11th NorPEN Meeting

Oslo 7 - 9 November 2018

From the Womb to the Grave - Life-course Pharmacoepidemiology

Program and Conference Booklet

NIPH Norwegian Institute of Public Health

EPINOR

BCPT Basic & Clinical Pharmacology & Toxicology

UiO : Universitetet i Oslo

Table of Contents

Welcome to the annual meeting for scientists in the Nordic countries working within Pharmacoepidemiology.
The aim is to present the latest results from scientific studies, to meet collaborators and to get new ideas and inspiration.

Certificate of participation: Any participant who need a certificate of participation from the 11th NorPEN Meeting, please contact Laila.torstveit@farmasi.uio.no

Program

Day 1 Wednesday 7th of November

Pre-meeting course:
11:00 – 15:30

An introduction to genetic epidemiology: Quantitative genetics, causal inference, and novel polygenic methods

The course has three modules:

1) Quantitative genetics
2) Causal inference
3) Molecular genetics

Organiser: Helga Ask, *Norwegian Institute of Public Health*

19.00-20:30	Reception at Oslo Town hall, Rådhuset, Oslo
20:30-	PhD and post doc social gathering

Day 2 Thursday 8th of November	The Womb and Youth
09:00-12:00	
Alternative I:	**An introduction to genetic epidemiology: Quantitative genetics, causal inference, and novel polygenic methods (continued)** Auditorium 1, Vilhelm Bjerknes' hus, Blindern Campus **Organiser: Helga Ask,** Norwegian Institute of Public Health
Alternative II:	**Meeting for Registry holders: Maintaining high quality and efficiency in prescription databases across the Nordic countries** Seminar room 123, Vilhelm Bjerknes' hus, Blindern Campus **Organiser: Kari Jansdotter Husabø**, Norwegian Institute of Public Health
11:30-17:40	**NorPEN Meeting** Auditorium 1, Vilhelm Bjerknes hus, Blindern Campus
11:30-12:30	Registration
12:30-12:45	Welcome! - Hedvig Nordeng, University of Oslo *Chair: Hedvig Nordeng, School of Pharmacy, University of Oslo*
12:45-13:30	Employing longitudinal trajectories to model exposure in perinatal pharmaco-epidemiology research – Kristin Palmsten, HealthPartners Institute (USA)
13:30-14:00	Mediation analysis - possibilities and pitfalls for medication safety studies in pregnancy–Jon Michael Gran, Department of Biostatistics, University of Oslo
14:00-14:15	Coffee break
	Chair: Angela Lupattelli, School of Pharmacy, University of Oslo
14:15-14:55	Pharmacoepi slam 1 (3 min presentation)
14:55-15:25	Medication Use from Cradle to Grave – the Nordic perspective Björn Wettermark, Regional Health Board, Stockholm (Sweden)
15:25-15:35	Break
15:35-16:35	Nordic collaborative studies and hot topics
15:35-15:50	Infections in children after prenatal exposure to opioids: Nordic registry study Milada Mahic (Norway)
15:50-16:05	Antidiabetic medication in pregnancy: an international drug utilization Ingvild Odsbu (Sweden)
16:05-16:20	Antipsychotic Drug Use in Pregnancy: a Multinational Database Study Johan Reutfors (Sweden)
16:20-16:35	Nordic use of antiepileptic drugs in pregnancy from 2006-2016 Jacqueline Cohen (Norway)
16:35-16:50	A meta-analysis proposal for Nordic collaborative studies - Pär Karlsson (Sweden)
16:50-17:00	Break
	Chair: Marte Handal, Norwegian Institute of Public Health
17:00-17:40	Pharmacoepi slam 2 (3 min presentation)
18:15	Meeting for departure to social dinner event
19:00-	Dinner at 'NedreLøkka Cocktailbar & Lounge'

Day 3 Friday 9th of November **Older and Wiser**
Auditorium 3, Sophus Bugges hus, Blindern Campus

Chair: Mollie Wood, School of Pharmacy, University of Oslo

09:00-09:45 Clinical epidemiology in the era of big data: new opportunities, familiar challenges – Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University Hospital (Denmark), ENCePP Steering Group 2017 - 2019

09:45-10:15 Making "RWD" a larger part of the regulatory decision-making process - with special focus on pharmacovigilance
Morten Andersen, Department of Pharmacy, University of Copenhagen

10:15-10:30 Coffee break

Chair: Milada Mahic, Norwegian Institute of Public Health

10:30-11:00 Academic Detailing using Health Registries–Harald Langaas, RELIS (Norway)

11:00-12:00 **Nordic collaborative studies and hot topics**

11:00-11:15 Association between use of azathioprine and risk of acute pancreatitis in pediatric inflammatory bowel disease: a Swedish-Danish nationwide cohort study - Bjørn Pasternak (Sweden)

11:15-11:30 Prescribed opioid analgesic use developments in the Scandinavian countries, 2006-2017 - Ashley Muller (Norway)

11:30-11:45 Non–aspirin NSAID use in the Nordic countries 2000–2016 from a cardiovascular risk perspective: a drug utilization study - *Kasper Bruun Kristensen (Denmark)*

11:45-12:00 Sodium-glucose cotransporter 2 inhibitors and risk of serious adverse events: cohort study using nationwide registers in Sweden and Denmark
Bjørn Pasternak (Sweden)

12:00-13:00 Lunch

Chair: Gun Peggy Strømstad Knudsen, Norwegian Institute of Public Health

13:00-14:40 Sharing sensitive data between the Nordic countries –
15 min presentation each + round table discussion:

15 min presentation:
TSD – revolutionizing services for sensitive data – Gard Thomassen, University of Oslo (Norway)
Tryggve – Antti Pursula, NeIC and CSC-it Center for Science (Finland)
NordMAN - Claus Göran Hjelm, Statistics Sweden (Sweden)
Statistics Denmark – Hans Ivan Thaulow, Research Services (Denmark)

Round table discussion:
Statistics Norway - Aksel Kvamme Vestfossen, Lin Hege Austad Dalen (Norway)
TSD – Gard Thomassen, University of Oslo (Norway)
Tryggve – Antti Pursula, NeIC and CSC - IT Center for Science (Finland)
NordMAN - Claus Göran Hjelm, Statistics Sweden (Sweden)
Statistics Denmark – Hans Ivan Thaulow, Research Services (Denmark)

14:40-15:00 Closing and introduction of next NorPEN Meeting in 2019

Program

About the speakers

Kristin Palmsten
HealthPartners Institute, Minneapolis, Minnesota, USA
Kristin Palmsten, ScD, is a Research Investigator at HealthPartners Institute. She earned her doctorate in Epidemiology from the Harvard T.H. Chan School of Public Health. Dr. Palmsten's research focuses primarily on evaluating the safety of medication use during pregnancy. She received a Career Development Award from the Eunice Kennedy Shriver National Institute of Child Health & Human Development to evaluate the impact of oral corticosteroid use during pregnancy on preterm birth risk. She was awarded the 2013 Abraham Lilienfeld Student Prize from the Society for Epidemiologic Research and the 2015-2016 University of California San Diego Chancellor's Postdoctoral Scholar Award.

Jon Michael Gran
University of Oslo, Norway
Jon Michael Gran is an Associate Professor at Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, University of Oslo, working on causal inference and survival analysis.

Björn Wettermark
Karolinska Institutet, Stockholm, Sweden
Björn Wettermark, M.Sc.Pharm, PhD works at the Regional Health Board in Stockholm, where he supports decision makers with various analyses on quality of care. He is currently leading a project with the aim to implement a new national system for guidelines development and quality improvement. Björn is also associate professor in pharmacoepidemiology at Karolinska Institutet with research focusing on drug utilization topics such as prescribing quality indicators, international comparisons of drug utilization, evaluation of prescribing doctors´ adherence to guidelines and intervention studies to promote rational use of drugs. He was the previous chair of the European Drug Utilization Research group.

Program

About the speakers

Vera Ehrenstein
Aarhus University, Denmark
Vera Ehrenstein is a Professor at Aarhus University, currently coordinating several international postauthorisation studies to assess benefits and risks of medicines. As a participant of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) under the aegis of the European Medicines Agency, she contributes to the development of European methodological standards in pharmacoepidemiology. She represents academia in the ENCePP Steering Group and in the Board of Directors of the International Society of Pharmacoepidemiology. Vera teaches graduate courses, supervises junior researchers and PhD students, and has more than 100 peer-reviewed publications.

Morten Andersen
University of Copenhagen, Denmark
Morten Andersen is Professor and head of the Pharmacovigilance Research Group at the Department of Drug Design and Pharmacology, University of Copenhagen, Denmark. He has a background as a clinical pharmacologist and more than 25 years of experience within pharmacoepidemiology, pharmacovigilance and drug utilisation research. His current research focus is method development in pharmacovigilance, in particular signal detection and proactive safety surveillance using big healthcare data and multi-country database networks.

Harald Chr. Langaas
Regional Medicines Information and Pharmacovigilance Centre (RELIS), Trondheim, Norway
Harald Chr. Langaas, MPharm, MPH, is head of the Regional Medicines Information and Pharmacovigilance Centre (RELIS) in Trondheim. His earlier experience includes work in hospital pharmacy, and as a manager for three primary care pharmacies. He is now also director of the Norwegian Academic Detailing Program in primary care. This program has completed two campaigns, on NSAIDs and antibiotics, and is starting the third campaign on diabetes type 2 in the autumn of 2018. Harald is working on a PhD based on evaluation of those programs.

Program

About the speakers

Gard Thomassen
University of Oslo, Norway
Gard Thomassen holds a PhD in Bioinformatics, and participated in the first exome and transcriptome sequencing of tumor/normal samples in Norway in 2010. In 2012 Thomassen became project leader for building a system for storage, analysis and collection of sensitive data (TSD) at the University of Oslo Centre for IT (USIT). TSD is now a national e-Infrastructure for research on sensitive data. TSD also delivers IT infrastructure for clinical deep sequencing at the Oslo University Hospital. Today, Thomassen is the Head of the Division for Research Computing and Assistant Director at the USIT at the University of Oslo, Norway.

Antti Pursula
NeIC and CSC - IT Center for Science, Finland
Antti Pursula works at the Finnish national e-infrastructure service center CSC as Project Director in the Research Infrastructures unit. In this role he supports research communities in solving their big data management challenges, including sensitive data management, especially in the area of health biomedical research. In addition, Antti is director of the Nordic sensitive data collaboration NeIC Tryggve that is developing and facilitating access to secure IT services for sensitive data in biomedicine on Nordic scale. His earlier work experience at CSC includes development and management of scientific software, working as Development manager and as Director for Application services unit, as well as several international project management roles over the years. He is also part of the ELIXIR Finland team.

Claus-Göran Hjelm
University of Örebro, Sweden
Claus-Göran Hjelm has worked as a IT Director at University of Örebro, Consultant Director at Sema Group, IT -Manager and Register Director at Statistics Sweden. The last year is dedicated to Research infrastructures on European and Nordic level. He has been a lecturer and consultant in more than 20 countries world-wide and has written articles and books about Register based statistics and metadata. He is also affiliated board member of international research groups and associations.

Abstracts - Invited Speakers

Thursday 8 November

Employing Longitudinal Trajectories to Model Exposure in Perinatal Pharmacoepidemiology Research
Kristin Palmsten, HealthPartners Institute (USA)

Studies of the safety of medication use during pregnancy typically classify exposures in a dichotomous manner (e.g., any use in pregnancy or by trimester) or by simple categories of dose (e.g., high vs low daily dose) or duration of use (e.g., many vs few days). However, recent studies have used clustering methods to summarize complex patterns of individuals' medication use during pregnancy. This presentation will highlight studies using longitudinal trajectory clustering methods to model medication exposure during pregnancy (i.e., oral corticosteroids, antidepressants) and will provide a review of standard statistical packages available, strengths, limitations, and future directions of the approach.

