disease-free survival (DFS) and overall survival (OS) rates were lower in ER negative and weakly ER positive BC patients when compared to strongly ER positive BC patients. In fully adjusted models, ER negative BC patients with (HR= 2.09, 95%CI: 1.43-3.04) and without (HR= 1.79, 95%CI: 1.39-2.29) AET had a poor 15-year DFS when compared to strongly positive ER BC patients with AET. Similar patterns of associations were observed for OS. No significant survival differences were evidenced among weakly positive ER BC patients who received AET. Strongly positive ER BC patients with AET had better survival outcomes comparatively to those without.

CONCLUSION: Our results indicate that AET provides no survival gains for ER negative and weakly ER positive BC patients. Given the potential side effects of AET, the current recommended threshold for ER positivity might be reconsidered

The Impact of Diabetes on Survival in Endometrial Cancer Patients: A Systematic Review and Meta-Analysis.

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BACKGROUND: Diabetes mellitus is a risk factor for endometrial cancer however, its impact on endometrial cancer prognosis is unclear. Epidemiological studies evaluating diabetes mellitus and endometrial cancer survival have to date appeared contradictory. We therefore conducted the first systematic review and meta-analysis of the association between diabetes and cancer-specific survival in patients with endometrial cancer.

METHODS: We conducted a systematic search of MEDLINE, EMBASE and Web of Science databases up to July 2020 for observational studies that evaluated the impact of pre-existing diabetes mellitus on survival in endometrial cancer patients. Titles, abstracts and full-texts were screened independently by at least two reviewers. A random-effects model was used to produce pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between diabetes status and endometrial cancer-specific survival. Secondary outcomes included overall survival and progression-free survival.

RESULTS: Twenty-five cohort studies were identified, 12 of which reported endometrial cancer-specific survival, 20 reported overall survival and 5 reported progression-free survival. Overall, there was a 22% increased risk of endometrial cancer-specific death in endometrial cancer patients with diabetes compared to endometrial cancer patients without diabetes (HR 1.22, 95% CI 1.01-1.48), with moderate heterogeneity observed (I2=68%). In sub-group analysis by study design, the increased risk of endometrial cancer-specific death was more marked in population-based studies (7 studies, HR 1.37, 95% CI 1.08-1.75, I2=55%) compared to institution-based studies (5 studies, HR 1.06, 95% CI 0.73-1.52, I2=73%). Further stratification by diabetes ascertainment found an attenuated increased risk for endometrial cancer-specific death when restricting to studies that used self-reported diabetes (5 studies, HR 1.52, 95% CI 0.87-2.66, I2=78%) compared to studies that used medical records to ascertain diabetes status (7 studies, HR 1.15, 95% CI 0.93-1.42, I2=61%). For secondary outcomes, risk of overall survival and progression-free survival were poorer in patients with diabetes compared to those without diabetes (overall survival: HR 1.45, 95% CI 1.31-1.60, I2=47%, progression-free survival: HR 1.25, 95% CI 1.03-1.51, I2= 0%).

CONCLUSION: Diabetes was associated with a worse cancer-specific survival in endometrial cancer patients, suggesting that diabetes may be an important prognostic feature in endometrial cancer. However, further large studies are required that include information on diabetes type, duration and severity.

The Use of Incretin-Based Therapies and Cancer-Specific Risk in Type 2 Diabetes Mellitus Patients: A Systematic Review

Niamh McGuckin[1], Chris Cardwell[1], Blánaid Hicks[1]
[1]*Centre for Public Health, Queens University Belfast*

BACKGROUND: Incretin-based medications including glucagon-like peptide 1 (GLP1) agonists and dipeptidyl peptidase-4 (DPP4) inhibitors are used for glycaemic control in type 2 diabetes mellitus patients. Evidence suggests incretin-based medications could have a role in cancer development through modulation of incretin receptors. We performed a systematic review to assess the available observational evidence of incretin-based medications and cancer risk.

METHODS: A literature search of the EMBASE, MEDLINE and Web of Science databases was conducted from January 2005 to June 2020 to identify all relevant studies that investigated incretin-based medications and cancer risk compared to other anti-diabetic drugs. Study quality and risk of bias were assessed using the ROBINS-I tool and additional pharmacoepidemiology-specific criteria. Pooled hazard ratios (HR) and 95% confidence intervals (CI) were calculated using a random effects model. Publication bias was assessed using a funnel plot.

RESULTS: 32 studies (28 cohort and 4 case-control) were included in the review. We found no association between the use of incretin-based medication and pancreatic cancer risk (14 studies, HR: 1.02, 95% CI: 0.85-1.23) or colorectal cancer (4 studies, HR: 1.03, 95% CI: 0.95-1.12). Analysis for other cancer sites (breast, thyroid, lung, bile duct, prostate) also showed no significant association. Large heterogeneity between studies was observed in some analyses and time-related biases were identified in 22 of the included studies.

CONCLUSION: No significant association was found between incretin-based medications and cancer risk. Further well-conducted studies that address time-related biases and confounding are needed to accurately determine the long-term cancer risk with the use of GLP1 agonists and DPP4 inhibitors.

