

# THE CANADIAN JOURNAL OF CLINICAL PHARMACOLOGY

JOURNAL CANADIEN DE PHARMACOLOGIE CLINIQUE

Published in the Canadian Journal of Clinical Pharmacology  
Online at [www.cjcp.ca](http://www.cjcp.ca)

## Second Canadian Therapeutics Congress Joint Scientific Meeting of

**CSCP/ SCPC**

Canadian Society for Clinical Pharmacology  
Société Canadienne de Pharmacologie Clinique

**CCCP**

Canadian College of Clinical Pharmacology  
Collège Canadien de Pharmacie Clinique

**CAPT/ ACTP**

Canadian Association for Population Therapeutics  
Association Canadienne de la Thérapeutique des Populations

**APRIL 13 - 19, 2005**

**Renaissance Vancouver  
Harbourside Hotel  
&  
BC Research Institute for  
Children's & Women's Health  
Vancouver, BC**

---

# ABSTRACTS

---

## SECOND CANADIAN THERAPEUTICS CONGRESS

April 13-19, 2005

Vancouver, British Columbia

### CAPT- ORAL PRESENTATIONS

1

#### **A Canadian economic analysis of the short and long-term cost effectiveness of the use of clopidogrel in reducing the risk of major cardiac event**

Kolm P, Yuan Y, Veledar E, Forte L, Amin M, Jackson J, Bouin O, Mehta S, Lamy A, Weintraub W  
Emory University, Atlanta, GA, USA

*Corresponding Author:* [paul.kolm@emory.edu](mailto:paul.kolm@emory.edu)

**Background:** Results from three pivotal studies, Clopidogrel in Unstable angina to prevent Recurrent Events (CURE), PCI-CURE, and Clopidogrel for the Reduction of Events During Observation (CREDO), demonstrated that up to 12 months of clopidogrel in combination with ASA significantly reduced the absolute combined risk of death, MI or stroke by 2-3%. We sought to determine the incremental cost-effectiveness per event prevented over one year and estimate the incremental cost-effectiveness per life year gained (LYG).

**Methods:** Canadian healthcare resource utilization costs were obtained from Case Mix Group costing from the 2003 Health Funding and Costing Branch of Alberta Health and Wellness Report. Cost effectiveness was expressed as the incremental cost effectiveness ratio of cost per event prevented (ICERep) or cost per life year gained (ICERlyg). 95% confidence intervals (CI) were obtained by bootstrap methods. The Canadian cost of clopidogrel was C\$2.40 per 75mg. Life expectancy in trial survivors was estimated from discounted Framingham and Saskatchewan data. Sensitivity analyses were performed for life expectancy reductions of 50% and 80%.

**Results:** Total per patient costs were higher in the clopidogrel arm in all three studies (C\$263, C\$333, C\$455 annually for CURE, PCI-CURE and CREDO respectively). All ICEReps were less than C\$16,000 and all ICERlygs were less than C\$5,000.

**Conclusions:** The results suggest that the use of clopidogrel in patients with acute coronary syndrome or undergoing percutaneous intervention is highly cost-effective in the Canadian healthcare system. Clopidogrel is also cost-effective relative to other cardiovascular therapies that are widely reimbursed in Canada.

**Key words:** *Clopidogrel, cardiovascular, cost-effectiveness*

2

#### **A comparison of asthma medication use in publicly versus privately insured children with asthma**

Ungar WJ, Kozyrskyj K, Paterson M, Mamdani M, Gunraj N, Ahmad F

The Hospital for Sick Children, Toronto, Ontario, Institute for Clinical Evaluative Sciences, Toronto, Ontario, Brogan Inc., Ottawa, Ontario, Manitoba Centre for Health Policy, Winnipeg, Manitoba, Canada

*Corresponding Author:* [wendy.ungar@sickkids.ca](mailto:wendy.ungar@sickkids.ca)

**Background:** Asthma is the most common chronic disease in childhood. To ensure optimal control, children must have access to necessary medications, including inhaled corticosteroids for maintenance and bronchodilators as needed. The objective was to compare asthma medication use in publicly insured social assistance children to privately insured children with asthma.

**Methods:** Identical case definitions were used to create public (n=12,767) and private (n=17,046) cohorts of asthmatic Ontario children aged 2-14 years using 2002 aggregate private sector claims and 1998-2001 Ontario Drug Benefits database claims. Use of bronchodilators (BD), inhaled corticosteroids (ICS), leukotriene antagonists (LA) and oral corticosteroids (OS) were compared between cohorts.

**Results:** In contravention of guidelines, 12% of social assistance children received BD monotherapy compared to 1% of privately insured children. Combined therapy of ICS+BD with or without LAs was observed in 70% of privately insured children compared to 44% of social assistance children. Despite apparently better management in the private group, OS use, indicating a severe exacerbation, was 16% in the private compared to 12% in the publicly insured group. While the average annual number of claims were similar in the private and public groups (7.3 vs. 7.1), privately insured children had more ICS claims (3.2 vs. 2.9) and fewer BD claims (2.9 vs. 3.9).

**Conclusions:** Privately insured children appeared to be better managed than social assistance children. Differences in socioeconomic status and formulary listings may explain observed differences. Policies governing public and private drug plans must ensure adequate access to necessary medications for children with asthma.

**Key words:** *Asthma medication use, medication insurance, children*

3

### Addressing Canada's national pharmaceutical strategy (NPS): electronic systems for pharmacosurveillance

Holbrook A,<sup>1,2,3,4</sup> Grootendorst P,<sup>2,4</sup> Willison D,<sup>2,3</sup> Sebaldt R,<sup>1,2,3</sup> Goldsmith G,<sup>2,3</sup> Keshavjee K,<sup>2</sup> Leung M,<sup>4</sup> Gaebel K<sup>2</sup>

<sup>1</sup>Division of Clinical Pharmacology & Therapeutics, <sup>2</sup>Centre for Evaluation of Medicines, St Joseph's Hospital, <sup>3</sup>Department of Clinical Epidemiology & Biostatistics- all at McMaster University, <sup>4</sup>Faculty Pharmaceutical Sciences, University of Toronto, Canada

Corresponding Author: [holbrook@mcmaster.ca](mailto:holbrook@mcmaster.ca)

**Background:** The NPS is to “strengthen evaluation of real-world drug safety and effectiveness” and “enhance analysis of cost drivers and cost-effectiveness”. We examined data needs for post-marketing risk: benefit and cost-effectiveness analysis for medications, investigated the ability of key electronic resources to meet these needs and the potential impact of evolving privacy guidelines and legislation on use of the data.

**Methods:** A nominal group consensus conference, representing 12 stakeholder groups involved in medication use, was held. Using the highly ranked data items as the “gold standard” dataset, the leading electronic healthcare data resources –large administrative databases (LADs), electronic medical records (EMRs) and patient registries (PRs)–were dissected to evaluate data availability and completeness. Privacy laws and research guidelines were reviewed for their impact on transfer and use of data from the data resources for research and regulatory purposes.

**Results:** 138 data items were declared necessary for routine pharmacosurveillance purposes, including 64 drug utilization variables. LADs had very complete data for a limited number of fields while EMRs with an e-prescribing link could contain all necessary fields but the missing data rate was high for many fields. The resources are frequently complementary but linkage between them is very rare in Canada. The interpretation by research ethics boards and data custodians of privacy legislation, meant to limit commercial use of health information, appears to have created barriers in the use and sharing of anonymized health data especially across provincial boundaries.

**Conclusions:** A “gold standard” dataset for pharmacosurveillance purposes has been created. Existing electronic health databases are inadequate on their own, but electronic health records with e-prescribing linkages are the best potential data source. The negative influence of privacy legislation on sharing information needs to be addressed.

**Key words:** *Pharmacosurveillance, databases, privacy*

4

### Canadian cost-effectiveness analysis of anastrozole versus tamoxifen in early breast cancer: the value of extrapolation

Verma S,<sup>1</sup> Rocchi, A,<sup>2</sup> Cheung, S<sup>3</sup>

<sup>1</sup>Ottawa Regional Cancer Centre, Ottawa, Canada,

<sup>2</sup>Axia Research, Hamilton, Canada, <sup>3</sup>AstraZeneca Canada, Mississauga, Canada

Corresponding Author: [angela@axiaresearch.com](mailto:angela@axiaresearch.com)

**Background:** Compared to tamoxifen, anastrozole (Arimidex) has demonstrated a 2% reduction in recurrence for post-menopausal, hormone receptor positive (HR+) women with early breast cancer over four years in the ATAC trial (Arimidex, Tamoxifen Alone or in Combination).

**Methods:** A Markov economic model was developed to extrapolate trial results over a lifetime horizon. Data were abstracted from the ATAC trial to assign events in the first three years of the model. Subsequently, event rates were estimated based on the literature and databases. Resource utilization was derived from Statistics Canada's Population Health Model (for breast cancer treatment), an expert panel and the literature. Prices were obtained from 2002 Canadian sources, using a health care system perspective and a 5% discount rate. Univariate and probabilistic sensitivity analyses were conducted.

**Results:** Anastrozole therapy had higher hormonal treatment costs compared to tamoxifen therapy in the short term (an additional \$7K per anastrozole patient), but later reduced costs by preventing downstream recurrences and deaths from breast cancer. Anastrozole patients were projected to experience a 7.6% absolute risk reduction of breast cancer recurrence and a 3.2% absolute risk reduction in breast cancer death, for a net cost of \$26K per quality-adjusted life year gained. Results were sensitive to the duration and extent of anastrozole benefit but were only modestly sensitive to other factors.

**Conclusions:** When compared to tamoxifen, anastrozole therapy is predicted to be cost-effective in post-menopausal, HR+ early breast cancer patients. Lifetime extrapolation was necessary to understand the clinical benefit observed over the four-year trial.

**Key words:** *Economic, anastrozole, breast cancer*

5

**Case control study of the association between use of acid suppression drugs and risk of gastric cancer**

Tamim HM, Duranceau A, Chen L-Q, LeLorier J  
CR-CHUM, Pharmacoepidemiology &  
Pharmacoeconomics Unit, University of Montreal,  
Montreal

*Corresponding Author:* [hani.tamim@elf.mcgill.ca](mailto:hani.tamim@elf.mcgill.ca)

**Background:** The objective of this study was to assess the association between exposure to acid suppression drugs and risk of gastric cancer.

**Methods:** We carried out a case-control study using data from the RAMQ. Cases included a 22% random sample of subjects with first time diagnosis of gastric cancer between 1995 and 2004. At least 4 controls were randomly selected and matched on age and sex. To be included in our study, cases and controls had to have a minimum of 5 years of coverage with the RAMQ prescription drug plan. The exposure definition was based on the summation of the defined daily doses (DDD) of either Histamine H2 receptor antagonist (H2RAs) or Proton Pump Inhibitors (PPIs) for each individual, which was further categorized into quartiles.

**Results:** During the study period, 1538 gastric cancer cases were identified in the RAMQ, who were matched to 12291 controls. The RRs for the association between the quartiles of the DDD of exposure to H2RAs and PPIs and risk of gastric cancer were: 1.42 (95% CI: 1.19-1.70) for the first quartile; 1.35 (95% CI: 1.13-1.61) for the second quartile; 1.51 (95% CI: 1.27-1.80) for the third quartile; and 1.17 (95% CI: 0.96-1.43) for the fourth quartile. The association between exposure to either H2RAs or PPIs alone gave similar results.

**Conclusion:** We conclude that this association is probably not causal but due to confounding by indication.

**Key words:** *PPI, cancer, case-control*

6

**Continued evidence for the suboptimal treatment of osteoporosis among older adults**

Maxwell CJ, Roberts M, Poss J, Hirdes JP, Hanley D, Vik SA, Hogan DB

Departments of Community Health Sciences & Medicine, University of Calgary and Institute of Health Economics, Department of Health Studies & Gerontology, University of Waterloo

*Corresponding Author:* [maxwell@ucalgary.ca](mailto:maxwell@ucalgary.ca)

**Background:** Past research indicates that fewer than 30% of patients with fragility fractures are being treated for osteoporosis. Our objective was to examine treatment coverage in a well-defined older home care population diagnosed with osteoporosis and/or a prevalent fracture.

**Methods:** We examined cross-sectional data available in the Ontario RAI-HC database for 48,689 home care (HC) clients aged 65+ years assessed initially between Feb-July, 2004 across all 42 agencies. The RAI-HC is a provincially mandated standardized assessment instrument employed by trained HC nurses and includes items regarding clients' socio-demographic, functional, health, medication and health service use characteristics. All prescribed and OTC medications used in the past 7 days were coded. Optimal osteoporosis treatment was defined as any use of the following: bisphosphonate, calcium with vitamin D, hormone replacement therapy, calcitonin, raloxifene, among clients with a diagnosis of osteoporosis, recent hip or other fracture. Descriptive and multivariate analyses were used to examine patient characteristics associated with sub-optimal treatment.

**Results:** Approximately 28% (13,580) had a diagnosis of osteoporosis and/or prevalent fracture. Among this sample, the mean age was 82 (7.1) years, 87% were women, 63% were widowed and 67% had 3+ comorbid conditions. Of those with osteoporosis/fractures, 39% were receiving optimal treatment (primarily, a bisphosphonate). After adjustment for relevant confounders, factors significantly associated with treatment (OR: 95%CI) included: being male (0.40: .35-.45), functional disability (0.73: .66-.81), a recent fall (0.89: .82-.96), 6+ comorbid conditions (0.38: .33-.43), health instability (0.83: .76-.89), being widowed (0.85: .79-.93) and depression (0.86: .77-.97).

**Conclusions:** Our findings illustrate continued sub-optimal treatment rates among older persons with osteoporosis and prevalent fractures. Treatment coverage was particularly poor among men and more socially and physically vulnerable clients.

**Key words:** *Osteoporosis, fracture, medications, home care, aged*

7

### Cost-effectiveness of the anglo-scandinavian cardiac outcomes trial-lipid lowering arm (ASCOT-LLA) in Canada

Lindgren P,<sup>1,2</sup> Jönsson B,<sup>2</sup> Merikle E,<sup>3</sup> Rinfret S<sup>4</sup>

<sup>1</sup>Karolinska Institutet, <sup>2</sup>Institute of Environmental Medicine, <sup>3</sup>Stockholm School of Economics, <sup>4</sup>Pfizer Canada, Inc., <sup>4</sup>Centre Hospitalier de l'Université de Montréal, Canada

Corresponding Author: [elizabeth.merikle@pfizer.com](mailto:elizabeth.merikle@pfizer.com)

**Background:** In the Anglo-Scandinavian Outcomes Trial (ASCOT), patients with normal or mildly elevated cholesterol and treated hypertension, treated with atorvastatin 10mg had significant reduction in CV events and procedures. The objective of this study was to evaluate the cost-effectiveness (CE) of this strategy in the Canadian health care system.

**Methods:** Cardiovascular events and procedures, number of non-fatal myocardial infarctions (MI) and cardiovascular deaths were the measures of effectiveness. Resources used (study drug, concomitant medications, hospitalization, ambulatory visits) were estimated based on data collected on the case report forms, and local costs for Canada (2004 CAD) were applied. Data from the intention-to-treat population were aggregated.

**Results:** The net incremental cost per-patient in the atorvastatin treatment group was \$958 (total cost of \$5 445 vs. \$ 4 487 in the placebo arm). Cost for the study drug was \$1,707. Approximately half of the cost of treatment was offset by savings due to reduced use of other resources, mainly hospitalisations. Treatment with atorvastatin was thus more expensive than placebo but also more effective, with a CE ratio of \$27,063 (95% C.I. \$12,507-\$65,348) per event avoided. As a benchmark value, primary prevention in hyperlipidemic men with pravastatin is considered cost-effective, with a cost per event avoided (cardiovascular events and procedures, MIs, CHD death, and stroke) of \$167,760 CAD.

**Conclusion:** Based on comparisons with other studies on lipid-lowering, we conclude that treatment as in the ASCOT study, with atorvastatin 10 mg, is a cost-effective treatment strategy.

**Key words:** *Cost-effectiveness, dyslipidemia, atorvastatin*

8

### Do proton pump inhibitors (PPI) infer additional gastrointestinal protection in patients given celecoxib? A retrospective cohort study

Rahme E, Barkun AN, Toubouti Y, Rochon S, LeLorier J

McGill University Health Centre Research Institute, Montreal

Corresponding Author: [elham.rahme@mcgill.ca](mailto:elham.rahme@mcgill.ca)

**Background:** Proton pump inhibitors are prescribed with non-selective NSAIDs to prevent and treat NSAID-associated gastropathy. It is unclear whether the utilization of a PPI with celecoxib confers additional gastrointestinal (GI) protection in elderly patients.

**Objectives:** To assess the association between GI hospitalizations and the use of celecoxib & PPI, celecoxib alone, NSAID& PPI or NSAID alone and to identify patient subgroups in whom the addition of a PPI to celecoxib is beneficial.

**Methods:** We conducted a population-based retrospective cohort study using Quebec government administrative databases. Patients 66 years of age or older were included at the dispensing date of their first filled prescription (index date) for celecoxib or an NSAID between April 1999 and December 2002. They were followed from the index-date until the occurrence of a GI hospitalization, death or the last day of supplied medication for either celecoxib or an NSAID in the study period. Cox regression models with time-dependent exposure were used to compare the hazard rates of GI hospitalization between the four groups: celecoxib & PPI, celecoxib alone, NSAID& PPI or NSAID alone, adjusting for patient characteristics at the index date.

**Results:** A total of 332,491 patients were included. The adjusted GI hospitalization hazard rate was significantly lower among patients given celecoxib & PPI compared to those given celecoxib alone (hazard ratio (HR) 0.69, 95% CI 0.52-0.93). The adjusted hazard rate among patients given NSAID & PPI was similar to that of patients given celecoxib alone (0.98, 0.67-1.45) while the rate among patients given NSAID alone was about twice as high as that of patients given celecoxib (2.18, 1.82-2.61). Stratified analyses showed that celecoxib alone was the GI-safest treatment option in patients 66-74 years of age, not taking aspirin and who did not have other GI risk factors. In all other groups the GI-risk associated with celecoxib seemed similar to that associated with NSAIDs & PPI. The results also showed that the use of a PPI with celecoxib may be beneficial in high-risk patients aged 75 or older and in patients using aspirin.

**Conclusions:** Celecoxib alone seemed as GI-safe as NSAIDs combined with a PPI in most patients. PPI conferred additional protection to celecoxib for older patients and for patients taking aspirin. The addition of a PPI to celecoxib did not seem beneficial for patients without these GI-risk factors.

**Key words:** *Gastrointestinal bleeding, celecoxib, proton pump inhibitor*

9

### **Economic evaluation of first-line treatments for depression in primary care: a Canadian probabilistic cost-effectiveness model**

Hemels ME,<sup>1</sup> Rocchi A,<sup>2</sup> Kennedy S,<sup>3</sup> Rousseau M<sup>4</sup>

<sup>1</sup>Lundbeck SA, Paris, France, <sup>2</sup>Axia Research, Hamilton, Canada, <sup>3</sup>University Health Network, Toronto, Canada <sup>4</sup>Lundbeck Canada, Montreal, Canada

*Corresponding Author:* [MEHH@Lundbeck.com](mailto:MEHH@Lundbeck.com)

**Objectives:** To assess the cost-effectiveness of escitalopram (10-20mg) vs. citalopram (20-40mg) and venlafaxine (75-150mg) in the first-line treatment of major depressive disorder in primary care in Canada.

**Methods:** A two-path decision analytic model was used. All patients started at the primary path and were referred to specialist care in the secondary path in case of insufficient response. Model inputs included drug-specific probabilities from a meta-analysis of four randomized direct-comparator trials, physician surveys and literature. Main outcome measures were success (remission, defined as Montgomery-Åsberg Depression Rating Scale  $\geq 12$ , and maintained for six months) and costs of treatment (drug costs, physician visits, hospitalizations). Patients were followed for six months after either remission or referral to secondary care. The analysis employed both the Ministry of Health (MoH) and societal perspectives. The Human Capital approach was used to estimate societal costs of lost productivity. Prices were from 2004 Canadian sources.

**Results:** After 6 months, expected success rate was 55% for escitalopram compared to 45% for citalopram, and 63% versus 62% for escitalopram and venlafaxine. Despite escitalopram's higher acquisition cost (\$1.55-\$1.65/day), expected cost from the MoH perspective per patient was \$11 higher for citalopram (\$0.875/day) and \$4 higher for venlafaxine (\$1.56-\$1.65/day). From the societal perspective, savings were \$249 and \$5 in favour of escitalopram respectively. Univariate and probabilistic sensitivity analyses demonstrated sensitivity only to the escitalopram remission rate.

**Conclusion:** Escitalopram demonstrated better clinical outcomes and cost equivalency compared with citalopram. Escitalopram demonstrated similar outcomes and costs compared to venlafaxine.

**Key words:** *Economic evaluation, escitalopram*

10

### **Economical impact of non-adherence to antidepressant treatment in the Quebec elderly population**

Moride Y, Galbaud du Fort G, Ducruet T, Crott R, Boivin JF, Perreault S, Laurier C, Monette J

Université de Montréal, Montreal, Canada

*Corresponding Author:* [yola.moride@umontreal.ca](mailto:yola.moride@umontreal.ca)

**Background:** The effectiveness of antidepressants in a real-life setting is compromised by low adherence. We hypothesize that, partly due to the somatization of depression, non-adherence results in higher costs of health services.

