NORPEN 2019

Abstracts for the 12th annual NorPEN meeting

held at Moesgaard Museum in Aarhus, Denmark

14-15 November 2019


Theme: Phase IV Studies and Beyond

Hosted by: Department of Clinical Epidemiology at Aarhus University and Aarhus University Hospital

Contact: norpen2019@clin.au.dk

AARHUS UNIVERSITY

midt Central Denmark Region

LUNDBECKFONDEN

BCPT Basic & Clinical Pharmacology & Toxicology

Abstracts – invited speakers

Nikolai Brun, director of division, MD, PhD
Danish Medicines Agency

Thursday 14 November, 11.15-11.45

MESSAGE FROM REGULATOR: REGULATORY APPROVAL TODAY AND IN THE FUTURE? A SHIFT IN PARADIGM?

We are currently at a crossroads as regulators: New technologies enable us to incorporate new data sources in our regulatory evaluation of drugs and devices. A true paradigm shift with continuous benefit risk assessment based on not only Randomised trials but also real world evidence data.

Marie Louise De Bruin, professor
University of Copenhagen

Thursday 14 November, 11.45-12.15

POST-MARKETING OBLIGATIONS IN THE EU, A REGULATORY SCIENCE PERSPECTIVE ON THE PERFORMANCE OF THE SYSTEM

In spite of extensive testing of medicines before authorization, knowledge of their benefits and risks is inherently limited at the time of marketing authorization, even more so when products are authorized under the Conditional Marketing Authorisation pathway. Specific obligations, including commitments to perform post-authorisation studies (PAS) can be agreed upon between regulators and companies to resolve uncertainties about benefits and risks after authorisation. Whether these studies are actually conducted, whether this happens in an acceptable and agreed-upon timeframe, and, ultimately, whether uncertainties are indeed resolved is subject to debate. It was the topic of interest of regulatory science studies on the performance of the regulatory system in this respect.

Abstracts – invited speakers

Hedvig M. E. Nordeng, professor
University of Oslo

Thursday 14 November, 12.15-12.45

PHARMACOVIGILANCE - A EUROPEAN REGULATORY PERSPECTIVE: A CASE OF MEDICATION SAFETY IN PREGNANCY

The lecture will give examples how the PRAC works using medication safety in pregnancy and lactation as the motivation example. The Pharmacovigilance Risk Assessment Committee (PRAC) is the European Medicines Agency's (EMA) committee responsible for assessing and monitoring the safety of human medicines. The PRAC is responsible for assessing all aspects of risk management of human medicines, including: the detection, assessment, minimisation and communication of the risk of adverse reactions, while taking the therapeutic effect of the medicine into account; design and evaluation of post-authorisation safety studies; pharmacovigilance audit.

Eleanor Murray, assistant professor, ScD
Boston University

Thursday 14 November, 13.30-14.15

GUIDELINES FOR CAUSAL INFERENCE FROM PRAGMATIC RANDOMIZED TRIALS REQUIRE ANALYTIC METHODS FROM OBSERVATIONAL STUDIES

Pragmatic randomized trials are designed to address real-world questions about options for care and to guide decisions. However, the characteristics which makes these trials pragmatic – including typical patients and care settings, clinically relevant comparators, unconcealed assignment to treatment, and longer follow-up – also make them vulnerable to post-randomization confounding from incomplete adherence and post-randomization selection bias. These sources of bias are

common in observational epidemiology, and the use of analytic approaches pioneered for observational studies can improve inference from pragmatic trials. We propose causal inference guidelines tailored for the analysis of pragmatic randomized trials using methods from observational research.

Morten Andersen, professor
Copenhagen University

Thursday 14 November, 14.15-14.45

REAL-WORLD EVIDENCE: STUDIES ADDRESSING THE COMPLEXITIES OF CLINICAL PRACTICE OR WANNABE RCTS – IS IT TIME TO RETHINK THE RCT PARADIGM FOR OBSERVATIONAL STUDIES?

Real-world evidence on drug safety and effectiveness is increasingly used to inform regulatory and policy decisions. Observational studies based on data from healthcare registers are often designed and analysed to mimic clinical trials. Cohorts of new users are followed, and confounding is dealt with using propensity score techniques. Studies focus mainly on differences between drugs and frequently do not address the variation among patients. Thus, they are not informative about important issues in real-world drug use, such as risk factors for adverse reactions or subgroups of patients who may experience little benefit from the drug.

Pål Hasvold, medical evidence science leader, PhD
AstraZeneca, Oslo

Friday 15 November, 9.00-9.30

Abstracts – invited speakers

ON-TREATMENT – IMPLICATIONS FOR ITT-LIKE AND PER-PROTOCOL LIKE INCARNATIONS FOR INTERPRETING SAFETY AND EFFECTIVENESS DATA IN OBSERVATIONAL STUDIES

Randomized clinical trials are commonly analyzed by the intention-to-treat (ITT) approach (participants analyzed in the group to which they were randomized, regardless whether they received or adhered to the allocated therapy) and per-protocol (PP) approach (only participants who fulfill the protocol requirements regarding inclusion, intervention, and outcome assessments). PP is a "best-case scenario" to reveal the actual effect of the investigated therapy, whereas ITT handles the bias associated with the non-random loss of participants. The approach with complementing ITT and PP/"on treatment" analyses is sometimes applied in observational, real-world studies. However, the implications for interpreting safety and effectiveness data based on this approach in a real-world setting might raise different challenges.

Henrik Støvring, associate professor, DrMedSci, PhD, MSc
Aarhus University

Friday 15 November, 9.30-10.00

METHODS TO ESTIMATE TREATMENT DURATION: WHY WE NEED DEDICATED STATISTICAL METHODS AND HOW THE WAITING TIME DISTRIBUTION PROVIDES NEW OPPORTUNITIES

In register-based pharmacoepidemiological studies of medication effects and side-effects it is essential to determine treatment exposure at specific time points. I will present new methodologic developments based on the parametric Waiting Time Distribution with a focus on how it can be used in common study designs (cohort, case-control) and discuss how it provides a foundation for further developments in methods and applications in pharmacoepidemiology. The ultimate aim is to make the use of decision rules for prescription durations obsolete by establishing a statistically valid method for estimating medication effects and side-effects, and I will show how close (or far) we are from reaching that goal.

Lars Pedersen, professor, MSc, PhD
Aarhus University

Friday 15 November, 10.00-10.30

THE POTENTIAL OF RESTRICTING STUDY POPULATIONS IN EPIDEMIOLOGICAL STUDIES OF TREATMENT EFFECTS

Large electronic health records (EHR) are a cost-effective resource for detection of intended and unintended treatment effects. Despite their advantages, these data have been criticized for their inability to include information on confounders related to the indication of use - a particular concern in epidemiological studies of drug effects. Traditionally, these studies rely on methods such as adjustment to minimize between-group differences and in the recent literature, the major focus has been on propensity scores methods that can make use of the growing number of variables from EHR data. The strength of restricting study populations, in the conduct of epidemiological studies of drug effects, is less well appreciated. The goal of restricting is ultimately to obtain less biased effect estimates by making patients more homogenous regarding potential confounding factors. The potential of restriction will be illustrated by the findings from a Danish cohort study mimicking the design criteria of a RCT.

