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ABSTRACTS / RÉSUMÉS

KNOWLEDGE TO PROVIDE EVIDENCE FOR HEALTH CARE DECISION-MAKERS: CLINICAL PRACTICE AND RESEARCH METHODOLOGY

APRIL 17TH – 19TH, 2011
OTTAWA, ONTARIO
THE WESTIN HOTEL

CAPT ACTP

The Canadian Association for Population Therapeutics / Association Canadienne pour la Thérapeutique des Populations

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CAPT ABSTRACTS

ORAL PRESENTATIONS

1

Antidepressant use during pregnancy and the risk of gestational hypertension

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Funding Source: FRSQ

Background: Despite growing knowledge on the impact of antidepressant use during pregnancy on fetal and neonatal outcomes, there is paucity of data on maternal outcomes. Our objective was to evaluate the impact of antidepressant use during pregnancy on the risk of gestational hypertension.
Methods: Using a nested case-control study design, we obtained population-based data from the Quebec Pregnancy Registry for 1,216 women with a diagnosis of gestational hypertension with or without pre-eclampsia, with no history of hypertension before pregnancy. We randomly selected 10 controls for each case, matched on case index date (date of diagnosis) and gestational age at time of diagnosis. Use of antidepressants was defined dichotomously. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) using conditional logistic regression models were calculated, adjusting for potential confounders including diagnosis of depression or anxiety before pregnancy, sociodemographic characteristics, and chronic conditions, antidepressant use, health care service utilization in the year before pregnancy.
Results: 45 (3.7%) women with gestational hypertension had at least 1 prescription filled for an antidepressant during pregnancy compared with 300(2.5%) in the control group (OR 1.52; 95% CI 1.10-2.09). After adjusting for potential confounders, use of antidepressants during pregnancy was associated with 58% increased risk of gestational hypertension with or without pre-eclampsia (OR 1.53; 95% CI 1.01-2.33).
Conclusions: These data indicate that women who use antidepressants during pregnancy have an increased risk of gestational hypertension with or without pre-eclampsia above and beyond the risk that could be attributed to their depression or anxiety disorders.
Keywords: *Pregnancy, antidepressants, gestational hypertension*

2

Association between use of antiretroviral therapy and risk of acute myocardial infarction: a nested case control study using Quebec's Public Health Insurance Database (RAMQ)

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Funding Source: Fonds de recherche en santé du Québec. Funds to acquire the dataset were provided by an unrestricted educational grant from Boehringer Ingelheim.

Background: Morbidity associated with cardiovascular disease is increasing in the HIV infected population. We aimed to study the impact of HIV and of antiretrovirals on acute myocardial infarction (AMI.)
Methods: We performed a cohort and a nested case-control study, using the dataset of the Regie de l'Assurance Maladie du Quebec. HIV-positive patients were identified using ICD-9 diagnostic codes, and matched to HIV-negative patients. Within the HIV-positive cohort, cases of AMI were identified and matched to HIV-positive patients without AMI. The co-primary outcomes were the risk of AMI associated with HIV exposure in the cohort study, and that associated with exposure to antiretrovirals in the case-

control study. Data were analysed using Poisson and conditional logistic regression.
Results: 7,053 HIV-positive patients were matched to 27,681 HIV-negative patients. Incidence rates of AMI in the HIV+ cohort was 3.88 95%CI [3.26-4.58] per 1000 patient-years, compared to 2.21 95%CI [1.93-2.52] per 1000 patient-years in the HIV- cohort (incidence rate difference 1.67 95%CI [0.96-2.37] p<0.001, incidence rate ratio 1.75 95%CI [1.41-2.18] p<0.001.) Among HIV+ patients, 125 AMI cases were matched with 1084 HIV+ patients. We found increased odds ratio [95%CI] of AMI associated with any exposure to abacavir 1.69[1.17-2.44] p=0.006, didanosine 1.68[1.14-2.49] p=0.009, stavudine 1.48[1.03-2.12] p=0.035, efavirenz 1.57[1.10-2.25] p=0.014, lopinavir 1.68[1.15-2.44] p=0.007, and ritonavir 1.78[1.25-2.54] p=0.002. Results were adjusted for use of anti-hypertensive, lipid-lowering, anti-diabetic, antiplatelet of anticoagulation drugs.
Conclusions: HIV+ individuals were at higher risk of AMI than the general population, and several antiretrovirals were associated with an increased risk of AMI.
Keywords: *HIV, myocardial infarction, drug safety*

3
Asthma-related direct medical costs in British Columbia from 2002 to 2007: a population-based cohort study

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Funding Source: This study was funded by AllerGen

Background: A better understanding of health care costs associated with asthma would allow us to estimate the economic burden of this increasingly common disease. The objective was to calculate the direct medical costs associated with asthma in British Columbia (BC).
Methods: BC asthma patients for years 2002-2007 were selected from the BC discharge abstract database, medical services plan, and PharmaNet. Patients 14-44 years old were stratified by level of asthma severity and control using a validated algorithm based on administrative data created for this age group (Firoozi et al.). Fee-for-service values for physician visits, government reimbursement fees for prescribed medications, and the case mix method was used calculate hospitalization costs. All costs were reported in inflation-adjusted 2008 Canadian dollars.
Results: 476,468 unique patients fulfilled the case definition of asthma (mean age 39.2 years at the time case definition was satisfied, 54.4% female). The identified cohort of patients was responsible for $462.9 M in direct health care costs during the 6-year period, corresponding to $77.1 M annually. Hospitalizations/ED visits, physician visits, and medication costs accounted for 13.4%, 12.7% and 73.9% of the total cost, respectively. When the broad definition of asthma-related resource used was employed, the total cost of asthma increased by 79% to $ 830.3 M. In this scenario the hospitalization/ED visits, physician visits, and medication accounted for 21.8%, 16.6%, and 47.3%, respectively.
Conclusions: Our results indicate the substantial burden of asthma, and the significant share of medications in the direct cost of asthma in BC.
Keywords: *Asthma, health care costs, retrospective study*

4
Beta-2-agonists use during pregnancy and the risk of congenital malformations

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L. Blais is the recipient of a Salary Award from the *Fonds de la recherché en santé du Québec* (FRSQ) and is the Endowment Pharmaceutical Chair AstraZeneca in Respiratory Health. L. Blais has received research support from AstraZeneca, Amgen, and GlaxoSmithKline.

Background: Short-acting inhaled beta-2-agonists (SABA) are routinely used as rescue medications and long-acting inhaled beta-2-agonists (LABA) are used as an add-on controller therapy for asthma during pregnancy.
Objective: To investigate the association between exposure to SABA and LABA in first trimester of pregnancy and the risk of congenital malformations among asthmatic women.
Methods: A cohort of pregnancies from asthmatic women was formed through linkage of three administrative databases from Quebec (Canada). The primary outcomes were major and any congenital

malformations and secondary outcomes were specific congenital malformations. The use of SABA and LABA was assessed in the first trimester of pregnancy. Using generalized estimating equation models, we estimated the association between congenital malformations and maternal exposure to SABA and LABA.

Results: From a cohort of 13, 117 pregnancies, we identified 1,242 infants with a congenital malformation (9.5%), of which 762 had a major malformation (5.8%). The adjusted odds ratios (95% CI) for any malformations associated with the use of SABA and LABA were 1.0 (0.9-1.2) and 1.3 (0.9-2.1), respectively. The corresponding figures were 0.9 (0.8-1.1) and 1.3 (0.8-2.4) for major malformations. Significant increased risks of cardiac malformations 2.4 (1.1-5.1), genital organ malformations 6.8 (2.6-18.1), and other congenital malformations 3.4 (1.4-8.5) were observed with LABA use in the 1st trimester.

Conclusions: Our study supports the evidence that the use of SABA during pregnancy is safe, but more research is required to validate the safety of LABA.

Keywords: *Asthma, administrative databases, congenital malformations*

5

Comparison of data from clinical trials versus small experimental studies for establishing the cognitive safety of anticholinergic drugs. a systematic review and meta-analysis using bladder antimuscarinic agents

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Funding Source: Canadian Institutes of Health Research

Background: Clinical uncertainty surrounds the cognitive safety of many centrally acting medications, including antimuscarinic treatment for overactive bladder. Central nervous system (CNS) side effects such as confusion or difficulty concentrating are arbitrarily screened for and rarely reported in clinical trials, hindering clinicians' ability to counsel patients on drug-associated cognitive risks.

Methods: Trial data from 32,009 patients with overactive bladder were compared with data from small experimental studies to determine the type and incidence of central nervous system adverse events reported by adults taking different antimuscarinic agents. Articles were identified from MEDLINE and EMBASE databases until 2010 using the search terms "clinical trial" or "cognition" AND (one of) "oxybutynin, tolterodine, fesoterodine, propiverine, solifenacin, darifenacin, and trospium". CNS adverse events included reports of confusion, somnolence, sedation, dizziness, drowsiness, asthenia, insomnia, and vertigo, or objectively measured decrements in neuropsychological performance.

Results: In trial data, dizziness was the most frequent adverse event, occurring in 3% of oxybutynin, 3.2% of propiverine and 1.8% of tolterodine users compared to 1.6% with placebo. Confusion was reported in <1% of cases. Meta-analysis of 15,273 patients by type of drug and dose indicated a lack of significant risk of increased CNS events with any antimuscarinic agent, except for dizziness with oxybutinin 15 mg/daily [OR 4.52 95% CI (1.10 - 18.59)]. This is in contrast to the results obtained with oxybutynin in small experimental studies using healthy volunteers and systematic cognitive testing.

Conclusions: Current screening methods used in clinical trials may inadequately detect cognitive adverse events, and need to be revised.

Keywords: *Cognitive safety, clinical trials, anticholinergic drugs*

6

Denosumab is cost-effective in the treatment of high risk postmenopausal osteoporotic women in Canada

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Funding Source: Amgen Canada Inc.

Background: Denosumab is a novel biologic agent approved in Canada for treatment of postmenopausal osteoporosis (PMO) in women at high risk for fracture, or who have failed, or are intolerant to other osteoporosis therapies. This study estimated the cost-effectiveness of denosumab from a Canadian healthcare system perspective compared to usual care.

Methods: A published Markov PMO cohort model1 was used to estimate cost-effectiveness of denosumab. Base case included women with demographic characteristics similar to those from the pivotal phase III trial2 (age 72 years, T-score -2.16 SD, vertebral fracture prevalence 23.6%). Three additional subgroups were examined including women: i) at high fracture risk, defined as having at least two of three risk factors

(age 70+; T-score ≤-3.0; prevalent vertebral fracture); ii) age 75+; iii) intolerant or contraindicated to oral bisphosphonates (BPs). Analyses were conducted over a lifetime horizon comparing denosumab to usual care (no therapy, alendronate, risedronate, and raloxifene [subgroup iii only]). The analysis considered treatment-specific persistence and post-discontinuation residual efficacy. Both deterministic and probabilistic sensitivity analyses were conducted for each subgroup.

Results: The multi-therapy comparisons resulted in incremental cost-effectiveness ratios for denosumab versus alendronate of $61,131 (2008 CDN$) (base case) and $28,868 (subgroup i) per quality-adjusted life year gained, while risedronate was dominated by denosumab in both the base case and subgroup i). Denosumab dominated all active therapies in subgroups ii and iii.

Conclusion: Denosumab is cost-effective compared to oral PMO treatments for women at high risk of fractures and those who are intolerant/contraindicated to oral BPs.

References:

1) Jönsson B, Ström O, Eisman JA, et al. Osteoporos Int 2010; [Oct 9; Epub ahead of print].

2) Cummings SR. San Martin J. McClung MR, et al. N Eng J Med 2009; 361(8):756-65.

Keywords: *Osteoporosis, cost-effectiveness, denosumab*

7

Documentation of human epidermal growth factor receptor-2 (HER2) testing and trastuzumab (TRA) treatment in Ontario breast cancer (BC) patients: a retrospective analysis

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Funding Source: Ontario Institute of Cancer Research (OICR), Cancer Care Ontario (CCO), Canadian Institutes of Health Research (CIHR)

Background: In Ontario, TRA is approved for early BC with HER2 overexpression. We studied documentation of HER2 testing and compliance with Canadian testing and TRA treatment guidelines in early BC using pathology information reported to CCO.

Methods: A population-based retrospective cohort of early BC patients diagnosed in 2006 and 2007 was identified using the Ontario Cancer Registry and for whom ≥1 pathology report was available from CCO. Information was collected from pathology reports, provincial and CIHI databases to determine surgical procedure, stage, hormone receptor status, HER2 testing, TRA treatment, income quintile, urbanicity, most responsible physician and regional cancer centre (RCC). Univariate odds ratios (ORs) were estimated to determine association of HER2 testing with covariates and multivariate logistic regression assessed HER2 documentation patterns.

Results: HER2 testing was documented for 66% of the 13,396 patient cohort from CCO-held pathology reports. No difference in test documentation was detected for patients across income quintiles (p>0.3550). Age was a significant predictor in univariate but not multivariate analysis. Rural residence predicted lower test documentation (adjusted OR 0.74 [0.63, 0.86]). Stage also predicted test documentation, with higher stage associated with greater likelihood of a documented test. Diagnosis outside an RCC was associated with significantly higher odds of test documentation (adjusted OR 1.23 [1.10, 1.39]).

Conclusions: The results suggest differential HER2 test documentation or pathology reporting patterns by treatment setting and disease severity, perhaps partially because HER2 status wasn't a mandatory reporting element for the CCO-maintained cancer registry. Adherence to guidelines for testing and treatment will be assessed.

Keywords: *HER2, practice patterns, retrospective cohort*

8

From priorities to action: improving cardiovascular prevention in primary care

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interventions en sciences infirmières du Québec (GRIISIQ), Canadian Institute of Health Research (CIHR); Pfizer Canada Inc., Réseau de recherche en santé des populations du Québec (RRSPQ), Réseau québécois de recherche sur l'usage des médicaments (RQRUM), Sanofi-Aventis.

Background: Cardiovascular disease (CVD) prevention in primary care (PC) needs to be improved to meet with the particular needs of the multimorbid patients, who require interprofessional care. The Chronic Care Model (CCM) is a guide to redesigning chronic care, yet it must be adapted to specific context.

Methods: Over 60 PC actors (physicians, nurses, pharmacists, nutritionists, kinesiologists, psychologists, tobacco cessation experts, clerical assistants, decision makers, patients and family members) are engaged in participatory research in Laval. Priorities for action to improving CVD prevention in PC among multimorbid patients were explored in an interactive workshop. Thereafter, those priorities were translated in a specific program of interventions by PC actors working in a large working group and sub-groups meetings.

