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"THERAPEUTICS EVOLVING: BRINGING THE SCIENCE OF INNOVATIVE TREATMENTS INTO OUR EVERYDAY WORLD"

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ABSTRACTS

THE CANADIAN THERAPEUTICS CONGRESS

"THERAPEUTICS EVOLVING: BRINGING THE SCIENCE OF INNOVATIVE TREATMENTS INTO OUR EVERYDAY WORLD"

MAY 10-13, 2006 - HILTON TORONTO
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CAPT ORAL PRESENTATIONS

1

A comparison of the net health benefits of three strategies for the surgical treatment of primary hyperparathyroidism (HPT)

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Funding Source: None

Background: Newer, less invasive surgical approaches to the treatment of HPT (Unilateral Neck Exploration (UNE), Minimally Invasive Parathyroidectomy (MIP)) have become commonplace in recent years, however the cost-effectiveness of these strategies has been questioned, given the well-documented effectiveness of the gold standard Bilateral Neck Exploration (BNE). The objective of our study was to determine the relative incremental cost-effectiveness of the BNE, UNE and MIP surgical techniques in treating patients with HPT.

Methods: Resource utilization and outcome data was collected prospectively on patients presenting to St. Paul's hospital for surgical treatment for HPT, 2002-2005. The primary measure of effectiveness was the rate of complications (hypocalcemia, paresthesias) post-surgery. Net Health Benefits were compared between the three treatment options (lambda=$15000). Non-parametric bootstrapping was applied to evaluate uncertainty around estimates of costs and effectiveness.

Results: Patient-level data on a total of 94 patients (50=BNE, 19=UNE, 25=MIP) provided estimates of mean costs between treatment arms (BNE=$4843; SE=(944), UNE=$4881 (519), MIP=$5954 (842)) as well as estimates of rates of complications (BNE=0.10, UNE=0.16, MIP=0.04). The gold standard BNE strategy displayed 1st-order stochastic dominance over the UNE strategy, and 2nd-order stochastic dominance over the MIP strategy (Incremental Net Health Benefits: UNE vs. BNE: -$723, 95% C.I. (-$3454, $1660); MIP vs. BNE: -$132 (-$1877, $1519)).

Conclusions: Our results suggest that in the experience of HPT surgery at St. Paul's Hospital, newer, costlier strategies of treatment of HPT may be less cost-effective than the gold standard Bilateral Neck Exploration.

Keywords: *Cost-effectiveness analysis, surgery, primary hyperparathyroidism*

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Adverse reactions associated with first-line anti-tuberculosis medications: A population-based analysis using time-dependent covariates and multiple events analysis

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Funding Source: None

Introduction: The standard first-line treatment of active tuberculosis (TB), isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (ETM), poses a significant challenge due to serious adverse reactions. We examined the incidence of major adverse events and their predictive factors associated with first-line anti-TB medications.g

Methods: Patients were identified from the provincial TB database from 2000 to 2005. Age, gender, ethnicity, co-morbidities, drug regimen, duration and the nature, severity and likelihood that the regimen caused the adverse event were evaluated. Cox regression using time-dependent covariates and multiple event methods was used to model the risk of adverse events in the first 100 days.

Results: 1061 patients received first-line treatment for active TB; mean duration 247.7 days (114.4 SD). At baseline, mean age was 50 years (SD 21), female (50%), mostly Asian (40%) had pulmonary TB (69%) and normal AST (80%). The incidence of all major adverse reactions was 16.7 events per 100 person-months of treatment (95%CI, 16.4-16.9). Females vs. males (adjusted hazard ratio[HR],1.8; 95%CI, 1.4-2.3), age 35-59 years (HR 1.5; 95%CI,1.1-2.2), age >60 years (HR 1.9; 95%CI, 1.4-2.7), baseline AST >80U/L (HR 3.1; 95%CI,1.8-5.1); PZA use (HR 2.6; 95%CI, 1.6-4.0); and multi-drug resistant TB (HR 1.7;95%CI 1.1-2.6) were independently associated with any major side effect. HIV positive serology (HR 0.4; 95%CI 0.2-1.0) was found to be protective.

Conclusions: Age>35 years, female gender, baseline AST>80 U/L, PZA use and viral hepatitis co-infection are independent risk factors for any major adverse event during therapy. Patients with these risk factors should be closely monitored.

Keywords: *Tuberculosis, adverse events, cox regression*

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Drug utilization review: combination therapy in asthma

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Funding Source: AstraZeneca Inc.
Conflict of Interest: relationship
Background: Combination therapy should be prescribed to patients with moderate to severe asthma after daily long-term treatment with ICS has been tried without obtaining adequate control and it is not indicated to be used as first line treatment in asthma.
Objectives: To describe the use of combination therapy for the treatment of asthma and to evaluate to which extent it is prescribed as recommended.
Methods: A cohort of 14 559 new users of a combination therapy identified between January 1, 2000 and September 30, 2003 was selected from beneficiaries of the Régie de l'assurance maladie du Québec. We evaluated whether the combination therapy was prescribed according to the Canadian Asthma Guidelines. A logistic regression analysis was also performed to identify patients' and physicians' characteristics associated with the adherence to the recommendations of the Canadian Asthma Guidelines for the prescription of a combination therapy.
Results: Only 40% of users of combination therapy filled a prescription of ICS in the year preceding the initiation of the therapy and this proportion decreased by 21.8 % from 2000 to 2003. Patients who received their first combination therapy in an emergency department were less likely to have used ICS previously, but patients treated by a respiratory physician and patients with co-morbidities, markers of asthma severity and markers of uncontrolled asthma were more likely to have used ICS previously.
Conclusion: Combination therapy has not been used according to the Canadian Asthma Guidelines in a large proportion of patients.
Keywords: *Asthma, combination therapy, short-acting â2-agonist, inhaled corticosteroids*

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Effectiveness of combination therapy in asthma

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Funding Source: Fonds de la recherche en santé du Québec
Background: Users of combination therapy (inhaled corticosteroids (ICS) and long-acting *f*Ò2-agonists (LABA) in the same inhaler) have been found to be more persistent and adherent than users of concurrent therapy. We wanted to investigate whether this observed difference in treatment adherence could result in an improved effectiveness for combination therapy as compared with concurrent therapy (ICS and LABA in two different inhalers) to prevent asthma exacerbations.
Methods: This retrospective one-to-one matched cohort included newly treated asthmatic patients aged 16-44 years with either a combination or concurrent therapy selected from the RAMQ database between 1999 and 2002. The main outcome was moderate to severe asthma exacerbations defined as either a filled prescription of oral corticosteroids, and ED visit or a hospitalisation for asthma. Treatment effectiveness was compared between combination and concurrent therapies using Poisson regression models adjusting for patient's socio-demographic characteristics, markers of asthma severity and control, and use of health care services.
Results: The matched cohort was formed of 2559 new users of combination and 2559 new users of concurrent therapy. The crude rate of asthma exacerbation was 0.3 and 0.4 per patient, per year for combination and concurrent therapy respectively. Combination users were found to be 17% less likely to have a moderate to severe asthma exacerbation (adjusted rate ratio= 0.83; 95% CI: 0.75-0.91) in the year following treatment initiation.
Conclusions: The reduction in the rate of moderate to severe asthma exacerbations is, at least in part, likely to be due to higher treatment persistence and adherence observed among combination users.
Keywords: *Asthma, effectiveness, combination therapy*

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Estimated risk of pregnancy and cost-effectiveness of emergency contraception in British Columbia

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Funding Source: BC Ministry of Health Services

Background: Emergency contraception (EC) has been shown cost-effective in a number of jurisdictions. However, recent findings suggest risk of pregnancy among women requesting EC is markedly less than previously reported. Consequently, effectiveness and cost-effectiveness of EC have been over-estimated. We report results of a population-based estimate of pregnancy risk among women requesting EC and the impact on cost-effectiveness.
Methods: De-identified patient-specific data on time since last menstrual cycle and time of unprotected intercourse were obtained from treatment consents for EC from pharmacists in 2001-2. These data were used to estimate pregnancy risk among Yuzpe or levonorgestrel regimen users. These risks were included in decision analytic models to assess potential cost-savings of the current level of EC use and of increased awareness and use. Sensitivity analyses included an estimate of the impact of risk of pregnancy on cost-savings associated with EC use.
Results: Using the method of Wilcox et al (Contraception 2001;63:211) for estimating risk of pregnancy, we observed the risk (<±>95%CI) to be 4.16% (3.71-4.65) among 7,160 Yuzpe users and 4.02% (3.48-4.63) among 4,635 levonorgestrel users. Current use of EC saves the province $2.20 million annually and varying the risk of pregnancy (3.1%-9.0%) resulted in estimated cost-savings of <$0.15 - $4.90> million/year. Increased awareness and use would result in further cost savings of <$0.22 – $5.75> million/year over the same range of pregnancy risk.
Conclusion: EC with Yuzpe and levonorgestrel regimens is cost-effective in BC when the estimated risk of pregnancy in the population is less than assumed in previous studies.
Keywords: *Cost effectiveness, emergency contraception, risk of pregnancy*

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Evaluating patients' preferences for asthma treatments using a discrete choice experiment

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Background: Previous work in asthma has revealed that there is an over-reliance on rescue therapies, which may be attributable to differences in patients' preferences. The objective of this study was to quantify patients' preferences for treatment-related risk and benefits in asthma using a discrete choice experiment (DCE).
Methods: One hundred fifty-seven asthmatics (35.0+7.9 years of age) participated in the study. The DCE was designed to measure preferences for treatment benefit (symptom free days), potential risk (oral thrush and tremor/heart palpitation), ease of use (frequency of daily administration and number of inhalers required), and cost. Each participant also underwent pulmonary function testing and provided information on disease severity, control, and socioeconomic status. A nested logit regression model was developed to calculate the relative utilities of each attribute, which facilitated the calculation of the marginal rates of substitution.
Results: A relationship between utilities and all attributes in the hypothesized directions was observed. Specifically, patients were willing to pay an additional $15 per month to receive one extra symptom free day (SFD). While a willingness to pay of $5 per year to avoid one episode of oral thrush was observed, patients were willing to pay $32 to avoid two and $69 to avoid three episodes per year. Participants were also willing to forego 0.3, 2.2, and 4.7 SFD per month to avoid one, two, and three annual episodes of oral thrush, respectively.
Conclusions: Although patients preferred an increase in treatment benefits, results indicated that they were willing to forego symptom relief to avoid greater frequencies of adverse events.
Keywords: *Asthma, patient preference, discrete choice experiment*

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Evaluating the costs and benefits of ramapril to prevent cardiovascular morbidity and mortality: a comprehensive analysis

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Funding Source: Sanofi-Aventis

Background: Although ramipril has been shown to prevent cardiovascular events and maintain renal function there are no pharmaco-economic analyses comparing the cost-effectiveness of therapy across different clinical indications. We completed a cost-effectiveness analysis comparing the costs and benefits of ramipril among individuals at high risk of cardiovascular disease [with and without diabetes], with previous congestive heart failure, and among individuals with non-diabetic chronic nephropathy and proteinuria.
Methods: The perspective of the analysis was that of the Canadian healthcare system. The Cardiovascular Life Expectancy model was used to estimate the benefits of ramipril based on the observed results of the following randomized clinical trials (RCT): HOPE, MICRO-HOPE, AIRE, and REIN. Quality adjusted life years saved (QALYs) were calculated based on the observed RCT outcomes including cardiovascular events, total mortality, and end-stage renal disease. Daily ramipril treatment costs ranged from $.97 to $1.21 while other direct health care costs were based on provincial and national cost data. Quality of life data were abstracted from published reports.
Results: Focusing only on the benefits observed during each RCT, QALY's ranged from 0.042 to 0.075, while the average cost-effectiveness of ramipril ranged from $3,900 to $20,000 per QALY. Forecasting over the remaining life expectancy of patients, QALY's ranged from 0.74 to 1.22 while cost-effectiveness ranged from cost savings to $14,000 per QALY. For each RCT, sensitivity analyses were completed for hypothetical patients including men and women age 55 to 75 and the cost-effectiveness ratios remained below $50,000 per QALY with few exceptions.
Conclusions: Ramipril appears economically attractive among Canadian patients when used for the clinical indications described in these four published RCT's.
Keywords: *Pharmacology economics, cardiovascular disease, renal disease*

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ENCORE PRESENTATION

Gestational exposure to paroxetine and cardiac malformations in the newborn: a nested case-control study

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Harm-benefit analysis of rofecoxib versus naproxen for the treatment of rheumatoid arthritis patients: a discrete event simulation

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Funding Source: None

Background: Patients with rheumatoid arthritis (RA) require chronic NSAID therapy; however, not all NSAIDs are effective in all patients. Rofecoxib was an effective treatment alternative for many patients. Despite a qualitative analysis by a Health Canada expert advisory panel that concluded that rofecoxib's benefits outweighed its risks, it was withdrawn from the market. The objective of this analysis was to quantitatively estimate the net-benefit of rofecoxib relative to naproxen in RA patients.
Methods: Using a discrete event simulation (DES) model, we estimated the incremental net-benefit in quality-adjusted life years (QALYs) of rofecoxib relative to naproxen over a one-year time horizon. Treatment risks included dyspepsia, peptic ulcer and gastrointestinal bleeding and perforation, and fatal and nonfatal MI. Benefits were evaluated using two approaches: assuming equal effectiveness, and based on reported differences in functional ability. All data were derived from the published literature. 10,000 hypothetical patients were simulated through each arm of the model using both first- and second-order Monte Carlo simulation, and the incremental net benefit was determined for each iteration of the model.
Results: Independent of the assumption of effectiveness, rofecoxib resulted in a small, positive incremental net benefit. Assuming equivalent effectiveness or slightly greater improvement in functional ability with rofecoxib resulted in 0.83 (SD 0.04) and 1.3 (SD 0.05) additional QALYs per 1000 patients treated for one year, respectively.
Conclusions: These results suggest that rofecoxib is at least equivalent to naproxen in terms net-benefit, which supports the conclusions of the Health Canada expert advisory committee.
Keywords: *Harm-benefit analysis, rofecoxib, rheumatoid arthritis*

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Impact of once-weekly bisphosphonates on persistence rate and adherence level with antiresorptive therapies used for secondary prevention of osteoporosis

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Background/Objectives: We assessed the impact of once-weekly bisphosphonates on persistence rate and adherence level with antiresorptive therapies (ART) among elderly women.

Methods: A cohort of 5,196 women was reconstructed from the RAMQ databases, from 2002-2004. Women were 70 years and older and had started ART (bisphosphonates, raloxifene, nasal calcitonin) for secondary prevention, defined as ICD-9 or medical procedure code for osteoporosis or fragility fracture recorded within 5 years before index date (date of first prescription). Persistence was defined as no medication uncovered interval >60 days. One-year persistence rates were evaluated with Kaplan-Meier analysis. Cox Proportional Hazards model was used to estimate the rate ratio (RR) of ceasing treatment adjusting for covariables. Adherence level at one year of follow-up was the proportion of days during which women possessed a supply of medication (<80% or >=80%).

Results: Mean age was 77.8; One-year overall persistence rate was 59.9%. Compared to those starting on once-weekly bisphosphonates, women starting on daily risedronate or alendronate (RR: 1.18; 1.07-1.31) or other ART (RR: 1.78; 1.60-1.98) had a higher RR of cessation. The RR of ceasing ART was significantly lower among women with bone mineral density testing done before index date or during follow-up, and among those suffering a fracture (reduction of 20%, 70% and 47%, respectively). Overall, 60.2% of women met the >=80% adherence level. Once-weekly bisphosphonates showed the highest proportion of women meeting the >=80% level.

Conclusions: Even though once-weekly bisphosphonates had a positive impact, persistence and adherence with ART for secondary prevention remain suboptimal.

Keywords: *Administrative databases, persistence, adherence*

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Impact of poor compliance with atypical antipsychotic agents on the risk of hospitalization and death for patients with schizophrenia in Quebec

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Background: Noncompliance, whether due to lack of efficacy or side effects, may limit the effectiveness of atypical antipsychotic agents for managing schizophrenia. The aim of this study was to determine the association between risks of hospitalization and all-cause mortality and compliance with atypical antipsychotics.

Methods: A cohort of patients with schizophrenia and at least one prescription for an atypical antipsychotic (risperidone, olanzapine, or quetiapine) between 1st July 2001 and 31st December 2004 recorded in the Quebec Prescription Drug Insurance Plan database was formed. Hospitalizations and deaths after the first anti-psychotic prescription were tabulated until 31st December 2004. Compliance was determined from the proportion of time medication was available (>80% good, 50-79% moderate, or <50% poor compliance). Risks of hospitalization and death (all-causes) in relation to compliance over the preceding 12 months were examined using Cox regression with a time-dependent definition of compliance, adjusting for baseline age and gender, antidepressant, lithium and benzodiazepine use (before or after the index atypical antipsychotic).

Results: Of 41,754 patients with schizophrenia identified, 50% were younger than 45 years. Over a mean follow-up of 2.6 years, 4.6% died, 20,868 hospitalizations were recorded. About 1 in 5 patients were poor compliers, and compared to patients with good compliance, this was associated with an increased risk of hospitalization (adjusted hazards ratio 1.72, 95% CI 1.52 to 1.96) and death (1.67, 95% CI 1.56 to 1.75).

Conclusion: In this study poor compliers had a higher risk of experiencing adverse outcomes. More studies are required to further investigate this association.

Keywords: *Adherence, atypical antipsychotic, cohort study*

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Impact of the socio-economic status on the probability to receive TZDS among patients who meet the criteria reimbursement

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Source of Funding: GlaxoSmithKline
Background/Objectives: Pioglitazone and rosiglitazone (TZDs) have exception drug status in the RAMQ formulary. One condition for reimbursement is failure to respond to maximal doses of conventional oral hypoglycemic agents (COHA). Among patients who met this reimbursement criterion, we studied the influence of different factors on the probability to receive the TZDs.
Methods: Among patients eligible for drug coverage under the RAMQ between May, 2000 and June, 2005, we selected those who received six consecutive dispensations of maximal doses of both metformine and sulphonylurea. The proportion of patients who received a TZD in the year following the index date was calculated and a logistic regression was used to estimate the impact of several factors on the probability to receive a TZD.
Results: There were 4,836 patients in the cohort. A TZD was dispensed to 24.9% (95% CI: 23.7%;26.2%) of the patients. Compared to the oldest group of patients (65 years and more), the probability to receive a TZD was higher for patients aged of 51 to 64 years (OR=1.33 95% CI: 1.11;1.59) and patients aged of 19 to 50 years (OR=1.81 95% CI: 1.40;2.33). Patients with the highest income had more than two times the probability to receive a TZD (OR=1.55 95% CI: 1.21;1.98) compared to patients with the lowest income.
Conclusion: Among patients susceptible to benefit from TZDs, the younger patients and those with a higher income are more likely to benefit from the drug.
Keywords: *Drug reimbursement, TZD, formulary*

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Improving prescribing practices for older adults with renal impairment living in long term care facilities

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Funding Source: Canadian Institutes of Health Research (CIHR), Knowledge Translation Grant
Background: Approximately 30-40% of medications prescribed to long-term care (LTC) residents are inappropriate based on creatinine clearance (CrCl). This places a substantial number of elderly individuals at unnecessary risk for toxicity. Our objective was to pilot a pharmacist-mediated computer Alert system for 25 medications requiring renal dose adjustments in 6 Ontario LTC facilities over 3-months.
Methods: Alert recommendations were created by using a consensus panel along with a review of pertinent literature. These recommendations were programmed into a patient database of a LTC pharmacy provider. The database printed an Alert for patients who were identified as having renal impairment along with a prescription order for one of the Alert medications. The Alerts were reviewed by the consultant pharmacist who made recommendations, if required, before forwarding to the appropriate Physician. Physician response was indicated via a) a note b) a phone-call, or c) a change in the drug order.
Results: At least one Alert was triggered for 320 of 1272 patients (25%). Of the 444 total Alerts, the pharmacist identified 60% as relevant. Physicians responded to 98% of the Alerts having a specific pharmacist recommendation, responding as follows: 13% indicated 'no change to order', 41% discontinued the order; 43% reduced the dose; 2% would 'monitor patient', and 1% made a change to a co-medication. The pharmacist recommendation and the physician response were identical in 78% of cases.
Conclusions: This study demonstrated that a pharmacist-mediated Alert system can be successfully incorporated into LTC facilities to reduce the potential for renal toxicity. This system had a high rate of acceptance by physicians, and qualitative interviews are being conducted to better understand this success.
Keywords: *Renal, prescribing, elderly*

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Income-based drug coverage in British Columbia: the impact on access to medicine

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Background: In May 2003, the British Columbian government adopted an income-based pharmacare program, replacing the previous age-based program. Stated policy goals included the maintenance or enhancement of access to necessary medicines. This study examines the policy impact on access to two widely used drugs for chronic risk factors (antihypertensives and statins).
Methods: Data on incident antihypertensive and statin prescriptions between 1997 and 2004 was extracted from PharmaNet. Incident antihypertensive users were those who filled a first prescription after residing in BC for at least two years prior to that initial prescription date. The number of patients who ceased to fill a contiguous series of prescriptions (within 120 days of one another) was used as a measure of apparent discontinuation or interruption of therapy. We used time series analysis to test for changes in incident use and discontinuation.
Results: Between 1997 and 2004, 530,167 BC residents initiated therapy with an antihypertensive and 264,904 BC residents initiated therapy with a statin. The 2003 policy change had no statistically significant impact on incident use of antihypertensives or statins, when stratified by age or socioeconomic status (SES). Similarly, the 2003 policy did not change the rate of apparent discontinuations with therapy across age and SES groups. However, a co-payment introduced in 2002 did increase end-of-year seasonality in apparent discontinuations—a finding deserving further research.
Conclusions: The 2003 transition to income-based pharmacare in BC did not result in significant changes in access to or continuation with use of prescriptions to treat leading chronic risk factors.
Keywords: *Pharmaceutical policy evaluation, access to medicines*

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Is statin therapy associated with a decreased risk for bleeding in patients with chronic atrial fibrillation who are receiving warfarin? A population-based nested case-control study

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Funding Source: This study was supported by the Institute of Clinical Evaluative Sciences core
Background: Recent observations in patients with atrial fibrillation who are receiving warfarin therapy have suggested that concomitant treatment with an HMG-CoA reductase inhibitor (statin) decreases the risk for bleeding complications.
Methods: We conducted a nested case-control study using the population-based administrative databases of Ontario, Canada, to assess whether statin use decreases the risk of bleeding in anticoagulated patients. Eligible individuals were Ontario residents, age 66 and over, with a history of atrial fibrillation, who were prescribed warfarin between April 1, 1994 and December 31, 2001. Patients were followed until the occurrence of a hospital admission for gastrointestinal or intracranial bleeding, study end (March 31, 2002), discontinuation of warfarin, or death. Cases were matched to controls by age and sex. Conditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between bleeding and statin use.
Results: We identified 79,207 warfarin users with a history of atrial fibrillation. There were 1,518 cases with a gastrointestinal or intracranial bleeding event and 15,100 matched controls without bleeding. Long-term (≥1year) statin use was associated with a lower risk for any bleeding (OR = 0.80; 95% CI: 0.66, 0.97). However, there was no association between bleeding and recent (<6 months) statin use (OR = 1.04 (0.74, 1.48) or statin use of any duration (OR: 0.91 (0.77-1.07).
Conclusion: Long-term statin use may be associated with a decreased risk for bleeding in warfarin users with atrial fibrillation. Additional research is needed to further explore this putative association.
Keywords: *Statins, bleeding, case-control study*

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Potential misuse of over-the-counter medications and natural products in patients with moderate and severe chronic renal insufficiency

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Funding Source: Unrestricted research grants from 9 pharmaceutical companies
Background: Misuse of over-the-counter medications (OTC) and natural products (NP) may be associated with serious health problems among patients with chronic renal insufficiency (CRI). The use of OTC and NP is described in CRI patients attending a pre-dialysis clinic.
Methods: In a 6-month cluster randomized controlled trial, patients with moderate (n=46) and severe (n=41) CRI were interviewed over the phone at baseline by a community pharmacist to document their use of OTC and NP. Baseline drug-related problems (DRP) were identified independently by two pharmacists based on the patients' pharmacy chart, clinical summary and telephone interview information. Pharmaceutical opinions related with OTC and NP were identified during the patient follow-up.
Results: 82.6% (95%CI: 71.6%-93.6%) and 68.3% (54.1%-82.5%) patients with moderate and severe CRI, respectively, reported using at least one OTC. Among them, 41.3% (27.1%-55.5%) of moderate and 39% (24.1%-53.9%) of severe CRI patients used at least one OTC considered as contra-indicated or to be used with precaution in CRI. NP were used by 21.7% (9.8%-33.6%) and 29.3% (15.4%-43.2%) of patients with moderate and severe CRI, respectively. Among those, 10.9% (1.9%-19.9%) and 12.2% (2.2%-22.2%) reported using a product considered as contra-indicated or to be used with precautions. Overall, 23 DRPs were identified and 2 pharmaceutical opinions were issued by community pharmacists.
Conclusions: The use of OTC and NP is highly prevalent in CRI patients and are often associated with a DRP. These results underline the importance for community pharmacists to closely monitor the use of OTC and NP by CRI patients.
Keywords: *Chronic renal insufficiency, OTC medications, natural products*

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Privacy and health research: what are the attitudes of the public?

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Funding Source: CIHR
Background: Obtaining patient consent for using personal health information in research studies is a complex issue. This study ascertained Canadians' attitudes towards use of personal health information for different types of health research.
Methods: 1230 Canadians were surveyed by telephone about attitudes toward privacy and health research, trust in different institutions to keep health information confidential, and the need for patient consent for use of health information for different types of research. We also asked about preferences for different ways of collecting health information for use in research – e.g., abstracting data from medical records.
Results: There was strong support for both health research and the protection of privacy of personal information. Support for health research was greatest when studying communicable diseases and quality of health care (85-89%). Trust in institutions was highest for: CIHI and Statistics Canada; university researchers; hospitals; and disease foundations (78-80%) and lowest for the insurance industry (35%). Many either strongly agreed (31%) or somewhat agreed (37%) that research beneficial to people's health is more important than protecting people's privacy. For medical record abstraction, 4% of respondents felt this information should not be used at all; 32% felt permission should be obtained for each use; 29% supported broad consent, 24% supported notification and opt out; and 11% felt no need for notification or consent.
Conclusions: The public generally supports using health information for research – particularly by academic researchers. Most are open to something less restrictive than a per-research-use consent but only a small minority support use of their information without their knowledge or consent. This raises important challenges for those designing new health privacy policies and laws in Canada.
Keywords: *Privacy, health research, attitudes*

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Risk of lower respiratory tract infection among users of inhaled corticosteroids

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Funding Source: Pfizer

Background/Objectives: Systemic steroids increase the risk of bacterial infections. This undesirable effect could also be present in patients with chronic airway disease (CAD) who receive high doses of ICs. We studied the effect of ICs on the incidence of lower respiratory tract infections (LRTIs) among patients with CAD.

Methods: The cohort included subjects covered by RAMQ between 1994 and 2003, aged 66 years or more, and who received 3 LABA/SABA, 3 theophylline or 3 ipratropium dispensations during 1 year. Cases were defined as subjects who received a diagnosis of LRTI (index date) and an antibiotic. One to 4 controls were matched to each case for age, sex, and date of entry in the cohort. Conditional logistic regression was employed.

Results: 4,482 cases and 17,441 controls were included. The risk of LRTI was higher for patients hospitalized (OR:1.28 ; 95%CI: 1.18-1.39) in the year preceding the index date, who visited a GP (OR:2.81 ; 95%CI: 2.47-3.20) and an ER (OR:1.39 ; 95%CI: 1.29-1.51), and who received a SABA (OR:1.10 ; 95%CI: 1.01-1.19). It also was higher for patients exposed to ICs between 61 to 120 days (OR:1.12 ; 95%CI: 1.01-1.25), between 121 to 209 days (OR:1.19 ; 95%CI: 1.06-1.33), and between 210 days and more (OR:1.36 ; 95%CI: 1.22-1.52).

Conclusions: We found a small and dose related increase in the risk of LRTIs among CAD patients treated with ICS. Further studies are in progress to determine if this is a causal effect or if it is due to confounding by indication.

Keywords: *Chronic airway disease, lower respiratory tract infections, databases*

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ENCORE PRESENTATION

Type 2 diabetes does not increase risk of depression

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A comparison study among Canadian provinces for prescription patterns of lipid-lowering therapeutics

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Funding Source: AstraZeneca

Background: The lipid-lowering therapeutics, particularly statins, are frequently used in the Canadian population. Statins compose approximately 10% of provincial medication budgets.

Objectives: To explore the similarities and dissimilarities among Canadian provinces regarding (1) characteristics of patients on the treatment, (2) prescription patterns and therapeutic indicators, and (3) community-based effectiveness of anti-hyperlipidemic drugs.

Methods: Patients filling a prescription for any anti-hyperlipidemia therapy in selected pharmacies in Ontario, Quebec, British Columbia and Nova Scotia. All eligible patients are interviewed over the telephone using CATI software. Physicians who are identified by the participating patients are requested to complete a questionnaire.

Results: The mean age for patients was more than 60 years old in all provinces [NS (61±11), PQ (63±10), ON (66±11), BC (65±10), P<0.0001]. Anti-hyperlipidemia therapy was associated with a decrease in LDL-C ($p < 0.001$) in all provinces, however on average only 55% of patients achieved the goal LDL level [NS (55%), PQ (54%), ON (58%), BC (54%), P>0.05]. The average lag time between the time when the diagnosis of hyperlipidemia was made and when drug treatment was started was 1.96 years ($p < 0.0001$) [NS (1.75±3), PQ (2.16±3), ON (2.17±4), BC (1.8±3), P>0.05]. Most patients had at least two cardiovascular risk factors [NS (86%), PQ (83%), ON (84%), BC (91%)]. On average 39% of patients were treated for secondary prevention [NS (37%), PQ (34%), ON (46%), BC (37%), P>0.05], and an additional 13% of patients were diabetics without previous cardiovascular events [NS (14%), PQ (11%), ON (12%), BC (16%), P>0.05]. Metabolic syndrome was observed in 32% of patients [NS (33%), PQ (24%), ON (35%), BC (38%), P>0.05].

Conclusions: Almost all patients fulfilled the guideline requirements for the use of anti-hyperlipidemic therapy. More than half the patients were high risk, either secondary prevention or primary prevention with diabetes. However, close to half of the patients did not achieve the recommended goals for LDL level. In general, there are no significant differences amongst provinces for patients' characteristics, prescription patterns, therapeutic indicators and effectiveness of lipid-lowering drugs.

Keywords: *Statins, anti-hyperlipidemia, population therapeutics*

CAPT POSTER PRESENTATIONS
Wednesday May 10, 2006

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A comparison between using data from community-based research (real world) with data from randomized controlled trials (RCTs) in economic evaluation of therapeutics

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Funding Source: Data obtained from a study which was supported by a fund from Wyeth Canada
Background: Data generated from RCTs are obtained under ideal experimental conditions (efficacy) and the applicability of this data when conducting a real world (cost-effectiveness) economic evaluation may be questionable.
Objective: To compare cost-effectiveness results obtained with RCT efficacy data with results derived from community-based clinical practice effectiveness data.
Methods: Using data from a community-based cohort study (Farahani 2006) and from a RCT (Moreland 2001), two cost-effectiveness analyses were performed with the same model, evaluating etanercept treatment in rheumatoid arthritis.
Results: Using an effectiveness-based analysis, the mean QALYs gained during the 12-month monitoring period were 0.45 and 0.35, for treatment and control groups respectively. The ICER for etanercept treatment was $174,200 (CDN) per QALY [95% CI, $119,500 to $285,000]. Incorporating RCT efficacy data into the analysis, the mean QALYs gained were 0.56 and 0.35, for treatment and control groups respectively. This reduced the ICER for etanercept treatment by more than 50%, $82,952 per QALY [95% CI, 66,500 to 103,430].
Conclusion: The source of clinical data used for has a significant impact on the ICER for etanercept treatment. This study highlights the potential concerns of using RCT data for estimating cost-effectiveness, and helps to explain the difference in cost-effectiveness reported in 2 previous modeling studies, one based on efficacy data (Brennan 2003) and the other on effectiveness data (Barton 2004).
Keywords: *Clinical outcomes studies, economic evaluation, rheumatoid arthritis*

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A comparison of three indirect utility measures and two disease-specific instruments for measuring quality of life in asthma

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Funding Source: BC Lung Association and Michael Smith Foundation for Health Research
Background: To assess management strategies, instruments used to measure the health-related quality of life (HRQL) of asthmatics must be able to discriminate between levels of control. The study objectives were to examine the cross-sectional construct validity of the HUI-3, SF-6D, and EQ-5D in terms of self-reported asthma severity, and to compare these with two valid and reliable disease-specific instruments, the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ).
Methods: One hundred fifty-seven asthmatics (35.0±7.9 years of age) participated in the study. Each participant completed all five questionnaires and provided self-reported HRQL, asthma severity, and asthma control level. Each participant also underwent pulmonary function testing and provided information on medication and healthcare use. Construct validity was assessed by comparing mean scores for each instrument across levels of self-reported asthma severity. Convergent validity of the instruments was evaluated using Spearman's correlations.
Results: Strong correlations were identified between the three generic instruments (rho = 0.61 to 0.72) and between the AQLQ and ACQ (rho = 0.82). However, there were only weak correlations between the generic and disease specific instruments (rho = 0.19 to 0.46). Although a monotonic decline in AQLQ and ACQ scores occurred with increasing severity, a similar relationship was not observed with the generic instruments.
Conclusions: There was no consistent relationship between the health utilities derived from the generic, preference-based instruments and increasing asthma severity, asthma control, or asthma-specific quality of life. This could have a significant impact on the results of any cost-utility analysis in asthma.
Keywords: *Asthma, utilities, preferences*

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A cost-effectiveness analysis of omitting chest radiographs in the diagnosis of bronchiolitis in infants in the emergency department

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Background: Viral bronchiolitis is the most frequent cause of infant admissions during winter and the conventional approach to diagnosis includes ordering a chest radiograph to eliminate alternative causes of the symptoms, such as bacterial pneumonia. It was hypothesized that the omission of the chest radiograph would result in savings through reduced radiographs and fewer antibiotics prescriptions, without adversely affecting outcomes. The objective was to quantify the economic and health benefits of omitting chest radiographs in the diagnosis of bronchiolitis in infants in the emergency department (ED).
Methods: A cost-effectiveness analysis was undertaken from the healthcare system perspective including only direct costs incurred during the acute episode of care. The data were obtained from a clinical study at the Hospital for Sick Children conducted from 2001 to 2005 that enrolled 311 patients with clinical presentation of typical (n=265) or atypical (n=46) bronchiolitis. ED physicians were asked to diagnose and recommend a treatment plan before and after chest radiographs were performed to determine if the radiograph altered the ED physicians' diagnosis. The radiographs were analyzed by an expert radiologist to assess the sensitivity and specificity of ED physicians' interpretations.
Results: Omitting chest radiographs from the diagnostic process for patients with typical bronchiolitis saved $5,908 per 100 patients diagnosed and treated for bronchiolitis. Including a chest radiograph improved the accuracy of diagnosis for atypical but not typical cases.
Conclusion: In a climate of rising healthcare costs, this study demonstrated potential cost-savings through omission of unnecessary chest radiographs.
Keywords: *Cost-effectiveness analysis, bronchiolitis, chest radiograph*

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A descriptive study of asthma medication users in Quebec in 2003: relative importance of various drug use profiles reflecting severity of asthma

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Funding Source: Novartis Pharma Canada (non restrictive grant)
Objective: The objective of the study was to describe asthma medications users covered by the Quebec public drug insurance plan, according to profiles that are likely to reflect asthma severity.
Methods: Individuals aged 5 to 44 years who received at least one prescription for an asthma medication in 2003 were drawn from the Quebec public drug insurance program database. This program covers individuals receiving provincial income supplement (PSRs) and those not covered by private insurance programs (adherents). Seven subgroups (profiles) of asthma medication users (AMU) were created according to the nature of the medication regimen received. The profiles are mutually exclusive and are designed to reflect asthma severity.
Results: More than 85% of AMU belonged to one of the 7 profiles. Profile 3 (Inhaled corticosteroids (ICS) with or without short-acting b2 agonists (SABA)) was the most prevalent profile (45% of AMU in PSRs, 47% in adherents). Patients in profile 6 (ICS, oral corticosteroids and one of either a long-acting b2 agonist or an antileukotriene with or without SABA) suggestive of severe persistent asthma with inadequate control, constituted 3% of AMU in adherents and 5% in PSRs, while profile 7 (ICS and oral corticosteroids with or without SABA) regrouped 6-7% of AMU.
Conclusions: Most AMU can be regrouped in one of 7 profiles. Patients who had to use oral corticosteroids despite ICS and adjunct therapy represent 3-5% of AMUs.
Keywords: *Asthma, utilization, medication*

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A typology of feedback interventions to modify prescribing practices

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Background/Objectives: Feedback, defined as a summary of clinical performance over a specified period of time that is given back to a professional for practice improvement, has been shown to have some impact on prescribing practices. However, no typology of feedback modalities exists to help sort out what kind of feedback is more useful and what is less useful. The objective of this presentation is to propose a typology of feedback interventions structured around a valid yet simple conceptual framework.