Jari Haukka, professor, PhD
University of Tampere and University of Helsinki

Friday 15 November, 12.45-13.05

THE PRIMARY CARE DATABASE IN FINLAND – CONTENT AND USE

The statistics on primary health care database (AvoHILMO) are based on care notifications that are collected from health care units in the public sector on the basis of personal identity numbers. Care notifications contain data on service provider and the client's/patient's municipality of residence as

well as information concerning admission, treatment, procedures and discharge. The National Institute for Health and Welfare (THL) can, on a case-by-case basis, grant permission to use registers for purposes of scientific research.

Inger Johanne Bakken, senior advisor, PhD
Norwegian Directorate of Health, Trondheim, and senior researcher, Norwegian Institute of Public Health

Friday 15 November, 13.05-13.25

THE NORWEGIAN REGISTRY FOR PRIMARY HEALTH CARE

The Norwegian Directorate of Health is responsible for two nationwide registries. These registries, the Norwegian Patient Registry (NPR) and the Norwegian Registry for Primary Health Care (NRPHC), together cover all governmental-funded health care. The NPR (specialist health care) was established in 2008, while the NRPHC (primary health care) was established in 2017. Data from the NPR are extensively used in a large variety of epidemiological studies. Data from the NRPHC will increase its importance when the registry covers a longer time period. In this talk, the NRPHC is presented as a possible future research tool.

Espen Jimenez Solem, associate professor
Copenhagen University

Friday 15 November, 13.05-13.25

THE HOSPITAL MEDICATIONS DATABASE AT COPENHAGEN UNIVERSITY

Drugs used in hospitals are often more expensive and more potent than those redeemed at community pharmacies. Still, databases containing in-hospital drug use are sparse and seldom validated. I will present our experiences with establishment and posterior validation of an in-hospital

database: EPM-research. EPM-research comprises the Capital Region of Denmark with 1.8 million inhabitants. We hope that by sharing our experience, including considerable challenges when ensuring data quality, we can help colleagues wanting to establish similar databases. Key variables and examples of relevant studies will be presented.

Kasper Adelborg, MD, PhD
Aarhus University Hospital

Friday 15 November, 13.05-13.25

THE LABORATORY INFORMATION SYSTEM DATABASES IN DENMARK

Biomarkers are used in everyday clinical practice in primary care and in the hospital setting for diagnosis, screening, monitoring, assessment of prognosis, and evaluation of treatment effects and safety. This talk provides an overview of the Danish healthcare research databases that contain information on routine individual-level biomarker data.

Helle Kieler, Professor, MD, PhD
Karolinska Institutet

Friday 15 November, 14.05-14.25

PHARMACOEPIDEMIOLOGY: QUO VADIS I

Abstracts – invited speakers

Jesper Halls, Professor, MD, DMSc
University of Southern Denmark

Friday 15 November, 14.25-14.45

PHARMACOEPIDEMIOLOGY: QUO VADIS II

Thursday 14 November, 14.45-15.30

TRIAL ELIGBILITY AND TREATMENT OUTCOMES OF CANCER MEDICINES IN A REAL-WORLD POPULATION: AN EXAMPLE FROM SCOTLAND

Tanja Mueller, Postdoctoral Research Assistant; Strathclyde Instititure of Pharmacy and Biomedical Sciences, University of Strathlcyde, Glasgow; tanja.muller@strath.ac.uk

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Jennifer Laskey, Lead Clinical Effectiveness Pharmacist; NHS Greater Glasgow & Clyde, Glasgow; Jennifer.Laskey@ggc.scot.nhs.uk

Marion Bennie, Professor of Pharmacy & Pharmacoepidemiology; Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow; marion.bennie@strath.ac.uk

INTRODUCTION
Medicines are introduced into clinical practice based on results obtained from randomised clinical trials. However, the real life clinical effectiveness of treatments can differ considerably to what has been reported from the trials.

OBJECTIVES
To describe a Scottish cohort of patients with metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide; identify potentially trial eligible patients using published criteria for enrolment in the respective clinical trials; and analyse treatment outcomes, both overall as well as for the trial-eligible subgroup of patients.

METHODS
Retrospective cohort study using routinely collected healthcare data (study period 02.2012 to 02.2017). Overall survival (OS) was analysed using Kaplan-Meier methods and Cox Proportional Hazard models.

RESULTS
Median OS in the full cohort (n=261) ranged from 10.8 (95% Confidence Interval 8.6 – 15.1) to 20.9 (14.9 – 29.0) months, depending on drug and indication (pre or post chemotherapy). Factors influencing survival included baseline performance status, and baseline prostate-specific antigen, alkaline phosphatase, and albumin levels. Only 46% of patients were potentially trial eligible; in this subgroup, OS survival was considerably higher – ranging from 13.9 (9.8 – 18.3) to 26.7 (20.4 – not reached) months.

DISCUSSION AND CONCLUSIONS
A majority of patients would not have been eligible for inclusion in the pivotal clinical trials upon which licenses for use were obtained, and poorer prognostics features of non-trial eligible patients affect real-world outcomes of cancer medicines. These are important aspects for clinicians and patients to consider in order to be able to make informed treatment decisions.

Thursday 14 November, 14.45-15.30

CHRONIC IMMUNE THROMBOCYTOPENIA IN DENMARK, SWEDEN AND NORWAY: THE NORDIC COUNTRY PATIENT REGISTRY FOR ROMIPLOSTIM

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INTRODUCTION

Population-based cohorts of immune thrombocytopenia (ITP) are useful for understanding occurrence, clinical characteristics and long-term clinical course.

OBJECTIVES

To describe the establishment and content of the Nordic Country Patient Registry for Romiplostim (NCPRR) and to provide prevalence and incidence estimates of chronic ITP (cITP).

METHODS

The NCPRR, a cohort study established in 2009, includes all adult (≥18 years) patients in Denmark, Sweden and Norway with cITP (defined as ITP lasting >12 months and platelet count <100x109/L), combining data from national health registries and medical records. The NCPRR currently includes

prevalent cITP patients diagnosed before 2009 and incident cITP patients diagnosed during 2009-2016. The registry obtains clinical information for cITP patients, including comorbidities, treatments, laboratory values, and complete follow-up for various outcomes.

RESULTS

The NCPRR currently includes 3,831 patients with cITP (1,258 prevalent; 2,573 incident). In 2009, the prevalence of registered cITP was 10.0/100,000 (95%CI: 9.1-11.0) adult persons in Denmark and 10.7/100,000 (95% CI: 9.9-11.4) adults in Sweden. During 2009-2016, the incidence rates of cITP per 100,000 person-years were 2.8 (95%CI: 2.6-3.0), 1.8 (95%CI: 1.7-1.9) and 2.1 (95%CI: 1.9-2.2) in Denmark, Sweden and Norway, respectively. Fifty-eight percent of cITP patients were women. At NCPRR inclusion, 30.2% were aged >=70 years, 23% had a platelet count <50x109/L, 17.4% were splenectomized, 41% had prior ITP therapy, and 8.6% had severe comorbidity.

DISCUSSION AND CONCLUSIONS

The NCPRR provides population-based data on the epidemiology and characteristics of almost 4,000 cITP patients and is a valuable resource for research.