Results: Priorities for action target three domains of the CCM: management of clinical information, organisation of care and services delivery, and self-management support. The program of interventions is based on interprofessional collaboration and centered around a PC case manager nurse. It is supported by a systematic follow-up protocol and collective prescriptions. To enhance self-management, a personalized CVD health booklet was created. In addition, to improve professional skills, clinicians will be trained to perform motivational interview and to use the computerized directory of health resources to improve access to community programs and to other PC clinicians.

Conclusions: Using a pragmatic randomized trial (TRANSIT project), two approaches will be tested to implement the program in 9 Family Medicine Groups: facilitation and passive diffusion.

Keywords: *Participatory research, clinical prevention, cardiovascular disease*

9
Generic drug pricing in Canada

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Funding Source: The Health Council of Canada commissioned the discussion paper, *"Generic drug pricing and access in Canada: What are the implications?"* The Health Council of Canada receives funding support from Health Canada. The views expressed here do not necessarily represent the views of Health Canada.

Background: Governments are trying to restrain the increasing cost of drugs which contribute to Canada's growing health care expenditure. The greater use of generic drugs accounts for a large portion of these rising costs. Canadians pay higher prices for generic drugs than many other countries. The Health Council of Canada's commissioned paper, *"Generic drug pricing and access in Canada: What are the implications?"* discusses the issues related to the high cost of generic drugs and the longstanding lack of transparency about how prices and drug plan reimbursement policies are set.

Methods: An extensive literature review on generic drug pricing and access was supplemented by interviews with a broad range of stakeholders and experts. Comparisons between Canada and five other countries that had similar pricing and reimbursement policies were made using data from the most recent country-specific, publicly available documents found and confirmed by international experts.

Results: Overall, there are many similarities between pricing and reimbursement policies in Canada compared to other countries. Key differences lie in the mechanisms and approaches used to determine drug plan reimbursement. Six critical success factors were identified to achieve greater affordability, accessibility, and sustainability, along with transparency of generic drug transactions. Potential options for governments were developed.

Conclusions: Creating a more sustainable drug system that meets the needs of patients and minimizes the negative impacts on stakeholders is challenging. Policy makers and drug-plan managers are encouraged to consider the various options presented and their impacts in bringing forward more affordable and transparent drug prices.

Keywords: *Generic drug pricing, reimbursement policy, drug access*

10
Health care costs of uncontrolled asthma: a population-based cohort study in British Columbia, 2002-2007

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Funding Source: This study was funded by AllerGen.

Background: Despite increased adoption of clinical guidelines by providers, many patients with asthma continue to exhibit poor symptom control. The objective was to calculate the health care costs associated with uncontrolled asthma in British Columbia (BC).
Methods: BC asthma patients for years 2002-2007 were selected from the BC discharge abstract database, medical services plan, and PharmaNet from 2002 to 2007. Patients 14-44 years old were stratified by level of asthma severity and control using a validated algorithm based on administrative data created for this age group (Firoozi et al.). Fee-for-service values for physician visits, government reimbursement fees for prescribed medications, and the case mix method was used to calculate hospitalization costs. All costs were reported in inflation-adjusted 2008 Canadian dollars.
Results: 210,233 unique patients fulfilled the case definition of asthma, contribution to a total of 1,092,832 patient-years. The identified cohort of patients was responsible for $288.0 M in direct health care costs during the 6-year period, corresponding to $48.0 M annually. Overall, 74.9%, 21.4% and 4.6% of patient-years were categorized as mild, moderate and severe asthma, respectively. Mild, Moderate and Severe asthma accounted for 14%, 26%, and 60% of this total cost, respectively. The ratio of annual costs per patient for uncontrolled versus controlled asthma was 5.7 for mild, 0.3 for moderate and 2.0 for severe disease. Asthma was poorly controlled in 39.3% of patients and responsible of 93% of the total cost.
Conclusions: Uncontrolled asthma is responsible for the majority of the costs attributed to asthma in BC.
Keywords: *Asthma, health care costs, retrospective study*

11
Income-related inequity in drug treatment following acute myocardial infarction

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Background: Income affects receipt of cardiac procedures following AMI; however little is known about the association between income and use of recommended medicines in this population.
Methods: Using administrative datasets, we identified all patients in British Columbia who survived for at least 120 days after their first AMI between January 1st 1999 and September 3rd 2006 (n=28,216), and calculated adjusted odds ratios of initiating on each medicine outlined above as well as all three medicines adjusting for age, general health status and urban residence using logistic regression. Among those who initiated we calculated concentration indices (commonly used measures of income inequality in health services use) and examined the income-related inequities in days of therapy and spending on each medicine.
Results: Our results reveal that men in the 3rd income quintile and above are significantly more likely to initiate on treatment with ACE-inhibitors, beta-blockers, and statins than men in the 1st (lowest) income quintile. Men in the highest income quintile had 37%, 50% and 71% higher odds of initiating than those in the lowest income quintile. Women in the highest income quintile were more likely to initiate on beta-blocker and statins. Concentration indices reveal that individuals of higher income were significantly more likely to receive more days of therapy use and to spend more on ACE-inhibitors, statins and all three medicines.
Conclusions: There are important inequities in treatment following AMI both in initiating on recommended therapies and, among those who initiated, in the days of use and spending on each of the therapies.
Keywords: *Equity, pharmaceuticals use, acute myocardial infarction*

12
Influence of birth month on diagnosis and treatment of attention-deficit/hyperactivity disorder in school-age children

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Funding Source: This work was funded by a grant from the Canadian Institutes of Health Research (CIHR) and from a 5-year renewable grant to the University of British Columbia from the British Columbia Ministry of Health Services.

Background: To explore the influence of birth month on diagnosis and treatment of attention-deficit/hyperactivity disorder in children, using large

databases containing most prescriptions and medical services in British Columbia, Canada.
Methods: The study cohort consisted of 994,100 children who were 6 to 12 years of age at any time during the study period. In British Columbia, the cut-off birth date for entry into kindergarten or grade one is December 31, so children born in January are the oldest in their grade. We categorized patients by calendar month of birth and calculated the fraction of patients prescribed methylphenidate, dextroamphetamine, amphetamine or atomoxetine and the fraction of patients diagnosed with this disorder by month. The study period was January 1, 1997, to December 31, 2008.
Results: If they were born in December as compared to January, the percentage of children prescribed an attention-deficit/hyperactivity disorder medication was 1.39% (95% CI: 1.12-1.66%) greater for boys and 0.72% (CI: 0.56-0.88%) greater for girls, and the percentage of children diagnosed with the disorder was 1.67% (CI: 1.34-2.00%) greater for boys and 1.07% (CI: 0.88-1.27%) greater for girls. If they were born in December as compared to January, boys were 41% more likely (relative risk 1.41; CI: 1.31-1.50) and girls 78% more likely (relative risk 1.78; CI: 1.57-2.02) to be prescribed an attention-deficit/hyperactivity disorder medication.
Conclusions: It is likely that in many cases normal differences in maturity are interpreted as symptoms of attention-deficit/hyperactivity disorder. These findings raise concerns about potential harms from over-diagnosis and over-prescribing.
Keywords: *Attention-deficit/hyperactivity disorder, cohort study, stimulants*

13
Interventions to increase influenza and pneumococcal vaccinations in community-dwelling adults: a systematic review and meta-analysis

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Funding Source: Alberta Innovates - Health Solutions, Canadian Institutes of Health Research

Background: Influenza and pneumococcal vaccination rates remain below national targets. How best to improve them - remains unclear.
Methods: We systematically reviewed effectiveness studies of quality improvement interventions for improving vaccination rates. Studies were identified by searching Medline, Embase, and other databases, and the bibliographies of included studies. Studies were included if they featured a parallel control group and targeted rates of influenza or pneumococcal vaccinations in community-dwelling adults. We performed a random effects meta-analysis.
Results: We analyzed 111 comparisons from 77 studies. Interventions were significantly associated with improvements in rates of any vaccination (pooled OR = 1.61), and of influenza (OR = 1.46) and pneumococcal (OR = 2.01) vaccinations. Patient outreach achieving personal contact was most effective (telephone reminders for influenza, OR = 2.74; point-of-care brochures for pneumococcus, OR = 5.86). Team changes were effective for promoting vaccinations (influenza OR = 1.44, pneumococcal OR = 2.09), especially where nurses administered vaccinations. Patient and clinician financial incentives improved influenza vaccination rates (OR = 1.98 and 1.52, respectively). Audit and feedback (OR = 1.83) improved influenza, but not pneumococcal, vaccinations. Conversely, clinician reminders were more effective for pneumococcal (OR = 2.27) than influenza (OR = 1.53) vaccinations. Study quality varied, but was not associated with outcomes. Some evidence of publication bias was detected.
Conclusions: Quality improvement interventions, especially those that assign vaccination responsibilities to non-physician personnel, or that activate patients through personal contact can modestly improve vaccination rates in community dwelling adults. To meet national targets more potent interventions should be developed.
Keywords: *Primary care, influenza vaccination, pneumococcal vaccination, quality improvement*

14
Medically assisted reproduction (MAR), including ovulation stimulators, and the risk of major congenital malformations: the AtRISK Study

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Funding Source: Canadian Institutes of Health Research (CIHR)

Background: Although limited data exist on the neonatal risk of major congenital malformation (MCM) associated with medically assisted reproduction (MAR), no such data are available for women using ovulation stimulators (OS) alone. Our objectives were to quantify and compare the risk of MCM associated with the use of MAR.
Methods: We conducted a case-control study using a pregnancy cohort built with the linkage of 4 sources of data: a self-administered questionnaire on history of use of ART including OS, and three administrative databases, the RAMQ, MedEcho and ISQ on health care utilization, diagnoses and hospitalizations data. All Quebec women having at least one live birth between years 2006-2008 were eligible to enter this cohort and were sampled from the RAMQ database. Cases were defined as a pregnancy resulting with at least one newborn with a MCM diagnosed in the first year of life. Controls were pregnancies that did not result in MCM or minor CM. The risk of MCM associated with the use of MAR was compared to the risk in spontaneously conceived pregnancies, stratified on multiplicity status.
Results: The cohort included 1407 singleton and 3580 multiple pregnancies with 465 cases and 4522 controls. The unadjusted risk of MCM associated with the use of MAR among singleton births was 1.43 (95% CI 0.88-2.30); and 1.55 (95% CI 1.19-2.02) among multiple births.
Conclusion: This study suggests that overall use of MAR increases the risk of MCM among pregnancies resulting in multiple births only.
Keywords: *Assisted reproductive technology, fertility therapy/ovarian stimulators, congenital malformation/ birth defect*

15
Public opinions on physician-pharmaceutical industry interactions: a Canadian survey

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Funding Source: Canadian Institutes of Health Research

Background: Many health professional and regulatory groups have guidelines for identifying, disclosing and managing potential conflicts of interest (COI). The opinions of the Canadian public regarding what constitutes COI, are unknown.
Methods: Bilingual telephone survey in all provinces using a validated questionnaire on physician-pharmaceutical industry interactions. Random digit dialing (RDD) with representative national sampling, including persons 18 years and older.
Results: 1041 participants (56.8% female, mean age 52.6 years (SD 16.5), 18.2% francophone, 85.5% graduated secondary school), completed the survey between May and September 2010. 64.8% had previously heard the term 'conflict of interest' in discussions about physicians and pharmaceutical companies. Median Likert scale ratings for the acceptability of various types of interactions ranged from: Very Acceptable for calling a drug company to request information on a particular drug; to Somewhat Acceptable for accepting free drug samples to give to patients; to Very Unacceptable for getting paid for recruiting patients to research studies, for accepting samples for personal use, or for using information not yet public about a new drug to make investment decisions. Opinions were divided regarding acceptance of small personal gifts, free dinner talks given by a drug company employee, or all-expenses-paid medical conferences. Age and gender influenced ratings of acceptability.
Conclusions: Public opinion on the acceptability of some types of physician-pharmaceutical industry interactions seems to differ from current guidelines and policies of professional organizations and government agencies. Further research is warranted to elucidate the reasons behind public opinions.
Keywords: *Conflict of interest, public opinion survey, physician-pharmaceutical industry interactions*

16
Quality assessment of clinical practice guidelines for the prescription of antidepressant drugs during pregnancy

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Background: Antidepressant use during pregnancy remains a controversial subject, mostly because of the lack of consensus on the maternal / neonatal risks and benefits associated with their use. Clinical practice guidelines (CPGs) for antidepressant use during pregnancy can optimize practice, facilitate the implementation of effective interventions and improve pregnancy outcomes. Objectives: To appraise the quality of the available CPGs that discloses recommendations on antidepressant use during pregnancy.
Methods: We systematically searched documents published from January 2000 to September 2010 in MEDLINE / TRIP database and on clearinghouses and scientific society's websites. Four appraisers evaluated each guideline using the AGREE II. Descriptive statistics were used to summarize the characteristics of the selected guidelines. Intra-class correlation coefficients (ICC) along with 95% confidence intervals (CI) were calculated as an overall indicator of agreement. All tests were two-sided and SPSS (v 18.0) was used to conduct the analysis.
Results: Twelve CPGs were chosen from a total of 539 references. Only two guidelines were specifically addressed to pregnant women. The overall agreement among reviewers was high (ICC: 0.94, 95%CI: 0.86-0.98). The mean scores and standard deviation (SD) for each of the AGREE domains were: scope and purpose: 84.4% (12); stakeholder involvement: 67.4% (29.8); rigor of development: 68.6% (19.8); clarity and presentation: 83.4% (17.4); applicability: 44% (37.3); and editorial independence: 62.1% (30.4).
Conclusions: CPGs containing recommendations for antidepressant use during pregnancy showed a moderate to high quality. Future guidelines should take into account the observed drawbacks in some domains, and specifically focus on depression during pregnancy.
Keywords: *Antidepressants, pregnancy, clinical practice guidelines*

17

Relapse of depression in pregnant users and discontinued users of antidepressants: results from the OTIS Antidepressants Study

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Background: To compare the risk of depressive relapse in pregnant women who discontinue/continue antidepressants during gestation and women who do not use antidepressants.
Methods: To be included in the OTIS Antidepressants Study, women had to 1) call a teratogen information service in Canada or the USA during 2006-2010, 2) be greater or equal to 18 years old, 3) less or equal to 14 weeks of pregnancy at the time of the call, and 3) be exposed to an antidepressant or any exposure considered non-teratogenic at the time of the call. Socio-demographic and lifestyle data, and comorbidity history were collected during the 1st and 2nd trimesters by telephone interviews. Validated measures of depression, anxiety, and QOL were also collected.
Results: A total of 367 pregnant women were included; 149 did not use antidepressants during pregnancy, 180 used antidepressants continuously, and 38 used antidepressants at the beginning of pregnancy but discontinued before the end of the 2nd trimester (17% discontinuation rate). On average, continued

users improved during pregnancy but 17% remained depressed even while using their medication. Adjusting for potential confounders, and compared to non-users, discontinued users were 10.5 times more at risk of depression (95%CI: 3.5, 32.1), and continued users were 3.5 times more at risk of depression (95%CI: 1.3, 9.2) during the 2nd trimester. Discontinued users were 3.1 times more at risk of depression compared to continued users (95%CI: 1.3, 7.1).
Conclusions: Discontinuation of antidepressants during pregnancy increases the risk of depression but those who continue taking antidepressants are also at a high risk of depressive relapse.
Keywords: *Relapse of depression, pregnant women, users and discontinued users of antidepressants*