**Objective:** In the Quebec elderly (age 65+) outpatient population, to assess the effect of non-adherence (<6 months) on the costs of prescribed medications, medical services, and hospitalizations.

**Methods:** A fixed retrospective cohort study was conducted using the Quebec health databases (RAMQ). Elderly users of newer antidepressants (fluoxetine, fluvoxamin, paroxetine, sertraline, nefazodone, venlafaxine; n=12 825) were randomly selected. If a switch occurred before 6 months, treatment with the initial product did not contribute to adherence but was accounted for in the costs. Cost of outpatient medical visits and medications over the 12 months after treatment initiation were obtained from the RAMQ databases, and hospitalizations through Med-Echo hospitalization database.

**Results:** 56% patients received at least 6 months of treatment with the same product, whether or not with the initial product. Non-adherent and adherent patients differed in the mean number of hospital-days for non-psychiatric diagnoses (5.63 v. 4.58). After controlling for age, gender, Chronic Disease Score, socio-economic status, prescriber's specialty, number of medical services and prescriptions in the previous year, log-transformed costs of medical services did not differ significantly across the two groups, and costs of non-antidepressant medications were greater for adherent patients.

**Conclusions:** In this population, we were unable to demonstrate that poor adherence resulted in higher health care costs, with the exception of hospitalizations.

**Key Words:** *Pharmacoeconomics, administrative databases, antidepressants*

11

### Factors influencing the initiation of an osteoporosis-related pharmacotherapy: a population-based analysis

Caetano CA, Metge CJ, Leslie WD

Faculty of Pharmacy, University of Manitoba, Manitoba,

Corresponding Author: [pcaetano@shaw.ca](mailto:pcaetano@shaw.ca)

**Objective:** Identify clinical and non-clinical factors influencing the initiation of an osteoporosis-related pharmacotherapy using population-based administrative and clinical databases.

**Methods:** Hospital, physician, pharmaceutical, clinical (bone mineral density results) and demographic data for women continuously residing in Manitoba from 1985 through 2002 were obtained from provincial administrative databases. Outcome variable: Initiation of an osteoporosis-related medication (OSRx; including hormone replacement therapy [HRT], bisphosphonates, selective estrogen receptor modulators [SERM], and calcitonin). Explanatory variables included: BMD test (yes/no), prior osteoporotic fracture (hip, spine, rib, or vertebral) after age 50, age, comorbidity level, number of other prescription drugs used, income quintile, and urban vs. rural residence. Likelihood of initiating an OSRx was analyzed by Cox proportional hazards regression.

**Results:** 112,464 women satisfied the inclusion criteria, of which, 14,031 women (12.5%) initiated at least one OSRx within the study period. Predictors of OSRx initiation included: prior BMD test (RR 9.00 (95%CL: 8.27, 9.80)), an osteoporosis-related fracture after age 50, higher income level, long-term oral corticoid steroid use, and the number of other prescription drugs used. Each of these factors strongly interacted with age. For instance, women aged 80 years and over were nearly 4.5 times more likely to initiate therapy subsequent to a BMD assessment than women aged 50-59. Women with BMD results indicating osteoporosis at the spine or hip were more likely to initiate an OSRx [RR=7.72 (95%CL: 6.77-8.79) and RR=6.14 (95%CL 5.44-6.92) spine & hip, respectively], compared to women with normal BMD.

**Conclusions:** Receipt of a BMD assessment increases the likelihood a woman will initiate an OSRx, particularly in older women diagnosed with osteopenia and/or osteoporosis according to their test results.

**Key Words:** Osteoporosis, administrative databases, treatment initiation

12

### Financial barriers to medication use in children with asthma: an analysis of private sector prescription medication claims

Ungar WJ, Ahmad F, Kozyrskyj A, Paterson M, Mamdani M

The Hospital for Sick Children, Toronto, Ontario, Canada, Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, Brogan Inc., Ottawa, Ontario, Canada, Manitoba Centre for Health Policy, Winnipeg, Manitoba, Canada

Corresponding Author: [wendy.ungar@sickkids.ca](mailto:wendy.ungar@sickkids.ca)

**Background:** The highest incidence of asthma occurs in children. Proper management requires treatment with multiple expensive medications. For private drug plan subscribers, deductibles and co-payments constitute a user fee which may impede access. The primary objective was to examine the impact of co-pay level on asthma medication use in asthmatic children in private drug plans.

**Methods:** A cohort of 17,046 asthmatic Ontario children from an aggregated private sector claims database were classified as zero (no co-payment), low (<20%) or high (>20%) co-payment. Use of bronchodilators (BD), inhaled corticosteroids (ICS), leukotriene antagonists (LA), oral corticosteroids (OS) and combinations were examined in 2003. Multiple linear and logistic regressions compared medication use between groups controlling for age and sex.

**Results:** Annual asthma medication claims per child were significantly lower in the high co-pay group (6.6) compared to the zero (7.0) and low co-pay (7.2) groups (p<0.0001). Children in the high co-pay group were less likely to receive concomitant BDs, ICSs and LAs compared to the low co-pay group, Odds Ratio 0.78 (95% CI 0.67, 0.86). As a marker for asthma exacerbation, children in the high co-pay group were more likely to receive an OS compared to the zero co-pay group, Odds Ratio 1.1 (95% CI 1.0, 1.2).

**Conclusions:** Cost-sharing level affected asthma medication utilization, with the highest cost-sharing group exhibiting significantly lower use of maintenance medications and higher use of medications for acute exacerbation than other groups. These results are valuable to inform decisions regarding Pharmacare and drug plan management.

**Key Words:** Asthma medication use, co-payments, children

13

**Improved clinical outcomes associated with metformin in diabetic heart failure patients: The other side of the patient safety coin**

Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA

Institute of Health Economics, University of Alberta, Edmonton, Canada

*Corresponding Author:* [deurich@ualberta.ca](mailto:deurich@ualberta.ca)

**Background:** Metformin is contraindicated in patients with heart failure (HF) due to concerns over lactic acidosis. However, there is growing debate around this issue and the clinical effects of metformin in patients with HF and type 2 diabetes remains uncertain. The aim of this study was to evaluate the association between metformin use and clinical outcomes in patients with HF and type 2 diabetes.

**Methods:** Using the Saskatchewan Health databases, 12,272 new users of oral antidiabetic agents were identified between the years 1991-1996. A cohort of subjects with incident HF (n=1,833) were identified through administrative claims based on ICD-9 code 428 and grouped according to antidiabetic therapy: metformin monotherapy (n=208), sulfonylurea monotherapy (n=773), or combination therapy (n=852). Multivariate Cox proportional hazards models were used to assess differences in all-cause mortality, all-cause hospitalization, and the combination (i.e., all cause hospitalization or mortality).

**Results:** Average age of subjects was 72 years, 57% were male, and average follow-up was 2.5 (SD 2.0) years. Compared to the sulfonylurea group, metformin therapy was associated with significantly fewer deaths [adjusted hazard ratio (HR) 0.70 (95% CI 0.0.54-0.91) for metformin monotherapy and 0.61 (95% CI 0.52-0.72) for combination therapy] and fewer deaths or hospitalizations combined [HR 0.83 (95% CI 0.70-0.99) for metformin monotherapy and 0.86 (95% CI 0.77-0.96) for combination therapy]. There was no difference in time to first hospitalization between study groups.

**Conclusion:** Metformin, alone or in combination, in subjects with HF and type 2 diabetes was associated with reduced morbidity and mortality compared to sulfonylurea monotherapy.

**Key Words:** *Health outcomes, diabetes, heart failure*

14

**Optimizing thromboembolic and stroke prevention: interim analysis of a randomized controlled trial of pharmacist-managed oral anticoagulothrapy (pharma trial)**

Lalonde L, Brassard J, Fournier M, Martineau J, Blais N, Blais L, Perreault L, Vanier M-C

Faculty of Pharmacy, University of Montreal, Research team in primary care, Centre de santé et de services sociaux de Laval, Laval Quebec, Canada

*Corresponding Author:* [lyne.lalonde@umontreal.ca](mailto:lyne.lalonde@umontreal.ca)

**Background:** 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 the PMAS of Cité de la Santé de Laval with a prescription of warfarin for at least 6 months were randomly assigned to the ICM or CCM when IRN were stabilized. Patients were followed for 6 months after initiation of treatment. Percent time in expanded therapeutic range was assessed. The health-related quality of life was evaluated at one month and six months after the initiation of treatment using the SF-36, the EuroQol, and a specific treatment-related questionnaire.

**Results:** 97 family physicians participated and 136 patients were randomized (ICM: 65; CCM: 71). On average patients were randomized after 9.9 weeks (SD: 4.3) of treatment. Mean number of weeks between INR was equal to two weeks (SD: 1.4) in each group. The mean percent time (SD) in therapeutic range was similar in each group: CCM: 91% (12%) and ICM: 90% (16%). The mean difference (95% CI) in the percent time in range between the two groups was equal to 0.8% (-4% to 6%). Similar changes in HRQOL were observed in the two intervention groups.

**Conclusion:** This analysis suggests that INR control is equivalent in the ICM and CCM models of care. In final analysis, health care cost of each model will be evaluated.

**Key Words:** *Anticoagulant treatment, randomized controlled trial, health care*



15

### Paediatric adverse drug reaction reporting in Canada - understanding and future directions

Carleton B, Smith A, Gelin M, Heathcote S

Faculty of Pharmaceutical Sciences, University of British Columbia, Pharmaceutical Outcomes Programme, Children's and Women's Health Centre of British Columbia, Canada

*Corresponding Author:* [bcrltn@interchange.ubc.ca](mailto:bcrltn@interchange.ubc.ca)

**Background:** Severe adverse drug reactions (ADRs) are an important cause of childhood morbidity and mortality. 95% of ADRs are likely not reported, less than 25% of marketed drugs can be advertised as safe and effective in children; yet over 50% of Canadian children receive prescription drugs annually. The purpose of this review was to increase understanding of reported ADRs in Canadian children.

**Methods:** A retrospective analysis of 1193 suspected ADRs in Canadian children (age 0-18 years) reported to Health Canada (January 1998 - May 2002). These data were a paediatric subset of the Canadian Adverse Drug Reaction Information System database.

**Results:** Drugs most frequently associated with suspected ADRs: isotretinoin (n=56); paroxetine (n=42); methylphenidate (n= 41); amoxicillin (n=40); valproic acid (n= 32); bupropion (n=26); carbamazepine, fexofenadine (n=25); acetaminophen and clarithromycin (n=19). 59% of reports involved children 13-18 years of age; 18% children 6-13 years. Serious reports accounted for 61% of cases; 41 associated deaths were reported. Drugs most frequently associated with death: olanzepine (n=3); cisapride, enoxaparin, fentanyl, isotretinoin, propafenone, propofol and venlafaxine (n=2 each). Causal links between these suspected ADRs and clinical outcomes have not been established. Careful interpretation of data with 95% of the cases missing is warranted.

**Conclusion:** The level of ADR reporting is insufficient to improve patient safety. These data provide only clues to the incidence and frequency of ADRs. More detailed reporting, including case outcomes, is needed. Mandatory ADR reporting is unlikely to improve underreporting. This may be due to lack of ADR recognition because of overlapping drug and underlying disease effects. The use of trained surveillance personnel located in major health centres, with primary responsibility for ADR reporting may provide a more accurate determination of ADRs in Canadian children.

**Key Words:** *Adverse drug reaction surveillance*

16

### Patterns of medication use among older adults: use of non-prescribed medicines

Fisher J, Ballantyne P

University of Toronto, Faculty of Pharmacy, Toronto, Canada

*Corresponding Author:* [judith.balfour@utoronto.ca](mailto:judith.balfour@utoronto.ca)

**Background:** There is a large literature regarding the growing numbers and increasing costs of prescription medications provided to older adults. Given the wide array of non-prescription medicines and the potential for adverse drug-related events among older adults, there is a need for knowledge about the patterns of use of these medicines in this population. This paper examines the use of non-prescribed medicines, i.e., over-the-counter drugs and natural health products among older adults to enhance our knowledge regarding overall drug use among the elderly.

**Methods:** Data from the National Population Health Survey (1996/97) was analyzed to generate frequencies indicating the prevalence and relative distribution of the use of non-prescription medicines. The data was analyzed using logistic regression to examine factors associated with the exclusive use of non-prescribed medicines.

**Results:** One-quarter (25.5%) of Ontario seniors report exclusive use of non-prescribed medicines during the two days previous to the survey interview. An additional 33% of Ontario seniors report taking combinations of prescribed and non-prescribed medicines. Better self-reported health, fewer physician visits and being separated/divorced or widowed are associated with increased likelihood of exclusive use of non-prescribed medicines. Being female and having lower levels of education are associated with decreased likelihood of exclusive use of non-prescribed medicines.

**Conclusions:** The findings indicate the extent of intentional self-care by older adults. The extent of use of non-prescribed medicines that are available without consultation with a health professional raises concerns regarding the potential for inappropriate use or adverse drug reactions resulting from combining various types of medicines.

**Key Words:** *Older adults, medication use, logistic regression*

17

**Persistence in coxib prescribing despite cautionary messages**Willison D, Marshall D, Kulin N

Dept. of Clinical Epidemiology and Biostatistics, McMaster University Faculty of Health Sciences, Canada

*Corresponding Author:* [willison@mcmaster.ca](mailto:willison@mcmaster.ca)

**Background:** The introduction of celecoxib (Celebrex ®) and rofecoxib (Vioxx ®) to the Canadian market in 1999 were associated with extremely rapid uptake. Within months, controversy emerged over each product. 1. The VIGOR trial revealed elevated risk for acute myocardial infarction in patients treated with rofecoxib, compared with those taking naproxen. 2. The CLASS study was criticized for presenting favourable 6-month data when 12-month less-favourable data were already available. Each controversy was associated with substantial coverage in both professional and public media. Research question: Did the cautionary messages have an impact on the writing of new prescriptions for either rofecoxib or celecoxib in 2001-2002?

**Methods:** New prescriptions for coxibs, non-selective NSAIDs and Arthrotec dispensed for patients  $\geq 65$  years old were identified between April 1999 and May 2003 in Quebec (RAMQ), Ontario (ODB), and British Columbia (PharmaCare and PharmaNet). The monthly incidence of new prescriptions for each of these drugs per 100 beneficiaries 65+ was plotted for each province. Superimposed were critical dates including: formulary listing; CLASS and VIGOR study publication; web posting of the FDA reports; and other reports critical of rofecoxib and/or celecoxib.

**Results:** Writing of new prescriptions for coxibs was unaffected by adverse publicity in professional and lay media.

**Conclusions:** The lack of effect of cautionary messages may be due to: aggressive marketing; attenuated messages of risk in prominent journals; and low-profile responses of the FDA (USA) and Therapeutic Products Directorate (Canada). This is very troubling for busy clinicians who rely upon the latter two sources for critical evaluation of new therapies.

**Key Words:** *Coxib, drug utilization, prescribing patterns*

18

**Testing the impact of censoring on healthcare decision-making: the case of atrial fibrillation follow-up investigation of rhythm management (AFFIRM)**Fenwick E, Levy AR, Marshall DA, Blackhouse G, Slee A,

University of York, UK

*Corresponding Author:* [ealf100@york.ac.uk](mailto:ealf100@york.ac.uk)

**Background:** Loss to follow-up is a substantial problem for trial-based economic evaluations. This paper examines the impact of alternative censoring methods, applied to a trial-based cost-effectiveness analysis comparing rhythm-control to rate-control treatment for atrial fibrillation, on healthcare decision-making.

**Methods:** The AFFIRM trial reported a non-significant mean survival gain (0.08 year survival gain) and lower cost (US\$5,077) for rate-control subjects. Three different levels of censoring were applied in the cost-effectiveness analysis: no censoring of cost or survival, censoring of survival only and censoring of both cost and survival. In each case the data were bootstrapped to estimate the uncertainty in costs and survival, with results presented on the incremental cost-effectiveness plane and as cost-effectiveness acceptability curves. The expected value of perfect information was calculated to determine the worth of further research to reduce uncertainty.

**Results:** For each level of censoring, the results suggest that the decision-maker would choose to adopt rate-control treatment (with no censoring the ICER is \$5m per life year, with partial and full censoring rate-control dominates). However, while there is no impact of censoring upon the adoption decision, this is not the case for the level of uncertainty surrounding the decision or the EVPI. For a maximum acceptable ceiling ratio of \$50,000 per life year gained the EVPI for the decision varies between \$0.15 (partial censoring) to \$28 (full censoring) per patient.

**Conclusions:** The method of censoring adopted can impact upon the decisions made by a healthcare decision-maker.

**Key Words:** *Censoring methods, value of information analysis, decision-making*

19

**The accuracy of a prescription claims database for determining medication profiles of heart failure patients**

Shalansky S, Yim J, Jang L, Lau J, Ignaszewski A, Jung L, Clark C

St. Paul's Hospital and the University of British Columbia, Vancouver

*Corresponding Author:* [sshalansky@providencehealth.bc.ca](mailto:sshalansky@providencehealth.bc.ca)

**Objective:** To quantify agreement between the British Columbia prescription database (PharmaNet) and an interview-based assessment of current prescription medication usage.

**Methods:** Outpatients taking prescription medications for heart failure were identified through hospital clinic and community pharmacy records. Consenting patients brought their prescription medications to an interview where PharmaNet profiles were reviewed, and a consensus was reached regarding current medication usage.

**Results:** Of the 194 patients interviewed, 138 (71%) identified at least one discrepancy. Patients indicated that they currently took  $1.0 \pm 1.9$  (mean  $\pm$  SD) more prescription medications than displayed in the active medication list on PharmaNet. Of the 1457 medications taken by study patients, there were 268 discrepancies relating to the number or type of medications currently consumed; most commonly the result of overdue refills (15%), recent dosage changes (15%), or recent discontinuation (12%). The majority of medications involved in these discrepancies were listed on PharmaNet, but appeared inactive based on refill records (76%). There were 85 dosing discrepancies identified, most commonly the result of side effects (13%), or ineffectiveness (11%). Diuretics were involved in discrepancies more frequently than other medication classes (22%), followed by beta-blockers (11%) and ACE inhibitors (8%).

**Conclusions:** Most medications consumed by heart failure patients appeared somewhere on the PharmaNet profile, however it was often difficult to determine which medications were still active, or what dose was currently being used. Clinicians and researchers using PharmaNet to determine current medication consumption should be aware that most profiles contain inaccuracies, thus the information should be confirmed using secondary sources whenever possible.

**Key Words:** *Prescription claims databases, accuracy*

20

**The cost-effectiveness of patient self-managed versus physician-managed oral anticoagulation: a Bayesian approach**

Regier D, Marra CA, Gin K, Carter C, Fung A, Sunderji R

Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute, University of British Columbia, Vancouver, British Columbia, Canada

*Corresponding Author:* [dregier@vanhosp.bc.ca](mailto:dregier@vanhosp.bc.ca)

**Objective:** To evaluate the incremental cost-effectiveness of patient self-management (SM) vis-à-vis physician management (PM) for the management of chronic warfarin therapy from the British Columbia (B.C.) Ministry of Health perspective.

**Methods:** A Bayesian discrete-state discrete-time Markov model tracked the costs and quality adjusted life years (QALYs) accrued to patients receiving SM care vis-à-vis PM care over five years. Five distinct health states were defined: no events; minor or major hemorrhagic events; thromboembolic events; and death. Transition to health states depended on time spent below, in, and above therapeutic range (TTR). Data used to inform TTR were derived from a randomized trial conducted in B.C. comparing SM to PM.[1]Clinical event rates were modeled from a cohort study [2] and a large randomized trial.[3] Canadian 2003 costs were modeled and utility estimates were obtained from various sources.[4][5][6] A Dirichlet prior distribution was specified for the multinomial data and probabilistic sensitivity analysis characterized uncertainty. The model was estimated using WinBUGS.

**Results:** Model results indicate that over a five year period SM resulted in 19 fewer thromboembolic and 3 fewer major hemorrhagic events per 1,000 patients. The discounted incremental cost of SM over PM was \$292 (95%CI, \$106 to \$454) and QALYs gained was .04 (95% CI, 0 to .06). The discounted incremental cost per QALY gained was \$8,375 (95%CI, \$7,494 to \$20,350). If decision makers are willing to pay \$20,000 per QALY, there is a 97% probability that SM is cost-effective.

**Conclusion:** SM appears to be an effective and economically attractive strategy.

(See author for References)

**Key Words:** *Cost-effectiveness analysis, Bayesian Markov model, oral anticoagulation*

21

### The impact of informed consent for administrative database linkage on the validity of pharmacoepidemiological studies

Pilette D, Moride Y, Weinstock D, Perreault S, Lachaine J, Kennedy W, Lesk M

University of Montreal, Montreal, Canada

Corresponding Author: [david.pilette@umontreal.ca](mailto:david.pilette@umontreal.ca)

**Background:** Administrative health databases are limited by absence of information on clinical characteristics and covariates. It is possible to supplement the information through linkage with population surveys, or medical records. Patient consent for linkage may introduce a bias.

**Objective:** To compare the socio-demographic characteristics and medical history of individuals who consent and who do not consent to database linkage.

**Methods:** Data were obtained from two different settings: i) a retrospective cohort study of 230 patients recruited at a glaucoma clinic in a Montreal university hospital; ii) a cross-sectional population survey conducted in Québec (Santé-Québec). In the glaucoma study, patients were contacted by mail at the end of the follow-up to seek consent for linkage of hospital chart data with the Quebec health databases (RAMQ). In the Santé-Québec survey, consent was sought at the time of the interview.