Thursday 14 November, 14.45-15.30

COMPARATIVE EFFECTIVENESS OF WARFARIN, DABIGATRAN, RIVAROXABAN AND APIXABAN IN NON-VALVULAR ATRIAL FIBRILLATION: A NATIONWIDE PHARMACOEPIDEMIOLOGICAL STUDY

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INTRODUCTION

Direct oral anticoagulants (DOACs) have been as effective and safe as warfarin for stroke prevention in non-valvular atrial fibrillation (NVAF) in clinical trials.

OBJECTIVES

Compare effectiveness and safety of DOACs (dabigatran, rivaroxaban and apixaban) versus warfarin for NVAF in routine care.

METHODS

From Norwegian registries, we identified treatment-naïve patients initiating warfarin or a DOAC for NVAF from July 2013 to December 2015. We assessed prescription duration using reverse waiting time distribution. Applying a Cox model, we estimated one-year adjusted hazard ratios (HRs) for a DOAC versus warfarin for thromboembolism (ischemic stroke, transient ischemic attack or systemic embolism) and bleeding (intracranial, gastrointestinal and other bleeding).

RESULTS

We included 30,820 patients. Compared to warfarin, the HRs for thromboembolism were 0.96 (95% CI 0.71–1.28) for dabigatran, 1.12 (95% CI 0.87–1.45) for rivaroxaban and 0.97 (95% CI 0.75–1.26) for apixaban. Correspondent HRs for bleeding were 0.73 (95% CI 0.62–0.86) for dabigatran, 0.97 (95% CI 0.84–1.12) for rivaroxaban and 0.71 (95% CI 0.62–0.82) for apixaban. Versus warfarin, there were fewer intracranial bleedings with dabigatran (HR 0.28, 95% CI 0.14–0.56), rivaroxaban (HR 0.40, 95% CI 0.23–0.69) and apixaban (HR 0.56, 95% CI 0.34–0.92); fewer gastrointestinal bleedings with apixaban (HR 0.70, 95% CI 0.52–0.93); and fewer other bleedings with dabigatran (HR 0.67, 95% CI 0.55–0.81) and apixaban (HR 0.70, 95% CI 0.59–0.83).

DISCUSSION AND CONCLUSIONS

All DOACs were similarly effective as warfarin in prevention of thromboembolisms, while safety from bleedings was similar or better.

Thursday 14 November, 14.45-15.30

ESTIMATING TIME ON TREATMENT USING WAITING-TIME DISTRIBUTION (WTD) AND FIXED DAILY DOSE ASSUMPTION AMONG INITIATORS OF WARFARIN WITH NON-VALVULAR ATRIAL FIBRILLATION IN DENMARK, NORWAY AND SWEDEN

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INTRODUCTION
In patients with non-valvular atrial fibrillation (NVAF), daily dose of warfarin varies by the international normalized ratio (INR). Neither INR nor prescribed daily dose is recorded in the Scandinavian prescription registries. When censoring follow-up at treatment discontinuation, the standard assumption of constant warfarin dose may cause misclassification, which can be alleviated by use of WTD-based methods.

OBJECTIVES
We examined discontinuation of warfarin therapy by methods based on WTD and on fixed daily dose, respectively.

METHODS
Using national registries in Denmark, Norway, and Sweden we assembled a population-based cohort of all 79,171 warfarin initiators with NVAF in 2013-2016, followed through 2016. We used a reverse WTD with a log-normal backward recurrence distribution with random index dates in 2015 to make parametric-based estimation of 80th and 95th percentile (WTD80/WTD95) of the interarrival density as discontinuation criteria. For the fixed daily dose method, we estimated the

average daily dose as age- and country-specific median of the mean usages, allowing for stockpiling, and adding a 30-day grace period before recording treatment discontinuation.

RESULTS

Using WTD80, WTD95 and the fixed daily dose method, the proportion of patients classified as discontinuers 76%, 54% and 48%. The corresponding mean on-treatment periods were 12, 18 and 18 months. Among the discontinuers, 70%, 51%, and 77% had a subsequent warfarin dispensing during the remaining follow-up, including 38%, 22% and 42% within 30 days of discontinuation.

DISCUSSION AND CONCLUSIONS

Prevalence of warfarin discontinuation varies among the WTD-based and fixed-dose based methods, indicating the need for further validation.

Friday 15 November, 10.50-12.00

ARE UNEXPLAINED ADVERSE HEALTH EVENTS FOLLOWING HPV VACCINATION ASSOCIATED WITH INFECTIOUS MONONUCLEOSIS? - A DANISH NATIONWIDE MATCHED CASE-CONTROL STUDY

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INTRODUCTION

The Danish vaccination program against HPV has been threatened by reports of adverse events (AE's). Epstein Barr Virus (EBV) infection is associated with long lasting symptoms similar to the reported adverse events.

OBJECTIVES

The aim of this study was to examine if EBV is a risk factor for reporting AE's after HPV vaccination.

METHODS

The study was a nationwide register-based matched case-control study. Cases were girls vaccinated with HPV in the period 2010 throughout 2017 who reported of AE's. For each case, five controls were selected among all HPV vaccinated girls. Information about EBV was obtained from the Danish Microbiology Database and assessed for three time periods: 1) before first HPV vaccination, 2) around time of HPV vaccination, 3) the total study period. Multiple logistic regression was used to calculate OR's (95% CI) for the association between EBV and reported AE's adjusting for the matching variables and region of residence.

RESULTS

We identified 1,406 cases and 7,030 controls. A higher proportion of cases 237 (17%) than controls 348 (5%) were tested for EBV in the study period. However, only 72 (1.0%) controls and 28 (2.0 %) cases had an acute/recent EBV infection. In all three time periods cases had higher odds for testing both positive and negative for EBV antibodies than controls.

DISCUSSION AND CONCLUSIONS

In conclusion, EBV cannot be excluded as an explanatory factor for a small proportion of females. However, the findings are more likely explained by the fact that a larger proportion of females reporting of AE's were tested for EBV.

Friday 15 November, 10.50-12.00

THE ROLE OF SOCIOECONOMIC FACTORS ON DISCONTINUATION OF INSULIN DURING PREGNANCY - METHODOLOGICAL CHALLENGES FROM A SWEDISH REGISTER BASED STUDY

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INTRODUCTION
In pregnancy, medication use is generally low. Lower socioeconomic status (SES) may be associated with low medication use. This is problematic since continuous antidiabetic medication use, especially with insulin, is crucial for diabetes management. However, little is known about discontinuation of insulin in pregnant women.

OBJECTIVES
To measure the association between SES factors and insulin discontinuation during pregnancy in women using insulin prior to pregnancy in Sweden.

METHODS
All pregnancies recorded in the Swedish Medical Birth Register from 2006 to 2016 in women receiving insulin prior to pregnancy were identified (N=6029). Discontinuation of insulin was defined by not receiving a refill within 120 days from the previous refill. Associations between discontinuation and SES factors were investigated via logistic regression. Sensitivity analyses were performed using different definitions of discontinuation.

RESULTS
In 34.2% of the pregnancies, women discontinued insulin use. The odds ratios of discontinuation of insulin were 1.17 (95% confidence intervals (CI): 1.01-1.37) for women with lower household disposable income, and 1.14 (95% CI: 1.01-1.29) for women with lower educational level. When a maximum refill gap change from 91 days to 180 days was tested, women with lower educational levels and born in non-Nordic countries showed greater associations with discontinuation.