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Streamlining drug coverage in Canada: an analysis of new drug products before and after the introduction of the Common Drug Review process

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Background: The Common Drug Review (CDR) was introduced in Canada to provide participating publically funded drug plans with a transparent, rigorous, and consistent approach for assessing the clinical and cost-effectiveness of new drugs. We conducted a detailed pan-Canadian comparison of drug coverage metrics before and after the introduction of the CDR.
Methods: Using IMS FAME database we identified new drug products in Canada five years before and after the CDR's first recommendation on May 27, 2004. For each province, we compared the median time-to-listing (TTL), the proportion of drugs listed, and the agreement (kappa) among drug plans in both pre-CDR and post-CDR time periods. Mann-Whitney tests were used to compare differences in TTL.
Results: We identified 196 new drugs (109 pre-CDR, 87 post-CDR) meeting our study criteria, of which 61 had a CDR recommendation. The change in median TTL between pre-CDR and post-CDR periods ranged by province from 717 fewer to 169 more days. The change in median TTL was not statistically significant for most provinces, except SK (increased TTL), and NB, PEI, and NL (all decreased TTL) ($p<0.025$). The proportion of drugs listed decreased substantially in the post-CDR period (43% vs. 26%, $p<0.05$). Kappa's ranged from 0.33 to 0.74 for agreement between CDR recommendations and provincial listing decisions.
Conclusions: The introduction of the CDR into the Canadian drug access process was not associated with a change in TTL for the larger provinces (BC, AB, ON) but may have influenced TTL for a number of smaller provinces (SK, NB, PEI, NL).
Keywords: *Drug coverage, time-to-listing, common drug review*

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Systematic review of low-molecular-weight heparins versus unfractionated heparin in chronic hemodialysis patients

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Wendy Lim received an investigator-initiated, arms-length grant from Leo Pharma evaluating LMWHs in patients with renal failure. Mark Crowther is on a Pfizer advisory board and he holds Leo Pharma chair in Thromboembolism at McMaster University.

Background: During hemodialysis, unfractionated heparin (UFH) is widely used for prevention of extracorporeal circuit thrombosis. Low-molecular-weight heparin (LMWH) may have advantages in terms of bleeding risk. The study objective was to review the effectiveness, safety and cost-effectiveness of LMWHs versus UFH in chronic hemodialysis to inform a hospital formulary policy decision.
Methods: A systematic review was conducted of randomized (RCTs) and non-randomized trials (non-RCTs) published to April 2010 evaluating the effectiveness, safety or cost-effectiveness of LMWHs for use in hemodialysis versus UFH. Outcomes included extracorporeal circuit thrombosis, bleeding events, vascular access compression time, heparin-induced thrombocytopenia, and cost-effectiveness. Where possible, data was pooled via a random-effects model.
Results: After reviewing 998 citations, 25 studies were included (1 systematic review, 12 RCTs, 12 non-RCTs). Meta-analysis of RCTs demonstrated no statistically significant differences between LMWHs and UFH for bleeding (relative risk (RR)=0.70, $p=0.66$) or compression time (weighted mean difference= -2.49 min, $p=0.31$). Pooled RR for circuit thrombosis was 1.32 ($p=0.05$) and 0.67 ($p=0.69$) in

studies assessing the number of dialysis session and patients, respectively. Pooled results for the non-RCTs were not significantly different between LMWH and UFH. No studies evaluating the cost-effectiveness of LMWHs versus UFH were identified; however, 4 cost analyses evaluated treatment costs. Despite higher drug acquisition costs with LMWHs, overall costs were lower or comparable when considering differences in nursing time associated with administration and monitoring.

Conclusions: LMWHs demonstrated no clear advantage over UFH in terms of effectiveness or safety, but may result in lower or comparable overall hospital costs.

Keywords: *Hemodialysis, anticoagulants, systematic review*

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The cost-utility and value of information of transcatheter aortic valve implantation compared to standard management and surgical aortic valve replacement in patients with severe symptomatic aortic valve stenosis

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Funding Source: Canadian Institutes of Health Research (CIHR) Strategic Training Fellowship in Drug Safety and Effectiveness

Background: The primary analysis was to estimate the cost-effectiveness of TAVI compared to standard management (SM) in inoperable patients with severe, symptomatic aortic valve stenosis (SSAVS). The secondary analysis was to estimate the cost-effectiveness and value-of-information of TAVI compared to surgical aortic valve replacement (SAVR) in operable patients with SSAVS.

Methods: A combined decision-tree and Markov model was developed to compare the costs, life-years (LYs) and quality-adjusted life-years (QALYs) of TAVI (transfemoral (TF) and transapical (TA) approaches) to SM and SAVR over a 5-year time horizon.

Results: In the primary analysis, comparing TF and SM resulted in an incremental cost-effectiveness ratio (ICER) of $126,874/LY and $222,378/QALY. Comparing TA and SM resulted in an ICER of $262,672/LY and $1,454,241/QALY. In the secondary analysis, TF and SAVR were compared, resulting in an ICER of $39,676/LY and $81,758/QALY. Comparing TA and SAVR resulted in an ICER of $183,454/LY. TA was dominated by SAVR when comparing QALYs. The total expected value of information was at a maximum at a WTP threshold of $80,000/QALY with a value of $6,928. The expected value of partial perfect information was highest for the 30-day clinical event rates when compared to 1-year, 2-year and >3-year event rates.

Conclusion: This economic evaluation suggested that TAVI is not cost-effective for inoperable patients in comparison to SM. The secondary analysis suggested that TAVI is cost-effective for operable patients compared to SAVR. To reduce uncertainty in our estimate, empirical evidence related to clinical event rates occurring 30-days post operation should be collected.

Keywords: *Economic evaluation, value of information analysis, aortic stenosis*

POSTER PRESENTATIONS

21

A cost-effectiveness analysis of two commercially available gene expression profiling tests: implications for reimbursement decision-making and policy

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Background: Oncotype Dx and MammaPrint are two commercially available gene expression (GEP) tests increasingly being used to guide treatment decisions in early stage lymph node-negative, estrogen receptor-positive breast cancer patients. Our primary objective was to evaluate the cost-effectiveness of treatment decisions using Oncotype DX as compared with treatment guided by MammaPrint from a third party payer's perspective.

Methods: A 10-year Markov model was developed to compare the costs and quality-adjusted life years (QALYs) of treatment decisions guided by either Oncotype Dx or MammaPrint in a hypothetical cohort of early stage lymph node-negative, estrogen receptor-positive breast cancer patients. Outcomes included no recurrence, recurrence, and death. Base case

probabilities included risk classification of patients based on Adjuvant! Online and risk re-classification referred to as recurrence score. Costs considered included gene tests, adjuvant chemotherapy, other chemotherapy costs including pre-medication, oncology visits, patient time, monitoring for adverse events, recurrence, and end of life. Sensitivity analyses were conducted at a range of ±25% to check the robustness of the model.
Results: The model showed that patients that had been offered Oncotype DX spent $18,549 USD and gained 7.009 QALYs, whereas patients that had used MammaPrint spent $15,713 USD and gained 7.142 QALYs. Sensitivity analyses demonstrated that the results were robust to changes in all parameters.
Conclusions: The model suggested that MammaPrint is a more cost-effective GEP test compared to Oncotype DX at a threshold willingness-to-pay of $50,000 USD. This finding has implications for health policy, particularly health insurance reimbursement decisions.
Keywords: *Pharmacogenomics, gene expression profiling, economics, Markov modeling, cost-effectiveness, reimbursement decisions*

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An environmental scan of graduate training programs in Canadian universities able to train post-market drug safety and effectiveness researchers

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Background: Current efforts to modernize the Food and Drugs Act have the potential to strengthen post-market surveillance of drug safety and effectiveness in Canada. With the proposed increase in post-market research requirements, it is essential to ensure that adequate training sites are available to build future research capacity. The objective of this educational institution inventory was to enumerate the universities currently able to train graduate students in post-market drug surveillance and determine the prevalence of essential core courses by institution.
Methods: A systematic web-based environmental scan was conducted of all Canadian educational institutions with academic health-related graduate programs. Details on course availability, annual graduates, program duration and contact information were abstracted. Core courses deemed essential for post-market drug surveillance were biostatistics; epidemiology; pharmacoepidemiology; health economics and/or pharmacoeconomics; pharmacogenetics and/or pharmacogenomics; and patient safety and/or risk management and/or pharmacovigilance.
Results: Twenty-three eligible institutions across Canada were identified: 20 in human health; two with separate human and veterinary health programs; and one for post-graduate veterinarians only. Of the estimated 900 students graduating annually in these programs, about 500 were thesis-based MSc and PhD degrees. Few students appear to receive training specializing in post-market drug evaluation research. No institution offered all six core courses; four offered five courses, four offered four courses, and the remaining 15 institutions offered three courses or less.
Conclusions: Many Canadian institutions able to train post-market drug surveillance researchers lack the necessary core courses to enable capacity building within Canada of researchers able undertake high-quality research in this area.
Keywords: *Graduate education, post-market drug safety and effectiveness, regulatory renewal*

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Assessing the prognostic value of technetium-99m in coronary artery disease screening with myocardial perfusion imaging in asymptomatic patients with type 2 diabetes: a systematic review, economic evaluation and policy analysis

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Background: The consistent availability of medical isotopes, including technetium-99m (Tc-99m), has become a concern. Coronary artery disease (CAD) is the leading cause of death amongst patients with type-2 diabetes mellitus (T2DM) and is commonly tested for using Tc-99m myocardial perfusion imaging (MPI). Objectives: This Master's thesis aims to assess the prognostic value of Tc-99m MPI screening for asymptomatic CAD in patients with T2DM through a cost-utility analysis
Methods: A systematic review was first conducted. Peer reviewed literature searches were conducted in a broad range of bibliographic databases; grey literature was also identified. A relevant Markov transition model was developed and populated using data from

the review; costs and utility values were determined from the literature. Sensitivity analyses were conducted using Monte-Carlo simulations.
Results: Analysis is ongoing. The systematic review shows no significant clinical benefit for the screening program. The cost utility of screening from a Canadian healthcare payer perspective will be presented.
Conclusions: Conclusions on the clinical effectiveness and cost utility of Tc-99m MPI as a prognostic tool for detecting asymptomatic CAD in patients with T2DM will be presented.
Keywords: *Diabetes, coronary heart disease, SPECT*

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Association of co-payments with compliance and employee sick days/short-term disability (ACCESS): The ACCESS Study

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Background: Private payers are increasingly turning to approaches such as co-payment increases for plan members in an effort to control rising drug costs. However, evidence suggests an inverse relationship between co-payment amount and medication compliance, with resulting negative clinical and economic outcomes. Given this, plus the importance of medication compliance and already existing poor compliance, more data to inform co-payment policies are warranted. The ACCESS Study is designed to evaluate whether eliminating co-payments for selected drugs is associated with better compliance. Secondary objectives are to measure the impact on persistence, sick days, and short-term disability claims. Study rationale, design, and implementation will be described.
Methods: From July 12, 2010 to July 11, 2011, enrollees (n=33,435: 12,675 employees, 8005 spouses, and 12,755 dependents) in the drug plan of TELUS Corporation will have the co-payment waived when filling prescriptions for selected drugs. Outcomes in the 12-month co-payment elimination period will be compared to the 12-month pre-implementation period. Outcomes include: compliance (measured by the Medication Possession Ratio), measures of persistence [i.e. days to discontinuation, 6-month discontinuation rates, and persistence rates (no discontinuations or gaps >30 days)], sick days, and short-term disability claims. Data analysis will be performed using data currently collected as part of prescription claims adjudication and casual absence/short-term disability data that are currently tracked by TELUS.
Discussion: To our knowledge, this is the first Canadian controlled trial of co-payment reductions. Results may provide evidence to support policy and innovative approaches with regards to drug benefit design and delivery.
Keywords: *Co-payments, compliance, database analysis*

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Canadian chronic phase chronic myeloid leukemia (CP-CML) treatment patterns and clinical outcomes study

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Background: In 2001, Health Canada approved a novel treatment for CP-CML, followed by the approval of two second-generation agents in the next 8 years. There exists little data regarding treatment of CP-CML patients in the real world. The objective of this analysis is to document patterns of care for CP-CML patients in Canada following the introduction of new treatment options.
Methods: Treatment patterns were obtained from the ONCO-CAPPS database, which includes treatment summaries of over 12,000 Canadian cancer patients. CP-CML patients eligible for the study were 18 years or older, received 400mg of imatinib as 1st-line treatment for at least 4 continuous weeks between October 2008 and December 2009.
Results: 301 patients met the selection criteria, 62% had a confirmed CP-CML diagnosis for at least 2 years. 49% of patients achieved a response on imatinib 400mg. Of the 51% (155/301) who received a 2nd line treatment option, the majority (77%) had an imatinib dose change. 32% (50/155) of these patients had an increase in imatinib dose to an average daily dose of 664 mg (66% increase in dose); average response times for these patients exceeded the Canadian Consensus Guidelines. Furthermore, 45% (69/155) of patients receiving a 2nd line treatment option had an imatinib dose decrease or interruption due to intolerance. Switching to a second generation TKI occurred in 20% of patients.
Conclusions: These results suggest that when 2nd-line treatment for CP-CML is indicated, consideration should be given to second-generation TKIs.
Keywords: *Canadian, chronic myeloid leukemia (CML), tyrosine kinase inhibitors (TKIs)*

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Canadian public drug program spending on seniors, 2002 to 2008

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Background: Seniors are estimated to account for about 40% of all Canadian retail spending on prescription drugs, and make up a significant proportion of public drug program expenditures. This analysis examines the types of drugs accounting for the majority of public drug program spending for seniors, and the distribution of program spending across seniors.
Methods: Claims-level data from the National Prescription Drug Utilization Information System (NPDUIS) Database were analyzed for 1,039,642 seniors on public drug programs in six provinces between 2002 and 2008. Public drug program spending on seniors refers only to the portion of prescription costs paid by the public drug program, including professional fees and markup.
Results: In 2008, the top 10 drug classes, in terms of public drug program spending, accounted for 48.3% of all spending on seniors in the six provinces. Statins accounted for the highest proportion of program spending for seniors, while 4 of the top 10 classes were used to treat hypertension. 45.5% of public drug program spending was for 14.7% of seniors, where the drug programs paid $2,500 or more of their annual drug costs. Tumour necrosis factor alpha inhibitors were the fastest growing drug class, in terms of spending, growing at 58.4% per year between 2002 and 2008.
Conclusions: Findings show almost half of drug program spending for seniors is on a small number of drugs. This suggests that cost saving initiatives that impact spending on these drugs could have a significant impact on overall public drug program spending.
Keywords: *Seniors, drug expenditure, drug claims analysis*