**Results:** In the glaucoma study, 45.7 % patients consented to linkage. Patients who consented were significantly using more dipivefrin, pilocarpine and timolol maleate as glaucoma medication and less dorzolamide, had entered the cohort at later years, and were less frequently diagnosed with psychiatric conditions during follow-up. In the Santé-Québec survey, 60.4 % respondents consented to linkage, and were significantly more likely to be female, younger, have a higher level of education and income, and use less prescribed and non-prescribed medication.

**Conclusion:** The differences between patients who consent and who do not consent may introduce a selection bias. Pathways for bias and impact on results of pharmacoepidemiologic studies will be presented.

**Key Words:** *Informed consent, database linkage, ethics*

22

### Treatment patterns and health care resources utilisation by patients with asthma and COPD

Lachaine J,<sup>1</sup> Zlateva G,<sup>2</sup> Charbonneau C<sup>3</sup>

<sup>1</sup>Faculty of Pharmacy, University of Montreal, Canada,

<sup>2</sup>Pfizer Inc., New York, NY, USA, <sup>3</sup>Pfizer Canada,

Kirkland, Quebec, Canada

Corresponding Author: [jean.lachaine@umontreal.ca](mailto:jean.lachaine@umontreal.ca)

**Background:** Asthma and COPD are chronic diseases affecting a large proportion of the adult population and are among the leading causes of morbidity and mortality worldwide. The objectives of this study were to assess treatment patterns and health care resources utilisation by patients with asthma or COPD

**Methods:** This study was performed using data from a random sample of patients covered by the RAMQ drug plan. Adult patients with a diagnosis of asthma or COPD in 2000-2001 were identified and analysed.

**Results:** A total of 5,789 patients had a diagnosis of asthma, 2,816 a diagnosis of COPD and 1,105 had both diagnoses. No systematic treatment approach was observed. Combinations of respiratory medications were used by 39% of asthma patients, 42% of COPD patients and by 67% of patients with both diagnoses. Of the patients who were initially treated with a single agent, 27% were using a combination one year later. Cost of medications, physician visits, hospitalisations and emergency visits were calculated for the three groups of patients. Average total cost over a two-year period was \$4,689, \$8,550 and \$11,395 for patients with asthma, COPD and both diagnoses respectively. At \$458 in asthma, \$837 in COPD and \$1,209 for both diagnoses, cost of respiratory medications is about 10% of total health care costs associated with these patients.

**Conclusions:** Asthma and COPD are not associated with definite treatment patterns. Significant health care costs are associated with asthma and COPD patients, but respiratory medications only represent a small proportion of these costs.

**Key Words:** *COPD, asthma, cost*

23

**Use of  $\beta$ -blockers for treating heart failure among the elderly in British Columbia, 1993-2001**

Levy AR, Johnston KM, Gustafson P, Palepu A, Reid R, McGrail K, Brophy J  
CHEOS, St. Paul's Hospital, Vancouver, Canada

*Corresponding Author:* [alevy@cheos.ubc.ca](mailto:alevy@cheos.ubc.ca)

**Background:** Until the mid-1990s, Canadian consensus guidelines identified  $\beta$ -blocker therapy as being contraindicated for persons with heart failure (HF). Based on placebo-controlled randomized trials and economic evaluations that appeared subsequently, more recent consensus statements reversed that recommendation and advocated widespread use of  $\beta$ -blockers for moderate to severe HF. Our goal was to estimate, among elderly persons discharged after a first HF hospitalization, the extent to which  $\beta$ -blocker use increased after the reversal in recommendations.

**Methods:** We carried out a retrospective cohort study using a linked administrative database of hospital separations and medication claims. Included were all residents of British Columbia (BC), aged 65 years and over, sent home after being hospitalized with a principal discharge diagnosis of HF during fiscal years 1990-2001. To eliminate prevalent hospitalizations, we excluded subjects discharged with any diagnosis of HF between 1990 and 1993. The proportion dispensed a  $\beta$ -blocker within 30 days of discharge was estimated for triennial periods and was modeled using logistic regression.

**Results:** For all subjects, the proportion dispensed a  $\beta$ -blocker after their first hospitalization for HF increased from 2.2% in 1993-95 through 4.0% in 1996-98 to 7.4% in 1998-2001 (crude odds ratio = 3.6; 95% confidence interval 3.3 to 3.9).

**Conclusions:** In the latter half of the 1990s, there was a three-fold increase in the use of  $\beta$ -blocker therapy after an initial hospitalization for HF, consistent with new guidelines. However, absolute rates of  $\beta$ -blocker use remained lower than 10% in BC, indicating that many patients may yet be receiving the benefit.

**Key Words:**  *$\beta$ -blockers, heart failure, time trends*

24

**Using and interpreting cost-effectiveness acceptability curves (CEACs): An example using data from a trial of management strategies for atrial fibrillation**

Fenwick E, Marshall D, Levy A, Nichol G  
University of York, UK

*Corresponding Author:* [ealf100@york.ac.uk](mailto:ealf100@york.ac.uk)

**Background:** The CEAC is an intuitive graphical method for summarizing information on uncertainty in cost-effectiveness. This approach is applied to a trial-based cost-effectiveness analysis comparing rhythm-control to rate-control treatment for atrial fibrillation.

**Methods:** The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial reported a non-significant mean survival gain of 0.08 years (95% CI:-0.10 to 0.24) for rate-control subjects, and rate-control was less costly than rhythm control \$5,077 (95% CI:\$1,100 to \$11,006). However, these estimates do not take the joint uncertainty of costs and effects into consideration. The CEAC is derived from the joint distribution of incremental costs and incremental effects to show the probability that the data are consistent with a true cost-effectiveness ratio falling below a specified ceiling ratio.

**Results:** Based on effectiveness data only, either treatment is equally effective, with a small and not statistically significant trend in survival favouring rate-control. Considering the joint distribution of costs and effects, rate-control is the favoured initial treatment approach because of the lower cost compared to rhythm-control, despite the absence of a statistically significant difference in survival. For a maximum acceptable ceiling ratio of \$100,000 per life year gained, the proportion of the re-samples that were cost-effective was found to be 99.42%. The CEAC shows that the decision uncertainty surrounding the adoption of rate-control is less than 0.6% regardless of the maximum acceptable ceiling ratio.

**Conclusions:** The CEAC is straightforward to calculate, construct and interpret and is increasingly becoming a part of economic evaluations for decision makers.

**Key Words:** *Cost-effectiveness acceptability curve, atrial fibrillation, uncertainty*

**CAPT- POSTER PRESENTATIONS**

25

**A Canadian economic evaluation of pegasys® rbv™ (peginterferon-alpha2a with ribavirin) for treatment of chronic hepatitis C: patient subgroup analyses**Marotta PJ<sup>1</sup>, Myers RP<sup>2</sup>, Jacobs P<sup>3</sup>, Adams J<sup>4</sup><sup>1</sup>Liver Unit, Univ. of Western Ontario, London, Ontario, <sup>2</sup>Liver Unit, Univ. of Calgary, Calgary, Alberta, <sup>3</sup>Dept. of Public Health Sciences, Univ. of Alberta, Edmonton, Alberta, <sup>4</sup>Health Outcomes, Hoffmann-La Roche Limited, Mississauga, Ontario,*Corresponding Author:* [Jim.Adams@Roche.com](mailto:Jim.Adams@Roche.com)**Background:** Pegylated interferon-based regimens form the mainstay of therapy for treatment naïve, hepatitis C virus (HCV) mono-infected patients with elevated alanine aminotransferase (ALT) levels. However, recent Canadian consensus guidelines (Sherman et al, Can J Gastro 2004) recommend that treatment should also be considered for other patient subgroups, such as those patients with normal ALT levels, previous relapsers/non-responders or HIV/HCV co-infected individuals.**Methods:** A previously published Markov model (Zou et al, Can J Gastro 2000) was employed to estimate the cost-effectiveness of peginterferon (PEG)-alpha2a versus no treatment (and active comparators, where applicable) in the above specified subgroups. Direct costs were obtained from the Alberta Health and Wellness database; transition probabilities and utilities were obtained from the literature. In the base-case analysis, a representative cohort of Canadian patients (based on age, gender, genotype, etc.) was analysed.**Results:** (Contact author for table of summary of efficacy data). For each of the specified subgroups, the incremental cost-utility ratio of PEG-alpha2a/RBV versus no treatment varied from \$1,000 to \$17,349 per QALY. For HIV/HCV co-infected patients, PEG-alpha2a/RBV was dominant over interferon-alpha2b/RBV and PEG-alpha2b/RBV, with lower expected lifetime costs and improved quality-adjusted life expectancy, due to enhanced SVR rates. Previous sensitivity analyses have shown that changes in the values of relevant parameters (including age, genotype, and disease severity) do not appreciably alter the model results (Aspinall et al, CAPT 2004).**Conclusions:** Further to overall results previously presented, PEG-alpha2a/RBV is also a cost-effective therapy in the analysed subgroups of Canadian patients, namely those with normal ALT levels, those who failed previous treatment(s) or those with concurrent HIV/HCV co-infection.**Key Words:** *Chronic hepatitis C, economic evaluation, pegylated interferon*

26

**A cost-effectiveness analysis of INH treatment of TB contact populations**Tan M.<sup>1</sup> FitzGerald JM,<sup>1</sup> Marra F,<sup>2</sup> Moran-Mendoza O,<sup>3</sup> Marra CA<sup>1</sup><sup>1</sup>Centre for Clinical Epidemiology and Evaluation, Vancouver, BC, Canada, <sup>2</sup>BC Center for Diseases Control, Vancouver, BC, Canada, <sup>3</sup>Faculty of Medicine, Universidad Autonoma de San Luis Potosi, San Luis Potosi, Mexico*Corresponding Author:* [mitan@vanhosp.bc.ca](mailto:mitan@vanhosp.bc.ca)**Background:** Most tuberculosis (TB) contacts with a tuberculin skin test (TST) size < 5 mm are not advised isoniazid (INH) treatment for latent tuberculosis infection (LTBI), but some are at high TB risk. We evaluated the incremental cost-effectiveness of advising standard LTBI treatment, versus not, for hypothetically defined at-risk populations of TB contacts grouped by TST induration.**Methods:** A decision analytic model was developed using published data and local costs (including indirect costs) evaluated from a societal perspective in Y2003 Canadian dollars (\$1 CDN=\$0.75 US). Effectiveness was measured as TB cases prevented and quality-adjusted life-years (QALYs) based on Health Utilities Index Mark 3 values obtained from a sample of latent and active TB patients.**Results:** By either effectiveness measure, advising INH to TB contacts with a TST size < 5 mm and advanced HIV was almost cost saving, and the threshold relative risk of reactivation at which advising INH became cost saving was 12.4.**Conclusions:** It appears economically attractive to advise INH to TB contacts with TST ≥ 5 mm and some with TST size < 5 mm.**Key Words:** *Latent tuberculosis CEA*

27

### A population-based, cost-effectiveness analysis of INH treatment of TB contacts in British Columbia

Tan M,<sup>1</sup> FitzGerald JM,<sup>1</sup> Moran-Mendoza O,<sup>2</sup> Marra F,<sup>3</sup> Marra CA<sup>1</sup>

<sup>1</sup>Centre for Clinical Epidemiology and Evaluation, Vancouver, Canada, <sup>2</sup>Faculty of Medicine, Universidad Autonoma de San Luis Potosi, San Luis Potosi, Mexico, <sup>3</sup>BC Centre for Disease Control, Vancouver, Canada

Corresponding Author: [Michael.Tan325@yahoo.com](mailto:Michael.Tan325@yahoo.com)

**Background:** Most tuberculosis (TB) contacts with a tuberculin skin test (TST) size < 5 mm are not advised isoniazid (INH) treatment for latent tuberculosis infection (LTBI), but some are at high TB risk. We evaluated the cost-effectiveness of standard LTBI treatment (compared to none) for at-risk groups within a population-based cohort of TB contacts.

**Methods:** Administrative health data on 40,581 TB contacts from the BC Division of TB Control over the period 1990-2001 were analyzed. We estimated the incremental cost-effectiveness of advising INH, versus not, while adjusting for TST size, socio-demographics, and TB-predisposing comorbidities. Direct and indirect costs were assessed from a societal perspective in Y2003 Canadian dollars (\$1 CDN=\$0.75 US). Effectiveness was measured as TB cases prevented and quality-adjusted life-years (QALYs) based on Health Utilities Index Mark 3 values from a sample of latent and active TB patients. Probabilistic sensitivity analysis was done.

**Results:** Advising INH to TB contacts with a TST size < 5 mm and malnutrition is cost saving (p-value <0.05).

**Conclusions:** It appears economically attractive to advise INH to TB contacts with TST size  $\geq$  5 mm and some with TST size < 5 mm.

**Key Words:** *Latent tuberculosis CEA*

28

### A population-based "atlas" of drug utilization patterns

Rahim-Jamal S, Schaub P, McMahon M, Mooney D, Yan L, Morgan S

Centre for Health Services and Policy Research, Vancouver, Canada

Corresponding Author: [sherin@chspr.ubc.ca](mailto:sherin@chspr.ubc.ca)

**Background:** Within British Columbia (BC), per capita expenditures on pharmaceuticals increased by 87% over the period 1996-2002. This is primarily driven by increases in the volume of drug treatment received. This study examines regional variations in the utilization of the top ten drug classes, by expenditure, across BC, and examines the use of these drugs relative to the provincial average.

**Methods:** PharmaNet, a population-based, patient-specific pharmaceutical dataset describing the type, quantity, and cost of every prescription drug purchased by BC residents, was used to analyze and map the variation in prescription drug use for five age categories in sixteen geographic regions of the province.

**Results:** There were significant variations in age-standardized utilization of and, therefore, expenditure on prescription drugs across regions of BC. Age-standardized regional variation in prescription drug use was greatest for psychoanaleptics (17.5%), analgesics (14.8%), and lipid-reducing agents (14.2%). Absolute differences in utilization across regions were highest among elderly cohorts, whereas percentage differences were highest among children and young adults. Despite these findings, overall variations across regions were driven by differences in utilization among the largest demographic: populations aged 45-64 (roughly speaking, the baby boomers).

**Conclusion:** The wide regional variation in the utilization of certain drug classes begs the question of whether current prescribing and utilization of these drugs is appropriate. Which regions are under- and over-utilizing these drugs, and why? The challenge for policy makers is to ensure that drug use is both appropriate and cost-effective. Our analysis can assist policy-makers identify therapeutic areas deserving of investigation for potentially inappropriate prescribing.

**Key Words:** *Regional variation, drug utilization, population-based, patient specific data*

29

**Antibiotic exposure in infants and the development of asthma: a systematic review and meta-analysis**

Marra CA,<sup>1,2</sup> Lynd L,<sup>1,2</sup> Coombes M,<sup>2</sup> Richardson K,<sup>2</sup> Legal M,<sup>1</sup> FitzGerald JM,<sup>1,2</sup> Marra F<sup>1,3</sup>

<sup>1</sup>University of British Columbia, Vancouver, Canada, <sup>2</sup>Centre for Clinical Epidemiology and Evaluation, Vancouver, Canada, <sup>3</sup>BC Centre for Disease Control, Vancouver, Canada

*Corresponding Author:* [fawziah.marra@bccdc.ca](mailto:fawziah.marra@bccdc.ca)

**Background:** Antibiotic exposure in early childhood is suggested to contribute to the increasing childhood asthma prevalence in industrialized countries. While a number of published studies have tested this hypothesis, the results have been conflicting.

**Objective:** To explore the association between antibiotic exposure prior to one year of age and development of childhood asthma.

**Methods:** Observational studies investigating the association between antibiotic exposure and the risk of asthma were identified. Studies of participants exposed to one or more courses of antibiotics during their first year of life and diagnosed with childhood asthma by a physician were included. Childhood asthma was defined as diagnosis after the age of 1 year and before the age of 18 years.

**Results:** Of fourteen studies identified, eight (four retrospective and four prospective) met our inclusion criteria. The random effects pooled odds ratio over the eight studies summarizing the overall risk was 2.05 (95% CI, 1.41 - 2.99). The association was significantly stronger ( $p = 0.02$ ) in the retrospective studies than the prospective studies (2.82, 95% CI, 2.07 - 3.85 vs. 1.12, 95% CI, 0.88 - 1.42). Using five of the eight studies that reported adjusted odds ratios across number of antibiotic courses taken in the first year of life, the pooled dose-response odds ratio was 1.16 (95% CI, 1.05 - 2.99).

**Conclusions:** These pooled results suggest that children with antibiotic exposure in the first year of life may have a 2-fold increased risk of developing childhood asthma. However, additional large-scale prospective studies are needed to confirm a causal link and dose-response.

**Key Words:** *Antibiotics, childhood asthma, meta-analysis*

30

**Assessing prescription medications for priority regulatory review**

Rawson, NSB

Center for Health Care Policy and Evaluation, Eden Prairie, MN, USA

*Corresponding Author:* [nigel.s.rawson@gsk.com](mailto:nigel.s.rawson@gsk.com)

**Background:** Poor concordance exists between priority-status medications in Canada and the US. The objectives of this study were to obtain an evaluation of the clinical significance of new drugs approved in both countries from expert clinical pharmacologists, and to examine the concordance of their aggregate assessment with actual review status.

**Methods:** Five experts assessed 146 new medications approved in Canada and the US between 1996 and 2001 for clinical significance and merit for priority status.

**Results:** Four experts evaluated all 146 products; the other evaluated only 86. Concordance between individual assessments was poor ( $\kappa$ : 0.11-0.21). When their assessments were aggregated, the experts identified 18 (49%) of the 37 Canadian priority-status medications as clinically significant and 92 (84%) of the other products as not significant; figures for the US were 41% (24/59) and 87% (76/87). The sensitivity and specificity of the aggregate assessment of merit for priority status were <30% and >94% in both countries.

**Conclusions:** Although their concordance was low, the aggregate evaluations suggested that several priority-status products did not warrant such a review. Regulatory agencies select new medications of potential significance to receive shorter review times to minimize the delay in access. However, these findings suggest a more appropriate strategy is for agencies to devote sufficient resources to reviewing most medications within their performance standards. Disclaimer: Opinions and conclusions expressed do not necessarily represent those of the Center for Health Care Policy and Evaluation (where the work was performed), my current employer, the clinical pharmacologists, or the funding organization.

**Key Words:** *Priority review, clinical significance, United States, Canada*



### Assessment of patient characteristics associated with statin use (preliminary report)

Farahani P,<sup>1</sup> Gaebel K,<sup>1</sup> LeLorier J,<sup>2</sup> Perrault S,<sup>2</sup> Gillis J,<sup>3</sup> Soon J,<sup>4</sup> Levine M<sup>1</sup>

<sup>1</sup>Center for Evaluation of Medicines, McMaster University, Hamilton, Canada, <sup>2</sup>Université de Montréal, Montreal, Canada, <sup>3</sup>Dalhousie University, Halifax, Canada, <sup>4</sup>University of British Columbia, Vancouver, *Corresponding Author:* [farahap@mcmaster.ca](mailto:farahap@mcmaster.ca)

**Background:** Several randomized controlled trials have demonstrated the efficacy of HMG Co-A reductase inhibitors i.e., Statins, to prevent cardiovascular morbidity and mortality in dyslipidemic patients. Statin therapy is more cost-effective in secondary prevention compared to primary prevention, and in patients at higher risk of cardiovascular events. There is also evidence in community use that the discontinuation rate for Statins is higher than anticipated, despite a low adverse effect profile.

**Objectives:** Primary: To assess the patient characteristics associated with Statin use in community-based clinical practice, in four geographic regions across Canada. Secondary: (a) To assess amongst Statin users the proportion of patients that would meet accepted dyslipidemia management guidelines. (b) To assess amongst patients who discontinue Statin therapy the reasons for stopping treatment.

**Methods:** Patients who are filling a prescription for any anti-hyperlipidemia therapy in selected pharmacies in Ontario, Quebec, British Columbia and Nova Scotia are invited by pharmacy staff to participate in the study. All eligible patients agreeing to participate in the study are then interviewed over the telephone using CATI software. All physicians who are identified by the participating patients are requested to complete a short questionnaire. The data that are collected from the patient telephone interview and the fax-back form completed by the physicians include age, gender, sex, duration and dose of Statin utilization, comorbid conditions, cardiovascular risk factors, lipids profile (total cholesterol, LDL-C, HDL-C, triglycerides), quality of life (SF-12) and dietary modifications.

**Results:** Over 60% of patients using anti-hyperlipidemia treatment are more than 60 years old. More than 90% of patients receiving anti-hyperlipidemia treatment are Statin users. Anti-hyperlipidemia therapy is associated with a decrease in LDL-C ( $p < 0.001$ ), total cholesterol ( $p < 0.001$ ) and triglycerides ( $p < 0.01$ ). A non-significant trend for increasing HDL level was observed. A significant lag time of more than two years was observed between the time that the diagnosis of hyperlipidemia was made and when drug treatment was started ( $p < 0.01$ ). The average patient receiving a Statin has three or more cardiovascular risk factors, although some of these patients would still be considered as receiving a Statin for primary prevention.

**Conclusion:** Preliminary data suggests that most Statin users are at sufficient increased risk for cardiovascular events regardless of whether the Statin use is for primary or secondary prevention. Statin therapy appears to be effective at improving lipid profiles amongst users in the community.