DISCUSSION AND CONCLUSIONS

The definition of discontinuation affects the level of association of SES factors and discontinuation. Nevertheless, discontinuation of insulin is common in Sweden especially in the lower socioeconomic groups. The inequality in insulin use behavior is worth noting.

Friday 15 November, 10.50-12.00

THE EFFECT OF PRENATAL EXPOSURE TO BENZODIAZEPINES AND Z-HYPNOTICS ON BIRTH WEIGHT AND OTHER PERINATAL OUTCOMES

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INTRODUCTION

Benzodiazepines (BZDs) and z-hypnotics are used in approximately 1% of pregnancies in the Nordic countries. Earlier studies have suggested that these medications may be associated with increased risk of preterm delivery.

OBJECTIVES

To estimate the effect of BZDs and z-hypnotics on immediate birth outcomes.

METHODS

We used self-reported exposure data (ever/never use, timing of use, and duration of use of BZDs/z-hypnotics during pregnancy) from the Norwegian Mother, Father and Child Cohort Study. Data on the outcome variables (birth weight, gestational age at delivery, z-score for birth weight relative to gestational age and sex, and other immediate birth outcomes) is from the Norwegian Medical Birth Registry. We used marginal structural models to account for confounding by baseline factors (maternal social and health-related covariates) and time-dependent factors (anxiety/depression and co-medication use during pregnancy).

RESULTS

We included 82 038 singleton pregnancies, of these 679 (0.8%) were exposed to BZDs/z-hypnotics during pregnancy. BZD/z-hypnotic use during pregnancy was associated with a reduction in birth weight by 79 gram (95 % CI: -127g, -32g) and a reduction in gestational age at delivery by 2.1 days (95% CI: -3.3, -0.9). We found no impact on the child's birth weight relative to gestational age (z-score) or on any other immediate birth outcomes.

DISCUSSION AND CONCLUSIONS

The absence of an effect on the z-score for birth weight relative to sex and gestational age suggests that the apparent reduction in birth weight is explained by earlier delivery rather than impaired intrauterine growth.

Friday 15 November, 10.50-12.00

SAFETY OF MODAFINIL IN PREGNANCY

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INTRODUCTION

The safety of modafinil during pregnancy is unknown due to limited data. A warning from the authorization holders of modafinil products was disseminated in June 2019. They found an increased 15% to have congenital malformations compared to 3% in the background population.

OBJECTIVES

To determine if use of modafinil during 1st trimester of pregnancy increases the risk of congenital malformations.

METHODS

In this cohort study we identified pregnancies during 1998 through 2017 with 1-year follow-up. Using Danish registries, we identified women with a pregnancy surpassing the anomaly scan at 18 weeks of gestation. We excluded women migrating within two years prior to delivery, unknown gestational age, diagnosis of chromosomal malformations, or exposure to known teratogenic drugs. Modafinil exposure was defined as ≥1 prescription overlapping with 1st trimester of pregnancy based on DDD per prescription. Methylphenidate was used as an active comparator. A second comparator group consisted of pregnancies unexposed to modafinil and methylphenidate. The main outcome was rates of major congenital malformations.

RESULTS

Looking at 1st trimester exposure, 49 women were exposed to modafinil, 965 to methylphenidate, and 1,209,331 were unexposed to modafinil and methylphenidate. Modafinil exposure was associated with increased risk of major malformations when comparing to methylphenidate (6/49 [12.2%] vs 42/965 [4.4%], adjusted odds ratio, 3.4, 95% CI, 1.2-9.7), and (43,099/1,209,331 [3.6%], adjusted odds ratio 2.7, 95% CI, 1.1-6.9) when compared to unexposed pregnancies.

DISCUSSION AND CONCLUSIONS

Modafinil seem to increase the risk of congenital malformations and should be avoided during pregnancy.

Friday 15 November, 10.50-12.00

COMPARATIVE SAFETY OF ANTIEPILEPTIC DRUGS AND RISK OF MAJOR CONGENITAL MALFORMATIONS

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On behalf of the Nordic Pregnancy drug Safety Studies (NorPreSS) Consortium

INTRODUCTION

The teratogenic potential of antiepileptic drugs (AEDs) has been recognized for decades but many patients require treatment during pregnancy. Direct comparison between AEDs will aid treatment decisions. Lamotrigine has the most evidence for safety in pregnancy and is used for a range of epilepsy types and other indications.

OBJECTIVES

To determine which AEDs are associated with an increased risk of any major congenital malformation (MCM), compared to lamotrigine monotherapy.

METHODS

We carried out a cohort study using data from birth and prescription registries from Denmark, Finland, Iceland, Norway, and Sweden. We compared first trimester use of monotherapy of carbamazepine, valproate, pregabalin, oxcarbazepine, levetiracetam, gabapentin, and topiramate to lamotrigine. MCMs were identified by ICD-9/10 codes mainly recorded within one year of birth. We estimated RRs and 95% confidence intervals, adjusted for maternal age, birth year, and co-medication. We pooled estimates with fixed-effects meta-analyses.

RESULTS

In total, n=6462 births were exposed to lamotrigine and n=8511 to other AEDs of interest as monotherapy. Compared to lamotrigine, there was an increased risk of MCM associated with valproate (pooled adjusted RR 1.7, 1.2-2.1) and topiramate (1.6, 0.9-2.3) with stronger estimates when we required at least two filled prescriptions. We found no differences for carbamazepine (0.8, 0.5-1.0), pregabalin (1.0, 0.7-1.4), oxcarbazepine (1.1, 0.6-1.5), or gabapentin (0.9, 0.5-1.4), and lower risk for levetiracetam (0.6, 0.3-0.9).

DISCUSSION AND CONCLUSIONS

Among the most commonly used AEDs, valproate and topiramate are associated with the highest risk of malformations, whereas levetiracetam is associated with the lowest risk compared to lamotrigine.

Friday 15 November, 10.50-12.00

THE ONE PERCENT

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Measures of inequality, such as the Gini coefficient and income shares, are frequently used when analysing economic data but have rarely been applied to drug utilisation. Large inequalities in drug utilisation have previously been shown to be a marker of drug misuse. Using these measures in large-scale health databases may thus identify drugs with an unsuspected misuse potential.
In this study we aimed to describe and screen the Danish population's drug use for unequal drug use patterns. Data from the Danish national prescription registry for the year of 2018 were analysed. Drugs administered intravenously or without a defined daily dose were excluded. The Gini coefficient, the fraction of cumulated drug use attributable to the highest percentile (1-percentile ratio) and their mean DDD used per day were calculated, and an inverse Lorenz curve was plotted for each drug. Signals were sorted in descending order according to Gini coefficient and 1-percentile ratio.

43,890,792 prescriptions and 2,474,195 individuals were analysed. The three drugs with the highest Gini coefficient were methylprednisolone, docusate sodium (administered rectally) and oxycodone. The highest 1-percentile ratio was found for methylprednisolone, cyclizine (sedating antihistamines) and loperamide.