Mediation analysis - possibilities and pitfalls for medication safety studies in pregnancy
Jon Michael Gran, Department of Biostatistics, University of Oslo (Norway)

Mediation analysis is a tool to better understand the mechanisms of how treatments work, by dissecting the total effect into a direct and indirect effects (through other variables). Methods for doing such analyses have been popular in fields like social science, and especially psychology, for decades, and increasingly in fields like epidemiology.

With the recent developments in causal inference, various limitations of the earlier approaches has been pointed out. New frameworks for causal mediation analysis have been developed based on concepts such as natural direct and indirect effects and controlled direct effects.

The aim of this talk is to give a short introduction to these concepts, and the framework of causal mediation analysis, before I discuss some particular possibilities and pitfalls that are relevant to medication safety studies in pregnancy.

Medication Use from Cradle to Grave – the Nordic perspective
Björn Wettermark, Regional Health Board, Stockholm (Sweden)

The Nordic countries have a long tradition of drug utilization research, with pioneering studies conducted already in the 1960s. We were also pioneers in epidemiology with unique identifiers given to all citizens and large population-based health registries. However, pharmacoepidemiologists had to wait until mid-2000s before individual level data on dispensed prescription medicines were available at a nationwide scale in all Nordic countries. This opened a new world of possibilities. The aim of this presentation is to present an overview of opportunities and challenges in the Nordic countries studying medication during different stages of life from pregnancy and children to the elderly.

Abstracts - Invited Speakers

Friday 9 November

Clinical epidemiology in the era of Big Data: new opportunities, familiar challenges
Vera Ehrenstein, Dep. of Clinical Epidemiology, Aarhus University Hospital (Denmark)

Clinical epidemiology is the study of the outcome of illness, and pharmacoepidemiology is the study of the outcome of treated illness. Nowadays pharmacoepidemiology relies primarily and increasingly on non-experimental studies based on routinely collected data for descriptive, predictive and causal research. Large data sets reduce the random error and often yield highly statistically significant and precise results. The danger is in succumbing to the fallacy that *precise* equals *valid* and *statistically significant* equals *clinically important*. The tried-and-tested remedies include transparency, use of valid tools and methods, applying expert knowledge, and bringing randomized trials closer to the real world.

Making "RWD" a larger part of the regulatory decision-making process - with special focus on pharmacovigilance
Morten Andersen, Department of Pharmacy, University of Copenhagen (Denmark)

Morten Andersen has a background as a clinical pharmacologist and more than 25 years of experience within pharmacoepidemiology, pharmacovigilance and drug utilisation research. His current research focus is method development in pharmacovigilance, in particular signal detection and proactive safety surveillance using big healthcare data and multi-country database networks.

Academic detailing using Health registries
Harald Langaas, RELIS (Norway)

Academic detailing combines interactive educational outreach with the best evidence for a specific therapeutic topic. Specifically trained personnel, who meet clinicians one-to-one in their practices during office hours, perform the visits. The Norwegian Academic Detailing Program have completed two campaigns in Norway using data from The Norwegian Prescription Database (NorPD) for evaluation, with a third campaign starting this autumn.

This presentation will include methods and results from the two first campaigns, and discussions of these findings. Possibilities and plans for further analyses will be also be presented.

Abstracts - Invited Speakers

Friday 9 November

TSD - revolutionizing services for sensitive data
Gard Thomassen, University of Oslo, Norway

The TSD system (Services for Sensitive Data) is a University of Oslo based national e-Infrastructure made to enable safe usage of personal (health) data within research. The system today hosts more than 400 research projects and 2000 researchers. One of the main goals of the TSD system has been to automate and digitize research processes to enable new and better research in a safe and secure manner. The talk will give a brief introduction to the TSD system, and then focus on actual ongoing research hosted and enabled by TSD.

Tryggve collaboration providing Nordic services for sensitive data management
Antti Pursula, NeIC and CSC - IT Center for Science (Finland)

Successful research on topics related to human health often requires accessing, combining and processing of sensitive data of various types from different sources. However, working with human data requires advanced security measures to ensure privacy of the research subjects. The ELIXIR nodes in four Nordic countries (DK, FI, NO, SE), together with the Nordic e-Infrastructure Collaboration NeIC, have worked for several years towards providing secure e-infrastructure for cross-border human data research in the Tryggve project (neic.no/tryggve).

This presentation briefly describes the secure computing and data environments, secure clouds and other services available within the Tryggve project. In addition, examples of supported scientific use cases are introduced.

NordMAN
Claus Göran Hjelm, Statistics Sweden (Sweden)

NordMAN is a project by the Nordic National Statistical Agencies (NSI) that aims to make register data more available and visible for Nordic research projects by making routines between the Nordic NSI's and building a metadata storage with population metadata from the Nordic countries. The project was performed between 2015-2018 and all the Nordic NSI's were involved in this. The hope and next step for these activities is to involve the Nordic National Boards of Health and Welfare, since one of the outcomes of the NordMAN is that most of the Nordic research projects contain data from them and we see the benefits of having the same routines and metadata from them included in the metadata storage. Website: nordman.network

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

Comparison of long-term clinical implications of beta-blockade in patients with obstructive airway diseases exposed to beta-blockers with different β1-adrenoreceptor selectivity: an Italian population-based cohort study - **Maurizio Sessa (Denmark)**

Association between antidepressant treatment during pregnancy and postnatal self-harm ideation: a cross-sectional, multinational study using the Edinburgh Postnatal Depression Scale - **Jennifer Vallee (Norway)**

Causal mediation analysis in sibling designs: an application to estimated effects of prenatal antidepressant exposure and toddler anxiety and depressive symptoms mediated by gestational age at birth - **Mollie Wood (Norway)**

Prescription drugs in fatal accidents – prescribed or not? - **Anna K Jönsson (Sweden)**

The risk of preterm birth and small for gestational age after exposure to phthalate containing drugs during pregnancy: a nested case-control study - **Anne Broe (Denmark)**

Proton pump inhibitor use and risk of breast cancer, prostate cancer and malignant melanoma: an Icelandic population-based case-control study - **Óskar ö. Hálfdánarson (Iceland)**

Association of prenatal paracetmol exposure with neurodevelopmental outcomes in five-year-old children and the role of unmeasured confounding - **Johanne Naper Trønnes (Norway)**

How do we measure child neurodevelopment after prenatal exposure to psychotropics and analgesics? – A systematic literature review - **Sarah Hjorth (Norway)**

DOAC use but no indication; to include or not to include? - **Maja Hellfritzsch (Denmark)**

Methamphetamine use during pregnancy and adverse neonatal outcomes - **Roman Gabrhelík (Norway/Czech Republic)**

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

Comparison of long-term clinical implications of beta-blockade in patients with obstructive airway diseases exposed to beta-blockers with different β1-adrenoreceptor selectivity: an Italian population-based cohort study

Maurizio Sessa, Postdoc, University of Copenhagen, maurizio.sessa@sund.ku.dk; Annamaria Mascolo, Postdoc, University of Campania «L. Vanvitelli», annamaria.mascolo@unicampania.it Cristina Scavone, PhD, University of Campania «L. Vanvitelli», cristina.scavone@unicampania.it Ilaria Perone, MPharm, University of Campania «L. Vanvitelli», ilaria.perone@unicampania.it Annalisa Di Giorgio, MPharm, Caserta Local Health Unit, annalisa77dg@virgilio.it; Michele Tari, MD, Caserta Local Health Unit, mc@aslcaserta1.it; Annamaria Fucile, MPharm, Caserta Local Health Unit, annamariafucile@virgilio.it; Antonella De Angelis, Postdoc, University of Campania «L. Vanvitelli», antonella.deangelis@unicampania.it; Daniel Bech Rasmussen, MD, University of Southern Denmark, daniel.rasmussen@live.dk; Magnus Thorsten Jensen, MD, Harlev and Gentofte University Hospital, magnustjensen@gmail.com; Kristian Kragholm, MD, Aalborg University Hospital, kdks@rn.dk; Francesco Rossi, Full Professor, University of Campania «L. Vanvitelli», francesco.rossi@unicampania.it; Annalisa Capuano, Associate Professor, University of Campania «L. Vanvitelli», annalisa.capuano@unicampania.it; Liberata Sportiello, MPharm, University of Campania «L. Vanvitelli», liberata.sportiello@unicampania.it

Introduction: Long-term clinical implications of beta-blockade in obstructive airway diseases (OAD) remains controversial.

Objectives: We investigated if within the first 5 years of treatment patients with heart failure (HF) and OAD using carvedilol have an increased risk of all-causes, cause-specific hospitalization or treatment discontinuation when compared to patients using metoprolol/bisoprolol/nebivolol.

Methods: Carvedilol users were propensity-matched 1:1 for co-treatments, age, gender, and year of inclusion in the cohort with metoprolol/bisoprolol/nebivolol users. Cox regression model was used to compare study outcomes between cohorts. The rate difference and the attributable risk were computed.

Results: Overall, 11,844 patients out of the 51,214 (23.1%) were exposed to carvedilol and 39,370 (76.9%) to metoprolol/bisoprolol/nebivolol. Carvedilol users had a higher hazard for heart failure hospitalization (HR 1.29; 95% Confidence Interval [CI] 1.18–1.40) with 106 (95%CI 76–134; p-value<0.001) additional cases of HF hospitalization per 10,000 person-years if compared to metoprolol/bisoprolol/nebivolol users. In all, 26.8% (95%CI 22.5%–30.9%; p-value<0.001) of HF hospitalizations in the study population could be attributed to being exposed to carvedilol. Carvedilol users had a higher hazard (HR 1.06; 95%CI 1.02–1.10) of discontinuing the treatment with 131 (95%CI 62–201; p-value<0.001) additional cases of discontinuation per 10,000 person-years. In all, 6.5% (95%CI 3.9%–9.0%; p-value<0.001) of discontinuation could be attributed to being exposed to carvedilol.

Discussion and conclusions: On long-term follow-up period, carvedilol was associated with a higher risk of HF hospitalization and treatment discontinuation if compared to metoprolol/bisoprolol/nebivolol users among patients with HF and OAD.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

Association between antidepressant treatment during pregnancy and postnatal self-harm ideation: a cross-sectional, multinational study using the Edinburgh Postnatal Depression Scale

Jennifer Vallee, Research Assistant, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, jennifrv@uio.no
Yih Wong, Research Assistant, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, yihw@uio.no
Eline Mannino, Research Assistant, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, elinemannino@gmail.com
Angela Lupattelli, Postdoc research fellow, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, angela.lupatelli@farmasi.uio.no

Introduction: Women with psychiatric disorders are currently making treatment choices during pregnancy without evidence on the preventative effects of antidepressants on postnatal self-harm ideation (SHI).

Objectives: To provide a preliminary estimate of the association between antidepressant use during pregnancy and SHI in the postnatal period.

Methods: Using the Multinational Medication Use in Pregnancy Study, a sample (n=187) of postnatal women who had a psychiatric disorder during pregnancy were included. Our outcome measure was frequency of SHI ('often/sometimes', 'hardly ever', 'never'), as measured by the Edinburgh Postnatal Depression Scale item 10. Antidepressant medication use in pregnancy was our exposure variable. We fit logistic models with a composite weight comprised of an inverse probability of treatment weighting (IPTW) multiplied by the sampling weight. The IPTW was generated using a propensity score.