**Key Words:** *Statins, anti-hyperlipidemia, population therapeutics*

### 32

#### Pharmacoepidemiogenomics—risks and benefits

Farahani P, Levine M

Centre for Evaluation of Medicines, St. Joseph's Healthcare, McMaster University, Hamilton, Canada

*Corresponding Author:* [farahap@mcmaster.ca](mailto:farahap@mcmaster.ca)

**Background:** Pharmacogenomics and pharmacogenetics can potentially revolutionized the field of medical therapeutics. An integrated, multi-dimensional approach is essential to explore the risks and benefits of for pharmacogenomics and pharmacogenetics at the population level.

**Objective:** To investigate and elaborate the impacts of pharmacogenomics and pharmacogenetics on health care delivery at the population level.

**Methods:** A systematic search through medical resources was conducted to identify the social aspects, economical frameworks and large-scale clinical application of genomic derived drugs.

**Results:** Despite advances in molecular medicine and biology for pharmacogenetics and pharmacogenomics, currently the population research in this area is well behind as a consequence of lack of practicality. Although scientific aspects of pharmacogenetics and pharmacogenomics therapeutics are exciting, cost-effectiveness, drugs pricing and pharmaceutical marketing should be addressed through research. Socio-epidemiological aspects of the pharmacogenetics and pharmacogenomics research call attention to data privacy and privacy protection, also availability of such a therapy for all individuals in the society and all geographical regions.

**Conclusion:** Dissemination and implementation of pharmacogenomics and pharmacogenetics for excellence of practical therapeutics at the population level requires an integrated action from various parties. This will be discussed in detail.

**Key Words:** *Pharmacogenomics, pharmacogenetics, pharmacoepidemiology*

33

### Assessment of provincial expenditures in depressed patients treated with venlafaxine XR vs SSRIs (APEX study)

Tahami Monfared AA, Sheehy O, Han D, LeLorier J  
Wyeth Pharmaceuticals, CR-CHUM (Hotel-Dieu), Canada

Corresponding Author: [amir.tahami@mail.mcgill.ca](mailto:amir.tahami@mail.mcgill.ca)

**Background:** Available pharmaco-economic data and RCTs published in recent years have suggested that achieving and sustaining remission of depression contributes to reductions in comorbidities and healthcare costs. Recent meta-analyses found venlafaxine, a dual-acting serotonin-norepinephrine reuptake inhibitor, produced significantly higher rates of remission compared with selective serotonin reuptake inhibitors (SSRIs). The objective of this study was to assess whether reductions in associated medical costs were observed in patients initiated treatment with venlafaxine XR (VXR) compared with SSRIs.

**Methods:** Using RAMQ claims databases, we identified a cohort of 17,144 patients who initiated therapy with an SSRI or VXR between 1996 and 2004. Using logistic regression, we identified differences in patients' socio-demographic and clinical characteristics. Overall direct medical costs during a 12-month period after the initiation of therapy were also estimated and compared using generalized linear models.

**Results:** The average acquisition cost of VXR was 20% higher than SSRIs, largely due to the availability of generic SSRIs. In contrast, the adjusted overall medical costs for patients treated with VXR was found to be 3% lower than those with an SSRI (cost ratio: 1.03 [95%CI: 0.99, 1.07]). Our study suggests that overall direct medical costs for patients who started antidepressant therapy with VXR are similar to, or lower than, those in SSRIs group. Fewer VXR recipients discontinued their initial therapy compared to SSRIs (persistence to treatment: 38.4% vs 29.4% at 6 months). Patients initially treated with VXR were less likely to require treatment switching. The compliance rate at 6 months was also statistically significant higher for VXR (57.5% vs 55.3%).

**Conclusion:** Offsetting of the higher acquisition cost of VXR compared with that of SSRIs may be accounted for by lower hospitalization and out-patient medical costs with VXR. Differences in the persistence in drug use may also, in part, explain the observed differences in average total healthcare costs between VXR and SSRIs.

**Key Words:** Antidepressants, utilization, administrative database

34

### Assessment of risks associated with short-term use of mefloquine in Canadian forces members: a descriptive cross-sectional study

Ma J, Vaillancourt R, Sampalis J  
Canadian Forces Health Services Group, Ottawa,  
Corresponding Author: [ma.j@forces.gc.ca](mailto:ma.j@forces.gc.ca)

**Background:** Media reports have implicated mefloquine as a contributor to adverse health effects experienced by military members serving in areas where chloroquine-resistant malaria is endemic. A systematic retrospective review has been undertaken to evaluate the health effects seen in members who received mefloquine for chemoprophylaxis against malaria.

**Methods:** Medical records of Regular Canadian Forces (CF) personnel who served in Somalia between 1992 and 1993 will be reviewed by trained data extractors. All health effects recorded during treatment with mefloquine will be assigned ICD-10-CA codes. Data extractors will also note if the effect has been reported with mefloquine, and rate the severity of the effect. Cohen's kappa will be calculated to determine concordance between extractors, and descriptive statistics used to report the health effects seen.

**Results:** The majority of the 1413 subjects identified were male (96%). A total of 2030 adverse health effects were recorded in the medical records, most of which were mild in severity. At least one adverse effect which could potentially have been related to mefloquine was reported in 39.2% of subjects. Of the adverse effects recorded, 13 were classified by the data extractors as major (12 cases of dizziness and 1 cardiac arrest). These results are consistent with those reported in other populations.

**Conclusions:** The results of this study have been applied to guide development of policies governing the provision of chemoprophylaxis during subsequent military missions. In particular, resources have been allocated to formalize the counselling provided to members regarding antimalarials and prevention of malaria infection.

**Key Words:** Mefloquine, adverse effects

35

### Associations between medication use and accident risk among members of the Canadian forces: a case-control study

Ma J, Vaillancourt R, Neutel CN, Sampalis J  
Canadian Forces Health Services Group, Ottawa, Canada

*Corresponding Author:* [ma.j@forces.gc.ca](mailto:ma.j@forces.gc.ca)

**Background:** Earlier studies evaluating the impact of medication use on accident risk are limited with regard to patient populations and drug classes. This study was undertaken to identify drugs which are consumed by generally healthy adults period prior to accidents.

**Methods:** A modified case-control design was used to allow to compare drug use in the two weeks preceding an accident. Subjects were employed as Regular members of the Canadian Forces (CF) between January 1999 and December 2001. Drug usage data was obtained from both CF pharmacies and an affiliated claims network. Accident data was gathered from three different reporting forms. Incidence risk ratios were calculated for both historical- and time-controlled analyses using the Mantel-Haenzel approach, and odds ratios employed to compare IRR from these two subanalyses.

**Results:** A total of 9921 subjects with 12,230 accidents were identified. Our final analysis identified 12 medication classes which were associated with accidents. The strongest associations detected were for antispasmodics and anticholinergics (OR 5.598, 95% CI 2.143 - 14.626). Unlike previous reports, other study identified some association which are not easily explained (e.g., estrogens and oral contraceptives). This suggests that mechanisms influencing accident risk in younger adults differ from those in the elderly.

**Conclusions:** Our study has identified classes of drugs which are more commonly consumed prior to accident occurrence. Where a direct pharmacological effect is probable, policies to discourage use of such medications in safety-critical occupations should be considered. Additional effort should be made to replicate these results with other databases of similarly-aged populations.

**Key Words:** *Drug-induced, accidents, case-control*

36

{ WITHDRAWN }

### Best practices and innovative approaches to academic detailing: a synthesis of Canadian and International experiences

Bacovsky R,<sup>1</sup> Maclure M,<sup>2</sup> Nguyen A,<sup>3</sup> Lopatka H,<sup>4</sup> Regier, L,<sup>5</sup> Bugden S,<sup>6</sup> Allen M<sup>7</sup>

<sup>1</sup>Integra Consulting Ltd, <sup>2</sup>School of Health Information Science, University of Victoria, <sup>3</sup>BC Community Drug Utilization Program, <sup>4</sup>Alberta Drug Utilization Program, <sup>5</sup>The RxFiles - Academic Detailing Program, Saskatchewan, <sup>6</sup>Prescription Information Service of Manitoba, <sup>7</sup>Dalhousie University CME, Canada

*Corresponding Author:* [bacovsky@telusplanet.net](mailto:bacovsky@telusplanet.net)

37

### Burden of Illness in Trauma Patients: a Canadian tertiary hospital perspective

Mittmann N, Seung SJ, Pisani N, Callum J, Smith T  
HOPE Research Centre, Sunnybrook and Women's  
College Health Sciences Centre, University of Toronto,  
Toronto, Ontario, Canada

*Corresponding Author:* [nicole.mittmann@sw.ca](mailto:nicole.mittmann@sw.ca)

**Background:** A burden of illness study was conducted to identify and quantify the resource utilization elements associated with the management of trauma patients

**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) for the resources used.

**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 ISS score was 41.3. Average total cost per patient was \$62,137. Disaggregated average total costs were \$44,861 (72.2%) for surgical procedures, \$13,691 (22.0%) for blood products and \$3,241 (5.2%) for laboratory/microbiology/ diagnostic procedures.

**Conclusion:** The average cost per trauma patient who received at least 10 units of blood was \$62,137. The cost drivers were the surgical procedures. Blood products represented 20% of the overall direct costs. Our results may have implications for the funding trauma centers in Canada.

**Key Words:** *Trauma, burden of illness, economics*

38

### Can NPDUIS be used to evaluate an educational outreach trial by the Canadian academic detailing collaboration? Lessons from BC's impact evaluation

Nguyen A, Maclure M, Roelants HWM, Carney G,  
Dormuth CR

BC Community Drug Utilization Program, Lions Gate Hospital; School of Health Information Sci., University of Victoria, Blue Thorn Research & Analysis, School of Health Information Sci., University of Victoria, Canada, Harvard Medical School & Harvard School of Public Health, USA

*Corresponding Author:* [anne.nguyen@vch.ca](mailto:anne.nguyen@vch.ca)

**Background:** In theory, a forthcoming randomized trial in BC, Alberta, Saskatchewan, Manitoba and Nova Scotia can be evaluated using the National Prescription Drug Utilization Information System (NPDUIS), which includes drug claims data from most provinces beginning January 2004. To determine data needs and a protocol for encryption and linkage with NPDUIS, we analysed a crossover trial by the BC Community Drug Utilization Program ([www.cdup.org](http://www.cdup.org)).

**Methods:** Participating GPs in Vancouver's North Shore were randomized to Group 1 or 2. In June 2000, Group 1 received a 2-page newsletter on congestive heart failure (CHF) while Group 2 received one on coxibs. 26 in Group 1 and 39 in Group 2 agreed to educational outreach visits by a pharmacist (AN) on their topic in the following 6 months. In January 2001, the interventions were reversed. A non-randomized control group of 334 similar GPs elsewhere in Vancouver received neither. We extracted encrypted data from PharmaNet and Ministry databases on 41,243 relevant patients seen by these GPs.

**Results:** Baseline characteristics of GPs and patients were similar, including prior use of ACE inhibitors, beta blockers, calcium channel blockers, NSAIDs and coxibs. The Ministry's algorithm for Majority Source of Care (MSOC) correlates with the primary prescriber as determined by claims data.

**Conclusions:** A large fraction of drug claims – refills or GPs' renewals of specialists' prescriptions – constitute noise that masks the impact of academic detailing. Assessing program impacts using NPDUIS, while feasible, will require focus on subgroups of patients where the signal-to-noise ratio is high.

**Key Words:** *Academic detailing, heart failure, administrative database*

39

### Chart audit of indicators for underutilization of effective drug therapy and drug related risk in primary care

Dolovich L, Kaczorowski J, Uppaluri A, Howard M, Gaebel K, Lau E, Jurcic J, Pottie K

Centre for Evaluation of Medicines and Faculty of Health Sciences McMaster University, Elizabeth Bruyère Research Institute, University of Ottawa, Canada

*Corresponding Author:* [ldolovic@mcmaster.ca](mailto:ldolovic@mcmaster.ca)

**Background:** Analysis of practice patterns can target areas for practice system improvements in medication prescribing and monitoring. This study determined the proportion of patients who met predetermined criteria for underutilization of effective drug therapy and drug related risk.

**Methods:** This was a descriptive cross sectional study. Charts from a random sample of patients 65 years old and older were reviewed in seven Ontario family practice networks between May and November 2004 as part of the Integrating Family Medicine and Pharmacy to Advance Primary Care Therapeutics (IMPACT) Project. Twenty-two indicators were chosen based on: established validity, high-expected potential for improving health or reducing drug related risk, high expected prevalence, and feasibility for data abstraction. Data were abstracted for the preceding year using a structured form. Overall proportions for data combined from all sites and minimum and maximum proportions from data across the seven practice sites are presented.

**Results:** Charts were reviewed for 1808 patients. Eighteen percent (n=319; min-max, 6-29%) of patients used more than 8 medications. Ten percent (n=177; min-max, 5-27%) were taking a potassium wasting diuretic, had no potassium levels recorded, or low potassium. The proportion of patients with diabetes and an A1C over 0.075 was 5% (n=88; min-max, 3-17%). Five percent (n=86; min-max, 2-7%) of patients had hyperlipidemia, elevated LDL, and no prescribed lipid lowering agent. Thirty-six percent (n=654; min-max, 24-56%) of patients met 3 or more criteria.

**Conclusions:** All indicators chosen identified areas of potential improvement in drug prescribing or monitoring. Considerable variability was seen across practice sites.

**Key Words:** *Prescribing indicators, primary care, chart audit*

40

### Community-wide implementation of a blood pressure monitoring program with feedback to family physicians

Karwalajtys T, Kaczorowski J, Chambers L, Hall H, McDonough B, Dolovich L, Sebaldt R, on behalf of the CHAP Working Group

McMaster University, Hamilton, Canada

*Corresponding Author:* [karwalt@mcmaster.ca](mailto:karwalt@mcmaster.ca)

**Background:** Primary prevention of cardiovascular disease can decrease morbidity, mortality, and health care costs.

Community-based programs have potential to improve BP monitoring among older adults, and overcome challenges associated with diagnosing/managing hypertension in family practice. Our objective was to implement and evaluate a community-wide program for BP monitoring and cardiovascular risk assessment, with feedback to family physicians (FPs), in Grimsby/Lincoln and Brockville/Prescott, Ontario.

**Methods:** The program relies on volunteer peer health educators to deliver sessions in pharmacies. All FPs and pharmacists in each community were asked to participate. Physicians chose up to three strategies for inviting patients: personalized letters, 'tickets' distributed opportunistically, and community-wide advertising. Sessions were held daily for ten weeks (March–May, 2004). Repeat visits were encouraged. Nearly all FPs (n=56) and pharmacists (n=16) participated, along with other community partners, ~90 older adult volunteers, and older adult residents. Volunteers helped participants measure BP using a validated, automated device, recorded cardiovascular risk factor information, and provided local resources for modifiable risk factors. Results were compiled using a computerized fax-to-database system and sent to FPs to augment in-office readings.

**Results:** Letters were sent to 4394 patients and there were 4171 visits to sessions by 2,375 patients. Overall, 60.5% of attendees were female. The mean age was 70.8 years. By self-report, 13.7% were diabetic, 10.3% had a history of heart attack and 7.3% of stroke, and 38.2% had high cholesterol. Recruitment, volunteer training, program promotion and delivery are described

**Conclusions:** This demonstration project provided important learning toward a large-scale program implementation.

**Key Words:** *Program implementation, blood pressure, peer volunteers*

41

### Primary care cardiovascular health promotion program: the community hypertension assessment trial (CHAT)

Kaczorowski J, Chambers LW, Dolovich L, Levitt C, Hogg W, Karwalajtys T, Hendriks A  
McMaster University, Hamilton, Canada, CHAT Working Group

Corresponding Author: [kaczorow@mcmaster.ca](mailto:kaczorow@mcmaster.ca)

**Background:** To determine the impact of primary care cardiovascular health promotion program to improve the monitoring and management of cardiovascular risk factors including blood pressure among older primary care patients.

**Methods:** The Community Hypertension Assessment Trial (CHAT) is a paired cluster-randomized controlled trial involving 28 randomly selected family physician practices in Ontario, Canada who were allocated to the intervention or control arm and a random sample of 1540 (55 per practice) community-dwelling patients 65 years of age and older attending these practices. Physicians in the intervention arm invited, by personalized letters, all of their patients 65 years and older to attend one, and preferably two, of four pharmacy sessions scheduled for each practice. Public health nurses trained older adult volunteer peer health educators to assist patients in using automated BP measurement devices, record readings and cardiovascular risk factors and provide accurate readings to physicians, patients and pharmacists.

**Results:** A total of 2493 patients from 14 practices allocated to the intervention arm (~180 per practice) were invited to attend at least one of four practice-specific sessions. A total of 56 four-hour sessions were held in 27 community pharmacies between May and December 2003. 39.4% (983/2493) of invited patients attended at least one session; 59% (589/983) of attendees returned for the second sessions.

**Conclusions:** The CHAT intervention proved feasible and was well accepted by older adults, physicians, pharmacists, and volunteers. The assessment of whether the program improved the control and management of high BP and cardiovascular risk factors will be presented.

**Key Words:** *Cardiovascular disease, health promotion, community pharmacy services*

42

### Comparable efficacy and safety of adalimumab (humira®) in Canadian and European practice: the canACT and the reACT trial

Cividino AA,<sup>1</sup> Guerette B<sup>2,3</sup>

<sup>1</sup>Department of Medicine McMaster University, Hamilton, Canada, <sup>2</sup>Abbott Laboratories Limited, Canada, <sup>3</sup>CanACT Investigators

Corresponding Author: [Benoit.Guerette@ABBOTT.com](mailto:Benoit.Guerette@ABBOTT.com)

**Background:** To evaluate the efficacy and safety of adalimumab in the Canadian practice setting, and to compare it with the results of ReAct, a similar trial that was conducted in Europe.

**Methods:** Canadian Adalimumab Clinical Trial was an open-label, multi-center, Phase IIIb study conducted in Canada. A total of 879 patients with moderate to severe rheumatoid arthritis (RA) who had an inadequate response to standard therapy, including MTX, were treated with adalimumab 40 mg SC every other week in addition to their preexisting but inadequate therapy. Efficacy and safety were assessed at baseline, 4, 8, and 12 weeks. This was a preliminary analysis of 236 patients. The sample size for each outcome variable is based on the data available at the time of the analysis. The data from this preliminary analysis were compared to the 12 weeks' assessments done in the ReAct trial (N=2008).

**Results:** The comparisons at 12 weeks of CanACT (N) with the ReAct (N=2008) results are: TJC\* (0-28): -10 (123) vs. -10; SJC\* (0-28): -7 (123) vs. -7; DAS28‡ -2.1 (116) vs. -2.1; HAQ‡ -0.55 (122) vs. -0.49; Moderate EULAR response (%): 78 (121) vs. 82; Good EULAR response (%): 18 (121) vs. 34. Four serious adverse events were reported, of which 2 (0.9%) were possibly related to adalimumab. The serious infection rates were comparable for both trials.

**Conclusion:** Canadian patients with RA receiving adalimumab consistently experienced substantial reductions in signs and symptoms of their disease. These results are consistent with results from the ReAct trial. \* Median Values; ‡ Mean Values (See author for reference)

**Key Words:** *rheumatoid arthritis, adalimumab, anti-TNF, CanACT, Canadian practice*

43

### Comparative study of the impact of irritable bowel syndrome on the quality of life of patients in Canada

Soule J,<sup>1</sup> Zdanowicz Y,<sup>2</sup> Moubazbaz T,<sup>2</sup> Barbeau M,<sup>3</sup> Garon E<sup>3</sup>

<sup>1</sup>University of Toronto, Toronto, Canada, <sup>2</sup>IPSOS-Insight, <sup>3</sup>Novartis Pharmaceuticals Canada Inc.

Corresponding Author: [martin.barbeau@pharma.novartis.com](mailto:martin.barbeau@pharma.novartis.com)

**Background:** Irritable Bowel Syndrome (IBS) is a chronic gastrointestinal disorder affecting over 1 in 10 Canadians aged 20 years and older. It is characterized by dysmotility symptoms such as abdominal discomfort/pain, bloating, constipation and/or constipation with occasional diarrhea (ABC/D).

**Objectives:** To quantify the Canadian impact of abdominal pain, discomfort, bloating, constipation and/or constipation with occasional diarrhea on the QOL of Canadian patients with (ABC/D) using the Medical Outcome Study Short Form (SF-36) questionnaire, and to compare scores with the Canadian population and patients with other chronic ailments.

**Methods:** Random telephone interviews, including the SF-36 questionnaire, were conducted in 2004 with 750 patients who had experienced ABC/D for 12 weeks or more over the last year, excluding patients with Crohn's disease, colitis or colon/rectal cancer. Mean SF-36 scores were compared to the general population and to scores reported by five published quality of life studies associated with other chronic illnesses (i.e., stroke, psoriatic and rheumatoid arthritis, sleep apnea and atrial fibrillation).

**Results:** Mean scores were significantly lower in ABC/D patients than in the general population for all domains ( $P < .001$ ). ABC/D patients had significantly lower scores for Bodily Pain than patients with either atrial fibrillation ( $P < .001$ ) or stroke ( $P < .01$ ). ABC/D patients also scored lower in General Health compared to patients with stroke ( $P < .001$ ), and lower in Social Functioning than patients experiencing psoriatic arthritis ( $P < .01$ ).

**Conclusion:** ABC/D dysmotility symptoms associated with IBS significantly reduces the quality of life of Canadian patients in all domains of the SF-36.