Of these, especially the signal for cyclizine warrants further investigation. Cyclizine can increase the sedating effect of alcohol and other drugs, can cause hallucinations in high doses and is sold as an over-the-counter drug, with only 6% of the drug's actual use being captured.

Thursday 14 November, 16.00-16.40 – Pharmacoepi Slam, session 1

RISK OF INFECTIONS AMONG INDIVIDUALS WITH PSORIASIS IN SWEDEN: A NATIONWIDE COHORT STUDY COMPARING SECUKINUMAB TO USTEKINUMAB

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INTRODUCTION

Psoriasis is a chronic inflammatory disease. Biologics secukinumab and ustekinumab are effective for psoriasis management. However, clinical trials of these biologics highlight safety concerns such as infections.

OBJECTIVES

To determine risk of infections among secukinumab users compared to ustekinumab users in an outpatient setting using dispensed systemic antibacterials as proxy for infections.

METHODS

Swedish population-based register-linked cohort study on individuals with psoriasis and psoriasis arthritis treated with secukinumab (2015 – 2017) and ustekinumab (2009 – 2017). Dispensed systemic antibacterials (ATC code J01 and subgroups) were used as proxy for any infection, respiratory tract infection, and urinary tract infection. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were estimated using Cox regression.

RESULTS

1955 new users of secukinumab and ustekinumab were identified. The incident rates for being dispensed systemic antibacterials per 1,000 person-days were 1.10 (95% CI 0.98 - 1.24) and 0.61 (0.56 - 0.66) for secukinumab and ustekinumab users, respectively. There was a slightly increased risk of infections in secukinumab users compared to ustekinumab users (aHR 1.28 [95% CI 1.09 - 1.50]). This increase was driven by increased risk of respiratory tract infections (aHR 1.23 [95% CI 1.03 - 1.48]). No association was observed for urinary tract infections. The majority of dispensed prescriptions were prescribed by physicians in primary care.

DISCUSSION AND CONCLUSIONS

We observed a slightly increased risk of infections treated in outpatient setting in secukinumab compared to ustekinumab users. Larger studies with longer follow-up are needed to draw conclusions on the safety of these drugs.

Thursday 14 November, 16.00-16.40 – Pharmacoepi Slam, session 1

STATIN THERAPY AND DEVELOPMENT OF NEUROPATHY IN DIABETES: A NATIONWIDE COHORT STUDY

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INTRODUCTION

Diabetic polyneuropathy (DPN) affects up to 50% of all patients with diabetes and is associated with major morbidity and mortality. It is plausible that statin therapy may prevent DPN through its lipid-lowering and pleiotropic anti-inflammatory effects. However, the impact of statin therapy on DPN risk remains controversial.

OBJECTIVES

To investigate the impact of statin therapy on development of DPN.

METHODS

Using data from Danish medical health databases, we conducted a 15-year nationwide population-based cohort study including all adults with a first-time diagnosis of diabetes, 2002-2016. Risk of developing DPN was assessed among new users, prevalent users, and never users of statins. DPN was defined by a newly validated algorithm including ICD-10 E- and G-chapter diagnosis codes. We followed patients from 6 months after initial diabetes diagnosis until first-time DPN, death, emigration, or study end, using Cox proportional hazard regression models to adjust for potential confounding factors.

RESULTS

Among 282,292 incident diabetes patients, 59,641 (21%) initiated new statin use within 6 months before to 6 months after their diabetes diagnosis, and another 75,587 (27%) were prevalent statin users before that time. Over mean follow-up of 6.7 years, incidence rates per 1000 person-years were 4.0 for new-users, 3.7 for prevalent users, and 3.5 for never users. Adjusted hazard ratio for DPN was 1.04 (95% CI, 0.98-1.11) in new users and 0.95 (95% CI, 0.89-1.01) in prevalent users, as compared with statin never-users.

CONCLUSION

Statin therapy, initiated before or around the time of first diabetes diagnosis, were not associated with subsequent DPN.

Thursday 14 November, 16.00-16.40 – Pharmacoepi Slam, session 1

FATAL LOPERAMIDE INTOXICATIONS IN SWEDEN, 2011 – 2017

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INTRODUCTION

Loperamide is a synthetic opioid. It is absorbed and concentrated in the gut and reduces peristalsis in the intestines, thus controlling symptoms of diarrhoea. It has a very low bioavailability and do not readily cross blood-brain-barrier. Thus in clinical doses it has no central nervous system activity. However when overdosed, there is a risk for central nervous effects and cardiac toxicity. During the last few years there has been several reports of fatal intoxications with loperamide.

OBJECTIVES

We aimed to described the prevalence of loperamide caused fatalities and post-mortem concentrations of the drug.

METHODS

The National Forensic Toxicology Database where used to identify Swedish residents, who died do to intoxications between 1/1/2011 and 31/12/2017 in who loperamid where detected. The same register where also used to obtain the post-mortem concentrations.

RESULTS

We found 35 cases where loperamide was causing or contributing to the death. In eleven cases loperamide intoxication was considered as the cause of death. In the other cases were poly-intoxications, or there were other pathological conditions contributing to the death. The eleven cases where the death was attributed to loperamide showed a concentration range between 0.07 – 0.78, median 0.12 microgram per gram blood. This is in accordance with other publications of series of loperamide-related deaths. In 14 cases pregabalin and/or gabapentin were found.

DISCUSSION AND CONCLUSIONS

When taken loperamide in high doses there is a real risk of fatal intoxication. The danger with a concomitant intake of other substances affecting P-glycoprotein should be considered.

Thursday 14 November, 16.00-16.40 – Pharmacoepi Slam, session 1

HIGH INAPPROPRIATE USE OF PRESCIPTION OPIOIDS IN PATIENTS WITH INCIDENT KNEE OR HIP OSTEOARTHRITIS

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INTRODUCTION

Opioids are not endorsed by clinical guidelines for early stage osteoarthritis (OA).

OBJECTIVES

To estimate the incidence of opioid dispensing within the first year of OA diagnosis.

METHODS

We used linked data on persons aged 35 years or older from Skåne Healthcare Register and the Swedish Prescribed Drug Register. Incident knee or hip OA was defined a new diagnosis between Nov 1st 2012 and Oct 31st 2014 (day of diagnosis = index date, randomly sampled for persons with no OA). The outcome was any dispensed opioid (ATC codes N02A) within first year of diagnosis. Persons with prior opioid dispensing (2 years) or a cancer diagnosis were excluded. Opioid dispensing within 30 days from knee (NG*) or hip (NF*) surgery was also excluded.Difference in proportions of opioid dispensing between persons with and without incident knee or hip OA was estimated using inverse probability weighted regression adjustment adjusted for age, sex, income,

level of education, residential area, civil status, country of birth and other comorbidities associated with opioid use.

RESULTS

In total, 5,866 of 399,670 and 2,359 of 414,216 persons developed knee and hip OA, respectively. 14.7% and 20.7% of knee and hip OA patients had an opioid dispensed within first year of diagnosis, respectively. The estimated proportion of knee OA patients with opioid dispensing attributable to knee OA was 7.4% (95%CI 6.5 to 8.4) and 12.8% (95%CI 11.1, 14.4) for hip OA.

DISCUSSION AND CONCLUSIONS

Half of opioids dispensed to patients with a new knee or hip OA diagnosis are inappropriate according to current treatment guidelines.