Results: Overall, 52% women were medicated with an antidepressant during pregnancy and 34% reported SHI as often/sometimes or hardly ever. Women medicated with antidepressants in pregnancy had a lower odds of reporting hardly ever SHI than the non-medicated counterpart (weighted OR: 0.39, 95% CI: 0.13, 1.14). This treatment did not seem to have a preventive effect on reporting sometimes/often SHI (weighted OR: 1.96, 95% CI: 0.61, 6.25).

discussion and conclusions: Among women with psychiatric disorders in pregnancy, antidepressant treatment appears to have a protective effect on occasional postnatal SHI. This association is not evident for more frequent SHI. This analysis is only a first step in providing evidence to inform psychiatric disorder treatment decisions for pregnant women.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

Causal mediation analysis in sibling designs: an application to estimated effects of prenatal antidepressant exposure and toddler anxiety and depressive symptoms mediated by gestational age at birth

Mollie Wood, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, & PharmaTox Strategic Research Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Norway; Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
Espen Eilertsen, Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway
Eivind Ystrom, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, & PharmaTox Strategic Research Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Norway; Department of Psychology, University of Oslo, Norway; Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway
Hedvig Nordeng, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, & PharmaTox Strategic Research Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Norway; Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway
Sonia Hernandez-Diaz, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Introduction: Prenatal antidepressant exposure has been previously linked to both shortened gestational age and anxiety/depressive symptoms in early childhood; however, no study has examined gestational age as a potential mediator for behavioral outcome in the offspring.

Objective: To estimate direct and indirect effects of prenatal antidepressant exposure, using a sibling-controlled study design.

Methods: The Norwegian Mother and Child Cohort Study was used to identify 25,776 pregnancies in 12,522 women. We estimated natural direct (NDE) and natural indirect (NIE) effects of antidepressant exposure on anxiety and depression symptoms in 3-year-old children, adjusting for potential confounders. Results are adjusted mean differences in z-scores for exposed versus unexposed children, with bootstrapped 95% confidence intervals (CI), and comparing results from the sibling analysis to those obtained without considering siblings.

Results: In the cohort design, the natural direct effects, without and with adjustment, were 0.21 (95% CI: 0.03, 0.38) and 0.04 (95% CI: -0.13, 0.22), respectively. In the sibling design, the natural direct effect, was 0.26 (95% CI: -0.02, 0.61) without adjustment and 0.18 (95% CI: -0.21, 0.47) with adjustment. Proportions mediated were 50% in the cohort design and 1% in the sibling design based on adjusted estimates.

Discussion and Conclusion: Adjustment for non-shared confounders attenuated cohort but not sibling estimates of the direct effect, while sibling models but not multivariable adjustment attenuated indirect effect estimates. A combination of multiple factors, including unmeasured shared confounding of the mediator and changes in confounders between pregnancies, may explain these results. Confidence intervals were wide, and these findings should be replicated in a larger sample.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

Prescription drugs in fatal accidents – prescribed or not?

Anna K Jönsson, PhD, forensic toxicologist, Department of Forensic Toxicology, National Board of Forensic Medicine and Linköping University, Linköping, Sweden; anna.jonsson@rmv.se
Johan Ahlner, Professor, senior physcian, Department of Forensic Toxicology, National Board of Forensic Medicine and Linköping University, Linköping, Sweden; johan.ahlner@rmv.se

Introduction: Impairment by ethanol and/or other psychoactive substances increases the risk of involvement in fatal accidents.

Objectives: The aim of this study was to describe prevalence of non-prescribed use of narcotic drugs among fatal accidents, split into road-accidents, drownings, falls, burns and other accidents.

Methods: The study population consists of Swedish residents, who died due to accidents between 1/6/2006 and 1/6/2016, where a prescription drug was identified in blood during postmortem analyses. For the included population information was retrieved from The Cause of Death Register, the National Forensic Toxicology Database and the Swedish Prescribed Drug Register.

Results: Preliminary results show that, 6022 prescription drugs were identified among the 2767 included fatalities. The majority of the prescription drugs were observed in males (N=4035, 67%), with a median age of 64 years. The most prevalent drug-classes present were opioids (N=775) and sedative and hypnotics (N=795). About half (53%) of the fatalities had a valid prescription for the drugs found. In traffic fatalities only 35% had a valid prescription whereas drowning fatalities had the highest prevalence of valid prescriptions (58%). Looking at different drug classes, for sedative and hypnotics the victims had a valid prescription in 60% of the cases, which is in contrast opioids, where only 36% had a valid prescription. However, within each class there was a huge variation between different substances.

Discussion and conclusions: This study shows that use of narcotic prescriptions drugs without a valid prescription was common among victims of fatal accidents in Sweden.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

The Risk of Preterm Birth and Small for Gestational Age After Exposure to Phthalate Containing Drugs During Pregnancy: A Nested Case-Control Study

Anne Broe, Post doc, Department of Clinical Biochemistry and Pharmacology, Odense University Hospital - Denmark, anbroe@health.sdu.dk
Anton Pottegård, Jesper Hallas, Thomas Ahern, Ronald F. Lamont
Per Damkier, Professor, Department of Clinical Biochemistry & Pharmacology, Odense University Hospital, Denmark & Department of Clinical Research, University of Southern Denmark, Denmark, pdamkier@health.sdu.dk

Introduction: Preterm birth (PTB) is a major cause of neonatal mortality and morbidity. Phthalates are thought to disrupt the human endocrine system and may increase the risk of adverse pregnancy outcomes.

Objectives: We aimed to explore the possible association between phthalate exposure from pharmaceutical drugs and risk of PTB or small for gestational age (SGA)

Methods: Using Danish Health Registries from 2004 to 2015, we identified 30,837 births in women exposed to our study drugs during pregnancy. The study drugs included 23 drugs marketed in both phthalate containing and phthalate free versions. Phthalate content of each prescription was identified, and date of prescription was used as a proxy for first day of exposure. Using conditional logistic regression, we calculated risk of PTB (birth before 37 completed weeks of gestation) and SGA (a birthweight below the 10th percentile by INTERGROWTH-21st size chart (SGA-I) or Marsal's expected birthweight chart (SGA-M).

Results: We included 1,960 PTBs, 1,314 SGA-Is, and 340 SGA-Ms, matched to 19,487, 12,002, and 2,633 controls, respectively. Diethyl phthalate exposure was associated with PTB and SGA-M, with adjusted ORs up to 1.31 (95% CI: 0.95-1.80) and 2.66 (CI: 0.86-8.17) depending on timing during pregnancy. No associations were seen for dibutyl phthalate. Exposure to polyvinyl acetate phthalate and hypromellose phthalate in late pregnancy was associated with risk of PTB with adjusted ORs up to 14.58 (CI: 2.75-77.29) and 3.48 (CI: 1.41-8.56) but reflected very few exposed individuals.

Discussion and conclusions: Exposure to phthalate-containing drugs during pregnancy is associated with adverse pregnancy outcomes.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

Proton pump inhibitor use and risk of breast cancer, prostate cancer and malignant melanoma: an Icelandic population-based case-control study

Óskar Ö. Hálfdánarson, Katja Fall, Margret H. Ogmundsdottir, Sigrún H. Lund, Eiríkur Steingrímsson, Helga M. Ogmundsdottir, Helga Zoega

Background: Increased expression of specific proton pumps, Vacuolar-type H+ ATPases (V-ATPases), in the plasma membrane of cancer cells has been suggested to contribute to the development of aggressive cancer phenotypes through generation of acidic tumour microenvironments. Accumulating data suggest that proton pump inhibitors (PPIs) may elicit a chemopreventive effect via inhibition of V-ATPases in some cancers, but evidence is still limited. Therefore, we aimed to explore a potential preventive role of PPIs in this study.

Methods: In this population-based case-control study, we identified all incident cases of breast cancer (n=1889), prostate cancer (n=2089) and malignant melanoma (n=428) in Iceland between 2004 and 2014 from the Icelandic Cancer Registry. We assessed varying levels of PPI use through record-linkages to the Icelandic Medicines Registry. For each case, we selected up to 10 birth-year - and sex-matched controls from the population. Using conditional logistic regression, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) controlling for NSAID use.

Results: Adjusted ORs associated with ever-use of PPIs were 1.04 (95% CI: 0.93-1.15) for breast cancer, 1.11 (95% CI: 1.00-1.23) for prostate cancer, and 0.88 (95% CI: 0.69-1.12) for malignant melanoma. A slight increase in prostate cancer risk was associated with increased PPI use, likely influenced by unmeasured confounding. For malignant melanoma, we observed a pattern of decreased risk with increased PPI use, but trend tests did not support a clear dose-response relationship.

Conclusions: Our findings do not support a chemopreventive effect of PPI use on breast cancer, prostate cancer or malignant melanoma.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

Association of prenatal paracetmol exposure with neurodevelopmental outcomes in five-year-old children and the role of unmeasured confounding

Johanne Naper Trønnes, PhD student, University of Oslo, j.n.tronnes@farmasi.uio.no
Mollie Wood, Post Doc, University of Oslo, mollie.wood@farmasi.uio.no
Angela Lupattelli, Post Doc, University of Oslo, angela.lupattelli@farmasi.uio.no
Eivind Ystrom, Professor, University of Oslo, eivind.ystrom@psykologi.uio.no
Hedvig Nordeng, Professor, University of Oslo, h.m.e.nordeng@farmasi.uio.no

Introduction: Recent studies have suggested an association between prenatal paracetamol exposure and adverse neurodevelopmental outcomes in children. However, these findings may be confounded by unmeasured factors.

Objectives: Investigate the association between prenatal paracetamol exposure and communication, externalizing and internalizing behavior, and temperament in 5-year-old children and explore the role of unmeasured confounding.

Methods: We used data from the Norwegian Mother and Child Cohort Study. Women were categorized according to duration of paracetamol use. Neurodevelopment was assessed using the Ages and Stages Questionnaire, the Child Behavior Checklist, and the Emotionality, Activity and Shyness Questionnaire. Linear and generalized linear models with inverse probability weights were used to evaluate continuous and categorical outcomes.

Results: Of the 32 934 children included in our study, 8374 (25.4%), 4961 (15.1%), and 1791 (5.4%) were prenatally exposed to paracetamol in one, two, and three trimesters, respectively. Children exposed to paracetamol in three trimesters had a moderately increased risk of internalizing behavior problems compared to unexposed children (relative risk [RR] 1.22, 95% confidence interval [CI] 0.93, 1.60). Children exposed to paracetamol in two trimesters scored lower on shyness traits compared to the unexposed children (β -0.62, 95% CI -1.05, -0.19). Sensitivity analyses indicated that unmeasured confounders play an important role.

Discussion and conclusions: Short-term use of paracetamol during pregnancy does not seem to pose any substantial risk of neurodevelopmental problems. Although we found an association between paracetamol use in multiple trimesters and greater internalizing behavior and lower shyness in 5-year-old children, we cannot rule out unmeasured confounding as a possible explanation for these findings.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

How do we measure child neurodevelopment after prenatal exposure to psychotropics and analgesics? – a systematic literature review

Sarah Hjorth, PhD student, Pharmacoepidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, s.h.andersen@farmasi.uio.no
Rebecca Bromley, research fellow, Division of Evolution and Genomic Sciences, School of Biological Sciences, University of Manchester, rebecca.bromley@anchester.ac.uk
Angela Lupattelli, post doc, Pharmacoepidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, angela.lupattelli@farmasi.uio.no
Eivind Ystrom, professor, Department of Psychology, and Pharmacoepidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, and National Institute of Public Health, Norway, eivind.ystrom@psykologi.uio.no
Olav Spigset, professor, Department of Clinical Pharmacology, St. Olav's University Hospital, and Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway, olav.spigset@legemidler.no
Hedvig Nordeng, professor, Pharmacoepidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, and National Institute of Public Health, Norway, h.m.e.nordeng@farmasi.uio.no

Introduction: There is to date no comprehensive review of studies on child neurodevelopment after prenatal exposure to psychotropic and analgesic medications.