Methods: A literature search was performed using the key words "feedback, interventions and prescribing". The different types of feedback modalities were classified according to the classical model of communication process developed by McGuire: who (Source) says what (Message), how (Channel), to whom (Target) and why (Purpose).

Results: The Source includes the characteristics of the organization that sends the feedback (e.g. government, professional, academic, national, local). The Message pertains to the nature of the feedback, the aggregation level, whether there are comparisons with peers or scientific norms, etc. The Channel by which the feedback is transmitted corresponds to the material means, frequency and whether there is an interactive process or incentive. The Target defines the types of professionals who receive the feedback, their performance level and their work setting. The Purpose specifies the approach (sanctional or formative) and the intention (modify, reduce or increase a given behaviour).

Conclusions: McGuire model of communication process provides a useful framework to guide both the design of feedback interventions and the study of their effectiveness.

Keywords: *Literature search, feedback, communication mode*

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An assessment of academic detailing, on congestive heart failure, using a prospective, randomized, cross-over design, in North Vancouver

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Background: Academic detailing (AD) involves an unbiased health professional visiting physicians in their offices to discuss evidence based recommendations. BC CDUP is an AD program. Congestive heart failure (CHF) affects over 350,000 Canadians. Appropriate pharmacotherapy can decrease associated morbidity and mortality. There are no Canadian randomized, cross-over studies published on the effects of AD.

Objectives: To determine whether AD increases appropriate prescribing, and decreases hospitalizations or deaths in CHF.

Methods: General practitioners (GPs) in North Vancouver were prospectively randomized to an Early or Delayed group. Between June-December 2000, the Early group received a newsletter and AD visit on CHF, the Delayed group received the same on a different topic. In January 2001, the interventions were reversed. Encrypted data were extracted using PharmaNet and Ministry databases. Prescribing preferences (probabilities) were compared in the Early and Delayed groups before, during and after the 6-month delay period. Probability ratios were analysed like relative risks.

Results: 39 in the Early group, and 26 in the Delayed group received an AD visit by a pharmacist on their topic. Results were from 1641 CHF patients with >50% of their care from GPs. The relative risk (and confidence intervals) of the Early group, divided by the Delayed group was as follows: starting ACE-inhibitors 1.2 (0.7-2.0), stopping alpha-blockers 0.3 (0.03-3.5), CHF hospitalization 1.2 (0.44-3.2). Mortality was not different.

Conclusion: There is a nonsignificant trend towards improved prescribing and decreased hospitalization. More data are needed to quantify the impact of AD, e.g. by pooling analyses of multiple interventions over time.

Keywords: *Academic detailing, randomized, heart failure*

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Antidepressant utilization in British Columbia

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Background: Expenditures on antidepressants in Canada are rapidly increasing. Yet few studies have analyzed the characteristics of incident and prevalent users of antidepressants. The objectives of this study were to investigate the prevalence and incidence of antidepressant use in British Columbia over an eight-year period.

Methods: Antidepressant utilization and demographic data were assessed for the population of BC from 1996 to 2004. Prescription drug claims for monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), tricyclics (TCA), bubroprion (categorized separately for smoking cessation and depression), and the 'novel' antidepressants such as venlafaxine, nafazodone, and trazodone, were identified within the PharmaNet database. Both incident and prevalent utilization rates were analyzed. Incident users were those who were dispensed their 'first' antidepressant therapy after a period of two years without antidepressant claims. All cohort subjects were required to have continuous registration with BC medical services for at least two years prior to their first recorded antidepressant prescription claim.

Results: Prevalence of antidepressant use almost doubled, from 34 to 72 users per 1000, between 1996 and 2004. The prevalence of particular classes of antidepressants also changed over time. Use of novel antidepressants and serotonin reuptake inhibitors (SSRI) increased overall, although incident use of SSRIs decreased over time. Use and incident use of bupropion for smoking cessation peaked in 1999 but then declined. Incident antidepressant use increased in 1998 and 1999, but decreased towards the end of 2004. No age gradient was observed for prevalence, although there was an obvious socio-economic gradient. Those in age groups of 20-44 and 45-64 showed the greatest peak in incident antidepressant use. A socio-economic gradient in incident antidepressant use was also observed.

Conclusions: Prevalence of antidepressant use in BC has increased dramatically since 1996. Incident use, however, increased from 1998 to 1999, but then decreased throughout 2004.

Keywords: *Prescribing patterns, drug utilization*

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Are there compelling cases for routine post-marketing surveillance of drugs?

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Funding Source: None

Background: As part of Canada's national pharmaceutical strategy, a committee of federal and provincial drug policy makers has been examining the merits of pharmaceutical post-marketing surveillance techniques. Input was requested on "compelling cases" where post-marketing surveillance could have significantly altered a drug's career on the market.

Methods: Five medications were selected to illustrate each of the following situations: 1) drug with both benefit and risk uncertain, 2) drug associated with adverse outcome where the background rate is a) common, b) unusual, c) rare, 3) drug associated with unexpected benefit. The "null hypothesis" was that only a high quality randomized trial (as opposed to case series, clinical database or prospective observational studies) could have significantly altered the history of the drug, either in final outcome or in time to gain approval or withdrawal from the market.

Results: Drugs (and outcomes) selected to illustrate the stated situations were, in order, t-pa for stroke (disability prevention versus intracranial bleeding), rofecoxib (vascular events), oral contraceptives (thromboembolic events), nefazodone (hepatic failure), and clopidogrel (acute coronary syndromes). In two cases (rofecoxib and clopidogrel), randomized controlled trials definitively answered the question of benefit:harm balance and dramatically changed the use of the relevant drug. In the other three cases, case series or planned observational studies inconclusively addressed benefit:harm issues but one drug (nefazodone) was withdrawn based on a case series alone.

Discussion: A mixture of rapidly deployable methodologies might well be helpful in shortening the time to definitive information. Practical randomized trials are the most valid but have feasibility issues to resolve.

Keywords: *Postmarketing surveillance, drug benefit, drug safety*

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Assessment of quality of life and health care resource utilization as a function of pain severity levels

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Funding Source: Pfizer Canada Inc.

Background/Objectives: To assess the impact of using physicians or patients' perception of pain severity in evaluating health related quality of life (HRQoL) and health care resource utilization associated with neuropathic pain (NeP).

Methods: A cross sectional, observational study was conducted at primary care sites across three Canadian provinces amongst NeP patients. Data was collected through patient self-administered questionnaires to measure HRQoL and investigator chart review to collect resource utilization. Patients' pain severity levels were assessed through the modified-Brief Pain Inventory. Physicians were asked to classify their perception of their patients' pain as mild, moderate or severe.

Results: 126 patients were enrolled. Severe pain was reported more often by patients (33%) than by physicians (22%). Overall, the two definitions of pain severity levels did not impact the HRQoL results (i.e., decreased HRQoL with increased pain severity). However, the number of GP visits over the three-month period prior to study visit increased with pain severity (mild:1.1 visits, moderate:2.3 visits, severe:3.0 visits) when using physicians' assessment of patients' pain severity while the number of GP visits was independent of pain severity (mild:2.1, moderate:2.2, severe:2.2) when using patients' ratings. Other discrepancies were observed regarding the number of specialist visits, and the use of diagnostic tests.

Conclusions: Results suggest that HRQoL assessment does not vary as a function of patients or physicians' perception of pain severity. However, as physicians are the main drivers of medical resource use, physicians' assessment of pain intensity should be used for identification of medical resource utilization per pain severity level.

Keywords: *Pain severity, HRQoL, resource utilization*

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Cost-effectiveness of pregabalin for the management of neuropathic pain (NeP) associated with diabetic peripheral neuropathy (DPN) in Canada

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Funding Source: Pfizer Canada Inc.

Objectives: To examine the cost-effectiveness of pregabalin, a new treatment approved in Canada for the management of NeP associated with DPN, versus gabapentin.

Methods: A published stochastic simulation Markov model was used to determine the 12-week incremental cost-effectiveness of pregabalin versus gabapentin. Based on patient-level data from randomized clinical trials of pregabalin (150-600 mg per day) and gabapentin (900-3,600 mg per day), the model simulated the daily pain experience of a hypothetical cohort of 1000 DPN patients in order to generate the expected mean numbers of days with no or mild, moderate, and severe pain over a 3-month time period as well as quality-adjusted life-years (QALYs). Resource utilization by level of pain severity was identified through a 2004 survey amongst 80 Canadian generalists and specialists treating DPN patients. The economic analysis was expressed in terms of incremental cost per day with no or mild pain and incremental cost per QALY gained.

Results: Compared to gabapentin, treatment with pregabalin saved $19 per patient over the 12-week period and resulted in 6 additional days with no or mild pain and an additional 0.0047 QALYs. Therefore, pregabalin was the dominant strategy as it was less costly and more effective than gabapentin (95% CI first analysis: dominant to $13 per day with no or mild pain; 95% CI second analysis: dominant to $15,708 per QALY). Sensitivity analyses are supportive of the robustness of model findings.

Conclusions: Pregabalin therapy for patients with NeP associated with DPN is dominant (cost-saving and more effective) when compared to gabapentin.

Keywords: *Cost-effectiveness, pregabalin, diabetic peripheral neuropathy*

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Association between the control of asthma during pregnancy and the incidence of asthma in the offspring

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Funding Source: CIHR
Background: It is unknown whether the incidence of asthma in children is influenced by the presence and control of maternal asthma during pregnancy. This study aims at evaluating the association between maternal's asthma control during pregnancy and the incidence of asthma in the offspring in the first 10 years of life.
Methods: A cohort of 32731 singletons born between 1990 and 2002 was constituted following the linkage of 3 Quebec's administrative health databases. Children were followed from birth until asthma diagnosis, end of governmental drug insurance coverage or December 31, 2002, which ever occurred first. Uncontrolled asthma during pregnancy was defined as the use of >10 doses/week of inhaled beta2-agonists, a filled prescription of oral corticosteroids, or an ER visit or hospitalization for asthma. Crude hazard ratios were estimated using Cox models.
Results: Asthma developed in 35.5% and 15.6% of children of asthmatic and non-asthmatic mothers, respectively. Children whose mothers had asthma during pregnancy were 2.5 times more likely to have asthma compared with children of non-asthmatic mothers (HR: 2.54 95%CI: 2.43-2.66). Moreover, we found that children whose mothers had uncontrolled asthma during pregnancy were 24% more at risk of developing asthma compared with children of mothers with controlled asthma (HR: 1.24 95%CI: 1.15-1.33) and had 3 times the risk of children of non-asthmatic mothers (HR: 2.97 95%CI: 2.77-3.18).
Conclusions: Results suggest that the incidence of asthma in children seems to be influenced by maternal's asthma control during pregnancy. Future analyses will consider potential confounders.
Keywords: *Pharmacoepidemiology, asthma, children*

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Availability of phototherapy services in Canada

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Funding Source: Amgen Canada Inc.
Background: To determine the number, location and availability of phototherapy services for psoriasis patients in Canada
Method: This analysis was conducted in two phases. Phase one consisted of contacting regional health offices of each Canadian province to determine the number of clinics offering phototherapy services. Phase two consisted of contacting dermatologists in each province listed in the Canadian Medical Directory (2004) by phone. The number of phototherapy services, location, hours of operations and staff operating phototherapy units was collected. Descriptive statistics were used to analyze the data.
Results: Preliminary results from Ontario and Alberta were available. The population of Ontario was 11,410,046. There were 50 regions and 177 dermatologists. There are 26 clinics that offer phototherapy services in Ontario. Only 14 regions (28%) offered phototherapy services and none of the clinics employed a specific individual to operate the phototherapy equipment. The majority of phototherapy services are in the greater Toronto area. In Alberta, there were 19 different regions and 41 dermatologists in a province of 2,974,807. There were 12 phototherapy clinics in the province. Only 4 regions (21%) offered phototherapy services. More updated information will be provided at the time of presentation.
Conclusions: Phototherapy services in Ontario and Alberta are centered in densely populated areas. Relatively, few individuals residing in rural committees have access to phototherapy services in Canada.
Keywords: *Psoriasis, phototherapy, accessibility*

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Can results from one geographic area be used to help inform health care decision making in another?

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Funding Source: Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
Background: There has been increasing pressure to consider using published economic evaluations or health technology assessments from other jurisdictions for local reimbursement decisions. Geographic transferability has the potential to facilitate assessments that would otherwise be infeasible and the potential to make more efficient use of global evaluation resources.
Objectives: To review and summarize the literature on: (i) factors affecting geographic transferability of economic evaluation data; (ii) criteria, guidelines or decision rules for determining transferability potential; and, (iii) approaches which have either been proposed or used in practice for transferability.
Methods: A systematic literature review on transferability was conducted. Electronic databases, hand searching and bibliographic searching techniques were utilized. Two classification systems were developed; one summarizing transferability factors, and another summarizing transferability approaches.
Results: Titles and abstracts of nearly 5,000 articles were reviewed and 808 in full text. There was a substantial literature identifying over 70 factors potentially affecting transferability. From these papers we developed a classification system which grouped these factors into 5 broad categories based on characteristics of the patient, the disease, the provider, the health care system and methodological conventions.
Conclusions: There is strong evidence indicating that transferability of economic evaluation data is complex and can result in misleading results. Approaches which have been used for transferability suggest that there is a need for country-specific substitution of practice pattern data as well as unit cost data. The results from this review will assist researchers and government decision making bodies when considering and conducting transferability studies.
Keywords: *Transferability, economic evaluation, HTA*

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Canadian cost-effectiveness of macugen compared to photodynamic therapy with verteporfin in the treatment of subfoveal wet age-related macular degeneration in the elderly

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Backround/Objective: To examine the cost-effectiveness of treatment with Macugen, a new treatment for age-related macular degeneration (AMD), compared to treatment with photodynamic therapy (PDT) with verteporfin for all lesion subtypes in the Canadian elderly population.
Methods: A Markov framework was used to model lifetime movement of an AMD cohort of elderly (age 65 and greater) through five health states based on visual acuity (VA): >20/40, 20/40 to >20/80, 20/80 to >20/200, 20/200 to >20/400, and lower than 20/400. The model incorporates patients across all lesion subtypes: predominately classic, minimally classic, and occult. All drug costs, procedure costs, and costs associated with declining VA (costs associated with depression, injuries, and nursing home admission) were derived from several Canadian sources including the RAMQ (Quebec) and the MOHLTC (Ontario) databases. Expert interviews were conducted to determine adverse event treatment patterns and vision rehabilitation resource use. Transition probabilities for Macugen were derived from published efficacy data from the VISION study, while data on treatment of all lesion subtypes with PDT were derived from the PDT TAP and VIP studies. Utilities were obtained from published sources similarly used in previous AMD models.
Results: For all lesion subtypes, the incremental cost per QALY gained for Macugen compared to PDT is $49,052 CAD. The incremental cost per vision years gained for Macugen compared to PDT is $20,401 CAD. Variations in model time horizon have the largest impact on results.
Conclusion: In elderly patients with subfoveal wet AMD and regardless of lesion subtype, Macugen is a cost-effective treatment when compared to PDT with verteporfin.
Keywords: *Cost-effectiveness, macugen, AMD*

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Canadian economic evaluation of pregabalin for the management of neuropathic pain (NeP) associated with postherpetic neuralgia (PHN)

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Funding Source: Pfizer Canada Inc.
Objectives: The objective of this evaluation is to examine the incremental cost-effectiveness of pregabalin, the first approved drug for the management of NeP associated with PHN in Canada, compared to gabapentin.
Methods: The analysis uses a previously published stochastic simulation Markov model to estimate the impact of pregabalin (150-600mg per day) versus gabapentin (900-3,600mg per day). The model simulates treatment strategies on a hypothetical cohort of 1000 patients with PHN and assesses their daily pain experience over time. Health benefit estimates were based on the results of two randomized clinical trials of pregabalin and gabapentin, respectively. Utility values and resource utilization were estimated from 126 Canadian patients, and 80 Canadian physicians, respectively. The analyses are expressed in terms of incremental cost per day with no or mild pain and incremental cost per quality-adjusted life-year (QALY) gained.
Results: Treatment with pregabalin (compared to gabapentin) results in 6 additional days with no or mild pain and an additional 0.0064 QALYs gained for the 12-week period. The incremental average medical savings of treating with pregabalin are estimated to be $62.39 per patient for the 12-week period. Consequently, pregabalin is the dominant strategy (more effective and less costly) over gabapentin (95% CI first analysis: dominant to $0 per day with no or mild pain; 95% CI second analysis: dominant to $158/QALY). Sensitivity analyses are supportive of findings from base case analyses.
Conclusion: Compared to gabapentin, pregabalin therapy is dominant in the management of NeP associated with PHN.
Keywords: *Cost-effectiveness, pregabalin, postherpetic neuralgia*

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ENCORE PRESENTATION

Collaborative management of allergic rhinitis in the Canadian Forces – a controlled clinical trial

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Community pharmacy pilot project on safety and quality improvement

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Background: Few interventions have been evaluated to improve safety and quality improvement (QI) in community pharmacies. The purpose of the pilot study was to determine if an educational and quality improvement intervention improved medication safety and the quality of care in community pharmacies.
Methods: Community pharmacies were recruited from 3 pharmacy corporations. 26 Alberta community pharmacies participated. Data was collected for 8 months. The multifaceted intervention consisted of pharmacist continuing education, provision of a practice tool / checklist, provision of a quality improvement model, a consultation visit from quality improvement expert and provision of comparative feedback reports. Data was collected (from surveys, pharmacist documentation, focus groups, interviews, project manager observations) to assess pharmacy safety scores, adherence to pharmacist practice standards, medication error reports, and improvements made. Pre and post intervention comparisons were made.
Results: Key findings include:
- The mean score on pharmacy safety assessments improved by 17.6%.
- 4164 practice adherence checklists were submitted. The average adherence to practice standards increased 9.0%.
- 577 error / near miss events were reported. Six event types accounted for 90% of events. There were 13.9 events per 100 pharmacist-patient encounters.
- Pharmacists reported 28 distinct operational improvements. Enhancements to patient counseling processes, improved communication processes regarding errors/ near misses and enhancements to inspection processes were cited most frequently.
- Lessons learned include: comparative feedback and one-on-one educational intervention improved interest; participant response was positive, but safety culture changes still are needed.

Conclusions: Community pharmacists' awareness of safety and QI processes improved. A decision will be made in 2006 about conducting an expanded project.
Keywords: *Safety, quality improvement, community pharmacy*

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Concordance between discharge prescriptions and insurance claims

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Background: Limited information exists on the accuracy of drug claims databases. Details on the characterization and time course of dispensation of medications as well as the concordance of days' supply and quantity in an administrative database for a homogenous patient population has not been previously explored. The purpose of this study was to assess the degree of concordance between the information (drug quantity and days' supply) recorded on hospital discharge prescriptions and what appears in a public drug insurance electronic claims database.
Methods: A retrospective chart audit of hospital discharge prescriptions with linkage to a prescription claims database was conducted. Three-hundred-forty-five post-myocardial infarction patients discharged from a university-affiliated teaching hospital were included. The percent of linkable records with perfect agreement between the written prescription and the insurance claim was our measure of concordance.
Results: Seventy-seven percent and 82% of discharge prescriptions were filled by seven days, and 120 days post-discharge, respectively. Of those dispensed and that contained adequate information, concordance was perfect for days' supply and quantity for 70.7% (95% CI 67.9%-73.4%) and 65.9% (95% CI 63.2%-68.7%) of prescriptions, respectively. For cardiac drugs, which comprised the majority of filled prescriptions, concordance was greater for days' supply than for quantity (75.5% [95% CI 72.6%-78.4%] vs 65.3% [62.3%-68.4%]). Concordance varied by medication type.
Conclusions: Most hospital discharge prescriptions were filled within one week. Concordance between discharge prescriptions and insurance claims was greatest for scheduled cardiac medications.
Keywords: *Prescriptions, accuracy, pharmacoepidemiology*

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Cost effectiveness of drug eluting stents in Ontario

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Background: Drug eluting stents cost more than bare metal stents, but may reduce the need for revascularizations. This study evaluates the cost-effectiveness of DES compared to BMS.
Methods: A decision analytic model with a 1 year time horizon was used to estimate costs and effects (QALYS, revascularizations) for patients receiving DES and BMS. Prospectively collected data from the Cardiac Care Network of Ontario was used to estimate revascularization rates along with other model parameters. Stent costs were obtained from manufacturers, while revascularizations costs were obtained from a southern Ontario hospital. Cost-effectiveness was assessed on 22 unique patient subgroups stratified by diabetes status, lesion characteristics and recent history of acute myocardial infarction (AMI).
Results: Using clinical outcome data from 7,953 PCI cases, the cost-effectiveness of DES was most favorable in non-post MI diabetes patients with long and narrow lesions $223,000/QALY ($9,869/revacularization). This subgroup had the greatest difference in estimated 1 year revascularization rates between BMS and DES (20.6% vs. 6.0%). Cost effectiveness was found to be greater than $500,000/QALY ($20,788/revascularization) in 17 of the 22 patient cohorts (85% of patients).
Conclusions: The current analysis found the cost-effectiveness of DES to be high in all patient subgroups. The primary strength of the analysis is that revascularization rates were based upon a large sample of "real world" patient data. Other published economic analyses of drug eluting and bare metal stents are at least partially based upon clinical trial data in which clinical benefits of DES are exaggerated compared to "real world" practice, thus providing more favorable cost-effectiveness results.
Keywords: *Cost-effectiveness, DES, HTA*

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Cost of corneal transplantation for the Quebec health care system

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Background: Although corneal graft is a common, long-standing procedure, little is known about its economic impact. The purpose of this study was to estimate resource use and costs associated with corneal transplantation according to a public third-party perspective.

Methods: The Régie de l'assurance maladie du Québec (RAMQ) provided medical and pharmaceutical data for a random sample of 75% of patients who underwent a corneal graft procedure between June 1, 1999 and May 31, 2002. Resource usage data, defined as medical interventions, physician visits and medication, were collected for a three year post-operative follow-up period.

Results: A total of 610 subjects were included in the study. Mean age was 54.8 years old (+/-20.4). The average costs per patient for graft and anaesthesia were $501 (+/-75) and $115 (+/-124) respectively. The cost per patient for physician visits was $276 (+/-146). The mean number of physician visits per patient during the follow-up was 14.9 (+/-9.1). The cost per patient for medication was $337 (+/-1,075). The average total cost per patient was $1,234 (+/-1,125). Graft and anaesthesia represent 51.0% of this total cost while medication and medical visits represent 27.0% and 22.0% of this cost respectively.

Conclusion: In Quebec, the number of patients grafted each year is estimated at 330; therefore, the annual cost assumed by RAMQ for corneal grafts would be approximately $370,000. Considering that the RAMQ spends over five billion dollars yearly to cover provincial medical and pharmaceutical services, the economic burden imposed by corneal transplantation would seem relatively low.

Keywords: *Corneal transplantation, health care costs, RAMQ administrative database*

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Cost-effectiveness analysis of port insertion using image guided therapy (IGT) compared to conventional operating room (OR) methods

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Funding Source: Unfunded student project

Background/Objectives: IGT has made significant contributions towards decreasing the invasiveness of surgical procedures, reducing morbidity and improving medical outcomes. Central venous port insertion is a procedure commonly performed on paediatric cancer patients using newer IGT techniques or conventional OR procedures. Costs and outcomes of these methods have not been compared. The study objective was to conduct a cost-effectiveness analysis of port insertion by IGT compared to conventional OR methods, from a societal perspective.

Methods: Retrospective chart and database analysis was performed on the first 30 paediatric cancer patients at the Hospital for Sick Children with new tumour diagnosis requiring a first-time port insertion in the period Jan-June 2000 (OR) and Jan-June 2004 (IGT) without concomitant procedures. Procedure, hospital, and travel costs, as well as productivity losses were calculated for 30 days following port insertion. An incremental cost-effectiveness ratio (ICER) was calculated.

Results: The total cost was greater for IGT ($630,677) compared to OR methods ($624,291), and the ICER was $773 per complication-free patient. There were significant differences between the two procedure groups in mean age (7.25 years IGT, 4.06 years OR), mean procedure duration (84.9 minutes IGT, 112.8 minutes OR), and number of complications post-procedure (2 IGT, 10 OR) (p-value less than 0.05). Sensitivity analyses concluded that the results were robust for complications but not for OR-related costs.

Conclusion: In this study, patients receiving a port insertion with IGT had fewer port-related complications compared to OR methods, at a greater cost. Future studies should assess society's willingness-to-pay for lower complication rates.

Keywords: *Cost-effectiveness, port insertion, paediatric oncology, image guided therapy*

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Cost-effectiveness of CADUET in the management of global cardiovascular risk in moderate to high risk hypertensive patients

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Background: The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated that concomitant treatment with amlodipine and atorvastatin significantly reduced the occurrence of cardiovascular events in hypertensive patients with d3 additional cardiovascular risk factors. CADUET (amlodipine besylate/atorvastatin calcium) is a new medication for the management of cardiovascular risk. The objective of this study was to examine the cost-effectiveness of CADUET in the treatment of patients with hypertension at risk for experiencing a CV event in a Canadian setting.

Methods: A stochastic Markov simulation estimated the cost-effectiveness of CADUET treatment vs. atenolol treatment plus atorvastatin and vs. amlodipine treatment plus atorvastatin in the ASCOT patient over lifetime treatment from a Ministry of Health perspective. Because CADUET is assumed to have equivalent efficacy to amlodipine-based treatment plus atorvastatin, a cost minimization analysis was also conducted.

Results: Model simulations demonstrate that CADUET treatment is cost-effective (QALY < $50,000) in comparison to atenolol treatment plus atorvastatin in 97% of simulated patients. Cost per LYG Cost per QALY CADUET vs. atenolol treatment plus atorvastatin $18,269 $9,360. When CADUET-based treatment is compared with amlodipine treatment plus atorvastatin, cost-savings of $2,748 (drug costs/patient over lifetime treatment) are achieved.

Conclusions: The present analysis demonstrates that CADUET is cost-effective in the treatment of hypertensive patients with at least 3 additional CV risk factors compared with atenolol-based treatment plus atorvastatin. Moreover, CADUET provides significant cost-savings compared with amlodipine-based treatment plus atorvastatin.

Keywords: *Cost-effectiveness, cardiovascular risk, ASCOT*

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Cost-effectiveness of venlafaxine extended release in major depressive disorder: a Canadian perspective

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Background: To estimate the incremental cost-effectiveness of venlafaxine extended-release (XR) compared to Selective Serotonin Reuptake Inhibitors (SSRIs) in the treatment of major depressive disorder (MDD) in Canada.

Methods: An existing analytical model was adapted to the Canadian clinical practice setting. Probabilities were derived from the literature and a Delphi panel consisting of two General Practitioners and two Psychiatrists. The Ontario Ministry of Health and Long-term Care perspective was used. All relevant direct medical costs (year 2005 values) were derived from the Ontario Health Insurance Policy and the Ontario Case Costing Initiative. The drug acquisition cost for venlafaxine-XR (Effexor XR) and SSRIs (generics) was derived from the Ontario Drug Benefit formulary. The treatment goal in the model was achieving remission and the primary outcome in the model was Symptom Free Days (SFDs). Time horizon of the model was six months; therefore costs and outcomes were not discounted. Various one-way sensitivity analyses were performed.

Results: The average six-month expected cost per patient for venlafaxine-XR and SSRIs were Cdn$4,156 and Cdn$4,224 respectively. The average six-month expected SFDs were 53.4 and 46.7 days for venlafaxine-XR and SSRIs respectively. The cost-effectiveness was Cdn$77.86/SFD for venlafaxine-XR and Cdn$90.36/SFD for SSRIs. The incremental cost-effectiveness analysis showed a treatment strategy using venlafaxine-XR as first line was dominant. Sensitivity analysis demonstrated results were robust to variations in drug acquisition cost/outcomes.

Conclusion: Despite a higher drug acquisition cost, venlafaxine-XR may be cost-effective and even cost saving compared to generic SSRIs in first line treatment of MDD in Canadian practice.

Keywords: *Cost-effectiveness, venlafaxine, major depressive disorder*

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Current prevalence and control of concomitant hypertension and dyslipidemia in the primary care setting

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Background: The burden of cardiovascular disease and associated risk factors are seen in primary care settings. Hypertension and dyslipidemia tend to co-occur. Patients with concomitant hypertension and dyslipidemia have a greater risk of developing cardiovascular disease. The Southwestern Ontario (SWO) database is a population-based prospective cohort of > 150,000 patients over 18 years in >35 family practice clinics in SWO. Clinic history of chronic diseases including date of onset, prescribed medications, procedures/interventions, laboratory results are collected on a quarterly basis. The objective of this study was to estimate the prevalence, treatment, and control of concomitant hypertension and dyslipidemia.

Methods: Patients with at least 4 quarters of data were included (N=42,496). Hypertension was defined as a recorded diagnosis of hypertension, >2 measurements of BP >140/90 mm Hg, or usage of anti-hypertensive drugs. Dyslipidemia was defined as a recorded diagnosis of dyslipidemia, a recorded measurement of lipids > the recommended targets, or usage of lipid lowering medication.

Results: The recorded prevalence of concomitant hypertension and dyslipidemia was 6.4%. Of these patients, 28.5% were untreated, 9.8% were treated for hypertension only, 6.4% were treated for dyslipidemia only, and 54.5% were treated for both risk factors. Of patients treated for both risk factors, only 12.7% were at both dyslipidemia and hypertension treatment targets.

Conclusions: Concomitant hypertension and dyslipidemia is prevalent in the primary care setting. The majority of these patients received treatment for both risk factors; however only a small percentage of these patients achieve both dyslipidemia and hypertension treatment goals.

Keywords: *Epidemiology, dyslipidemia, hypertension*

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Demographic and clinical characteristics of patients with Alzheimer's disease receiving cholinesterase inhibitors

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Background: Estimates for the cost-effectiveness of cholinesterase inhibitors (ChEIs) are based on clinical trial (CT) data and are dependent on assumptions concerning the patients' initial MMSE score and mortality rate. We examined and compared the demographic and clinical characteristics of Alzheimer's disease (AD) patients who were dispensed a ChEI under the Saskatchewan Health and Alberta Health & Wellness Exception Drug Status (EDS) Program with those included in the ChEIs CTs.

Methods: Based on linked de-identified administrative data provided by SK Health and AH&W, descriptive statistics were calculated for all patients with an index (first) prescription for a ChEI during the first year of coverage under the EDS program (2000-01 and 1999-00, respectively). These estimates were compared to published data from participants in the ChEI CTs.

Results: In SK and AB, 1086 and 2079 patients received 1+ claim(s) for a ChEI. Both samples had a mean age of 79.8 (sd ~7) with 25% aged 85+ years and with >60% of patients being female. At the time of the index prescription, the mean (sd) MMSE scores were 20.8 (4.4) and 20.9 (5.7) for SK and AB samples, respectively. In the Phase III ChEI CTs, the mean age of participants was 73.8, 60.8% were female and the mean baseline MMSE score was 17.1.

Conclusions: Compared to subjects in the critical CTs of these agents, AD patients receiving ChEIs in SK and AB, were, on average, almost 7 years older and showed less cognitive impairment. Differences in patient characteristics could have implications on the likelihood of benefit with therapy and cost-effectiveness.

Keywords: *Alzheimer's disease, cholinesterase inhibitors, prescription drug claims*

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Depiction of confounding by episode duration in a discrete event simulation model

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Funding Source: None

Background: Antidepressant medications are efficacious treatments for major depression and are among the most frequently prescribed medications. However, their effectiveness in "real world" populations has been difficult to confirm. Although antidepressant medications should shorten the duration of major depressive episodes, observational data have paradoxically reported that treated subjects tend to have longer episodes than untreated subjects. One potential explanation for the paradox is confounding by episode duration. Since depressive episodes are variable in their duration, and delays in seeking treatment can occur, subjects with long episodes may be more likely to receive treatment.

Methods: In this preliminary analysis, the plausibility of this explanation was explored using a discrete event simulation model. The software Arena® was used. This software provides a graphical interface for the development of SIMAN models. Based on earlier epidemiological work using data from the Canadian Community Health Survey, episode duration was depicted using the Weibull distribution.

Results: For plausible rates of treatment seeking, even a dramatic improvement in episode remission frequencies in treated subjects was found to result in longer episodes being observed. The expected pattern of recovery in treated and untreated subjects was found to be dependent on the rate at which treatment was sought.

Conclusions: Models that can adjust for this type of confounding may ultimately be useful for describing the impact of depression treatment on population health. However, effective calibration of such models to available sources of data will be challenging.

Keywords: *Major depressive disorder, simulation models, confounding*

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Depression and quality of life in new onset wet AMD subjects: a case-control analysis

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Background: Age-related macular degeneration (AMD) is characterized by a loss of function in the part of the eye responsible for central vision. The objective of the study was to determine the difference in depression (HADS scale) and quality of life (NEI-VFQ 25 score: eye visual function questionnaire) in patients with new onset wet AMD compared to a group of patients with acute posterior vitreous detachment (PVD).

Methods: A cross-sectional case-control study was performed. PVD subjects (controls, n=48) demonstrated similar levels of visual acuity (VA) (greater than 20/40). AMD subjects (cases, n=50) maintained different levels of VA. ANOVA was used to determine the differences between AMD and PVD subjects with similar VA in depression and quality of life and to examine differences in quality of life among AMD subjects.

Results: Depression was higher in the AMD population than in the PVD group (HADS scores 8.24 vs. 5.04, p=0.0427), with a larger proportion of patients in the AMD group having HADS score of 8 or greater (52% vs. 23%). Quality of life was lower in the AMD than in the PVD group (NEI-VFQ score 70.6 vs. 91.1; p=0.0001). In the AMD population, a lower VA corresponded systematically to a decrease in quality of life. No statistical differences were seen for depression between the AMD VA sub-groups.

Conclusion: In subjects with similar VA, subjects with new onset wet AMD were more likely to be depressed and had a lower quality of life than patients with PVD. Quality of life was related to VA and was sensitive to different levels of VA.