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Number and type of drugs used by seniors on public drug programs in Canada, 2002 to 2008

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Background: The use of multiple medications can increase the risk of adverse effects, drug interactions and non-compliance, all of which may result in less-than-optimal health outcomes. Seniors are at particularly high risk of adverse effects. This analysis examines the number and types of drugs being used by seniors, and how utilization changes as seniors age.
Methods: Claims-level data from the National Prescription Drug Utilization Information System (NPDUIS) Database were analyzed for 1,039,642 seniors on public drug programs in six provinces between 2002 and 2008. Drug classes were defined using the World Health Organization's Anatomical Therapeutic Chemical classifications.
Results: In 2008, 21.4% of seniors on public drug programs had claims for 10 or more drug classes, a slight increase from 2002 (18.6%). The number of drug classes used by seniors increased with age. The most commonly used drug classes were used to treat chronic conditions such as high cholesterol, hypertension, heart failure, and emphysema. Statins were the most commonly used drug class among seniors aged 65 to 84, while single-ingredient ACE inhibitors were the most commonly used class among those aged 85 and over.
Conclusions: Findings suggest a high proportion of seniors may be at risk for drug interactions and other adverse events due to the number of medications they are taking. Although it may be appropriate for a patient to be taking a high number of medications, this illustrates the importance of medication management strategies for seniors, and the need for communication between health care providers regarding seniors' drug regimens.
Keywords: *Seniors, polypharmacy, drug claims analysis*

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Challenges in the economic evaluation of topical anti-rosacea agents: an illustration using azelaic acid

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Background: Conducting an economic evaluation of topical anti-rosacea agents presents unique challenges with regard to quantifying volumes and duration of use of the comparators. Here, we illustrate one approach to address these challenges using an analysis of azelaic acid vs. metronidazole 0.75% as topical treatment of rosacea.
Methods: A cost-minimization analysis (CMA) was conducted over a 1- year time horizon from the

perspective of a publicly funded health care system. Clinical inputs were based on a head-to-head trial of topical azelaic acid vs. topical metronidazole 0.75%. Inputs on volume and duration of use were based on the trial and expert opinion. All costs were reported in 2009 Canadian dollars (CAD).
Results: Neither market data (e.g. IMS) nor dosing protocols confirmed daily volumes or length of time the products are used. Thus, assumptions were made for both comparators based on the trial and expert opinion. The acquisition cost (List Price) of azelaic acid ($0.60/gram) is lower than that of metronidazole 0.75% ($0.66/gram). The economic analysis demonstrated that azelaic acid represents a cost-savings of $21.90 per patient compared to metronidazole 0.75% over a 1-year time horizon.
Discussion: Generally, published guidelines or product monographs can be referenced for therapy regimens and/or volume and duration of use can be derived from market data. In this case, the topical format of the products created challenges for quantitative validation. Subsequently, other data sources informed our assumptions for the economic evaluation. Our analysis demonstrated that azelaic acid offers cost-savings compared to metronidazole 0.75% in the topical treatment of rosacea.
Keywords: *Cost-minimization analysis, rosacea, azelaic acid*

ENCORE PRESENTATION

29

Changing patterns of androgen deprivation therapy use in prostate cancer patients in Ontario from 1995 to 2005

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Common Drug Review recommendations: analysis of predictors

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Background: The Common Drug Review (CDR) was created to provide a single process to review the comparative clinical efficacy and cost-effectiveness of new drugs, and to make formulary listing recommendations to Canadian publicly funded drug benefit plans.
Objective: The objective was to conduct an in-depth analysis of CEDAC recommendations, to explore predictors associated with negative recommendations.
Methods: Final recommendations were identified from inception to December 31, 2009. Recommendations were analyzed under the following categories: submission specifics, drug characteristics, clinical factors and economic factors. Descriptive analyses were conducted, followed by statistical analyses to determine which factors independently predicted a 'Do Not List' (DNL) recommendation.
Results: The database consisted of 138 unique final recommendations. The overall DNL rate was 48%. Significant differences in DNL rates were observed between therapeutic areas, from 0% for HIV antivirals up to 88% for analgesic drugs. In the multivariate regression, four factors were significantly predictive of a DNL recommendation: clinical uncertainty (odds ratio = 14), price higher than comparators (odds ratio = 9), request for reconsideration (odds ratio = 10) and price as the only economic evidence used (odds ratio = 18). Incremental cost-effectiveness thresholds were not predictive of recommendations.
Conclusions: This review documented an evidence-driven process that simultaneously weighted multiple factors. Clinical uncertainty and price considerations, but not economic results, had a strong impact on the recommendations. Insufficiency of clinical evidence may have resulted from the gap in evidence available at the time of product launch, and the absence of demonstrated benefits to support innovative drugs.
Keywords: *Decision-making, reimbursement, drug policy*

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Comparative net cost impact of the utilization of Nplate® (romiplostim) and Intravenous Immunoglobulin (IVIg) for the treatment of patients with Immune Thrombocytopenia (ITP) in Ontario

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Background: ITP is an autoimmune disorder characterized by bleeding due to low platelet counts (thrombocytopenia). Nplate® safely increases and sustains platelet counts in most adults with chronic ITP. IVIg, another treatment approved for ITP, is an expensive and occasionally scarce blood product. Using Nplate® instead of IVIg can result in savings to the provincial healthcare budget.
Methods: A net cost impact model was developed to provide a detailed analysis of the cost implications of Nplate® utilization compared with IVIg. Expert consultation was used to define treatment algorithms including all health resource utilization required when using Nplate® and IVIg. Costs were assigned to direct (e.g., drugs, medical supplies, laboratory testing, healthcare professionals' time) and indirect (e.g., productivity) healthcare resources.
Results: Based on the median weekly dose observed in the pivotal clinical trial (3mcg/kg), the annual cost of Nplate® per patient was $50,950. The annual per patient cost of IVIg was $107,041 based on an average dose suggested by a clinical expert (1g/kg every 4 weeks and average administration time of 3.5 hours). Lower costs for preparing, administering and indirect costs were attributed to Nplate® compared to IVIg .
Conclusion: Treating ITP patients with Nplate® can provide a lower cost alternative to IVIg for the overall provincial healthcare budget. Compared with IVIg, using Nplate® results in less direct costs, health care resource utilization and indirect costs. Finally, the use of Nplate® can allow for improved healthcare resource allocation where IVIg, can be reserved for use in other areas of greater need.
Keywords: *Nplate®, immune thrombocytopenia, net cost impact*

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Comparison of amiodarone-treated to antiarrhythmic naïve elderly patients with atrial fibrillation: an observational study

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Background: Amiodarone is the most frequently used antiarrhythmic agent for atrial fibrillation (AF). However, its use is somewhat limited by potentially serious side-effects, particularly in elderly patients. Our objective was to characterize and compare health-care resource utilization in elderly AF patients with and without amiodarone therapy.
Methods: A random sample of 3,711 patients with AF >75 years of age and newly prescribed amiodarone (A-group) between January 1998 and April 2009 was obtained from RAMQ. Patients on amiodarone were age and sex-matched to controls with AF who were antiarrhythmic naïve (N-group). The index date (iDate) was defined as the date of initiating amiodarone therapy or the matching date for N-group patients.
Results: Mean follow-up time was 37.2 months .In the year prior to the iDate, patients in the A-group had more frequent medical resource utilization (35.6 versus 24.3, $p<0.001$).. The following diagnoses were statistically more frequent in the A-group: bradycardia, cardiomyopathy, endocardium disorder, mobitz type II atrioventricular block and ventricular arrhythmia. Of particular interest was the fact that pulmonary fibrosis (1.6% versus 0.4%, $p<0.001$) and dysthyroïdism (17.0% versus 7.1%, $p<0.001$) were also more frequent in the A-group. However, the incidence of dermopathy and hepatic dysfunction were similar. Mortality was lower in the A-group ($p<0.05$). Fifty percent of the A-group had discontinued amiodarone therapy after 10.3 months.
Conclusions: More potentially amiodarone-related diagnoses were present in the A-group. This could be in part due to the fact that this group was already sicker at the iDate. However, mortality was lower in the A-group.
Keywords: *Atrial fibrillation, antiarrhythmia agents, administrative data*

33
Concordance between preconceptional and periconceptional vitamin/folic acid supplementation and the joint SOGC-MOTHERISK clinical guidelines

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Background: Folic acid deficiency during embryogenesis is known to be an environmental risk factor for neural tube defects (NTD). In 2007, the Society of Obstetricians and Gynaecologists of Canada (SOGC)-MOTHERISK introduced new guidelines aimed at reducing the occurrence and recurrence of NTDs among women at intermediate to high risk (obese, diabetics, family history of NTD). The objective of this study is to identify predictors of adequate folic acid supplementation in women of childbearing age.
Methods: From May to July 2010, pregnant women attending the outpatient clinic at CHU Ste-Justine were recruited during the second trimester of pregnancy. Data on socio-demographic factors, lifestyles, and folic acid supplementation before and during pregnancy were recorded using a self-administrated questionnaire. Statistical analysis was performed using t-tests for continuous variable and Chi-square tests for categorical variables.
Results: Women with postsecondary education (68% vs. 38%, $p<0.0001$), women in a stable relationship (64% vs. 19%, $p<0.0001$), and women with a family income greater than $60 000 (compared to women with a family income < $40 000 (72% vs. 41%, $p<0.001$)) were more likely to have folic acid supplementation before conception compared to others.
Conclusions: Women with a higher socio-demographic status were more likely to have folic acid supplementation preconceptionally than others.
Keywords: *Pregnancy, folic acid, neural-tube defects*

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Cost eEffectiveness Analysis of Intranasal Live Attenuated (LAIV) versus Injectable Inactivated (TIV) Influenza Vaccine for Canadian children and adolescents

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Background: Although influenza affects all age groups, influenza is common in children. Between 15% and 42% of preschool and school-aged children experience influenza each season. Recently, LAIV has been approved in Canada for use in eligible persons aged 2-59 years of age. The objective was to determine the cost-effectiveness of LAIV compared to TIV in Canadian children and adolescents from a Ministry of Health perspective and a societal perspective.
Methods: A previously published US cost-effectiveness model using patient-level data to compare LAIV and TIV was supplemented by secondary (e.g. literature) and primary data (i.e. survey of 144 Canadian physicians). To compare the costs and benefits of LAIV and TIV, a cost-utility analysis was conducted. Parameter uncertainty was addressed through probability sensitivity analysis.
Results: Although LAIV increased vaccination costs compared to TIV, LAIV reduced the number of influenza illness cases and lowered the number of hospitalizations, ER visits, outpatient visits and parents' days lost from work. The estimated offsets in direct costs saved were $4.19 per vaccinated child aged 2-17 years. Societal savings were $35.33 per vaccinated child. When costs and outcomes were considered, LAIV was the dominant strategy when compared to TIV. At a willingness to pay of $50,000 per QALY gained, the results of the PSA indicated that the probability of LAIV being cost-effective was almost 1.
Conclusions: LAIV reduces the burden of influenza in children and adolescents. Consistent with US results, vaccinating children with LAIV instead of TIV is the dominant strategy from a societal and MoH perspective.
Keywords: *Flu, vaccine, cost-effectiveness*

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Evaluation of a workplace health program for British Columbia public service agency (Canada) - an example of partnership in employee health

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Background: To evaluate the My Health Matters! (MHM) program, a multifaceted workplace intervention relying on education and awareness, early detection and disease management with a focus on risk factors for metabolic syndrome.

Methods: The MHM program included a health risk assessment combined with an opportunity to attend an on-site screening, face-to-face and call back visits as well as related on-site educational programs. The MHM program was offered to 2,000 public servants working in more than 30 worksites in British Columbia, Canada. Clinical and economic outcomes were collected over time in this one-year prospective study coupled with administrative and survey data.
Results: Forty three per cent of employees (N=857) completed the online HRA and 23 per cent (N=447) attended the initial clinical visit with the nurse. Risk factors for metabolic syndrome were identified in more than half of those attending the clinical visit. The number of risk factors significantly decreased by 15 per cent over six months (N=141). The cost per employee completing the HRA was $205 while the cost per employee attending the initial clinical visit was $394. Eighty-two per cent of employees would recommend the program to other employers.
Conclusions: This study supports that workplace interventions are feasible, sustainable and valued by employees. As such, this study provides a new framework for implementing and evaluating workplace interventions focusing on metabolic disorders.
Keywords: *Workplace intervention, metabolic syndrome, employee satisfaction*

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The burden of illness of osteoporosis in Canada

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Background: Since the 1993 estimate of the burden of osteoporosis in Canada, the population has aged and new treatment options have been introduced. The study purpose was to estimate the current burden of illness due to osteoporosis in Canadians aged 50 and over.
Methods: Analyses were conducted using five national administrative databases from the Canadian Institute for Health Information for the fiscal-year ending March 31 2008 (FY 2007/08). Gaps in national data were supplemented by provincial data extrapolated to national levels. Osteoporosis-related fractures of the hip, humerus, vertebra, wrist, other sites and multiple sites were identified using a combination of most responsible diagnosis and intervention codes. Fractures associated with severe trauma codes were excluded from the analysis. Costs, expressed in 2010 dollars, were calculated for osteoporosis-related hospitalizations, emergency care, same day surgeries, rehabilitation, continuing care, home care, long-term care, prescription drugs, physician visits and productivity losses. Sensitivity analyses were conducted to measure the impact on the results of key assumptions.
Results: Osteoporosis-related fractures were responsible for 57,413 acute care admissions and 832,594 hospitalized days in FY 2007/08. Acute care costs were estimated at $1.2 billion. When outpatient care, prescription drugs and indirect costs were added, the overall yearly cost of osteoporosis was over $2.3 billion for the base case analysis and as much as $3.9 billion if a proportion of Canadians were assumed to be living in long-term care facilities due to osteoporosis.
Conclusion: Osteoporosis is a chronic disease that results in a substantial economic burden to the Canadian society.
Keywords: *Osteoporosis, burden of illness, Canada*

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Cost-effectiveness of febuxostat in managing Hyperuricemia in gout patients in Canada

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Background: Febuxostat is a xanthine oxidase inhibitor indicated to lower serum uric acid (sUA) levels in patients with gout. Studies have indicated a positive correlation between elevated sUA and outcomes, such as flare and quality of life.
Methods: A Markov model was developed to compare the cost-effectiveness of febuxostat 80mg versus allopurinol from the Canadian public payer perspective. Data on the efficacy of febuxostat and allopurinol in managing sUA levels were derived from febuxostat phase III trials. Patient results were stratified by renal function. Risk of gout flare per sUA level was obtained from published literature. Drug cost and gout management costs were derived from Ontario Drug Benefit Formulary and a Canadian health records database. 5% discount rate and 30-year time horizon was applied in the base case analysis. The model predicts cost and quality adjusted life years (QALYs) gained for a representative patient with gout.