Objectives: To provide an overview of the use and validity of neurodevelopment outcome measures in studies on prenatal exposure to psychotropics or analgesics. A secondary aim was to provide guidance on how to conduct and interpret such studies.

Methods: A systematic review was conducted in the MEDLINE, Embase, PsycINFO, Web of Science, Scopus and Cochrane databases from inception to January 2018, including controlled studies on prenatal exposure to psychotropics or analgesics and child neurodevelopment, measured with psychometric instruments or by diagnosis of neurodevelopmental disorder. The review management tool Covidence was used for data-extraction. Outcomes were grouped as psychomotor, cognition, behaviour, emotionality or "other".

Results: Of 98 eligible papers, the majority focused on antidepressants (54 papers) and paracetamol (21 papers). A variety of neurodevelopmental outcome measures were used, including psychometric instruments administered by health care professionals or parents, and diagnoses of developmental disorders. In 22 papers, no comments were made on the validity of the outcome measure.

Discussion and conclusions: Studies use both psychometric instruments and medical diagnosis to measure child neurodevelopmental after prenatal exposure to psychotropics and analgesics. Authors should to a greater extent report on the validity of these outcome measures. Combining of data across studies in meta-analysis may be inappropriate due to inherent heterogeneity of neurodevelopmental outcome measures. There is urgent need for international consensus on how to assess child neurodevelopment in medication safety in pregnancy studies.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

DOAC use but no indication; to include or not to include?

Maja Hellfritzsch[1], Erik Lerkevang Grove[2&3], Simone Bonde Haastrup[3], Lotte Rasmussen[1], and Anton Pottegård[1]
(1) Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark, (2) Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark, and (3) Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

Background: In observational studies exploring the safety and effectiveness of direct oral anticoagulants (DOAC), the indication for DOAC treatment serves an important in- or exclusion criterium. Indications are usually captured using specific hospital diagnoses, e.g., ICD-10 code I48 for atrial fibrillation (AF). However, when using this approach about 1/3 of Danish DOAC initiators are excluded, as no reason for treatment can be identified in hospital-based registries.

Methods: Using Danish health registries, we compared the characteristics of new DOAC users (August/2011-June/2017; n=133,588) according to classified indication: AF (n=62,262), venous thromboembolism (VTE) (n=17,300), VTE prophylaxis after arthroplastic surgery (n=13,420), or unknown indication (n=40,238). To identify DOAC users with unknown indication likely treated for AF, we searched for presence of pre-defined proxies for AF (e.g., use of an antiarrhythmic drug) in these patients.

Results: DOAC users with unknown indication were most comparable to DOAC users classified with AF. Also, a proxy for AF could be identified in 35% of users with unknown indication. The most common proxies were ischemic stroke and digoxin use. However, the results also supported presence of users with other indications than AF in the “unknown indication” group.

Discussion and Conclusion: A large proportion of DOAC users in whom the treatment indication cannot be identified according to current practice are likely using DOAC due to non-captured AF. While systematic inclusion of all DOAC users classified with “unknown indication” may introduce misclassification, inclusion of users with a proxy for AF seems reasonable when constructing cohorts of patients using DOACs for AF.

Pharmacoepi slam 1

Thursday 8 November, 14:15 - 14:55

Methamphetamine use during pregnancy and adverse neonatal outcomes

Roman Gabrhelík[1,2], Svetlana Skurtveit[3,4], Blanka Nechanská[1], Marte Handal[3], and Viktor Mravčík[1,5]
[1]Department of Addictology, First Faculty of Medicine, Charles University, Prague, Czech Republic
[2] Department of Addictology, General University Hospital in Prague, Czech Republic
[3]Norwegian institute of Public Health, Oslo, Norway
[4]Norwegian Centre for Addiction Research at the University of Oslo, Norway
[5]National Monitoring Centre for Drugs and Addiction, Office of the Government of the Czech Republic

Aims: We aimed to compare neonatal outcomes in new-borns exposed to methamphetamine (MA) with new-borns of mothers from the general population and opioid dependent mothers.

Design: Nationwide register-based cohort study using personalized IDs assigned to all Czech citizens for data linkeage.

Participants: A total of 258 women diagnosed with ICD-10 F15 during pregnancy and their children. The comparison group consisted of women (n=199) diagnosed with ICD-10 code F11 (all sub-codes) and women (n= 1,511,310) with no ICD-10 F10 to F19 diagnosis (general population) and children of women from both groups.

Measurements: We used data from nationwide registries to identify neonatal outcomes. We performed multivariate linear regression and binary logistic regression to explore the associations between MA and neonatal outcomes. Regression coefficient (b) and Odds ratio (OR) were estimated.

Findings: Women using MA during pregnancy had worse socio-economic characteristics as compared to the general population of pregnant women and mother using opioids during pregnancy. Relative to the non-using population of women, MA reduced birth weight (adjusted b = 102.8 grams, 95% confidence interval (CI) = -164,2--41,4), birth length (adj b = 0.5 cm, 95% CI = -0.8--0,2), head circumference (adj b = 0.3 cm, 95% CI = -0.5-0.0) and increased the odds of preterm birth (adj OR = 2.0, 95% CI = 1.5-2.9) and the odds of low Apgar score at 1 minute.

Conclusions: ew-borns of women using MA had slightly better anthropometric data as new-borns of opioid using women and significantly worse than women from the general population.

Corresponding author: Roman Gabrhelík, Charles University, First Faculty of Medicine, Department of Addictology, Apolinářská 4, 120 00 Prague 2, Czech Republic.
Email: roman.gabrhelik@lf1.cuni.cz

Nordic collaborative studies and hot topics

Thursday 8 November, 15:35 - 16:35

Infections in children after prenatal exposure to opioids: Nordic registry study

Milada Mahic[1,2], Sonia Hernandez-Diaz[2], Mollie Wood[2], Ingvild Odsbu[3], Mette Nørgaard[4], Buket Öztürk[4], Helle Kieler[3], Vidar Hjellvik[1], Svetlana Skurtveit[1], and Marte Handal[1].
Norwegian Institute of Public Health, Oslo, Norway[1], Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, US[2], Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark[4], Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden[3]

Background: Little is known about long-term consequences of in-utero opioid exposure. Opioids modulate the immune system; hence prenatal exposure may increase susceptibility to infections in childhood.

Objectives: To examine susceptibility to infections in childhood following prenatal opioid exposure.

Methods: We conducted separate analysis for opioids used in maintenance therapy (OMT) and analgesic opioids. Use of opioids during pregnancy was identified from linkage between Birth and Prescription Registries. OMT exposure during pregnancy was compared to OMT discontinuation before pregnancy. For children prenatally exposed to analgesic opioids, the risk was assessed for short versus long term use. Risk of infections was measured as Incidence rate ratios (IRRs) for antibiotic prescriptions using Poisson regression, and Hazard ratios (HRs) for infection diagnosis using Cox regression. Standardized mortality ratio weights were applied to adjust for confounding.

Results: During the study period, 522 and 371 OMT exposed infants were compared with 156 and 821 OMT discontinuers in Norway-Sweden, and Denmark, respectively. In Norway-Sweden, adjusted IRR for antibiotic prescription during childhood was 1.08 (0.81-1.44), and in Denmark adjusted IRR was 0.79 (0.68-0.9). Adjusted HRs for diagnosis of infections were 0.83 (0.55 – 1.26) in Norway-Sweden and 0.89 (0.70-1.13) in Denmark.

We didn't find differences neither in the risk for antibiotic prescriptions nor the risk for diagnosis of infections between short and long term use of analgesic opioids. Adjusted IRRs were 1.01 (0.97-1.04) and 1.06 (1.00-1.12), and HRs 0.97 (0.93-1.00) and 0.98 (0.89-1.09), in Norway-Sweden, and in Denmark, respectively.

Conclusions: Our study suggests that children prenatally exposed to opioids don't have higher risk for infections in childhood.

Nordic collaborative studies and hot topics

Thursday 8 November, 15:35 - 16:35

Antidiabetic medication in pregnancy: an international drug utilization study

Carolyn E Cesta, postdoctoral researcher, Karolinska Institutet, Stockholm, carolyn.cesta@ki.se
Jacqueline M Cohen, postdoctoral researcher, Norwegian Institute of Public Health, Oslo, jacqueline.cohen@fhi.no
Ingvild Odsbu, research coordinator, Karolinska Institutet, Stockholm, ingvild.odsbu@ki.se
On behalf of the Nordic Pregnancy drug Safety Studies (NorPreSS) Consortium

Introduction: Type II diabetes and gestational diabetes (GDM) are becoming increasingly prevalent. Consequently, the need for antidiabetic medication (ADM) use in pregnant woman has increased.

Objectives: To assess the prevalence of different classes of ADM use in pregnancy from 2006 up to 2015 in the Nordic countries and insurance claims databases from the US and Australia.

Methods: The prevalence of ADM use in each country was calculated as the proportion of pregnancies in which women filled at least one prescription for an ADM in the 90 days before or within the three trimesters of pregnancy (T1-T3).

Results: Approximately 5 million pregnancies were included. ADM use remained stable in Sweden (1.1-1.3%) and in the US-MarketScan (5.2-5.4%), and increased in Norway (1.3-2.0%), Denmark (1.4-2.0%), Iceland (1.6-3.2%), Finland (1.91-3.4%), US-MAX (3.0-3.9%), and in Australia (3.7-5.9%). Insulin was the most commonly used ADM in pregnancy except for in Denmark and US MarketScan, where biguanides use was higher. In women with dispensations in PRE and T1, the majority continued dispensing the ADM class used pre-pregnancy. For women who initiate ADM treatment in T2 or T3, the most common first dispensation was insulin, except for in the US databases, where sulfonylureas accounted for 40-60% of first dispensations.

Discussion and conclusions: Since 2006, ADM use in pregnancy has increased in most countries. Insulin remains to be the most common ADM used. For treatment of gestational diabetes, sulfonylureas are increasingly the preferred agent in the US, whereas the preference for insulin has remained stable over time in all other countries.

Nordic collaborative studies and hot topics

Thursday 8 November, 15:35 - 16:35

Antipsychotic Drug Use in Pregnancy: a Multinational Database Study

Johan Reutfors, Associate Professor, Karolinska Institutet, Stockholm, Sweden. johan.reutfors@ki.se
Helga Zoega, Professor, University of New South Wales, Sydney, Australia and University of Iceland, Reykjavik, Iceland. helga.zoega@gmail.com
Carolyn E Cesta, Postdoc, Karolinska Institutet, Stockholm, Sweden. carolyn.cesta@ki.se

Introduction: Little is known about how use of antipsychotic drugs during pregnancy varies between countries and over time.

Objectives: To quantify and compare the prevalence of AP drug use during pregnancy in ten populations worldwide.