Keywords: *Depression, quality of life, AMD*

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Development and impact of profil, a training and communication network program for community pharmacists, on the clinical follow-up of moderate to severe chronic renal insufficiency patients: a cluster randomized controlled trial

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Funding Source: Unrestricted research grants from nine pharmaceutical companies
Background/Objective: In chronic renal insufficiency (CRI) patients, clinical follow-up may delay or prevent renal failure. PROFIL program provides community pharmacists with a 3-hour training workshop, clinical information (creatinine clearance) on their patients, access to a consultation service and pharmaceutical opinion forms. The relevance and potential impact of the program were assessed.
Methods: In a 6-month cluster randomized controlled trial involving 42 pharmacies, 101 pharmacists and 90 CRI patients, pharmacies were assigned to the intervention (PROFIL) or control group. The relevance was evaluated by the change in pharmacist's knowledge before and after the workshop and the number of drug-related problems (DRP) at baseline. Using multilevel analysis, the impact was evaluated based on the mean number of pharmaceutical opinions and refusal issued per patient, the mean changes in clinical variables and patient satisfaction.
Results: 42 (84%) PROFIL pharmacists attended the workshop. Mean knowledge score improved from 54% to 88% (p<0,001). A mean of 4.1 DRPs/patient were identified. A total of 29 and 2 pharmaceutical opinions and refusal were issued in the PROFIL and control group, respectively. The adjusted mean difference in the number of opinions issued (primary outcome) was 78.3/100 patients (p=0,001). No differences in the change in clinical variables and patient's satisfaction were observed.
Conclusion: PROFIL program is relevant and significantly increase in the number of pharmaceutical opinions and refusal, suggesting that community pharmacists may intervene more frequently when having access to clinical information. Such program may improve the management of patients with chronic disease in primary care.
Keywords: *Chronic renal insufficiency, community pharmacist, cluster RCT*

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Development and validation of database measures of asthma severity and control

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Funding Source: None
Background: We developed and validated two database measures to classify currently treated asthmatic patients into categories of severity and control.
Methods: The database measures of asthma severity (3 categories) and control (2 categories) were derived from the definitions found in the Canadian Asthma Guidelines and were based on dispensed prescriptions (controller therapies, short-acting beta2-agonists, oral corticosteroids) and medical services for asthma (ED visits and hospitalizations) recorded in the RAMQ and MED-ECHO databases over 12 months. For validation purposes, 56 asthmatic patients were randomly selected from an asthma clinic in 2001-2002 and their FEV1 and FEV1/FVC ratio were retrieved from their medical chart. For these patients, we also obtained data on prescriptions and medical services from the databases. The measures of asthma severity and control were validated against the pulmonary function test results using t-tests.
Results: According to the database measures, 54%, 32% and 14% of patients were found to have mild, moderate and severe asthma, respectively and 59% were found to have controlled asthma. The mean predicted value of FEV1 went from 92% for mild to 61% for severe asthma (p-value=0.001) and from 92% for controlled to 68% for uncontrolled asthma (p-value<0.0001). The FEV1/FVC ratio went from 0.76 for mild to 0.62 for severe asthma (p-value=0.03) and from 0.75 for controlled to 0.66 for uncontrolled asthma (p-value =0.0009).
Conclusions: In the absence of clinical data, our measures could be used in epidemiologic studies in the field of asthma using administrative databases to validly assess the severity and control of asthma.
Keywords: *Asthma severity, asthma control, administrative databases*

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Direct medical cost of severe acute respiratory syndrome (SARS) at one hospital

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Background: The primary objective of this study is to identify and quantify the direct medical costs associated the hospital management of Severe Acute Respiratory Syndrome (SARS).
Methods: There were a total of 48 patients admitted into Sunnybrook and Women's College Health Science Centre between March 13, 2003 and August 13, 2003. Resource utilization variables associated with the direct medical costs of SARS management were: (1) Hospitalization, (2) Discharge Team (3) Physician visits, (4) Nursing, (5) Allied Health, (6) Respiratory therapists, (7) Medication, (8) Laboratory and Diagnostics and (9) Infection Control costs. Resource utilization was available from patient medical records, computerized hospital databases or provincial databases. Costs (2003 $ CAN) were standard provincial and hospital. Descriptive statistics (mean, standard deviation, maximum, minimum, range and median) will be used to characterize the resource utilization and costs for each direct medical resource variables. An average cost per patient was calculated.
Results: The overall direct medical costs came to total of $2,621,987.92, which amounted to $54,624.75 per patient. The highest cost was hospitalization costs, 45%, followed by infection control costs, 28%, medication costs, 11% and laboratory test costs 7%. The least costly was the discharge team, 0.7%. Nursing costs are still pending due to the irregularity of the nursing situation during SARS, costs are difficult to quantify.
Conclusion: The results of this study will support improved management decision-making and the development of hospital funding methodologies. This type of information can be used to predict costs in simulated epidemiologic models for future outbreaks.
Keywords: *SARS, economics, burden of illness*

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Direct medical costs of severely bleeding trauma patients: a Canadian tertiary hospital perspective

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Background: To determine the cost and resource utilization in severely bleeding trauma patients receiving mores then 10 units of red blood cells.
Methods: A retrospective analysis of a trauma registry database (1992-2001) that included patients with a major trauma and who receive at least ten units of red blood cells within the first 24 hours was conducted. Resource utilization elements collected were: Blood products; laboratory, microbiology and diagnostic procedures; surgical procedures, medications; and allied health professionals. Hospital and provincial sources were used to calculate costs (2003 Canadian dollars).
Results: A total of 371 patients were included in the registry. Seventy percent of eligible patients were male; the average age was 42.3 years. The hospital mean length of stay was 25 days and an overall 50% mortality rate. Sixty-nine percent of the fatalities were within the first 24 hours. The mean Injury Severity Score (ISS) score was 41.3. Average total cost per patient was $67,469. Disaggregated average total costs were $44,861 (73.0%) for surgical procedures, $13,771 (20.4%) for blood products, $5,252 (8.5%) for allied health professionals and $3,241 (4.8%) for laboratory/microbiology/ diagnostic procedures.
Conclusions: The average cost per severely bleeding trauma patient was $67,469. The main cost driver was the surgical procedures. Blood products represented 20% of the direct costs measured. Our results may have implications for the funding trauma centers in Canada.
Keywords: *Trauma, burden of illness, economics*

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ENCORE PRESENTATION

Economic evaluation of a primary care-based medication management program to reduce the risk of osteoporosis-related fractures

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Exploring elderly patients' perceptions about strategies to improve adherence to medications: a qualitative study

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Background/Objective: Medication non-adherence rates for elderly patients taking multiple medications for chronic conditions ranges from 26% to 59%. Interventions to improve adherence are not always effective although the reasons for this are unclear. The objective of this study was to explore the experiences, perceptions, and expectations of elderly patients regarding strategies used to improve medication adherence.

Methods: This study used qualitative methods. Patients 65 years of age or older who were taking 2 or more prescription medications were recruited from family physician practices and community pharmacies to participate in focus groups. A semi-structured interview guide was used with questions that explored the importance of adherence, facilitators and barriers to adherence, and usefulness of strategies for improving adherence. Focus group sessions were digitally recorded and transcribed verbatim. Data analysis of primary themes was conducted by 2 research team members independently and in duplicate.

Results: Forty-two participants attended 1 of 7 focus groups. The mean age of participants was 73.7 (SD 6.0) years, 55% were female, and the mean number of medications taken was 6.1 (SD 2.9). Facilitators to adherence included: having trust in the physician, feeling comfortable discussing medications with healthcare providers, awareness of the consequences of not taking medication, and accepting responsibility for one's
health. Barriers to adherence included: having a negative perception of medication-taking, feeling overmedicated, fear
of side effects, lack of support from healthcare providers, and receiving conflicting information about medications. The main adherence strategies patients used were medication organizers, integrating medication-taking into their daily routine, and consulting with their physicians when they encountered side effects.

Conclusions: There were a wide range of barriers and facilitators that influenced elderly patients' medication adherence. By understanding the patient perspective, more effective interventions can be designed to improve medication adherence.

Keywords: *Medication adherence, elderly, qualitative*

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Economic evaluation of symbicort® (budesonide/formoterol) single-inhaler maintenance and reliever therapy (SMART) in asthma

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Objectives: To compare the cost-effectiveness of budesonide/formoterol in a single inhaler used as maintenance and reliever medication (Symbicort SMART) versus clinician directed titration of maintenance fluticasone/salmeterol (Advair) plus as-needed salbutamol in controlling asthma in adults and adolescents.

Methods: An economic evaluation was conducted based on the results of a large (N=2,143), open-label, randomized, controlled effectiveness trial in which health resource utilization was prospectively collected. Primary outcome measurements included time to first exacerbation and number of severe exacerbations. Costs included direct medical costs (physician/emergency room visits, hospitalizations, asthma drug costs) and productivity (absenteeism). The time horizon was one-year which corresponded to the duration of the trial. Prices were obtained from 2005 Canadian sources. Both healthcare (HC) and societal (Soc) perspectives were considered. Deterministic univariate sensitivity analyses were conducted.

Results: In the clinical trial, Symbicort was superior to Advair for the number of exacerbations, lung function and use of as-needed rescue. The annualized rate of severe exacerbations was 0.24 in the Symbicort arm and 0.31 in the Advair arm (p=0.0025). From the HC perspective, the mean cost per patient-year was $1,315 in the Symbicort arm versus $1,541 in the Advair arm. From the Soc perspective, it was $1,538 for Symbicort and $1,854 for Advair. Symbicort SMART was dominant (more effective, less expensive) in the base case analysis from both the HC and Soc perspectives. The results were robust under sensitivity testing.

Conclusions: The strategy of Symbicort SMART which allows the combination of budesonide/formoterol to be used as both maintenance and reliever medication is dominant over a strategy of clinician directed titration of Advair (fluticasone/salmeterol) therapy.

Keywords: *Asthma, economic evaluation, budesonide/formoterol, salmeterol/fluticasone*

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Economic evaluation of voriconazole for the treatment of candidemia in Canada

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Funding Source: Pfizer Canada Inc.

Background: Candidemia is a bloodstream infection caused by the Candida species that may complicate the hospital management of immunocompromised, surgical and critically ill patients in the intensive care unit. The objective of this study was to evaluate the cost-effectiveness of voriconazole in comparison to conventional amphotericin B followed by fluconazole (CAB/fluconazole) for the treatment of candidemia in non-neutropenic patients.

Methods: A decision analytic model was designed to reflect the clinical events that can occur when treating candidemia with voriconazole or CAB/fluconazole. Switching to another antifungal in the event of an inadequate response or toxicity was allowed. The time horizon was 98 days after initiating therapy. Resource use data were collected from a randomized clinical trial and supplemented with data from a panel of Canadian experts. Costs were obtained from Canadian sources. Incremental cost-effectiveness ratios were calculated for cost per surviving patient, cost per patient avoiding toxicity and cost per patient cured.

Results: Average cost per patient was CDN $1,121 higher for voriconazole than CAB/fluconazole. Incremental cost per surviving patient and incremental cost per patient avoiding toxicity at day 98 were CDN $17,744 and CDN $9,300, respectively. In the case of cost per patient cured, voriconazole had a slightly higher cost ($1,121) than CAB/fluconazole but cure rates were equivalent in both arms (40.7% vs 41.0%, respectively). Deterministic and probabilistic sensitivity analyses demonstrated that the model was robust.

Conclusions: For primary treatment of candidemia, voriconazole has similar efficacy to a CAB/fluconazole but improves survival, lowers toxicity and is expected to be a cost effective strategy.

Keywords: *Candidemia, voriconazole, cost-effectiveness*

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Economic impact of tibolone compared with continuous-combined hormone replacement therapy in the management of climacteric symptoms in postmenopausal women

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Funding Source: None

Background: Deciding whether to treat postmenopausal women suffering from climacteric symptoms with Continuous Combined Hormone Replacement Therapy (CCHRT) has become increasingly difficult after the release of the Women's Health Initiative results. As a result, the research is actually focusing on development of alternatives to CCHRT. Tibolone, which is a synthetic steroid that has estrogenic, progestogenic and androgenic properties, could be a promising alternative. It has been used in Europe, in the same indication as CCHRT, for approximately twenty years but is not yet available in Canada.

Objective: We carried out a cost-utility analysis comparing three-year treatment course with Tibolone 2.5mg and Conjugated Equine Estrogen (CEE)/Medroxyprogesterone Acetate (MPA) [0.625mg/5mg] in the management of postmenopausal women with climacteric symptoms.

Methods: A Markov model, considering compliance, vaginal bleeding and climacteric symptoms, was elaborate to compare the different options in term of cost and Quality Adjusted Life-Year (QALYs). This modelling study was performed from a public third-party payer perspective.

Results: Compared with CEE/MPA, Tibolone lead to an increase in cost ($161.74 for Tibolone vs. $77.21 for CEE/MPA) and a slight increase in QALYs (2.08 for Tibolone vs. 2.05 for CEE/MPA). Consequently, the incremental cost per QALY gained ratio was $3065.93.

Conclusions: According to the results, Tibolone seems to be a cost-effective alternative to CEE/MPA. However, those results should be interpreted with caution insofar the difference in term of QALY might or might not be significant depending on the clinical meaning granted to that difference. Moreover, limited data on Tibolone's long-term innocuity should be taken into account.

Keywords: *Hormone replacement therapy, tibolone, menopause*

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Effect of restricted access to clopidogrel on patient health outcomes following cerebrovascular event in the elderly

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Background: In the province of Quebec, clopidogrel is reimbursed for patients who had a cerebrovascular accident (CVA), only if the CVA occurred while on acetyl-salicylic acid (ASA).

Objective: To determine the impact of the special authorization process on the real-life use of clopidogrel and on health outcomes.

Methods: We analyzed all-cause mortality in the year following hospital discharge in patients who had a CVA while on ASA. Data from the administrative databases from Régie de l'assurance maladie du Québec (RAMQ) were used. The Time Delay Attributable to the Approval Process (TDAAP) was defined as the number of days between the first claim made for a non restricted cardiovascular preventive drug (NRCPD) and the first claim made for clopidogrel. We postulated that if clopidogrel had not been restricted, the patient would have filled the clopidogrel prescription at the same time as the NRCPD prescription.

Results: 8,299 patients were identified with a new CVA on ASA. Of these, 4,091 patients (49.2%) received clopidogrel and NRCPD during their follow-up. The median TDAAP was 35, 5 days (25% quartile: 10 days and 75% quartile: 125 days). After controlling for potential confounders, time-dependent exposure to clopidogrel was protective (RR=0.71, 95%CI=0.53-0.96).

Conclusion: Half of the patients experiencing a CVA while on ASA received clopidogrel while the other half did not. Exposure to clopidogrel was associated with a risk reduction of 29% for all-cause mortality. The results suggest that the restrictive access could be responsible for sub-optimal use of clopidogrel in this population.

Keywords: *Cerebrovascular event, clopidogrel, restrictive access*

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Elective endovascular repair (EVAR) compared to open surgical repair (OSR) of abdominal aortic aneurysms (AAA): a cost-utility analysis

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Background: Untreated AAAs are a serious health concern due to risk of rupture and death.
Objective: Estimate the cost-utility of elective EVAR compared to OSR for treating non-ruptured AAAs.
Methods: A 1 year decision analytic model was constructed to represent the cost-effectiveness of EVAR for the treatment of AAA. A systematic review of the literature was conducted for estimates of key model parameters and was supplemented with a prospective follow-up of patients from a large tertiary hospital for information on costs and health-related quality of life. Deterministic sensitivity analyses were used to assess the impact of methodological and modeling uncertainty and probabilistic sensitivity analyses was used for parameter uncertainty.
Results: The identified 59 comparative studies suggest the technical and clinical success rates are lower for EVAR patients; however, EVAR treated patients tended to have a higher surgical risk than OSR trial patients. Our prospective study showed success rates for both OSR and EVAR are very high and complication rates are much lower than reported in the published literature. Cost-utility based on success and complication rates from the literature suggests EVAR cost $160,176/QALY compared to OSR. However, results from our prospective study suggest EVAR costs only $59,485/QALY in all AAA patients and may even dominate OSR in high surgical risk patients.
Conclusions: Using results from literature reviews of non-randomized trials for input into an economic model can be misleading. The predominance of non-randomized trials comparing EVAR and OSR highlights the importance of adjusting for baseline imbalances in patient risk.
Keywords: *Cost-utility analysis, abdominal aortic aneurysm repair, systematic review*

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Estimating the wait times for physiotherapy and occupational therapy of hospitalized ischemic stroke patients

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Background: Stroke recovery is dependent on the amount of rehabilitation therapy – a Canadian expert consensus panel recommended a minimum of 2 hours of therapy per day. Prompt access to physiotherapy (PT) and occupational therapy (OT) services can be evaluated by determining wait times.
Methods: We conducted a retrospective database analysis of ischemic stroke patients admitted to a university teaching hospital in Toronto, Ontario over a four-month period (July – October 2003). Using an allied health professional database (INFOMED), the number of PT and OT hours, and the number of days between admission date and date of first PT/OT encounter was calculated.
Results: There were 71 ischemic stroke admissions (mean age 77 years and 44% male). Mean length of hospital stay was 18.0±21.8 days. Eighty-six percent (61/71) received PT and 87% (62/71) received OT assessments and/or therapy. A total of 345 hours of PT and 278 hours of OT was provided, averaging to 4.9±6.0 hours and 3.9±2.8 hours per patient, respectively. The average wait time was 2.3±1.7 days for PT and 3.2±2.2 days for OT.
Conclusions: In this sample, hospitalized ischemic stroke patients received an average of 1 hour of PT over 3.7 days and 1 hour of OT over 4.6 days which falls below current recommendations. The Ontario Wait Times Strategy currently does not include rehabilitation services as one of the five key services that it is reporting. These results should prompt hospitals and health ministries to monitor the duration, frequency and wait times of rehabilitation services provided to stroke patients.
Keywords: *Ischemic stroke, rehabilitation, wait times*

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Estimation of the care gap in the management of patients with chronic obstructive pulmonary disease by primary care physicians in Québec and Ontario: results from the CAGE study

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Funding Source: This study was sponsored by Pfizer Canada Inc. and Boehringer-Ingelheim Canada Ltd.
Background: CAGE is a prospective cross-sectional study of the "care gap" in patients treated for chronic obstructive pulmonary disease (COPD) in primary care practice in Québec (QC) and Ontario (ON).
Methods: Primary care physicians each recruited up to 8 successive patients treated for COPD in their routine practice in each of 4 sequential 8-week cycles. "Care gap" is defined as the percentage of patients not receiving pharmacologic treatment consistent with the Canadian Thoracic Society's 2003 COPD Guidelines, which differ by disease stability and symptom severity. We report results from the first cycle about the baseline care gap, before feedback was provided to physicians.
Results: 161 physicians (44 QC; 117 ON) recruited 1090 (320 QC; 770 ON) consecutive patients. Mean age was 69.9 years, 40.3% were smoking, and the majority had stable COPD of moderate (451; 157 QC; 294 ON) or mild (351; 96 QC; 255 ON) symptom severity on the Medical Research Council dyspnea scale. 56% (48% QC; 59% ON) had at least one spirometry evaluation. In patients with mild stable COPD, the "care gap" was 86% (70% QC; 92% ON); in those with moderate or severe stable COPD, it was 55% (59% QC; 53% ON) and 58% (60% QC; 57% ON), respectively.
Conclusions: A substantial "care gap" compared to "best care" exists in the current treatment of COPD patients in primary care in QC and ON and depends on patient disease severity. Subsequent study cycles will reveal whether these care gaps can be reduced.
Keywords: *COPD treatment, primary care, care gap*

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ENCORE PRESENTATION

Expert MD™ osteoporosis: baseline patterns of practice

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Funding Source: EXPERT MD™ OSTEOPOROSIS is a health education program funded by Merck Frosst Ltd.

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Exploring family physicians' attitudes and beliefs towards insulin therapy in elderly patients with type 2 diabetes: a qualitative study

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Background/Objectives: Approximately 16% of seniors (aged 65 year and over) have been diagnosed with type 2 diabetes. In Ontario, insulin alone or insulin in combination with other treatments are the least popular prescribing choices for this population. The objective of this study was to explore the attitudes, beliefs, and rationale for prescribing decisions of family physicians when treating patients over the age of 65 years with type 2 diabetes.
Methods: A qualitative design using a grounded theory approach was used. Data was collected through individual in-person interviews with a purposeful sample of family physicians in Ontario. Data analysis was iterative to ensure that emerging themes were explored in subsequent interviews. Analysis was completed by 3 researchers, collating and corroborating themes. A model examining the factors influencing the prescribing of insulin was developed.
Results: Twenty-one physicians were interviewed (mean age 53 years [SD 9], 76% male, mean 26 years in practice [SD 10]). The resultant model demonstrated 4 factors influencing prescribing of insulin for elderly patients: 1) patient's support system, 2) type of elderly person ('young' old vs.'old' old), 3) need to individualize the 'aggressiveness' of therapy, and 4) need to prepare for insulin therapy. Though physicians indicated that they would prescribe insulin allowing for the above factors, there was some conflict between actual prescribing reported and intended prescribing.
Conclusions: Physicians' rationale for prescribing (or not prescribing) insulin is mediated by a variety of factors. The 'disconnect' around practitioners' beliefs and their subsequent prescribing requires further exploration.
Keywords: *Insulin, physician perspective, grounded theory*

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Health care resource use in type 2 diabetes: a retrospective cohort study of antihyperglycemic users in Québec

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Background/Objective: Type2 diabetes represents a significant economic burden. Little is known, however, on how treatment costs evolve over time and according to the intensity of diabetes care management. The objective of this study was to estimate cost of type2 diabetes treatment over time and to compare costs of well versus poorly-managed patients with diabetes (defined based on incidence of diabetes complications and annual number of physician visits) in current clinical practice.
Methods: This cohort study retrospectively analyzed data on medical and pharmaceutical services, obtained from the Régie de l'Assurance Maladie du Québec (RAMQ), for a random sample of patients who received an antihyperglycemic agent between September 2003 and August 2004. A 10-year observation period, from January 1994 to August 2004, was applied.
Results: The number and the average dose of antihyperglycemic medications increased over time as well as the cost of antihyperglycemic treatment. On average, the medication cost for the initial year was $99 (SD=148), which more than doubled over a 5-year period to an average cost of $229 (SD=326). Average medication cost during the 12-month period ending in August 2004 was $425 (SD=241). Average annual cost of hospitalizations, emergency room and physician visits were higher for poorly managed patients compared to well managed patients with diabetes, and to patients without diabetes ($3,393 vs. $1,902 vs. $1,136; p<0.001).
Conclusion: Total treatment costs of type2 diabetes increases over time. On average patients with diabetes consume more health care resources than patients without diabetes, but well managed patients consume fewer resources than poorly managed patients.
Keywords: *Diabetes, antihyperglycemics, cost*

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How common are the provincial/territorial public drug formularies?

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Funding Source: None

Background: There have been many discussions about "National Pharmacare" and "National Formulary" over the past few years. Many experts have speculated about how close we are, what is meant, what needs to be done to get there and the benefits that would be realized. These are difficult questions to address due to the lack of basic analysis of the formularies that currently exist. The following analysis acts as the foundation to begin to address complicated policy-related questions.
Methods: An environmental scan of the drug products on the market, review of the monthly changes and a comparison of the listings across 10 jurisdictions were conducted using the Anatomical Therapeutic Chemical (ATC) classification system. The "September 2005 Extract of the Health Canada Drug Product Database" was used to identify "current Marketed Human" medications assigned an ATC on 10 Provincial/Territorial formularies "Expensive Drugs" were defined by a threshold of $5,000 per drug per person per year using Manitoba drug claims.
Results: There are more than 15,000 drug products on the market and an average of 93 new ones per month. The analysis performed indicates a common core of medications is available on the public drug formularies. At ATC level 4, there is 55% commonality amongst 8, 9 or 10 jurisdictions are combined. The coverage distribution of 106 "Expensive" chemicals identified is consistent across jurisdictions with an average listing of 78.
Conclusions: The analysis indicates a common core of medications is available and provides insight into the comparability of these public drug formularies. Detailed utilization data will is necessary to provide a complete understanding of the relationship between coverage and utilization.
Keywords: *Formulary, ATC, NPDUIS*

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Identifying persons with treated asthma using health services utilization data: developing a case definition via latent class modelling

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Funding Source: Canadian Institutes for Health Research
Background/Objectives: Researchers and health system planners frequently use health services utilization data (HSUD) to study the prevalence and burden of chronic conditions, conduct population health surveillance and implement and evaluate interventions. An important problem in selecting cohorts from HSU databases is the occurrence of misclassification errors. There is a paucity of research on comparison and validation of existing HSUD-based case definitions for asthma. Latent class modeling (LCM) offers a way to address the lack of a gold standard in assessing HSUD-based case definitions. The primary objective of this study was to develop a parsimonious model of the patient population in British Columbia (BC) with respiratory diagnosis, using treatment markers derived from event records in provincial databases.
Methods: Seven indicators related to physician, hospital and medication use were computed for each of BC's 1.9 million respiratory patients aged 5-55 for each year (1996/97-2000/01), and 2-, 3- and 4-class models were fitted. Annual asthma prevalence was estimated. Conventional (literature-based) case definitions were assessed relative to LCM-based criteria.
Results: The 2-class model was the superior LCM model. Indicators of general practitioner use for asthma management (ICD-9 code 493) and prescription of short-acting beta agonists had the best sensitivities (0.60 and 0.80). Indicators' specificities ranged from 0.98 to 1.0. The estimated prevalence in 1996/97 of asthma among BC respiratory patients is 830/10,000. The a priori "treated asthma" definition had a sensitivity of 0.65 relative to LCM-based case selection.
Conclusion: LCM provides a useful probability-based approach to developing HSUD case definitions and estimating case prevalence.
Keywords: *Health services utilization data, case definition, latent class analysis*

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Impact of a dyslipidemia management workshop on community pharmacists' knowledge: team workshop

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Background/Objective: In Quebec, pharmacists may initiate and adjust drug therapy in accordance with a prescription and request laboratory analyses when needed. In a eight-hour interactive dyslipidemia management workshop, treatment guidelines, pharmacotherapy management, treatment protocol and specific clinical tools were presented. The impact of the workshop on pharmacists' knowledge was assessed.
Methods: In a cluster randomized controlled trial, 15 clusters involving 77 physicians and 104 pharmacists were randomized to the usual care (UC) or pharmacist's management care (PMC) groups. 95% of PMC pharmacists (n=58) attended the workshop. UC and PMC pharmacists (n=104) completed a knowledge questionnaire at entrance into the study and PMC pharmacists completed the same questionnaire after the workshop (n=56). Overall and specific knowledge scores were compared at baseline across the study groups (T-test). Changes in knowledge before and after the workshop were measured (paired T-test).
Results: At baseline the mean overall knowledge score was equal to 45.2% and 45.8% (p=0.8) in the UC and PMC group, respectively. Specific knowledge scores were low in both groups; treatment guidelines knowledge (UC: 61.6%, PMC: 63.1%; p=0.7) and pharmacotherapy management knowledge (UC: 39.5%, PMC: 40.0%; p=0.8). After the workshop, the mean overall PMC pharmacists' knowledge score improved from 45.8% to 89.0% (p<0.0001). Specific knowledge scores also improved: treatment guidelines (63.1% and 94.4%; p<0.0001) and pharmacotherapy management (40.0% and 85.2%; p<0.0001).
Conclusion: TEAM workshop significantly improves community pharmacists' knowledge on treatment guidelines and pharmacotherapy management. These results suggest that adequate training is relevant prior to implementing a pharmacist's management care program.
Keywords: *Pharmacy practice research, dyslipidemia, cluster randomized controlled trial*

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Impact of antihypertensive (AH) adherence level on coronary artery disease (CAD) among patients in primary prevention

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Funding Source: CIHR

Background/Aim: Despite evidence that the control of blood pressure may reduce morbidity and cardiovascular mortality, there are still a high proportion of hypertensive patients whose blood pressure is not controlled. Non-adherence to AH therapy is a major issue in health care and may have significant negative consequences for clinical outcome. The consequences of non-adherence on the real-life efficacy of drugs needs more study.
Objective: To evaluate the impact of AH adherence on the rate of non fatal CAD.
Methods: A cohort of 34,608 patients was reconstructed using the RAMQ databases. All patients aged from 45 to 75 years old who were newly treated with AH agents between 1999 and 2000 were eligible. A nested case-control design was used. Every case of non fatal CAD was matched for age and period with 15 controls. Adherence level was reported as the percentage of the prescribed doses of AH used during follow-up period, and was classified as equal or more than 80% or < 80%. Conditional logistic regression models were used to estimate the rate ratio (RR) of non fatal CAD adjusting for several covariables.
Results: The overall rate of non fatal CAD was at 12.4%. Among patients followed up for more than one year, those with adherence level of equal or more than 80% had less CAD (RR: 0.86; 0.79-0.93). Male patients (RR: 1.38; 1.27-1.50), patients with diabetes (RR: 1.38 (1.24-1.53), dyslipidemia (RR: 1.39; 1.28-1.52), and higher chronic disease score (RR: 1.77; 1.62-1.95) had a significantly higher risk of CAD.
Conclusion: This analysis indicates that adherence of equal or more than 80% for more than one year is essential to reduce non fatal CAD among patients in primary prevention. Our results confirm the importance of a long term therapy with AH agents.
Keywords: *Adherence, antihypertensive agents, non fatal coronary artery disease*

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Impact of antihypertensive (AH) adherence level on heart failure among patients in primary prevention

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Background/Aim: Despite evidence that the control of blood pressure may reduce morbidity and cardiovascular mortality, there is high proportion of hypertensive patients whose blood pressure is not controlled. Non-adherence to AH is a major issue in health care and may have a significant negative consequences on clinical outcome. The consequences of non-adherence on the real-life efficacy of drugs needs more study.
Objective: To evaluate the impact of AH adherence on the rate of heart failure.
Methods: A cohort of 34,608 patients was reconstructed using the RAMQ databases. All patients aged from 45 to 75 years old who were newly treated with AH agents between 1999 and 2000 were eligible. A nested case-control design was used. Every case of heart failure was matched for age and period with 15 controls. Adherence level was reported as the percentage of the prescribed doses of AH used during follow-up period, and was classified as equal or more than 80% or < 80%. Conditional logistic regression models were used to estimate the rate ratio (RR) of heart failure adjusting for several covariables.
Results: The overall rate of heart failure was at 2.8%. Among patients followed up for more than one year, those with adherence level of equal or more than 80% had less heart failure (RR: 0.59; 0.46-0.76). Patients with diabetes (RR: 2.05; 1.53-2.75) and higher chronic disease score (RR: 2.76; 2.12-3.60) had a significantly higher risk of heart failure.
Conclusion: This analysis indicates that adherence of equal or more than 80% for more than one year is essential to reduce heart failure among patients in primary prevention. Our results confirm the importance of a long term therapy with AH agents.
Keywords: *Adherence, antihypertensive agents, heart failure*

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Impact of antihypertensive (AH) adherence level on non fatal strokes among patients for primary prevention

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Funding Source: CIHR

Background/Aim: Despite evidence that the control of blood pressure may reduce morbidity and cardiovascular mortality, there are a high proportion of hypertensive patients whose blood pressure is not controlled. Non-adherence to therapy is a major issue in health care and may have significant negative consequences on clinical outcome. The consequences of non-adherence on the real-life efficacy of drugs needs more study.
Objective: To evaluate the impact of AH adherence on the rate of non fatal strokes.
Methods: A cohort of 34,608 patients was reconstructed using the RAMQ databases. All patients aged from 45 to 75 years old who were newly treated with AH agents between 1999 and 2000 were eligible. A nested case-control design was used. Every case of non fatal stroke was matched for age and period with 15 controls. Adherence level was reported as the percentage of the prescribed doses of AH used during follow-up period, and was classified as equal or more than 80% or < 80%. Conditional logistic regression models were used to estimate the rate ratio (RR) of non fatal strokes adjusting for several covariables.
Results: The overall rate of non fatal strokes was at 4%. Among patients followed up for more than one year, those with adherence level of equal or more than 80% had less non fatal stroke (RR: 0.82; 0.71-0.95). Male patients (RR: 1.41; 1.22-1.64), patients with diabetes (RR: 1.21 (1.00-1.46), and higher chronic disease score (RR: 2.46; 2.11-2.86) had a significantly higher risk of non fatal stroke.
Conclusion: This analysis indicates that adherence of equal or more than 80% for more than one year is essential to reduce non fatal strokes among patients in primary prevention. Our results confirm the importance of a long term therapy with AH agents.
Keywords: *Adherence, antihypertensive agents, non fatal stroke*

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Impact of once-weekly bisphosphonates on persistence rate and adherence level with antiresorptive therapies in primary prevention: a population-based study among elderly women

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Background/Objectives: We investigated the impact of once-weekly bisphosphonates on persistence rate and adherence level with antiresorptive therapies (ART) used in primary prevention of osteoporosis.
Methods: A cohort of 2,962 women was reconstructed from the RAMQ databases, from 2002-2004. Women were 70 years and older and had started ART (bisphosphonates, raloxifene, nasal calcitonin) for primary prevention, defined as no ICD-9 or medical procedure code for osteoporosis or fragility fracture recorded within 5 years before index date (first prescription). Persistence was defined as no medication uncovered interval >60 days. Persistence rates were estimated using Kaplan-Meier analysis. Cox Proportional Hazards model was used to estimate the adjusted rate ratio (RR) of nonpersistence to treatment. Adherence level at one year of follow-up was the proportion of days during which women possessed medication (<80% or >=80%).
Results: Mean age was 78.5; One-year overall persistence rate was 53.9%. Compared to those starting on once-weekly bisphosphonates, women starting on daily alendronate or risedronate (RR: 1.20; 1.05-1.38) or other ART (RR: 1.99; 1.76-2.26) had a higher RR of cessation. The RR of discontinuing ART was lower among women with BMD testing done before index date or during follow-up, and among those suffering a fracture (reduction of 23%, 55% and 55%, respectively). Overall, only 54.4% of women met the >=80% adherence level. Once-weekly bisphosphonates showed the highest proportion of women meeting the >=80% level.
Conclusions: Considering low persistence and adherence with ART and limited data supporting their efficacy in primary prevention, reasons for their use in this population should be explored.
Keywords: *Administrative databases, persistence, adherence*

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Impact of restrictive access to clopidogrel on patient health outcomes following coronary stent placement in Quebec

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Background: In Quebec, the provincial drug plan needs to review a faxed Special Authorization form prior to approving any reimbursement for clopidogrel. The impact of this restricted accesson outcomes following coronary stenting is unknown.
Methods: We analysed all-cause mortality in the year following coronary stent placement in a large cohort of elderly patients who underwent this procedure between January 2000 and September 2004. We used administrative data from Régie de l'assurance maladie du Québec (RAMQ). We postulated that the time interval between the first claim for any Non-Restricted Preventive Cardiovascular Drug (NRPCD) and the first claim for clopidogrel was attributed to the special authorization process.
Results: The cohort was composed of 13,663 patients who had not filled a clopidogrel prescription in the year preceding stenting and who also had filled a prescription for another NRPCD following stent implantation. In the 2,745 patients (20.1% of the study cohort) who experienced a delay of at least one day in filling their clopidogrel prescription, we observed a significant increased risk in all-cause mortality (HR=2.03). After controlling for potential confounders, at least one day of delay between the first claim for other NRPCD and clopidogrel was still associated with a significant increase in all-cause mortality (HR=1.47 95% CI=1.20-1.80). Time-dependent exposure to clopidogrel was protective (HR=0.61, 95%CI=0.49-0.77).
Conclusion: This study suggests that restrictive access to clopidogrel increases the risk in all-cause mortality following coronary stent placement.
Keywords: *Coronary stent implantation, clopidogrel, restrictive access*

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Impact of the exception drugs status on access to clopidogrel in Quebec

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Background: In Quebec, clopidogrel is reimbursed only in patients who meet specific criteria and only if the special authorization form submitted by the physician is approved.
Objective: To estimate the percentage of patients who received clopidogrel among those who met the criteria and assess the proportion with Time Delay Attributable to the Approval Process (TDAAP).
Methods: Data from the administrative databases from Régie de l'assurance maladie du Québec (RAMQ) were used. Four algorithms using ICD-9 codes, RAMQ procedure codes and drug claims were developed to identify patients who met the clopidogrel reimbursement criteria. For each sub-population, only patients with at least one claim for a Non-Restricted Cardiovascular Preventive Drug (NRCPD) were selected. The TDAAP was assessed for each patient and defined as the number of days between the first claim for a NRCPD and the first claim for clopidogrel. We postulated that if clopidogrel had not been restricted, the patient would have filled the clopidogrel prescription at the same time as the NRCPD prescription.
Results: The percentage of patients with at least one claim for clopidogrel was 88.5% for Coronary Stent (CS), 50.5% for Cerebrovascular Accident (CVA), 24.1% for Acute Coronary Syndrome (ACS) and only 6.1% for patients with Peripheral Arterial Disease (PAD). The proportion of patients with TDAAP was: 9.8% for CS, 30.2% for ACS, 44.8% for CVA and 70.3% for PAD.
Conclusion: The restrictive access to clopidogrel in Quebec appears to be associated with sub-optimal use and with significant delay in access to care.
Keywords: *Exception drug status, clopidogrel, delay to access*

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In-hospital management of osteoporosis in patients with hip fractures

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Background: Hip fracture in the elderly is primarily related to osteoporosis and falls. The objective of this study is to examine the pharmacologic management of osteoporosis in patients admitted with hip fractures during the acute care phase.
Methods: This is a cross sectional survey of a consecutive cohort of elderly patients who were admitted to the Capital Health Region (Edmonton) with a primary diagnosis of hip fracture. Patients were interviewed 3 to 5 days after surgery. Data on the use of osteoporosis medications was abstracted from the medical chart. Osteoporosis medications included bisphosphonates, calcium and vitamin D, hormone replacement therapy, or calcitonin.
Results: Of the 382 patients recruited into the study, the mean age was 81 + 8 yrs. The majority were female, 268 (70%), 231 (56%) resided in the community; 2 deaths occurred during hospital stay. The median length of stay was 10 days. One hundred four (27%) of the patients demonstrated severe cognitive deficits (MMSE<18). One hundred sixty one (43%) received hip arthroplasties while 213 (57%) were fixated with pins/plates. Two hundred twenty nine (57%) patients had treatment for osteoporosis ordered in hospital of which 207 (54%) received the medications as ordered in hospital. Female patients who received hip arthroplasties were more likely to receive treatment for osteoporosis. The longer one stayed in hospital regardless of complications, the more likely one would also receive treatment for osteoporosis. Cognitive status, comorbidities and type of residence from which the patient was admitted were not factors associated with drug use.
Keywords: *Hip fracture, osteoporosis, medications*

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Medication use and awareness of risk factors for falls in patients with Parkinson's disease

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Background: This pilot study was to evaluate the awareness of fall risk factors in a high risk patient population who attended a Movement Disorder Clinic (MDC). We also wanted to examine the relationship between medication use and awareness of risk factors for falling.
Methods: A cross-sectional survey of patients with Parkinson Disease was conducted between January-March, 2003. Behavioural, medication, physical, environmental, and medical risks were included. Demographics, medical status and medication use were collected from the medical charts using a standardized form. The Falls Risk Awareness Questionnaire was used as the survey instrument.
Results: Twenty-eight patients completed the survey. Twenty-three patients reported a history of falls, with 7 having fallen in the past month, 7 in the past 6 months, and 7 in the past year. Twenty-three of the 28 patients were taking at least 1 anti-parkinsonian medication. Falls were reported by 10 of the 12 patients taking Sinemet, 9/9 on Sinemet CR, 5/7 taking dopamine agonists, and 2/2 on amantadine. Three of the 5 patients who were not taking any anti-parkinsonian medications had fallen. Eight patients reported using sedative hypnotics, and six reported using a medication for mood. Half of participants identified taking more medications as a risk for falling.
Conclusions: Patients with Parkinson's disease have high rates of falls. However, only half of the patients identified medications as risk factors for falling. This high risk population requires careful management of medications as well as education regarding medication risk factors for falling.
Keywords: *Falls, Parkinson's disease, medication risk*

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Isotretinoin and the risk of depression in patients with acne: a case-crossover study

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Background: The potential association between isotretinoin and depression is controversial and remains unclear. We determined whether isotretinoin increases the risk of depression and whether guidelines changes initiated after 1997 are effect modifiers.