Results: Base case results show febuxostat to be cost-effective when compared to allopurinol with an incremental cost-effectiveness ratio (ICER) of $18,395 per QALY gained for patients with normal renal function. The model shows febuxostat to be moderately more cost effective in the population with impaired renal function, (ICER of $15,468 per QALY gained). Probabilistic sensitivity analyses show febuxostat to be cost-effective in the population with normal renal function under various conditions with less than 5% probability of the ICER to exceed $33,000 per QALY gained.
Conclusions: Results suggest febuxostat is a cost-effective treatment in the Canadian healthcare setting for the management of hyperuricemia in patients with gout.
Keywords: *Febuxostat, hyperuricemia, Markov*

ENCORE PRESENTATION

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Currently available platelet function tests are highly variable when used to identify patients who are resistant to clopidogrel

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Decision-making for rare diseases: developing evidence-based clinical practice guidelines for growth hormone therapy in Prader-Willi syndrome using the EVIDEM framework

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Funding Source: None

Background: Prader-Willi syndrome (PWS) is a rare and complex multisystem disorder, with serious long-term consequences. Use and coverage of growth hormone (GH) in patients with PWS vary widely across Canada and there is a need to clarify its benefits.
Objective: To test a pragmatic framework (EVIDEM) to: 1) clarify the state of knowledge regarding GH therapy in PWS and 2) facilitate compliance with the recommendations of the AGREE collaboration in developing clinical practice guidelines (CPG) to support evidence-based decision-making.
Methods: An extensive literature review was performed to identify and synthesize available evidence on GH for PWS for each criterion of the EVIDEM framework. The framework was adapted to include a CPG module, complying with AGREE requirements, which was used to identify questions for CPG development. Experts were involved in the process of validation.
Results: Evidence was compiled and validated for 13 scientific criteria covering disease impact, therapeutic context, treatment outcomes (efficacy/effectiveness, safety, patient-reported outcomes), type of benefits and economic impact. The efficacy criterion was subdivided into sub-criteria for each type of outcome measured including growth, body composition, exercise tolerance, metabolic effects, bone health, cardiovascular health, psychomotor development and behavioral outcomes. Relevance and validity of evidence were assessed. Data for six contextual and ethical criteria were also summarized. CPG questions were aligned with each decision criterion, using the CPG module, to develop international CPG during a consensus workshop.
Conclusions: The framework provides a pragmatic means for systematic assessment of evidence and identification of questions to guide clinical practice and evidence-based decision-making.
Keywords: *Decision-making, evidence-based medicine, health technology assessment*

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Designing a national eHealth Drug Safety and Effectiveness Research Network

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Background: Health information technology has not met its potential to improve drug safety, effectiveness or quality of use. Our objective was to evaluate the potential merits and challenges of a national eHealth data network.
Methods: Focus group and key informant feedback on a prototype data platform linking primary care electronic medical records (EMRs), community pharmacy databases, and hospital electronic health records (EHR). We sought input on data architecture as

well as network governance, privacy and methodology development.
Results: Experts in EMR /EHR/pharmacy data use or structure or research; large database management or research; and health information privacy (n = 65) noted that no such national network exists internationally. While EMRs and EHRs contain relevant data elements additional to health administrative databases, they currently require extensive cleaning, organizing, de-identification and validation for research purposes. Much more work on eHealth standards is required for the dozens of EMRs and EHRs in healthcare to communicate. A distributed data network (rather than one central database) appears to deal with health information privacy most effectively, but will require significant statistical and data management planning and expertise. Community pharmacy data linkages with prescribers were seen as a potential quality of care gain, but requiring further incentives and a shared person identifier. Governance was judged to depend on degree of autonomy of the network. Methodology priorities included data quality validation and extraction interface templates for researchers.
Conclusion: Development of a national eHealth network design suitable for drug safety and effectiveness research is underway.
Keywords: *Drug safety and effectiveness, network design, health information technology*

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Determinants of adherence to antidiabetes treatment among newly treated patients with oral antidiabetes drugs

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Background: Lack of adherence to drug treatment is a major barrier to the control of type 2 diabetes.
Objectives: To measure the proportion of new OAD users still on an antidiabetes treatment after 365 days and, among them, the proportion of those who are compliant. To identify the determinants of persistence and those of compliance.
Methods: We performed a population-based cohort study using the Quebec Health Insurance Board databases. We included new users of OAD aged 18 years or over. Those still treated with any OAD or insulin 365 days after their first claim, were considered persistent. Among them, those with a supply of OAD or insulin for at least 80% of the days were deemed compliant. Characteristics associated with both outcomes were identified using a multivariate logistic regression model.
Results: Among the 151,173 individuals included in the cohort, 119,832 (79.3%) were persistent and 93,418 (78.0% of those who persisted) were compliant. Individuals were more likely to be persistent if they were: aged more than 53 years (adjusted odds ratio: 1.44; 95%CI:1.39-1.51), lived in a rural region (1.67; 1.13-1.21), received guaranteed income supplement (1.10;1.07-1.14), were initiated on metformin (1.34; 1.30-1.39), were prescribed their initial OAD by general practitioner (1.21;1.16-1.26), if they had used more than 5 drugs (1.41;1.36-1.45) and had less than 7 physician visits (1.26; 1.21-1.31) in the year before initiating OAD therapy. Determinants of compliance were similar to those of persistence.
Conclusions: Results could help tailoring interventions aimed at optimizing the use of OAD treatments.
Keywords: *Oral antidiabetes drugs persistence, compliance, determinants*

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Direct cost of schizophrenia in Quebec, Canada: an incidence-based microsimulation Monte-Carlo Markov model

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Background: Pharmacological strategies for schizophrenia have received increasing attention due to the development of new and costly drug therapies.
Objectives: To estimate the direct healthcare and non-healthcare cost of schizophrenia and to simulate cost reductions potentially obtained with a new treatment, over the first 5 years following diagnosis.
Methods: A microsimulation Monte-Carlo Markov model was used. Costs and individual probabilities of transition were estimated from the Regie de l'assurance maladie du Quebec and Med-Echo databases and all

analyses were performed under the government perspective.
Results: A total of 14,320 individuals were identified in the study cohort as newly diagnosed patients with schizophrenia. The mean direct healthcare and non-healthcare cost of schizophrenia over the first 5 years following diagnosis was estimated $36,701 Canadian (CAN) (95% CI: 36,264 to 37,138). The direct healthcare cost accounted for 56.2% of the total cost, welfare assistance for 34.6% and long term care facilities for 9.2%. In the case where a new treatment with 20% increase of effectiveness will be available, the direct healthcare and non-healthcare costs can be reduced up to 14.2%.
Conclusions: This model is the first Canadian model incorporating transition probabilities adjusted for individual risk-factor profiles and costs using real-life data.
Keywords: *Costs of schizophrenia, direct healthcare and non-healthcare cost, Markov Model with Monte-Carlo microsimulations*

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Effectiveness of adherence to antihypertensive agents after ischemic stroke

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Background: Antihypertensive agents have been shown to reduce the risk of major cardiovascular events. However, there are no large effectiveness studies which have assessed adherence to antihypertensive medications and major cardiovascular outcomes in high risk individuals who have recently suffered an ischemic stroke.
Objective: Our primary aim was to evaluate the relationship between antihypertensive drug adherence and non-fatal vascular events in a cohort of older patients hospitalized for an ischemic stroke and discharged in the community.
Methods: A cohort of 14, 227 patients with an ischemic stroke was reconstructed from individuals 65 years and older who were treated with antihypertensive agents between 1999 and 2007. A nested case-control design was conducted to evaluate the occurrence of non-fatal major cardiovascular outcomes including stroke or myocardial infarction. Every case was matched by age and duration of follow-up with up to 15 randomly selected controls. The adherence to antihypertensive drugs was measured with the medication possession ratio. Conditional logistic regression models were performed to estimate the rate ratio of non-fatal vascular events associated with adherence to antihypertensive agents, adjusting for various potential confounders.
Results: Mean patient age was 75 years, 54% were male, 23% had diabetes, 47% dyslipidemia, 38% coronary artery disease, and 14% atrial fibrillation or flutter. Adherence to antihypertensive therapy over than 80% decreased the risk of non-fatal vascular events RR: 0.74 (0.67-0.83), compared to an adherence of <80%. A reduction in all cause mortality RR: 0.52 (0.47-0.58) was also associated with higher adherence. Male gender and cardiovascular disease were also risk factors for non-fatal vascular events.
Conclusions: Our study suggests that higher adherence to antihypertensive medication is associated with a risk reduction of non-fatal vascular events and all-cause mortality among patients with a recent ischemic stroke.
Keywords: *Stroke, antihypertensive drugs, adherence to treatment*

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Effectiveness of interventions to improve the detection and treatment of osteoporosis in primary care settings: a systematic review and meta-analysis

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Funding Source: None

Background: The objective of this study was to evaluate the effectiveness of primary care interventions to improve the detection and treatment of osteoporosis.
Methods: Eight electronic databases and six grey-literature sources were searched. Randomized controlled trials, controlled clinical trials and quasi-randomized trials from 1985 to 2009 were considered. Eligible studies had to include patients at risk (women 65 years or older, men 70 years or older, and men/women 50 years or older with at least one major risk factor for osteoporosis) or at high risk

(men/women using oral glucocorticoids or with previous fragility fractures) for osteoporosis and fractures. Outcomes included bone mineral density (BMD) testing, osteoporosis-treatment initiation and fractures. Data were pooled using random-effect models when applicable.
Results: Thirteen studies were included. The majority were multifaceted and involved patient educational material, physician notification, and/or physician education. Absolute differences in the incidence of BMD testing ranged from 22% to 51% for high-risk patients only and from 4% to 18% for both at-risk and high-risk patients. Absolute differences in the incidence of osteoporosis-treatment initiation ranged from 18% to 29% for high-risk patients only and from 2% to 4% for both at-risk and high-risk patients. Pooling the results of six trials showed an increased incidence of osteoporosis-treatment initiation (risk difference (RD)=20%; 95%CI: 7%-33%) and of BMD testing and/or osteoporosis-treatment initiation (RD=40%; 95%CI: 32%-48%) for high-risk patients following intervention.
Conclusions: Multifaceted interventions targeting high-risk patients and their primary care providers may improve the management of osteoporosis, but improvements are often clinically modest.
Keywords: *Meta-analysis, osteoporosis, primary care*

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Estimating the cost effectiveness of ramipril in the prevention of new diagnoses of type 2 diabetes

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Background: Type 2 diabetes (T2D) is a growing public health problem. The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that ramipril was associated with fewer new diagnoses of T2D in high-risk individuals than placebo. The objective of this analysis was to examine the cost effectiveness of ramipril in the prevention of new T2D diagnoses and subsequent acute myocardial infarctions (AMI) and strokes among a high-risk population from the perspective of the Ontario Ministry of Health and Long-Term Care (MOHLTC).
Methods: In this hypothetical cohort, high-risk Ontarians (i.e., ≥ 55 years with the Metabolic Syndrome [MetS]) were identified. Patients were randomized 1:1 to receive ramipril (10 mg/day) or no intervention for 5 years. The incidence of new diagnoses of T2D in each group was obtained from the HOPE study. Direct healthcare costs related to AMI, stroke, and diabetes care were obtained from the literature. It was assumed that the MOHLTC would cover the costs of ramipril for all patients in the cohort.
Results: Over 5 years, the number of T2D diagnoses made in the ramipril and no intervention arms were 6,400 and 9,469, respectively. The incremental cost effectiveness ratio (ICER) for ramipril was $18,154/diagnosis averted. The model was most sensitive to the exclusion of coverage of ramipril therapy for patients between 55 to 64 years of age (ICER: $5,750).
Conclusions: This analysis demonstrated that ramipril was associated with fewer diagnoses of T2D and a moderate ICER. This intervention may be interest to health policy decision makers to help prevent new diagnoses of T2D.
Keywords: *Cost effectiveness analysis, ramipril, type 2 diabetes prevention*

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Ethnic variation in the quality of asthma management in British Columbia

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Background: Despite the wide dissemination of international as well as national asthma clinical guideline, asthma imposes a substantial burden on Canadian health care expenditure and patient health. We have currently very little knowledge with regard to the role of patient ethnicity in influencing the quality of asthma management. Our study objective was to investigate the extent of ethnic variation in the quality of asthma management in BC.
Methods: We identified 2,591 asthma patients from BC linked health administrative databases and respondents to the Canadian Community Health Survey. We used the Canadian asthma clinical guidelines to assess the quality of asthma management (defined through rescue medication overuse). Self- or family-based ethnic identity (White, Chinese, South Asian, other Asian, mixed, and all other ethnicity) was our main independent variable. We used a logistic regression within an extension of Generalized Estimation Equation (GEE) framework and adjusted for general health status, income, age/gender, area-level ethnic concentration, and socio-economic status at the census dissemination area level.

Results: Our study showed a considerable ethnic variation in the quality of asthma management. In particular, patients of Chinese ethnicity had 45% higher likelihood of engaging in optimal quality of management, compared to White ethnicity. (Adjusted OR=0.54; 95% CI: 0.35-0.84). The Chinese-White disparity in the quality of asthma management was even greater in the neighborhoods with <5% concentration of Chinese ethnicity (Adjusted OR=0.39; 95% CI: 0.23-0.69).
Conclusions: Our results demonstrated that individual-level as well as area-level ethnicity has a significant influence on the quality of asthma management in BC.
Keywords: *Chronic disease management, ethnicity, cohort study*

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Generic comparators - what is the best approach?