Methods: Individually linked data from health registers in Denmark (2000-2012), Finland (2005-2014) Iceland (2003-2012), Norway (2005-2015), Sweden (2006-2013), Germany (2006-2015), Australia (New South Wales, 2004-2012), Italy (Lombardy, 2005-2010), and the US (Medicaid Analytic eXtract, 2000-2013, and Truven Health MarketScan, 2012-2015) were used in this study. The prevalence of AP use was calculated as the proportion of pregnancies in which the woman filled at least one prescription for an AP in the period from three months before pregnancy until birth.

Results: We included 7 563 399 pregnancies. The prevalence of first-generation AP and second-generation AP were lowest in the Italian population (0.03% and 0.07%, receptively), and highest in the US Medicaid population (1.8% and 1.5%, respectively). In most countries, prochlorperazine was the most commonly used typical AP and quetiapine the most common atypical. Typical AP use remained stable or decreased over time in all ten populations. Atypical AP use increased markedly over time in all populations except Italy and US MarketScan, reaching 2% in both the Australian (2012) and the US Medicaid population (2013).

Discussion and conclusions: Antipsychotic use during pregnancy varied considerably between countries, but explaining factors are yet to be understood. Most countries showed an increased use of second-generation AP use over time.

Nordic collaborative studies and hot topics

Thursday 8 November, 15:35 - 16:35

Nordic use of antiepileptic drugs in pregnancy from 2006-2016

Jacqueline Cohen, Postdoctoral Fellow, Norwegian Institute of Public Health, jacqueline.cohen@fhi.no
Carolyn Cesta, Postdoctoral Fellow, Karolinska Institutet, carolyn.cesta@ki.se
Kari Furu, Senior Researcher, Norwegian Institute of Public Health, kari.furu@fhi.no
On behalf of the Nordic Pregnancy drug Safety Studies (NorPreSS) Consortium

Introduction: While continuous treatment with antiepileptic drugs (AEDs) is often required, important pregnancy safety concerns exist. Thus, it is important to understand the prevalence and patterns of AED use surrounding pregnancy.

Objectives: To describe the utilization of AEDs in pregnancy from 2006-2016 in the Nordic countries.

Methods: Using linked birth and prescription registers, we defined pregnancy exposure based on drugs dispensed from 3 months before pregnancy to birth. We examined the prevalence by country and year of birth, AED polytherapy use, and patterns of use by trimester.

Results: AED use in over 2.8 million pregnancies was 7.3 per 1000 and ranged from 6.4 in Sweden to 10.7 in Iceland. Use of AED polytherapy in pregnancy was lowest in Iceland (9%), and highest in Finland (13%). Lamotrigine was the most commonly used AED, with use increasing over time. Valproate use decreased over time, but use in Finland remained substantial. Pregabalin use increased substantially to become the second most commonly used drug. Pregabalin and gabapentin were most commonly discontinued in early pregnancy, whereas leviteracetam and oxcarbazepine were least likely to be discontinued. 22% of exposed only filled an AED prescription before pregnancy while 36% filled prescriptions in all three trimesters.

Discussion and conclusions: With increased use of AEDs in pregnancy in recent years there is even more pressing need for comparative safety studies to inform the balance of risks and benefits for use. Combining data from across the Nordic countries will increase the power of such studies to produce conclusive results.

Nordic collaborative studies and hot topics

Thursday 8 November, 15:35 - 16:35

A meta-analysis proposal for Nordic collaborative studies

Pär Karlsson[1], Laura Pazzagli[1]
[1]CPE, Karolinska Institutet, Stockholm, Sweden;

Introduction: Data transfers regulations may limit the possibility of pooling individual data in international collaborations. Meta-analysis techniques can be a useful tool to provide pooled estimates of parameters of interest when these type of problems occurs.

Objectives: To propose a meta-analysis approach in presence of sparse data also adjusting for potential confounders.

Methods: Within each country, the data is adjusted by propensity score (PS) stratification, to obtain a 2x2 table were the control group is standardized to the exposed group. The standardized 2x2 tables from each country are pooled with a Mantel-Haenszel approach retraining information from countries with no exposed events. To account for the dependency introduced in the data by the PS method, a correcting factor is used to produce a more robust confidence interval (CI) for the Mantel-Haenszel estimate.

Results: The approach shows that data from countries with no exposed events may add information to the pooled meta-analysis estimates. The correcting factor used in the CI of the Mantel-Haenszel estimate provide an estimate of the extra variability introduced in the data by the PS techniques.

Discussion and conclusions: PS methods are useful tools to attempt to adjust for potential confounding factors. Those methods may introduce further variability in the data due to the dependency created among observations. A correcting factor accounting for such variability can provide a more conservative measure of the uncertainty of the final pooled estimate.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Folate use in Pregnancy and Risk of Gestational Diabetes - **Carolyn E Cesta (Sweden)**

Weight and weight change and risk of atrial fibrillation – the HUNT study - **Tingting Feng (Norway)**

Association between adherence to lipid-lowering medications and risk of cardiovascular disease and mortality among patients with type 2 diabetes - **Sofia Axia Karlsson (Sweden)**

Prenatal exposure to benzodiazepines or z-hypnotics and child behavior problems at 5 years - **Lene Maria Sundbakk (Norway)**

Cross national collaborative study of oral anticoagulant use in atrial fibrillation to inform a more stratified approach to drug selection - **Marion Bennie (Sweden/Scotland)**

Methods for estimating treatment episodes - dosage assumptions versus real prescribed dosage accounting for treatment gaps and overlaps - **Laura Pazzagli (Sweden)**

Factors influencing the choice of direct oral anticoagulants and vitamin k antagonists in non-valvular atrial fibrillation patient and evaluation of channeling **- Mia Aakjær (Denmark)**

Use of some psychotropic drugs before and after start of biologic treatment for rheumatoid arthritis - **Anders Sundström (Sweden)**

Carcinogenic and chemopreventive effects of prescription drugs: A register-based screening approach - **Bettina Kulle Andreassen (Norway)**

Scandinavian multi-registry study of antiepileptic drug teratogenicity: the SCAN-AED study **Marte-Helene Bjørk (Norway)**

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Folate use in Pregnancy and Risk of Gestational Diabetes

Carolyn E Cesta, post-doctoral researcher, Karolinska Institutet, carolyn.cesta@ki.se
Laura Pazzagli, post-doctoral researcher, Karolinska Institutet, laura.pazzagli@ki.se
Ingvild Odsbu, research coordinator, Karolinska Institutet, ingvild.odsbu@ki.se
Helle Kieler, professor, Karolinska Institutet, helle.kieler@ki.se
Olov Andersson, senior researcher, Karolinska Institutet, olov.andersson@ki.se

Introduction: Findings from animal and clinical studies suggest it is plausible to hypothesize that individuals with higher levels of folate intake may, to some degree, be protected from the development of diabetes. Women are advised to take folic acid supplements prior to and during pregnancy, and gestational diabetes mellitus (GDM) is one of the most common complications in pregnancy, but their association has never been explored.

Objectives: To examine whether folate supplementation during pregnancy is associated with a reduced incidence of GDM.

Methods: An observational cohort study of pregnant women without pre-existing diabetes will be conducted using data from the Swedish National Population Registers, including the Medical Birth Register, the Prescribed Drug Register, and the National Patient Register, from 1998 to 2015. Folate use will be assess from maternal-reported use in early pregnancy and dispensations of folate prescriptions. Gestational diabetes will be identified by diagnosis or initiation of antidiabetic medication use in the 2nd or 3rd trimester. Data will be analyzed taking into account a number of covariates including maternal country of birth, BMI, comorbidities and co-medication dispensations.

Results: The cohort will include over 1.5 million pregnancies in Sweden.

Discussion and conclusions: Results from this study have the potential to suggest unique pathways for the development of GDM. While there are known risk factors for GDM, aside from lifestyle modification, there is limited knowledge on possible prevention strategies.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Weight and weight change and risk of atrial fibrillation – the HUNT Study

Tingting Feng, PhD student, NTNU, tingting.feng@ntnu.no
Imre Janszky, professor, NTNU, imro.janszky@ntnu.no

Introduction: Obesity has reached epidemic proportions globally and the last few decades have also witnessed a global rise in the incidence of atrial fibrillation (AF).

Objectives: The aims of the study were to explore the effects of long-term obesity and long-term weight change on AF development.

Methods: We conducted a population-based cohort study of 48,846 community-dwelling individuals who were followed from 2006-2008 until 2015 with measurements of cardiovascular risk factors and common chronic disorders. Weight and height were directly measured repeatedly over decades (at baseline in 2006-2008, 10, 20 and 40 years prior to baseline). From these measurements, we estimated the effects of average weight and weight change on AF risk.

Results: For weight averaged over 40 years, obesity (HR: 1.6 , 95% CI: 1.2-2.0) group had higher AF risk compared to the normal weight group. For the total weight change during around 40 years, there was a greater than 3-fold increase in AF risk among those with weight gain more than 5.0 kg/m2 (HR: 3.1, 95%CI:1.6-6.2). Early life obesity and weight change presented cumulative effects on AF development even after accounting for the most recent BMI.

Discussion and conclusions: Long-term obesity and high degree of weight change were associated with increased AF risk. Our findings may have important clinical and public health implications and may highlight the potential for weight control strategies to decrease the increasing AF incidence.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Association between adherence to lipid-lowering medications and risk of cardiovascular disease and mortality among patients with type 2 diabetes

Sofia Axia Karlsson, MSc, University of Gothenburg, sofia.karlsson@gu.se
Stefan Franzén, PhD and statistician, Swedish National Diabetes Register, stefan.franzen@registercentrum.se
Ann-Marie Svensson, PhD, Swedish National Diabetes Register, ann-marie.svensson@registercentrum.se
Mervete Miftaraj, MSc, Swedish National Diabetes Register, mervete.miftaraj@registercentrum.se
Björn Eliasson, PhD, University of Gothenburg, bjorn.eliasson@medic.gu.se
Karolina Andersson Sundell, PhD, University of Gothenburg/AstraZeneca AB, karolina.a.sundell@gu.se

Introduction: High refill adherence to lipid-lowering medications is associated with lower risk of cardiovascular disease (CVD) and mortality among type 2 diabetes (T2D) patients. Impact of treating healthcare providers' guideline adherence on patients' risk of CVD and mortality is unclear.

Objectives: Analyze refill and guideline adherence to lipid-lowering medications in relation to risk of CVD and mortality among T2D patients.

Methods: We included T2D patients ≥18 years, who initiated lipid-lowering medications during 1/7 2006–31/12 2012. Patients were followed from when the first supply of lipid-lowering medications ceased until migration, CVD, death or 31/12 2016. The study period was divided into 4-month intervals through 2014, followed by annual intervals through 2016. Risk of CVD and mortality for primary and secondary prevention was analyzed for each interval using Cox regression with refill adherence from the precedent interval and guideline adherence from the interval prior to that as exposures.

Results: Totally 123,460 patients (12% secondary prevention) registered by 1338 healthcare providers were included. Mean first supply was three months. Mean study period was 6.5 years for primary prevention and 5 years for secondary prevention. Risk of CVD was 56–65% higher in primary prevention and 22–24% higher in secondary prevention with low refill adherence, independent of guideline adherence level. Risk of mortality was doubled among patients with low refill adherence independent of prevention group or guideline adherence level.

Discussion and conclusions: Refill adherence has greater impact on risk of CVD and mortality compared to guideline adherence and prevention type.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Prenatal exposure to benzodiazepines or z-hypnotics and child behavior problems at 5 years

Lene Maria Sundbakk, PhD candidate, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, l.m.sundbakk@farmasi.uio.no.

Jon Michael Gran, Associate Professor, Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, University of Oslo, j.m.gran@medisin.uio.no.

Mollie Wood, Postdoc, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, mollie.wood@gmail.com.