Methods: We conducted a case-crossover study among welfare recipients who received ≥1 isotretinoin prescription between 1984 and 2003. Data were obtained from RAMQ and Med-Écho administrative databases. Cases were defined as subjects receiving a first antidepressant with a diagnosis of depression (ICD-9: 296.x-301.x, 309.x or 311) during the study period. The index date (ID) was the earliest calendar date of either a filled prescription of an antidepressant or the depression diagnosis. Cases had to be covered by the RAMQ drug plan and have ≥1 acne diagnosis (ICD-9: 706.1) in the 18 months prior to ID. Exclusion criterion was a depression diagnosis at any time prior to ID. Exposure to isotretinoin in a 5-month risk period immediately prior to ID was compared with 2 previous 5-month control periods. Relative risks (RR) were estimated using conditional logistic regression adjusting for time-dependent variables: number of different medications, dermatologic and non-dermatologic MD visits, and emergency department visits/hospitalizations. Analyses were repeated after stratifying on calendar date: before and after 1997.

Results: A total of 107 patients met the inclusion criteria. The adjusted RR of exposure to isotretinoin in the risk versus control periods was 3.00 (95%CI: 1.20, 7.49). The adjusted RR was 7.43 (95%CI: 1.86, 29.66) before versus 1.25 (95%CI: 0.33, 4.78) after 1997.

Conclusions: We found a positive association between isotretinoin and depression before but not after 1997. The guidelines changes initiated after 1997 appear to be effect modifiers.

Keywords: *Isotretinoin, depression, case-crossover*

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Making your curriculum vita numerical and graphical for promotion, tenure and career awards

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Funding Source: None

Background: Academics are interested in tenure, promotion and career awards. Training and productivity of a researcher are summarized in a Curriculum Vita (CV). This paper shows how to convert productivity into tables and graphs.

Methods: Tables of output on the CV such as articles, abstracts, reports and total are sorted into those that are and are not peer reviewed. Presentation tables are sorted into invited or contributed and also whether local, national, international and total. Each table row has important signposts in a person's career: first contribution year, PhD year, Assistant Professor appointment year. Contribution date (y) is subtracted from the current year to get the contribution interval (y). Table entries are three numbers: c,w,m (where *c* is the count, w is the weighted sum and *m* is the mean). While there are different weighting systems, I use triangular weights. For each entry, w/y is the productivity per year. If the second of consecutive pairs of productivities per year is ≥ the first, indicate with a + sign to show increased productivity; or else – for a decrease.

Results: These tables are converted into a Leadership Index, an Improvement Index and a frequency table of productivity per year. Smoothed productivity data are plotted versus year to show career patterns. Career examples and criteria are applied to make recommendations for promotion, tenure and career awards.

Conclusions: These tables and indices are helpful in making recommendations as to which people should be given tenure, promoted, and get a career award.

Keywords: *CV evaluation, tenure, promotion, productivity*

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Methicillin-resistant staphylococcus aureus: a public health issue with economic consequences

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Background: Methicillin-resistant Staphylococcus aureus (MRSA) has become endemic worldwide in hospitals and community-associated MRSA (CA-MRSA) is spreading into the community at large. The objectives of the study were to estimate the current cost of MRSA in Canada and assess the magnitude of this public health issue.

Methods: An extensive review of the literature was conducted to gather epidemiology, healthcare resource utilization and cost data for MRSA in Canadian settings. Current burden of MRSA was estimated using available cost and epidemiological data.

Results: The rate of MRSA in Canadian hospitals increased more than 10 fold between 1995 and 2004 while CA-MRSA, which exhibits specific characteristics, continued to spread into the community. Patients harboring MRSA required prolonged hospitalization varying between 14 to 36 days per patient in isolation, special control measures, expensive treatments and extensive surveillance. Total cost per patient incident of MRSA infection averaged $12,216 with hospitalization the major cost driver (81%) followed by barrier precautions (13%), antimicrobial therapy (4%) and laboratory investigations (2%). Most recent epidemiological data suggest that direct Canadian healthcare cost attributable to MRSA, including management of MRSA-infected and -colonized patients and MRSA infrastructure, ranges between CAN$54 million to CAN$110 million annually. Although there is limited data on costs of CA-MRSA and outbreak management, those can only add to the overall financial burden of MRSA.

Conclusions: MRSA is a costly public health issue that should be tackled to limit the growing burden of this disease in Canadian hospitals and in the community.

Keywords: *Methicillin-resistant staphylococcus aureus, review, costs*

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Methodology of the Canadian quality circle (CQC) national project to improve physician adherence to the osteoporosis Canada 2002 clinical practice guidelines

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Background: The 2-year CQC National project assesses and monitors changes in family physicians' (FPs) practice patterns compared to the Osteoporosis Canada 2002 clinical practice guidelines. It uses multiple knowledge dissemination strategies, including chart audits, small group learning and case-based discussion.

Methods: 340 FPs in 7 Canadian provinces were recruited as members in 34 Quality Circles (QCs) lead by a FP facilitator and an osteoporosis specialist. Facilitators received training prior to each QC meeting during national train-the-trainer meetings. Each member completed standardized data collection forms (DCFs) on 25 patient charts during baseline. Inclusion criteria were women 55 years or older with more than two visits to the FP in the last 2 years. Data included the FP's awareness of patient risk factors, rates of BMD and x-ray testing, and treatment. At QC meeting 2, members received performance feedback through individual profiles comparing member, circle and national data, and participated in a CME osteoporosis workshop designed to help them understand and improve on their results. Members then completed DCFs after seeing 25 other patients. These follow-up data are currently being analyzed and will inform members of changes in their practice patterns since baseline.

Results: A total of 340 members collected baseline data on 8,376 patient charts. Of these members, 300 (88%) collected follow-up data on 7,355 patients. All 34 circles continued into the follow-up phase.

Conclusions: Follow-up results are required to confirm whether this methodology can change physicians practice patterns. However, the number of members continuing was high, suggesting that this project was well received.

Keywords: *Osteoporosis, education, guidelines*

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National active surveillance network for adverse drug reactions

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Background: Severe adverse drug reactions (ADRs) are an important cause of childhood morbidity and mortality. 95% of ADRs are likely unreported. Current models of ADR surveillance do not offer pragmatic value to clinicians.

Objectives: Establish a national network of trained full-time surveillance clinicians to identify, assess and report paediatric ADRs and collect DNA samples from ADR patients and controls (who take medications but do not have ADRs). Use network surveillance results to identify and validate genomic markers predictive of ADR risk. Develop pragmatic ADR risk management strategies for clinicians.

Methods: ADR active surveillance by 9 clinicians in 7 academic Canadian pediatric hospitals. Recruitment of children from inpatient/outpatient wards and emergency departments. Network development included establishing inter-institutional service agreements, developing on-line case ascertainment and data warehousing, developing site-specific protocols for surveillance within hospital departments and establishing web-based communication linkages between network centres.

Results: ADR surveillance in the 6-month ramp up phase at the first hospital site - before national network implementation - has resulted in 70 ADR and 311 control patients recruited. ADRs have been reported for 28 distinct drugs. Most frequent suspected ADRs are serious skin reactions (n=21) including 3 cases of Stevens Johnson syndrome, cardiotoxicity (n=13), and ototoxicity (n=8). Implicated drugs include doxorubicin (n=11), methotrexate (n=10), cisplatin (n=8), vincristine (n=4) and trimethoprim/sulphamethoxazole (n=4). Other national sites begin patient enrollment in 2006.

Conclusion: Early results demonstrate increased and more thorough ADR case ascertainment as a result of an active surveillance network for ADRs.

Keywords: *Adverse drug reaction surveillance, active pharmacosurveillance, patient safety*

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Osteoporosis care gaps among nursing home residents in Canada

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Funding Source: Unrestricted research grant, Merck Frosst Canada
Conflict of Interest: have received research funds and speaking fees from MFCL and other industry.

Introduction: The Osteoporosis Society of Canada (OSC) has established clear, evidence-based guidelines for the diagnosis and management of osteoporosis (OP) in Canada (CMAJ Nov 2002). Elderly persons are at the highest risk of fragility fracture and have the best evidence of effectiveness with OP diagnosis and therapy. Our study evaluates the quality of OP care delivered in Long Term Care (LTC) facilities. We investigated the prevalence of OP risk factors, frequency of diagnosis and the use of guideline-based interventions in 2 LTC facilities in BC. Informed consent was obtained from all participants.

Results: Our findings indicate deficiencies in the diagnosis and management of OP in the LTC setting. We observed full guideline-based care in only 1 of 67 (3.6%) residents after the diagnosis of OP. Frequency of care after hip or spine fracture (5%), in 65-84 year olds (3.1%), and in those with 3 or more risk factors (1.6%) was similarly low. Calcium and vitamin D intakes were insufficient in 90% and 97.3% of residents at each of the 2 facilities surveyed. Medications were infrequently prescribed for OP with only 5.4% and 10% of patients receiving recommended care. Age, prior fracture, OP diagnosis, and the presence of more than 3 risk factors did not affect the use of OP medications, calcium or vitamin D.

Conclusion: We conclude that among BC LTC facility residents there is low adherence to OP guidelines. The high prevalence of OP in this population, poor access to bone density testing, and obstacles to accessing evidence-based therapies may account for this large care gap.

Keywords: *Osteoporosis, care gap, long term care*

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Paediatric drugs: use of multi-jurisdictional prescription drug data

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Background: There is growing evidence of increased psychopharmacologic treatment in Canadian children, despite effectiveness and safety concerns. Little information is available to show the extent of psychostimulant and antidepressant use. This research was undertaken to describe drug utilization in BC and MB, with the intent of identifying children at risk of adverse drug reactions (ADRs).

Methods: All stimulant and anti-depressant prescription records (1997/98-2003/04) were obtained for children <18 years from BC PharmaNet and MB Drug Programs Information Network. Data were analyzed to show population trends by age, gender, and drug classes.

Results: Rates of stimulant use increased by 13.2% in BC (14.4-16.3 users/1000 population/yr) and 45.3% in MB (14.8-21.5 users/1000 population/yr). Most stimulant prescriptions were for immediate-release and long-acting methylphenidate (38.0% and 24.2%) in BC and (61.8% and 18.3%) in MB. Rates of use were highest in children 11-14 yrs. 78.6-83.0% of all users were male. Antidepressant use increased by 73.7% in BC (7.6-13.2 users/1000 population/yr) and 80.9% in MB (6.8-12.3 users/1000 population/yr). Rates of antidepressant use were highest in BC and MB in 2002/03. SSRIs were the most frequently prescribed antidepressants in BC (53.14%) and in MB (59.7%). Antidepressant use was highest in children >15 years. 49.1-58.8% of all users were female.

Discussion: In order to evaluate ADR risk and effectiveness of psychopharmacologic drugs in Canadian children it is important to understand patterns of use. Collaboration among researchers in different provinces with similar data sources enhances ability to identify areas of safety and effectiveness concern and plan for evaluation.

Keywords: *Multi-jurisdictional drug data, psychopharmacology, paediatrics*

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Paper stamp checklist tool enhances asthma guidelines knowledge and implementation by primary care physicians

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Background: We evaluated Quebec primary care physicians' knowledge of the Canadian Clinical Practice Guidelines CPGs and patient outcomes before and after introducing physicians to a new clinical tool consisting of a memory aid in the form of a self inking paper stamp checklist summarizing CPG criteria and guidelines for assessing asthma patient control and therapy. A prospective randomized-controlled study of 104 physicians located in four Quebec regions was conducted. Each MD initially responded to questions on their knowledge of the CPGs and was randomly allocated into four groups which received information about the CPGs while implementing an intervention (the stamp tool) aimed at supporting their decision-making process at point of care. Six months later the physicians were retested and patient outcomes were obtained for approximately one year through the Quebec RAMQ. The stamp significantly improved the MDs knowledge of the CPGs in all Quebec regions tested. Controls improved their knowledge by only 6% whereas those that received the stamp improved by 60 to 87%, depending on the intervention associated with the stamp. Emergency room visits were significantly less in the patients that were followed by the physicians who received the stamp (7.8% vs. 13.5%, p=0.009) and hospitalizations tended to be lower (2.2% vs 4%, p=0.09). A paper stamp summarizing CPGs for asthma can be employed effectively to increase physician's knowledge and affect patient's outcomes positively.

Keywords: *Asthma education, tool, paper stamp*

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Perceptions of the barriers and facilitators of Herceptin® use in three Canadian provinces: a multi-method approach

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Funding Source: Canadian Breast Cancer Research Alliance (CBCRA)
Background: Little is known about how rapidly shifting evidence, guidelines and resources affect new genetically targeted medications. Methods were developed to assess changes in perceptions of the barriers and facilitators to using Herceptin® (trastuzumab) for the treatment of women with metastatic breast cancer in three Canadian provinces from the time of approval for use to the present.
Methods: Prescribers of Herceptin and key informants who were involved in guideline or policy development were interviewed. These interviews were used to develop a quantitative survey of all prescribers of Herceptin in Ontario, British Columbia, and Quebec.
Results: A total of 19 participants were interviewed individually. Interviews were analyzed for major themes relating to potential barriers and facilitators. These factors were then used to develop the survey sent to all Herceptin prescribers in the three provinces, with an overall response rate of 68%.
Conclusions: Perceptions towards Herceptin have changed since 1999 when it was approved for use in Canada. Evolving clinical evidence, testing procedures, cost, resource availability, funding policies and patient demand were dynamic factors that shifted perceptions of the barriers and facilitators of Herceptin use.
Implications: A multi-method approach has been developed to plot the emergent trajectory of perceptions of new, genetically targeted medications. Understanding how and why perceptions change is critical for understanding current patterns of use and for promoting optimal use of new therapies in clinical practice.
Keywords: *Prescribing decisions, breast cancer, multi-method*

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Predictive value of health economic models: similarity in lifetime results using three-year versus five-year observations from the ATAC trial

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Funding Source: Partially funded by an unrestricted grant from AstraZeneca Canada Inc.
Background: Compared to tamoxifen, anastrozole (Arimidex) has demonstrated a reduced risk of recurrence in post-menopausal, hormone receptor positive (HR+) women with early breast cancer in the ATAC trial (Arimidex, Tamoxifen Alone or in Combination). We originally conducted a health economic analysis using three-year interim data (ID) and have now finalized the analysis using recently released completed-treatment (CT) five-year data.
Methods: A Markov model extrapolated trial results over a lifetime horizon for the typical ATAC trial patient. Data from the HR+ subset of the ATAC trial defined rates of recurrence, death and adverse events for 3 years (ID) or 5 years (CT). Tamoxifen recurrences were based on the 2005 EBCTCG overview; recurrences for anastrozole were based on the hazard ratio of disease-free survival from the ATAC trial. Anastrozole benefit was assumed to last 10 years (tamoxifen benefit, 15 years).
Results: Minor differences were observed in adverse events and recurrences over the additional two year observation period. Over a lifetime extrapolation, the ID analysis predicted an incremental difference of 7.6% in the total recurrence rate and 3.2% in the breast cancer mortality rate; the CT analysis predicted 5.7% and 2.8% respectively. The cost-utility ratio remained stable at CDN$26K/QALY (ID) and CDN$28K/QALY (CT). In the CT analysis, the sensitivity analysis was much more robust, with a narrow 95% confidence interval, since the anastrozole benefit was proven to be consistent and durable.
Conclusions: Three year observations were highly predictive in determining economic conclusions regarding anastrozole use in postmenopausal women with HR+ early breast cancer.
Keywords: *Anastrozole, breast cancer, economic evaluation*

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Preferences for the NovoFine® 32 gauge 6 mm tip in the treatment of diabetes mellitus

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Background: The objective was to obtain patient-reported outcomes for the NovoFine® 32 G 6 mm Tip needle, used with a pen injector or doser, in the administration of insulin by participants with diabetes mellitus, compared to their current needle.
Methods: A total of 1339 participants were enrolled by 251 pharmacists across Canada. A pre-post design was used where participants completed a self-administered survey for their current needle, then completed a second survey after using 10 NovoFine® 32 G 6 mm Tips.
Results: Of all participants, 981 (73%) were included in the analysis (eligible and returned both surveys). For all needle characteristics, the percent of participants who experienced an "improvement" with the NovoFine® 32 G 6 mm Tip compared to their current needle was statistically significantly higher (all $p < 0.0001$) than the percent of participants who experienced a "worsening". The largest percent of participants with "improvement" were for bruising, bleeding, pain intensity, smoothness, pain frequency, and overall satisfaction (38% to 52% of participants). Fear or anxiety, leakage, and force had between 18% and 29% of participants who experienced an "improvement". Less than or equal to 6% of participants indicated a "worsening" when using the NovoFine® 32 G 6 mm Tip for any of the needle characteristics. If given a choice, 73% of participants would prefer to use the NovoFine® 32 G 6 mm Tip instead of their current needle.
Conclusions: The results demonstrate that the new NovoFine® 32 G 6 mm Tip performs better than participants' current needle in all needle characteristics.
Keywords: *Diabetes, patient-reported outcomes (PROs), NovoFine® 32 G 6 mm Tip needle*

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Prevalence and management of depression in the community dwelling elderly: mail-out survey combined with a medical chart review

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Background: Depression in the elderly is under-recognized and undertreated. Our objective was to estimate the prevalence of self-reported depressive symptoms in the community-dwelling elderly and to examine medication management.
Methods: This cross-sectional study utilized two data sources: 1) a mailed survey and 2) a structured medical chart audit. Participants were recruited from an academic community family practice and included patients 65 years of age and older who had at least 1 visit in the previous year identified from computerized billing data. The survey included demographic information, attitudes around mental health and the validated Short Geriatric Depression Scale (GDS15). GDS scores ≥ 5 suggest the presence of depressive symptoms. The management of depression was determined through chart audit.
Results: Survey response rate was 64% (411/642). Mean age of respondents was 74.7 (SD 5.9), 68% were female and 77.5% completed at least secondary school. Mean GDS15 score was 2.4 (SD 2.8). Scores ≥ 5 occurred in 15.7% (n=64) of respondents. The adjusted Odds Ratio of elevated GDS scores for those respondents who rated their health as fair/poor was 14.2. One hundred and eighty-eight charts were audited (62 elevated GDS, 64 normal GDS, 62 non-responders). A diagnosis of depression was recorded for 21% of individuals. Respondents took an average of 6.4 (SD 4.3) medications. Antidepressants were prescribed for 25.8%; and of those 61% were prescribed an SSRI.
Conclusions: Prevalence of depressive symptoms was similar to rates reported in the literature. Self-rated health status was significantly correlated with GDS score. Approximately one-quarter of patients with elevated GDS scores were prescribed antidepressants.
Keywords: *Depression, elderly, cross-sectional*

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Prior authorization process to access inhaled combination therapies containing corticosteroids and long-acting beta2-agonists did not affect asthma treatment in the province of Quebec

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Background: There are concerns that prior authorization process (PAP) may affect appropriateness of drug utilization. Our objective was to assess impact of PAP for inhaled combination therapies containing corticosteroids and long acting beta2-agonists (LABA), introduced in October 2003 in the province of Quebec, on asthma treatment use.
Methods: Using administrative databases for each of the two periods (pre and post PAP), three cohorts based on the first study drug found were formed. Study drugs were inhaled corticosteroids (ICS), LABA and short acting beta2-agonists (SABA). Were included individuals aged 5 to 45 years, who have had an asthma diagnosis in the year preceding the first prescription and who were eligible for the public drug insurance plan for the entire period. Statistical analyses were performed to compare pre and post PAP for three treatment endpoints: use of high doses of ICS without LABA (monotherapy), use of LABA without ICS (monotherapy) and overuse of SABA.
Results: There were 3 836 users (11.3%) of high ICS doses in the pre and 4 392 (11.7%) in the post PAP ICS cohorts. Among those, 77.1% and 72.6% used ICS in monotherapy respectively ($p< 0.01$). There were 458 (13.9%) and 437 (9.3%) users of LABA in monotherapy in the pre and post PAP periods ($p<0.01$). Overuse of SABA remained constant (about 30%) for the two periods.
Conclusions: PAP did not affect three important endpoints of asthma treatment use. However, there is still a gap between optimal asthma treatment and the observed situation.
Keywords: *Asthma medication, drug use, databases*

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Process and outcome evaluation of academic detailing in five Canadian provinces

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Background/Objectives: Academic detailing (AD) is an educational intervention for improving professional practice. Evidence based information is provided to health care providers in their practice environment through one-to-one visits by trained educators. Programs in five provinces have created a national collaboration to create synergies and study selected processes and outcomes of the collaboration model.
Methods: Qualitative and quantitative methods were employed to assess the following elements of the collaboration: 1) a synthesis of Canadian and international experience, 2) a needs assessment of physicians, 3) co-production and analysis of printed educational materials (PEMs), 4) a study of dissemination logistics, 5) an assessment of the feasibility of outcome evaluation, and 6) an evaluation of the process of collaboration.
Results: The following were selected key findings for the above elements.

1) International programs usually are not stand alone and are integrated with pharmaceutical policies and programs. Credibility is a key critical success factor.
2) Physician participation is encouraged by the evidence based focus, complementary handouts, and follow-up. Inconvenience and non-physician educators discouraged participation.
3) The application of information design concepts and principles improved the effectiveness of PEMs and physician performance.
4) Time and motion analysis identified the baseline costs of program delivery with the initial collaborative model.
5) Rigorous evaluations of impacts are feasible through randomized design-delay trials. Important operational barriers must be overcome.
6) Short term benefits include increased information sharing and quality improvements. Potential long term gains include efficiency, innovation and evaluation.

Conclusions/Discussion: The collaboration model showed promise as a means of improving the efficiency and effectiveness of individual provincial programs.
Keywords: *Academic detailing, process and outcome evaluation*

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Public health impact model: quantifying the number of strokes that can be prevented by optimizing anticoagulation in atrial fibrillation in Canada

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Background: The risk of stroke is increased in patients with atrial fibrillation (AF) and strokes in this setting tend to be more severe. The efficacy of Warfarin (WA) is well documented, yet there is a gap between clinical trials and usual care outcomes. WA underutilization and suboptimal WA control account for this gap. The purpose of this study is to determine the number of strokes that may be avoided in Canada by optimizing anticoagulation in AF.

Methods: An Excel spreadsheet compared the annual number of strokes in a "suboptimal" usual care setting versus an "optimal" clinical trial-like setting among Canadian AF population. Canadian specific AF prevalence (2005), treatment patterns, usual care and clinical trial event rates were taken from published literature. The "suboptimal" scenario assumed that usual care outcomes with WA treated patients would be similar to large observational studies and a proportion of patients are not being anticoagulated. The "optimal" scenario assumed that all WA treated patients are achieving clinical trials-like control and all the non-anticoagulated patients eligible for WA would receive well controlled WA.

Results: Optimizing anticoagulation may prevent an estimated 4,805 strokes in 2005 alone: 2,181 from increasing WA control and 2,624 from increased anticoagulant use.

Conclusions: There is an opportunity to further prevent strokes within the Canadian population by increasing WA control among WA treated patients and by anticoagulating the untreated AF patients. As the senior population increases, the burden of stroke also increases dramatically. More aggressive stroke prevention must be a public health priority.

Keywords: *Anticoagulation, stroke, outcomes*

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Quality of life and resource utilization of patients with advance non-small-cell lung cancer: a Canadian perspective

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Funding Source: Roche Canada

Background: There is limited information on Health Related Quality of Life (HRQoL) and resources utilization in the Canadian population with Non Small Cell Lung Cancer (NSCLC). The objective of the analysis was to determine the HRQoL and resource utilization components in Canadian patients with stage III/IV NSCLC.

Methods: A face-to-face survey was conducted on a cohort of 32 patients with stage III/IV NSCLC from the lung cancer clinic at Princess Margaret Hospital in Toronto. HRQoL was assessed using disease specific tools (FACT-L). Utility scores were assessed by EQ-5D US English version. Socio-economic, clinical, and resource utilization data were collected using a self-administered questionnaire. Participants' clinic charts were reviewed for supportive data and verification.

Results: Patient age was 63.03±10.39 years on average, 23 were females and 68.8% were smokers. Mean time since cancer diagnosis was 24.1±17.7 months, 78.1% had metastasis. The average FACT-L score was 99.64 (range: 90-130), the FACT-L/TOI score was 57.43. The average EQ-5D score was 0.533, the score for Current Health State was 9.38 (0-10 scale). The mean number of visits to oncology clinic was 1.1±0.7/month, and 0.9±0.9/month for family physicians. Patients had been hospitalized for 4.1±4.3 days in previous year. The average cost of medical imaging was CAD403.2±CAD81.3, the mean cost of lab test was CAD44.7±CAD9.0, and the mean cost of non-chemotherapy drugs was CAD44.5±CAD65.3. The average cost of chemotherapy drugs was CAD460.0±CAD100.2.

Conclusion: Advanced NSCLC patients on chemotherapy use substantial health care resources in Canadian setting.

Keywords: *Oncology, quality of life, NSCLC*

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The economic burden of ischemic stroke study ("BURST"): Canadian preliminary results

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Background: There is a paucity of comprehensive, accurate, up-to-date data on the costs of ischemic stroke in Canada.
Methods: A cohort (N=200) of ischemic stroke subjects will be recruited in a consecutive manner at sites across Canada (N=10). Baseline, 3-month and 6-month questionnaires will be completed to capture information about stroke severity (National Institutes of Health Stroke Scale [NIHSS]), treatment, functional impairment (Barthel Index [BI] and modified Rankin Scale [MRS]), depression (Hamilton Depression Rating Scale [HAM-D]), utility (Health Utilities Index Mark 3 [HUI3]) and resource utilization. Data collected will be entered electronically via a secure website (www.burststudy.ca).
Results: As of February 1st 2006, nine (Ottawa, Toronto, Calgary, Quebec City, Edmonton, Halifax, Vancouver, Saint John and Thunder Bay) sites received ethics approvals and 33 subjects were consented for the baseline questionnaire: 70% were male and the average age was 65.3±14.0 years. Co-morbidities included hypertension (79%), hyperlipidemia (64%), diabetes (39%) and atrial fibrillation (15%). Outpatient stroke clinic follow-up was the discharge destination for 45% of subjects. The majority of subjects were retired (45%) and had visited their general practitioner an average of 5.6±6.4 times the year prior to their stroke. Nine subjects required a mobility aid (cane, walker, wheelchair) after their stroke, and the spouse was the primary unpaid caregiver for 64% of all subjects.
Conclusions: The BURST study has been launched and is ongoing. Interim results will be available in summer 2006. This prospective study will determine current resource utilization and overall costs of treating ischemic stroke in Canada.
Keywords: *Ischemic stroke, burden of illness, prospective study*

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Quality of pharmacist-managed anticoagulation service: a randomized controlled trial

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Background/Objective: In an integrated care model (ICM), patients on oral anticoagulant are initially followed at a pharmacist-managed anticoagulation service (PMAS) and transferred thereafter to their physician. ICM may be as effective as a centralized care model (CCM) where patients are followed only at a PMAS.
Methods: Patients referred to a PMAS with a prescription of warfarin for at least 6 months were randomly assigned to the ICM or CCM when INR were stabilized. Patients were followed for 6 months after initiation of treatment. Percent time in expanded therapeutic range and number of hospitalizations and emergency visits associated with thromboembolic or hemorrhagic events were assessed. The SF-36, the EuroQol, and a specific treatment-related questionnaire were administered at entrance into the study and six months after the initiation of treatment.
Results: 138 physicians participated. 250 patients were randomized (ICM: 122; CCM:128). Mean number of weeks between INR was equal to 2.7 (SD=1.1) and 2.4 (0.96) in the ICM and CCM, respectively. The mean percent time in therapeutic range was equal to 91% in the CCM and 90% in the ICM group. The mean difference (95% CI) in the percent time in range between the two groups was equal to 1.2% (-3.2% to 5.6%). A total of 7 and 10 hemorrhagic and thromboembolic events were reported in the ICM and CCM groups, respectively. Similar changes in HRQOL were observed in the two intervention groups.
Conclusion: INR control is equivalent in the ICM and CCM models of care.
Keywords: *Pharmacy practice research, anticoagulant treatment, randomized controlled trial*

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Real-world utilization patterns of cyclosporine ophthalmic emulsion 0.05% within managed care

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Background: Assess utilization patterns of cyclosporine ophthalmic emulsion 0.05% within managed care using a claims database.
Methods: Patients with at least one prescription for cyclosporine over a three-month enrollment period and at least one refill prescription over the 12-month follow-up period were included. Classification of new or continuing patients were determined whether or not the patient received at least one cyclosporine prescription 12 months prior to enrollment. Per FDA-approval, the recommended use is 2 vials daily (2 trays/month or 24 trays/year, each tray containing 32 vials) to receive the prescribed dosage of 1 drop in each eye twice daily. Daily, monthly, and annual utilizations were assessed. Based on this retrospective approach, no efficacy data were available for analysis.
Results: 38,164 patients met the inclusion criteria. The majority of patients were female (82%), 50 years or older (77%), and new to therapy (59%). Prescription refill patterns demonstrated 73% of patients used 1 tray/month. Annual data was similar as 80% of the patients used 11 trays or less per year. Daily utilization differed between continuing and new patients. New patients had a bimodal use pattern. Over 30% were using ¡Ÿ1.75 vials/day and approximately 55% were using 0.25 to 1.25 vials/day. The majority of continuing patients (approximately 80%), however, used 0.25 to 1.25 vials/day.
Conclusions: While some new patients use 2 vials of cyclosporine daily, the majority of continuing patients follows a utilization pattern of 1 vial/day. As such, the impact on a managed care budget may be significantly less than originally estimated.
Keywords: *Cyclosporine, dry eye, utilization patterns*

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Recent patterns of medicine use among community-dwelling elderly: focus on quantity and type

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Background: Prescription drug costs are a key driver of rising health system expenditures. Explanations of the increasing cost of drugs typically include reference to population aging and an assumption of high use of drugs by the elderly. However, no Canadian studies illustrate the extent of medicinal drug use in this population. We examine quantity of drug use among community dwelling elderly.
Methods: Data are from the National Population Health Survey Cycle 2. Bootstrap weights are applied to illustrate population estimates of self-reported quantity of drugs used in 'last two days' by community-dwelling Ontarians aged 65 and over, by gender and age categories, and type of drug (prescription, over-the-counter and natural health products).
Results: Nearly one quarter of community-dwelling elderly report using no drugs. Most individuals report using three drugs or fewer. About twenty-three percent report using four or more, and only one percent report using ten or more drugs concurrently. Use is distributed among prescription and non-prescription drugs and natural health products. We describe statistical differences among key sub-groups (age, sex, drug type, quantity-category).
Conclusions/Discussion: The implications of the use-patterns are considered in light of a) assumptions about the impact of the aging population on rising costs of drugs; b) the out-of-pocket costs of non-prescription drugs; and c) health professional responsibility for appropriate and safe use of drugs by the elderly.
Keywords: *Elderly, drug use, population estimates*

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Reduction of GI drugs intake following tegaserod use

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Background: The primary symptoms of irritable bowl syndrome are abdominal pain/discomfort, bloating and constipation. In the treatment of this poorly understood disorder, tegaserod has shown efficacy in relieving these primary symptoms. However, it is not known if the costs of tegaserod are incremental to other GI drug costs. The aim of the present database analysis was to determine whether tegaserod use reduces the use and ultimately costs of other GI drugs.

Methods: Between July 2002 and October 2004, a total of 18,469 patients (88% women) were identified as first-time users of tegaserod in the Brogan Inc. private payer database. Drug utilization data on these patients were gathered for 12 months pre and post their first prescription of tegaserod provided that they were still in the database at the end of this period. Consumption of GI medication was measured by the number of claims submitted, the tablets prescribed and days and number of patients using these medications pre and post tegaserod use.

Results: On average, patients were using tegaserod for almost 80 days over a period of one year. After patients starting to use tegaserod, there was a 10.64% reduction in the number of patients using other GI medications ($p<.0001$). In addition, the total cost reduction due to reduced concomitant GI drug use was calculated to be $17/patient per year.

Conclusion: These results indicate that the costs of tegaserod are not strictly incremental as the use of other GI drugs is reduced following tegaserod use.

Keywords: *Tegaserod, utilization, IBS*

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Relationship between stroke severity and INR control

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Background: Warfarin's efficacy for stroke prevention in atrial fibrillation (AF) depends highly upon INR control. Strokes that occur at an INR below 2 are associated with more severe neurologic deficit and increased 30-day mortality. The purpose of this study is to assess the relative risk of these more severe strokes between poor vs moderate vs good INR control groups.

Methods: A discrete event simulation was developed using Arena® to compare stroke outcomes from the three INR control groups. They were defined according to time spent in therapeutic range (TTR) of 2-3 ($\geq$ 76 % of time = good; 60-75% of time = moderate; < 60 % = poor control). Daily INR scenarios were generated from individual patient reported INRs. Other model assumptions were taken from the literature. A one-year analysis was performed by assigning a hypothetical patient cohort in each of the three control groups. Individual patient stroke risk was assigned daily according to daily simulated INR values.

Results: The rate of severe stroke occurring at an INR below 2 was higher in the poor control group: 1.45 vs. 0.55 vs. 0.22 strokes/100 patient-years. This translates to a 6 fold greater risk of severe stroke in poorly controlled patients compared to the good INR control group and a 2.6 fold greater risk vs. the moderate control group.

Conclusions: Obtaining good anticoagulation control should be a public health concern as patients with poor INR control experience a greater number and more severe strokes than those well or moderately controlled.

Keywords: *Anticoagulation, stroke, simulation*

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Risk of clostridium difficile diarrhea among medical intensive care patients receiving proton-pump inhibitors

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Funding Source: None

Background: Proton pump inhibitors (PPI) could cause bacterial overgrowth in the gastrointestinal tract. Increased PPI use has raised concerns that it could contribute to the increasing Clostridium difficile epidemics by favouring its acquisition and development.
Methods: A 27-month cohort study was conducted on all patients admitted to the medical intensive care unit. Risk factors associated with incident CDAD cases were identified from patients' medical records.
Results: Out of the 832 patients cohort, 118 (14.2%) developed C. difficile diarrhea. Prior use of a PPI or H2 blocker did not correlate with a significant increase in the risk of developing of CDAD. Major risk factors were the presence of an enteric tube (OR, 3.21; 95% CI, 1.85-5.68), high risk antibiotic use (OR, 2.02; 95% CI, 1.09-3.74), and age ≥ 65 years (OR, 1.56; 95% CI, 1.01-2.41). Mean duration of high-risk antibiotic treatment for CDAD patients was longer (6.70 vs. 4.61 days, p=0.01) than the control group.
Conclusion: Prior use of a PPI or H2 blocker did not correlate with a significant increase in the risk of developing CDAD. Tube feeding, high risk antibiotic use and older age are associated as risk factors.
Keywords: *Proton-pump inhibitors, clostridium difficile, diarrhea*

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Role of medication in emergency department (ED) revisits

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Objective: The objective of the study was to determine the role of medications in predicting ED revisits
Methods: A random sample of files of patients who visited the ED of a large Montreal ultraspecialized hospital between October 2000 and March 2001 (period 1) or between October 2002 and March 2003 (period 2) was drawn. Files were reviewed to establish the occurrence of an ED revisit within 30 or 90 days of the index visit. Socio-demographic characteristics, co-morbidities and medications taken at the index visit years were retrieved from the files. Diagnoses were used to calculate a score according to the Charlson index of co-morbidity. Multiple logistic regression analyses were performed to verify the relationships between medication use and likelihood of an ED revisit within 30 and 90 days
Results: Of the 884 ED visits, 132 (15.2%) were followed by a revisit to the ED within 30 days and 209 (23.6%) by a revisit within 90 days. Number of drugs taken was a predictor of revisits. After adjusting for age, gender, Charlson index and hospitalization at the index ED visit, the OR associated with taking 3-6 medications compared to none was 11.5 (CI 95% 2.6-51.4) for a revisit within 30 days and 2.9 (1.3-6.4) for 90 days. The OR associated with taking 7 medications or more were respectively 20.8 (4.5-97.3) and 5.8 (2.5-14.0).
Conclusions: Patients taking multiple medications who visit the ED are more at risk of making revisits and should draw close attention from the healthcare professionals.
Keywords: *Emergency department, medication, revisit*

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Rural and urban primary care physcians (PCPs) asthma patterns of practice

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Background/Objectives: Despite the dissemination of guidelines for asthma, there are concerns that care is suboptimal. The purpose of this study was to compare practice patterns of asthma care in relation to the Canadian Guidelines between urban and rural primary care physicians (PCPs).