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Funding Source: Amgen Canada

Background: An economic evaluation must be included in a reimbursement submission for new medical technologies. The Canadian guidelines for conducting economic evaluations state that the appropriate comparator should include the most commonly used and lowest cost alternatives. If a new product has an efficacy and/or safety advantage over the existing standard of care, justification can often be made for a premium price over a generic comparator. With pending legislation mandating a substantial reduction in generic drug prices, it will become more difficult for new products to demonstrate value versus generics. The Province of Quebec is working on a strategy to address this issue, but no announcements have been made. A public discussion is necessary to ensure a common understanding of the methodology options that exist.
Methods: The framework utilized is the principle that an economic evaluation is intended to guide the efficient allocation of scarce healthcare resources.
Results: There is a paucity of methodology research comparing new medicines with generics. One option is to include all comparators and to use the weighted-average for existing treatments since the new medicine will displace patented and generic products. Other reimbursement options that do not address the comparator issue include confidential pricing agreements, risk-sharing schemes, and coverage with evidence development. Finally, manufacturers may focus on private payers to the detriment of patients without private plan coverage.
Conclusions: Pharmaceutical policy and reimbursement policy will have to be coordinated to stimulate innovation of new medicines and to improve patient outcomes through better access to effective medicines.
Keywords: *Generic, value, innovation*

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History of regular hormonal contraceptive use among emergency contraceptive users in British Columbia

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Background: The relative effectiveness of the Yuzpe and levonorgestrel regimens of emergency contraceptives (ECs) is being estimated in an ongoing observational study. History of hormonal contraceptive (HC) use can impart protection from pregnancy and is a potential confounder.
Methods: A cohort of 7493 women who received pharmacist-prescribed ECs in British Columbia between December 2000 and December 2002 was identified. The provincial prescription database was used to assess the presence of HC prescription(s) in the 12 months prior to the first (index) EC of each woman in the cohort. Women were considered to have been current HC users on the day of requesting EC if they were possibly receiving HC based on dispensing date and quantity. The chi square test was used to assess differences between the Yuzpe (n = 3023) and levonorgestrel (n = 4470) groups.
Results: Among the 7493 women in the cohort, 1759 (23.5%) received HC within 12 months prior to index EC. Of these, 1563 (88.9%) received oral contraceptives, 175 (9.9%) received depot medroxyprogesterone, and 20 (1.1%) received both types. The frequency of HC dispensing was 24.7% and 22.6% in the Yuzpe and levonorgestrel groups, respectively (p = 0.03, odds ratio 1.1). In principle, 7.1% and 6.9% of women, respectively, were possible current HC users (p = ns).
Conclusions: The observed history of HC prescriptions among EC users suggests a potential

difference in fertility, behaviour, and access to medical services that could affect evaluation of the relative effectiveness of the Yuzpe and levonorgestrel regimens.

Keywords: *Contraception, postcoital, drug prescriptions, comparative effectiveness research*

ENCORE PRESENTATION

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Impact of process characteristics on quality related event reporting in Nova Scotia community pharmacies

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Increased risk of intra-cranial hemorrhage in HIV infected subjects is mainly due to AIDS and comorbidities: a population-based study

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Background: HIV infection and antiretrovirals have been associated with intracranial hemorrhage (ICH). We performed a cohort and nested case-control study to study this risk.
Methods: We selected all HIV-positive individuals from the RAMQ database from 1985 to 2007. Each HIV-positive subject was matched with four HIV-negative individuals. We used a Poisson regression model to calculate rates of ICH according to HIV status. We conducted a case-control study nested within the cohort of HIV-positive patients to look at the effect of antiretrovirals. Cases were defined as ICH in an HIV-positive, and were matched to HIV-positive controls without ICH. Odds ratios for antiretroviral exposure were obtained using conditional logistic regression.
Results: There were 7053 HIV-positive and 27 681 HIV-negative patients available, representing 138,704 person-years. There were 49 incident ICH, 29 in HIV-positive and 20 in HIV-negative patients. Adjusted hazard ratio for ICH in HIV+ patients compared to HIV- was 3.28 95%CI[1.75-6.12]. The effect was reduced to 1.99 [0.92-4.31] in the absence of AIDS-defining conditions, and increased to 7.64 [3.78-15.43] in patients with AIDS-defining conditions. Hepatitis C infection, illicit drug or alcohol abuse, intracranial lesions and coagulopathy were all strongly associated with ICH (all p-values<0.001). In the case-control study, 29 cases of ICH in HIV+ individuals were matched to 228 HIV+ controls. None of the antiretroviral classes was associated with increase OR of ICH.
Conclusions: Risk of ICH in HIV-positive patients seems mostly associated with AIDS-defining conditions, other co-morbidities or adverse habits. No association was found between use of antiretrovirals and ICH.
Keywords: *HIV, intra-cranial hemorrhage, drug safety*

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Initiation of ACE inhibitors and angiotensin receptor blockers in elderly patients taking oral antidiabetes drugs

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Background: Canadian guidelines recommend that ACE inhibitors (AECI) or Angiotensin II receptor blockers (ARB) be used by elderly patients with diabetes.
Objectives: To estimate the rate of initiation of AECI/ARB among elderly patients using oral antidiabetes drugs (OAD) and to identify factors associated with this initiation.
Methods: Using the Quebec Health Insurance Board databases, we conducted a population-based cohort study of individuals aged over 64 years who were newly dispensed an OAD between 2000-01-01 and 2008-12-31. The rate of AECI/ARB initiation was calculated and factors associated with AECI/ARB initiation were identified with multivariable Cox regression.
Results: In this cohort of 52,293 new users of OAD, AECI/ARB was initiated at rate of 24.3 cases per 100 patient-years. Patients who had initially received metformin and secretagogue vs metformine alone (Adjusted hazard ratio: 1.36; 95% CI: 1.29-1.44) and those who were admitted to hospital (1.22; 1.17-1.26) in the year before receiving OAD therapy were more likely to have AECI/ARB initiated. In contrast, patients

who were aged 75-79 (0.92; 0.89-0.95) as opposed to 65-69 years, who were prescribed an OAD by general practitioner vs. internist (0.93; 089-0.98), and who received in the year prior to receiving OAD 4 to 7 (0.85: 0.82-0.87) or more than 8 (0.74; 0.72-0.77) different medications as opposed to less than 4 were less likely to have AECI/ARB initiated.
Conclusions: The initiation rate of AECI/ARB in elderly patients receiving OAD is low. Several factors are associated with this initiation and could be considered in future interventions.
Keywords: *ACE inhibitors or Angiotensin II receptor blockers, type 2 diabetes, determinants*

ENCORE PRESENTATION

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Innovation deficit or imitation deficit in drug development?

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Insulin and cancer outcomes in patients with type 2 diabetes: a systematic review and meta-analysis of observational studies

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Background: Epidemiologic studies suggest that individuals with type 2 diabetes (T2DM) are at an increased risk of cancer outcomes. Insulin is a known growth factor and hyperinsulinemia is the leading hypothesis for the underlying biologic mechanism for this association. Our objective was to determine whether data summarized from observational studies supported the hypothesis of an increased risk of overall and site-specific cancers among individuals with T2DM using exogenous insulin.
Methods: A comprehensive search of nine key biomedical databases for all years up to December 2010 was conducted. Searches were restricted to English language and reference lists of relevant studies were scanned. Data from published observational studies were abstracted and entered into RevMan (v. 5.0) for meta-analysis of cancer outcomes associated with insulin use versus no insulin use in patients with T2DM.
Results: The search yielded 3043 unique citations and 12 studies were selected for inclusion. There was no clear trend in overall cancer risk for insulin users compared those using other therapies. For site-specific cancers there was an increased risk of pancreas (OR=2.86 [1.96, 4.15], I2=0%, n=3), colorectal (OR=1.16 [0.45, 3.00] I2=76%, n=3) and liver cancers (OR=1.87 [1.14, 3.08], I2=0%, n=2), whereas there was a decreased risk of prostate cancer (OR=0.61 [0.37, 1.00], I2=0%, n=2) among insulin users.
Conclusions: In people with T2DM, insulin use was associated with an increased risk of several site-specific cancers, but a decreased risk of prostate cancer. Further evaluations of insulin exposures and risk and potential confounding factors are required.
Keywords: *Cancer, insulin, systematic review*

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Maternal prenatal and parental postnatal stress in a cohort of depressed women and their partners

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Background: Studies have shown that perinatal stress is associated with unfavourable outcomes. Our objective was to evaluate parental stress in a cohort of pregnant depressed women who continue or discontinue antidepressant (AD) treatment, and their partners.

Methods: The OTIS Antidepressants in Pregnancy Study cohort was used. Women were recruited through North American Teratogen Information Services and at the outpatient clinic of CHU Ste Justine (Montreal). To be included, women had to be >18 years old, <15 weeks pregnant, using AD (exposed group) or any non-teratogenic drugs (non-exposed group). Women were excluded if they were using a known teratogen or other psychotropic drugs or taking AD in the year prior to pregnancy (for the non-exposed group). Parental stress was assessed by telephone interview using the validated 4-items perceived stress scale during the 1st trimester of pregnancy (TP) for mothers and at 2 months postpartum for both parents. To compare stress levels between groups, statistical analyses were conducted using t-tests and ANOVA with posthoc tests.
Results: Overall, 249 women and 138 men were recruited for this study. During the 1st TP, women exposed to AD, and especially those who discontinued their AD, had a higher level of stress than women in the non-exposed group ($p<0.001$). After pregnancy, exposed women as well as their partners also had a higher level of stress than parents in the non-exposed group ($p<.05$).
Conclusions: These results indicate that depressed women taking AD while pregnant and their partners have higher levels of stress during and after pregnancy than those not taking AD.
Keywords: *Perinatal, stress, antidepressant*

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Modelling the lifetime costs of insulin glargine and insulin detemir in type 1 and type 2 diabetes patients in Canada: a meta-analysis and a cost-minimization analysis

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Background: Two basal insulin analogues, insulin glargine (Lantus ®) once daily and insulin detemir (Levemir ®) once or twice daily are marketed in Canada. The objective of this analysis was to estimate the long-term costs of insulin glargine compared to insulin detemir for type 1 (T1DM) and type 2 (T2DM) diabetes mellitus from the perspective of a Canadian provincial government.
Methods: A meta-analysis was done to compare the efficacy and safety results for IGlarg and IDet and to obtain T1DM and T2DM patients' characteristics and daily insulin doses per patient. Based on the meta-analysis results, a cost-minimization analysis comparing insulin glargine (IGlarg) to insulin detemir (IDet) was conducted using the CORE Diabetes Model. Lifetime direct medical costs were projected. Costs were discounted at 5% per annum and reported in 2010 Canadian dollars.
Results: The meta-analysis showed no difference in efficacy and safety for T1DM and T2DM patients receiving IGlarg or IDet. For an equivalent efficacy, the daily insulin doses per T1DM patient were IGlarg QD 26.2 IU; IDet BID 33.6 IU; T2DM patient were IGlarg QD 47.2 IU and IDet 74.5 IU (QD and BID combined). From this cost-minimization analysis, using IGlarg is cost-saving ($4,231 per T1DM patient; $6,757 per T2DM patient) compared to IDet for a lifetime under the perspective of a Canadian provincial government.
Conclusions: From this economic analysis, the greater the proportion of patients with T1DM and T2DM that are treated by IGlarg compared to IDet, the greater the savings realised by Canadian health authorities.
Keywords: *Long acting insulin analogue, cost-minimization, diabetes*

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Patterns of osteoporosis medication prescribing in British Columbia and Ontario, 1995/96-2008/09: impact of public drug coverage

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Background: Approved therapies for treating osteoporosis in Canada include bisphosphonates, calcitonin, denosumab, raloxifene and teriparatide. However, significant variation in public drug access to these medications exists across Canada. We sought to compare patterns of osteoporosis medication prescribing between British Columbia (BC) and Ontario (ON).
Methods: Using dispensing data from BC (PharmaNet) and ON (Ontario Drug Benefits), we identified all new users of osteoporosis medications aged 66 or more years from 1995/96-2008/09. We summarized the number of new users by fiscal year, sex and index drug for each province. BC data were also stratified as provincial PharmaCare accepted or not.

Results: We identified 578,977 (n=123,376 BC) eligible new users. Overall patterns of prescribing were similar between provinces: 1) over 97% of all dispensings were for an oral bisphosphonate; 2) etidronate prescribing declined after 2001/02, reaching a low of 41%BC and 8%ON of new users in 2008/09; 3) the number of males treated increased over time, from 8%BC and 6%ON of new users in 1996/97, to 23%BC and 26%ON of new users in 2008/09. We note differences in access to second-generation bisphosphonates in BC when stratified by whether or not drugs were covered by BC PharmaCare; <2% (PharmaCare) versus 78% (non-PharmaCare) of medications dispensed were for second-generation bisphosphonates.
Conclusions: Oral bisphosphonates are the primary drugs used to treat osteoporosis in Canada. Prescribing practices changed over time as newer medications came to market: etidronate prescribing declined and a larger percentage of males were treated. Access to second-generation bisphosphonates through BC PharmaCare was limited.
Keywords: *Osteoporosis, public drug coverage, bisphosphonates*

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Persistence to antidepressants and quality of their use in adults diagnosed with major depression in Quebec: a cohort study from 2005 to 2009

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Funding Source: None

Background: Substantial increases in antidepressant prescribing have been observed over time. The present study was designed to assess persistence to antidepressants and quality of their use among beneficiaries of Quebec's Public Prescription Drug Insurance Plan who were diagnosed with major depression.
Methods: A descriptive, retrospective cohort study was conducted using administrative databases of the Régie de l'assurance maladie du Quebec, from 2005 to 2009. New users of antidepressants aged 18 or older and diagnosed with major depression were identified. Persistence to the antidepressant treatment was evaluated using the Kaplan-Meier method. Quality of use was evaluated using criteria established under Canadian guidelines.
Results: Persistence to the antidepressant treatment for periods of 30 days, six months and one year after starting treatment was 72.6%, 46.3% and 33.1% respectively. More than 85% of the 50 662 new antidepressant users with major depression started their treatment with a first-line agent and 80.7% of the doses taken three months after starting treatment complied with the recommendations. Only 35.9% of new treatment episodes lasted eight months or more. The medical follow-up of major depression was problematical, since only 18.7% of new users with major depression had eight or more medical consultations in the year following the start of their treatment.
Conclusions: These results show the need to improve the persistence to antidepressant treatment and the follow-up of patients with major depression. More exhaustive studies would be relevant to determine the reasons inhibiting the optimal use of antidepressants in Quebec and to implement interventions targeting specific problems.
Keywords: *Cohort studies, antidepressants, drug utilization review*

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Pharmaceutical sales representatives' activities in Canada, France and the U.S.: opinions of key stakeholders on the effectiveness of current regulatory practices