Hedvig Nordeng, Professor, PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, and PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, h.m.e.nordeng@farmasi.uio.no.

Introduction: Little is known about the long-term effect of benzodiazepines and z-hypnotics exposure during pregnancy on behavioral problems. One recent study using propensity score (PS) adjusted sibling-matched linear regression found a significant effect of benzodiazepine anxiolytics exposure and internalizing problems at age 3 (β=0.26, CI=0.002-0.52).

Objectives: To examine whether prenatal exposure to benzodiazepines and z-hypnotics may increase the risk of externalizing and internalizing behavior problems in children at 5 years, while controlling for the potential impact of the underlying maternal psychiatric disorder.

Methods: This study used data from the Norwegian Mother and Child Cohort Study and the Medical Birth Registry of Norway. The study population consisted of 36,401 children. Children's behavior was measured by maternal report on the Child Behavior Checklist at age 5. Children with T-score>63 were considered to have clinically relevant behavior problems. We applied PS weighting methods and regression models to estimate risk ratios (RR) and robust 95% confidence intervals (CI). In addition, censoring weights were applied to account for drop out.

Results: In our sample, 266 (0.7%) children were exposed to benzodiazepines or z-hypnotics during pregnancy. PS-weighted analyses showed no significant increased risk of internalizing behavioral problems (16.5% among exposed, 10.4% among unexposed, RR: 1.35, 95% CI: 0.74-2.45), or externalizing behavioral problems (16.9% among exposed, 9.9% among unexposed, RR: 1.58, 95% CI: 0.93-2.70).

Discussion and conclusions: Among this cohort of Norwegian children, there was no evidence that prenatal exposure to benzodiazepines or z-hypnotics increase the risk of externalizing and internalizing behavior problems by age 5 years.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Cross national collaboative study of oral anticoagulant use in atrial fibrillation to inform a more stratified approach to drug selection

Marion Bennie, Professor of Pharmacy and Pharmacoepidemiology, University of Strathclyde, Scotland
Bjorn Wettermark, Associate Professor, Centre for Pharmacoepidemiology, Karolinska Institutet and Stockholm County Council

Introduction: There is an increasing use of oral anticoagulants (OA) globally but real world evidence studies involving multiple countries are sparse. Scotland (population 5.4m) has an established individual level prescribing dataset covering all primary care prescribing. An analysis of Swedish and Scottish data is planned, and the opportunity to extend this study through the NORPEN network is proposed .

Objectives: To assess across different geographies the use of OA therapy (including treatment trajectories / sequencing), permit deeper phenotyping and enable generation of more precise prediction algorithms to inform both treatment choice and predict treatment outcome.

Methods: Patients receiving OA for the management of atrial fibrillation over the period 2010-2017 will be included. Drug use will be assessed at an aggregate (drug incidence/prevalence) including the influence of policy factors and at an individual level (adherence, discontinuation and persistence). Risk modelling methods will include Bayesian hierarchical approaches for multiple outcomes and other data science methods being developed as part of a wider project (MRC/HDR (UK).

Results: This study will provide insights into the differences in the use of OA across geographical regions in Europe, from changes in prescribing patterns over time to patients' adherence to treatment options available. The expected results will build on current analysis to give more precise prediction methods and algorithms to inform treatment management.

Discussion and conclusions: This study presents an opportunity to evaluate the feasibility of moving towards standardisation of drug utilisation research methods/measurements and to develop predictive algorithm approaches.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Methods for estimating treatment episodes - dosage assumptions versus real prescribed dosage accounting for treatment gaps and overlaps

Laura Pazzagli[1], Lena Brandt[1], Marie Linder[1], Anders Sundström[1], Emese Vago[2], David Myers[2], Morten Andersen[1,3], Panagiotis Mavros[2], and Shahram Bahmanyar[1]
[1]CPE, Karolinska Institutet, Stockholm, Sweden; [2]Johnson & Johnson/Janssen Companies; [3]Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark

Introduction: Exposure definition is crucial to reduce bias in treatment effect estimates. When constructing treatment episodes in observational studies, information about dosage, duration, and presence of gaps and overlaps among prescriptions should be properly considered.

Objectives: To compare treatment episode durations estimated using real prescribed dosage versus different assumptions on prescribed dosage and different approaches to account for gaps and overlaps among prescriptions.

Methods: Data from the Swedish Prescribed Drug register were used to estimate treatment episodes for patients exposed to citalopram and mirtazapine during 2006-2014. Three methods were used: Method A, used as gold standard, is based on real dosage extracted from free text format. Methods B and C are based on 1 unit of drug and 1 DDD per day assumptions, respectively. Moreover the methods accounted for different assumptions on gaps and overlaps between prescriptions.

Results: For citalopram users the cumulative duration in days (median 260, interquartile range IQR 612) is underestimated using Method C (median 230, IQR 618) and overestimated using Method B (median 294, IQR 668). The cumulative durations for mirtazapine users (median 130, IQR 340) derived using Method C is underestimated (median 100, IQR 300) and it is well estimated with Method B (median 130, IQR 346).

Discussion and conclusions: Depending on the research question and the therapeutic area, dosage assumptions involved in the exposure definition require careful evaluation. When considering a time-varying exposure, the presence of gaps and overlap need to be taken into account in the treatment episode estimation.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Factors influecing the choice of direct oral anticoagulants and vitamin k antagonists in non-valvular atrial fibrillation patient and evaluation of channelling

Trine Skjærbæk Christiansen, Research assistant, Pharmacovigilance Research Group, University of Copenhagen, trine.christiansen@sund.ku.dk
Mia Aakjær, PhD student, Pharmacovigilance Research Group, University of Copenhagen, mia.aakjaer@sund.ku.dk
Marie Louise De Bruin, Professor, Copenhagen Centre for Regulatory Science (CORS), University of Copenhagen, marieke.debruin@sund.ku.dk
Morten Andersen, Professor, Pharmacovigilance Research Group, University of Copenhagen, morten.andersen@sund.ku.dk

Introduction: Channelling is a form of allocation bias where newly launched drugs, with same or similar indications, are prescribed to patients with different severity or risk, which may lead to biased treatment effect.

Objectives: This study aimed to investigate factors that influence the choice between direct oral anticoagulants (DOAC) and vitamin K antagonists (VKA) and if channelling has occurred.

Methods: We conducted a retrospective, cross-sectional study in non-valvular atrial fibrillation (NVAF) patients aged 18 and over, who were naïve DOAC or VKA users between August 2011 and December 2015. We used logistic regression to investigate predictors for DOAC choice including age, sex, comorbidity and co-medications. Propensity scores were calculated to investigate channelling.

Results: We included 41,597 patients of which 24,167 (58%) were DOAC users. Eleven thousand five hundred and thirty-tree (47%) of DOAC and 7,582 (43%) of VKA users were female. Mean age (SD) were 73.7 (11.26) and 72.4 (11.49) for DOAC and VKA users, respectively. Predictors for DOAC choice were being female (OR 1.19; 95 % CI 1.14-1.23), over 80 years (1.39; 1.30-1.47), history of stroke (1.28; 1.21-1.35) and intracranial hemorrhage (1.38; 1.03-184). VKA choice was associated with renal disease (0.49; 0.45-0.54), heart failure (0.81; 0.78-0.85), and co-medications such as aspirin (0.66; 0.61-0.71) and clopidogrel (0.73; 0.69-0.78). We identified nearly identical distribution of propensity scores over time.

Discussion and conclusion: We identified differences in sex, age, comorbidity, and co-medications between the choice of DOAC and VKA. However, these factors are not frequent enough to observe major channelling.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Use of some psychotropic drugs before and after start of biologic treatment for rheumatoid arthritis

Philip Brenner, MD, PhD, PostDoc, Karolinska institutet, Stockholm Sweden. Philip.Brenner@ki.se
Anna Citarella, PhD, Karolinska Institutet, Stockholm Sweden. Anna.Citarella@ki.se
Anders Sundström, PhD, Karolinska Institutet, Stockholm Sweden. Anders.Sundstrom@ki.se

Introduction: Rheumatoid arthritis (RA) is an autoimmune disorder that can have considerable effects on mental health

Objectives: To analyze extent of use of some common psychotropics before and after first time treatment with anti tnf-alfa inhibitors (anti-tnf) for RA; and to correlate such use with randomly selected population controls.

Methods: Subjects with a diagnosis of RA were identified in the Patient Register, and their treatment with anti-tnf was extracted from the Prescribed Drug Register. Up to ten randomly selected population controls were identified for each diseased. Prescriptions of anti-depressants (AD) and benzodiazepine related drugs (ZOPZOL) were then extracted. Proportions of subjects filling such prescriptions from two years before start of treatment (index-date), and two years thereafter were estimated.

Results: During the two years preceding index, a clearly higher proportion of the 3,697 diseased subjects filled prescriptions for AD and ZOPZOL (from 10.5% to 11.3% AD, 9.1% to 11.2% ZOPZOL) than did their 36,866 matched controls (from 9.8% to 10.1% AD, 7.3% to 8.1% ZOPZOL). The rate of use rose during the pre-index period for both groups. During two years after index, however, the proportion of diseased users decreased (from 11.4% to 11.0% use of AD, 11.1% to 9.8% use of ZOPZOL) thus approaching that of the population controls, whose rate of use in contrast continued to increase (from 10.3% to 11.0% for AD and 8.1% to 8.8% for ZOPZOL).

Discussion and conclusions: Starting a potent and efficient treatment for RA entails a decreasing use of anti-depressants and benzodiazepine related preparations.

Pharmacoepi slam 2

Thursday 8 November, 17:00 - 17:40

Carcinogenic and chemopreventive effects of prescription drugs: A register-based screening approach

Bettina Kulle Andreassen[1], Nathalie Støer[1], Giske Ursin[1], Hege Thoresen[2], Karen Boldingh Debernard[3], Øystein Karlstad[4], Kari Furu[4], Anton Pottegård[5], Søren Friis[6]
[1]Department of Research, Cancer Registry of Norway, Oslo, Norway
[2]Department of Clinical Pharmacology, University of Oslo, Norway
[3]Regional Medicines Information and Pharmacovigilance Centre (RELIS), Department of Pharmacology, OUS, Oslo, Norway
[5]Department of Clinical Pharmacology and Pharmacy, University of Southern Denmark
[6]Danish Cancer Society, Copenhagen, Denmark

Unintended effects of drugs may include increased or decreased risk of cancer, typically occuring after a long induction period. The excess risk of breast cancer induced by menopausal hormone replacement therapy becomes apparent only after 5-10 years of continuous use, and chemoprevention of colorectal cancer by aspirin use also requires long-term regular use. Knowledge of such potential carcinogenic or chemopreventive effects of drugs is sparse at the time of drug approval due to limited follow-up time in pre-marketing clinical trials and a limited number of exposed individuals. Postmarketing surveillance (pharmacovigilance) is therefore crucial for identification of long-term effects of new drugs, such as cancer occurrence. However, the discipline is challenging due to the long latency of cancer development and limited statistical power in traditional pharmacoepidemiological approaches.

The main aim of this study is to identify carcinogenic or chemopreventive effects of prescription drugs on the incidence of cancer of various types and at different sites, using a large-scale register approach based on existing Norwegian nationwide health and demographic registries. We will develop a surveillance tool, which may in coming years be used for efficient periodic screening and identification of novel drug-cancer associations in the entire Norwegian population.

This work is a collaboration between the Cancer Registry of Norway, the Danish Cancer Registry, the Norwegian Prescription Registry and the University of Oslo (Department of Pharmacology). As this project is work in progress, in my presentation, I will focus on the (statistical) methods used in this project.