Methods: The Alberta Strategy to Help Manage Asthma (ASTHMA) invited all PCPs practicing in rural and urban Alberta to participate in a chart review. From each practice, charts were randomly selected and reviewed using a standardized data collection form.

Results: A total of 3,072 patient charts (401 rural, 2671 urban) from 45 PCPs were reviewed. The rural group had more pediatric patients (36% rural, 28% urban, $p<0.001$). More urban patients were female (55% urban, 42% rural, $p < 0.001$). No diagnostic tests were documented in 53% of rural patients and in 42% of urban patients ($p < 0.001$). Asthma education was not documented in 61% of the rural and 54% of urban patient charts ($p = 0.01$). The use of written action plans was low in both groups. Rural patients (38%) visited the emergency department or were admitted to hospital more often than urban patients (17%; $p=<0.001$). This may be related to a paucity of "urgent" after-hour clinics or reflect a different pattern of use.

Conclusions/Discussion: Asthma care is suboptimal in both urban and rural settings, particularly in the use of diagnostic tests, education, and written action plans. This study highlights the need for improvement in asthma care.

Keywords: *Asthma, primary care physicians, chart reviews*

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Saskatchewan medication assessment for risk reduction target treatments (SMART2)

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Background: Many high risk vascular patients (stroke, ACS and CABG patients) do not achieve published Canadian goals for risk reduction strategies, i.e., hypertension, cholesterol, diabetes, nor do they receive complete bundles of preventative agents (i.e., antiplatelet, statin, ACE inhibitor and others as necessary). Complicating the matter is a low rate of adherence at one year to these preventative therapies.

Objective: To test whether a physician-pharmacist collaboration will significantly increase utilisation of risk reduction medications, adherence, and control of physiologic variables compared to standard care within a high risk vascular population.

Methods: Following hospitalisation for a vascular event (ischemic stroke, ACS, CABG) and after obtainment of informed consent, patients will be randomised to normal care or the collaborative model. Patients randomised to the collaborative model will be followed by a hospital pharmacist either in person or by phone at: 3-7 days post discharge, 3, 6, 9 and 12 months. Issues related to medication use, smoking and exercise therapy will be assessed with solutions provided. If patients are not receiving target therapies or are not at published goals, the pharmacist will collaborate with the patient, specialist and community based physician in attempts to optimise pharmacotherapy.

Conclusions: Knowledge management and transfer via a physician-pharmacist collaboration and patient should result in improved patient care, health service outcomes, and changes in health policy. Anticipated completion date is March 2007.

Implications: Translating this research into action should improve the use and adherence of evidence based therapies, patient safety, quality of life, and pharmacist, physician, patient integration.

Keywords: *Collaboration, secondary prevention, outcomes*

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ENCORE PRESENTATION

Selection of a preferred proton pump inhibitor in the Canadian forces: a drug use evaluation

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Short-lived influence on prescribing trends following publication of the ALLHAT trial

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Background: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) strongly supported the use of thiazide diuretics. Its publication in (2002) was associated with an immediate change in the class of antihypertensive drugs purchased by elderly and insured populations in favour of thiazide diuretics. We examined whether this change was also experienced in British Columbia (BC), and the duration of time for which it was sustained.

Methods: Antihypertensive drug use, stratified by evidence of co-morbidities, was analyzed for all residents of BC from 1996 to 2004, inclusive, through administrative data describing medical, hospital, and pharmaceutical use. The antihypertensive drug (or drugs) purchased on the date that a resident filled their first antihypertensive prescription (after at least one-year without any AH prescriptions) was defined as the 'first-line' therapy.

Results: The publication of ALLHAT was associated with an immediate change in antihypertensive prescribing patterns across the entire population of BC, with an abrupt increase in use of thiazides and a decrease in the use of ACE-inhibitors as first-line therapies. However, within one year of ALLHAT publication, first-line antihypertensive prescribing for uncomplicated patients began to revert to pre-ALLHAT trends. Similar, though less dramatic results were found among the 28% of antihypertensive drug users with identified co-morbidities. The proportion of incident users that received thiazides increased following ALLHAT publication, while the proportion that received ACE-inhibitors decreased.

Conclusions: The changes in prescribing patterns following the publication of ALLHAT were short-lived. The increase in thiazide use amongst incident antihypertensive users observed in the first six months of 2003 was lost to ACE-inhibitors in the year that followed. Thus, while it is encouraging that well-publicized trial results influence prescribing patterns, long-term trends may reflect the significant financial interests in hypertension treatment as much as (or perhaps more than) scientific evidence.

Keywords: *Drug utilization patterns, prescribing behaviours, hypertension*

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Persistence with statin therapy in British Columbia

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Background: Although the benefits of statin therapy occur only after at least one year of therapy, few patients persist with statin therapy, and little is known about factors predictive of persistence with statins. The purpose of this study was to identify factors predictive of persistence with statin therapy one year after initiation of therapy.

Methods: British Columbia PharmaCare data was used to determine persistence (prescriptions filled within < 120 days of one another for 1 year) with statin therapy for new users from 1999 to 2003. Medical, hospital and prescription drug claims were examined for evidence of clinical (medical history, drug, dose, number of medications) and sociodemographic (age, socioeconomic status, year of prescription) characteristics predictive of persistence with statins, as determined from multiple logistic regression methods.

Results: Of 168,161 adults that filled a first statin prescription from 1999-2003, 61,177 (36.4%) were persistent for one year. Evidence of the co-morbid conditions of coronary artery disease, diabetes or peripheral vascular disease, a greater number of co-prescribed medications, increasing age, higher socioeconomic status, and use of simvastatin or atorvastatin increased the likelihood of persistence with statins, ($p<0.05$) while statin dose, sex and year of first prescription did not.

Conclusions: Factors predictive of persistence with statins include: medical history, age, socioeconomic status and drug prescribed. However, persistence with statins remains low, even in patient groups who could benefit from long term therapy.

Keywords: *Persistence, prescription drugs*

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Statin prescribing in British Columbia

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Background: Expenditures on cholesterol-lowering medications in Canada are rapidly increasing. Yet few studies have explored indications for incident use of cholesterol drugs. The objectives of this study were to investigate the prevalence and incidence of HMG-CoA reductase inhibitor ('statin') use, and the underlying cardiovascular comorbidities of statin users, in British Columbia over an eight-year period.
Methods: Incident and prevalent statin utilization rates were assessed for the population of BC by identifying all prescriptions for HMG-CoA reductase inhibitors from BC PharmaNet between 1996 and 2004. Medical services and hospital claims for identified statin users were retrospectively examined for evidence of ischemic heart disease (IHD), diabetes mellitus (DM), atherosclerosis, cerebrovascular disease (CVD), peripheral vascular disease (PVD), and hyperlipidemia in the three years prior to the first statin prescription.
Results: Prevalence of statin use increased from 9 to 51 users per 1000 between 1996 and 2004. The prevalence and incident use of particular classes of statins also changed over time. Use of atorvastatin increased overall. Incident use of atorvastatin and rosuvastatin use also increased, while new use of other statins decreased. Of incident statin users, 36% had evidence of IHD; 20% had DM but no IHD; 5% had no DM or IHD, but atherosclerosis, CVD or PV; 22% had hyperlipidemia; and 17% had none of the listed medical conditions.
Conclusions: Prevalence and incidence of statin use in BC has increased dramatically since 1996. Although many statin users had evidence of medical conditions that indicate appropriate use, a significant proportion of users remain at low risk for cardiovascular disease. The benefit of statins for this group remains small.
Keywords: *Prescribing patterns, drug utilization*

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Systemic exposure to ethanol correlates with oleic ethyl ester in hair

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Objective: To compare the incorporation rate (ICR) of individual FAEE in hair between guinea pigs and humans, and to assess the relationship between FAEE and systemic ethanol exposure.
Methods: Published data from pregnant guinea pigs (including peak blood ethanol concentration and total hair FAEE) were compared to published data from alcoholic patients (including total ethanol dose and total hair FAEE). Mean values of ethanol Vmax for pregnant guinea pigs and humans were obtained from published data (26.2 mg/dl/h, and 24 mg/dl/h, respectively).
Results: Individual FAEE ICRs, defined as the ratio of hair FAEE to the area under the blood ethanol concentration-time curve (total systemic ethanol exposure), were found to be on average an order of magnitude lower in the guinea pig than in the human. The profiles of ester incorporation differed slightly between species with ethyl stearate being highly incorporated in guinea pig hair, and less so in human hair. Ethyl oleate was found to correlate with total systemic ethanol exposure for both guinea pigs and humans, correlation coefficients equaling 0.67 ($P < 0.05$), and 0.49 ($P < 0.05$), respectively.
Conclusion: Our results confirm that when extrapolating FAEE concentrations in hair from guinea pigs to humans, an order of magnitude difference should be considered, with humans incorporating more FAEE per unit of ethanol exposure, and that caution should be applied when interpreting single ester values because of differential incorporation between species. Lastly, our data suggest that ethyl oleate may be of significant interest in FAEE hair analysis, particularly across species.
Keywords: *FAEE, ethanol, ethyl oleate*

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Tegaserod is appropriately used in the medical management of IBS in Canada

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Background/Objectives: Tegaserod, a selective 5HT4 receptor agonist, is effective and well tolerated in patients with symptoms of abdominal pain, bloating and constipation associated with Irritable Bowel Syndrome (IBS).
Methods: This prospective, observational, single-cohort study conducted under conditions of routine practice by 85 community-based physicians in Canada evaluated 500 patients at the time of prescription. Physicians completed a case report form with information on the symptoms, diagnosis, age and gender of patients prescribed tegaserod (new or repeat).
Results: The majority (87%) of patients were female and 63% were 35 to 64 years of age. The most frequently reported symptoms were abdominal pain (87%), bloating (80%) and, constipation (75%) and many patients also had upper GI symptoms, including sensation of fullness (41%), heartburn/acid regurgitation (27%) and retrosternal pain (9.0%). The majority of patients were diagnosed with IBS (78%), including IBS with constipation and IBS with symptoms alternating between constipation and diarrhea. A small proportion (14%) of patients was diagnosed with functional dyspepsia or chronic constipation. Based on the presence of female gender and a diagnosis of IBS-C or presence of symptoms of abdominal pain and constipation, 67% of patients were appropriately prescribed tegaserod according to the label. When all patients with a diagnosis of IBS were included, the proportion rose to 87%. As a result, only 13% of patients received tegaserod for a diagnosis or symptom not consistent with IBS.
Conclusion: The vast majority of patients are prescribed tegaserod for IBS based on symptoms and/or a specific diagnosis. Decision makers should be reassured that tegaserod is appropriately prescribed to patients who are most likely to benefit based on labeling.
Keywords: *Tegaserod, utilization, IBS*

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The care gap between optimal and actual osteoporosis diagnosis and treatment following a fragility fracture: the Saskatoon Atraumatic Fracture Elimination (SAFE) Program

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Background: The clinical manifestation of osteoporosis is the occurrence of fragility fractures. Individuals who have had a prior fragility fracture may represent the population at greatest risk for a future fragility fracture and those that would benefit most from anti-fracture therapy. However, it is probable that only one in ten patients who require anti-fracture therapy receive it.
Methods: The Saskatoon Atraumatic Fracture Elimination (SAFE) Program has retrospective and prospective arms with the purpose to first determine and then diminish the osteoporosis care gap following fragility fracture. The retrospective arm is designed to document the rate of osteoporosis diagnosis and the prescription of anti-fracture treatment in the Saskatoon Health Region (Saskatchewan) for those who suffered a fragility fracture between the years 2001-2004. This analysis will be completed with the use of medical databases and be stratified for age and sex. All men and women must have been 45 years of age or older at the time of fracture and all pathologic or traumatic fractures will be excluded from the analyses.
Results: The results of the retrospective arm will be presented. Based on previous investigations, it is anticipated that the rates of osteoporosis diagnosis and anti-fracture treatment following a fragility fracture will be within the 20-40% and 10-20% range, respectively.
Conclusions: The findings from the retrospective arm of SAFE will provide a baseline reference for the prospective arm of SAFE which will attempt to diminish the care gap.
Keywords: *Osteoporosis, fragility fracture, medical databases*

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The depletion of susceptibles effect in the assessment of burden-of-illness for pharmacoeconomic studies: the case of Macugen

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Introduction: Burden-of-illness (BOI) data, such as health services use and incidence of adverse events, may be obtained through administrative databases and are often used in economic evaluations of new medicines. However, failure to account for duration of illness may bias comparisons across patient subgroups.

Objectives: Using the economic evaluation of Macugen (macular degeneration treatment) as a case study, this study aimed to assess the risk of fracture, institutionalization, depression, and death among community-dwelling elderly patients diagnosed with visual impairment.

Methods: A retrospective cohort study was conducted over the years 2000 to 2004. Data were obtained through the Quebec health databases (RAMQ). The 5-year hazard rate of fracture, depression, institutionalization, or death in a cohort of elderly patients (age 65+) with visual impairment (either moderate (n= 2,454), or severe/blindness (n=2,609)) was compared to a cohort of elderly patients without visual impairment (n=16,932). Associations were quantified through Cox proportional hazard models.

Results: Adjusting for age, gender, overall health status (Chronic Disease Score), and history of depression, the hazard ratio for all outcomes was greater for visual impaired patients than for referents. However, the risk of fracture, institutionalization, or death showed a trend to be greater for patients with moderate than severe visual impairment; consistent with a depletion of susceptibles effect.

Conclusion: Crude BOI data should be used in economic evaluations. However, if the objective is to determine the risk of adverse events according to an etiological perspective, failure to account for the depletion of susceptibles effect may bias results.

Keywords: *Burden of illness, depletion of susceptibles*

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The immediate and long-term costs of diabetes and diabetes-related complications: results from a large prospective cohort study

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Background: Previous studies have shown that diabetes is a costly chronic condition due mainly to the treatment of complications that occur with increasing frequency and severity as the disease progresses. However, results vary greatly primarily because they rely on different modeling techniques, secondary data sources and/or on numerous assumptions to project potential long-term costs. The objective of this study is to estimate the short-term and long-term healthcare costs of diabetes and diabetes-related complications for a large cohort of patients followed prospectively.

Methods: All prevalent cases of diabetes in Ontario from 1992 to 2002 were followed for up to 10 years, until death, or out migration. This Ontario Diabetes Database was linked to various healthcare resource utilization administrative datasets. Seven diabetes-related complications were tracked over time (e.g. ischemic heart disease). Outpatient services, pharmaceuticals, long-term care, homecare and hospitalizations were all included.

Results: Of the 734,113 diabetics in the database, there were over 1.26 million non-fatal cardiovascular-related events during the 10-year follow-up period. Costs of complications were higher than previously believed (e.g. amputation $34,469 first year and $4,721 subsequent years; renal failure $22,116 first year and $10,033 subsequent years).

Conclusions: The results confirm that diabetes is a costly condition due largely to the high incidence and cost of secondary complications. Our large sample and ability to link administrative databases provide a unique opportunity to estimate the high cost of diabetes and related complications.

Keywords: *Diabetes, costs, regression analysis*

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The influence of health status on healthcare utilization and costs: results from the Canadian community health survey (CCHS) cycle 1.1

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Funding Source: Canadian Institutes of Health Research Team Development Grant
Background: The Canadian Community Health Survey Cycle 1.1 is a cross-sectional representative survey of health determinants, status, and healthcare utilization (HCU) for the Canadian population (2000/2001). Health status may influence HCU and HCU costs but this has not been investigated. Our objective was to measure the association between HCU/HCU costs and health status as estimated by the Health Utilities Index Mark 3 (HUI3) global utility score.
Methods: Data were extracted on age, sex, chronic conditions, HUI3, and HCU during the previous 12 months. HCU costs were estimated from published sources. The relationship between HUI3 and HCU costs was estimated using generalized linear modelling to determine a cost ratio (CR) and health professional visit ratio (VR) measuring the effect of a unit change in HUI3 score.
Results: The study population represented 3,647,791 persons > 65 years of age, 56 % were women, median age was 73.0 years. 25% reported no chronic conditions, 20% reported Ý3 chronic conditions. The weighted mean (std) HUI3 score was 0.78 (0.26). Mean HCU cost over the previous 12 months was $1,688.61. The overall CR and VR was 0.90 (99% CI: 0.89-0.91) and 0.93 (0.91-0.93) respectively. The CR for people age 65-74 was 0.89 (0.88-0.91) and 0.91 (0.90-0.92) for those >75 years. The VR for people age 65-74 was 0.92 (0.91-0.93) and 0.93 (0.92-0.99) for those >75 years. Confounding variables for age, sex, and chronic conditions had little effect.
Conclusion: The HUI3 score is a predictor of HCU costs. The impact of age, sex, and chronic conditions is not significant.
Keywords: *Cost estimation, health status, quality of life*

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The lack of individualization of harms and benefits reported in randomized controlled trials

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Background: For optimal decisions regarding medications, clinicians and patients need to know the patient's own expected benefit and harm with treatment, in addition to average population statistics. The objective of this study was to evaluate the reports of high quality randomized controlled trials (RCTs) to determine the degree of individualization of harm and benefit data.
Methods: We used ACP Journal as a screening tool for high quality RCTs and considered all trials published between May 2003 and May 2005 (n = 357). Articles were ineligible if not drug-related and if not RCTs or meta-analyses of RCTs (n = 150). Eligible articles were rated based on their reporting of a drug's harm(s) and benefit(s): were both harm and benefit examined? analyzed dependently? analyzed at a population/sub-group/individual level? All articles were rated by a single reviewer; a second reviewer rated a random subset of 60 articles to ensure inter-rater reliability.
Results: 207 eligible articles were included in this review. 166 (80%) examined both a drug's harms and benefits though none examined risks and benefits dependently in the same analysis. All articles included population analyses of a drug's risks and/or benefits, while 64 (31%) included subgroup analyses and 4(2%) extended to individual patient data analysis.
Conclusions: While the current reporting of drug RCTs in medical journals typically includes both harm and benefit assessment, these are analyzed separately and rarely involve an analysis beyond the population level. This makes it virtually impossible for physicians to predict benefit/harm ratios for specific patients.
Keywords: *Benefit, harm, RCT*

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The rate of gastrointestinal prophylaxis in Nova Scotia Seniors' Pharmacare beneficiaries starting nonsteroidal anti-inflammatory (NSAID) therapy

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Funding Source: B. Superceanu received funding from CHSRF/CIHR/NHSRF

Background: NSAIDs are one of the most widely used classes of drugs and they can cause serious gastrointestinal (GI) side effects. In patients at increased risk of NSAID related GI complications, either a non-selective NSAID plus gastroprotective agent (GPA) or a cyclooxygenase-2 selective inhibitor (Coxib) is recommended. The objective was to describe coprescribing of non-selective NSAIDs and GPAs.

Methods: N.S. Seniors Pharmacare beneficiaries were studied for the fiscal years 1998-2002. A cohort of incident NSAID and GPA users was selected (no NSAID use 12 month before index month, no GPA use 2 months before the index prescription) from all non-selective NSAID users with at least 13 months of Pharmacare eligibility. Monthly coprescribing rates were calculated as the number of patients in the cohort using GPAs divided by the number of NSAID users. Gastrointestinal prophylactic coprescribing was the coprescribing rate in the first month (index month).

Results: Our cohort consisted of 12,906 patients. Most of the non-selective NSAID prescriptions were short, 75% up to two months. Only 2.3% were longer than one year. In only 3.8% of NSAID users was gastrointestinal prophylaxis given. The rate of Histamine-2 Receptor Antagonist (H2RA) coprescribing increased with the number of consecutive months on an NSAID, from 3.5% in the first month to 24.1% in month 48.

Conclusion: In Nova Scotia seniors using non-selective NSAIDs, the rate of gastrointestinal prophylaxis is low. Most patients (93%) receive H2RAs as GPAs despite limited evidence that they protect against gastric ulcers.

Keywords: *NSAID drug utilization*

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The use of practice management strategies to optimize patient care: the EPIC initiative

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Background/Objectives: EPIC (Enhancing Practice to Improve Care) was initiated to determine if primary care management of chronic conditions (e.g., Chronic Kidney Disease (CKD)) can be improved via implementation of practice management strategies.

Methods: Prospective, multi-centre study of the routine use of patient registries and recall systems for the management of CKD patients. 43 primary care physician's (MDs) offices in 4 regions of British Columbia agreed to participate and identifed eligible patients with confirmed or suspected CKD. Consent was obtained and charts were audited pre- and post-intervention. Information collected included patient characteristics and clinical variables. This abstract reports on the baseline measurements of the study.

Results: 378 eligible baseline case report forms were received from 41 sites. MD routine use of patient registries and formal recall systems were 22% and 7% respectively. Patient characteristics were: 52% female, 91% Caucasian, average age 72 years, BP 133/74, LDL 2.7, TC/HDL ratio 3.5. 76% had a past diagnosis of CKD. 73% used ACEI/ARB and 55% cholesterol lowering agents. Routine monitoring of Na, K, and Hgb were 83%, 85% and 79% respectively. Serum albumin, phosphorus, iPTH and transferrin saturation: 28%, 25%, 16%, and 12% respectively.

Conclusions/Discussion: Formal practice management strategies are not routinely utilized in this cohort. ACEI/ARB use was higher than anticipated but may be due to the high % of hypertensive patients and past CKD diagnosis. A significant percent of patients do not receive routine monitoring of important CKD parameters. Implementation of practice management strategies is expected to enhance patient care in follow-up measurements.

Keywords: *Chronic kidney disease, self-audit, care gap*

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Theophyllines, long-acting beta-2 agonists and inhaled corticosteroids and the risk of death among patients with chronic obstructive pulmonary disease: a nested case-control study

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Background: A few observational studies and one meta-analysis have suggested that inhaled corticosteroids (ICS) alone or in combination with long-acting beta-2 agonists (LABA) may reduce COPD mortality, but no study has investigated the effect of theophyllines. The aim of this study was to compare the relative effectiveness of theophyllines, LABA and ICS to reduce mortality rate.
Methods: Using data from the RAMQ and MED-ECHO databases we performed a nested case-control study. We first selected a cohort of 36,492 patients between 1996 and 2000. Patients were included in the cohort if they were 50 years and older, filled at least 6 prescriptions of an inhaled bronchodilator, received at least one medical service for COPD and did not receive any diagnosis of asthma over a 12-month period. From the cohort, we then identified 7,792 cases of death, and selected 77,920 controls using density sampling. Adjusted mortality rate ratios comparing the three medications under study were estimated from a conditional logistic regression model.
Results: We observed an increased rate of death among patients treated with theophyllines as compared with LABA (adjusted RR = 1.31; 95% CI: 1.04-1.65) and ICS (adjusted RR= 2.12; 95% CI: 1.90-2.37). However, patients treated with theophyllines plus ICS were not found to be more at risk of death than patients treated with LABA plus ICS (adjusted RR = 0.84; 95% CI: 0.70-1.02).
Conclusion: ICS and LABA were found to be associated with a reduction in mortality rate as compared with theophyllines among patients with COPD.
Keywords: *COPD, pharmacoepidemiology, mortality*

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Treatment patterns in type 2 diabetes management: a retrospective cohort study of antihyperglycemic users in Québec

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Background/Objective: Type2 diabetes represents a significant public health issue, however the management path patients follow once diagnosed with type2 diabetes remains unclear. Study objectives were to describe characteristics of patients with type2 diabetes, in terms of age, gender and comorbidities, and to identify treatment patterns in current clinical practice.
Methods: This cohort study retrospectively analyzed data on medical and pharmaceutical services, obtained from the Régie de l'Assurance Maladie du Québec (RAMQ), for a random sample of patients who received an antihyperglycemic agent between September 2003 and August 2004. A 10-year observation period, from January 1994 to August 2004, was applied.
Results: Incidence of selected comorbidities, based on medication use, was higher in patients with diabetes compared to a control group of patients without diabetes matched for age and gender: heart diseases (61.4% vs. 30.1%; p<0.001), hypercholesterolemia (44.9% vs. 21.6%; p<0.001), hypertension (68.9% vs. 46.8%; p<0.001), and glaucoma (8.1% vs. 5.4%; p<0.001). Majority of patients (93.7%) was initially treated with one oral antihyperglycemic medication but over time a larger proportion of patients (31.8%) required a combination of medications. For most medications, the average dose increased by up to 120% of the initial dose. A few patients received an oral agent and insulin (0.4%) as initial antihyperglycemic treatment. After 10 years, the proportion of patients to whom insulin was added to their antihyperglycemic treatment reached 19.1 %.
Conclusion: Over a 10-year observation period, patients with type2 diabetes were prescribed more aggressive treatments. Insulin was added to the treatment regimen of an important number of patients.
Keywords: *Diabetes, antihyperglycemics, treatment patterns*

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Trends in the diagnosis and treatment of hypertension in Canada

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Background: Understanding recent trends in the awareness and treatment of hypertension among Canadians represents an important public health issue.

Methods: We examined the prevalence and treatment of hypertension in adult Canadians prior and subsequent to the implementation of the Canadian Hypertension Education Program (CHEP) in 1999. Data were obtained from respondents aged 20+ (residing in the 10 provinces) included in the NPHS (1994/95, 1996/97, 1998/99) and the CCHS (2000, 2003) survey cycles. Subjects were asked whether they had ever received a diagnosis of hypertension and whether they received antihypertensive medication in the past month. Prevalence rates were age-standardized to 2003 and weighted to reflect the Canadian population. Piecewise linear regression was used to calculate the average annual increase (AAI) in rates, pre/post 1999.

Results: Between 1994 and 2003, the percent of the Canadian population aware of being diagnosed with hypertension increased by 51% (12.4 vs. 18.7%) and the percentage prescribed antihypertensives increased 65% (9.6 vs. 15.9%). Following 1999, the rate of increase in the diagnosis of hypertension doubled (AAI: 0.51% vs. 1.03%. $p<.001$ pre vs. post) and the rate of increase in percentage prescribed antihypertensives almost doubled (AAI: 0.54% vs. 0.97%, $p<.001$ pre vs. post). There was a greater increase in the awareness of hypertension and use of antihypertensives among men compared with women after 1999; although prevalence estimates were lower among men than women.

Conclusions: There has been a significant increase in the diagnosis and treatment of hypertension in Canada between 1994 and 2003. The greater AAI in the diagnosis and utilization of antihypertensives post-1999 suggests a potential beneficial effect of the CHEP program.

Keywords: *Hypertension, medication, Canada, community health survey*

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Understanding regional variation in prescription drug use: do British Columbia and Ontario physicians make different choices about who should take statins?

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Background: Though statins are fully reimbursed by the provincial drug benefit plans for seniors in British Columbia (BC) and Ontario, Canada, population-based rates of statin use are markedly higher in Ontario. Are Ontario seniors prescribed statins for less appropriate indications? The purpose of this study was to assess whether Ontario and BC seniors newly treated with statins differ in terms of their risk for future coronary heart disease (CHD) events.

Methods: For the period 1998-2001, we collected information on demographics, outpatient prescriptions, physician visits, hospital admissions, and vital status from linked health administrative databases in BC and Ontario to compare the proportions of new statin users aged 66 years and older who had prior evidence of an acute coronary syndrome (ACS), chronic CHD, neither ACS nor CHD but diabetes, or none of the above.

Results: Approximately 15% and 20% of BC and Ontario seniors, respectively, had filled a statin prescription by 2001. Among new statin users in the two provinces, virtually identical proportions had prior evidence of ACS, chronic CHD, and diabetes -- 8%, 25%, and 14%, respectively -- for an overall proportion of roughly 50% at high risk for future CHD events.

Conclusions: New statin users in BC and Ontario were at similar risk for future CHD events. Poorer case selection is an unlikely explanation for the relatively higher population-based rates of statin use in Ontario.

Keywords: *Health policy, population health, geographic variation, prevention, statins*

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Use of bland-altman plots to assess agreement for clinical assessments: a new method that adjusts for chance agreement

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Background: Studies of the agreement between pairs of clinical assessments measured on a continuous scale often utilize Bland-Altman (B-A) plots. However, these plots are often misinterpreted when scales have fixed lower and upper bounds. We propose a new method to adjust for the agreement that occurs by chance alone.
Methods: 10,000 randomly simulated, independent pairs of responses bound between 0 and 1 were used to generate a B-A plot (average vs. difference). A new method that considers the observed difference as a proportion of the maximum possible difference (PMPD) was developed. This method was applied to an empirical dataset of 320 rheumatoid arthritis (RA) patients comparing two quality of life measures (HUI2 and the standard gamble).
Results: Due to range of scale limitations, B-A plots of concordance for pairs of bound clinical assessments are subject to end-of-scale bias as illustrated by the diamond shaped pattern from the simulated data. This leads to erroneous reports of better agreement at the scale ends and worse agreement in the middle. By using the PMPD, this bias is no longer apparent as the results no longer converge at the lower and upper scale ends. When applied to the RA HUI dataset, the PMPD method was useful in determining agreement beyond chance.
Conclusions: B-A plots are useful in examining agreement between pairs of clinical assessments. However, when assessment scales have a lower and upper bound, B-A plots are subject to misinterpretation. Our method adjusts for chance agreement and is useful for many types of clinical assessments.
Keywords: *Agreement, Bland-Altman plot, quality of life*

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Using healthcare administrative data to identify children at risk for influenza related complications

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Funding Source: Alberta Children's Hospital Foundation
Objective: To develop a population based method for identifying children with chronic high risk medical conditions (CHRMC) that place them at high risk of influenza-related complications. These data are needed to monitor target group vaccine coverage.
Method: We conducted a retrospective analysis of all fee for service physicians' claims for all children aged less than 18 years old (n = 41171) born in Alberta, Canada during the fiscal year 1984/85. CHRMC related physician visits were identified by using Ninth Revision of the International Classification of Diseases-Clinical Modification (ICD-9 CM) codes for cardiovascular, pulmonary, metabolic, anemias/hemogobinopathy, immunossupression/ immunodefficiency, cancer, central nervous system and renal diseases. A child was classified as having CHRMC using two criteria: CRITERION A: greater than 2 related claims from a family physician or greater than 1 claim from a pediatrician/other specialists or greater than 1 emergency room visit or greater than 1 hospitalization; or CRITERION B: claims from a combination of any two of the providers listed in criterion A.
Results: Preliminary findings are that 38.9% of children had at least one CHRMC by Criterion A versus 10.9% by Criterion B. The proportion of children that could be classified as having greater than 2 CHRMC was 6.3% (CRITERION A) and 0.7% (CRITERION B).
Conclusions: By using a defined set of criteria based on different types of providers, children with CHRMC can be identified from health care administrative data. These data can be used in monitoring influenza vaccine uptake. Further validation of our methods is ongoing.
Keywords: *Administrative data, vaccine coverage, children*

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Validation of maternal self-report and report of infant health care utilization for the first six months postpartum

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Background: In studies of maternal and infant health care utilization, data are often based on maternal report. However, the validity of maternal self- and proxy reporting needs to be examined.
Objective: To examine the validity of maternal self-report and report of infant health care utilization by comparing reports to services billed through the Ontario Health Insurance Plan (OHIP).
Methods: Physician and ED visit data were collected from 113 women interviewed at three and six months postpartum regarding services received by themselves and their infants. Using each individual's unique health card number and birth date, data were linked to the OHIP database. Cross-tabulation tables (OHIP vs. maternal report) were generated and agreement between the two sources was assessed with Cohen's kappa statistic.
Results: Kappa statistics indicated moderate to substantial agreement between maternal self-report and the OHIP database for general practitioner, psychiatrist, obstetrician, other specialist physicians, and ED visits. Agreement between maternal proxy report and the OHIP database for infant ED and other specialist visits was substantial. There was only slight agreement for infant general practitioner/pediatrician visits. There were no differences in the quality of reporting by women with and without depression, or for primiparous versus multiparous women.
Conclusion: Maternal report is a valid source of health care utilization data in this population. These results can be generalized to other studies that rely on patient self-report, or maternal report of infant health care utilization.
Keywords: *Validation study, self-report, proxy report, health care utilization*

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Validity of a modified scoring index to assess severity of nausea and vomiting of pregnancy (NVP); effect of antiemetic utilisation

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Background: The only existing validated NVP severity index is the Motherisk PUQE. However, PUQE covers symptoms that occurred within 12h, not necessarily accurately measuring first trimester NVP. We sought to assess the validity of a modified-PUQE index that covers the entire first trimester of pregnancy by comparing NVP severity classification between the PUQE-12hr and our modified version.
Methods: A prospective study was conducted between 2004-2005 on the population of pregnant women attending their first prenatal visit to the outpatient clinics of Ste-Justine's Hospital or René-Laennec Clinic. Women were eligible if they were at least 18 years, ≤16 weeks of pregnancy, and able to read French or English. Eligible women were asked to fill out the PUQE-12hr and the modified-PUQE simultaneously. Weighed Kappas were performed to evaluate agreement on the classification of NVP severity between the two indexes.
Results: Among participants (n=185), 67% vs. 53% were classified as having mild NVP, 31% vs. 44% as having moderate NVP, and 2% vs. 3% as having severe NVP, on the PUQE-12hr and modified-PUQE, respectively ($p \leq .01$). There was moderate agreement between the two indexes (weighted-kappa=0.55). Women who took antiemetics were more likely to report NVP similarly on the two indexes. However, multivariate linear regression models showed that antiemetic use, adjusted for maternal and gestational age, was a confounder rather than an effect modifier in the relationship between the two indexes.
Conclusions: Although the modified-PUQE tended to classify women's NVP as more severe than the PUQE-12hr, the two indexes agreed.
Keywords: *Nausea and vomiting of pregnancy (NVP), severity scoring index, validation*

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Warfarin utilization trends among elderly patients with atrial fibrillation

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Funding Source: None
Background: Several RCTs published between 1989 and 1993 showed that warfarin (W) could reduce by 60-70% the risk of stroke in patients with atrial fibrillation (AF). A number of non-Canadian surveys of clinical practice have shown that as few as 25% of patients with AF receive W.
Methods: We determined the usage of W in ONT patients 65 years of age or older who were discharged from a hospital with a diagnosis of AF between 01/1993-03/2005. Population -based administrative databases (Can.Institute for Health Info, ON Drug Benefit Plan, Reg.Persons Data Base, and ON Health Insurance Plan) covering over 1.5 million residents of ON were used to confirm the diagnosis, drug usage and co-morbidities.
Results: W usage in AF (N=53,988) increased steadily from 38.1% in Jan '94 to 69% in Jan '05. W usage in the highest stroke risk group (>80 yrs of age) increased over the same period from 17% to 49%. No significant gender differences were detected. The incidence of stroke decreased significantly from 8.7% to 6.4% over the same time period. The GI bleeding complication rate increased significantly from 4.2% to 5.6%.
Conclusions: W usage for stroke prophylaxis in AF has increased significantly over the last decade in ON but may still be under-utilized, especially in those with the highest risk of stroke.
Keywords: *Warfarin, afib, usage*

CSCP Trainee Oral Presentations

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Hepatic CYP2A6 levels and nicotine metabolism are influenced by CYP2A6 genetic variation and sex, but not age

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Background: Substantial interindividual variability exists in the rates of nicotine clearance in humans. Age, sex, and genetic variation in the main nicotine metabolic inactivating enzyme CYP2A6 might influence this variability.
Methods: Liver samples (n=28) were assessed for their CYP2A6 levels, nicotine metabolism activity, and CYP2A6 genotype (CYP2A6*2, *4, *9, *12). The CYP2A6 alleles investigated are frequent in Caucasians and associated with decreased (or loss of) CYP2A6 function.
Results: Liver samples with at least one CYP2A6 variant allele (n=9) had substantially lower CYP2A6 levels (0.8±0.5 vs.2.4±2.5, p=0.02) and Vmax/Km (catalytic efficiency, 0.29±0.23 vs. 0.58±0.58, p=0.04), and trended towards lower Vmax (maximum nicotine metabolism, 17.7±9.7 vs. 30.6±31.4, p=0.2) compared to homozygous wildtype livers (n=19). In those livers without genetic CYP2A6 variants, to limit biases from genetic variation, the impact of age and gender was examined. The wildtype livers in three different age groups (2-9 {n=6}, 16-23 {n=6}, and 31-53 {n=7}) had similar CYP2A6 levels (1.9±1.8, 3.4±3.9, 1.9±1.2) and activity (28.2±20.5, 46.6±49.5, 18.9±11.9) respectively. However female (n=9) compared to male livers (n=10) had significantly higher CYP2A6 levels (3.5±3.0 vs 1.4±1.1 p=0.04), Vmax (45.8±40.3 vs.16.9±9.5 p=0.02) and Vmax/Km (0.85±0.7 vs. 0.34±0.2 p=0.04). The Km (affinity for nicotine) was similar in all comparisons.
Conclusions: These results indicate that the higher rates of nicotine clearance observed in wild type individuals, particularly women, is likely due to up regulation of CYP2A6 levels suggesting steroid hormone regulation of CYP2A6-mediated metabolism. Faster CYP2A6 metabolism has been associated with higher levels of smoking, increased failure on nicotine patch, and higher cancer risk.
Keywords: *CYP2A6, nicotine metabolism, gender*

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The effect of N-acetylcysteine on ifosfamide-induced nephrotoxicity

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Background: Ifosfamide (IF) nephrotoxicity is a serious adverse effect in pediatric patients undergoing chemotherapy despite concurrent administration of MESNA. Previous studies have shown that in addition to the renal production of chloroacetaldehyde (CAA), a toxic metabolite of IF, lower levels of glutathione (GSH) may predispose the kidney to damages by CAA. The antioxidant N-acetylcysteine (NAC) is used extensively as an antidote for acetaminophen poisoning in children. Since it has been safely and effectively used clinically, the goal of this study was to test whether reversal of ifosfamide-induced nephrotoxicity can be achieved by administering NAC.
Methods: LLC-PK1, a porcine renal tubular proximal cell line, was pre-treated with either 50uM BSO or 2.5 mM NAC alone followed by the addition of 100uM IF and 50uM BSO. Cellular viability was assessed by alamarBlue assay at 24 and 96 hours. Intracellular and extracellular GSH and GSSG levels were determined by GSH/GSSG ratio kit and high performance liquid chromatography (HPLC), respectively. Statistical differences were assessed by
one-way ANOVA.
Results: There was no significant cellular death with BSO and IF at 24 hours. In contrast, there was a significant increase in cellular viability when cells were treated daily for 96 hours. This decrease was reduced when cells were concurrently treated with NAC. Intracellular and extracellular GSH levels in the cells receiving concurrent treatment of NAC remained significantly lower as compared to the controls.
Conclusions: NAC protects renal tubular cells from ifosfamide nephrotoxicity. It is unlikely that NAC is protecting the cells by acting as a precursor for GSH synthesis. NAC may protect the cells by direct conjugation with CAA, acting alternatively as a nucleophile.
Keywords: *Ifosfamide nephrotoxicity, pediatric, chemotherapy, N-acetylcysteine*

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Involvement of PXR in ABC transporter expression during pregnancy

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Background: Dramatic increases in the circulating levels of hormones such as progesterone and estrogen occur in pregnancy. Hormones are activating ligands for nuclear receptors, such as the Pregnane X Receptor (PXR). PXR regulates the expression of numerous ABC transporters by altering transcriptional pathways. Thus we hypothesize that PXR is involved in the regulation of drug transporters during pregnancy.
Methods: Hepatic and placental tissues from pregnant (gd17) and non-pregnant animals were harvested from PXR +/+ and PXR-/- C57BL/6 mice and the RNA extracted. Gene expression of various ABC transporters including BCRP, MRP1, MRP2, MRP3, Mdr1a was quantified utilizing semi-quantitative RT-PCR and normalized to Gapdh.
Results: In the PXR+/+ mice, a three-fold increase was observed in the expression of BCRP in the liver samples of the pregnant as compared to the non-pregnant females, while no such changes were detected in the PXR-/- mice. MRP3 mRNA levels were undetectable in the liver of all mice. BCRP expression was increased by approximately 40% and MRP3 was increased by 80% in the placenta of the PXR+/+ mice as compared to the levels found in the placenta of PXR-/-mice
Conclusions: The differential expression of BCRP and MRP3 in hepatic and placental tissues of PXR+/+ versus PXR-/- mice suggests a possible role of PXR in the regulation of these drug transporters during pregnancy. This involvement could help elucidate in part the regulation of drug transport across the placenta as PXR may also play an important role in regulation of other ABC transporters during pregnancy.
Keywords: *PXR, placenta, BCRP*

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Sustained intraperitoneal delivery of paclitaxel on the regulation of p-glycoprotein in ovarian tumors

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Background: In ovarian cancer, chemotherapy is often ineffective due to a phenomenon known as multidrug resistance (MDR). MDR is conferred through the over-expression of the drug efflux transporter, P-glycoprotein (Pgp). We hypothesized that sustained intraperitoneal delivery of paclitaxel (PTX) could improve chemo-responsiveness of ovarian tumors by attenuating the expression of Pgp/MDR1.