Cost-Effectiveness of Direct Oral Anticoagulants (DOAC) Versus Low-Molecular Weight Heparin (LMWH) for Treatment of Venous Thromboembolism (VTE) in Gastrointestinal (GI) Cancer Patients

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BACKGROUND: GI cancer patients are at high risk for development of cancer-related VTE. Though LMWH are the current standard treatment of VTE, clinical trials have shown that DOACs are non-inferior to LMWH in cancer patients. It is unclear whether DOACs are cost-effective in GI cancer patients as there is an increased risk of bleeding.

OBJECTIVE: To assess the cost-effectiveness of DOACs for treatment of VTE in American gastrointestinal cancer patients.

METHODS: A cost-utility analysis was conducted using a Markov model over 60 months in a hypothetical cohort of gastrointestinal cancer patients with active malignancy who were eligible to receive either rivaroxaban/edoxaban

or dalteparin. Transition states for the model included on anticoagulant treatment, off anticoagulant treatment, recurrent deep vein thrombosis (DVT), recurrent pulmonary embolism (PE), major bleeding (MB), clinically relevant non-major bleeding (CRNMB), PE-related death, MB-related death, and non-PE/non-MB-related death. Transition probabilities, costs, and utilities were obtained from literature. The main outcome of this study was the incremental cost-effectiveness ratio (ICER), expressed as cost in U.S. dollars per QALY. ICER was calculated from a United States payer's perspective, including direct medical cost related to drugs and complications. Univariate and probabilistic sensitivity analyses were performed to test the robustness of the results.

RESULTS: DOACs compared to dalteparin were associated with incremental cost savings of $70,388 and incremental QALY reduction of 0.62, with an ICER of $114,319 saved per QALY lost. In the univariate sensitivity analysis, the cost of DOACs starting from month 2 influenced the incremental cost difference the most while the utility value for one cycle of dalteparin treatment influenced the incremental QALY difference the most. Sensitivity analyses indicated that results were robust over a wide range of inputs.

CONCLUSION: The model projects that DOACs could be a cost-effective alternative to LMWH for treatment of VTE in GI cancer patients over 60 months when the willingness-to-pay is approximately $115,000 or lower. This analysis can help professional organizations and healthcare systems decide how GI cancer patients would benefit from different anticoagulants for treatment of VTE.

Incidence and Determinants Associated with Retransitioning from Biosimilar SB4 to Originator Etanercept

Rosanne Meijboom[1], Helga Gardarsdottir[1], Matthijs Becker[2], Saskia ten Wolde[3], Toine Egberts[1], Thijs J. Giezen[2]

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BACKGROUND: The market entry of the etanercept biosimilar SB4 (BS-ETA) reduced prices; and, therefore, many patients in clinical practice are transitioned from originator etanercept (OR-ETA) to BS-ETA. However, previous observational studies demonstrated that 2.7-17.1% of patients who transitioned from OR-ETA to BS-SB4, retransitioned to OR-ETA (i.e. restarted originator), which might reduce the (financial) benefits of biosimilars. Insight in the incidence of retransitioning and characteristics of patients who are most likely to retransition, can provide lessons to clinicians for successful introduction of biosimilars.

OBJECTIVE: To assess the incidence of retransitioning from BS-ETA to OR-ETA in patients with a rheumatic disease (RD) and to identify determinants thereof.

METHODS: All patients diagnosed with RD who transitioned in 2016 from OR-ETA to BS-ETA in a Dutch general teaching hospital (the Spaarne Gasthuis, Haarlem/Hoofddorp) were included in this cohort study. All patients were followed until retransitioning, switching to another biological, discontinuing of biological treatment death, loss to follow up or until the censor date (April 30, 2019). The incidence of retransitioning and duration of BS-ETA use was assessed using the Kaplan-Meier method Potential determinants for retransitioning, including age, gender, BS-SB4 dosing interval, use of other biologicals prior to OR-ETA, duration of OR-ETA treatment, initiation or intensification of corticosteroids or

immunomodulators, hospitalizations and the number of outpatient visits to the rheumatology department, were assessed in a nested case control study, using (multivariate) conditional logistic regression.

RESULTS: In total, 342 patients (median age 57.8 years, 53.5% females, median follow-up 2.7 years) were included. 9.4% of patients had retransitioned to OR-ETA one year after transitioning. Additionally, one year after transitioning 69.7% of patients were still treated with BS-ETA, 3.8% switched to other treatment and 17.1% discontinued all biological treatment. At the end of follow-up (median 2,7 years), 46 patients (13.5%) had retransitioned to OR-ETA; median time until retransitioning was 0.50 (IQR 0.98) years.

Univariate determinants for retransitioning included female gender (OR 2.37, 95% CI 1.18-7.74), initiating or intensifying corticosteroid or immunomodulator treatment (OR 3.24, 95% CI 1.38-7.63) and the number of visits to the rheumatology department (OR 2.32, 95% CI 1.70-3.17). Based on the multivariate analysis, only the number of visits to the rheumatology department was associated with retransitioning (OR 2.19 95% CI 1.60-3.00).