Scandinavian multi-registry study of antiepileptic drug teratogenicity: the SCAN-AED study

Marte Helene Bjørk, associated professor/consultant Neurologist, University of Bergen and Haukeland University Hospital, Norway
Silje Alvestad, post doctor/consultant Neurologist, University of Bergen and Oslo University Hospital, Norway
Jakob Christensen, PhD, consultant Neurologist, Aarhus University Hospital, Denmark
Julie Werenberg Dreier, post doctor, Aarhus University, Denmark
Nils Erik Gilhus, professor/consultant Neurologist, University of Bergen and Haukeland University Hospital, Norway
Mika Gissler, professor, THL, Finland
Maarit Leinonen, MD, PhD, project manager, Drugs and Pregnancy Project, THL, Finland
Yuelian Sun, Aarhus University, Denmark
Torbjörn Tomson, professor, Karolinska Institutet, Sweden

Introduction: It is unknown why antiepileptic drug (AED) exposure in pregnancy harms some children and others not. A significant problem is lack of statistical power when studying rare outcomes for AEDs used in a small groups of the population, or new AEDs.

Objectives: The SCAN-AED is a study in progress aimed to link Nordic population registers to study the effects of in utero exposure of AEDs on congenital malformations, neuropsychiatric disorders, somatic morbidity and survival of the offspring. We will also study whether teratogenic effects of in utero AED exposure are influenced by co-medication, doses, folic acid supplements, comorbidity and socioeconomic factors.

Methods: We will link individual level data from the Medical Birth Registries, the National Prescription Databases, the Patient Registries, and socioeconomic data from the National Statistical Agencies in Denmark, Norway, Sweden and Finland. Exposure is determined as ≥1 redeemed prescription of ≥1 AED between conception and delivery. The pooled data will be stored and accessed from the research server at Statistics Denmark.

Results: The population will be approximately 4 700 000 children, of whom 23 000 have been exposed to AED in pregnancy. The study is approved by regulatory authorities including the Ethics committees and the Data inspectorate/ombudsman in all countries. NordForsk and Helse Vest have funded the project.

Discussion and conclusions: Joint Nordic registry studies can contribute cohorts large enough to study complex causes of AED teratogenicity. Cooperation between strong clinical and epidemiological research groups, NordForsk and the NordMAN Network is important to realize the project.

Nordic collaborative studies and hot topics

Friday 9 November, 11:00 - 12:00

Association between use of azathioprine and risk of acute pancreatitis in pediatric inflammatory bowel disease: a Swedish-Danish nationwide cohort study

Viktor Wintzell, MSc; Henrik Svanström, PhD; Ola Olén, MD, PhD; Mads Melbye, MD, DrMedSci; Jonas F. Ludvigsson, MD, PhD; **Björn Pasternak**, MD, PhD
Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden (VW, HS, OO, BP); Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (HS, MM, BP); Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (MM); Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA (MM); Department of Pediatric Gastroenterology and Nutrition, Sachs' Children and Youth Hospital, Stockholm, Sweden (OO); Department Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (JFL); Department of Pediatrics, Örebro University Hospital, Örebro University, Örebro, Sweden (JFL); Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, UK (JFL); Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA (JFL).

Introduction: Whereas studies have shown an association between azathioprine use and increased risk of acute pancreatitis in adult inflammatory bowel disease (IBD), it is unclear if there is a similar association among pediatric patients.

Objective: To investigate if there is an association between azathioprine use and risk of acute pancreatitis in pediatric IBD patients.

Methods: We conducted a Swedish-Danish cohort study based on nationwide registers, identifying all pediatric patients (<18 yrs) with IBD during the study period (Sweden: July 2006-2016, Denmark: 2000-2016). Episodes of new azathioprine use and no use of any thiopurine were propensity score-matched (1:1 ratio). Incident cases of acute pancreatitis occurring in the risk period of 90 days following treatment initiation were identified through outpatient and inpatient hospital diagnoses.

Results: The cohort included 3378 matched pairs of azathioprine and no use episodes. During the first 90 days following azathioprine initiation, 40 patients experienced acute pancreatitis (incidence rate 49.0 events per 1000 person-years) compared with 6 patients among non-users (incidence rate 8.5 events per 1000 person-years). The risk was significantly higher in patients with azathioprine use, incidence rate ratio 5.80 (95% confidence interval [CI] 2.46-13.68), corresponding to an absolute difference of 1.0 (95% CI 0.3-2.7) event per 100 patients during the 90-day risk period.

Conclusion: Use of azathioprine was associated with an increased risk of acute pancreatitis in pediatric IBD during the first 90 days following treatment initiation. The risk of acute pancreatitis needs to be considered when deciding on optimal treatment strategies in pediatric IBD.

Nordic collaborative studies and hot topics

Friday 9 November, 11:00 - 12:00

Prescribed opioid analgesic use developments in the Scandinavian countries, 2006-2017

Ashley Elizabeth Muller, Researcher, Norwegian Centre for Addiction Research, ashely.muller@medisin.uio.no
Thomas Clausen, Centre leader, Norwegian Centre for Addiction Research, thomas.clausen@medisin.uio.no
Per Sjøgren, Clinical Professor, University of Copenhagen, Per.Sjoegren@regionh.dk
Ingvild Odsbu, Research Coordinator, Karolinska Institute, ingvild.odsbu@ki.se
Svetlana Skurtveit, Senior Researcher, Norwegian Institute of Public Health, Svetlana.skurtveit@fhi.no

Introduction: While the Scandinavian countries have considerably stricter controls on opioid prescribing for chronic non-cancer pain, previous research has warned that prescription of weak opioids is increasing, and new groups of problematic users are developing.

Objectives: This study examines the Scandinavian populations' consumption of and developments in the use of weak and strong opioid prescribed to individuals receiving ambulatory care from 2006-2017, using publicly available data from each country's complete prescription registries.

Methods: Repeated, cross-sectional design. One-year prevalence of the strong opioid oxycodone and the weak opioids tramadol and codeine were reported for an eleven-year period. The mean defined daily dose (DDD) per user per year, an estimate of the amount of opioids prescribed, was reported for each of the three opioids in 2016.

Results: Norway exceeded Sweden and Denmark in opioid prescribing prevalence, with 12% of the Norwegian population receiving at least one opioid prescription as an outpatient in 2016. Patterns of strong and weak opioid prescribing differ greatly between 2006 and 2017 and between countries, with codeine declining across the board, tramadol increasing in Norway, and opioid oxycodone increasing in Sweden. Sweden's high oxycodone prescribing is tempered by low doses, while Norway prescribes the highest amounts.

Discussion and conclusions: The increased availability of oxycodone in all three of these countries needs to be addressed, particularly given that oxycodone-related deaths are increasing along with availability, in settings with both low and high average doses. The ambulant prescription of opioids for chronic non-cancer pain must be critically re-considered, and prescription registries provide awealth of publicly available data that can be used to inform prescribing policies.

Nordic collaborative studies and hot topics

Friday 9 November, 11:00 - 12:00

Non–aspirin NSAID use in the Nordic countries 2000–2016 from a cardiovascular risk perspective: a drug–utilization study

Kasper Bruun Kristensen, medical doctor[1], Øystein Karlstad, research fellow[2], Jaana E. Martikainen, head of medicine research[3], Anton Pottegård, associate professor[1], Jonas W. Wastesson, research fellow[4], Helga Zoega, professor[5,6], Morten Schmidt, research fellow[7,8]
[1]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark. E-mail: kaskristensen@health.sdu.dk
[2]Department of Chronic Diseases and Aging, Norwegian Institute of Public Health, Oslo, Norway
[3]Research Unit, The Social Insurance Institution (Kela), Helsinki, Finland
[4]Aging Research Center, Karolinska Institutet & Stockholm University, Stockholm, Sweden
[5]Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[6]Medicines Policy Research Unit, Centre for Big Data Research in Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[7]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
[8]Department of Cardiology, Regional Hospital West Jutland, Herning, Denmark

Introduction: The cardiotoxic potential of non–aspirin non–steroidal anti–inflammatory drugs (NSAIDs) – particularly diclofenac and the newer selective COX–2 inhibitors – has been increasingly recognized during the last decade.

Objectives: To examine whether the use of NSAIDs in the Nordic countries changed as evidence on the cardiotoxicity of specific NSAIDs accumulated.

Methods:
Design: A drug–utilization study using nationwide wholesale statistics and prescription registries. **Setting:** Denmark, Finland, Iceland, Norway, and Sweden 2000–2016. **Main outcome measures:** Yearly total sales expressed as defined daily doses (DDD) sold per 1,000 inhabitants per day and yearly prevalence of prescription use as prescription users per 1,000 inhabitants.

Results: Total sales of NSAIDs increased in all countries and were highest in Iceland with 74.3 DDDs/1,000 inhabitants/day sold in 2016, followed by Finland (73.9), Sweden (54.4), Norway (43.8), and Denmark (33.1 in 2015). Diclofenac use declined after 2008 in all countries. Nonetheless, diclofenac remained the most widely prescribed NSAID in Norway with 63 prescription users/1000 inhabitants in 2016 and diclofenac sales remained high in Iceland (12.7 DDD/1,000 inhabitants/day), Norway (8.1), and Sweden (7.8). Since its introduction in 2003, the use of etoricoxib, a newer selective COX–2 inhibitor, increased in all countries except Denmark with highest sales in Finland (6.7 DDD/1,000 inhabitants/day in 2016).

Discussion and conclusions: The persistent high use of diclofenac in Iceland, Norway, and Sweden and increasing use of etoricoxib in most of the Nordic countries pose a cardiovascular health concern.

Nordic collaborative studies and hot topics

Friday 9 November, 11:00 - 12:00

Sodium-glucose cotransporter 2 inhibitors and risk of serious adverse events: cohort study using nationwide registers in Sweden and Denmark

Peter Ueda, MD, PhD; Henrik Svanström, PhD; Mads Melbye, MD, DrMedSci; Björn Eliasson, MD, PhD; Ann-Marie Svensson, PhD; Stefan Franzén, PhD; Soffia Gudbjörnsdottir, MD, PhD; Kristian Hveem, MD, PhD; Christian Jonasson, PhD; **Björn Pasternak**, MD, PhD.
Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden (PU, HS, BP); Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (HS, MM, BP); Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (MM); Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA (MM); Department of Molecular and Clinical Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden (BE, SG)
The Swedish National Diabetes Register, Västra Götalandsregionen, Gothenburg, Sweden (AMS, SF, SG); K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Science, NTNU—Norwegian University of Science and Technology, Trondheim, Norway (KH, CJ); HUNT Research Center, Faculty of Medicine, NTNU—Norwegian University of Science and Technology, Levanger, Norway (KH, CJ)

Introduction: There are concerns that sodium-glucose cotransporter 2 (SGLT2) inhibitors may be associated with several serious adverse events.

Objective: To assess the association between use of SGLT2 inhibitors and seven serious adverse events of current concern.

Methods: We conducted a cohort study using an active-comparator new-user design and nationwide register data from Sweden and Denmark, July, 2013, through December, 2016. The propensity score-matched cohort included 17,213 new users of SGLT2 inhibitors and 17,213 new users of the active comparator, glucagon-like peptide 1 (GLP1)-receptor-agonists.