**Key Words:** SF-36, IBS, comparative study

44

### Comparison of cost-effectiveness ratio across individual antidepressants in the Quebec elderly outpatient population

Moride Y, Ducruet T, Galbaud du Fort G, Boivin JF, Perreault S, Crott R, Laurier C, Monette J, Champoux N  
Université de Montréal, Montreal, Canada

Corresponding Author: [yola.moride@umontreal.ca](mailto:yola.moride@umontreal.ca)

**Background:** While new antidepressants have a more desirable cost-effectiveness ratio than tricyclics, few data exist on the comparisons of new products among themselves in a real-life setting.

**Objectives:** In the Quebec elderly (age 65+) outpatient population: i) to compare health services use and associated costs over a period of 12 months after treatment initiation; ii) to compare cost-effectiveness ratio using adherence as an indicator of effectiveness.

**Methods:** A fixed retrospective cohort study was conducted using the Quebec health databases (RAMQ). Elderly users of the following products were randomly selected from the prescription database: fluoxetine (n=380), fluvoxamin (n=883), paroxetine (n=2,353), sertraline (n=2,269), nefazodone (n=360), venlafaxin (n=1,937). Adherence was defined as use of > 6 months with the initial product only. Cost of outpatient medical visits and medications over the 12 months after treatment initiation were measured according to a third-party perspective.

**Results:** Controlling for covariables, the proportion of adherence was higher for SSRIs (46.9%) and venlafaxine (46.5%) than for other products (35.4%). Nefazodone was associated with the least favorable cost-effectiveness ratio overall (\$6,574), and specifically for antidepressant medications (\$622), and outpatient medical services (\$2,323). The best cost-effectiveness ratio was found with paroxetine overall (\$4,840), non-antidepressant medications (\$2,560), and medical services (\$1,679).

**Conclusions:** The products with lower cost per unit are not necessarily associated with more favorable cost-effectiveness ratio due to non-adherence to treatment and higher use of health services.

**Key Words:** Pharmacoeconomics, administrative databases, antidepressants

45

**Comparison of health care resource utilization obtained from patient recall, chart review and administrative data for SMART economic analysis**

Blackhouse G, Goeree R, Kaczorowski J, Sellors J, Sellors C, Dolovich L, Howard M

Program for Assessment of Technology in Health (PATH), Hamilton, Canada

*Corresponding Author:* [blackhou@mcmaster.ca](mailto:blackhou@mcmaster.ca)

**Background:** In prospective health economic evaluations, resource utilization is usually identified through chart review patient recall or administrative datasets. The impact of choosing one source over another is unclear. This study compares resource utilization collected from various sources: chart reviews (CR), patient diaries (PD), and administrative data (AD).

**Methods:** This study is based on secondary analysis of the Seniors Medication Assessment Research Trial (SMART), a randomized trial of a pharmacist consultation program for family physicians and their elderly patients. Chart reviews, patient diaries, and administrative data were used to obtain resource use for trial participants related to hospitalizations, physician services, ER visits and X-rays. The utilization of resources and resultant patient costs estimated by the different sources are calculated and compared.

**Results:** Based on administrative data, the intervention group was found to have statistically significantly fewer GP visits compared to the control group (-1.26) however no statistical differences were found in GP visits when using data collected from CR or PD. The mean cost per patient was found to be \$177 less in the intervention group when based on CR, \$106 less based on AD, and \$178 more when costs are based on PD.

**Conclusions:** Health care resource utilization identified in prospective economic evaluations can vary depending on the sources used. Using data sources from SMART, different conclusions on differences in mean number of GP visits and mean costs between intervention and control groups were found. What is less clear is which source should be considered the 'gold standard'.

**Key Words:** Economic analysis, resource utilization, data collection

46

**Compliance with lipid-lowering drug treatment in members of the Canadian Forces: an observational cohort study**

Groves S, Vaillancourt R, Ma J

Canadian Forces Health Services Group, Ottawa, Canada

*Corresponding Author:* [groves.sv@forces.gc.ca](mailto:groves.sv@forces.gc.ca)

**Background:** Non-compliance with lipid-lowering therapy has been documented in many populations. Our group has implemented several initiatives which were intended to enhance uptake of lipid-lowering treatment. This study aims to measure the current compliance rates among members of the Canadian Forces (CF), and to identify potential predictors of non-compliance that may refine future interventions to improve adherence.

**Methods:** An observational study will be performed using data from the pharmacy database. All CF members who received a lipid-lowering drug between 1 April 2003 and 1 June 2003 will be included in the analysis, provided that a minimum follow-up time of three months following the initial prescription is represented in the database. Subjects will be categorized as compliant if the pharmacy records indicate at least 80% consumption of doses prescribed. Statistical tests will be performed to determine the impact of patient characteristics, drug characteristics, and time upon compliance rates.

**Results:** The compliance rates identified in our population will be compared to those reported in other patient groups, as well as to the rates observed in previous studies among CF personnel. Predictors of compliance will also be compared to those known from the clinical literature.

**Conclusions:** The results of this investigation will be used to guide the development of additional interventions to enhance lipid compliance, and may enable justification of additional expenditures or reallocation of funds for different initiatives.

**Key Words:** Antilipemic agents, dyslipidemia, patient compliance



47

**Evaluation of health products used by the Canadian forces health and lifestyle information survey respondents**

Groves S, Vaillancourt R, Roy M, Sampalis J  
Canadian Forces Health Services Group, Ottawa, Ontario, Canada

*Corresponding Author:* [groves.sv@forces.gc.ca](mailto:groves.sv@forces.gc.ca)

**Background:** In the Canadian Forces (CF) Health and Lifestyle Information Survey, information was gathered regarding use of medications and nutraceuticals. Responses obtained during this survey were reviewed to obtain information on patterns of nutraceutical use among CF members.

**Methods:** A cross-sectional survey of Regular Force CF members was performed in 2000. Open-ended questions were used without limiters to obtain information on products consumed. Detailed searches were performed in an attempt to identify and classify all products reported. Descriptive statistics were employed to represent respondent characteristics and frequency of health product usage. Logistic regression analysis was performed to identify predictors of nutraceutical use.

**Results:** Information was analyzed for all 6841 respondents who completed the survey. Respondents were relatively young (mean age 37.2, SD 7.52 years), with a large number rating their health status (41.3%) as very good. Consistent with trends seen in the general Canadian population, use of nutraceuticals was common in the CF, with 44.1% of all respondents self-reporting the use of such items on a regular basis and 31.2% having used a nutraceutical in the previous two days.

**Conclusions:** A range of natural health products are used informally by CF members, which likely mirrors the use of such items among the general population. The high prevalence of nutraceuticals among agents consumed should be borne in mind by health care providers when treating individual patients. Further study should be undertaken to determine patient sources of both the products consumed and information guiding such consumption.

**Key Words:** Natural remedies, health surveys

48

**Cost of illness study of nausea and vomiting of pregnancy in Canada**

Piwko C, Ungar WJ, Einarson TR, Koren G  
The Hospital for Sick Children, Department of Clinical Pharmacology, Toronto, Canada, Department of Health Administration, University of Toronto, Canada

*Corresponding Author:* [charles.piwko@utoronto.ca](mailto:charles.piwko@utoronto.ca)

**Background:** Nausea and vomiting of pregnancy (NVP) is the most common medical condition in pregnancy affecting an estimated 80% (50–90%) of all pregnancies. Even with mild symptoms, NVP generates costs to society, patients and the healthcare system, and reduces quality of life. However, its costs are largely unknown. We estimated the total cost per woman-week associated with the onset of NVP in Canada, stratified by severity (mild, moderate, severe) from the perspectives of society, Ministry of Health (MoH), and patients.

**Methods:** Data were collected from 139 pregnant women, who called the Motherisk Program at the Hospital for Sick Children in Toronto. We estimated resource utilization for direct costs (drugs, physicians, hospitalizations) from interviews. Costing was conducted with Ontario price lists and fee schedules. Indirect costs, calculated using the human capital approach, included absences from work/usual activities and reduced productivity at work.

**Results:** From the societal perspective, the costs per woman-week were \$124, \$334 and \$610 for mild, moderate and severe NVP, respectively. From the MoH perspective, they were \$4, \$36, and \$87, respectively. From the patient perspective, costs were \$110, \$253 and \$375, respectively. Costs from all perspectives increased with increasing NVP severity. Productivity costs constituted the largest cost component.

**Conclusion:** NVP in Canada is associated with substantial costs to society, patients, and the MoH. Indirect costs were in all cases higher than direct costs.

**Key Words:** Nausea and vomiting of pregnancy, cost of illness, Canada

49

### Cost-effectiveness of pegylated interferon treatments in hepatitis C (HCV) patients in Canada

Einarson TR, Iskedjian M, Piwko C

Leslie Dan Faculty of Pharmacy, University of Toronto

Corresponding Author: [t.einarson@utoronto.ca](mailto:t.einarson@utoronto.ca)

**Background:** To compare the cost-effectiveness of combination ribavirin plus pegylated interferon alfa-2b (PEG2b+R (i.e., PEGETRON)) or pegylated interferon alfa-2a [PEG2a+R (i.e. PEGASYS RBV)] treatment in patients with genotype 1 HCV. Randomized phase III trials comparing both pegylated interferon to standard interferon plus ribavirin (INF+R) have yielded comparable sustained viral responses (SVR). However based on reports of 12-week early viral responses (EVR) in clinical use, the decision to discontinue eventual nonresponders may affect overall cost-effectiveness.

**Methods:** A decision analysis model was constructed to compare PEG2b+R and PEG2a+R per approved label doses. Base-case assumed that 48% of patients weigh less than 75kg. The length of therapy was reflective of the current treatment algorithm for genotype 1 patients, i.e., they receive an initial 12 weeks of therapy. An approximate two-log drop in the quantitative HCV RNA value or an undetectable qualitative HCV RNA value at 12 weeks is required to continue therapy until week 48. Prices were from standard sources in Canadian dollars.

**Results:** Evaluating EVR leads to lower overall treatment costs for INF+R and PEG2b+R than PEG2a+R. The incremental cost per SVR ratios of PEG2b+R and PEG2a+R compared to conventional INF+R are \$5,713 and \$16,810, respectively. PEG2b+R was dominant over PEG-2a+R, with a lower expected treatment cost and a higher chance of achieving an SVR.

**Conclusions:** These results indicate that treating HCV patients with PEG2b+R maximizes the cost-effectiveness of HCV treatment since PEG2b+R is a better predictor of sustained viral response, and therefore enables treatment discontinuation in those unlikely to respond with further therapy.

**Key Words:** Hepatitis C (HCV), cost effectiveness, pegylated interferon

50

### Cost sharing of prescription drugs and demand for doctor and hospital visits – evidence from a natural experiment

Li X, Guh DP, Lacaille D, Esdaile JM, Anis AH

University of British Columbia, Centre for Health Evaluation and Outcome Sciences, Arthritis Research Centre of Canada, Vancouver, British Columbia, Canada

Corresponding Author: [xin@hivnet.ubc.ca](mailto:xin@hivnet.ubc.ca)

**Background:** To evaluate the impact of changes in cost sharing policies for prescription drugs on overall health resource use among seniors with rheumatoid arthritis (RA) in British Columbia (BC), Canada.

**Methods:** Medication, physician and hospital visit data between 2001/01/01 and 2002/12/31 for all seniors were selected from a population-based RA cohort. Under the BC drug insurance program, prior to 2002, seniors paid 100% of their dispensing fee of each prescription to an annual maximum of \$200 (Plan A). Starting in 2002, this plan was split into Plans A and A1 (Premium Assistance) whereby seniors paid a maximum of \$25 and \$10 per prescription to an annual maximum of \$275 and \$200, respectively. Only seniors who either reached or did not reach the annual deductible in both years were included. Patients were classified into 4 groups based on reaching the annual deductibles and their Plans. Own-price and cross-price elasticities were estimated using mixed effect models.

**Results:** A total of 5,227 patients were included in the study. All four groups had negative own-price elasticities of demand for prescription drug, negative but insignificant cross-price elasticities of demand for hospital visits, and positive and significant cross-price elasticities of demand for physician visits. The positive estimates suggested that when cost sharing for prescription drugs increased, so did the demand for physician visits.

**Conclusions:** In a predominantly publicly funded health care system, the introduction of market driven cost containment concepts such as a patient cost-sharing might have the unintended impact of increasing overall utilization.

**Key Words:** Rheumatoid arthritis, economics, medicare policy analysis

51

**Cost-effectiveness of infliximab for ankylosing spondylitis (AS) in Canada**

Kobelt G, Andlin-Sobocki P, Maksymowych WP  
Karolinska Institute, Stockholm Sweden, Stockholm Health Economics, Stockholm, Sweden, Division of Rheumatology, University of Alberta, Edmonton

*Corresponding Author:* [Gisela.Kobelt@Heeurope.com](mailto:Gisela.Kobelt@Heeurope.com)

**Background:** To estimate the cost-effectiveness of infliximab therapy in patients with AS.

**Methods:** Using a BASDAI/BASFI-based Markov model, we projected the results from 1) a 3-month placebo-controlled clinical trial with 2-year open extension, and 2) a 4-year follow-up study of clinical practice in Canada to forward estimate the long-term costs and quality-adjusted life expectancy of AS patients. Costs and utility, estimated from an observational study in 545 Canadian AS patients, using a regression model including age, gender, disease duration, disease activity and functional status, were assigned to individual patients. Costs were based on Canadian pricing. AS costs and effects were discounted at 5%.

**Results:** Mean annual cost per patient was estimated at \$9,008 (ranges \$4,000-\$30,000) and mean utility was estimated at 0.67 (ranges 0.2-0.87). Over a 30-year timeframe, the model assumes that after the first year patients on treatment progress at the same rate as non-treatment patients, a conservative estimate. The cost per QALY gained is \$84,780 (5mg/kg q 6). Using the dosing regimen of the Canadian study (75% at 3mg/kg q 8, 15% at 3mg/kg q 6, and 10% at 5mg/kg q 8) the cost per QALY is \$30,809. Under the assumption that patients' BASFI would remain stable on treatment, the cost-effectiveness ratios are reduced by 20%. The results are sensitive to the dosing regimen adopted, the continuation rate and assumptions concerning disease progression while on treatment.

**Conclusions:** Our results suggest that infliximab therapy for patients with active AS should be cost-effective (ranges \$30,809-\$84,780 per QALY) in a Canadian setting.

**Key Words:** Infliximab, ankylosing spondylitis, cost-effectiveness

52

**Cost-effectiveness of irbesartan 300 mg given early or late in patients with type 2 diabetes, hypertension and renal disease**

Coyle D, Levin A, Muirhead N, Palmer A, Rene de Cotret P, Soroka S, Amin M, Chen R, Dupont D, Forte L, Rodby R

Department of Epidemiology and Community Medicine, University of Ottawa, Canada

*Corresponding Author:* [dcoyle@uottawa.ca](mailto:dcoyle@uottawa.ca)

**Background:** Both the IRMA-2 and the IDNT trials have demonstrated that irbesartan is beneficial in hypertensive patients with type 2 diabetes and renal disease. The objective of this study was to assess whether treatment with irbesartan was cost effective and whether it was more cost effective to treat patients early rather than later in the development of disease.

**Methods:** Analysis compares three alternative strategies for the treatment of patients: standard pharmaceutical treatment of patients, the early addition of irbesartan to treatment (initiated with microalbuminuria) and the late addition of irbesartan (initiated with overt nephropathy). A Markov model was used to simulate the progression of type 2 diabetes. Transition probabilities were derived from the two randomized controlled trials. A cost effectiveness analysis was conducted with outcome measured in life years gained.

**Results:** The early addition of irbesartan during microalbuminuria is shown to be both cost saving and more effective than both delaying irbesartan treatment to advanced overt nephropathy and to no irbesartan use. This is due to delays in both the development of overt nephropathy and the subsequent delay to end-stage renal disease (ESRD). The addition of irbesartan during advanced overt nephropathy is also cost saving and more effective compared to no irbesartan use. Sensitivity analysis confirms the robustness of the study results.

**Conclusions:** The early use of irbesartan for patients with type 2 diabetes who have yet to develop overt nephropathy is cost effective and will lead to both costs savings and an increase in life years gained.

**Key Words:** Cost-effectiveness, nephropathy, diabetes

53

### Cost-effectiveness of surgery plus radiotherapy vs. radiotherapy alone for treatment of metastatic spinal cord compression (MSCC)

Thomas KC,<sup>1</sup> Fisher CG,<sup>2</sup> Nosyk B,<sup>3</sup> Dvorak M,<sup>2</sup> Boyd M,<sup>2</sup> Kwon B,<sup>2</sup> Patchell R,<sup>4</sup> Regine W,<sup>5</sup> Lablaw D,<sup>2</sup> Bansback N,<sup>3</sup> Guh D,<sup>3</sup> Sun H,<sup>3</sup> Anis AH<sup>3,6</sup>  
<sup>1</sup>Calgary Health Region, Calgary, Canada, <sup>2</sup>Vancouver Hospital and Health Sciences Center, Vancouver, Canada, <sup>3</sup>Centre for Health Evaluation and Outcome Sciences, <sup>4</sup>Neurosurgery, University of Kentucky, <sup>5</sup>Radiation Oncology, University of Maryland, <sup>6</sup>University of British Columbia

Corresponding Author: [bnosyk@hivnet.ubc.ca](mailto:bnosyk@hivnet.ubc.ca)

**Background:** Radiotherapy is central to the palliative treatment of MSCC. With the evolution in medical imaging, surgical technique and biomaterials, surgical indications for these patients have broadened. A randomized trial comparing surgery plus radiotherapy (S+RT) to radiotherapy (RT) alone in patients with MSCC has shown S+RT to be the superior treatment. Our objective was to perform a cost-effectiveness analysis based on this trial for the treatment of metastatic spinal cord compression (MSCC).

**Methods:** 101 patients were randomized to receive S+RT or RT alone. Clinical effectiveness was measured by ambulation and survival time until death. A Weibull regression was applied to extrapolate outcomes to the lifetime of the cohort in the presence of censored clinical effectiveness data. Costs related to treatment and post-treatment care were estimated from a variety of sources. An incremental cost-effectiveness analysis was performed from a societal perspective.

**Results:** Patients randomized to S+RT had greater expected mean number of days of ambulation and greater overall costs than those treated with RT alone. From a societal perspective, the baseline incremental cost-effectiveness ratio (ICER) was found to be \$56 per additional day of ambulation. Probabilistic sensitivity analysis resulted in 95% of all ICERs below \$239 per additional day of ambulation.

**Conclusions:** We found strong evidence for improved functional outcomes and cost-effectiveness of treatment of MSCC with surgery in addition to radiotherapy. Whether the addition of surgery is cost-effective depends on the value placed on ambulatory function by the patient, by society, and on the alternative use of scarce healthcare resources.

**Key Words:** Cost-effectiveness, metastatic spinal cord compression, Weibull

54

### Cost-effectiveness of etanercept in the treatment of patients with moderate to severe ankylosing spondylitis

Sadri H,<sup>1</sup> Mittmann N,<sup>1</sup> Base C,<sup>2</sup> Chau D,<sup>3</sup> Bell M<sup>2</sup>  
<sup>1</sup>HOPE Research Center, <sup>2</sup>Sunnybrook & Women's College Health Sciences Centre, <sup>3</sup>Amgen Canada, Canada

Corresponding Author: [hamid.sadri@swri.ca](mailto:hamid.sadri@swri.ca)

**Background:** To assess the cost-effectiveness of etanercept in patients with moderate to severe ankylosing spondylitis (AS).

**Methods:** A cost-effectiveness analysis was used to determine the cost per improvement in disease activity using a decision tree over a one-year time horizon. Long-term incremental cost/QALYs was calculated over a 10-year time horizon, using a spreadsheet model. Ontario provincial perspective was used. Direct medical costs were in 2003/04 Can\$. Comparator was standard-therapy (NSAIDs, DMARDs, steroids). Clinical outcomes were functional status measure (ASAS20) and AS disease activity index (BASDAI).

**Results:** Clinical charts of 20 AS patients at Sunnybrook & Women's Health Sciences Centre were reviewed. Mean age was 43.6±12.6 years, 9 were male. Mean AS duration was 13.8±7.3 years. 7 patients had spine involvement, 2 had peripheral involvement, and 11 had both. Majority of patients were using NSAIDs/COXIBs alone, or in combination with sulfasalazine. Mean annual cost: 1) for drugs and monitoring was \$1589.80±\$601.70, 2) for medical-imaging cost was \$140.20±\$65.80, and 3) for physician visit was \$303.40 (average 2.4±1.4 visits). The one-year incremental cost-effectiveness for etanercept compared to standard therapy was \$36,622/ASAS20 and \$47,474/BASDAI50. The cost per severity avoided, using BASDAI, decreased over time from \$880/severity avoided at year one to \$368/severity avoided at year ten. Similarly, the cost per QALY decreased from \$129,000/QALY in year one of treatment to \$76,000/QALY in year ten.

**Conclusions:** Short-term results show a reasonable incremental cost-effectiveness ratio when etanercept was compared to standard therapy. Moreover, long-term results with etanercept demonstrate an improvement in the cost per QALY over time.