Methods: Intermittent or sustained administration of PTX using PTX solution (PTXcrel) or a novel sustained PTX implant system (PTXfilm) was examined in vitro in SKOV-3 cells and in vivo in a human ovarian xenograft murine model. Animals were implanted intraperitoneally with the PTXfilm and tumors were analyzed for Pgp/MDR1 expression. Pgp/MDR1 expression was examined by real-time quantitative PCR, flow cytometry and immunohistochemistry. H&E staining was performed to assess overall tumor health.

Results: In vitro, PTXcrel treatments (5-250 ng/ml) induced MDR1 mRNA levels by 3-4 fold in SKOV-3 cells ($P<0.05$), whereas the PTXfilm treatments did not induce MDR1 or Pgp expression. Likewise, we did not detect significant changes in the in vivo expression of MDR1/Pgp in tumors of mice treated for 14 days with sustained PTXfilm which delivered doses of 0.841-84.1 mg/kg/week of PTX. Increased necrosis was observed in tumors obtained from animals implanted with PTXfilm delivering a PTX dose of 84.1 mg/kg/week.

Conclusions: Overall, this is the first study demonstrating that sustained intraperitoneal administration of PTX attenuated development of MDR by repressing MDR1/PGP over-expression. As a result, novel methods of delivering chemotherapeutic agents intraperitoneally with a sustained release may improve current treatment strategies for ovarian cancer.

Keywords: *Ovarian cancer, paclitaxel, intraperitoneal*

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CYP2B6 genetic variation alters abstinence rates in smoking cessation treatment with bupropion

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Background: CYP2B6 genetic variants alter the rates of bupropion (Zyban) metabolism to hydroxybupropion; smoking cessation rates may be altered by differing rates of metabolism. The CYP2B6*6 allele has been associated with decreased activity for bupropion. We hypothesized that the CYP2B6*6 allele would decrease smoking cessation abstinence.

Methods: We haplotyped Caucasian 423 smokers and created two groups according to estimated CYP2B6 activity: CYP2B6*1 group (CYP2B6*1/*1, 54.8% of population, normal activity) and CYP2B6*6 group (CYP2B6*1/*6, 38.1% of population, and CYP2B6*6/*6, 7.1% of population, altered activity).

Results: In the placebo treatment, the CYP2B6*6 group did more poorly than the CYP2B6*1 group at EOT (14% vs. 32%, p=0.01). However, among those in the CYP2B6*6 group, bupropion treatment significantly increased abstinence compared to placebo at the end of treatment (EOT, 33% vs. 14%, p=0.01) and at the 6-month follow-up (31% vs. 13%, p=0.008). In contrast, the CYP2B6*1 group did not benefit from bupropion treatment, compared to placebo, at EOT (32% vs. 31%, p=0.96) or at 6 months (22% vs. 22%, p=0.91). There was a significant CYP2B6 genotype by bupropion treatment effect at EOT (p=0.043) and a trend at the 6 month follow-up (p=0.057). There were no significant differences in baseline measures (cigs/day, age of initiation, FTND score, craving, urge to smoke, withdrawal symptoms or side effects) between the CYP2B6*1 and CYP2B6*6 group nor between the bupropion and placebo arms within the CYP2B6*6 group.

Conclusions: CYP2B6 genotype alters abstinent rates in bupropion treatment; smokers with a CYP2B6*6 genotype receive greater benefit from bupropion than CYP2B6*1/*1 smokers.

Key words: S*moking, bupropion, CYP2B6*

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The effect of endotoxin on the regulation of hepatic drug transporters in pregnant rats

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Background: Bacterial endotoxin-mediated inflammation is known to down-regulate the expression of a number of rodent hepatic drug transporters and CYP3A. However, virtually no information exists as to the impact of endotoxins on the regulation of these drug transporters and metabolizing protein in pregnancy. Thus, our objective was to examine the effects of inflammatory response on the regulation of several key drug transporters and CYP3A in liver of gestational rats.

Methods: Acute inflammation was induced in pregnant Sprague-Dawley rats on G18 through administration of endotoxin (LPS) in doses of 0.1, 0.5 and 1.0 mg/kg, with saline as control. Hepatic expression levels of PGP, MRP2, BCRP, OATP2, and CYP3A were measured at 6 hours by RT-PCR and were normalized to GAPDH.

Results: A significant downregulation of MRP2, OATP2 and CYP3A mRNA levels ($p<0.05$) was observed in the liver of pregnant rats at all administered LPS doses in comparison to controls. Meanwhile, mdr1b and BCRP expression was induced at all doses of LPS ($p<0.05$) as compared to controls. The extent of down- or up-regulation appeared to be dose-dependent in all animals. On the other hand, mdr1a expression was up-regulated at the 0.1 mg/kg dose of LPS, but downregulated by 50% at higher doses.

Conclusions: LPS-induced inflammation significantly modified the expression of key ABC drug transporters, as well as the expression of OATP2 and CYP3A in the liver of pregnant rats. As a consequence, infection and inflammation during pregnancy likely affect maternal as well as fetal drug disposition.

Key words: *Pregnancy drug-transporters , RT-PCR*

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Sucrose reduces pain during intramuscular vitamin K injection in newborns

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Background: Sucrose has been demonstrated to reduce pain in young infants undergoing painful procedures such as venipuncture and heel lance. To date, no studies have evaluated its analgesic effectiveness during intramuscular injection of vitamin K in the newborn. The objective was to determine the analgesic effectiveness of sucrose for intramuscular injection of vitamin K in newborns.

Methods: Double-blind randomized controlled trial in healthy full-term neonates. Neonates received either sucrose or water on the tongue two minutes prior to vitamin K injection. Pain was assessed from videotapes using facial grimacing (FG; brow bulge, eyes squeezed shut and naso-labial furrow) and cry duration (CD).

Results: 119 infants participated. There were no significant differences in characteristics between groups; mean (SD) gestational age and birthweight was 39 weeks (1 week) and 3.4 kg (0.4 kg), respectively for both the sucrose and water groups. Repeated measures ANCOVA revealed a statistically significant main effect of treatment group for facial grimacing ($p = 0.018$) and for cry duration ($p = 0.028$), a significant main effect of procedure phase for both FG and CD (both $p<0.001$), and no significant group x phase interaction for either FG or CD. Overall, the sucrose group showed 19% less facial grimacing and a 28% reduction in crying time than the water group.

Conclusions: Sucrose reduced pain during intramuscular injection of vitamin K in newborn infants and is recommended for routine use in clinical practice.

Key words: *Randomized -controlled trial, sucrose, vitamin K, painful procedures, neonates*

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Time and dose dependent effects of maternal inflammation on the expression of ABC transporters in placenta

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Background: ABC transporters are expressed in placenta, and play a protective role for the fetus from maternal blood-born toxins. Bacterial endotoxin lipopolysaccharide (LPS)-induced inflammation alters transporters expression in the liver, intestines and the brain, but is not fully investigated yet in placenta. We compared the effect of LPS treatment on transporter expression in rat placenta in a time- and dose-dependent manner.

Methods: Pregnant Sprague Dawley rats (17 days) were administered LPS (0.1, 0.5 or 1.0 mg/kg, i.p.) or equal volume of saline as control. The rats were sacrificed at 6 or 24h, and placentas were collected. ABCB1 (Pgp) and ABCG2 (BCRP) expression was determined at the mRNA and protein level by RT-PCR and Western blotting, respectively.

Results: LPS doses of 0.1, 0.5 and 1.0 mg/kg caused down-regulation of mdr1a/Pgp mRNA to 63.5 ± 6.2% ($p < 0.05$), 43.1 ± 3.0% ($p < 0.01$) and 12.5 ± 4.1% ($p < 0.01$) of control at 24h, respectively. BCRP mRNA was also down-regulated to 80.4 ± 3.5%, 14.8 ± 7.8% ($p < 0.01$) and 1.0 ± 0.1% ($p < 0.01$) of control at 24h, respectively. Corresponding reduction in protein levels of Pgp and BCRP was seen in the LPS treated rats at the 24h time point. However, significant changes were not observed at the 6h time point.

Conclusions: LPS-induced inflammation significantly suppresses placental Pgp and BCRP, which are important in efflux of numerous drugs and toxins. Therefore, inflammation-imposed changes in Pgp and BCRP in placenta may increase fetal exposure to toxins.

Keywords: *ABC transporter, placenta, RT-PCR*

CSCP POSTER PRESENTATIONS

Wednesday May 10, 2006

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ENCORE PRESENTATION

The accuracy of using computerized medical records in detecting adverse drug events: a meta-analysis

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Safety and maintenance of effect of orally disintegrating risperidone tablets in patients with major depressive disorder, bipolar disorder or dementia, results of an open-label study

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Background: Safety and maintenance of clinical effect in subjects transitioned from compressed risperidone tablets to orally disintegrating risperidone tablets.

Methods: Patients >= 18 years with DSM-IV diagnosis of Major Depressive Disorder (MDD), Bipolar Disorder (BP) or Dementia (D) with baseline CGI-Severity <= 3 (mildly ill) and minimum 2 weeks prior risperidone therapy at a stable dose of 0.5, 1.0 or 2.0 mg/day were recruited and switched to equivalent doses of orally disintegrating risperidone tablets and assessed 4 weeks later. All MDD patients had been previously stabilized on an anti-depressant, most BP patients (16/21) were taking a mood stabilizer and most Dementia patients (13/20) were on a cholinesterase inhibitor.

Results: N=25 MDD, N=21 BP and N=20 Dementia . Mean age was 49.2+/-13.8 years (MDD), 45.7+/-13.2 (BP), 77.6+/-8.7 (D). Mean baseline CGI-S score was 2.5 +/- 0.7 (MDD), 2.3 +/- 0.7 (BP) and 2.8 +/- 0.4 (D) with a mean improvement observed at Week 4 of -0.13 +/- 0.45 (MDD), -0.17 +/- 0.4 (BP) and -0.3 +/- 0.6 (D) respectively. On a Visual Analogue Scale for acceptability of treatment, all diagnostic groups favourably rated orally disintegrating risperidone tablets, with patients rating acceptability at 6.4/10 (MDD), 8.2/10 (BP) and 7/10 (D) respectively. The most frequent AE reported was headache.

Conclusions: Orally disintegrating risperidone tablets offer an alternative, well-tolerated method of drug delivery with no evidence of symptom decompensation when transitioned from the previous risperidone formulation.

Key words: *Depression, bipolar disorder, dementia*

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Long-term effectiveness of CONCERTA®: 6 and 8 month analyses in children with attention deficit hyperactivity disorder (ADHD)

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Objective: To determine whether symptomatic remission/overall improvement experienced in an 8 week, open label effectiveness trial with once daily OROS™ methylphenidate (Concerta™) in ADHD children is maintained in the longer-term.

Method: N=109 with DSM-IV diagnosed ADHD (based on KSADS and clinical interview). Children who completed a previous 8 week, open label study randomizing patients to Concerta™or IR-MPH could participate in a 6 month, open label extension trial. At the beginning of this 6 month study, children could continue taking the medication they were randomized to in the 8 week trial or switch to the other treatment arm. The results reported here represent 2 cohorts, as follows: i) 6 month extension study only, ii) combined 8 week and 6 month studies=8months of ongoing Concerta™ treatment.

Results: For cohort i) N=109. 54/109 patients continued on Concerta™CON/CON group) and N=55 switched to Concerta™ from IR-MPH(IR-MPH/CON group). Remission, the primary outcome measure, was defined as a score<=1on each item of the 18 item SNAP-IV assessment. At Month 6, 52%(CON/CON) and 30%(IR-MPH/CON) met criteria for remission of ADHD symptoms. For cohort ii) N=54 patients continued on Concerta™ treatment. Remission was maintained over 8 months, at every time point measured, in 29% of patients with continuing Concerta™ treatment. Mean change in total SNAP-IV-26 item score(ADHD + ODD sub-items) continued to reflect statistically significant symptom improvement at every time point measured including endpoint($p<0.0001$).

Conclusions: These data suggest continuing treatment with once daily OROS™ methylphenidate (Concerta™ offers sustained symptom control in the longer-term treatment of children with ADHD.

Keywords: *Attention deficit hyperactivity disorder, OROS™, methylphenidate*

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The efficacy and tolerability of initiating Concerta® treatment in children with attention deficit hyperactivity disorder (ADHD)

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Funding Source: Janssen-Ortho Inc.

Background: CONCERTA™ was developed to overcome dosing limitations of immediate release and inconsistent efficacy noted with slow release methylphenidate. Once-daily CONCERTA™maintains efficacy over 12 hours and minimizes compliance problems by eliminating the stigma associated with in-school dosing.

Objective: To evaluate efficacy/tolerability of initiating CONCERTA™ in drug naïve ADHD children or those not currently taking ADHD medications.

Methods: Children 6 – 12 years with an ADHD DSM-IV diagnosis of any subtype who were drug naïve or not on medications for a 4 week minimum pre-study and a baseline CGI-Severity score of at least "moderate" illness (CGI-S >= 4), necessitating pharmacotherapy treatment, were enrolled. Patients began on 18 mg CONCERTA™ for 1 week. Stepwise titration, based on clinician's discretion regarding response/tolerability occurred weekly thereafter (to 36 mg followed by 54 mg if necessary). Patients were assessed weekly for symptom reduction and tolerability.

Results: N=47 patients enrolled (77% male, 23% female) with the majority of combined sub-type (57.5%) and mean age of 8.4 +/- 2.3 years. Mean baseline CGI-S score = 4.9 +/- 0.9. At Day 28/final visit, an improvement in CGI-S score was noted (–2.4 +/- 1.3 points) and an improvement in total score on the 18 item SNAP-IV (-21.7 +/- 10.7 points). The most commonly reported adverse events were insomnia (12.5%), abdominal pain (7.5%), decreased appetite (5%), and irritability (5%).

Conclusions: Initiating ADHD treatment with CONCERTA™ in drug naïve patients or those not currently taking ADHD medications is efficacious and well tolerated.

Keywords: *Attention deficit hyperactivity disorder, CONCERTA™, children*

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Cocaine detection in maternal and neonatal hair

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Background: Cocaine use during pregnancy is difficult to ascertain. Although the extent of the risk is controversial, fetal exposure is potentially damaging. Cocaine and its metabolite benzoylecgonine accumulate and can be detected months after exposure in maternal and neonatal hair.

Methods: We developed a hair immunoassay for cocaine and benzoylecgonine at Motherisk laboratory in Toronto. The aim of the study was to find evidence of cocaine exposure during pregnancy using hair measurements, and the relationship between maternal and fetal exposures.

Results: We identified 110 mother-child pairs who had cocaine and/or benzoylecgonine positive hair. Mean cocaine concentrations in hair was 12.92 ng/mg in the mothers and 1.96 nm/mg in the neonates ($p<0.001$). Mean benzoylecgonine values were 3.74 ng/mg in the mothers and 1.05 ng/mg in the babies ($p<0.001$). Forty-two (38.2%) babies had negative cocaine and benzoylecgonine results even though their mothers were positive. None of the pairs identified included mothers with negative results. Sensitivity of the test for maternal use of cocaine using neonatal hair was 61.8% (95% CI 51% – 70%).Neonatal cocaine and benzoylecgonine concentrations in hair were significantly correlated with maternal cocaine and benzoylecgonine concentrations ($P<0.001$ for all comparisons).

Conclusions: Fetal hair grows in the last trimester. A positive result in the neonate's hair may indicate maternal use after pregnancy became known and therefore maternal addiction. Transplacental exposure to cocaine of babies of addicted mothers seems extensive. The significant dose response relationship between maternal and neonatal hair cocaine suggests that neonatal hair may predict maternal dose of cocaine.

Keywords: *Drugs of abuse, placenta, fetal toxicology*

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Mass spectrometry versus flame ionization detection of meconium fatty acid ethyl esters in the context of neonatal screening for fetal alcohol exposure

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Background: The analysis of fatty acid ethyl esters (FAEE) in meconium as a biomarker for prenatal ethanol exposure has emerged as a novel approach to neonatal screening with the ultimate goal of early detection and intervention of individuals at risk for Fetal Alcohol Spectrum Disorder (FASD). FAEE meconium analysis was applied to a large population-based neonatal sample to assess its effectiveness as a neonatal screening tool.

Methods: FAEE were extracted from meconium by liquid-liquid and solid-phase extraction and analyzed by GC-FID. Fifty samples were confirmed by GC-MS. Ethyl palmitate, ethyl palmitolate, ethyl stearate, ethyl oleate, ethyl linolate, ethyl linolenate, and ethyl arachidonate were measured.

Results: GCMS confirmation demonstrated no false negative analyses and confirmed the presence of FAEE in 18 of 37 samples. GC-FID analysis followed by GC-MS confirmation exhibited a sensitivity of 100% and specificity of 96.99% in the entire study population for the determination of FAEE concentrations above the established baseline of 2.0 nmol/g cumulative FAEE. GC-FID exhibited the highest sensitivities for the detection of ethyl palmitate and ethyl linolate (100%). Ethyl palmitoleate displayed the lowest sensitivity (66.67%). The highest specificity was shown for ethyl linolenate (92.86%). The GC-FID method exhibited the lowest specificities (~60%) for the detection of ethyl linolate and ethyl arachidonate.

Conclusions: GC-FID is a highly sensitive method, suitable for primary screening of FAEE in meconium. Due to the lower specificity of this method, subsequent GC-MS analysis should be conducted in order to confirm the presence of meconium FAEE in positive samples.

Keywords: *Meconium, FAEE, alcohol*

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A meta-analysis of prenatal multivitamin supplementation and the rates of congenital anomalies

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Background: Folic acid supplementation prior to and during pregnancy is associated with a decreased risk of neural tube defects. Several studies have suggested that folic acid-fortified multivitamins are also effective in preventing other birth defects. To date this association has not been systematically examined.

Objective: A systematic review and meta-analysis was conducted to evaluate the effect of prenatal supplementation with folic acid-fortified multivitamins on congenital anomalies.

Methods: Studies published in all languages from 1966-July 2005 were identified by searching Medline, PubMed, EMBASE, Toxline, Healthstar, Cochrane databases, and reviewing the references from all collected articles. Two blinded, independent reviewers extracted data using predetermined inclusion and exclusion criterion. Rates of congenital anomalies in babies born to multivitamin supplemented women were compared with a control group of unsupplemented women using a random effects model.

Results: Forty-two of the ninety-two articles collected met the inclusion criteria. Supplementation resulted in a decreased risk for neural tube defect (OR=0.64, CI 95%=0.56-0.73), cleft palate (OR=0.74, CI 95%=0.61-0.91), oral cleft with/out palate (OR=0.63, CI 95%=0.54-0.73), urinary tract anomalies (OR=0.48, CI 95%=0.31-0.74), cardiovascular defects (OR=0.74, CI 95%=0.66-0.84), limb defects (OR=0.52, CI 95%=0.35-0.76), congenital hydrocephalus (OR=0.36, CI 95%=0.24-0.54), and gastrointestinal abnormalities (OR=0.43, CI 95%=0.19-0.98).

Conclusions: Prenatal multivitamin supplementation is associated with a decreased risk of several congenital anomalies including neural tube defects. In light of these findings and its health implication, a new approach should be adopted. Pregnant women should use a folic acid fortified prenatal multivitamin rather than just folic acid.

Keywords: *Prenatal multivitamins, congenital anomalies, meta-analysis*

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Fatal toxicity in a breastfed infant of a codeine using mother

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Funding Source: CIHR

Background: Thousands of Canadian women breastfeed while on codeine, prescribed for pain post caesarian section or epiphysiotomy. The drug is labeled as "compatible with breastfeeding" by the American Academy of Pediatrics. Patients who are ultra-rapid 2D6 metabolizers may experience life-threatening toxicity due to over production of morphine.

Methods: A full term healthy male infant, delivered vaginally, exhibited from potential day 7 intermittent periods of difficulty in breastfeeding and lethargy. At Day 13 he exhibited grey skin and decreased milk intake. Subsequently, he was found dead.

Results: Postmortem analysis showed no anatomical anomalies and blood morphine concentration of 70 ng/mL by GC/MS. Neonates breastfed by mothers receiving codeine-typically have morphine serum concentrations of 0-2.2 ng/mL(2). The mother was prescribed Tylenol 3 (codeine 30 mg and acetaminophen 500 mg) after birth for severe epiphysiotomy pain (initially 2 tab. 6 hourly and half the dose from Day 7 due to somnolence and constipation). She continued codeine for two weeks. Due to poor neonatal feeding, she stored milk at postnatal day 13 which was measured for morphine by specific ELISA and GC/MS at 86 ng/mL. Typical milk levels after repeated maternal codeine range from 1.9 to 20.5 ng/mL at doses of 60 mg q6H. Genotype analysis was conducted for cytochrome P450 2D6 (CYP2D6), the enzyme catalyzing the O-demethylation of codeine to morphine(3). The mother was heterozygous for a CYP2D6*2A allele with CYP2D6*2x2 gene duplication, classified as an ultra-rapid metabolizer. This genotype leads to enhanced formation of morphine from codeine, consistent with the somnolence and constipation experienced by her(4). Both the father and infant possessed two functional CYP2D6 alleles(CYP2D6*1/*2 genotypes).

Conclusions: The clinical and toxicological picture in this case is consistent with opioid toxicity leading to neonatal death. The high milk levels of morphine, (86 ng/mL) corroborate the clinical picture in the infant. Milk was available only at half codeine dose; conceivably peak milk concentration of morphine was higher.Our case reveals that polymorphism in CYP2D6 may be life threatening for some breastfed babies. Given that a CYP2D6 ultra-rapid metabolizer genotype occurs in 1% in Caucasians and up to 30% in some parts of Asia and Africa(5), this polymorphismis clinically important. Several clinical approaches may be considered: Informing mothers on potential toxicity, monitoring the mother and baby for signs of opioid toxicity, limiting codeine dose, duration and genotyping for CYP2D6 to identify ultra rapid metabolizers (Table). This is the first record of a breastfed baby succumbing to toxicity through breastmilk.

Keywords: *Codeine, breastfeeding, opioid toxicity*

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Topiramate-induced weight loss in schizophrenia: A case series

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Funding Source: None

Background: Obesity is more prevalent in schizophrenia than the general population. Weight gain is a common side effect of antipsychotic treatment. Excessive body weight may lead to de novo or worsening medical comorbidity and can have severe consequences in patients with schizophrenia. Excessive weight gain may also lead to non-compliance with pharmacological treatment. Case reports suggest that topiramate can help reduce weight. This study sought to determine if topiramate's effects on antipsychotic-induced weight gain in patients with schizophrenia and schizoaffective disorder could be replicated in a larger case series over longer treatment duration.

Methods: 10 patients from our 300-outpatient schizophrenia clinic were identified as topiramate-treated. Body Mass Index (BMI) before and after topiramate was compared using a paired t-test. Pearson correlations between BMI difference (BMI-d) and age, as well as between BMI-d and topiramate dose, were calculated.

Results: BMI significantly decreased after topiramate treatment (p=0.005; mean BMI-d =3.2, 95% CI= 1.3-5.1), with 9/10 patients demonstrating weight reduction. Patients treated for >6 months had significantly greater reduction in BMIs than those treated for shorter periods (BMI-d>6months = 5.1 ± 2.4; BMI-d<6months = 1.2 ± 2.3; p= 0.015).

Conclusions: Topiramate significantly reduced antipsychotic-induced weight gain in this case series. Furthermore, topiramate's efficacy appears to increase with longer durations of treatment suggesting both a continued and sustained response. A placebo-controlled trial with a larger sample is needed to corroborate these findings.

Keywords: *Schizophrenia, weight gain, topiramate*

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Acceptability and potential for use of complementary and alternative medicine in children with cancer

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Background: No previous studies have examined attitudes of Canadian paediatric haematologist-oncologists (PaedH-Os) towards complementary and alternative medicine (CAM) use in patients, and CAM research. Our objective was to determine extent of use of CAM in PaedH-Os and their patients, to explore attitudes of PaedH-Os towards CAM use and research, and to elucidate concerns about participating in CAM research.

Methods: A mailed survey was sent to 89 PaedH-Os in Canada.

Results: There were 63 responders (71% response rate), of which 59 were practicing PaedH-Os. Thirty-seven % had used CAM and 93.2% reported that their patients had or were receiving CAM, most commonly naturopathic (79.7%) and homeopathic (55.9%) medicine. Only 1.7% of physicians were very opposed to CAM use in their patients, and 39.0% were neither supportive nor opposed. Physicians who knew friends, coworkers or relatives who had used CAM with successful results were more likely to be supportive or somewhat supportive of CAM use (P=0.039), and were more likely to advise patients to use CAM (P=0.009). Physicians who used CAM were more likely to advise patients to use CAM (P=0). Prior to participating in CAM research, physicians wanted information on possible interactions with chemotherapy or other drugs, beneficial and adverse effects, cost, mode of administration and taste, and worried about drug interactions, adverse effects, and cost.

Conclusions: CAM use is common among Canadian paediatric cancer patients, as perceived by PaedH-Os. Prior to supporting participation in CAM research, most physicians expressed the need for rigorous RCTs on the specific CAM in question.

Keywords: *Complementary and alternate medicine, cancer, paediatrics*

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Neuroprotection from Parkinson's disease by nicotine and smoking; a role for brain CYP2D6

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Background: CYP2D6 is an enzyme that metabolizes a number of clinically used centrally acting drugs such as antidepressants, opioids and endogenous neural compounds (e.g. catecholamines). There is evidence suggesting a link between the expression of certain forms of CYPs and toxin-induced Parkinson's Disease (PD). For example, reduced expression of CYP2D6 has been shown to increase the risk for PD. CYP2D6 is able to detoxify compounds, such as MPTP, that create reactive oxygen species that contribute to the development of PD. Neuroprotective effects of smoking are also well documented for PD; smokers are 50% less likely to develop the disease. The protective mechanisms are unclear but may involve receptor and enzyme alterations. As CYP2D6 can deactivate many PD causing neurotoxins, we hypothesized that the neuroprotective effects of smoking against PD are mediated in part by increased CYP2D6 in the brain.
Results: Here we show that CYP2D6 levels are elevated in most brain regions of human smokers, including substantia nigra, a region affected by PD. We also show that in African Green monkeys, chronic nicotine treatment (0.3 mg/kg bid., s.c, 18 days) increases CYP2D in brain regions such as cerebellum (1.3-fold, $p<0.02$) and frontal cortex (1.7-fold, $p<0.001$).
Conclusions: These findings suggest that nicotine is a component of cigarette smoke that may contribute to neuroprotection against PD, through induction of the protective metabolic actions of CYP2D6. Supported by CIHR MOP14173, CAMH, CRC.
Keywords: *Nicotine, Parkinson's disease, brain CYP2D6*

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ENCORE PRESENTATION

Drug ordering in pediatric critical care: A prospective, observational study

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Valproic acid is a major human teratogen: Systematic review and meta-analysis

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Background: Scientific reports on major congenital malformation (MCM) rates in neonates exposed to valproic acid (VPA) in utero are not consistent. The aim of this study was to ascertain the rates of MCM in children exposedto VPA using meta-analysis.
Methods: Medline, EMBASE and Cochrane databases were searched for all relevant articles until December 2005. Controlled cohort studies reporting on the use of VPA during the first trimester of pregnancy were selected if they had at least one of the following comparison groups: women treated with other antiepileptic drugs, women with untreated epilepsy, or healthy pregnant women who represented the general population. To be included, the studies also had to describe rates of MCM within the study and comparison groups. Relative risks (RR) were calculated using the Mantel-Haenszel random effect method.
Results: Eleven studies of exposed babies (n=1,740) were analyzed. A RR of 2.6 (95% CI 2.11-3.17) for MCM was associated with VPA monotherapy when compared to other antiepileptic drug monotherapies. Eight studies n=1,351) of VPA monotherapy versus untreated epilepsy showed a RR of 3.2 (95%CI 2.2 to 4.6) for MCM. Three studies (n=185) of VPA monotherapy versus healthy controls resulted in a RR of 3.77 (95% CI 2.18-6.52) for MCM. When comparing VPA polytherapy to other antiepileptic drug polytherapies, untreated epilepsy, or healthy controls, a RR of 1.8 (95%CI 1.3-2.5), 3.2 (95%CI 2.1-5.1) and 3.4 (95%CI 1.9-6.0) respectively, was found.
Conclusions: VPA is associated with a 3-fold increase of MCM above the general population when used in early pregnancy.
Keywords: *Antiepileptic drugs, drug-induced abnormalities, valproic acid*

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Minimizing the adverse events of multivitamin supplementation of pregnant women

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Background: Periconceptional and prenatal multivitamin supplementation improves pregnancy outcome, particularly reducing the risk of neural tube defects and potentially other malformations. Many pregnant women experience adverse events due to the high iron dose and large tablet size of common multivitamins. PregVit®, a different type of prenatal multivitamin, has a lower iron dose and smaller tablet size. We want to determine if compliance is improved and adverse events are minimized among pregnant women taking PregVit® compared to those taking a standard prenatal multivitamin, Orifer F®.

Method: Consenting pregnant women, who contacted the Motherisk program and who did not start or discontinued any type of multivitamins, were randomized to try either Orifer F® or PregVit®. Upon enrolment, medical and baseline information were recorded. Participants were interviewed monthly until the end of their pregnancy to document vitamin intake, adverse events, and changes in health.

Results: Since October 2004, 160 pregnant women were enrolled in the study. 72 were randomized to take Orifer F® and 88 were randomized to take PregVit®. Around 50% of participants discontinued Materna® or a generic version prior to enrolling in the study. Preliminary analysis shows that compliance rates for either Orifer F® or PregVit® ranges from 40-60%. Commonly reported adverse events for both supplements are nausea, vomiting, and constipation, although the severity varies.

Conclusions: The current data suggests that PregVit® and Orifer F® are equivalent in rates of compliance and adverse events, although improving compliance and adverse events also requires discussing with women ways to comfortably incorporate multivitamin supplementation into their prenatal care.

Keywords: *Prenatal multivitamins, tolerability*

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Child neurodevelopment following in utero exposure to venlafaxine, unexposed siblings as comparison groups: Preliminary results

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Background: Venlafaxine (VLF) is widely used to control depression in women of childbearing age. VLF crosses the placenta, and its possible adverse effect on fetal CNS development has not been studied. The present study will fill the knowledge gap on long-term VLF safety following in utero exposure.

Objective: To assess long term neurodevelopment of children exposed to VLF during gestation.

Methods: Prospective, controlled, matched, blinded cohort. Assessment of 5 groups of mother-child pairs: exposed to VLF (n=41), exposed to other antidepressants (n=37), healthy controls (n=30), and 2 groups of siblings not exposed to antidepressants (n=15). Primary outcome: WPPSI-III Scales of Intelligence. This outcome will be compared with those of children in control groups and their non-exposed siblings.

Results: There were no differences between the groups in maternal physical characteristics, child physical characteristics, maternal IQ or SES. There were no significant differences in Full Scale IQ between the 2 groups of children exposed to antidepressants (104+13 vs.103+10) and their non-exposed siblings (101+9 vs. 103+8). Full Scale IQ of healthy controls was significantly higher (113+12) than in all 4 other groups (P= 0.007). Children of healthy parents achieved significantly higher on Verbal IQ (P=0.014), Performance IQ (P=0.043) and PLS scores (P=0.05).

Conclusions: Exposure to VLF does not adversely affect cognitive development of preschool children. VLF, if indicated, should be used to prevent postpartum depression. The inclusion of siblings in this study helps to verify the impact of genetic and environmental factors and is possibly the strongest evidence of VLF safety.

Keywords: *Venlafaxine, pregnancy, child development*

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Use of novel redox sensitive green fluorescent proteins to measure changes in intracellular redox status following treatment of cells with unconjugated bilirubin

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Background: Deposition of unconjugated bilirubin (UCB), the end product of heme catabolism, in the central nervous system causes kernicterus in some severely jaundiced neonates. The molecular mechanisms that contribute to UCB toxicity remain unknown, however, at elevated concentrations UCB has been shown to be pro-oxidant.

Objectives: To employ novel, mutated, redox sensitive, green fluorescent proteins (roGFP2) to measure time- and concentration-dependent changes in the intracellular redox status of murine hepatoma cells mediated by treatment with UCB.