Results: Use of SGLT2 inhibitors, as compared with GLP1-receptor-agonists, was associated with an increased risk of lower limb amputation (incidence rate, 2.7 vs. 1.1 events per 1000 person-years; hazard ratio, 2.32 [95% confidence interval [CI], 1.37-3.91]) and diabetic ketoacidosis (1.3 vs. 0.6 per 1000 person-years; hazard ratio, 2.14 [95% CI, 1.01-4.52]) but not with bone fracture (15.4 vs. 13.9 per 1000 person-years; hazard ratio, 1.11 [95% CI, 0.93-1.33]), acute kidney injury (2.3 vs. 3.2 per 1000 person-years; hazard ratio, 0.69 [95% CI, 0.45-1.05]), serious urinary tract infection (5.4 vs. 6.0 per 1000 person-years; hazard ratio, 0.89 [95% I, 0.67-1.19]), venous thromboembolism (4.2 vs. 4.1 per 1000 person-years; hazard ratio, 0.99 [95% CI, 0.71-1.38]) or acute pancreatitis (1.3 vs. 1.2 per 1000 person-years; hazard ratio, 1.16 [95% CI, 0.64-2.12]).

Conclusion: In this analysis of nationwide registers from two countries, use of SGLT2 inhibitors, as compared with GLP1-receptor-agonists, was associated with increased risk of lower limb amputation and diabetic ketoacidosis but not with other serious adverse events of concern.

Participants

First name	Last name	Institution	Position
Aksel Kvamme	Vestfossen	Statistics Norway	
Anders	Sundström	Karolinska Institutet	Pharmacoepidemiologist
Anders	Engeland	Norwegian Institute of Public Health/University of Bergen	Researcher/Professor
Angela	Lupattelli	University of Oslo	Post doc research fellow
Anita	Haugan	Norwegian Institute of Public Health	Senior Advisor
Anja Maria Steinsland	Ariansen	University of Bergen	Post doc
Anna	Jönsson	National Board of Forensic Medicine	PhD, Forensic toxicologist
Anne	Broe	Odense University Hospital	post doc
Antti	Pursula	NeIC	Project Director
Ashley	Muller	University of Oslo	Researcher
Bettina Kulle	Andreassen	Cancer Registry of Norway	Senior Researcher
Björn	Pasternak	Karolinska Institutet	Senior researcher
Björn	Wettermark	Karolinska Institutet	Associate professor
Carolyn	Cesta	Karolinska Institutet	Post-doctoral researcher
Christian	Jonasson	NTNU	Senior Researcher
Claus-Göran	Hjelm	Statistics Sweden	R&D
David	Medved	Senter for rus- og avhengighetsforskning	Prosjektmedarbeider
Eivind	Ystrøm	School of Pharmacy, University of Oslo	Professor of psychology
Elviira	Linask	State Agency of Medicines	Specialist
Eva	Skovlund	NTNU / FHI	Professor
Gard	Thomassen	University of Oslo	Assistant Director, University Senter for IT
Hanna-Mari	Jauhonen	Finnish Medicines Agency	MD, PhD, research physician
Harald	Langaas	Regional Medicines Information and Pharmaco-vigilance Centre (RELIS)	Director
Gunn Peggy	Strømstad Knudsen	Folkehelseinstituttet	Executive Director
Hedvig	Nordeng	School of Pharmacy, UiO	Professor
Heidi	Taipale	University of Eastern Finland	Academy Research Fellow
Helle	Wallach Kildmeoes	University of Copenhagen	Affiliate Associate Professor

Participants

First name	Last name	Institution	Position
Ida Henriette	Caspersen	Folkehelseinstituttet	Postdoctoral researcher
Ingebjørg	Buajordet	Norwegian Medicines Agency	M.sc.Pharm, PhD/Scientific Director
Ingvild	Odsbu	Department of Medicine	Research coordinator
Jacqueline	Cohen	Norwegian Institute of Public Health	Postdoctoral Fellow
Jennifer	Vallee	University of Oslo	Research Assistant / Master's Student
Johan	Reutfors	Department of Medicine	Associate professor
Johanna	Jyrkkä	Finnish Medicines Agency	Researcher
Johanne Naper	Trønnes	University og Oslo	Phd student
Jon Michael	Gran	University of Oslo	Associate Professor
Kari	Furu	Norwegian Institute of Public Health	Senior Researcher
Kari Jansdotter	Husabø	Norwegian Institute of Public Health	Senior adviser
Kasper Bruun	Kristensen	University of Southern Denmark	MD, PhD student
Katrine Hass	Rubin	University of Southern Denmark	Associate professor
Kristin	Palmsten	HealthPartners Institute	Research Investigator
Kristin	Tomren	Folkehelseinstituttet	Seniorrådgiver/ Prosjektkoordinator
kristine	vejrup	FHI	PhD Senior rådgiver
Lars	Kjerpeseth	NTNU / FHI	PhD student
Larus	Gudmundsson	University of Iceland	Associate Professor
Laura	Pazzagli	Karolinska Institutet	Post doc
Laura	Saarelainen	Epid Research-StatFinn	pharmacoepidemiologist
Leena	Saastamoinen	The Social Insurance Institution, Finland	Senior researcher
Lene Maria	Sundbakk	University of Oslo	PhD student
Leon	Berge	Kreftregisteret	PhD Stipendiat
Lin Hege	Austad Dalen	Statistics Norway	
Maarit	Leinonen	National Institute for Health and Welfare	Project Manager
Maja	Hellfritzsch Poulsen	Clinical Pharmacology and Pharmacy, Public Health, University of Southern Denmark	MD, PhD-student

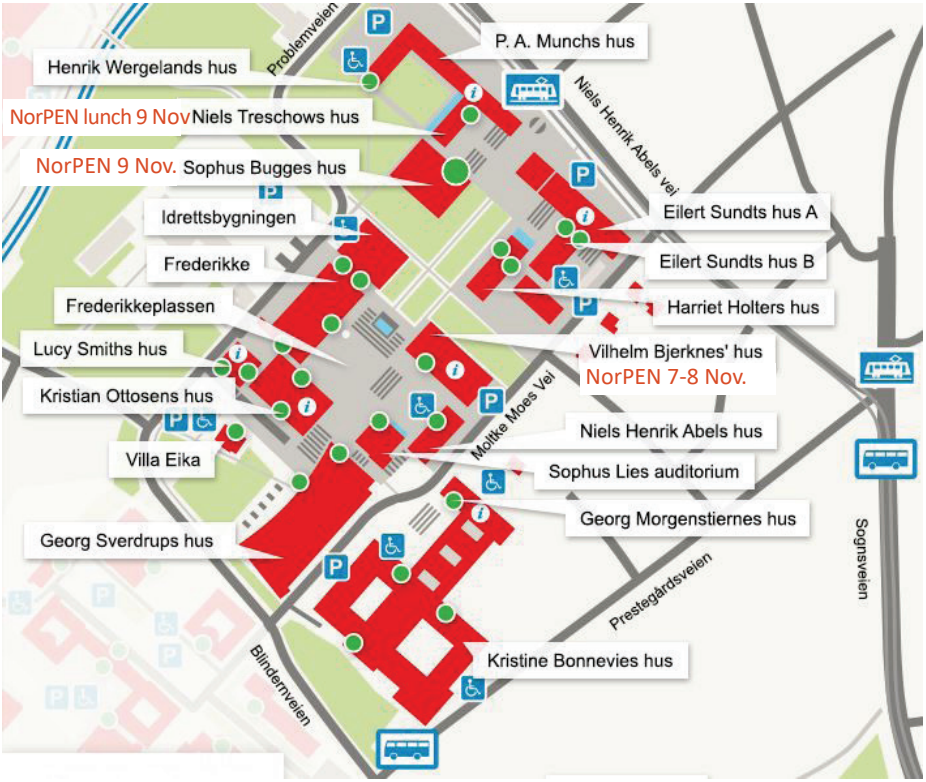
Participants

First name	Last name	Institution	Position
Maja	Laursen	Sundhedsdatastyrelsen	Specialkonsulent
Malene	Nielsen	Leo Pharma	Professional, Pharmacoepidemiology
Maria	State	The Swedish National Board of Health and Welfare	Manager, Unit of Epidemiology and Methodology
Maria	Magnus	Norwegian Institute of Public Health	Researcher
Maria	Sjölander	Umeå University	Post doc
Marion	Bennie	University of Strathclyde	Professor of Pharmacy and Pharmacoepidemiology
Marit	Waaseth	Institutt for farmasi, UiT Norges arktiske universitet	Associate professor
Marthe Helene	Bjørk	University of Bergen	Associated professor/ neurologist
Marte	Handal	Norwegian Institute of Public Health	Senior Reseacher, MD, PhD
Maurizio	Sessa	University of Copenhagen	Post doc
Merete	Eggesbø	FHI	Senior researcher
Mette	Bliddal	University of Southern Denmark	Post doc
Mia	Aakjær	Department of Drug Design and Pharmacology	PhD student
Miia	Artama	National Institute for Health and Welfare	Senior researcher
Mikael	Hoffmann	Stiftelsen NEPI - nätverk för läkemedelsepidemiologi	Chef
Milada	Mahic	Norwegain Institute of Public Health	Post doc
Mollie	Wood	Harvard TH Chan School of Public Health	Post doc
Morten	Andersen	University of Copenhagen, Dept. of Drug Design and Pharmacology	Professor
Natalja	Balliu	The Swedish National Board of Health and Welfare	Statistician
Nina	Iszatt	FHI	Researcher
Olaug	Fenne	Folkehelseinstituttet	Senioradvisor
Óskar	Hálfdánarson	University of Iceland	PhD student
Per-Jostein	Samuelsen	RELIS	Post.doc., adviser
Pia	Vattulainen	EPID Research Statfinn	Statistician
Pinelopi	Lundquist	Swedish Medical Products Agency	Manager

Participants

First name	Last name	Institution	Position
Pär	Karlsson	CPE/KI	Statistician
Randi	Selmer	Norwegian Institute of Public Health	Senior researcher
Roman	Gabrhelík	Charles University, 1st Medical Faculty	Head of Research and Development
Sarah Hjorth	Andersen	University of Oslo	PhD student
Silje	Alvestad	Universitetet i Bergen	Post doc
Sirpa	Hartikainen	University of Eastern Finland	Professor
Sissel	Torheim	Folkehelseinstituttet	Seniorrådgiver
Sofia Axia	Karlsson	University of Gothenburg	PhD student
Svetlana	Skurtveit	Folkehelseinstitutt Oslo	Senior reasearcher
Synnve	Schjølberg	NIPH- Oslo	Researcher
Tania	Schink	Leibniz Institute for Prevention Research and Epidemiology - BIPS	Head of Drug Safety Unit
Tingting	Feng	NTNU	PhD student
Trude Eid	Robsahm	Kreftregisteret	Researcher
Vera	Ehrenstein	Department of Clinical Epidemiology	Professor
Vidar	Hjellvik	Norwegian Institute of Public Health	Researcher
Yih	Wong	University of Oslo	PhD candidate
Yury	Kiselev	OsloMet	Associate professor

Map of Blindern Campus



Lunch
The registration fee includes lunch Friday 9 November. Lunch will be served in Kafe Niels, in the building named Niels Treschows Hus.

Lunch is not included 7-8 November. In the Fredrikke building you will find several places to choose from:

- Frederikke Spiseri: the largest cafeteria with the best selection
- Deiglig: bakery
- Diggbar: yoghurt and porridge bar, sandwiches and salads
- Japanese Ramen: noodles and wok
- Tacoteket: tacos, burritos and bowls

Thursday 8 November

18:15 Meeting time for departure to social dinner event
19:00- Dinner at “Nedre Løkka Cocktailbar & Lounge”
Address: Thorvald Meyers gate 89, 0550 Oslo