**Key Words:** Cost-effectiveness, ankylosing spondylitis, etanercept

55

**CTS COPD recommendations: the Dalhousie continuing medical education academic detailing service**

Allen M,<sup>1</sup> Mclean-Veysey P,<sup>2</sup> Fleming I,<sup>1</sup> Hernandez P,<sup>2,3</sup> McIvor RA<sup>2,3</sup>

<sup>1</sup>Dalhousie University, <sup>2</sup>QE II Health Sciences Center, <sup>3</sup>Dalhousie University Department of Medicine, Halifax, Canada

*Corresponding Author:* [michael.allen@dal.ca](mailto:michael.allen@dal.ca)

**Background:** Significant gaps in COPD care highlight the need to disseminate and implement the 2003 Canadian Thoracic Society (CTS) Recommendations for Management of COPD. Academic detailing is a form of continuing medical education (CME) in which a trained professional (e.g. physician, nurse, or pharmacist) visits a physician in their office to provide evidence-based, educational messages. The Dalhousie Office of CME has had an academic detailing service for three years. We used academic detailing to enhance adoption of the recent COPD recommendations in clinical practice.

**Methods:** To develop our evidence-based, educational messages we critically appraised the CTS recommendations and other published COPD guidelines. Guided by an advisory panel (4 FPs and a Respiriologist), we developed handouts, including a double-sided, laminated sheet of key messages. Key educational messages included: using spirometry to confirm the diagnosis; smoking cessation; encouraging regular exercise; appropriate utilization of short and long-acting bronchodilators and inhaled corticosteroids; identification of key outcomes; and distinguishing between clinical and statistical significance in COPD trials.

**Results:** The academic detailers have visited 365 FPs. Evaluation forms (N=175) indicate overall satisfaction was high (4.7 on a 5-point Likert scale). FPs indicated that they are more likely to use spirometry to establish a diagnosis (4.2/5); encourage patients to exercise regularly (4.3/5); and assess response to long-acting bronchodilators (4.3/5).

**Conclusions:** A local initiative, lead by respected peers, using an established process (Dalhousie Academic Detailing Service) is an important tool to assist with dissemination and implementation of COPD guidelines and adoption of evidence-based recommendations in clinical practice.

**Key Words:** CME, guidelines, evidence-based medicine

56

**Family physicians' perceptions of academic detailing**

Allen M, Fleming I, Ferrier S

Dalhousie University CME, Halifax, Canada

*Corresponding Author:* [michael.allen@dal.ca](mailto:michael.allen@dal.ca)

**Background:** Academic detailing is a form of continuing medical education (CME) in which a trained professional (e.g. physician, nurse, or pharmacist) visits a physician in their office to provide evidence-based, educational messages. Dalhousie CME has had an Academic Detailing Service since 2001. Records show that 414 (46%) family physicians have never used the Service, 110 (12%) have used it once, and 375 (42%) have used it more than once. Our purpose was to determine the factors that encourage and discourage physicians from using academic detailing and how we can make it better meet their CME needs.

**Methods:** Questionnaire mailed to each of the three groups (never used, used once, used > once) and telephone interviews with 10 physicians from each group.

**Results:** Overall response rate to the questionnaire was 33% (N=288). Response rate among the groups varied widely: never used group - 17%; used once group - 27%; used > once group - 52%. Factors most likely to encourage participation are 1) adopting an evidence-based approach; 2) covering topics useful to practice; and 3) providing useful handout material. Factors most likely to discourage participation are 1) spending office time doing CME; 2) scheduling time for the academic detailer; and 3) having access to CME in other ways. We have conducted but not yet analyzed six interviews and will present complete data at the conference.

**Conclusions:** Preliminary data indicate that all three groups value evidence-based information. Scheduling time to see the detailer and spending office time for CME discourage some physicians from using academic detailing.

**Key Words:** Continuing medical education, academic detailing, evidence-based medicine

57

### Current prevalence and control of dyslipidemia in the primary care setting

Petrella RJ,<sup>1</sup> Merikle E,<sup>2</sup> Tarride J-E,<sup>2</sup> Jones J<sup>1</sup>

<sup>1</sup>Faculty of Medicine and Dentistry, Schulich School of Medicine, University of Western Ontario, Canada,

<sup>2</sup>Outcomes Research Pfizer Canada Inc., Canada

*Corresponding Author:* [elizabeth.merikle@pfizer.com](mailto:elizabeth.merikle@pfizer.com)

**Background:** The burden of cardiovascular disease and associated risk factors are seen in primary care settings. The most recent prevalence and control estimates of dyslipidemia in Canada (1986-1992) may not be reflective of more recent clinical evidence and practice guidelines. The SWO is a population-based prospective cohort of > 150,000 patients over 18 years in > 35 family practice clinics in Southwestern Ontario. 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 dyslipidemia.

**Methods:** Patients with at least 4 quarters of data were included (N=42,496). Dyslipidemia was defined as usage of lipid lowering medication, at least one chart entry of a diagnosis of dyslipidemia, or a recorded measurement of LDL-C or TC/HDL-C greater than the recommended targets.

**Results:** The overall prevalence of dyslipidemia was 14.0% with a similar gender distribution of which 63.2% were untreated, 17.3% were treated but not controlled, and 19.4% were treated and controlled. For patients > 65 years the prevalence of dyslipidemia was over 38% but most (57.2%) were treated and controlled. Seventy-three percent of treated patients used statin therapy.

**Conclusions:** Dyslipidemia prevalence in the primary care setting is high. Despite clinical evidence and treatment guidelines, dyslipidemia is largely untreated in family practice. Educational supports to improve detection, diagnosis and treatment compliance are needed.

**Key Words:** Dyslipidemia, retrospective database analysis, primary care

58

### Employee disability days associated with cardiovascular disease using the Canadian community health survey (CCHS)

Merikle E, Tarride J-E, Montpetit M

Outcomes Research Pfizer Canada Inc., Canada

*Corresponding Author:* [elizabeth.merikle@pfizer.com](mailto:elizabeth.merikle@pfizer.com)

**Background:** CVD cost the Canadian economy over \$18 billion per year which includes direct costs of \$6.8 billion and indirect costs of \$11.6 billion. Approximately 30% of the indirect costs are the result of disability of employees. The objective of this study was to compare disability days for adults with and without CVD.

**Methods:** Using the CCHS Cycle 1.1 (September 2000-November 2001), we selected individuals between 30 and 70 years reporting either full time employment status or not working due to illness. Individuals were classified as having no CVD (no reported use of medications for CVD or CHD or stroke), CHD (reported at least one of the following: heart disease, myocardial infarction or angina), stroke (reporting suffering a stroke). Disability days were calculated as the number of days in the past 2 weeks that individuals reported staying in bed or cutting down on activities due to illness or injury.

**Results:** The presence of CVD is associated with a substantial increase in the number of reported disability days. On average, individuals without CVD, with CHD and with stroke reported 0.8, 2.1 and 3.0 disability days respectively. A similar pattern of results was found for men and women. With age the number of disability days tends to increase.

**Conclusion:** The presence of CVD increases the number of disability days reported by employees. Managing cardiovascular risk factors can provide substantial benefits to employers by reducing the disability days associated with cardiovascular disease.

**Key Words:** Indirect costs, retrospective database analysis, cardiovascular disease

59

**Decrease in health care resource utilization (HCRU) by patients started on olanzapine for treatment of bipolar affective disorder (BPD) using régime de l'assurance maladie du québec (RAMQ) administrative databases**

Sheehy O,<sup>1</sup> Marshall D,<sup>2</sup> Brazier N,<sup>2</sup> MacLeod S,<sup>2,3</sup> LeLorier J<sup>1</sup>

<sup>1</sup>Pharmacoepidemiology and Pharmacoeconomics Research Unit, Université de Montreal, Montreal, Canada, <sup>2</sup>Innovus Research Inc., Burlington, Canada, <sup>3</sup>British Columbia Research Institute for Children's & Women's Health, Vancouver, Canada

*Corresponding Author:* [odile.sheehy@umontreal.ca](mailto:odile.sheehy@umontreal.ca)

**Background:** To estimate the change in HCRU and costs associated with initiation of olanzapine treatment in patients with BPD.

**Methods:** Retrospective administrative database analysis comparing HCRU and costs in patients diagnosed with BPD before and after start of olanzapine treatment. The study cohort included patients with a diagnosis of BPD, who had been prescribed other antipsychotic drugs, lithium, or anticonvulsants at least 1 year prior to the first dispensation of olanzapine between January 1994 and June 2002, and who had 1-year follow-up after the first olanzapine dispensation (index date). HCRU was estimated from three Québec health insurance databases administered by RAMQ that recorded all diagnostic and therapeutic procedures and drug prescriptions for RAMQ beneficiaries. Costs were estimated using Québec provincial fee schedules for physician and hospital services and drug reimbursement. Mean differences in HCRU by major category before and after the index date were tested using Student's t-tests.

**Results:** In 909 olanzapine users who met inclusion criteria, psychiatric emergency visits, psychiatric hospitalizations, and psychiatric office visits decreased per patient per year by 45% ( $p < 0.001$ ), 52% ( $p < 0.001$ ) and 33% ( $p < 0.001$ ) respectively in the post index period. Drug costs increased by \$877 in the post-index period, however, the overall decrease in mean total health care costs decreased \$5,484 (34%) per patient per year.

**Conclusions:** Olanzapine treatment in routine practice for BPD is associated with a decrease in HCRU and costs compared to treatment with antipsychotic drugs, lithium, or anticonvulsants. These findings should be confirmed in the context of a prospective controlled trial.

**Key Words:** Bipolar affective disorder, cost analysis, olanzapine, antipsychotics

60

**Decreasing hospitalizations for heart failure in British Columbia, 1993-2001**

Levy AR, Johnston KM, Gustafson P, Palepu A, Reid R, McGrail K, Brophy J

CHEOS, St. Paul's Hospital, Vancouver, Canada

*Corresponding Author:* [johnston@stat.ubc.ca](mailto:johnston@stat.ubc.ca)

**Background:** Heart failure (HF) is a debilitating chronic condition characterized by steady deterioration that is punctuated with acute episodes of decompensation requiring hospitalization. It is among the most costly conditions, consuming between 2 and 3% of healthcare budgets in western countries, 2/3 of which is spent on hospitalizations. During the 1980s, increasing age-specific hospitalization rates of HF were observed. However, there is little Canadian information on trends in HF hospitalizations during the 1990s, a period when efficacious therapies for HF, including angiotensin converting enzymes and  $\beta$ -blockers, were being progressively incorporated into clinical practice.

**Methods:** Using the hospital separations database, we obtained abstracts of all residents of British Columbia (BC), aged 40 y and over, having a principal discharge diagnosis of HF during fiscal years 1990-2001. To eliminate prevalent hospitalizations, we excluded subjects who were discharged with any diagnosis of HF between 1990 and 1993. Age- and sex-specific, and directly age-standardized, rates of initial HF hospitalization were estimated using population denominators. Poisson regression was used to model changes over time.

**Results:** For both women and men, age-standardized rates decreased 37% from 1993 to 2001. Decreases of this magnitude were observed over all ages.

**Conclusions:** Declines in rates of initial hospitalization for HF occurred in BC at the same time that efficacious therapies were incorporated into practice. While this finding is encouraging, alternative explanations such as concurrent hospital downsizing that restricted admission to more severe cases, must be ruled out before concluding that persons with HF were managed better.

**Key Words:** Heart failure, time trends, British Columbia

61

### Determining the prevalence and predictors of blood pressure self-management in community-dwelling seniors

Lau E,<sup>1</sup> Dolovich L,<sup>1,2</sup> Kaczorowski J,<sup>2</sup> Karwalajtys T,<sup>2</sup> Levine M<sup>1,2</sup>

<sup>1</sup>Centre for Evaluation of Medicines, St. Joseph's Healthcare, Hamilton, Canada, <sup>2</sup>Faculty of Health Sciences, McMaster University, Hamilton, Canada

Corresponding Author: [lau@mcmaster.ca](mailto:lau@mcmaster.ca)

**Background:** High blood pressure is highly prevalent in Canada and its prevalence increases with age. Patient self-management of hypertension may lead to improved control of this frequently under-diagnosed and undertreated condition. The objectives of this study were to determine the extent to which elderly patients are involved in blood pressure (BP) self-management and to identify factors predictive of self-management practices.

**Methods:** This was a cross-sectional survey study. Community-dwelling seniors (65 years of age) from family physician practices in Hamilton, Ontario completed a 37-item self-administered written questionnaire with 9 domains: perceived need to manage BP, positive health practices (lifestyle modification and self-monitoring), knowledge, self-awareness of BP, healthcare provider interactions, decision-making style, self-efficacy, medication adherence, and external factors. Scores were calculated within each domain and a composite score was calculated across all domains. Multivariate regression models will be used to identify independent predictors of self-management behaviour. A target sample size of 1000 patients is anticipated.

**Results:** Preliminary results are available for 142 patients (mean age 74.0 years, 58.5% female) of 485 surveys sent (30% initial response rate). Patients scored highest in BP knowledge (mean score 86.0%) and medication adherence (mean score 93.8%), and lowest in positive health practices (mean score 57.3%). Although more than half of patients felt very sure about how to take their medications, less than one third felt very sure of the important side effects of their medications. Seventy-six percent expressed willingness to adjust the dose of their medications if guided by their physician. Respondents had a mean composite score of 73.0% for overall self-management willingness and ability.

**Conclusions:** Preliminary results suggest that although elderly patients have some degree of knowledge and skill necessary for BP self-management, not all patients are prepared to take a more active role.

**Key Words:** *Blood pressure, self-management, survey*

62

### Exploring patient perceptions about strategies to improve adherence to osteoporosis therapies: a qualitative study

Lau E,<sup>1</sup> Papaioannou A,<sup>2</sup> Dolovich L,<sup>1</sup> Adachi J,<sup>3</sup> Sawka A,<sup>3</sup> Nair K,<sup>1</sup> Burns S,<sup>1</sup> Pathak A,<sup>2</sup> Kennedy C<sup>2</sup>

<sup>1</sup>Centre for Evaluation of Medicines, St. Joseph's Healthcare, Hamilton, Canada, <sup>2</sup>Department of Medicine, Hamilton Health Sciences, Hamilton, Canada, <sup>3</sup>Department of Medicine, St. Joseph's Healthcare, Canada

Corresponding Author: [lau@mcmaster.ca](mailto:lau@mcmaster.ca)

**Background:** Non-adherence to osteoporosis medications is common. Strategies to improve adherence have resulted in limited improvements in patient adherence and treatment outcomes, although the reasons for this are unclear. The objective of this study was to explore the experiences, perceptions, and expectations of post-menopausal women regarding strategies used to improve adherence to osteoporosis therapies.

**Methods:** This was a qualitative study that utilized a phenomenological approach. Focus groups will be conducted with a purposeful sample of post-menopausal women who are taking osteoporosis medications, recruited from physician practices and community pharmacies in Hamilton, Ontario. Eight focus groups, with 6-8 participants each, are planned. A semi-structured interview guide was used with questions about 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 at least 2 research team members.

**Results:** From preliminary analysis of the first focus group, adherence to osteoporosis medications was viewed as important among all participants. Non-intentional non-adherence was a more prominent theme than intentional non-adherence since patients generally did not perceive they had a choice in taking osteoporosis medications. Facilitators to adherence included trust in the prescribing physician, receiving adequate information about osteoporosis and its treatment, and seeing the positive effects of medication on their condition. Barriers to adherence included fear of long-term side-effects, complex administration schedules, and changes in daily routine. Patients often consulted their physicians to determine if other options were available if they encountered problems with taking their medications. The main adherence strategies patients perceived as useful were planning ahead, using medication organizers, and integrating medication-taking into their daily routine.

**Conclusions:** Patient's unique experiences may affect their responsiveness to a given adherence strategy. Adherence strategies are most useful when they are individualized to the type of non-adherence behaviour encountered.

**Key Words:** *Osteoporosis, adherence, qualitative*



63

### Development and evaluation of a workshop to disseminate Canadian clinical practice guidelines on the diagnosis and treatment of osteoporosis in primary care

Lalonde L, Goudreau J, Rodrigues I, Fournier M  
Research team in primary care, Centre de Santé et de services sociaux de Laval, Québec

Corresponding Author: [martine.fournier\\_csl@ssss.gouv.qc.ca](mailto:martine.fournier_csl@ssss.gouv.qc.ca)

**Background:** A tool kit on the prevention of fragility fractures has been developed and presented during a workshop to family physicians in their medical clinic to disseminate the Canadian osteoporosis practice guidelines.

**Objectives:** To measure the change in participant physician's knowledge and identify factors influencing the use of the tool kit in clinical practice.

**Methods:** Forty-four family physicians working in private practice and in local centre of community services in Laval (suburb of Montreal) attended the workshop and have completed a knowledge questionnaire based on a clinical vignette before and after the workshop. A semi-structured interview was conducted with twelve physicians, three to six months after the workshop to document their use of the tool kit and a content analysis have been realised.

**Results:** An improvement in the knowledge of risk factors (before the workshop: 80% versus after the workshop: 100%;  $p = 0.002$ ), diagnostic tests (40% versus 100%;  $p < 0.001$ ), and available community resources (0% versus 50%;  $p = 0.001$ ) have been observed. All interviewed physicians agreed on the quality and potential usefulness of the tool kit. Eight physicians have used at least one section of it. Reasons for not using it were: (1) forgetting about it; (2) feeling knowledgeable about its content; and (3) lack of time.

**Conclusions:** A workshop based on a tool kit improves family physician knowledge on osteoporosis diagnosis and treatment and has been judged as useful by users. A subsequent study to measure the impact of the workshop on clinical practice is ongoing.

**Key Words:** *Osteoporosis, practice guidelines, clinical workshop*

64

### Differential risks of death for users of carvedilol according to the specialty of the prescriber

Dorais M, LeLorier J

Centre de recherche Hôtel-Dieu-CHUM, Montreal

Corresponding Author: [marc.dorais@umontreal.ca](mailto:marc.dorais@umontreal.ca)

**Background:** Randomised controlled trials have shown that carvedilol decreases mortality and morbidity in patients with cardiac failure. However, carvedilol has a narrow therapeutic index and its titration requires a great deal of clinical expertise. We studied the mortality of patients on carvedilol according to the specialty of the prescriber.

**Methods:** Subjects (age 42–91) were eligible for drug coverage under the RAMQ and were carvedilol users with an index date (initial dispensed prescription) between January, 1997 and June, 2003. The study was restricted to patients who consulted the same specialty of physician for the renewal of carvedilol prescription. The proportion of patients who died during the carvedilol therapy was analysed using survival curves and Cox Regression methods.

**Results:** There were 198 patients in the final cohort. Cardiologists were the carvedilol prescribers for 62% of patients, general practitioners (GP) for 31%, and internists for 7%. The median number of days where the patients were continuously under carvedilol therapy was 211. Compared to patients receiving their carvedilol from a cardiologist, the survival rates were lower for patients with an internist (adjusted RR of death: 61.53; 95% CI: 3.94-960.22) and for patients with a GP (RR: 33.03; 95% CI: 2.75-396.97). Patients aged 73 years or more and patients who visited an emergency room in the year prior to the index date also had a lower survival rate.

**Conclusion:** Physicians who prescribed carvedilol to patients with heart failure should be aware of the required expertise to properly administer this drug.

**Key Words:** *Prescriber, cardiac failure, drug prescription*

65

**Impact of exception drug status on the appropriate use of TZDs**Dorais M, LeLorier J

Centre de recherche Hôtel-Dieu-CHUM, Montreal, Canada

*Corresponding Author:* [marc.dorais@umontreal.ca](mailto:marc.dorais@umontreal.ca)

**Background:** Pioglitazone and rosiglitazone (TZDs) have exception drug status in the RAMQ formulary. The conditions for reimbursement are renal insufficiency and failure to respond to maximal doses of conventional oral hypoglycemic agents (COHA). We evaluated the proportion of patients who received a prescribed dispensation of a TZD among those who met the reimbursement criteria.

**Methods:** Among patients eligible for drug coverage under the RAMQ between July, 1997 and June, 2001, we selected those who received three consecutive dispensations of maximal doses of both metformine and sulphonylurea: Cohort 1; and those who received at least one oral antidiabetic agent and who had a diagnosis of chronic renal failure: Cohort 2. In both cohorts, we evaluated the proportion of patients who received a TZD in the year following the index date.

**Results:** There were 5,216 patients in Cohort 1 (high doses) and 3,183 in Cohort 2 (renal failure). A TZD was dispensed to 12.1% (95% CI: 11.3%;13.0%) of the patients in the cohort of high doses and to 7.9% (95% CI: 7.0%;8.9%) in the cohort of renal failures. The average time to receive a TZD was 233 days for the cohort of high doses and 199 days for the cohort of renal failures.

**Conclusion:** As a result of the bureaucratic hurdle imposed by RAMQ, only about 10% of the patients susceptible to benefit from TZDs received these drugs.

**Key Words:** *RAMQ formulary, pioglitazone, rosiglitazone*

66

**Direct medical costs (2004) of acute care for stroke in Ontario, Canada**Seung, SJ,<sup>1</sup> Mittmann, N,<sup>1</sup> Haiderali A<sup>2</sup><sup>1</sup>HOPE Research Centre, <sup>2</sup>AstraZeneca Canada,*Corresponding Author:* [Amin.Haiderali@astrazeneca.com](mailto:Amin.Haiderali@astrazeneca.com)

**Background:** The Heart & Stroke Foundation of Canada estimates that there are between 15,000 to 20,000 strokes annually in the province and in 1994-5, the total cost of stroke was \$857 million. The objective of this study was to update the annual cost of acute care for stroke from a provincial perspective.