Methods: Hepa 1c1c7 cells expressing roGFP2 were exposed to elevated concentrations (10-50 ìM) of UCB. roGFPs can form a reversible, intramolecular disulphide bond between two introduced cysteine residues near the chromophore of the GFP under oxidizing conditions. Formation of an intramolecular disulphide alters the excitation properties of the fluorescent molecule. Changes in roGFP fluorescence were assayed by confocal microscopy.

Results: In the present study, treatment with 50 µM UCB resulted in a biphasic change in intracellular redox status characterized by an early reduction of the intracellular compartment, peaking at 2 h followed by significant oxidation from 3 to 4.5 h. By 6 h adherent cells were starting to rebound. Treatment with 10 µM UCB resulted in a similar biphasic change in redox status, however the observed oxidation was less severe.

Conclusions: These results demonstrate that elevated concentrations of UCB cause a concentration- and time-dependent decrease in intracellular redox status in murine hepatoma cells. These results also demonstrate the use of roGFPs as novel indicators of intracellular redox status in intact mammalian cells treated with the mitochondrial toxin, UCB.

Keywords: *Oxidative stress, bilirubin, redox sensitive green fluorescent proteins*

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Longitudinal study of depression, anxiety, irritability and stress in pregnancy

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Background: Many women suffer from depression during pregnancy and must use antidepressant medication to treat this condition.

Objectives: This study sought to determine whether depression increased during pregnancy and the post-partum period despite treatment with antidepressant therapy; anxiety, irritability and stress were also followed throughout pregnancy.

Methods: Depressed women who were pregnant and taking antidepressant medication participated in four telephone interviews; one in each trimester and one in the post-partum period. Depression, anxiety, irritability and stress scales were completed at each call.

Results: 58 women enrolled in the study; 38 completed 75% of follow-ups. 14% of women stopped their medication at some point during the study. Depression scores were highest in the first trimester and decreased as pregnancy progressed. When all women irrespective of dose adjustments, were analyzed, a statistically significant difference existed between depression scores in the first trimester and third trimesters (mean ± SD = 7.6 ± 4.1 vs. 5.6 ± 3.4 respectively, p = 0.02). No differences in depression scores were found between remaining trimesters. Statistically significant differences in mean depression scores were found between the first trimester and postpartum for women remaining on the same dosage of medication during the study (6.7 ± 3.6 vs. 3.6 ± 3.0 respectively, p = 0.04). No significant differences found between remaining trimesters. No significant differences found in irritability, anxiety or stress scores during pregnancy.

Conclusion: When depressed women remain on antidepressant therapy during pregnancy their depression remains well controlled. Irritability, anxiety and stress remained at low levels throughout pregnancy.

Keywords: *Depression, pregnancy, antidepressants*

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Specialized follow-up of amiodarone therapy may increase success of atrial fibrillation therapy

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Background: Amiodarone is an inexpensive, highly effective therapy for atrial fibrillation. However, fear of potential adverse effects often leads avoidance or premature discontinuation of therapy. We hypothesized that follow-up by a clinician experienced in identifying true toxicity in combination with therapeutic drug monitoring to adjust dose and reduce adverse effects would increase therapeutic success.

Objective: Study differences in discontinuation and rates of success in maintaining sinus rhythm in two groups of patients randomized to care in a specialized outpatient clinic vs. standard care in the community.

Methods: Two groups consisted of: A-35 patients followed in the specialized clinic, coached and reinforced regarding the true risks and benefits of amiodarone and educated on how to avoid problems with the drug, regularly monitored ALT and fT4, and dose adjusted by therapeutic monitoring; B-36 patients followed in the community, given same initial education as Group A and their physicians provided with same suggested schedule for monitoring.

Results: Group A, 69% completed 2 years of follow-up vs. 44% Group B. No medication was stopped because of an objectively documented adverse effect of amiodarone in either group, but 17% had amiodarone stopped in A vs. 39% in B. Mean amiodarone dose of 235 + 65 mg/d achieved serum concentrations in an effective range with evidence for reduced toxicity (0.75 to 1.5 mg/L). All patients remaining on amiodarone achieved control without toxicity (92% sinus 8% rate). Median baseline ALT=24 and fT4=15.7 unchanged at 24 months.

Conclusions: Difference between clinic management and community management appears to be ability to coach patients through uncertainties concerning amiodarone and adjust medication for efficacy and toxicity avoidance. Relative risk of stopping amiodarone was 2.3 for community care vs clinic care patient (p = 0.037, Chi-square). Preliminary results suggest potential to reduce toxicity and improve care of atrial fibrillation.

Keywords: *Amiodarone, atrial fibrillation, education, adverse events*

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Pediatric neurocognitive development following in utero exposure to labetolol

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Background: Hypertensive disorders in pregnancy require pharmacotherapy to prevent target organ damage. Selection of anti-hypertensive drugs in pregnancy is limited due to the risk of teratogenicity. Methyldopa remains the treatment of choice in pregnant women, although many clinicians prefer labetolol. For both drugs there are no long-term neurodevelopmental studies.

Objectives: To evaluate the neurodevelomental outcomes of children following in utero exposure to labetolol, as compared to 2 controls groups; methyldopa-exposed or a non-teratogen group.

Methods: Observational cohort study of children with at least 3 weeks of in utero exposure to either labetolol, methyldopa or, an agent without known teratogenic effect. All children were identified through one of two sources:1) The Obstetrical Medicine Clinic at Women's College Hospital, and 2) The Motherisk Program at Hospital for Sick Children using records of women previously counseled, between January 1996 and July 2001. In total 32 children of labetolol, 27 of methyldopa and 57 in controls were tested.

Results: There were no significant differences in Full Scale and Performance IQ between children exposed to labetolol and healthy controls (110±9; 112±11 and 106±10; 109±13) respectively. However, children exposed to methyldopa achieved significantly lower on Full Scale and Performance IQ (106±12 and 99±15) P¨T 0.038. Regression analysis revealed that maternal IQ was a significant predictor (P¨T0.019) of child Full Scale IQ measured with WPPSI & WISC tests. Analysis is in progress.

Conclusions: Exposure to labetolol does not adversely affect cognitive development of preschool children. Labetolol if indicated can be used to control maternal hypertension.

Keywords: *Labetolol, child development, methyldopa*

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Morphine and tetracaine for pain in neonates undergoing central line placement

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Funding Source: Canadian Society of Hospital Pharmacists, Restracomp, CIHR
Background: Systemic analgesia and local anesthesia have been recommended to manage procedural pain in hospitalized newborn infants without sufficient clinical investigation. The objectives were to determine the effectiveness and safety of tetracaine, morphine, and morphine plus tetracaine for alleviating pain duringpercutaneous central venous catheter (PCVC) placement.
Methods: Randomized controlled trial in ventilated neonates undergoing PCVC insertion. A separate group of neonates that received no analgesia served as a control group. Prior to PCVC insertion, randomized infants received tetracaine, morphine, or morphine plus tetracaine. Facial grimacing (brow bulge), heart rate, and oxygen saturation responses were monitored during the procedure. In randomized infants, blood pressure, ventilatory support, and ocal skin reactions were monitored during and after the procedure.
Results: There were 132 participants; mean gestational age at time of study was 30.6 weeks (SD=4.6) and 57% were male. Facial grimacing and heart rate differed among the 4 study groups ($p<0.001$). The sequence in neonatal pain response was: no analgesia > tetracaine > morphine > morphine plus tetracaine. Compared to infants without morphine, infants given morphine required larger increases in ventilation rate in the first 12 hours after the procedure ($p=0.012$). They did not differ, however, in blood pressure ($p=0.215$), frequency of hypotension ($p=0.45$), and oxygen requirements ($p=0.105$). Local skin reactions occurred in 30% of infants treated with tetracaine compared to 0% of those treated with placebo-tetracaine ($p<0.001$).
Conclusions: Morphine alone or morphine plus tetracaine are superior to tetracaine alone and no analgesia for decreasing pain from PCVC placement in ventilated neonates.
Keywords: *Tetracaine, morphine, pain management*

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How do pediatricians manage immunization pain?

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Funding Source: Canadian Pain Society
Background: Routine immunizations are the most common source of iatrogenic pain in healthy children. Previous studies have demonstrated that needle poke pain is effectively managed with topical anesthetic agents whereas post-immunization pain is best managed with oral analgesics. To date, the frequency of utilization of specific interventions in clinical practice has not been investigated. The objective was to assess pediatricians' practices regarding analgesic use to prevent needle poke pain and post-injection pain.
Methods: Self-administered mailed survey of pediatricians in the Toronto area (Ontario, Canada) who administer immunizations.
Results: 70% (138/197) of eligible pediatricians responded: 68.9% were male; the median duration of practice was 18.5 years. Analgesics were 'rarely' or 'never' used to relieve pain during the needle poke in 57.9% and when used, 80.2% and 45.5% of the respondents used acetaminophen and ibuprofen, respectively. Lidocaine-prilocaine and tetracaine were used by 12.1% and 2% of respondents, respectively. Non-pharmacologic methods of reducing pain during the needle poke were reported by 96% of pediatricians. Post-immunization pain was managed with either acetaminophen or ibuprofen by 88.8% of respondents.
Conclusions: The use of analgesics for post-immunization pain has been well integrated into clinical practice by pediatricians. In contrast, topical anesthetics remain underutilized for managing pain during the needle poke. Non-pharmacologic interventions during needle poke are utilized by almost all pediatricians. Knowledge translation strategies designed to increase the utilization of topical anesthesia for injection pain are recommended.
Keywords: *Infant/child, pain management, immunizations*

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Paediatric labeling in drug monographs contained in the Canadian compendium of pharmaceuticals and specialties

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Background: It has been suggested that the therapeutic needs of children are not well served by drug licensing regulations. We evaluated the information in drug monographs contained in the 2005 Canadian Compendium of Pharmaceuticals and Specialties (CPS).

Objective: To describe the indications, pediatric safety data, and availability of pediatric formulations in the 2005 CPS.

Methods: Detailed drug monographs in the 2005 electronic CPS were identified and included in the study. We abstracted information about indications, safety, drug-associated fatalities, and preparations for patients <18 years. Data was gathered from the indications, warnings, precautions, adverse effects, dosage and supplied sections of each monograph.

Results: 1548 detailed monographs were studied; 87% of indications did not exclude children. Paediatric safety information was absent in 808(52%) drugs, not established in 567(37%) drugs, limited in 148(10%) drugs, and established in 25(2%) drugs. Drug-associated fatalities in adults were described in 570(37%) monographs; 213(37%) had an absence of paediatric safety information vs. 595(61%) of monographs not describing a fatal harm ($p<0.0001$). Oral-liquid or parenteral preparations that could be administered to children were listed in 514(37%) monographs; 222(43%) had dosing guidelines that could be used in children despite absent paediatric safety information.

Conclusions: The legal documentation of licensed drugs in Canada is selective. The indications for prescription were broad and inclusive, and pediatric compatible preparations plus dosing information were provided for many drugs. In marked contrast, paediatric safety information was absent in more than half of the monographs. In summary, the 2005 CPS does not appear to be meeting the pharmacotherapeutic needs of children.

Key words: *CPS, monographs, labeling*

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PK/PD study of the effects of midodrine on blood pressure, the autonomic nervous system, and plasma natriuretic peptides

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Funding Source: FRSQ

Background: Midodrine is an alpha agonist pro-drug of desglymidodrine (DGM) that has been shown to be of clinical benefit in patients with neurocardiogenic syncope. Its effects may be mediated by its hypertensive properties but also by its neurohumoral influences. The present study aims to simultaneously characterize the effects of midodrine on blood pressure, sympathovagal balance, and plasma ANP in healthy volunteers.

Methods: This study is a prospective, randomized, placebo-controlled, simple-blind, 2-period crossover study of single dose midodrine 5 mg. The wash out period between placebo and midodrine was 1 week long. Study days involved 12 measurements of all parameters before and over 8 hours after drug administration. Measured parameters were plasma DGM, systolic and diastolic blood pressure, heart rate, plasma catecholamines, and plasma ANP.

Results: Fifteen male subjects were randomized. No treatment effect was found at each measurement time nor for 8-hour averaged results. A treatment effect was found at maximal DGM concentration for norepinephrine ($p=0.011$) and heart rate ($p=0.022$) but not for ANP and blood pressure. A significant correlation was found between DGM concentration and heart rate ($\tilde{n}=0.61$, $p=0.014$).

Conclusions: Midodrine has sympatholytic influences that appear to be independent of its arterial and venous vasoconstrictive properties. These effects could explain clinical benefits without increase in blood pressure.

Keywords: *Clinical pharmacology, midodrine, orthostatic hypotension*

CSCP POSTER PRESENTATIONS
Thursday May 11, 2006

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Exploring potential biases that may contribute to discordant results of clinical studies on receptor genetic polymorphism of the rennin-angiotensin-aldosterone system (RAAS)

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Background: Although several candidate genes of RAAS relating to pharmacokinetic and pharmacodynamic effects upon ACE-I and ARBs have been investigated, the drug gene relationship remains unclear.

Objective: To appraise the elements of research methodology and explore potential biases which may be contributing to discordant results in the gene-drug interaction assessment for RAAS.

Method: Systematic review of studies involving candidate polymorphisms, searching PubMed and EMBASE and reference citations.

Results: Sixteen studies were identified. Nine studies had a genomic evaluation as the primary question. Six studies investigated more than one gene. A gene-drug interaction was evaluated in two studies and only one of the studies had a placebo arm for accurately exploring the interaction. 87.5% of the studies explored the gene-effect only in the drug users. 87.5% of the studies had sample sizes of less than 500 patients. 4 studies combined the allele frequencies of the heterozygotes group with one of the homozygotes groups. 26% of the studies combined different therapeutics in one group. 5 studies included patients in one group from previous studies in which selection criteria were not quite similar. Only one study used the hard endpoint; the others measured various surrogate endpoints.

Conclusions: Most studies contain several methodological limitations including candidate genes approach, population admixture, sample size issues, multiple comparisons. They also included biases driven from patient selection, combining alleles frequencies, combining different therapeutics and the selected end-point. These limitations and biases may contribute to inconsistency of the results of these studies.

Keywords: *Pharmacogenomics, renin-angiotensin-aldosterone system, clinical studies*

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ENCORE PRESENTATION

Probing the brain reward system in co-morbid major depressive disorder and alcohol dependence

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Funding Source: Internal Source

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Association of DRD2 gene taqi polymorphism with schizophrenia in an Iranian population

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Background: D2 dopamine receptor (DRD2) gene has been reported to be one of the most relevant candidate genes in schizophrenia. In this study we investigated the association between TaqI A and TaqIB dopamine D2 receptor polymorphisms and psychopathology of schizophrenia.

Methods: The study subjects were 38 acutely exacerbated schizophrenic patients who were all Iranian descent. Control population consisted of 63 healthy individual within the same range of age as patients. The TaqIA and TaqI B genotypes, the A1 and A2 alleles and, the B1 and B2 were determined by Restriction Fragment Length Polymorphism (RFLP) of the amplified DNA fragments by Polymerase Chain Reaction (PCR). For each polymorphism (A or B) the patients were divided into three genotype groups; i.e., the patients with A1/A1 allele (n=3), B1/B1 (n=2); those with A1/A2 allele (n=39), B1/B2 (n=20); and those with A2/A2 allele (n=21), B2/B2 (41)

Results: We found a relatively higher frequency of the A1/A1 genotype and A1 allele in women subjects with schizophrenia compared to men subjects and unaffected controls. These differences were not observed between controls and patients in male subjects.

Conclusions: A significant association between DRD2 gene TaqI polymorphism with schizophrenia in women patients was observed.

Keywords: *DRD2 gene, schizophrenia, polymorphism, human, TaqI*

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The potential role of oxidant stress in the involvement of apoptosis in Jurkat cells induced by sulphamethoxazole hydroxylamine

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Background: Adverse Drug Reactions (ADRs) have been implicated as a major cause of morbidity and mortality associated with drug therapy. Although, the precise mechanisms of ADRs are unclear, it has been proposed that drug metabolism is a critical determinant. SMX is frequently used as a model drug for the study of ADRs due to the high incidence of ADRs.

Objectives: The first objective was to identify the cause of cell death mediated by treatment with differential concentrations sulphamethoxazole hydroxylamine (SMX-HA) and its mechanism of action. Accordingly, the next objective was to provide supporting data implicating role of apoptosis as the mechanism of cell death induced by SMX-HA treatment.

Methods: Exposure of Jurkat E6.1 cells to increasing concentrations of SMX-HA (200, 400, 600 and 800 μM) and subsequently stained 2', 7' dichlorfluorescein-diactate (DCFH-DA) to quantify the production of reactive oxygen species (ROS). To confirm the contribution of apoptosis in SMX-HA-mediated cell death, the detection of cytochrome-c release and caspase-3 activation by western blot analysis was employed.

Results: The formation of ROS in Jurkat cells treated with SMX-HA increased in a time-and concentration-dependent manner ($p<0.05$). Furthermore, SMX-HA-treated Jurkat cells demonstrated a translocation of cytochrome c from the mitochondrial fraction into the cytosolic fraction and a proportional depletion of the intensity of the procaspase-3 band was observed, however, activated caspase-3 was not detected.

Conclusions: The mechanism of cell death appears to involve apoptosis triggered by the production of ROS following SMX-HA treatment. However, the data suggests a caspase-independent apoptotic pathway involved in SMX-HA toxicity.

Keywords: *Sulphamethoxazole hydroxylamine, adverse drug reactions, apoptosis*

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Homocysteine metabolism in end-state renal disease using peripheral blood mononuclear cells as a model

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Background: Homocysteine (Hcy) a ubiquitous thiol amino acid, is an independent risk factor for atherosclerosis and thrombosis. Over 85% of patients with end-stage renal disease (ESRD) have vitamin-resistant hyperhomocysteinemia (tHcy ≥ 15 μmol/L). Despite its prevalence the mechanism by which Hcy remains elevated is elusive and controversial. We hypothesized that export of Hcy from cells is increased in ESRD either by increased methylation demand or decreased catabolism. Alternatively, whole body clearance may be inhibited. Export of Hcy was evaluated using PBMC as an in vitro model of complete Hcy metabolism.

Methods: PBMC isolated from five vitamin-replete ESRD patients and five healthy controls were cultured with mitogens and catechol-O-methyltransferase substrate, 3, 4-dihydroxybenzoic acid at 37°C for up to 72 hours. Intracellular Hcy production and export from PBMC were measured by HPLC-FD and normalized to protein concentration.

Results: The rate Hcy export remained linear between 12 and 72 hours. Intracellular Hcy levels are increased in uremic PBMC by 1.7 fold over controls. However, the rate of Hcy export from uremic PBMC was 63.9% lower than healthy controls.

Conclusions: The results of this study with PBMC are consistent with those of previous studies with erythrocytes. Stimulated PBMC of patients with ESRD export Hcy at a lower rate than controls, leaving Hcy elevated intracellularly. These results do not support the hypothesis that hyperhomocysteinemia in ESRD is due to elevated homocysteine export. This leads to the possibility that the accumulation of Hcy in ESRD may be due to a deficiency in whole body clearance.

Keywords: *Homocysteine, end-stage renal disease, peripheral blood mononuclear cells*

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ENCORE PRESENTATION

Methadone maintenance patients with comorbid major depressive disorder experience more negative opioid effects

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Effect or oral mesna (sodium2-mercaptoethanesulfonic acid) on plasma total homocysteine concentrations in healthy subjects

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Funding Source: CIHR / LHRI

Background: Elevated plasma total homocysteine (tHcy) is an independent risk factor for atherosclerosis. Water-soluble vitamins effectively normalize tHcy in most patients however, certain groups are refractory to this simple treatment and thus remain at high risk. Mesna is a thiol-containing drug normally used to prevent ifosfamide-induced hemorrhagic cystitis in cancer patients. A potentially beneficial side-effect of IV mesna infusion is a lowering of plasma cysteine and Hcy. The objective of this study was to determine if single oral doses of mesna can lowers plasma tHcy in healthy subjects.
Methods: Eleven subjects with normal kidney function were recruited to the study. After voiding urine and drinking a glass of orange juice (control), 2 X 5 mL blood samples were drawn for baseline tHcy and serum creatinine. Hcy and creatinine were then measured in plasma and urine over the next 2.5 hours to determine control Hcy clearance and excretion. For the treatment phase, subjects voided urine and a single, oral 10 mg/kg dose of mesna was given in juice. Hcy and creatinine measurements in plasma and urine were performed again at selected intervals post-mesna.
Results: Plasma tHcy decreased by 24.2% (P<0.0001) following oral mesna with no undesirable effects. Exretion of Hcy was significantly greater with mesna (3.9 +/- 2.4 ìmol) compared to vehicle control (0.4 +/- 0.1 µmol), P<0.01.
Conclusions: Oral mesna consistently decreases plasma tHcy by increasing its renal excretion. Although 10 mg/kg oral mesna transiently decreases plasma tHcy, an appropriate dosing schedule is required to achieve a sustained decrease.
Keywords: *Mesna, homocysteine, atherosclerosis*

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Novel method for detection of glyburide by HPLC UV detection in human plasma

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Background: Glyburide is a potent second generation sulfonylurea oral hypoglycemic agent used for the treatment of type II diabetes mellitus. However, recent advances in chromatography have rendered most previous methods obsolete and irreproducible given that the majority of the materials employed became unavailable.
Objectives: To develop a rapid, accurate, specific and sensitive UV HPLC assay with single step sample preparation of human plasma samples.
Method: Serum samples to which glyburide (100ng/ml) has been added as internal standard were treated with a chloroform liquid-liquid extraction. Following centrifugation, separation and reconstitution in mobile phase, the redissolved residue was eluted from a 3µm Luna C8 (2) reversed phase column at ambient temperature using a mobile phase consisting of acetonitrile-ammonium phosphate (55:45 v/v) at pH 5.26 and pumped at a flow rate of 1ml/min. The effluent was monitored at 254 nm and glyburide elution time is 6.3 min.
Results: A linear relationship between peak height ratio and concentration was obtained for the range of 5-400 ng/ml. A typical calibration curve has an excellent regression curve (r2 = 0.996). The detection limit of gluburide in serum is 5 ng/ml. Within day and between day coefficients of variation are 6% and 3% respectively. The lower limitof quantitation of glyburide was set at 10ng/ml.
Conclusions: This is a simple, rapid and sensitive method suitable for pharmacokinetic, bioavailability and bioequivalence studies.
Keywords: *Type II diabetes, glyburide, HPLC*

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Effect of ganoderma lucidum on cells of the immune system

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Background: Ganoderma lucidum (Ling-zhi, Reishi mushroom) has been used in Traditional Chinese Medicine for over 5000 years. It has been suggested that PSGL can be used as an adjunctive to chemotherapy in paediatric patients undergoing chemotherapy to enhance the immune system and decrease the risk of infections. We evaluated the proliferative effects and toxicities of three different extracts: PSGL, GL, and Reishi.
Objective: The objective of these experiments was to determine the toxicity and proliferative effects of PSGL, GL, and Reishi in Jurkat E6.1 cells and LG2 cells, and in peripheral blood nuclear cells (PBMCs) obtained from healthy adults, healthy children and children undergoing chemotherapy.
Methods: A thiazolyl blue tetrazolium bromide (MTT) toxicity assay was used to measure percent cell viability as compared to control. Cells were incubated with PSGL, GL or Reishi ranging from 1 µg/mL to 200 µg/mL for 24 hours and 48 hours. After overnight incubation, cell viability was assessed using a spectrophotometer. Statistical significance was assessed using a one-way analysis of variance followed by a Dunnett multiple comparison test ($p<0.05$).
Results: In general, low doses (1 - 10 µg/mL) of the three extracts resulted in increases in cell viability and higher doses (100 - 200 µg/mL) resulted in decreases in cell viability in Jurkat E6.1 cells and LG2 cells. In PBMCs obtained from healthy subjects, the PSGL extract appears to have the most immunostimulatory effect; whereas, in PBMCs obtained from children undergoing chemotherapy, the Reishi extract appears to be more immunostimulatory.
Conclusions: Extracts of Ganoderma lucidum may enhance proliferation of cells of the immune system; however, these same extracts may also cause toxicity.
Keywords: *Ganoderma lucidum, chemotherapy, MTT toxicity assay*

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Fetal exposure to alcohol in Uruguay as measured by fatty acid ethyl esters in medonium

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Background: High social tolerance to alcohol consumption and an increasing trend of consumption among females of childbearing age in Uruguay leads to a major public health concern. Fetal alcohol exposure can result in fetal alcohol spectrum disorder (FASD), a preventable cause of mental and growth retardation, and numerous neurodevelopmental deficits. By measuring fatty acid ethyl esters (FAEE) in neonatal meconium, the rate of heavy alcohol consumption during the latter two-thirds of pregnancy can be estimated. Understanding the fetal exposure rate and associated risk factors will assist with future FASD prevention planning.
Methods: Meconium samples (n=900) were collected from two public hospitals in Montevideo that characteristically serve women of low socioeconomic status and educational level. Maternal interviews were also completed. FAEEs were extracted from meconium using solid-phase extraction and analyzed using gas chromatography with a flame ionization detector (GC-FID). A sample was considered positive if the cumulative concentration of seven FAEEs was $\geq$ 2 nmol/g. All positive samples will be confirmed by GC-MS prior to completion of the study.
Results: Of 14% of the samples analyzed (n=125), 54% tested above the positive cut-off. Seventy-two percent of positive samples had total FAEE concentrations double the positive cutoff. Ethyl oleate (E18:1) and ethyl linolate (E18:2) were found in 100% and 94% of the positive samples respectively. Low levels of FAEEs were detected in 40% of the negative samples.
Conclusion: From preliminary meconium analysis, approximately half of infants born within this population are at high risk of fetal alcohol exposure, necessitating future prevention strategies.
Keywords: *Alcohol, pregnancy, gas-chromatography*

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In vitro modeling of intravenous meropenem [500 milligrams every 6 hours versus 1 gram every 8 hours] in acinetobacter bacteraemia

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Background: The objective of this study was to determine, using an in vitro model of infection, whether the rate and extent of killing of a sensitive and multi-drug resistant strain of Acinetobacter baumannii differed when meropenem was administered at a dose and frequency modeling 500mg IV q6h vs. 1g IV q8h infused over 30 minutes.
Methods: An in vitro model of infection using a 1-compartment model for meropenem was used. Two clinical isolates of A. baumannii were tested, a sensitive and multi-resistant strain. 24-hour experiments were run using concentrations that resembled meropenem given by intravenous infusion over 30 minutes for 500mg q6h and 1g q8h regimens. Samples were taken throughout the 24 hours for quantification of meropenem and A.baumannii growth.
Results: There was no statistically significant difference in % of time spent above the MIC (%T>MIC) between 500mg q6h and 1g q8h (p=0.48, 95% CI -34.94 to 52.38). When looking at the resistant strain only, meropenem remained above the MIC for a longer period of time in the 500mg q6h regimen compared to the 1g q8h regimen (p=0.0004, 95% CI 9.95 to 23.43). No difference was found for the sensitive strain. The extent of kill of A. baumannii was not statistically different between the two regimens (p=0.85, 95% CI -2056.85 to 2405.59). The 500mg q6h regimen achieved a 3 log reduction (99.9% kill) in less time than the 1g q8h regimen (p=0.0006, 95% CI-131.70 to -60.43).
Conclusions: Meropenem 500mg q6h has at least equal antimicrobial activity as 1g q8h against a sensitive and multi-drug resistant strain of A.baumannii.
Keywords: *Acinetobacter, meropenem, in vitro model*

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Vacuolar-atpase-dependent cell vacuolization induced by topical cationic drugs from several classes

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Background: Several basic amine drugs are applied to mucosae or into confined anatomical regions under the form of concentrated solutions. Inflammation and cell vacuolization has been reported as a consequence. On the basis of previous investigations based on procainamide-related drugs, we investigated the cytopathology induced by an α-adrenoceptor decongestant and mydriatic, phenylephrine, and a local anesthetic, lidocaine.
Methods: Cultured smooth muscle and other cells were used to study the vacuolization in response to the amines. Mitotic arrest was examined and bafilomycin A1 (V-ATPase inhibitor) and receptor antagonists were used to evaluate the role of the V-ATPase and the adrenergic receptors, respectively, during ion trapping.
Results: Several classes of drugs were active at mM concentration to induce massive cell vacuolization (α -adrenoceptor agonists, local anesthetics, etc). The swelling of the Golgi and other acidic compartments was reversed by washout and prevented by bafilomycin A1 co-treatment. Phenylephrine-induced vacuolization was not inhibited by treatment with an α-adrenoceptor antagonist (phenoxybenzamine) or uptake-1 and-2 inhibitors (desipramine and decynium-22). In amine-treated cultured cells, mitotic arrest was observed in presence of vacuoles and this was not blocked by bafilomycin A1, since this drug also caused this effect. Cell mortality observed during vacuolization was negligible (for drug concentrations ≤ 5 mM).
Conclusion: Cell changes in response to phenylephrine and lidocaine occur well within the topically used concentration. (decongestants, mydriatics, local anesthetics). The study of the ion trapping and its consequences could be important in the understanding of the tissue reactions induced by concentrated amine drugs from several classes.
Keywords: *Vacuolization, vacuolar-ATPase, bafilomycin A1*

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Contrasting nicotine dependence diagnosis in African Canadian smokers: DSM-IV, ICD-10 & FTND

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Background: Investigating nicotine dependence is particularly important in African North Americans smokers because this community has significantly higher rates of most smoking related diseases (e.g., lung cancer) for any given level of smoking. Nicotine dependence is often measured with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the International Classification of Diseases (ICD-10) or the Fagerström Test for Nicotine Dependence (FTND). The central constructs of DSM-IV and ICD-10 are based on generic definitions of substance dependence. In contrast, the FTND focuses heavily on behavioral aspects of dependence and is intended to measure the degree of physical nicotine dependence.

Objectives: To evaluate nicotine dependence in African Canadians using these three standard tests: DSM-IV, ICD-10 and FTND.

Methods: The study population is composed of 138 African Canadian smokers.

Results: Smoking is light (median 8 cigarettes per day) in this population and concordance between the three measures of nicotine dependence is poor. The majority of African Canadians (88%) were diagnosed as nicotine dependent by DSM-IV. Approximately half of the population (47%) was diagnosed as nicotine dependent by ICD-10. Very few African Canadians were classed as highly dependent (7%) by FTND.

Conclusions: In light smoking adult populations, tests for nicotine dependence need to be developed further. More research is needed to examine the validity of these tests in populations of different ages, ethnicity and cigarette consumption. A valid questionnaire to measure nicotine dependence would be useful in identifying individuals suitable for treatment and distinguishing cases in epidemiological investigations.

Keywords: *Nicotine dependence, African Canadian, light smokers*

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Efficacy of phenol, menthol 1% formula in mustard gas induced chronic skin lesions

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Objective: Chronic skin lesions are common late complications of sulfur mustard intoxication resulting in numerous complaints including pruritus, skin dryness and burn feeling. Our objective was evaluation of efficacy of topical phenol, menthol 1% formula in treatment of chemical warfare injured patients (especially for pruritus) in comparison with placebo.

Methods: This clinical trial performed in chemical warfare injured patients with mustard gas induced pruritus. 80 subjects with such injury were sampled randomly and divided to 2 same groups, one receiving phenol, menthol 1% formula and other placebo.

Results: Pruritic score in case group had significant difference with control group ($P=0.026$). Furthermore, there was a significant correlation between pre and post-treatment pruritic score in case group ($P<0.05$).

Conclusions: Phenol, menthol 1% formula has significant therapeutic effects for mustard gas induced pruritus in chemical warfare injured patients.

Keywords: *Phenol and menthol, chronic skin lesions, sulfur mustard*

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Hair levels of cortisol and testosterone in non-obese, obese and aging subjects

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Background: Measuring the change in hormonal status over time may be important for both diagnosing and treating a variety of conditions. Hair gives the advantage over serum or urine since it provides a long-term perspective of exposure to xenobiotics and endogenous substances, as it grows (~1cm/month). We hypothesized that hair levels of cortisol (C) and testosterone (T) will reflect systemic concentrations of these hormones over time in healthy and obese individuals.

Methods: Healthy and obese participants (≥ 18 yrs) were recruited via local advertising. Blood pressure (BP), height, weight and waist circumference were measured. C was measured in 24H-urine, in fasting blood sample and in a hair sample. T and Free Androgen Index (FAI) were measured in the males' serum and T in hair. C and T were measured using salivary C and serum T immunoassay (ELISA) kits modified for hair matrix.

Results: Analyzing all participants combined (n=56), hair cortisol correlated positively with systolic BP (r=0.27; P=0.048), but not with diastolic BP (r=0.24, P=0.078), urine/serum cortisol or BMI. In males (n=25), hair testosterone levels correlated negatively with age (r= -0.47, P=0.02), waist (r=-0.57; P<0.01) and BMI (r= -0.40; P=0.048) (Spearman).

Conclusions: This study demonstrates that C and T are present and can be measured in hair in humans. Hair C positively correlated with systolic BP and hair T decreases with age, waist circumference and BMI. As hair is not influenced by acute responses and collection is non-invasive, the measurement of steroid hormones in hair may become a useful tool in research and possibly in clinical practice.

Keywords: *Hair testing, ELISA, cortisol, testosterone*

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ENCORE PRESENTATION

Amantadine acetylation as a biomarker for malignancy

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Neuroprotective effects of maguk inhibitors in permanent focal cerebral ischemia with severe hyperthermia

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Funding Source: CIHR & NIH to MT (CIHR Clinician Scientist)HSS: a Focus On Stroke Fellow (CSN)

Background: Stroke is a cause of major socioeconomic burden worldwide. Hyperthermia (fever) and hyperglycemia are common in stroke victims (25% and 20-50%, respectively), and indicate a poor prognosis. No clinical or experimental treatment has been shown to improve outcome from stroke in the setting of hyperthermia. We report here the efficacy of neuroprotective peptides termed MAGUK (membrane-associated guanylate kinase) inhibitors, which dissociate NMDA glutamate receptors from downstream neurotoxic signals, against severe stroke in hyperthermia.

Methods: Male SD rats were not fasted overnight and subjected to permanent middle cerebral artery occlusion (pMCAO) which, owing to the large infarct produced, also induces severe hyperthermia. Animals were treated with a single intravenous injection of the MAGUK inhibitor 1h after stroke onset. Body temperature was continuously monitored using a telemetric system. Infarct volume was assessed using standard techniques. The procedures and analyses were performed in a blinded manner.

Results: Animals subjected to sham surgery or to drug administration without pMCAO did not exhibit a fever. All animals subjected to pMCAO exhibited sustained hyperthermia (>39°C) for the 24h post-ischemic period. Two different MAGUK inhibitors, SDV and TDV (0.3nM/g and 3nM/g) reduced infarct size by approximately 50%, without affecting postischemic hyperthermia.

Conclusions: Both MAGUK inhibitors significantly reduced infarct volumes in the most severe animal stroke model that recapitulates the fever and hyperglycemia which are so commonly seen in stroke patients. This raises the possibility that these compounds may have clinical utility in stroke victims, in which fever and hyperglycemia are common.

Keywords: *Neuroprotection, stroke, hyperthermia*

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Identification of a novel SLC22 transporter

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Backgrounds: A number of transporters which translocate various compounds were identified and functionally characterized over the last 20 years. SLC22 transporters are expressed predominantly in liver, intestine, and kidney and play a pivotal role in absorption and excretion of drugs, xenobiotics and endogenous compounds. Here we report the cloning of a novel SLC22 transporter, BOCT, abundantly expressed in brain.
Methods: Using several sequences of SLC22 transporters as queries, a BLAST search was performed. The obtained data were further analyzed with web-based data and programs. A human multiple tissue Northern blot was used to confirm tissue distribution of BOCT. To more precisely study BOCT location, we performed in situ hybridization using mouse brain slices.
Results: Through database searches, a novel SLC22 transporter, BOCT, was identified. The BOCT gene is located on chromosome 14q11.2 and encodes a 520-amino acid protein. Typical features of SLC22 transporters, such as 12 transmembrane domains and N-Glycosylation sites are conserved. Northern blot analysis revealed that BOCT mRNA was abundantly expressed in brain and in situ hybridization showed wide distribution across the brain except for in the thalamus region which showed relatively weak signals. More specifically, strong signals were detected in neurons and choroids plexus, while glial cells showed comparatively weak signals.
Conclusions: We cloned a novel SLC22 transporter BOCT which appears to be strongly expressed in neurons and the choroids plexus. This transporter may play a physiologically and clinically important role in the transport of endogenous substrates or drugs.
Keywords: *SLC22, transporter, brain*

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Modulation of multidrug resistance-associated protein (MRP) 3 and 4 by retinoic acids: The role of xenobiotic nuclear receptors

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Background: Multidrug resistance-associated proteins (MRPs) are plasma membrane ATP-dependent transporters which extrude a myriad of endogenous and exogenous toxic compounds from the cell. Upregulation of MRPs, which contributes to drug resistance, represents an adaptive component of cellular defense against xenobiotic insults. To better understand how this adaptive system works, we determined the transcriptional regulation of these transporters, which presently remains largely undefined. Retinoic acids, the biologically-active vitamin A derivatives and drugs used in chemotherapy and skin diseases, were chosen in this investigation as they are activators for xenobiotic-responsive transcriptional factors such as retinoid X receptors (RXRs) and, potentially, nuclear factor erythroid 2-related factor 2 (NRF2).
Methods: We treated the liver (HepG2 and Hepa-1c1c7) and intestinal (C2bbE1) cells with all-trans, 9-cis and/or 13-cis retinoic acids. mRNA transcripts of MRP1-7, MDR1 and BCRP were analyzed by real-time quantitative RT-PCR. To elucidate the involvement of transcriptional factors (RXR and NRF2) as transcriptional regulators, we devised RNA interference strategy to knockdown respective receptors and the magnitude of gene induction was compared.
Results: Significant induction of MRP3 and MRP4 mRNAs (>3 folds) by all retinoic acids was noted. The silencing of NRF2, but not RXR-alpha and -beta, was found to alleviate the magnitude of gene induction of these transporters
by retinoic acids.
Conclusions: Upregulation of MRP3 and MRP4 by retinoids is dependent on NRF2. Because NRF2 is a cellular sensor and protector against free radical attack, the upregulation of these transporters pinpoints a cellular adaptive defense mechanism in combating oxidative stress.
Keywords: *Multidrug resistance-associated protein, retinoic acid, nuclear receptor*

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Activation of PXR protects mice against cholic acid-induced hepatotoxicity by induction of CYP3A11 and MRP3 expression

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Background: The pregnane X receptor (PXR) regulates genes involved in bile acid biosynthesis, metabolism and transport. PXR has been shown to be involved in the defense against cholestatic liver injury, however the protective mechanism of PXR remains unclear. We therefore examined the effect of PXR activation on hepatotoxicity and hepatic gene expression in a cholic acid model of cholestasis.