Thursday 14 November, 16.00-16.40 – Pharmacoepi Slam, session 1

USE OF PSYCHOTROPIC DRUGS AND OTHER TIC SUPPRESSING MEDICATIONS IN CHILDREN AND ADOLESCENTS WITH A TIC DISORDER IN DENMARK

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INTRODUCTION

There is limited evidence available to guide the choice of treatment of tics and treatment mostly relies on clinical experience and individual preferences.

OBJECTIVES

To describe the use of psychotropic drugs and other tic suppressing medications in children with a newly diagnosed tic disorder in Denmark.

METHODS

Using the Danish nationwide health registries, we identified all children 6-17 years old who were diagnosed with a tic disorder for the first time during 2006-2017. We extracted data on filled prescriptions for psychotropic drugs and other tic suppressing medications.

RESULTS

The one-year prevalence proportion for the use of psychotropic drugs and other tic suppressing medications was 36.3%. The most common medications used were ADHD medication (24.8%) and antipsychotics (10.5%). Use varied according to age, sex and type of tic disorder. Over time less children with tic disorders were medicated (31.8%) and aripiprazole played a larger role at the expense of risperidone. Treatment was mainly initiated by specialists.

DISCUSSION AND CONCLUSIONS

The majority of children with tic disorders were not medicated during the first year after diagnosis, however the need for medication extended beyond the first year. Contrary to what has been observed in children with other neurodevelopmental disorders, there was a decrease in the number of children who was medicated over time. The shift from risperidone towards aripiprazole is in line with the emerging evidence for the efficacy of aripiprazole to treat tics. Treatment of tics was mainly handled by specialists which is reassuring giving the lack of national guidelines.

Thursday 14 November, 16.00-16.40 – Pharmacoepi Slam, session 1

THE USE OF MEDICINES THAT SHOULD BE AVOIDED AMONG OLDER PERSONS IS DECREASING IN FINLAND

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INTRODUCTION

Fimea collects yearly register data on the use of medicines and their costs among Finnish older population. We follow changes that occur in polypharmacy and the use of medicines that should be avoided in older persons (D-class in Meds75+ database). Meds75+ is a consensus-based tool for evaluating the appropriateness of medicines for the use of older persons. It supports the clinical decision-making and improve the medication safety in primary health care.

OBJECTIVES

The aim of our report was to produce information on the prevalence of excessive polypharmacy (10 or more medicines in use) and the use of D-class medicines among Finnish population aged 75 years or older.

METHODS

Data on reimbursed medicine purchases are from prescription register maintained by the Social Insurance Institution, Finland. Indicators were: 1) proportion of those who have purchased 10 or more medicines during a 4-months period and 2) proportion of those who have purchased D-class medicines during a 1-year period.

RESULTS

Every tenth older persons had excessive polypharmacy, and this proportion have remained same over the four-year follow-up period between 2015 and 2018. Every fourth had purchased D-class medicines in 2015. This proportion is decreasing, thus every fifth had used these medicines in 2018.

DISCUSSION AND CONCLUSIONS

Based on the indicator data the quality of medication in older persons seems to be improving, especially the use of D-class medicines is decreasing. This positive trend may be reflection of the long time work and efforts done by many stakeholders in promoting rational use of medicines in Finland.

Thursday 14 November, 16.00-16.40 – Pharmacoepi Slam, session 1

METFORMIN FOR TREATMENT OF GESTATIONAL DIABETES AND RISK OF DELIVERY BY CAESAREAN SECTION

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INTRODUCTION

In 2015, Swedish guidelines adopted metformin as a suitable antidiabetic medication (ADM) for treatment of gestational diabetes mellitus (GDM). Thus, there is a need for studies on the safety and effectiveness of metformin compared to insulin with regards to obstetrical outcomes.

OBJECTIVES

To determine whether there is an association between the use of metformin and delivery by caesarean section compared to insulin for the treatment of GDM.

METHODS

All singleton pregnancies registered in the Swedish Medical Birth Register from 2006-2016 were linked to the Prescription Drug Register. Women with a first dispensation of ADM in the second or third trimester were identified. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for the association between the class of ADM (insulin, metformin, or both) and caesarean section, adjusted for potentially relevant confounders.

RESULTS

Of all pregnancies pharmacologically treated for GDM (n=5,269), 93%, 4%, and 3% were dispensed insulin, metformin, or both, respectively. Metformin use increased substantially from 2014 onward. The adjusted OR for caesarean section in metformin users was 0.72 (95%CI 0.52–0.98) and 1.39 (95%CI 0.96–1.99) in pregnancies using both insulin and metformin, compared to pregnancies with insulin use only.

DISCUSSION AND CONCLUSIONS

Use of metformin alone did not lead to a higher odds of delivery by caesarean section. However, the severity of GDM, as indicated by use of both ADM, may influence the mode of delivery. As the use of metformin in pregnancy continues to rise, the influence on additional obstetrical outcomes should be evaluated.

Thursday 14 November, 16.00-16.40 – Pharmacoepi Slam, session 1

PRENATAL EXPOSURE TO NSAIDS AND RISK OF ADHD DIAGNOSIS AND SYMPTOMS: A FOLLOW-UP STUDY IN THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT STUDY

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are used in 5-15% of pregnancies and have the potential to affect child neurodevelopment. It is unknown whether prenatal exposure to NSAIDs increases the risk of child attention deficit hyperactivity disorder (ADHD).

OBJECTIVES

First, to investigate the association between timing and duration of prenatal exposure to NSAIDs and risk of ADHD diagnosis and symptoms in children in the Norwegian Mother, Father and Child Cohort (MoBa). Second, to investigate whether associations differed by maternal indication for NSAID use.

METHODS

Mother-child pairs from MoBa were included if the mother reported indications for NSAID use in pregnancy. NSAID exposure was identified by maternal self-report. Children's diagnoses of ADHD were obtained from national registries. Children's symptoms of ADHD at 5 years were measured using Conners' Parent Rating Scale-Revised. To account for time-varying exposure and confounders, marginal structural models were fitted to estimate hazard ratios and mean difference in z-scores.

RESULTS

The analyses on ADHD diagnoses and symptoms included 56 340 and 34 961 mother-child pairs respectively. There was no increased risk of ADHD diagnosis or symptoms in children exposed to NSAIDs prenatally regardless of timing. No duration-response relationship was observed for either outcome. Associations did not differ by maternal indication for NSAID use.

DISCUSSION AND CONCLUSIONS

Though it cannot be ruled out that non-differential misclassification of the exposure may have attenuated results, these findings are reassuring. The findings suggest no substantially increased risk of ADHD diagnosis or symptoms in children prenatally exposed to NSAIDs, regardless of timing or duration.

Thursday 14 November, 16.50-17.30 – Pharmacoepi Slam, session 2

BETA-BLOCKER CHOICE AND EXCHANGEABILITY IN PATIENTS WITH HEART FAILURE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE: AN ITALIAN REGISTER-BASED COHORT STUDY

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INTRODUCTION

Clinical guidelines suggest that for patients with heart failure (HF) and concurrent chronic obstructive pulmonary disease (COPD), metoprolol/bisoprolol/nebivolol should be preferred over carvedilol. However, studies suggest a high proportion of carvedilol usage that remains unexplained.