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Background: Contact with pharmaceutical sales representatives (PSR) affects prescribing quality and cost, but little is known about the effectiveness of differing approaches to regulation.
Objectives: To compare the regulation of PSR activities in Canada, France and the U.S. and the opinions of key stakeholders on the effectiveness of current regulatory practices.
Methods: A literature review and document synthesis were performed to identify key stakeholders from government and affected sectors, and to describe national regulations. Semi-structured open-ended interviews were carried out, and a qualitative analysis used to compare regulatory approaches between countries, and barriers and enablers contributing to perceived effectiveness.
Results: In Canada, regulation of PSRs is largely delegated to the industry via a Code of Conduct and voluntary pre-approval of promotional materials. Pre-approval is seen as an enabler to effectiveness; identified barriers are lack of formal monitoring, voluntary compliance, weak enforcement, and lack of transparency. In France, regulation is partly delegated to the industry via certification of companies that

conform to the Sales Visit Charter. The French regulatory agency also approves promotional material a posteriori. Enablers include publication of violations and financial penalties; barriers include omission of information quality from certification criteria. The U.S. FDA also requires a posteriori approval of materials and encourages voluntary industry compliance. Enablers include proactive monitoring and enforcement; barriers are monitoring difficulties and pressures on staff time from direct to consumer advertising.
Conclusions: Voluntary compliance by industry is encouraged in these three countries. However, proactive monitoring and strong enforcement procedures are seen as essential to effective health protection.
Keywords: *Regulation, pharmaceutical sales representatives, Canada, United States, France*

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Pharmacist intervention for glycemic control in the community (The RxING Study)

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Background: Approximately 1.9 million Canadians are living with diabetes and this is estimated to increase by 75% over the next few decades. Pharmacists are front line primary healthcare professionals who see patients with diabetes frequently and in Alberta, they recently have been granted authority to prescribe medications and order laboratory tests. As such, pharmacists could systematically identify poorly controlled patients and provide greater access to interventions to improve glycemic control. The aim of this study is to determine the effect of a community pharmacist intervention on glycemic control in patients with poorly controlled diabetes.
Methods: Pragmatic (practice-based), before-after design, based in 10 community pharmacies in Alberta. Pharmacists will systematically identify potential candidates by inviting patients receiving oral hypoglycemic medications to check their HbA1c using validated point of care technology (DCA Vantage ®). The pharmacist will prescribe insulin glargine for the patients whose HbA1c is 7.5 to 9.5%. The patient will be given 10 units at bedtime, adjusted by increments of 1 unit daily to achieve a morning fasting glucose of <5.5mmol/L. Oral hypoglycemic medications will be adjusted accordingly. The 100 patients will be followed at 2, 4, 8, 14, 20, and 26 weeks. The primary outcome is the change in HbA1c from baseline to week 26. Other outcomes include fasting blood sugar, quality of life, economic analysis, adverse events (including hypoglycemic events), adherence and titration of the insulin regimen.
Conclusions: This ongoing multicentre study should demonstrate pharmacists' ability to improve glycemic control and improve access to care.
Keywords: *HbA1c, multicentre before-after design, glycemic control*

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Pharmacotherapeutic management of chronic non-cancer pain in primary care

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Background: Chronic non-cancer pain (CNCP) is prevalent. Although, management guidelines have been developed, pharmacological treatment remains challenging, particularly in primary care where most of these patients are followed-up. The objectives of this study were to describe the medications used to control CNCP and to manage their adverse drug reactions in primary care.
Methods: In a cohort study, patients reporting CNCP since six months or more, at least twice weekly with a severity of at least 4 on a 0-10 scale (10 represents the worst possible pain), and having an active analgesic prescription from a family physician were recruited in 82 pharmacies in Quebec. They completed a telephone interview and a self-administered questionnaire. Using the RAMQ database and the pharmacies' charts, medications used for pain management in the previous year were documented.
Results: A total of 486 patients participated. The mean age was 58.4 years (SD=12.5). The mean pain intensity

in the past week was 6.5. Medications used for pain were acetaminophen (28%), non-steroidal anti-inflammatory drugs (NSAIDs) (72%), antidepressants (50%), anticonvulsants (61%), muscles relaxants (26%), and opioïds (65%). The prevalence of gastro-intestinal effects associated with pain medications was high: 90%. Among patients reporting these effects, 42.7% did not have received medication to relieve constipation, stomach aches or nausea. Patients' satisfaction with pain management was generally low, especially regarding information about pain and treatment.

Conclusions: In this population of patients with moderate to severe CNCP, opioids and NSAIDs use is frequent and associated with a suboptimal management of gastro-intestinal side effects.

Keywords: *Pain, non-cancer chronic pain, primary care, pain medication*

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Post-market surveillance of drug safety and effectiveness: international approaches and lessons for Canada

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Funding Source: The Health Council of Canada commissioned the discussion paper, *"Keeping an Eye on Prescription Drugs, Keeping Canadians Safe."* The Health Council of Canada receives funding support from Health Canada. The views expressed here do not necessarily represent the views of Health Canada.

Background: Approved drugs, once they reach the market, tend to be used by a wider range of individuals than in clinical testing, often for multiple medical conditions and for a more prolonged period of time. Canada faces challenges in regulating post-market drug surveillance. The Health Council of Canada's commissioned paper, *"Keeping an Eye on Prescription Drugs, Keeping Canadians Safe"*, compares strategies used by various international regulators in order to develop appropriate recommendations for Canada.

Methods: Best practice models of pharmacovigilance were identified in five international jurisdictions (US, EU, France, UK, New Zealand) selected for their relative similarity while allowing for a spectrum of approaches. Documentary analyses and structured interviews were used to collect information. The strengths and weaknesses of these models on specific dimensions were compared. Based on this analysis, recommendations were developed to address challenges in pharmacovigilance strategies in Canada.

Results: Only 1-10% of adverse drug reactions are captured through Health Canada's voluntary reports once prescription drugs have been approved for public use. International approaches for active post-market surveillance of drugs have been identified, many of which hold potential for Canada. Our recommendations offer options for developing active systems of research, regulation, and risk warning that lead to safer and more effective use of medications.

Conclusions: Although medications offer many benefits, the risks associated with their use in the real world remain largely unknown. Developing more effective and active systems of surveillance of real-world drug use will ensure that we move toward safer and better health care.

Keywords: *Pharmacovigilance, post-market surveillance, best-practice models*

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Potentially inappropriate prescribing in the elderly from the EGB database in France

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Background: Inappropriate prescribing is a risk factor of adverse drug events occurrence in the elderly. Several studies have used drug prescription databases to estimate the prevalence of potentially inappropriate medications (PIM) with explicit PIM lists. Recently, drug reimbursement data of the French Health Insurance, have become accessible, making it possible to assess the quality of drug use in France. Our objective was to evaluate the prevalence of PIM use in the elderly ≥75 years in France, using the consensual French PIM list and the EGB database (Echantillon Généraliste des Bénéficiaires).

Methods: The list of drugs reimbursed to patients ≥75 years has been extracted from the EGB database (1/3/2007-29/2/2008). This database is a representative sample of 1/97th of the French population. Drugs were classified as inappropriate using the French PIM list.

Results: In France, 53.6% (IC95%:53.0-54.1) of the elderly ≥75 years consumed at least one PIM. The three main criteria identified were cerebral vasodilators (19.4%), drugs with antimuscarinic properties (19.3%) and long half-life benzodiazepines (17.8%). There was an important disparity of PIM use between the French

regions (from 46.4% in Basse-Normandie to 61.6% in Limousin), as well as significant differences according to the considered criteria.
Conclusions: PIM use in the elderly is a worrying problem in France. The recent accessibility to reimbursement databases makes it possible to create indicators, useful for the Regional Health Agencies which manage the public health policy within each French region.
Keywords: *Inappropriate prescribing, reimbursement database, France*

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Programme ACCORD: priorities for action to improve the management of patients with non-cancer chronic pain (NCCP) in primary care (PC)

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Background: The prevalence of NCCP is high and will increase with the aging of the population. The management of NCCP in PC is not always optimal. A one-day workshop was conducted to explore the perception of PC actors regarding changes that could be implemented in the PC system to provide better care to these patients.
Methods: Physicians(6), pharmacists(6), nurses(6), physiotherapists(6), psychologists(6), pain specialists(6), patients(3), family members(3), decision makers(4) and researchers(7) attended the workshop. In seven parallel focus groups framed according to the Chronic Care Model (CCM) and including participants with similar background (e.g. pharmacists), specific proposals to improve the management of NCCP were identified and presented to all participants in a plenary session. Thereafter, five nominal groups including participants with various backgrounds (e.g. physician, pharmacist, patients') were conducted. In two voting rounds, five priorities for action were identified in each group. In a plenary session, the priorities were presented and a final vote was conducted to identify the top five priorities.
Results: The five priorities were: 1) provide interprofessional continuing education program supported by clinical tools; 2) implement interprofessional approach supported by a case manager; 3) create well defined corridors of service between PC and the second and third lines of treatment; 4) identify regional champion; and 5) improve patient's self-management.
Conclusions: To improve the management of NCCP in PC every element of the CCM needs to be considered. Implementing these proposals will need to take into account regional context and will require the involvement of the whole community.
Keywords: *Primary care, non cancer chronic pain, continuity of care, accessibility of care, chronic care model*

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Providing evidence to inform decision making: do economic evaluations of targeted therapy follow economic evaluation (EE) guidelines?

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Background: Payors as decision-makers are often faced with making decisions without complete information. EEs using decision-analytic modelling provide a framework to reduce and assess decision uncertainty when local data are used and the variability of all model inputs is considered concurrently, per the recommendations of national and international evaluation guidelines. The extent to which these recommendations have been used in EEs of targeted therapy is unknown. We reviewed EEs of trastuzumab as an example of targeted therapy because of the growing use and costs associated with these medicines, particularly in cancer therapy.
Methods: We systematically reviewed EEs of adjuvant trastuzumab treatment in early breast cancer (BC).

Evaluation criteria were derived from Canadian, UK and USA EE guidelines. Data extraction considered the use of local data sources for model parameters, methods of sensitivity analysis (scenario, univariate, multivariate and probabilistic) and uncertainty representation (cost-effectiveness plane, scatterplot, confidence ellipses, tornado diagrams, cost-effectiveness acceptability curve).
Results: We identified 10 EEs of trastuzumab in early BC. Local data were most frequently used to estimate costs (10/10). Utilities (2/10) and trastuzumab efficacy (0/10) were informed by local data rarely. Univariate sensitivity analysis was common (8/10), probabilistic analysis was less frequent (6/10) and only half of surveyed studies provided visual representation of results and decision uncertainty.
Conclusions: Local data beyond costs is rarely used in EEs of trastuzumab in early BC. Parameter and decision uncertainty quantification did not meet guideline recommendations and highlights areas that can be improved for decision-making support.
Keywords: *Systematic review, personalized medicine, trastuzumab*

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Quality of medication use in chronic kidney disease patients: development and pilot testing of a web-based training program for community pharmacists

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Background: To improve the quality of medication use in chronic kidney disease (CKD) patients, a Web-based training program for community pharmacists was developed. The program is based on the Pharmacotherapy Assessment In chronic Renal disease PAIR criteria; a list of clinically significant drug-related problems requiring a pharmaceutical intervention in CKD patients. The impact of the training program on the knowledge and skills of pharmacists and their satisfaction were evaluated.
Methods: Pharmacists were randomly assigned to the training program or the control group. The program included a 60-minute web-based interactive training supported by a clinical guide. Each pharmacist completed a knowledge and skills questionnaire at baseline and after one month. Trained pharmacists completed a satisfaction questionnaire. Semi-directed telephone interviews were conducted with eight pharmacists.
Results: Seventy pharmacists (Training: 52; Control: 18) were recruited. They were mainly women with less than 15 years of experience in pharmacy. Compared to the control group, an adjusted incremental increase in knowledge score (22%; 95% confidence interval (CI): 16%-27%) and skill scores (24% CI 16%-33%) were observed in the training group. Most pharmacists (87%-100%) rated as excellent or very good each aspect of the program. Many pharmacists would appreciate receiving additional training in this field. Adding a discussion forum was proposed to complement the program.
Conclusion: The program was appreciated by pharmacists and improved their knowledge and skills. Its impact on clinical practices and quality of medication use remain to be evaluated.
Keywords: *Progression of renal disease, diabetes mellitus, drug-induced nephropathies*

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Quality of medication use in chronic kidney disease patients: development and validation of the pair criteria

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Background: Explicit criteria for judging the quality of medication use in chronic kidney disease (CKD) patients are lacking. We developed and validated a list of clinically significant drug-related problems (DRPs)

requiring a pharmaceutical intervention in CKD patients; the Pharmacotherapy Assessment In chronic Renal disease or PAIR criteria.
Methods: Using the RAND appropriateness method, nephrologists (n=4), family physicians (n=2), hospital pharmacists (n=4) and community pharmacists (n=2) developed the PAIR criteria. These criteria were applied to 90 CKD patients in a cluster randomized pilot study. The prevalence of the DRPs and the reliability, validity and responsiveness of the PAIR criteria were assessed.
Results: The PAIR criteria include 50 DRPs grouped into six categories. A mean of 2.5 DRPs/patient (95% Confidence interval (CI): 2.0-3.1) were identified. Inter-raters reliability coefficients (kappa) by category varied from 0.8 to 1.0 with an intra-class correlation coefficient (ICC) of 0.93 (95% CI: 0.89-0.95) for total DRPs/patient. Test-retest reliability coefficients by category varied from 0.74 to 1.00 with an ICC of 0.91 (95% CI: 0.82-0.96) for total DRPs/patient. A total of 3.5 DRPs/patient were identified by consensual evaluation based on implicit judgments. During the study, the mean number of DRPs/patient did not change significantly. However, the number of DRPs resolved by improved medication adherence was higher in the intervention group (0.5DRP/patient versus 0.2 DRP/patient; p=0.037).
Conclusions: The PAIR criteria can reliably be used to detect clinically significant DRPs requiring the intervention of a community pharmacist, but their responsiveness remains to be demonstrated.
Keywords: *Progression of renal disease, blood pressure, drug-induced nephropathies*

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Stitching the gaps in the Canadian drug coverage patchwork: have provincial pharmacare policies converged towards a national standard?

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Background: Despite the absence of a federal pharmaceutical strategy, provincial policy changes have the potential to address interprovincial inequities in public coverage of prescription medicines. To assess progress towards a national standard, we aimed to describe recent changes and identify emerging trends in provincial drug benefit policies.
Methods: We collected coverage information for four beneficiary groups: social assistance beneficiaries, seniors, the general population, and cancer patients. We obtained provincial plan information from historical editions of the CPhA periodical Provincial Drug Benefit Programs, provincial websites, and government personnel. We used data on eligibility, deductibles, co-payments, and out-of-pocket limits to construct a historical timeline of changes in benefit structures from 1990 to 2010.
Results: Over the study period, six provinces instituted a universal income-based "catastrophic" plan. In BC, SK, and MB, catastrophic programs replaced some or all senior's benefits. Catastrophic thresholds, co-payments/co-insurance, and out-of-pocket limits vary widely across provinces. NB and PEI have not introduced coverage for the general population. While new catastrophic programs limit expenses on cancer medicines, specific cancer coverage ranges from universal first-dollar in BC to no coverage for the general population in NB - a gap that may be exacerbated by industry trends towards expensive specialized cancer therapies.
Conclusions: Province by province, public pharmacare programs are moving towards an income-based catastrophic model. Wide inconsistencies in coverage generosity prevent this convergence from truly mending interprovincial disparities in coverage. Federal action to create national standards for public drug coverage is necessary to uniformly protect Canadians against high drug costs.
Keywords: *Pharmacare, access, historical policy analysis*

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Sustained cost savings and fewer dose administration errors in hemodialysis patients converted from epoetin alfa to darbepoetin alfa in a community hospital setting

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Funding Source: Jordan J received funding from Amgen Canada Inc. for research support.