**Methods:** The acute care for stroke involves six health care services: emergency departments, ambulance transport, hospitalizations, inpatient rehabilitation, physicians and allied health professionals (physiotherapy, occupational therapy and speech language therapy). Resource utilization information was based on Canadian Institute for Health Information (CIHI) databases and Sunnybrook & Women's College Health Sciences Centre's Emergency Department Information System while costing data was based on provincial fee schedules, the Ontario Case Costing Initiative and published literature.

**Results:** An estimated \$372.4 million is being spent annually by Ontario to provide six acute care services to stroke patients. Hospitalizations account for 76% (\$283.1 million) of the total acute care cost followed by 13% (\$48 million) for inpatient rehabilitation, 4% (\$13.4 million) for physician services, 3% (\$13.6 million) for emergency departments, 2% (9.3 million) for allied health professionals and 2% (\$6 million) for ambulance transport.

**Conclusions:** The results suggest that the acute care component of stroke care is resource intensive and thus costly. This study is part of a multi-phase study to determine the total cost of stroke in Canada that will also include a prospective study focusing on outpatient stroke care at secondary stroke prevention clinics.

**Key Words:** *Neurology, databases, costs*

67

**Rate and quality of anticoagulation in Canadian patients with CNVAF**Caro JJ, Payne KA, [Haiderali A](#), Lordan N, El-Hadi S, Ishak I, Proskorovsky I, Hollowell J

AstraZeneca Canada Inc., Ontario, Canada

*Corresponding Author:* [amin.haiderali@astrazeneca.com](mailto:amin.haiderali@astrazeneca.com)**Background:** Patients with CNVAF require anticoagulation (AC) to reduce their 5-fold increased risk of stroke. Objectives: To estimate the rate and quality of AC in Canadian patients with CNVAF.**Methods:** A retrospective chart review study of patients with newly diagnosed or existing EKG confirmed CNVAF was conducted in 3 Canadian provinces. Rate of AC and INR time in therapeutic range (TR: INR 2.0-3.0) over a 15 month study period were primary outcomes.**Results:** Only 60% of CNVAF patients received a minimum of 60 days of AC. Reasons for no AC were: 28% because treatment was contraindicated, 26% because of physician discretion, 16% due to successful cardioversion, 12% because of patient refusal, and for 18% of patients, the reason was unknown. In the 225 patients (62% male; mean age 73 years) who did receive AC, 78% were prescribed warfarin, 6% an unspecified AC, and 16% nothing at the start of the study period. Overall, patients spent 63% of study time within TR, but results were poorest (53%) for those at highest risk for stroke. 25% of test results fell below 2.0 and 12% were above 3.0. AC was temporarily discontinued in only 26% of INRs >5.**Conclusions:** The routine medical care of Canadian patients with CNVAF is sub-optimal leaving a significant proportion of these patients at high risk for serious and costly outcomes such as bleeds and strokes. Newer AC therapies with better management profiles are clearly warranted.**Key Words:** *Anticoagulation, CNVAF, Canada*

68

**Duration of hospital stay for treatment of methanol and ethylene glycol poisoning in British Columbia 1996-2001**[Lepik KJ](#), Levy AR, Daws DE, Sobolev B, Purssell RA  
Department of Health Care and Epidemiology,  
University of British Columbia, Canada*Corresponding Author:* [klepik@dowco.com](mailto:klepik@dowco.com)**Background:** Methanol (ME) and ethylene glycol (EG), constituents of automotive antifreeze, are a common source of poisoning. ME and EG produce similar toxic effects and require treatment with an antidote (ethanol or fomepizole) and/or hemodialysis (HD). As the resources devoted to treatment have not been well characterized in Canada, our goal was to estimate the length of hospital stay for persons poisoned with ME and EG in BC.**Methods:** We retrospectively reviewed medical charts of persons diagnosed with ME or EG poisoning admitted to nine BC hospitals with HD units between 1996 and 2001. Treatment duration (from admission to completion of antidote and/or toxin-clearing HD treatment), post-treatment hospitalization (end of treatment to discharge) and total hospital stay were collected.**Results:** The series comprised 70 ME and 48 EG poisonings. Although the mean (SD) treatment duration was similar for both ME and EG, 1.3 (1.2) and 1.4 (1.1) days respectively, post-treatment hospital stay was shorter for ME 3.5 (6.3) than EG 12.5 (15.0) days. This resulted in a shorter mean length of stay for ME, 4.8 (6.5), than for EG poisoning, 13.9 (15.2) days.**Conclusions:** The treatment time for ME and EG poisoning is less than half the hospital stay. The large differences in post-treatment hospital stay between ME and EG poisonings may be due, in part, to increased medical complications in EG-poisoned patients. These data comprise the largest Canadian case series of ME and EG poisonings and will be used to more fully characterize the economic burden of illness.**Key Words:** *Methanol, ethylene glycol, hospital stay*

69

**Economic burden of moderate to severe chronic-plaque psoriasis in Canada**

Einarson TR, Piwko C, Desjardins O, Tan J, Shear N, Dorkalam M, Iskedjian M  
PharmIdeas Research & Consulting Inc., Oakville, Canada

*Corresponding Author:* [t.einarson@utoronto.ca](mailto:t.einarson@utoronto.ca)

**Background:** Psoriasis is an immune-mediated disorder of which the chronic plaque type is the most common form. This condition affects about 1 million Canadians, 25% of whom are afflicted from a moderate to severe extent. The objective of this study was to determine average annual direct and indirect costs in these patients from a societal perspective.

**Methods:** Data were collected in two phases: chart review and patient interview. Inclusion criteria were adults <sup>3</sup>18 diagnosed with moderate-to-severe disease. We obtained utilization patterns for direct costs (drugs, physicians, hospitalizations) and indirect costs (time off work) from patients in 4 Ontario dermatology clinics. Chart data were collected for the previous 2 years, interview data for 1 year. Annual costs/patient were calculated in 2004 Canadian dollars. Results were projected to the population using published Canadian epidemiologic estimates.

**Results:** Direct medical costs/patient/year as derived from 80 charts were \$3,726±\$1,496; translating to a total estimated burden for Canada of \$745±\$299 million/year. From 104 interviews, the average direct and indirect costs/patient/year were \$5,546±\$5,935 and \$3,281±\$7,223, respectively. The total estimated Canadian burden was \$1.765±\$2.632 billion/year. Projected from these two separate estimates, the overall burden of illness for moderate-to-severe chronic plaque psoriasis in Canada was \$1.255 billion/year.

**Conclusions:** This study estimates the economic burden of moderate-severe chronic plaque psoriasis in Canada. This condition is associated with a substantial economic burden on both the healthcare system and society. The introduction of new biologic drugs is expected to add to drug related costs, but potentially decrease other direct and indirect costs.

**Key Words:** *Cost of illness, chronic plaque psoriasis, Canada*

70

**Economic impact of reduced incidence of diabetes in patients with left ventricular dysfunction treated with enalapril**

McLachlin DT, Rindress D, Desjardins B, Tardif J-C  
BioMedCom Consultants, Inc., Montreal, Canada

*Corresponding Author:* [derek.mclachlin@biomedcom.org](mailto:derek.mclachlin@biomedcom.org)

**Background:** In a subgroup of patients participating in the Studies of Left Ventricular Dysfunction (SoLVD) trials, the angiotensin-converting enzyme inhibitor enalapril was found to reduce incidence of new-onset diabetes by 78% relative to standard care alone. This work predicts the economic consequences of this reduced incidence of diabetes in patients with heart failure who receive enalapril, from a Canadian Ministry of Health perspective.

**Methods:** A 10-year Markov decision model was generated, incorporating published incidence data from the SoLVD trials and Canadian direct costs. The timeframe of the model reflects the life expectancy of patients in the SoLVD prevention trial.

**Results:** On average over 10 years, patients treated with enalapril incurred Can\$13,015 per person in treatment costs relating to diabetes and heart failure; those who did not receive enalapril incurred costs amounting to Can\$16,952. Therefore enalapril was predicted to save \$3,938 per patient in diabetes and heart failure treatment costs over 10 years. Of patients surviving at model termination, 45.4% of those who did not receive enalapril and 82.4% of those who received enalapril were nondiabetic. These results were robust to changes in the model assumptions.

**Conclusions:** Use of enalapril in patients with heart failure was projected to reduce treatment costs over 10 years as a consequence of reduced incidence of diabetes. When the benefits of reduced new-onset diabetes are added to the previously established benefits of enalapril resulting from reduction of cardiovascular outcomes, enalapril therapy in patients with heart failure becomes even more clinically and economically attractive.

**Key Words:** *ACE inhibitor, diabetes mellitus, health economics*

71

### Effectiveness evaluation of population therapeutics & provincial health databases in Canada – a systematic review

Tricco AC, Pham B, Rawson NSB, Robson RC  
BioMedical Data Sciences, GlaxoSmithKline, Canada

Corresponding Author: [andrea.tricco@utoronto.ca](mailto:andrea.tricco@utoronto.ca)

**Background:** The lack of effectiveness evidence continues to plague technology assessment (e.g., cost-effectiveness analyses), especially in submissions for publicly-funded drug programs. Some effectiveness evidence has been derived from readily available population-based data using different approaches (e.g., cohort design). These and their relative merit are assessed in a systematic review of studies addressing research questions using the Saskatchewan and Manitoba (SK&MB) databases.

**Methods:** PUBMED, EMBASE, BIOSIS and CINAHL were searched, keywords “Saskatchewan”(exploded:1969-2004) or “Manitoba”(exploded:1970-2004), to identify studies using SK&MB data. Two reviewers independently screened citations. Data abstraction independently conducted included study design, research type (e.g., validity and reliability studies, V&R), and disease area.

**Results:** 3637 citations were identified and screened, 492 full-text articles retrieved, and 302 included (136 SK, 166 MB). These studies spanned a variety of approaches, which are summarized below. In total, 26% (n=80) studies addressed a stated hypothesis using a case-control (n=39, 72%SK, 28%MB) or cohort design (n=41, 73%SK, 27%MB). Less than 10% assessed V&R (6%SK, 7%MB). Major types of studies included exposures and health outcomes (48%SK, 18%MB), disease surveillance (17%SK, 24%MB), and health services utilization (27%SK, 48%MB). The main clinical areas were respiratory (18%SK, 7%MB), circulatory (16%SK, 10%MB), and neoplasms (17%SK, 9%MB). Clusters of similar studies were found in both sources.

**Conclusion:** There is a large body of literature on studies using SK&MB data. The V&R of both SK&MB is well established. Precedence for proper effectiveness evaluations is common (e.g., optimal use of therapeutic interventions, most effective treatment for a subpopulation). Clusters of similar studies indicate a potential for wide application of these sound approaches; others appear to be multiple publications.

**Key Words:** *Effectiveness, systematic review, provincial databases*

72

### Evaluation of patient access to diabetic medications

Abushomar H, Gaebel K, Levine M

The Centre for Evaluation of Medicine, Hamilton, Canada

Corresponding Author: [abushoht@mcmaster.ca](mailto:abushoht@mcmaster.ca)

**Background:** Rosiglitazone (Avandia) and pioglitazone (Actos) are two new generations of oral hypoglycemic medications known as thiazolidinediones (TZD). They are available to Ontario Drug Benefit (ODB) eligible patients according to specific reimbursement criteria. This study sought to evaluate patient access to TZD therapy through ODB program.

**Methods:** Type 2 diabetes patients > 68 years who were using an oral hypoglycemic were recruited through community pharmacies in Ontario. Data were obtained from patient telephone interviews and medical forms completed by the treating physicians.

**Results:** 77 patients did not receive a TZD even though they met the ODB eligibility criteria for TZD reimbursement. 27 patients who met the criteria received a TZD, which would have been reimbursed either by the ODB or by a non ODB source, or not reimbursed at all (i.e., cost borne by the patient). Females comprised 51% of non-TZD users but only 33% of TZD users. 48% of non-TZD users had an annual income of < \$30,000 whereas 33% of TZD users were at that low level of income. Patient visits to a diabetic clinic were more frequent amongst TZD users (26%) than non-TZD users (17%), even though both groups had similar age, duration of illness and co-morbidities. The most recent HbA1c, mean (s.d.), was slightly higher in non-TZD users 0.074 (0.012) than in TZD users 0.071 (0.012).

**Conclusion:** The ODB policy to limit TZD reimbursement to specific conditions of appropriate use may have been applied in a non-uniform manner, resulting in reduced access for woman, the poor and those not attending diabetes clinics. This may also lead to negative effects on blood glucose control.

**Key Words:** *Prescribing, drug utilization, diabetes*

73

**Graphs in pharmacoepidemiology - are they in need of improvement?**Goldsmith C

McMaster University, Hamilton, Canada

*Corresponding Author:* [goldsmi@mcmaster.ca](mailto:goldsmi@mcmaster.ca)

**Background:** Statistical packages permit easy production of graphs. However, this ease means that the graph may not always use good graphic perception principles.

**Objectives:** This presentation will review the common principles of graphic perception, apply them to graphs examples in Pharmacoepidemiology and Drug Safety (PDS) in 2003:12, and suggest how these graphs could be improved.

**Methods:** Graphic perception principles are: Position along a common line; Position along identical but nonaligned scales; Length; Angle or Slope; Area; Volume; Colour hue, Colour saturation, Density. Violating these principles has resulted in many poorly constructed graphs in the scientific literature. All graphs from PDS 2003:12 will be used to illustrate improvements to better enable the reader to see the key messages. Counts and percentages are used to describe the improvements.

**Results:** Of 80 articles, 28(35%) contained at least one graph. Of these 28, 14 (50%) had 1 graph, 4 (14%) had 2 graphs, 6 (21%) had 3 graphs, 3 (11%) had 4 graphs, while 1 (4%) article had 24 graphs!, for a total of 76. One graph (1%) had no suggested graphical improvements! However, 48 (63%) could have included a right-hand axis to make the graph easier to interpret, 33 (43%) could have included the data values below the group label, 31 (41%) could have made the y axis label horizontal rather vertical, 31 (41%) could have put the legend outside the data region to be less confusing, 17 (22%) had no x axis, 10 (13%) had extra zeros in the numbers on the y axis, 10 (13%) had no y axis label, 9 (12%) had no x axis label, 7 (9%) used a 3 dimensional plot when there was no information in the 3rd dimension, with lower counts and percentages of graphs with 10 other suggestions for improvement. A selection of graphs are redrawn to show how these graphs might be improved to become visual aids rather than impediments.

**Conclusions:** Pharmacoepidemiology graphs could be improved by paying attention to good graphic perception principles.

**Key Words:** *Graphs, graphic perception, misleading plots*

74

**High cost users of pharmaceuticals: who are they?**Kozyrskyj AL, Dahl ME, Soodeen RA, Lix LM

Manitoba Centre for Health Policy, Dept Community Health Sciences, Faculty of Medicine, Faculty of Pharmacy, University of Manitoba, Canada

*Corresponding Author:* [kozyrsk@cc.umanitoba.ca](mailto:kozyrsk@cc.umanitoba.ca)

**Background:** This population-based study characterized high cost users of pharmaceuticals in Manitoba in terms of prescription costs and utilization, underlying conditions, health care system use and health outcomes.

**Methods:** On the basis of annual prescription costs, 3 groups were identified from Manitoba's prescription database: Persistent High Cost Users (PHUs - top 5% of expenditures in each year from FY1997/98 to FY2000/01), Intermittent High Cost Users (IHUs - top 5% in FY2000/01 and episodically since 1997/98) and Non High Cost Users (NHUs) in FY2000/01. Linkages were made to other health care databases (eg. physician claims, hospital abstracts) to determine morbidity and health outcomes.

**Results:** PHUs and IHUs consumed 41% of total prescription expenditures. Hypertension, diabetes, depression, schizophrenia and peptic ulcer disease were 3-6 times more prevalent in PHUs/IHUs than in NHUs. 40% of PHUs/IHUs had two or more major conditions and over 85% received 6 or more different medications (7% and 16% in NHUs, respectively). PHUs had a higher level of cardiovascular comorbidity (28%) than IHUs (20%) and NHUs (1%). IHUs were more likely than PHUs to have cancer or multiple sclerosis. PHUs and IHUs had greater physician utilization and hospitalization rates than NHUs in FY2000/01. Hospitalization and institutionalization rates were also higher in the subsequent year for PHUs and IHUs; this finding was not completely explained by increased comorbidity.

**Conclusions:** A large share of prescription medications are being used by persons with a high level of comorbidity, but the use of multiple medications predisposes high cost users to adverse events.

**Key Words:** *Pharmaceuticals, cost, high*

75

**Predictors of transition to high cost use of pharmaceuticals**

Lix LM, Dahl ME, Soodeen RA, Kozyrskyj AL  
 Manitoba Centre for Health Policy, Dept Community Health Sciences, Faculty of Medicine, Faculty of Pharmacy, University of Manitoba, Canada

*Corresponding Author:* [kozyrsk@cc.umanitoba.ca](mailto:kozyrsk@cc.umanitoba.ca)

**Background:** This was a population-based study which identified predictors of transition from being a low to high cost user of pharmaceuticals.

**Methods:** A case-control design was used to test predictors of transitioning to first-time high cost pharmaceutical use (HU = top 5% of annual prescription costs in Manitoba's prescription database in FY2000/01, but not FY1997/98 - FY1999/00). Controls were age and sex matched Manitoba residents who were not high cost users (NHU) in the study period. Using multiple logistic regression, predictors of the probability of transition were derived from Manitoba's health care databases in the year prior to high cost pharmaceutical use: first-time hospital use, first-time hospital long-stay use, first-time home care use, and first-time multiple physician and prescription drug use.

**Results:** A much larger proportion of HUs than NHUs had contact with home care, hospitals, and physicians, used multiple drugs and saw multiple practitioners even three years before becoming high users. However, there was a sharp increase in prevalent and first-time health care use in the year prior to transition. For example, HUs with low comorbidity were more likely (OR=4.1, 95%CI: 3.5-4.8) than NHUs to be hospitalized for 7 or more days, or to receive home care (OR=1.8, 95%CI: 1.5-2.1) for the first time in the year prior to high use.

**Conclusions:** Hospitalization and home care can be viewed as opportunities for intervention in the transition to high cost pharmaceutical use. They provide the time, physical and human resources for conducting medication reviews and discontinuing unnecessary medications.

**Key Words:** *Pharmaceuticals, high-use, transition*

76

**Impact of a pharmacist telephone follow-up intervention on patients receiving antibiotic treatment in community: microbe study**

Lachance-Demers H, Beaucage Krystel, Ngo TTT, Vachon C, Lamarre D, Guévin J-F, Martineau A, Desroches D, Brassard J, Lalonde L

Faculty of Pharmacy, University of Montreal, Research Team in Primary Care, Centre de Santé et de services sociaux de Laval, Aventis Pharma endowment Chair in Ambulatory Pharmaceutical Care, Faculty of Pharmacy, University of Montreal, Canada

*Corresponding Author:* [heldemers@hotmail.com](mailto:heldemers@hotmail.com)

**Background:** Community-pharmacist telephone-follow-up intervention (PTFI) for patients undergoing antibiotic treatment may optimize the efficacy of treatment. Aim: To evaluate the impact of a PTFI on clinical outcomes, pharmaceutical care, and cost among adult patients undergoing a short antibiotic treatment.

**Methods:** A randomized, controlled trial in 6 community pharmacies in the area of Montreal to compare the PTFI to the usual pharmacist intervention (UPI).

**Results:** As compared to the UPI group (n = 129), in the PTFI group (n = 126), drug-related-problems (DRPs) were identified in more patients (PTFI: 53%, UPI: 8%; p < 0.001). Verbal recommendations (PTFI: 52%, UPI: 6%; p < 0.001) and pharmaceutical advices were also given for more patients (PTFI: 15 %, UPI: 3 %; p < 0.05). The mean difference (95% CI) in the change in the number of infectious symptoms and the infection-severity score across the two groups were equal to -0.24 symptom (-1.22 to 0.74) and -0.05 unit (-0.35 to 0.25), respectively. Adherence to treatment and patient satisfaction did not differ across the two treatment groups. The direct costs of the intervention vary from \$2.68 CAD and \$5.08 CAD per patient depending on whether cognitive services are reimbursed.

**Conclusion:** A PTFI provides an excellent opportunity to detect and manage DRPs. In this study, no improvement in clinical outcomes was detected. This may be attributable to the difficulty of measuring clinical outcomes without laboratory culture, to the high level of pharmaceutical care offered to all study patients, and to the relatively small number of patients.

**Key Words:** *Antibiotic, drug-related problems, pharmaceutical care*

**Impact of private drug-plan changes on beneficiaries**

Polygenis D,<sup>1</sup> Polk G,<sup>2</sup> Fishman R,<sup>1</sup> Mihai A<sup>1</sup>

<sup>1</sup>Phase 4 Health Inc., Canada, <sup>2</sup>Ontario Round Table on Appropriate Prescribing (ORTAP) & AstraZeneca, Canada

*Corresponding Author:* [dpolygenis@phase4health.com](mailto:dpolygenis@phase4health.com)

**Background:** The impact of employer-sponsored drug plan changes (i.e., cost-containment) on employee drug/health care utilization and health status is not known. The purpose of this study was to explore the impact of drug plan changes in order to better inform choices/discussion regarding cost sharing policies and drug plan design.

**Methods:** Employees from two large employers were randomly surveyed and asked to comment on their: 1) understanding of their private drug plan; 2) health and medical conditions and impact on daily activities; and 3) medication taking behaviour pre- and post- drug plan change. 727 surveys were analysed and compared with 367 surveys from a sub-population suffering from multiple health conditions, using regression techniques. Corresponding claims data was examined to assess utilization pre-/post-drug plan change.