OBJECTIVES

We aimed to investigate the predictors of carvedilol choice in patients with both diseases.

METHODS

Caserta databases (Italy) were used as data sources. Age, sex, chronic/acute comorbidities, and co-medications were included in a logistic regression model to assess predictors of carvedilol choice. Chronic comorbidities all hospitalizations within two years before the first beta-blocker (BB) prescription. Comedications include all redeemed prescriptions within one year before the BB prescription. Kernel density estimations were used to assess the overlap in propensity/preference scores distributions for receiving carvedilol and thereby potential BB exchangeability.

RESULTS

Totally, 10091 patients composed the study population; 2011 were exposed to carvedilol. The overlapping of propensity scores distributions was 57%. Accordingly, the exchangeability was not reached. Atrioventricular block (Odds Ratio, OR 8.20; 95% Confidence Interval, 95% CI 1.30–51.80), cerebrovascular thrombosis (OR 7.06; 95% CI 1.14–43.68), chronic kidney disease (OR 4.32; 95% CI 1.16–16.02), and acute HF (OR 1.97; 95% CI 1.28–3.03) hospitalizations were statistically significantly associated with carvedilol choice. Analogously, human insulin (OR 3.00; 95% CI 1.24–7.24), fondaparinux (OR 2.47; 95% CI 1.17–5.21) or strontium ranelate (OR 2.03; 95% CI 1.06–3.90) redeemed prescriptions.

DISCUSSION AND CONCLUSIONS

We found the absence of BBs exchangeability and a preferential choice of carvedilol in specific clinical scenarios.

Thursday 14 November, 16.50-17.30 – Pharmacoepi Slam, session 2

PRELIMENARY RESULTS: GP ATTENDANCE IN PROXIMITY TO HPV VACCINATION: A CASE-COHORT STUDY ON EXPERIENCING SUSPECTED ADVERSE EVENTS

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INTRODUCTION

Studies on girls experiencing suspected adverse events after HPV-vaccination show increased morbidity prior to vaccination compared to other HPV-vaccinated. This may indicate that their symptoms have not occurred recently, and it is therefore important to examine whether there is a temporal link between vaccination and experiencing symptoms.

OBJECTIVES

To examine whether possible changes in GP attendance occurs following vaccination, and whether possible changes in GP attendance occurs in temporal link to vaccination.

METHODS

Cases were referred to an HPV-center and matched with HPV-vaccinated controls on selected variables. Negative binomial regression were used to examine GP attendance patterns prior to and after vaccination. An interaction term between case/control status and GP contacts before/after

vaccination was used to estimate possible changes in GP attendance. Analyses were stratified on vaccination year (2008-2009, 2010-2012 and 2013-2014) and 12 months prior to and after vaccination.

RESULTS

GP contacts for cases rise in the first year after vaccination, with incidence rate ratios (IRR) between cases and controls increasing 35% [31% ; 39%] after vaccination compared to prior. Stratification on vaccination year show similar increases in IRR. Restricting to 12 months prior to and after vaccination show that increase occurs 0-3 months after vaccination.

DISCUSSION AND CONCLUSIONS

This study shows that cases increase in GP contacts in close proximity to HPV-vaccination. It is however not possible to conclude a causal link to HPV-vaccination. Symptoms may be of temporal coincidence and would have occurred irrespectively, or vaccination may trigger unknown pathways for increased illness. Note this is preliminary results and should be cautiously interpreted.

Thursday 14 November, 16.50-17.30 – Pharmacoepi Slam, session 2

THE DANISH NATIONAL MULTIPLE MYELOMA REGISTRY (DMMR): A COMPREHENSIVE CLINICAL DATABASE

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Denmark has a long tradition for recording healthcare information in administrative and healthcare registries, and among these are the Danish clinical quality databases covering the entire Danish population. The clinical quality databases cover a large number of different specialties including cardiovascular disease, surgery and emergency room contacts, cancer and cancer screening, psychiatry, gynaecology and obstetrics and chronic disease. The haematological malignancy database is one example of a nationwide population-based clinical quality database. This database was established in 2005 and contains information on all new cases of lymphoma, leukaemia, chronic myeloproliferative disorders and multiple myeloma in Denmark. The Danish National Multiple Myeloma Registry (DMMR), part of the haematological malignancy database, holds information on all new cases of multiple myeloma, smoldering multiple myeloma, solitary plasmacytomas and plasma cell leukaemia in Denmark accumulating altogether 350 new cases annually. The DMMR comprises a large number of clinically relevant variables including information on patient demographics, performance status, cancer cytogenetics, disease stage and complications such as hypercalcaemia, anaemia, renal impairment and lytic bone disease. Moreover, detailed information on anti-myeloma treatment at diagnosis and at relapse, and treatment response are recorded. The DMRR can be linked with other healthcare registries in Denmark to obtain information on relevant variables such as comorbidity, supportive care, hospital admissions, and skeletal-related events. The DMMR is a comprehensive clinical database, which can facilitate accurate descriptions of the epidemiology of multiple myeloma in Denmark and is an important tool for research and a source for data from standard clinical practice.

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Thursday 14 November, 16.50-17.30 – Pharmacoepi Slam, session 2

THE UTILIZATION OF FIRST AND SECOND-GENERATION ANTIPSYCHOTIC DRUGS IN DENMARK FROM 1999 TO 2017: A STUDY USING POPULATION-BASED DATA.

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INTRODUCTION

Both first generation antipsychotics (FGA) and second-generation antipsychotics (SGA) are known to cause serious adverse events, that may eventually cause relapses of the psychotic disorders. Despite the wide usage of antipsychotic drugs, little information is available on longitudinal utilization patterns and the use in specific-age groups.

OBJECTIVES

To analyze the consumption of antipsychotic drugs in Denmark with a focus on the transition from FGA to SGA and the utilization pattern of SGAs.

METHODS

Nationwide data on outpatients' purchase of antipsychotic drugs was obtained from national statistics on the total drug sales in Denmark (Medstat.dk) during the period 1999 - 2017. The annual use in million DDDs (MDDD) and the number of users was retrieved for FGA, SGA, and single substances (ATC codes), stratified on 5-year age groups and sex. The one-year prevalence of use and average consumption in DDD/user/year was calculated for all strata.

RESULTS

The total consumption of FGA decreased from 9.180 in 1999 to 2.743 MDDDs in 2017. Conversely, SGAs consumption significantly increased from 3.481 to 18.209 MDDDs). During the study period, amongst the five most used SGAs- clozapine, olanzapine, quetiapine, aripiprazole and risperidone, there was a distinct increase in preference towards quetiapine (0.021 in 2001 to 5.926 MDDDs in 2017) and aripiprazole (0.154 in 2004 to 2.696 MDDDs in 2017) when compared to the other SGAs.

DISCUSSION AND CONCLUSIONS

Our study explored the longitudinal use of antipsychotics showing a transition from FGA to SGA and an increasing preference for quetiapine and aripiprazole during later years.

Author Disclosure Information:

Abstracts - slammers

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EXAMINATION OF PEDIATRIC PRESCRIPTIONS FOR DIABETES MELLITUS SUBGROUPS IN PRIMARY CARE

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INTRODUCTION

While initial diagnosis is mostly established by specialist physicians, primary care plays an important role in the routine management of children with diabetes mellitus (DM).