Background: In January 2005, the hemodialysis (HD) unit at Toronto East General Hospital switched all patients from IV epoetin alfa (EPO) to IV darbepoetin alfa (DPO). The research purpose was to quantify erythropoiesis stimulating agent (ESA) utilization, cost implications and medication administration errors (MAE) before and after the EPO to DPO switch.
Methods: The study design was a 15 month retrospective observational study. ESA weekly doses and MAEs were collected for 6 months pre-conversion

and 9 months post-conversion. A follow-up 6 month sub-group analysis was performed 5 years after the conversion.
Results: Thirty-seven patients underwent conversion to DPO and the sub-group analysis consisted of 16 patients. During the study, hemoglobin and iron indices were in accordance with the 2001 NKF KDOQI guidelines while median DPO dose decreased from 50 to 20mcg (P=0.026, Wilcoxon signed-rank test). Further DPO dose reductions were seen after 5 years (30mcg in 2005 versus 20mcg in 2010, P=0.0006 using Wilcoxon singed-rank test) with an estimated annual cost savings of $3100 per patient. Thirty MAEs were observed after DPO conversion compared to 106 during EPO pre-conversion (P<0.0001, Fisher exact test). Thirty-four patients had at least one or more MAE while on EPO compared to 17 patients after DPO conversion. The absolute risk of a medication discrepancy was reduced by 8% after conversion to DPO.
Conclusion: This dosing evaluation study showed continued cost savings after 5 years and fewer medication administration errors when hemodialysis patients were switched from EPO to DPO, while maintaining clinical targets.
Keywords: *Darbepoetin alfa, medication administration error, cost-effectiveness analysis*

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Systematic review to assess the quality of published health economic evaluations

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Background: Health economic (HE) evaluations are intended to provide decision-makers with information on the comparative efficiency of medical technologies. The quality of a study is critical to the useful application of its findings. The objective of this study was to systematically review all studies assessing the quality of published HE evaluations (QA studies) and investigate how quality has changed over time.
Methods: Following a systematic search, all QA studies meeting inclusion criteria were obtained from public domain sources (e.g. PubMed, conference proceedings). Data from retrieved studies was systematically extracted using a data extraction template. Issues pertaining to the quality of HE evaluations were tabulated and analyzed both quantitatively and qualitatively. An issue was defined as a problem noted in at least 20% of the HE evaluations reviewed in each QA study.
Results: From over 2,700 abstracts screened, 66 QA studies were included for data extraction. Issues most commonly identified pertained to perspective (by 50% of QA studies), sensitivity analyses/uncertainty (50%), discounting (32%), types of costs included (23%), sources of funding/conflict of interest (18%), time horizon (14%) and outcome measures (14%). Results were equivocal: some QA studies found evidence that quality is slowly improving, whereas others found no or little improvement over time and sub-optimal adherence to standards.
Conclusions: Despite a wealth of available guidelines for their conduct and reporting, the quality of HE evaluations is lacking and needs to be improved if they are to be optimally useful to decision-makers.
Keywords: *Health economic evaluations, quality, decision-making, literature review*

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Trends in anti-infective drugs use during pregnancy in Canada

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Background: Development of knowledge in understanding the use of antibiotics during pregnancy has been limited by difficulties in testing medications in pregnant women and lack of good evidence-based data. Overuse of broad spectra antibiotics is associated with development and spread of bacterial resistance, a problem that is faced as a significant threat to the public health. In this study, we describe trends in prescription of general and broad spectrum anti-infective drugs during pregnancy.
Methods: We used the Quebec Pregnancy Registry to analyze trends for prescriptions of oral anti-infectives dispensed during pregnancy for the five-year period comprised between January 1998 and December 2002. Trends in use were assessed for classes of anti-infectives and for broad-spectrum drugs. Descriptive statistics were used to summarize the characteristics of the study population. Annual trends for anti-infective prescriptions were analyzed using the Cochran-Armitage test.
Results: The use of anti-infective drugs and broad spectrum agents during pregnancy decreased from 1998 to 2002 ($p \leq 0.05$ for trends). The classes that showed increasing trend for use were: macrolides, quinolones, tetracyclines, urinary anti-infective drugs

and antimycotics. Use of penicillins and sulfonamides decreased. Azithromycin showed a remarkable increase in its use: 0.04% of all anti-infective prescriptions in 1998, compared to 10.16% in 2002.
Conclusions: Decrease of broad-spectrum anti-infective drugs use may have been caused by a positive impact of data issue from evidence in everyday life clinical practice. More data are needed to evaluate the impact of the knowledge transfer from evidence-base studies on prescription's trends during pregnancy.
Keywords: *Anti-infective drugs, pregnancy, trends*

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Understanding treatment gaps in warfarin management of stroke prevention in atrial fibrillation

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Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects approximately 400,000 Canadians. Notably, AF causes up to 15% of all strokes. Therefore, guidelines recommend oral anticoagulation therapy, such as the vitamin K antagonist (VKA) warfarin, in AF patients to prevent stroke. However, studies suggest that approximately 50% of AF patients may not be adequately treated and the reasons behind these treatment decisions are not well characterized. The purpose of this study is to: a) determine the reasons why Canadian AF patients at moderate to high risk of stroke do not receive VKA treatment despite guideline recommendations, and b) understand the reasons why some VKA-treated patients are considered "difficult to manage."
Methods: A retrospective chart review of approximately 240 AF patients at moderate to high risk of stroke managed by general/family practitioners was conducted in Ontario, Quebec, and British Columbia. Three patient groups meeting the inclusion/exclusion criteria were examined:
1) Eligible for VKA but not treated with VKA,
2) Eligible for and previously treated with VKA, but subsequently discontinued VKA,
3) Eligible and currently VKA-treated, but considered "difficult to manage."
Results: AF patients' future risk of stroke as per validated criteria will be mapped against their physician-documented rationales for not initiating or discontinuing VKA treatment, along with physician reasons for perceiving some VKA-treated patients as being "difficult to manage."
Conclusions: This study provides a snapshot of the various reasons why Canadian AF patients may not be optimally managed with VKAs to prevent stroke.
Keywords: *Warfarin, atrial fibrillation, retrospective chart review*

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Use of ovulation stimulation (OS) alone, intrauterine insemination (IUI) and assisted reproductive techniques (ART) and the risk of multiplicity - The TWINPREG Study

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Background: Very little is known about the risk of multiplicity associated with the use of OS alone, without IUI or other ART.
Objectives: We aimed to estimate the risk of multiplicity associated with the use of: OS alone, without IUI or other ART.
Methods: Between years 2006-2008, all multiple pregnancies in Quebec were identified by the Regie de l'assurance maladie du Quebec (RAMQ), and defined as the study cases. Three singleton pregnancies (controls) were randomly selected among all Quebec pregnancies and matched to each case on maternal age and year of delivery. Cases and controls were contacted by mail to collect information on infertility history, use of OS, IUI, ART, and lifestyles. Data from the questionnaires were linked to their health services utilization data (RAMQ), hospitalization data (MedEcho), and Quebec's birth data. The risk of multiplicity in all exposure groups were quantified and compared using multivariate logistic regression models, adjusting for potential confounders.
Results: A total of 4,987 women were studied. After adjustment, pregnant women who used oral OS alone and those who used injectable OS were respectively 4.5 times (95%CI 3.1, 6.3), and 11.3 times (95% CI 2.9, 44.1) more at risk of multiplicity than those who

spontaneously conceived. OS with IUI and ART were also increasing the risk of multiplicity (p<.05).
Conclusions: Although the risk associated with ART can be decreased by implementing Single Embryo Transfer (SET), the risk associated with OS alone or with IUI is directly attributable to the medication taken and much more difficult to prevent.
Keywords: *Multiple pregnancies, ovarian stimulation (OS), assisted reproductive techniques (ART)*

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Utilization of drugs and the risk of falls in a long term care facility

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Background: Falls are the leading cause of injury among adults 65-years old. Multiple drug classes are associated with increased occurrence of falls in the elderly, yet the risk/benefit for individuals has not been well studied. Our objective was to conduct a descriptive analysis of the relationship between drug use and falls in a long term care facility in Halifax, Nova Scotia.
Methods: The study included all individuals admitted to the facility within a 16 month period (January 2009-April 2010) who had a Fall Risk Tool (FRT) completed within 48 hours of admission (n=42, mean age = 86, age range= 79-94). Although frequently used in practice, The Falls Risk Tool has not been validated. Prescribed drugs were identified from pharmacy records, assigned WHO Anatomical Therapeutic Chemical codes and categorized according to risk based on the literature and facility recommendations.
Results: Approximately 70% of drugs prescribed for all participants during the study period were classified as low risk. Yet, most (98%) participants received at least one drug characterized as increasing the fall risk, e.g. antihypertensive/diuretic, sedative hypnotic. The proportional hazards analysis suggested that the use of high risk drugs did not predict fall occurrence.
Conclusions: Almost all patients received a high risk drug. Further work is needed to assist healthcare professionals to determine risks and benefits of drugs associated with increasing risk of falls and to implement intensive early intervention prevention programs targeted at those at greatest risk. Further validation of the FRT will support the use of this measure.
Keywords: *Risk, falls, drugs, veterans*

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Utilization of regular contraceptives among rural northern youth in British Columbia: an ethnographic study

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Background: In northern communities, teen pregnancy rates are up to 100% higher than the provincial average. To better understand youth decision-making related to contraceptive use, we compared prior and current contraceptive usage patterns among young female study participants.
Methods: During ethnographic fieldwork in two communities, in-depth semi-structured interviews were conducted with 47 female English-speaking youth (aged 15 - 24) with varied socio-cultural and economic backgrounds and diverse contraceptive experiences. Participants completed a sociodemographic survey, and documented the type of past and current contraception used by themselves or their sex partner. Contraceptive effectiveness was classified into four categories: most effective; very effective, moderately effective and not effective.
Results: Among the 47 participants (mean age 18.3 years), self-described relationship status was single (44.7%), boyfriend (38.3%), married/common-law partner (12.8%), multiple partners (2.1%), and friends with benefits (2.1%). In this group, 40 (85.1%) participants reported currently using a form of contraception with comparable or lower effectiveness than in the past. Seventeen (36.2%) participants had used EC. Thirteen (27.7%) participants had a history of pregnancy, of which, 11 (84.6%) had previously used contraception in the most effective or very effective categories.
Conclusions: A substantial proportion of young women had a history of pregnancy, despite a large number having used effective contraception in the past. Potential gaps in youth sexual health services, including any barriers to access to contraception, will be explored through detailed analysis of interview transcripts.
Keywords: *Contraception, adolescent, health surveys*

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Validation of warfarin pharmacogenetic algorithms in real clinical practice

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Funding Source: Groupe de recherche universitaire sur le médicament (GRUM) Centre for Excellence in Personalised medicine (CepMED).

Background: Warfarin is the most widely prescribed oral anticoagulant for the treatment and prevention of thromboembolic diseases. However, warfarin has a narrow therapeutic range and a certain dose has a large interindividual variation.The goal of this study was to evaluate the performance of three warfarin pharmacogenetic algorithms in a real clinical setting, namely the algorithms of Gage et al., Michaud et al., and the IWPC algorithm.

Methods: Data was obtained retrospectively for 605 patients who had initiated warfarin therapy at the Montreal Heart Institute. Stable therapeutic warfarin dose was obtained from hospital charts and CYP2C9 and VKORC1 polymorphisms were genotyped. Pearson's correlation coefficient and mean absolute error (MAE) were used to validate and compare the algorithms. Clinical accuracy of the predictions was assessed by computing the proportion of patients in which the predicted dose was under-estimated, ideally estimated, or overestimated.

Results: The Gage algorithm explained most of the variation (adjusted R2=44% and MAE=1.41) and predicted 43.8% of patients within plus or minus 20% of their observed stable warfarin dose. Michaud's and the IWPC algorithms respectively had a MAE of 1.37 and 1.48 mg/day and a coefficient of determination of 45% and 43%.

Conclusions: Gage's algorithm was the most accurate for predicting stable warfarin dose in our study population. Despite the accurateness of these pharmacogenetic warfarin dosing algorithms, the routine use of genotyping for patients newly started on warfarin should not be promoted before conducting prospective clinical trials.

Keywords: *Warfarin, pharmacogenetics, algorithms*

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When can self-controlled crossover studies of only cases be used for rapid pharmacosurveillance?

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Objectives: Mini-Sentinel aims to facilitate development of a national surveillance system to detect adverse effects of medical products by developing and piloting methods for rapid analysis of de-identified data from the Mini-Sentinel distributed database covering over 60 million Americans. Mini-Sentinel's Working Group on Case-Based Approaches addressed the title's question.

Methods: We searched PubMed for 'case-crossover' (CCO), 'self-controlled case-series' (SCCS), 'case-time-control' (CTC) or 'sequence symmetry analysis' (SSA), and reviewed papers related to medical product safety. We compared unidirectional and bidirectional designs with real and simulated data.

Results: Both CCO and SCCS have been used to study drug and vaccine safety. The original CCO was unidirectional (right-censored at outcome to avoid reverse-causation bias) and assumed prior exposure trends were negligible. The CTC is a CCO that adjusts for prior exposure trends measured in non-cases. The original SCCS, like bidirectional CCOs and SSAs, assumed reverse-causation and immortal-time bias were negligible or controllable by restriction or modeling. The designs converge when using identical person-time. Estimates from bidirectional SCCSs tended to be slightly higher than from unidirectional SCCSs, suggesting outcomes sometimes reduce subsequent exposure propensity. Simulation shows, at medication inception, when exposure trend is only upward, unidirectional CCO estimates are biased and become less biased as populations approach steady states of starting and stopping.

Conclusions: Strengths and limitations of case-based designs often complement those of cohort designs. Needing no data on time-invariant characteristics (unless for effect modification), they support privacy and efficiency. Mini-Sentinel should capture

bidirectional data for cases contributing both exposed and unexposed time.

Keywords: *Methodology, study design, pharmacosurveillance*

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