CONCLUSION: When introducing BS-SB4 in clinical care, clinicians should anticipate on about one in seven patients retransitioning to OR-ETA. These patients might be identified prior to retransitioning based on their contacts to the rheumatology department. Information specifically aiming for their concerns might prevent them from retransitioning. However, more qualitative studies are needed to explore patients' underlying reasons for retransitioning, in order to improve the introduction of biosimilars in clinical care.

Comparative Safety of TNF-Alpha Inhibitors in Patients with Rheumatoid Arthritis in Administrative Health Databases: A Systematic Review and Meta-Analysis

Djanilson Barbosa Santos[1], Caroline T. Castro[2], Roberto Carreiro[1], Daniella C. Rodrigues[1], Mauricio Barreto[1], Wânia C. [1], Flávia Albuquerque[3], Celmário Brandão[3], Mariana Queiroz[3], Jessé Azevedo[3], Wenderson Andrade[3], Sandra Barros[3]

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BACKGROUND: The tumor necrosis factor inhibitors (TNFi) are biological drugs used to treat rheumatoid arthritis (RA) that, despite the therapeutic effect, may increase the risk of some adverse events like cancer, tuberculosis, cardiovascular events and serious infections. It was hypothesized a higher incidence of adverse events would be observed in rheumatoid arthritis (RA) patients using biologic anti-tumor necrosis factor (TNFi) agents compared with traditional disease-modifying antirheumatic drugs (tDMARDs) or other biological drugs (bDMARDs).

OBJECTIVE: This study is aimed to assess the safety of TNFi use by patients with rheumatoid arthritis in administrative health databases .

METHODS: We performed a systematic review and meta-analysis of studies containing real-world data (RWD) from administrative health databases, to evaluate the risk of adverse events with the use of TNFi (adalimumab, etanercept and infliximab). The search was performed using the electronic databases: PubMed, Embase, Ovid, Scopus, Web of Science, and BVS databases . We included all RWD studies that assessed the risk of adverse

events in TNFi users compared to non-users and considered the following outcomes: occurrence of serious adverse events and adverse events leading to treatment discontinuation (cancer, tuberculosis, serious infection and cardiovascular events). We assessed the studies according to MOOSE guidelines and their quality according to a methodological index for non-randomized studies (MINORS) by two independent researchers. Pooled risk ratios (RRs) were calculated using random-effects meta-analysis for safety outcomes with 95% confidence intervals. The study protocol was registered at PROSPERO [CRD42020190838].

RESULTS: Fifteen studies (6 retrospective cohorts, 4 prospective cohorts and 5 case-controls) enrolling 277,253 participants (mean age: 53.3 years; female sex: 64.7%) among which 2,311 experienced adverse events were included (5 studies on cancer, 2 on tuberculosis, 6 on serious infection and 4 on cardiovascular events). They were all considered high quality studies. The risk ratio (RR) for adverse events was 1.26 [95% confidence interval (CI): 1.12 – 1.30) among anti-TNF users, compared with non-users. TNFi increases the risk of tuberculosis (2.25; 95%CI 1.46-3.45), cardiovascular events (1.18; 95%CI 1.03-1.36) and serious infections (1.11; 95%CI 1.04-1.19). No statistical significance was found between TNFi and cancer (0.99; 95%CI 0.86-1.15).

CONCLUSION: Our results partly support the existing literature, indicating increased risk of adverse events associated with the use of TNFi compared to tDMARDs. Short and long term safety-related factors are critical in determining appropriate therapy for RA patients. Although biological agents are clinically effective, physicians should be mindful of potential safety concerns associated with their use. Key words: pharmacoepidemiology, rheumatoid arthritis, safety, TNF-alpha inhibitor, administrative health databases, meta-analysis

Observational Real-World Study of Patients with Rheumatoid Arthritis Treated with Baricitinib and/or Tofacitinib in a Tertiary Hospital, Collected in the Register of Patients and Treatments.

Elena Guillén[1],Mónica Sabaté[1], Elena Ballarin[1], Esther Espartal[2], Maria Lopez[2], Montserrat Bosch[1], Núria Boixareu[3], Carmen Alerany[1], Eduard Diogene[1], Immaculada Danes[1]

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BACKGROUND: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease. Management is aimed to achieve remission or a low level of clinical activity, with disease-modifying antirheumatic immunosuppressive drugs (DMARD), which have demonstrated high efficacy with an acceptable profile of adverse events. Many of them are prescribed in the hospital setting, mostly biological therapies (bDMARD) and directed DMARD (dDMARD) such as JAK inhibitors. However, data on follow-up and safety in routine clinical practice is scarce. In 2014, The Catalan Health Service (CatSalut) implemented the Register of Patients and Treatments (RPT), where most of the hospital outpatient treatments have to be registered in order to be refunded. bDMARD or dDMARD are recommended if conventional synthetic DMARD (csDMARD) are ineffective. Although choosing one or the other depends on medical criteria, given the greater clinical experience of use, bDMARD are suggested first.

OBJECTIVES: To describe, in clinical practice, the line of treatment and the use of baricitinib and/or tofacitinib in patients with RA treated at Vall d'Hebron University Hospital (VHUH).

METHODS: All patients included in VHUH's RPT who started treatment with baricitinib and/or tofacitinib for RA between September 2017 (date of their commercialization in Spain) and November 2019 were analysed. Data was extracted from the RPT and patients' medical records. A descriptive analysis was performed with REDCap and SPSS software.