OBJECTIVES

We aimed to investigate the drugs in DM prescriptions of family physicians for their pediatric patients.

METHODS

We analyzed pediatric (0-17-year-old) prescriptions (n=1062) with single diagnosis of DM (ICD-10 Codes: E10 to E14.9) managed by family physicians selected by systematic sampling in Istanbul in 2016.

RESULTS

We determined DM prescriptions as most frequently generated for children at 17, 14, and 15 years (12.3%, 11.1%, and 10.8%; respectively), and 37.9% of these belonged to 3-11 years of age. The mean age of the patients was 12.2 ± 3.8 years and 50.1% of them were girl. In all prescriptions, those with diagnosis of type-1 DM constituted 38.0%, type-2 DM 6.8%, and the remaining 55.2% were in "other specified/unspecified DM" (E13-E14). We found that 86.2% of prescriptions contained insulin compared to 11.0% of those containing oral antidiabetic medication. Insulin glargine (37.8%), insulin lispro (20.1%) and insulin aspart (13.9%) were the most commonly prescribed drugs for type-1 DM whereas metformin ranked the number one (31.1%) in type-2 DM, followed by insulin glargine (23.3%) and insulin lispro (15.5%).

DISCUSSION AND CONCLUSIONS

Family physicians seem to prescribe antidiabetic medications using comparably vague DM diagnostic codes other than type-1/type-2 in at least one of every two encounters in pediatric population. While higher prescribing of insulin could be well expected in type-1 DM, substantial prescribing rates in type-2 DM could be regarded as remarkable in primary care.

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THE ROLE OF CARDIOVASCULAR, ANTILIPEMIC AND ANTIDIABETIC DRUGS IN RISK OF DEATH IN ELDERLY USERS OF ANTIPSYCHOTIC MEDICATIONS: PHARMACOEPIDEMIOLOGIC STUDY

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INTRODUCTION

Recent research on elderly patients suggests that use of antipsychotics may increase risk of hospitalization or death. These drugs have significant side effect burdens, many of them relating to cardiovascular health. Few observational epidemiologic studies looked at the major cardiovascular issues that arise in patients taking antipsychotic medication.

OBJECTIVES

The aim of this study was to determine mortality risk in elderly patients treated with antipsychotics in relation to the use of cardiac drugs, antilipemic and antidiabetic agents.

METHODS

We conducted a retrospective cohort study involving 26,639 patients 65 years of age or older who had drug insurance benefits in Gdansk voivodship and who began receiving a conventional or atypical antipsychotic medication between 2008 and 2012. Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death with different groups of antipsychotic medication, cardiovascular drugs, antilipemic and antidiabetic medications. We controlled for potential confounding variables with the use of traditional multivariate Cox models.

RESULTS

The use of cardiac medications and antilipemic drugs was associated with significantly reduced risk of death in this population (HR 0.88; 95 % CI 0.83 to 0.93 and HR 0.66; 95 % CI 0.58 to 0.75, respectively) but not antidiabetic drugs (HR 1.09; 95 % CI 0.96 to 1.24). Between 2008 and 2012, atypical antipsychotic medications were not associated with a higher adjusted risk of death than were conventional antipsychotic medications (hazard ratio [HR], 0.99 ; 95 percent confidence interval [% CI], 0.95 to 1.04).

DISCUSSION AND CONCLUSIONS

These results suggest that results suggest that attention should be paid to patients with antipsychotics with regard to proper therapy of cardiovascular diseases.

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A DOSE-DEPENDENT INCREASE IN MORTALITY IN MULTIMORBID AND NON-MULTIMORBID PATIENTS PRESCRIBED HYPNOTICS/ANXIOLYTICS. A LONGITUDINAL COHORT STUDY IN PRIMARY CARE

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INTRODUCTION

Earlier studies on mortality associated with use of hypnotics/anxiolytics have shown inconsistent results.

OBJECTIVES

To assess the risk of mortality in primary care patients, multimorbid (≥2 chronic conditions) or not, prescribed hypnotics/anxiolytics.

METHODS

Medical records from 114,084 primary care patients in the Reykjavik area (10 to 79 years of age, average 38.5, SD 18.4) were analysed according to multimorbidity or not, regular long-term use of hypnotics/anxiolytics for three consecutive years or not, defined as low dose (1-300 DDDs/3 years), medium dose (301-1,095 DDDs/3 years) and high dose (>1,095 DDDs/3 years). Those neither multimorbid nor using hypnotics/anxiolytics (55,759) comprised the reference group. Mortality was analysed in these groups, cancer patients excluded. Hazard ratios (HR) were calculated, using Cox proportional hazard regression, adjusting for age, sex and comorbid conditions.

RESULTS

During a 516,358 person-years follow-up, in total, 1,926 persons died. Mean follow-up was 4.6 years. For all multimorbid patients who took no drugs the HR was 1.14 (95% CI = 1.00 to 1.30) compared to those without multimorbidity. HRs varied from 1.49 to 3.35 (95% CI ranging from 1.03 to 4.11) with increasing doses of hypnotics/anxiolytics among participants without multimorbidity and varied correspondingly from 1.55 to 3.52 (95% CI ranging from 1.18 to 4.29) in multimorbid patients.

DISCUSSION AND CONCLUSIONS

Mortality increased in a dose-dependent manner among both multimorbid and non-multimorbid patients taking hypnotics/anxiolytics. Their use should be limited to the recommended period of two to four up to six weeks; long-term use may incur increased risk and should be re-examined.

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EXAMINATION OF GENERIC DRUG PRESCRIBING IN PRIMARY HEALTH CARE INSTITUTIONS IN TURKEY

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INTRODUCTION

Generic drug (GD) use is encouraged and special policies are developed worldwide for strategies to mitigate economic burden of drugs.

OBJECTIVES

We aimed to investigate the prescription of GDs in primary care.

METHODS

We analyzed electronic prescriptions registered to national Prescription Information System by primary care physicians in Turkey in a four-year period (2013-2016). For each year, we evaluated the number of prescriptions and drugs, cost, GD rates with their distribution by gender and age groups.

RESULTS

In total, 518,335,821 prescriptions and 1,457,034,275 drugs (annual average 364,258,569) were prescribed. Women constituted 59.3% of the population and 21.9% were <18 years. The years of the highest and lowest percentages of GDs were 2016 (54.4%) and 2014 (53.6%). This value ranged between 53.7-54.7% for women and 53.4-54.1% for men in each of the four years examined. In each year, the percentage of GDs decreased as the age group increased [highest observed in <18-year-old group (range: 64.0-64.5%) and the lowest (range: 46.0-47.1%) in >75-year-old group. The

average annual cost of all drugs was €4,211,819,844 (range: €3.93-4.46 billion), while the average cost of GDs was €1,577,245,225 (range: €1.49-1.64 billion). The ratio of generics among drug costs was highest in 2013 (37.8%) and lowest in 2014 (36.9%).

DISCUSSION AND CONCLUSIONS

In Turkey, GD prescription trends in primary care exhibits some fluctuations according to year, gender, and age group. While GDs account for slightly more than half of all prescribed drugs and approximately 37% of the cost. Cost share of GDs is noted to be higher than that reported in the literature.