Methods: Wild-type (PXR+/+) and PXR-null (PXR-/-) mice were fed a 1% CA-supplemented diet with or without the PXR activator, PCN (50 mg/kg). Hepatotoxicity was determined by serum enzymes and histochemical analysis, and mRNA expression was measured by real-time quantitative RT-PCR.

Results: CA caused significant hepatotoxicity as indicated by elevated ALT, AST and ALP levels. Toxicity was substantially attenuated by co-treatment with PCN in PXR+/+ but not PXR-/- mice. CA induced CYP3A11, MRP2, MRP3, MRP4, BSEP, OATP2 and PXR but down-regulated NTCP and CYP7A1 mRNA expression in PXR+/+ mice. Administration of PCN in CA-fed PXR+/+ mice further induced the expression of CYP3A11 and MRP3 as compared to CA alone. In PXR-/- mice, CYP3A11, MRP3, and OATP2 induction by CA were abolished, whereas levels of MRP2, MRP4 and BSEP were significantly lower compared to CA-fed PXR+/+ mice.

Conclusions: The PXR activator PCN protects PXR+/+ but not PXR-/- mice against CA-induced hepatotoxicity. This is associated with an induction of CYP3A11 and MRP3 expression. Thus increased metabolism and basolateral transport of CA appear to be major protective pathways mediated by PXR.

Keywords: *PXR, transporters, bile acids*

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A tonicity-controlled human CYP3A expression

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Background: Expression of CYP3A is regulated by transcriptional factors such as PXR. However, an entire spectrum of its regulation remains elusive. Based on our recent findings that tonicity controls CYP3A expression, we hypothesize that the tonicity responsive enhancer binding protein (TonEBP) mediates the CYP3A transcriptional control. Further, we investigated effects of tonicity changes on major drug transporters.

Methods: Human intestinal C2bbe1 cells were exposed to various tonicity. Real-time RT-PCR and western blotting were used to analyze gene and protein expression. TonEBP expression plasmid, siRNA, and dominant-negative TonEBP were used for gain- and loss-of-function assays based on Luciferase reporter constructs.

Results: The C2bbe1 cells showed significant tonicity-dependent increase in CYP 3A4, 7 and 5 mRNA (5-10-fold increase at 400 mOsm/kg) and protein expressions with no appreciable change in PXR. This was confirmed in the primary culture of human colon and other cell lines of human intestinal and hepatic origins. PXR overexpression had no influence. Screening of the CYP3A gene region revealed an active TonE sequence within a CYP3A7 intron.Transporter expression showed only mild changes.

Conclusions: Human CYP3A expression is under the influence of external tonicity changes, which is distinct from the PXR pathway. We propose that binding of the tonicity-activated TonEBP to the TonE element in the CYP3A gene cluster is responsible for this phenomenon.

Keywords: *TonEBP, NFAT5, enhancer*

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Novel drug delivery system for paclitaxel increases tolerability and therapeutic efficacy in a human ovarian cancer model

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Background: Paclitaxel (PTX) is a widely utilized chemotherapeutic, however, severe adverse reactions are associated with its administration, due to its formulation vehicle, Cremophor EL (CrEL). This study compared the safety, toxicity, biocompatibility and anti-tumour efficacy of a novel chitosan-egg phosphatidylcholine (ePC) implantable delivery system that provides controlled and sustained release of PTX versus commercial PTX formulated in CrEL (PTXCrEL).
Methods: Toxicity studies were conducted in healthy CD-1 female mice, whereas efficacy studies were performed in SKOV-3 xenograft models of ovarian cancer. Treatments consisted of intraperitoneal (IP) implantation of drug-free or PTXePC formulations, IP bolus PTXCrEL, or CrEL/dehydrated ethanol vehicle. Toxicity was assessed as number of deaths, weight loss, hepatic enzyme function and histopathological changes.
Results: Mice implanted with drug-free or PTXePC implants did not exhibit observable toxicities, local inflammation or fibrous encapsulation of the implant. In contrast, mice receiving PTXCrEL displayed significant weight loss and lethality with abnormal peritoneal organ morphology and hepatic inflammation. The maximum tolerable dose (MTD) of PTXCrEL was 20 mg/kg/week, whereas PTX doses of more than 280 mg/kg/week were well tolerated when administered as PTXePC. Interestingly, significant hepatotoxicity and mortality occurred in the CrEL treated controls. Anti-tumour efficacy of 100% was achieved with PTXePC, in contrast to only 45% with PTXCrEL utilizing the same dose (20 mg/kg/week for 21 days).
Conclusions: The novel ePC formulation is a safer and better tolerated method of PTX administration, with a significant increase in MTD and enhanced anti-tumour efficacy, suggesting improved therapeutic index with possible clinical implications in the treatment of ovarian tumours.
Keywords: *Paclitaxel, maximum tolerable dose, efficacy*

CCCP ORAL PRESENTATIONS

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ENCORE PRESENATION

Type of antidepressant therapy and risk of type 2 diabetes in people with depression

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Effect of educational initiatives and pharmacare policy change on wet nebulization respiratory drug therapy and portable inhaler utilization at the Queen Elizabeth II Health Sciences Centre (QEII HSC), Halifax, Nova Scotia

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Funding Source: None

Background: Wet nebulization (WN) respiratory drug therapy was changed to an exception status benefit and a spacer device was added to the Nova Scotia Community Services and Seniors Pharmacare Programs, effective August 1, 2000. Concurrently, multifaceted interventions at QEII HSC (1000-bed teaching hospital) promoted conversion of WN therapy to portable inhalers (PI). We evaluated the effect of educational initiatives and Pharmacare policy change on use of salbutamol and ipratropium bromide WN, PI, and Aerochamber® devices at QEII HSC.
Methods: Monthly drug utilization data from QEII HSC's pharmacy database was expressed using the World Health Organization's ATC/DDD system for the period before (August 1998 to July 2000) and after (August 2000 to July 2005) the intervention. Time series graphs were plotted to determine trends in DDD/respiratory admission and DDD/100 bed-days.
Results: Interventions and policy change significantly increased PI use, but did not decrease WN use. Mean (SD) DDD/respiratory admission for the year preceding and following policy change were: salbutamol PI: 256.59 (63.61), 328.97 (87.56), $p = 0.03$; ipratropium bromide PI: 219.30 (53.75), 293.81 (80.71), $p = 0.01$; salbutamol WN: 66.19 (17.90), 71.37 (20.10), $p = 0.51$; ipratropium bromide WN: 161.53 (49.27), 195.18 (43.84), $p = 0.09$. Mean (SD) Aerochamber® units/respiratory admission did not increase (3.74 (1.17), 4.59 (1.22), $p = 0.10$). Time series analysis is in progress.
Conclusions: These findings may reflect the acuity of hospitalized patients necessitating WN use and increased conversion from WN to PI in Pharmacare patients before discharge.
Keywords: *Wet nebulization, drug utilization, time series plots*

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High levels of satisfaction reported by patients receiving services provided by pharmacists integrated into family practice

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Background: Successful integration of pharmacist services into family practice is an emerging role for pharmacists. Patient evaluation of this new role can provide important information to improve service and patient outcomes. The objective of this study was to determine patient satisfaction with services provided by a family practice pharmacist.
Methods: A cross sectional survey of patients who had an initial consultation and at least 1 follow-up assessment with one of seven pharmacists working in a collaborative care model with seven family practice sites in Ontario. A validated 30-item, 4 domain questionnaire, the Pharmaceutical Care Satisfaction Questionnaire (PCQS), was mailed to each patient. Unlike other satisfaction surveys, the PCSQ contains patient evaluations of medication understanding and empowerment. Items were rated on a 5-point Likert-type scale. Multivariate linear regression analyses that included age, sex, number of medical problems, number of medications, practice site, and referral strategy were tested as predictors of patient satisfaction.
Results: Response rate was 77% (223/289). Mean overall patient satisfaction score was 121.7/150 (SD, 15.8). Subscales scores were: patient understanding 33.5/45 (SD, 5.2); provision of pharmaceutical care 50.6/60 (SD, 7.0); patient empowerment 21.2/25 (SD, 2.9); and pharmacist-patient relations 16.4/20 (SD, 3.4). There were no differences in patient satisfaction dependent on the strategy used to refer patients and no variables tested were significantly associated with satisfaction score.
Conclusions: The high level of patient satisfaction suggested a smooth integration of pharmacist service into family practices. The association between satisfaction and patient outcomes will be evaluated in future analyses.
Keywords: *Patient satisfaction, questionnaire, pharmacist practice*

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ENCORE PRESENTATION

Implementation and a randomized controlled evaluation of pharmacist medication assessments in a surgical pre-admission clinic

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CCCP POSTER PRESENTATIONS

Wednesday May 10, 2006

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The impact of pharmacist counseling on patient knowledge of medications in patients attending an outpatient diabetes clinic

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Funding Source: None
Background: Diabetic patients take many medications to reduce complications associated with diabetes. Improved understanding of medications should improve medication adherence thus contributing to fewer micro and macrovascular complications.
Objective: To determine if diabetic patients who receive pharmacist counseling in a diabetes outpatient clinic change their knowledge regarding medications used to prevent diabetic complications and attitudes towards self care compared to before they received counseling and are satisfied with pharmacist service.
Methods: This pre-post pilot study includes outpatient diabetes clinic patients prescribed diabetes related medications along with insulin and antidiabetic agents. Patients were excluded if they did not speak English, were less than 18 years of age or were blind. Patients answered questionnaires about diabetes knowledge (maximum score = 23) and attitudes towards self-care (maximum score = 50) before and one month after pharmacist appointment. The post questionnaire set included the validated Client Satisfaction Questionnaire (CSQ-8; maximum score = 32). Descriptive statistics are provided. Before and after comparisons were conducted using paired t-tests.
Results: Twenty-two patients were included in the study. There was an average increase of 3.3 (p=0.0008) for the 16 patients who completed both knowledge questionnaires and an increase of 2.0 (p=0.40) for the 11 patients who completed both attitudes questionnaires. The mean (SD) score for the 16 patients who completed the CSQ-8 was 27.8 (3.9).
Conclusions: Patients receiving pharmacist counseling had an increased understanding of diabetes medications and no change in attitudes one month after meeting with the pharmacist. Patient satisfaction was high.
Keywords: *Pharmacist education, diabetes, patient knowledge*

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Reliability testing of an adapted case leveling framework for assigning level of difficulty of the pharmacist's task in conducting initial patient medication assessments in the impact study

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Background: Older adults have an average of 3.2 drug related problems identified after pharmacist assessment however little is known about the complexity of the patients assessed by pharmacists.

Objective: To test the reliability of an adapted case leveling framework to assign the level of difficulty of the pharmacist's task in conducting an initial patient medication assessment.

Methods: This cross sectional study included a convenience sample of patients seen by pharmacists integrating into family practice clinics. The adapted case leveling framework consisted of descriptions for three levels of difficulty of pharmacists' tasks (I, II and III). Two assessors independently reviewed pharmacist generated documentation notes and used the case leveling framework to rate the level of each case. Level of agreement was estimated using the kappa statistic.

Results: The average case level assigned for the 53 IMPACT cases sampled was 1.83 (SD, 0.67). Thirty-two percent (17/53) of cases were assigned Level I, 53% (28/53) Level II and 15% (8/53) Level III. Complete agreement occurred in 41/53 (77%) of cases. All disagreements were within 1 level of difference. The kappa statistic was 0.62 (95%CI, 0.44 to 0.798; $p < 0.0001$).

Conclusions: There was good level of agreement between raters. Feedback generated refinements to the descriptors and level examples. This method can be used to reliably assign level of difficulty of the pharmacist's task in conducting patient medication assessments. Better understanding of patient case complexity related to the task of medication assessments would be beneficial for pharmacy curriculum design, training of family practice pharmacists and estimation of pharmacist workload.

Keywords: *Pharmacists, primary care, reliability study*

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Self reported risk for drug related problems in ambulatory elderly patients referred for family practice pharmacist assessment

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Background: Tools to help clinicians and patients identify medication-related risk can reduce poor health outcomes. The objectives of this study were to determine the risk for drug related problems based on patient self-report using a structured tool and to identify patient characteristics associated with this risk in elderly ambulatory patients.

Methods: This was a cross sectional study of consecutive patients referred for pharmaceutical care assessments who self-completed the previously validated 10-item Medication Risk Questionnaire (MRQ; scored 0-10). Descriptive statistics were calculated. Multivariable regression analyses used MRQ score as the dependent and age, gender, SF-12, number of medications and medical conditions as independent variables.

Results: There were 573 patients (mean age 71.2 yr, SD 11.4), taking a mean 7.9 (SD 4.3) medications daily with a mean of 5.1 (SD 2.4) medical conditions. The mean MRQ score was 3.4 (SD 1.9; median 3) with 79.9% of subjects taking 5 or more medications daily. Three or more medical conditions were reported in 78.8% and 58.8% took 12 or more medication doses daily. Twenty-six percent were unclear about the reason for taking their medications and 19% reported adherence problems. Multivariable analysis found that age, gender, Mental Composite Score of SF-12 and number of medications were significant in their associations with MRQ score.

Conclusions: Three areas of focus for clinicians working with the elderly were identified: seamless care, patient education and adherence strategies. Age, number of medications and quality of life can help identify patients potentially at risk for drug related problems.

Keywords: *Elderly, screening tool, drug related problems*

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Survival and cost-effectiveness of docetaxel (D) and paclitaxel (P) in patients with metastatic breast cancer (MBC): a population-based evaluation

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Background: A randomized comparison between P and D for MBC reported superior overall survival (OS) for D. We report a population-based comparison of P to D in MBC patients who failed anthracycline in terms of OS and cost-effectiveness (CE).
Methods: MBC patients treated with P or D (Jan 1999-Dec 2002) were retrospectively reviewed. OS (time from taxane initiation to all-cause death) was expressed as Kaplan-Meier plots and compared with a 2-tailed log-rank test. A CE analysis, including cost of drug (list price $CDN), labour and supplies, was performed using median cost/patient and median OS (MOS). Incremental CE ratios (ICERs) were compared in a sensitivity analysis varying MOS to the extremes of the 95% confidence interval (CI).
Results: 435 patients met eligibility criteria. MBC prognostic factors were balanced between the two groups. MOS was significantly longer for D (10.9 mos) vs. P. (8.3 mos), with HR 0.76 (95% CI, 0.62-0.92, P=0.006). The median treatment cycles were 4 (D) and 3 (P). The respective cost/month of MOS is $805 (D) and $303 (P). The ICER of D vs. P was $2,434/month MOS gained. The range of ICERs in the sensitivity analysis was $1,121 to 7,361/month MOS gained. These results were robust except that P dominates when the low end of the 95% CI of MOS for D is compared to the high end for P.
Conclusion: This population-based study corroborates the randomized trial's conclusion that for patients with MBC, D provided superior survival than P. Each additional month of survival had an incremental cost of $2,434.
Keywords: *Docetaxel, paclitaxel, survival*

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Anticholinergic load in residents of a long-term care facility

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Background: Anticholinergic (ACH) agents are associated with adverse effects in seniors. As such, clinical guidelines recommend these drugs be avoided. We completed a retrospective drug use evaluation in a long-term care facility to determine ACH drug use & estimate total ACH load over a one year period.
Methods: Computerized prescription drug records were searched for use of regularly scheduled ACH agents. Drugs were considered regularly scheduled if used > 3 times/week. The Modified Clinician Rated ACH Scale was used to identify & classify ACH activity (low to moderate, 1 to 3 respectively). Total ACH load was determined based on ACH activity & dose, quantified by tertiles of the maximum recommended daily dose (scale 1 to 3). ACH activity was multiplied by the dose rating to determine ACH load for a specific agent. If more than one ACH agent was used, they were summed to determine total ACH load.
Results: Mean age of residents using ACH agents was 83 years (range 71-97), 94% were male, & 61% were diagnosed with dementia. 15.9%(33/207) were receiving at least one scheduled agent with moderate or high ACH activity. Common agents were amitripyline, oxybutynin, dimenhydrinate, flavoxate, & loxapine. Total ACH load was < 8 in 7%, 8-15 in 27% & >15 in 52%.
Conclusion: While the overall number of residents receiving agents with ACH activity was low, total ACH load among those prescribed these agents was high. Opportunity exists to reduce ACH load in this group.
Keywords: *Drug use evaluation, long-term care, anticholinergic load*

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ENCORE PRESENATION

A pilot project of community pharmacy based influenza immunization clinics

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Severe thrombotic reaction and amputation following initiation of celecoxib: a case report

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Background: A 70-year-old woman developed bilateral leg pain and a skin rash on both legs two days after initiating celecoxib therapy for left hip pain. She had no history of autoimmune disease or drug allergy but reported a remote pulmonary embolism post-surgery. In hospital, laboratory tests showed a positive cryoglobulin and cold agglutinin, elevated IgM and elevated liver function tests consistent with cryoglobulinemia. An erythrocyte sedimentation rate (ESR) was zero. She was treated with steroids, intravenous immunoglobulin and plasmapheresis. Despite treatment, the rash progressed to extensive ischemic necrosis, resulting in bilateral above knee amputation. A skin biopsy was consistent with ischemic changes and small vessel deposition with no evidence of inflammation or vasculitis. The differential diagnosis included hypercoagulable states such as cryoglobulinemia, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, paroxysmal nocturnal hemoglobinuria, protein C deficiency and antiphospholipid antibody. The necrosis and lack of mucosal involvement was considered not consistent with toxic epidermal necrolysis. The cryoglobulin was immunoglobulin M (IgM) kappa (monoclonal) consistent with Type I cryoglobulinemia, usually linked to lymphoproliferative disorders (i.e., multiple myeloma, Waldenström macroglobulinemia), however this was never diagnosed.
Results: It is well documented in the literature that COX-2 inhibitors may cause a prothrombotic state by decreasing prostacyclin (PGI2) production. To date, there are no reports of celecoxib-induced cryoglobulinemia. There is evidence that COX-2 inhibition increases the risk of developing thrombotic cardiovascular events.
Conclusion: This is the first report of ischemic necrosis requiring limb amputation associated with the initiation of celecoxib. COX-2 inhibition is a possible cause of the hypercoagulable state and resulting ischemia.
Keywords: *Celecoxib, COX-2 Inhibitors, adverse effects*

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Pain management decision-making among long-term care physicians and nurses

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Background: Little research has been conducted in pain management among older adults living in long term care (LTC). Our objective was to explore attitudes and beliefs that affect decisions about prescribing and administering pain medications in older adults living in LTC with special emphasis on those with cognitive impairment.
Methods: This qualitative study utilized and grounded theory approach and three data sources: 1) physicians, 2) registered nurses (RNs), and 3) registered practical nurses (RPNs). Participants were recruited from four LTCs. Focus group discussions were held with RNs and RPNs, while individual interviews were conducted with the physicians. Structured interview and focus group guides were used. Member checking was conducted. Data were first analyzed separately by two individuals who compared findings then presented findings to the team for further discussion. Themes emerged leading to the creation of a model.
Results: Nine physician interviews and four RN and four RPN focus groups were conducted (median number of participants was 7). The model highlighted critical decision points for nurses and physicians around pain management. The major themes emerging from the data concerned pain assessment (lack of recognition of pain, uncertainty about the accuracy of pain assessment and diagnosis), and treatment (reluctance of health care providers to use opioids, working to individualize pain treatments, issues relating to physician trust of the nurse on prescribing patterns).
Conclusions: These findings will be useful in the development and evaluation of innovative approaches to pain management by facilitating effective decision making and collaboration among health care providers in LTC settings.
Keywords: *Pain management, long-term care, qualitative*

CCCP POSTER PRESENTATIONS
Thursday May 11, 2006

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Health professionals' perceptions of pharmacist and family physician's contributions to medication-related processes: changes over time as pharmacists integrated into family practice

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Funding Source: Ontario Ministry of Health and Long-Term Care (OMHLTC) through the Primary Health
Background: Contribution to medication related processes (MRP) in family practice is important to successful integration of pharmacists. The objective of this study was to measure how different professionals/staff perceived their own and others' contributions to MRP over time as pharmacists integrated into family practice clinics.
Methods: The 22- item Family Medication Use Processes Matrix (MUPM) with 5 subscales (diagnosis & prescribing, monitoring, administrative/documentation, education and medication review) was mailed to physicians, pharmacists and office staff in 7 sites at the 3rd and 12th month of pharmacist integration. Paired sample T-tests were conducted to determine change over time in each subscale. One-way ANOVA analysis with Tukey's post-hoc test was conducted to compare perceptions between occupation groups and change over time.
Results: There were 91 surveys (58%) returned at the 3rd month and 85 (54%) at the 12th month. There was a significant increase in the mean score of pharmacist's contribution in the Diagnosis & Prescribing subscale among all respondents ($p<0.01$) and a separate analysis of physicians' responses ($P<0.05$). There was a significant increase in the mean score of the physicians' contribution to the Administration & Documentation subscale ($P<0.05$) from the pharmacists' perspective. ANOVA analysis revealed more consensus among occupation groups in some subscales while other differences persisted over time.
Discussion: Changes in perceived contributions of health care professionals to medication-related processes suggest exploration and increased understanding of their own and others' roles. The full effect of pharmacist integration may take longer than one year to perceive clearly.
Keywords: *Pharmacist, family medicine, quantitative questionnaire*

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Collaborative working relationships between family physicians and pharmacists: changes over time as pharmacists integrated into family practice

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Funding Source: OMHLTC through the Ontario Primary Health Care Transition Fund
Background: Collaborative working relationships (CWR) may be influenced by many factors as health care professionals learn to work together in the primary care setting. This study used a quantitative questionnaire to evaluate change over time and predictors of change as pharmacists integrated into family practice settings.
Methods: A CWR questionnaire validated with family physicians and community pharmacists (covering a variety of participant variables, professional interactions, exchange characteristics and collaborative practice) was administered at 3 and 12 months. Family physicians completed the questionnaires considering their practice pharmacist and pharmacists completed questionnaires regarding each physician with whom they worked. Paired sample T tests were conducted for physician-completed questionnaires. Effect sizes were calculated for each pharmacist and meta-analytically combined. Hierarchical linear regression analysis was performed to identify significant predictors of collaborative relationship development.
Results: Response rate was 87% and 88% for the two survey administration times. Paired sample T test revealed significant increase in physicians' collaborative practice score ($P<0.05$) over time. Regression analyses showed significant predictors (e.g. role specification) of the development of collaborative working relationships at the 12 month point. Meta-analytically combined effect sizes of the pharmacist-completed questionnaires showed small positive effects in four variables and a large negative effect in one variable.
Conclusion: We successfully used this questionnaire to measure CWR between pharmacists and physicians, working together in family practice and to evaluate change over time. Role specification as a predictive factor of CWR development highlights the importance of clear roles and responsibilities as pharmacists integrate into family practice.
Keywords: *Pharmacist, family medicine, quantitative questionnaire*

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Effect of District Health Authority (DHA) pharmacy policies on fluoroquinolone use in Nova Scotia hospitals

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Funding Source: Andrea Kent and Ryan Sommers were research associates funded by a Chair provided

Background: Fluoroquinolones are useful against a variety of bacterial infections, yet may be subject to misuse. Many hospitals in Nova Scotia (NS) implement district pharmaceutical policies to improve antimicrobial prescribing; however the impact of these policies on utilization is unknown.
Objectives: To describe the use of fluoroquinolones using the World Health Organization (WHO) / Anatomical Therapeutic Chemical (ATC) Defined Daily Dose (DDD) methodology in the NS hospitals and examine the influence of DHA pharmacy policies on fluoroquinolone use for community acquired pneumonia (CAP).
Methods: NS has nine district health authorities (DHAs) and 31 hospitals which administered fluoroquinolones during the study period. Hospital administrative data, hospital characteristic information and pharmaceutical purchasing data were aggregated using the WHO/ATC DDD system for fiscal years 1997- 2002. District pharmacy directors were surveyed regarding hospital pharmacy antibiotic policies. Descriptive statistics, univariate regression and multilevel analyses were performed.
Results: Mean overall fluoroquinolone use increased over study period: 47 DDD/1000 bed days/yr (1997) to 163 DDD/1000 bed days/yr (2002) ($p<0.01$). Between 1998 and 2002 mean respiratory fluoroquinolone increased by more than seven fold; from 14.1 DDD/1000 bed days/yr to 108.4 DDD/1000 bed days/yr. Hospital fluoroquinolone use did not differ between hospitals with multiple pharmacy policies and those with no policies.
Conclusion: Our study found that drug purchasing, hospital administrative and diagnostic data could be combined to provide benchmarks for fluoroquinolone use. The number of antibiotic policies had little effect on the amount, type or route of fluoroquinolone use.
Keywords: *Drug utilization, fluoroquinolones, policies*

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Sharing the workload while improving therapeutic outcomes – a trial of a warfarin nomogram with collaborative roles for pharmacy and nursing

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Background: Physician warfarin management yields a Time in Therapeutic Range (TTR) of 33-64%. Warfarin nomograms can produce higher TTRs, however small hospital pharmacies lack the time needed to operate a nomogram and nurses are reluctant to assume this responsibility without pharmacy assistance. The goal of this study was to find a warfarin nomogram that improves TTR while sharing the workload between pharmacists and nurses.
Methods: A retrospective chart review of 61 randomly selected internal medicine inpatients was completed to assess current physician management of warfarin. The key outcome variable collected was TTR for INR=2-3. A PubMed literature review yielded no suitable nomogram, accordingly a new nomogram was developed and trialed with 60 non-randomly selected inpatients. The TTRs for the two groups were then compared using a t-test.
Results: The retrospective review of physician warfarin management revealed an average TTR=49%. The nomogram produced a TTR=62% (t-test: $p < 0.05$). Despite this result, several challenges were identified: the ~150 users limited flawless execution of the nomogram, and the nomogram managed all patients equally which is not ideal given patients at different levels of bleed and thrombosis risk.
Conclusions: The nomogram did appear to improve TTR, but the large user base necessitated close monitoring to assure its proper use. Hence a nomogram operated by a large group of individuals cannot be recommended. A better alternative is a small group of pharmacists and/or nurses providing an anticoagulation management service using either paper or computer based nomograms as an aid to making dosing recommendations.
Keywords: *Warfarin Nomogram Trial*

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e-Therapeutics: clinical decision support tools to improve patient outcomes

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Background: In the 2005 report to Canadians the Health Council of Canada recommended investment in the development of unbiased, evidence-based drug information for physicians, pharmacists and patients. Managed by the Canadian Pharmacists Association (CPhA), e-Therapeutics is a decision support tool for primary care practitioners that provides evidence-based Canadian drug and therapeutic information to be used at the point of care. The purpose of e-Therapeutics is to support best practices in appropriate drug therapy and improve safety by providing busy practitioners with evidence to help them answer their drug therapy questions.

Methods: Delivered through a web portal, with some content downloadable to a handheld, e-Therapeutics offers content published by CPhA and is augmented with Health Canada drug alerts; links to abstracts, reviews and other references; clinical practice guidelines; and public drug plan formularies and other key content to create a centralized resource. e-Therapeutics is being developed using accepted technical and information standards.

Results: The potential impact on primary care includes better patient outcomes; fewer medication errors; improved communication of formulary status and new drug safety information; and better value for the money spent on pharmaceuticals. This presentation will demonstrate these e-tools and describe the results of user experiences and pilot testing.

Conclusions: e-Therapeutics provides busy health care providers with access to the right information at the right time to make the right therapeutic decision, allowing them to manage drug therapy efficiently. Patient safety, outcomes and cost effectiveness are supported by evidence-based decision making.

Keywords: *Knowledge translation, evidence based medicine, decision support*

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Evaluation of warfarin patient education

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Funding Source: None

Background: Adverse patient events post-discharge have been linked to poor communication between patients and practitioners. Warfarin is a common, high-risk drug whose safety requires clear understanding by the patient. This involves both accurate and relevant content as well as presentation at an appropriate reading level where written communication is utilized. The objectives of this study were to determine the accuracy of warfarin patient information sheets provided to patients and to assess their reading level.

Methods: Surveys were sent to the 47 members of the Thrombosis Interest Group of Canada (TIGC) to establish a "Canadian Consensus" of important items for inclusion in a warfarin education sheet. Patient information sheets representing those distributed by more than 90% of community pharmacies in Ontario were collected. Their content was evaluated by comparison to the "Canadian Consensus" and the reading level was assessed using standardized formulas.

Results: The consensus of the TIGC survey was used to create a checklist of 53 important items against which other information sheets were compared. Analysis of the individual information sheets for 3 categories of item options (essential or important and accurate, incorrect, missing) is currently in progress and will be completed by the meeting; one commonly distributed sheet contained 35 deficiencies and 2 incorrect statements.

Conclusions: Warfarin patient information sheets fail to address essential patient information and contain deficiencies or incorrect statements that may compromise patient safety and lead to unnecessary lifestyle restrictions.

Keywords: *Warfarin, education, evaluation*

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Influence on adherence of "health inform", a series of periodiceducational mailings on disease and drug from the pharmacy and manufacturer

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Background: Medication non-adherence is a major health care problem costing billions of dollars annually. “Health Inform” is a program developed by Rx Canada to improve adherence; it is a series of educational mailings to reinforce other efforts. Review of prescription data provided by the participating pharmacies led to the opportunity to determine persistence rate differences for both enrolled and control patients.
Methods: Anonymized prescription records were collected for the period of January to November 2005 for 16 products. Patients on these medications were asked to enrol in the program; other patients on these medications who were not approached were considered controls.
Results: Data were organized on the tens of thousands of patients as follows: drop out points at 6, 9, 12, 15 and 18 months determined persistence. Average days supply per month (ADSM) was also used as an adherence measure. Persistence rates varied widely, but were higher for repeat prescriptions. For the antihypertensives, persistence at 12 months (P-12) was approximately 53% in the enrolled groups, 43% in the control group, an improvement of about 10% (up to 20% higher for prescription renewals). For bisphosphonates, P-12 rose from 39.5 to 49% .For statins, P-12 increased from 43 to 54 (an 11 % difference). ASDM increased proportionately. Limitations are listed, but the results are very strong statistically.
Conclusion: Health Inform increases P-12 by about 10%, even more for repeat prescriptions and increases ADSM proportionately. Higher persistence rates may be achievable with the introduction of other adherence-inducing interventions.
Keywords: *Adherence, prescription data, compliance*

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Evaluation of a self-medication program on a geriatric assessment unit

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Background: This study was designed to evaluate the use of a self-medication program (SMP) on a Geriatric Assessment Unit (GAU) and to identify characteristics associated with patient success or failure in the program.
Methods: A retrospective chart review was conducted on a consecutive sample of 107 patients who had been admitted to the GAU between October 1999 and April 2005, and who had been enrolled in the SMP. Using a standardized chart review form, demographic and medical information, medication use, health service utilization, and patient outcomes on the SMP were gathered.
Results: Of 107 patients enrolled in the program, 25 successfully completed the SMP, 24 did not complete, 12 discontinued prematurely, and 46 had no documented outcome. No statistically significant differences were seen between the patients who had documented outcomes and those who did not ($p>0.05$). Patients who had succeeded (n=25) had higher MMSE (27.0 vs. 25.4, p=0.02), fewer medications (13.5 vs. 17.6, p=0.02), higher number of days enrolled in the SMP (12.2 vs. 5.6, p=0.007), and fewer self-medicated errors (1.8 vs. 4.6, p=0.002) than those who did not complete (n=24).
Conclusion: We were unable to provide a comprehensive evaluation of the program because of the high proportion of undocumented outcomes. Further research is required to determine appropriate SMP guidelines. Trends indicated that patients who have low MMSE, high numbers of medications, and high numbers of errors will likely have difficulty completing a SMP. Further study is required to determine which patients would benefit from enrollment in a SMP.
Keywords: *Self-medication, assessment, pharmacy*

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Efficacy of indomethacin in treatment of Patent Ductus Arteriosus (PDA) in neonates; a chart review from St. Joseph's Hospital, London, Ontario

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Funding Source: none

Background: Patent ductus arteriosus (PDA), a vascular connection between the main pulmonary artery and the aorta, persists after birth in approximately 20-40% of newborns. Presentation can range from clinically asymptomatic to severe complications including heart failure and respiratory distress. Use of cyclooxygenase inhibitors such as indomethacin is generally accepted treatment for symptomatic PDA. The major side effect noted in these patients is decreased renal function.The efficacy of Indomethacin in PDA closure at St Joseph's Hospital has not been measured to date. Little conclusive data is available to describe predictors of success. We aim determine the PDA closure rate following treatment with indomethacin at our institution. We also examine factors correlating with success and observe.

Methods: A retrospective chart review was conducted of neonates treated with indomethacin for PDA ligation at St. Joseph's hospital. Data were collected to represent diagnostic, treatment, and monitoring parameters. SPSS 12.0 database was used to calculate ratios, means and other statistical outcomes. Factors identified apriori were included in a logistic regression model to determine predictors of success.

Results: Efficacy with indomethacin was found to be 54.7 % in our population. Trends observed indicate that indomethacin may be most effective in patients with greater gestational age and birthweight, and a longer treatment course. We observed minimal adverse effects in our patient population.

Conclusions: Our results indicate that the benefits of using indomethacin for treatment of PDA outweigh the risks posed to the patient. Further investigations with larger study groups and a prospective design may determine the best treatment regiment and ideal patient for treatment of PDA with indomethacin.

Keywords: *Patent ductus arteriosus (PDA), indomethacin, chart review*

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ENCORE PRESENTATION

Retrospective methods of measuring practice change of pharmacists in continuing education

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ENCORE PRESENTATION

Systematic protocol for managing drug information requests

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Use of LABAs adversely affects resting heart rate in CHF patients receiving Beta-blocker Therapy

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Funding Source: None

Background: Short-acting beta agonists have been shown to increase the risk of hospital admission for congestive heart failure (CHF) in patients with left ventricular (LV) systolic dysfunction. Long-acting beta-agonists (LABAs) (i.e., salmeterol and formoterol) are recommended for management of obstructive airways disease but the potential aggravant effect of these agents in patients with CHF is unknown.

Method: A retrospective cohort study involving 67 outpatients with LV systolic dysfunction (31 LABA users and 36 controls), matched for age, gender, LV ejection fraction and index date was performed to compare resting physiologic parameters (i.e., heart rate [HR], rate-pressure product [RPP]) and hospital admissions between the two groups.

Results: During a mean follow-up period of 2.5 years, no differences were detected in terms of HR, RPP or hospitalizations between LABA users and controls (mean HR of 76.5 + 15 bpm versus 70.5 + 16.2 bpm and mean RPP of 9276 + 2806 bpm×mmHg versus 8784 + 2597 bpm×mmHg respectively). No difference in the number of patients hospitalized for any reason was noted between the groups (68% versus 67% respectively). Subgroup analysis demonstrated that in patients who received beta-blocker therapy, the HR was greater (74.8 + 10.5 bpm) in LABA users than in controls (64.9 + 11.9 bpm) (p=0.014).

Conclusion: LABA therapy in patients with CHF was not associated with increased resting HR, RPP or hospitalizations. In patients who received beta-blockers, HR was greater in patients who received LABA therapy than in controls.

Keywords: *Long-acting beta-agonists, heart failure*

AUTHOR INDEX
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