RESULTS: Out of 58 patients, 42 met the inclusion criteria (10 had other rheumatological conditions and were mislabelled as RA, 5 were out of study period and one did not receive JAK inhibitors). The study included 30 patients who were prescribed tofacitinib, 7 baricitinib and 5 patients received both sequentially. Most were women (90.5%), and the median age (IQR) was 56 years (29-78). More than 78% had one or more comorbidities, mainly dyslipidemia (35.7%) and hypertension (33.3%). All patients had previously received at least one csDMARD, mainly methotrexate (41) and leflunomide (33), and 93% had received two or more csDMARD. Thirty-three (78.6%) had previously received at least one biological DMARD, mainly etanercept (25), tocilizumab (20) and abatacept (20). Nine patients (21.4%) were treated directly with JAK inhibitors after csDMARD failure, and 8 (19%) started another bDMARD before JAK inhibitors when these drugs were already available in Spain. Treatment was withdrawn in 9 patients: 5 due to lack of efficacy (one patient withdrew sequentially both tofacitinib and baricitinib), 2 due to toxicity (one case of abdominal pain and pustules and another case due to anaemia) and 2 were lost to follow-up. Ten adverse events were observed in 5 patients who had received tofacitinib, mostly gastrointestinal and skin disorders. None were severe or life-threatening.

CONCLUSION: JAK inhibitors were used according to CatSalut criteria. All treated patients had previously received several csDMARD, and four out of five at least one bDMARD before JAK inhibitors, in some patients even when these drugs were already available. Withdrawal due to adverse effects was rare. This study reflects the usefulness of patient registries for new and expensive drugs.

Breakout Room 3: Capturing The Real World: Design, Reporting & Analysis in Pharmacoepidemiology

Tuesday 20 April | 9:50 AM – 10:20 PM

Abstracts In Presentation Order

Presenting Author Highlighted In **Bold**

Estimation of Adverse Drug Reaction Reporting in Iran: Correction for Underreporting

Malahat Khalili[1], Bita Mesgarpour[2], Hamid Sharifi[1], Asieh Golozar[3], Akbar Haghdoost[1]

[1]HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran; [2]National Institute for Medical Research Development, Tehran, Iran; [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

BACKGROUND: Identifying and reporting suspected adverse drug reactions (ADRs) is a vital patient safety activity, but underreporting of ADR is a crucial drawback of the pharmacovigilance system.

OBJECTIVE: We described ADR reporting and its trend from 1999 to 2017 and estimated the underreporting of ADR in the Iranian Pharmacovigilance Center.

METHODS: We identified the number of ADR reporting per inhabitants and admissions and their trends. Then, ADR underreporting was estimated by three methods. First, a three-month prospective study was carried out in two

tertiary hospitals of Iran to identify suspected ADR per admission as the expected proportion of reporting. The number of reported ADR per admission in the three months before the study was used as the observed proportion in each hospital. In the second method, we determined the proportion of ADR per admission in the Iranian hospitals through a literature review as the expected proportion and used the national proportion of ADR reporting in 2017 as the observed proportion. In the third method, we stratified the country into three strata based on patients' specialized medical services. In each stratum, the sensitivity of reporting in provinces with the highest proportion of ADR reporting per admission was assumed 100% and consider as the expected proportion. This reporting proportion in the rest provinces considers as observed proportions. Finally, in each method, the expected proportion is subtracted from the observed proportion, the difference is divided by the expected proportion to calculate the percentage of underreporting. The median of these estimated underreporting percentages was used as the best estimation.

RESULTS: The proportion of ADR reporting was 15.3 per 100,000 inhabitants (95% CI: 15.2, 15.8) and 10.0 per 100,000 admissions (95% CI: 9.8, 10.2) in 2017, and its trend was increasing with 16.3% average change per annum during 19 years. The lowest and highest underreporting percentages were estimated from prospective studies and literature review methods; 71.9% (95% CI: 69.0-74.9) and 99.7% (95% CI: 99.69 - 99.73), respectively. According to the three methods, the median of the estimated underreporting percentages was 76.0% (IQR: 64.32-81.35) in the stratification of the country' method. After the correction, the mean proportion of ADR reporting for 19 years reached from 5.87 to 10.33 per 100,000 inhabitants.

CONCLUSION: The trend of ADRs reporting in Iran has been increasing over the 19 years but is still low. This study showed a considerable underreporting of ADR, and only about one of four detected ADRs were reported to the pharmacovigilance center. Our research suggests that more education and training are needed for healthcare professionals and patients to understand ADRs reporting and their pivotal role in successfully implementing this process.

Is Pharmacovigilance Unpopular in Lithuania? Barriers to Reporting of Adverse Drugs Reactions by Community Pharmacists and General Practitioners

Agne Valinciute-Jankauskiene[1], Loreta Kubiliene[1]

[1]*Department of Drug Technology and Social Pharmacy, Lithuanian University of Health Sciences*

BACKGROUND: All medicines have potential side effects, and unfortunately, they are an important cause of patient morbidity and mortality. As they frequently lead to hospital admission, hospitalization prolongation, and emergency room visits, ADRs have substantial economic and health costs. Several studies were performed to investigate the knowledge, perception, and barriers towards ADR reporting by community pharmacists (CPs) and health care providers (HCP) worldwide. However, very little is known about the factors which influence CPs and HCPs in Lithuania from reporting ADR. According to our knowledge, this is the first qualitative research to explore and understand barriers of the adverse drug reaction reporting in Lithuania that could lay the foundation for wider investigation in the future.

A qualitative research approach was selected to perform this study. A semi-structured interview guide was developed after reviewing previous studies on ADR reporting. The interviews were

carried out from March 2020 – December 2020. Written informed consent was obtained from each of the GPs and CPs before participation in the interview. All interviews were audio-recorded and transcribed verbatim, and thematically analyzed.

During the thematic content analysis, six barriers were identified. The identified barriers to reporting ADR found in this study with suggested interventions to remove these barriers are listed in table 1.

Table 1. Identified barriers and suggested interventions.

Identified barriers	Suggested interventions
Lack of information and education	Educational sessions: theoretical and practical
Heavy workload	Time management training; Establishment of drug safety department/staff
Complicated ADR reporting procedure	Educational sessions: theoretical and practical; Computerized registration; Revision and reorganization of the reporting procedure
Limitations of the e-health system	Computerized registration
Organizational culture	Provision of communication training; Awards and financial incentives; Educational sessions: theoretical and practical; Teambuilding initiatives
Lack of trust in authority	Provision of active feedback and support; Initiation of open discussions; Educational sessions: theoretical and practical

The spontaneous reporting system depends on the voluntary submission of ADR reports; therefore, the reporting needs continuous stimulations. The recent scoping review showed that the most impact had educational interventions, including theoretical and practical sessions, intensive monitoring system, and computerized registration. It was demonstrated that applied multiple interventions have a higher impact compared to single ones. Even though Lithuania is leading in three Baltic countries, there is room to grow. Considering the identified barriers, we suggested interventions that could be most effective in the current situation of pharmacovigilance in Lithuania.

Trends in Opioid-Related Adverse Reactions Declared to Health Canada Since 1965: Can We Do Better?

Maude Lavallée[1], Carolina Galli da Silveira[2], Samuel Akinola[3], Julie Méthot[4], Marie-Ève Piché[5], Anick Bérard[6], Magalie Thibault[1], Jennifer Midiani Gonella[2], Fernanda R. Gimenes[2], Jacinthe Leclerc[1]

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BACKGROUND: Opioids are frequently used to treat acute and chronic pain. However, opioid-related adverse reactions (AR) are common and have been associated with worse outcomes. Only 5% of drug-related AR (including opioids) would be reported to health authorities. The opioid crisis is raging in Canada and the government has issued specific clinical recommendations and policies. However, little is known regarding the declaration and investigation of opioid-related AR at the Canadian population level. It is therefore of the utmost importance to assess how reports of opioid-related AR have evolved over time.

OBJECTIVE: To investigate how rates of opioid-related AR declarations occurring in and out of hospitals have evolved since 1965 in Canada.

METHODS: We conducted a retrospective study examining the trends of opioid-related AR declared to Health Canada from January 1, 1965 to October 31, 2019. Of note, AR can be reported by hospitals' staff, health care professionals in clinics, manufacturers and patients. Once investigated for causality and coded by Health Canada, each denominated AR are made publicly available into the Canada Vigilance database. Data were extracted from the following databases: 1) Canada Vigilance, and 2) Statistics Canada. Descriptive analyzes were performed and yearly rates of AR declarations per 100,000 person-year were computed: the numerator was the number of opioid-related AR (from Canada Vigilance) while the denominator was the Canadian population (from Statistics Canada). Stratification by sex was performed, as well as a log-linear Joinpoint regression analysis to identify and quantify variations of rates of declared AR over time. A post-hoc sensitivity analysis was also performed.

RESULTS: Opioid-related AR were common (n= 18,407, 1.1 per 100,000 person-years). AR were mostly declared after the use of oxycodone (22.0%), while the least (0.1%) declaration was as a result of normethadone use. The lowest rate of AR declaration to Health Canada was observed at the beginning of the study period (1965: 0.1 per 100,000 person-years), while the highest rate was observed in 2012 (3.8 per 100,000 person-years). The Joinpoint regression model permitted to quantify that rates annually increased by 4.2% [95% confidence interval: 3.1 to 5.2] throughout the study period, but fluctuated as: 1) +22.3% [12.0% to 33.6%] between 1965-1974, 2) -4.1% [-5.3% to -2.9%] between 1974-2000, 3) +30.3% [22.6% to 38.4%] between 2000-2008, 4) +4.1% [-1.5% to 10.1%] between 2008-2014, 5) -26.0% [-44.7% to -0.9%] between 2014-2017 and finally, 6) +35.4% [3.8% to 76.7%] between 2017-2019. Sex stratification revealed that opioid-related AR seemed more declared for female patients throughout the study period, with the exception of 2008 to 2013. Unforeseen and yet unresolvable technical issues with the Canada Vigilance Database have hindered our ability to extract some opioid-related AR's data. Nevertheless, the post-hoc sensitivity analysis' results were aligned with our main findings.

CONCLUSION: Trends of declared opioid-related AR increased since 1965, even though huge fluctuations were observed in the last 20 years. Knowing that the absolute number of opioid-related AR might be seriously underestimated, upcoming studies should investigate how to overcome this gap, as well as the sex differences in opioid-related AR declarations.

Incidence, Characteristic and Risk Factors of Drug-Induced Liver Injury in Hospitalized Patients: A Matched Case-Control Study

Xianghao Kong[1], Daihong Guo[1], Siyuan Liu[1], Yu Zhu[1], Chengxuan Yu[1]

[1]*Chinese PLA General Hospital*

BACKGROUND: The diagnosis of drug-induced liver injury (DILI) is relatively complex, involving a wide variety of drugs. Liver injury was usually associated with severe COVID-19, some drugs prescribed in COVID-19 patients are potentially hepatotoxic.

OBJECTIVE: The purpose of this study is to use algorithms to quickly screen DILI patients, count incidence rates and find risk factors.

METHODS: The Adverse Drug Events Active Surveillance and Assessment System-2 was used to extract the data of hospitalized patients in 2019 according to the set standards, then the RUCAM was used to evaluate patients who meet the standards. A retrospective case-control study was conducted according to suspected drugs, length

of hospital stay, height and weight matched controls, and logistic regression was used to find risk factors.

RESULTS: Among the 156,570 hospitalized patients, 480 patients (499 cases) of DILI were confirmed, and the incidence of DILI was 0.32%. Anti-infective agents, antineoplastic agents, non-steroidal anti-inflammatory drugs (NASIDs) were the major category of causative drugs causing DILI, and the highest incidence of DILI caused by agent of voriconazole(1.33%). The latency period and hospital stay of patients with cholestasis was relatively long. Patients with hyperlipidemia (AOR: 1.884), cardiovascular disease (AOR: 1.465), pre-existing liver disease (AOR: 1.827) and surgical history (AOR: 1.312) were likely to be risk factors for DILI.

CONCLUSION: The incidence of DILI in hospitalized patients was uncommon (0.32%), and its pathogenic drugs were widely distributed. LiverTox's information could assist in the diagnosis of DILI. The incidence of DILI in many drugs was seriously underestimated. It is recommended to focus on patients with hyperlipidemia, cardiovascular disease, pre-existing liver disease, and surgical history.

Validation of Diagnostic Algorithms for the Identification of Patients with Inflammatory Bowel Diseases: Analysis of Administrative Data from a Local Health Unit in Southern Italy

Valentina Isgrò[1], Ylenia Ingrasciotta[1], Valentina Ientile[1], Luca L'Abbate[1], Saveria Serena Foti[1], Gabriele Puglisi[1], Michele Tari[2], Angela Alibrandi[3], Gianluca Trifirò[4]

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BACKGROUND: Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic diseases associated with increased morbidity and reduced quality of life. Claims databases are an important source to conduct observational research on drug utilization of biologics in IBD in a real world setting. Case validation is necessary to ensure accurate disease investigation using these databases and to accurately identify separately cohorts of CD and UC patients. The objective of this study is to validate diagnostic algorithms aiming to identify patients with CD or UC within a cohort of biological drugs users in gastroenterological setting, using claims database of a Local Health Unit (LHU) of Southern Italy.

METHODS: Among one million inhabitants from Caserta LHU, patients with at least one dispensing of biological drugs indicated for CD or UC were identified in the years 2015-2018. Confirmed diagnoses of CD and UC were available for a subpopulation of biological drug users, using electronic therapeutic plans (gold standard cohort). Biological drug users receiving electronic therapeutic plans with indication for use related to other diseases other than IBDs were excluded. Biological and non-biological drugs dispensing

with exclusive indication for CD or UC from electronic therapeutic plan, IBDs-related ICD9-CM codes (CD:555.xx; UC:556.xx) as primary/secondary causes of hospital admissions and exemption codes (009.555 for CD and 009.556 for UC) were the variables considered for IBDs coding algorithms development. Five algorithms for each disease (i.e. CD or UC) were developed. Sensitivity (Se), specificity (Sp), accuracy as well as positive (PPV) and negative (NPV) predicted values were estimated.

RESULTS: Among a total population of about 1 million inhabitants from Caserta LHU in the study period, 855 (0,1%) had at least an electronic therapeutic plan associated with the use of a biologic drug for treatment of IBDs. 138 (16.1%) biological drug users had IBD diagnosis reported in at least one electronic therapeutic plan; among these, 83 (60.1%) subjects had a certain indication of use for CD and 51 (36.9%) for UC. The algorithm 1 for CD, based on specific diagnosis code (i.e. ICD-9 555.xx) OR exemption code (009.555 OR 555),showed a good Se (91.6%), Sp (98.6.0%), accuracy (97.9%), NPV (99.1%) and PPV (87.4%). The algorithm 5 for UC, based on specific diagnosis code (i.e. ICD-9 556.xx) OR non-biological drugs dispensing with exclusive indication for CD (i.e. mesalazine, balsalazide, budesonide), showed Se (74.5%), Sp (96.9%), accuracy (95.6%), NPV (98.4%) and PPV (60.3%).

CONCLUSION: Diagnostic and exemption codes in combination with drug-utilization patterns can be used to identify IBDs and further differentiate patients with CD or UC within a cohort of biological drugs users in gastroenterological setting.

Difficulty of Validating Real-World Data Findings Due to Insufficient Details of the Publication – An Example of Replicating a Real-World Data Study

Yu-Chia Hsu[1]

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BACKGROUND: Data transparency and replicability are essential for real-world data (RWD) to be trusted and recognized as real-world evidence (RWE), especially when comparing the results from randomized clinical trials. Published RWD studies should have sufficient details for other researchers to validate the findings with another dataset. Stapff et al (World J Diabetes. 2018 Dec 15; 9(12): 252–257) used an Electronic Health Records (EHR) dataset to assess the results of EMPA-REG OUTCOME (NCT01131676). Stapff attempted to show that Sodium-Glucose Co-Transporter-2 inhibitors (SGLT-2 inhibitors) decrease incidence of stroke or myocardial infraction (MI) than Dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitors). However, EMPA-REG OUTCOME trial found no significant differences in the incidence of stroke or MI between empagliflozin and placebo.

OBJECTIVE: The objectives are to validate Stapff's study and to identify the difficulties that might occur during the replication of this published RWD study.

METHODS: The RWD source was an EHR dataset from a large Midwest health system in the US. We followed Stapff's protocol to define our cohort. The outcome of interest is the composite cardiovascular event (stroke or MI). Relative Risk (RR) were calculated by dividing the risk of composite cardiovascular event in SGLT-2 inhibitor users by the risk of DPP-4 inhibitors users. Five potential confounders (age >60, hypertension (HTN), chronic kidney disease (CKD), insulin use and metformin use) suggested by Stapff were

used as subgroup analysis to examine the RR across strata. While Stapff didn't use propensity score (PS) matching, we further examined the results robustness with 1:1 PS matching with all covariates (age, gender, low- and high-density lipoprotein cholesterol, CKD, HTN, metformin user and insulin use). All data analysis was done in Python v3.9 and Microsoft SQL v18.

RESULTS: A total of 11,495 patients were identified: 3454 SGLT-2 inhibitors users and 8041 DPP-4 inhibitors users. Compared to the RR 0.63 [0.60-0.66] found from Stapff, we found the RR to be 0.47 [0.40-0.56]. In all strata, the RR ranged between 0.44 to 0.58, which is similar with 0.62 to 0.81 found from Stapff. The RR after PS matching is 0.76 [0.62-0.93]. In each strata after PS matching: RR = 0.89 [0.68-1.18] for age >60; RR = 0.83 [0.65-1.05] for HTN; RR = 0.79 [0.46-1.37] for CKD; RR = 0.72 [0.49-1.05] for insulin users; and RR = 0.61 [0.41-0.91] for metformin users. Major difficulties we encountered were 1) Drug ingredient codes not provided (RXCUI codes). 2) Insufficient/limited ICD-10-CM codes provided, no ICD-9-CM codes supplied for outcomes/comorbidities. 3) The timeframe to assess co-medications and cholesterol not defined. 4) Limited information to handle patients with both SGLT-2 and DPP-4 inhibitors.

CONCLUSION: Despite the information provided in the paper is mostly sufficient for replicability, some assumptions are still needed because of the limited level of details. We found similar RR as Stapff suggested, but all RR relatively moved toward the null (or 1) after PS matching. Further RWD studies with a well-defined protocol and confounding adequately controlled are warranted to assess the effects of SGLT-2 inhibitor versus control on the risk of stroke and MI.

Quality Assessment of Clinical Trials About Stab Minimally Invasive Therapy with Needle Knife: A Systematic Review

Yunjing Zhang[1], Shengfeng Wang[1], Yuanyuan Chen[2], Mengze Liu[2], Zhi Lin[2], Yutong Song[2], Ying Chen[2], Wanqian Guo[2], Lin Zhuo[1], Siyan Zhan[1]

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BACKGROUND: Stab Minimally Invasive Therapy with Needle Knife (SMITNK) stands for a typical acupuncture treatment in traditional Chinese Medicine. It has been long-term applied to treat tonsillitis and pharyngitis and improved by Professor Xie Qiang, featured by puncturing the affected part with needles and causes bloodletting in small quantities. A couple of clinical trials have been conducted to evaluate the effectiveness, but no quality assessment on extant studies has been completed.

METHODS: We searched Web of Science, PubMed, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wan Fang database, Chinese Biomedical Literature Database (CBM) and the Chongqing VIP Chinese Science and Technology Periodical Database (VIP) between their inception and 14 December, 2020, using the keywords "needle knife" and "Xie Qiang" both in Chinese and in English. Randomized controlled trials (RCTs) or quasi-trials associated with SMITNK were included if they reported effectiveness and their full texts were available. The Cochrane Collaboration's tool for assessing risk of bias was used for each trial. The data extraction and evaluation were conducted independently by two reviewers.

RESULTS: Of the 241 unique records identified, 12 trials in Chinese were included in our review. All authors of 12 trials were merely clinicians without methodologist involvement. Only four trials (33.3%, 4/12) had funding supports. SMITNK

was mainly used to treat acute tonsillitis (25.0%, 3/12), chronic tonsillitis (33.3%, 4/12) and acute pharyngitis (16.7%, 2/12). The primary outcome was efficacy rate defined with the decrease of syndrome scores (quantitative but based on subjective scoring) (66.7%, 8/12) or improvement of symptoms and signs (qualitative) (33.3%, 4/12). Most of the therapies received by control groups were western inventions (58.3%, 7/12). In addition, 10 claimed to be RCTs and two to be quasi-trials, but actually eight (66.7%, 8/12) misused retrospective data. Ten trials (83.3%, 10/12) mentioned randomization but only three described the detailed process (with SPSS). Besides, allocation concealment was not mentioned in any trial. Only one research (8.3%, 1/12) claimed to be single-blind but without any detail. Participants were assigned at 1:1 ratio into experimental and control groups in 10 trials (83.3%, 10/12). The sample sizes ranged from 60 to 120, but five trials (41.7%, 5/12) had insufficient sample sizes according to their reported efficacy rates and the sample size calculation formula of RCT (assuming α=0.05, β= 0.10).

CONCLUSION: Few clinical trials are about Stab Minimally Invasive Therapy with Needle Knife. However, all of them have relatively low quality, especially contain methodological errors such as misuse of retrospective data. It reflects the lack of methodological knowledge for traditional Chinese medicine clinicians and the absence of methodological experts. High-quality randomized controlled trials with enough sample sizes and standard procedures and emerging real word studies are urgently needed. Keywords: Stab Minimally Invasive Therapy with Needle Knife; clinical trials; quality assessment; systematic review

Propensity Score Matching: Why Do My Results Differ When Using SAS vs R?

Lexi René[1], Wayne Weng[1], Charlene Wong[1]

[1]*Johnson & Johnson, Medical Device Epidemiology and Real-World Data Sciences*

BACKGROUND: Researchers who run propensity score matching (PSM) in SAS® and R® may notice unexpectedly different results in matched treatment and control groups. There is little documentation explaining key differences between the function and computational methods of PSM used in SAS® and R®.

OBJECTIVE: To examine the discrepancies in the matching methodologies using the greedy nearest neighbor method with a set caliper between the PSMATCH in SAS® and MATCHIT in R®.

METHODS: PSMATCH and MATCHIT were used to perform PSM to match control and treated patients (1:1) in a dataset containing 424 records of patients with atrial fibrillation. PSMATCH and MATCHIT perform a logistic regression that create the propensity score for each patient. The greedy nearest neighbor algorithm with a caliper=0.1 was used to match treated and control patients based on 13 patient demographic and comorbidity covariates. In SAS®, the match selection prioritizes the proximity within the caliper; a caliper of 0.1 provides a maximum distance for matching treated and control patients when matching by propensity score, while R® prioritizes the highest propensity score rather than the proximity within the caliper. Standardized mean differences (SMDs) was used to examine the covariate balance distribution between the two groups; matched covariates with an absolute SMD value >=0.1 were considered imbalanced. To ensure consistency between SAS® and R®, the treatment variable was sorted in descending order setting the reference level to '1'. Unlike SAS®, sorting the treatment variable is not necessary in R®.

RESULTS: Based on the propensity scores resulting from PSMATCH in SAS® and MATCHIT in R®, the number of matched treatment (n = 97) and control (n = 97) patients were the same. However, the unique patient identifiers in the resulting matched groups differed between SAS® and R®. Similar SMD ranges were observed between the software programs (PSMATCH range, SMD 0-0.2034 vs. MATCHIT range, 0-0.2648), SMD values for select covariates differed for each software. Among the 13 covariates, both SAS® and R® had 5 common balanced covariates (SMD< 0.1) and 4 common covariates that were imbalanced (SMD >=0.1); PSMATCH resulted in one additional imbalanced covariate, while MATCHIT produced 3 additional imbalanced covariates. For further comparison, we took the absolute difference of the SMDs between the software programs, per covariate. This showed that ~70% of these differences were < 0.1, with the largest difference being 0.232.

CONCLUSION: This verification analysis highlights the differences in the PSM matching methodology used in each software program. PSM results from SAS® and R® may not provide the same matches, however, the results are similar in balancing the covariate distribution for the matched groups.

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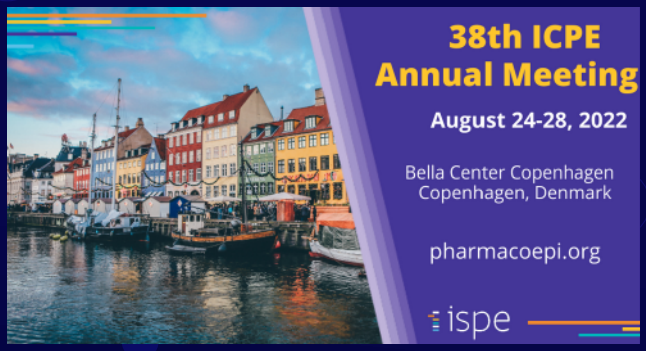

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