**Results:** Few employees adequately grasp drug plan policy (33%-44% considered the drug plan unchanged). Following drug plan change, the majority of employees increased their usage of both prescription (65%-73%) and over-the-counter drugs (63%-72%). Claims data revealed little change in the type and quantity of drugs used. Few employees reported drug cost-cutting measures and negative health outcomes, and fewer linked these to restricted drug coverage. Severely ill, low income and female employees are the most vulnerable.

**Conclusions:** Drug plan changes have direct consequences on drug utilization and health status. Although few employees resort to cost-cutting measures or incur negative health outcomes immediately following implementation of cost-containment measures, the true impact of these changes may take a long time to emerge. 'High-need' beneficiaries are those at greatest risk for engaging in undesirable medication-taking behaviour.

**Key Words:** *Cost-sharing/containment, utilization, health outcomes*

**Poster Session II**

**Price benchmark evaluation of recent innovations in the setting of stroke prophylaxis**

Polygenis D,<sup>1</sup> Liovas A,<sup>2</sup> Chandra K<sup>1</sup>

<sup>1</sup>Phase 4 Health Inc., <sup>2</sup>AstraZeneca Canada Inc

*Corresponding Author:* [dpolygenis@phase4health.com](mailto:dpolygenis@phase4health.com)

**Background:** There are a number of treatments with benefits in stroke prevention. Since these treatments are primarily used to treat other conditions (i.e., hypertension, atrial fibrillation, hyperlipidemia), head-to-head comparisons are difficult to make and the cost of stroke prophylaxis difficult to quantify. The purpose of this study is to benchmark the cost and stroke avoidance profiles of recent innovations in the setting of stroke prophylaxis.

**Methods:** Drugs meeting the following criteria were selected: 1) recent innovation; 2) available in Canada; 3) published stroke data. These were identified a priori as Plavix®, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and HMG-CoA reductase inhibitors (STAT). An extensive literature search was performed and all placebo controlled, randomised clinical trials reporting stroke events as an outcome were identified and analysed. Weighted averages for cost and strokes prevented for each drug class were calculated and cost per stroke avoided was compared across drug classes.

**Results:** Eighteen trials were included in this comparative analysis. ACEIs averted the most events preventing 0.57 strokes per 100 persons per year. They were followed by ARBs, Plavix® and STATs which prevented 0.29, 0.25 and 0.20 strokes per 100 persons per year respectively. The cost per stroke averted for ACEIs, ARBs, STATs and Plavix® was \$521, \$1,348, \$2,912 and \$3,570 respectively.

**Conclusions:** Although there are limitations with indirect comparisons, (i.e., different patient populations and risk factors), adjusted comparisons may provide useful insight into the treatment of multifactorial diseases such as stroke (BMJ 2003;326:472-5).<sup>1</sup> A meta-analysis is underway to confirm these results.

**Key Words:** *Literature evaluation, price benchmarking, stroke*



79

### Impact of statin adherence on coronary artery disease (CAD) among middle aged patients for primary prevention

Bouchard M-H, Dragomir A, Perreault S  
University of Montreal, Montreal, Canada

*Corresponding Author:* [sylvie.perreault@umontreal.ca](mailto:sylvie.perreault@umontreal.ca)

**Background:** Clinical trials have previously demonstrated that statins can reduce cardiovascular (CVD) morbidity and mortality among patients having hyperlipidemia. These trials showed benefits only after 1 to 2 years of continuous treatment. Observational studies have demonstrated that more than 50% of patients stop their therapy after 2 years, but no study has evaluated the impact of statin adherence on coronary events for primary prevention.

**Objective:** To evaluate the impact of statin adherence on coronary events.

**Methods:** A cohort of 9,184 patients was reconstructed using the RAMQ databases. All patients aged from 50 to 64 years old who were newly treated for hyperlipidemia with statins between 1998 and 2001 were eligible. The date of the first prescription of statin was defined as the index date. Patients with history of CVD 3 years before the index date were excluded. The primary endpoint was CAD. Adherence was calculated by the proportion of days covered (65, 70, 80, 90%). Cox proportional hazards models with time-dependent covariates were used to estimate the rate ratio (RR) of CAD adjusting for age, sex, socioeconomic status, diabetes and hypertension.

**Results:** Among patients followed up for more than two years, those with adherence of more than 70% had less CAD (RR: 0.68; 0.47-0.99). Moreover, the impact of statin therapy was greater with a higher adherence, at 80% (RR: 0.67; 0.45-0.99) and at 90% (RR: 0.56; 0.36-0.87). This effect was not present at adherence of less than 70%. Patients with hypertension (RR: 1.74; 1.18-2.56) and with low socioeconomic status (RR: 1.54; 1.03-2.29) had a significantly higher risk of CAD.

**Conclusion:** This analysis indicates that adherence of more than 70% and for more than 2 years is essential to reduce CAD among middle aged patients in primary prevention. Our results confirm the importance of a long term therapy with statins.

**Key Words:** *Statin, effectiveness*

80

### Persistence and determinants of statins therapy among middle aged patients free of cardiovascular disease

Perreault S, Blais L, Dragomir A, Bouchard M-H, Lalonde L, Laurier C, Collin C

University of Montreal, Montreal, Canada

*Corresponding Author:* [sylvie.perreault@umontreal.ca](mailto:sylvie.perreault@umontreal.ca)

**Background:** In clinical trials, statins have been shown to reduce cardiovascular (CVD) morbidity and mortality among high risk patients and in patients with hyperlipidemia. Statins demonstrated benefit only after 1 to 2 years of continuous treatment. It is important to identify which subgroups of patients and when they are at most risk of statin discontinuation.

**Objective:** To evaluate the persistence rate in patients initiating statin therapy, and its relation to patient's characteristics.

**Methods:** A cohort of 13,630 patients was reconstructed from prescription data recorded in the RAMQ administrative database. All patients aged 50 to 64 years old who received at least 1 statin prescription between Jan 1998 and Dec 2000 for a new intention of treatment were included in the cohort and followed up until June 2001. The date of the first prescription of statin was defined as the index date. The cumulative persistence rate was estimated using a Kaplan-Meier analysis. Cox regression models were used to estimate the rate ratio of ceasing statins after adjustment.

**Results:** Persistence with statin therapy fell to 65% in the first 6 months after treatment and continued to decline over the next 3 years to 35%. At 3 years, persistence varied significantly with statin agents. After controlling for individual patients' demographic and clinical characteristics, we found patients who were prescribed fluvastatin, lovastatin and atorvastatin to have a higher rate of cessation compared with those on pravastatin. Adjusted rate ratio of ceasing statin agents in patients with other risk factors of CVD, such as age (RR:0.99; 0.98-0.99), diabetes (RR:0.87; 0.81-0.94), or hypertension (RR:0.77; 0.73-0.81) demonstrated a lower cessation rate. We observed lower persistence in patients who used the greatest number of pharmacies and prescribing physicians.

**Conclusion:** This analysis indicates that barriers to persistence occur early in the therapeutic course. Overall persistence with statins is low, and particularly among patients with few other CVD risk factors.

**Key Words:** *Statin, persistence, determinants*

81

### The impact of the WHI publication on incidence rate of hormone replacement users, persistence rate and its determinants in post menopausal women

Guay MP, Dragomir A, Pilon D, Moride Y, Perreault S  
University of Montreal and University of Sherbrooke,  
Montreal, Canada

Corresponding Author: [sylvie.perreault@umontreal.ca](mailto:sylvie.perreault@umontreal.ca)

**Background:** The WHI stopped prematurely because of an increased risk of breast cancer, stroke and cardiovascular diseases (CVD) in the estrogen and progestin (HRT) arm of the trial. Few studies have evaluated the impact of the WHI publication.

**Objective:** To determine the impact of the WHI publication on the utilization rate of HRT, the persistence rate and its determinants.

**Methods:** Two cohorts of women were reconstructed from prescription data recorded in the RAMQ administrative databases. Women aged 45 to 55 years old who received at least one HRT prescription: Pre-WHI cohort (10052 women) was recruited between Jan 1998 and Dec 2001, and Post-WHI cohort (1049 women) was enrolled between Sept 2002 and May 2003 for a new intention of HRT therapy, and followed up for a period of until 9 months. The date of the first prescription of HRT was defined as the index date. We estimated the trends of prevalence and incidence rate of HRT users by 30 days-period. The cumulative persistence rate was estimated using a Kaplan-Meier analysis. Cox regression models were used to estimate the rate ratio of ceasing HRT after adjustment.

**Results:** After the WHI publication, we noted a decrease of 30% in the prevalence and a 50% in the incidence rate of HRT users. A significant change was seen in the proportions of women using other dosages than 0.625 mg of estrogen; and for those having an established osteoporosis or being users of antidepressant. The rate of persistence of Pre-WHI cohort was 63% compared to 53% Post-WHI ( $p < 0.0001$ ). In Pre-WHI cohort, women having risk factors of CVD (HR: 0.89; 0.83-0.96) or coronary artery disease (CAD) (HR: 0.87; 0.77-0.99) or being user of antidepressant (HR: 0.84; 0.76-0.92) or anxiolytic (HR: 0.88; 0.81-0.95) agents were less likely to cease HRT; but these figures were non significant in Post-WHI cohort.

**Conclusion:** Substantial decrease occurs in the prevalence and incidence rate of HRT user. Significant change in the determinants was observed in women having risk factors of CVD, CAD, antidepressant or anxiolytic users.

**Key Words:** *Hormone replacement, utilization rate, persistence*

82

### Incorporating pharmacosurveillance in provincial drug formulary decision-making

Bassett K,<sup>1,2,3</sup> Wright J,<sup>1,3,4</sup> Carney G,<sup>1</sup> Cassels A,<sup>5</sup> Warren L,<sup>6</sup> Anderson G,<sup>7,8</sup> Mamdani M,<sup>7,9</sup> Naglie G,<sup>8</sup> Laupacis A,<sup>7,8</sup> Paterson M<sup>7,10</sup>

<sup>1</sup>Therapeutics Initiative, <sup>2</sup>Centre for Health Services and Policy Research, Departments of <sup>3</sup>Medicine and <sup>4</sup>Pharmacology & Therapeutics, University of British Columbia, Canada, <sup>5</sup>Department of Health Information Sciences, University of Victoria, Canada, <sup>6</sup>British Columbia Ministry of Health, Canada, <sup>7</sup>Institute for Clinical Evaluative Sciences, Faculties of <sup>8</sup>Medicine and <sup>9</sup>Pharmacy, University of Toronto, Canada, <sup>10</sup>Department of Family Medicine, McMaster University, Canada

Corresponding Author: [paterson@ices.on.ca](mailto:paterson@ices.on.ca)

**Background:** Prescription drug plan managers seek 'real world' evidence regarding the safety and effectiveness of drugs and drug coverage policies. We sought to: i) work with drug plan managers in Ontario and BC to define priorities for pharmacosurveillance evidence; ii) develop techniques for producing such evidence; and iii) assess its impact on formulary decision-making.

**Methods:** We established links with drug plan staff in Ontario and BC and developed a research team comprised of investigators and analysts in both provinces. We used semi-structured interviews with plan staff and advisors at the outset (30 from 9 provinces/territories) and conclusion (2 each from BC and ON) to collect information about use of evidence and the drug categories of greatest concern, and then developed common computer programs and analytic plans to study the drugs using administrative data. Initial cross-provincial studies involved data on prescriptions and costs paid by the provincial drug plans for seniors, and information from BC's PharmaNet Database on prescriptions paid by others. Closing interviews asked for feedback on the impact of independent and cross-provincial studies, areas for improvement, and directions for future research.

**Results:** It is possible for researchers and drug plan managers in two provinces to agree upon priority areas and to undertake research using common methods. Interprovincial research in which ideas and methods are shared, rather than data, can build local research capacity and improve efficiency. Data transfer to one site raises privacy and logistical issues. Local researchers have links with drug plan staff, access to provincial administrative data, and know their data best. Impact of pharmacosurveillance evidence is greatest when it is designed to inform/evaluate a specific decision or policy, available at the right time in the decision-making process, and presented in a manner that makes application easy. Existing administrative databases provide useful information, but do not capture many important patient characteristics or outcomes. Work is needed to develop ways to fund, collect, and link information (from patients, medical records) to administrative data to permit better characterization of therapies, patients, and outcomes.

**Key Words:** *Prescription drug insurance, pharmacoepidemiology, pharmacovigilance*

83

### Increase in prevalence of antidepressant use in Quebec within all age groups and persons diagnosed with depression, panic or generalized anxiety disorders

Barnard L

Conseil du médicament of Québec, Quebec, Canada

*Corresponding Author:* [louise.barnard@mss.gouv.qc.ca](mailto:louise.barnard@mss.gouv.qc.ca)

**Background:** Considerable increase in the use of antidepressants in Quebec has occurred since 1999. Were prescribing habits affected by the controversy concerning possible increased risk of suicide associated with the use of selective serotonin reuptake inhibitors (SSRIs) and related Health Canada's warnings?

**Objectives:** To determine the annual prevalence of antidepressants use, the diagnosis of users and the type of antidepressants prescribed, the use of other central nervous system drugs including benzodiazepines (BDZs). To determine the treatment duration in depression, panic or generalized anxiety disorders.

**Methods:** A retrospective study using provincial database. Five annual cohorts of persons insured for the whole year 1999, 2000, 2001, 2002 or 2003 were formed. A 2004 cohort of six months starting in June 2004 was formed. Those who had received at least one antidepressant during the year were considered as users and those without antidepressants in preceding 395 days as new users. Annual prevalence was determined according to sex, age-group and insured categories (non employed, employed, seniors). Use of other drugs was considered on a yearly basis. Diagnosis by prescribing doctors captured in the provincial database.

**Results:** From 1999 to 2003, prevalence of antidepressant use increased from 8.1% to 10.4%. In 2003, prevalence is twofold higher in women vs men (13.5% vs 6.8%) and in 40-64 year old non employed vs employed women (30.8% vs 14.4%) as well as men (17.1% vs 6.7%). In 2000, 67.2% of persons diagnosed with depression used an antidepressant vs 69.2% in 2003; for persons with panic or generalized anxiety disorders, the percentages are 35.9% and 42.0%. From 2000 to 2004, the percentage of new users diagnosed with depression prescribed a SSRI decreased from 68.3% to 55.0% while the percentage of those receiving mirtazapine, trazodone or bupropion increased from 8.1% to 26.4%; simultaneously changes occurred within the various SSRIs: paroxetine, from 27.4% to 12.7%; citalopram, from 15.5% to 28.3%. Use of paroxetine is lower in new users diagnosed with depression younger than 18 years old (7.8%) or older than 75 (9.8%). In 2003, 66.1% of senior antidepressant users and 28.4% of non users have used BDZs. The percentage of BDZ users varied with the group of antidepressants used: 59.6% of tricyclic users, 68.0 % of SSRI users and 70.5% of SNRI users. In 2000, 33.7% of antidepressant users with depression used them for at least 9 months vs 36.1% in 2003. The percentage in adults increases with age-group from 25.1% in 18-39 to 47.6% in 75 or older and increases with the number of medical visits in the first three months of treatment from 19.8% for no visits to 41.3% for 4 visits or more.

**Conclusion:** The duration of treatment with antidepressants in persons with depression under that recommended by the Canadian guidelines, that is, at least 9 months. Results show shifting from paroxetine to other antidepressant particularly in young and old persons consistent with Health Canada's warnings but the impact is not so important on others that were later identified as also having

an increased suicide risk. Antidepressant senior users seem to be using BDZs frequently.

**Key Words:** *Antidepressant use, depression, descriptive study*

84

### Inreased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or exogenous insulin compared to metformin

Bowker S.<sup>1</sup> Majumdar S,<sup>2</sup> Veugelers P,<sup>2</sup> Johnson, J<sup>1,2</sup>

<sup>1</sup>Institute of Health Economics, Edmonton, Canada,

<sup>2</sup>University of Alberta, Edmonton, Canada

*Corresponding Author:* [sbowker@ihe.ca](mailto:sbowker@ihe.ca)

**Background:** Numerous epidemiologic studies have identified an increased risk of cancer in people with type 2 diabetes. We sought to explore the association between antidiabetic therapies and cancer-related mortality in patients with type 2 diabetes.

**Methods:** This was a population-based retrospective cohort study using administrative databases from Saskatchewan Health. We identified new users of metformin or sulfonylureas from January 1, 1991 to December 31, 1996, with follow-up until December 31, 1999. Cancer-related mortality was compared between cohorts of metformin users (alone or in combination with sulfonylurea) to sulfonylurea monotherapy users. Multivariate Cox regression models were used to estimate the hazard ratio (HR) of cancer-related mortality, after adjusting for age, sex, and insulin use.

**Results:** We identified 10,309 new users of metformin or sulfonylureas, with an average follow-up of 5.4 (1.9) years. The mean age for the cohort was 63.4 (13.3) years and 55.1% were men. Unadjusted cancer mortality was 4.9% (162/3340) for sulfonylurea monotherapy users and 3.5% (245/6969) for metformin users ( $p = 0.001$ ). After adjusting for age, sex, and insulin use, the sulfonylurea cohort had significantly greater cancer-related mortality compared with the metformin cohort (HR: 1.3; 95% CI: 1.1-1.6,  $p=0.012$ ). Insulin use was associated with an adjusted hazard of cancer-related mortality of 1.9 (1.5-2.4;  $p<0.0001$ ).

**Conclusions:** Patients with type 2 diabetes exposed to sulfonylurea and exogenous insulin had a significantly increased risk of cancer-related mortality compared to patients exposed to metformin. It is uncertain whether this increased risk is related to a protective effect of metformin or a deleterious effect of sulfonylurea and insulin.

**Key Words:** *Type 2 diabetes, cancer, administrative databases*

85

### Is adherence to antidepressant treatment guidelines for depressive disorders associated with lower or higher cost of health services?

Partlova H,<sup>1</sup> Blais R,<sup>1</sup> Lachaine J,<sup>2</sup> Sewitch M<sup>3</sup>

<sup>1</sup>GRIS, University of Montreal, Canada, <sup>2</sup>Faculty of Pharmacy, University of Montreal, Montreal, Canada, <sup>3</sup>Department of Medicine, McGill University, Montreal  
Corresponding Author: [hana.denis@videotron.ca](mailto:hana.denis@videotron.ca)

**Background:** Depressive disorders are a major public health problem with significant medical and economic consequences. Prescribing guidelines were developed to improve patient care, but treatment is often suboptimal.

**Objectives:** The objectives were to assess whether the use of antidepressants according to Canadian guidelines (CANMAT, 1999) is associated with higher or lower cost of health care services and to identify other cost predictors.

**Methods:** A population-based retrospective drug utilization review was performed using the Quebec public prescription plan and medical services database (RAMQ). Patients treated for a new diagnosis of depression were eligible (n=2750). Conformity to guidelines was defined by the type of prescribed medications, their dosage and duration of treatment. The cost of health services was assessed over a year and measured in terms of medications, physician and hospital services. Patients' and physicians' characteristics were examined as potential cost predictors.

**Results:** Total costs of health services were not associated with conformity to prescribing guidelines. Conformity was associated with savings in outpatient visits to other physicians than the prescribing physician. No association was found between conformity and the cost of hospitalisations, emergency department visits and visits to the prescribing physician. The total costs of health services are higher for men and increase with age and comorbidity. Chronic illness is associated with higher costs of every type of care.

**Conclusion:** Treating depressed patients according to prescribing guidelines is not necessarily associated with savings in general, but for specific items (e.g. visits to other physicians). Long term impact of conformity to guidelines on patient health and health system costs should be assessed.

**Key Words:** Depression, treatment guidelines, costs

86

### Is there a relationship between socioeconomic status and use of medications?

Raymond C, Kozyrskyj A, Mignone J  
University of Manitoba, Winnipeg, Canada

Corresponding Author: [umraymoc@cc.umanitoba.ca](mailto:umraymoc@cc.umanitoba.ca)

**Background:** A socioeconomic gradient in health is well described, but the relationship between socioeconomic status (SES) and medication use remains unclear. We sought to evaluate a SES-medication relationship within universal healthcare systems. We expected to observe greater medication use with low SES at the population level, (greater disease burden) and similar medication use across SES in studies of specific disease states or treatments, (explained by similar diagnostic rates).

**Objectives:** A systematic review was conducted to identify studies evaluating a SES-medication relationship. Variables assessed included: location, population, type of data, SES measure, medication measure, outcomes and observed SES-medication relationship. Studies were categorized according to the population studied (population level or specific disease), and assessed for the presence of a prescribing gradient. A prescribing gradient was observed if there was i) no difference in prescribing across SES for population level studies or; ii) a difference in prescribing across SES for studies of specific diseases or drugs.

**Methods:** Thirty two studies were located evaluating a SES-medication relationship. Of 24 studies in specific populations, 10 observed a prescribing gradient. Of studies assessing cardiovascular disease (CVD), most (6/7) showed no prescribing gradient. All studies evaluating asthma (4) and most (4/6) evaluating pediatric antibiotic use observed a prescribing gradient. Of 8 studies at a general population level, 6 demonstrated a prescribing gradient. Most (6/7) studies evaluating appropriateness showed greater inappropriate prescribing with low SES.

**Results:** Although no clear SES-medication relationship was observed, studies indicated some inappropriate medication use with decreasing SES. Further research that assesses a SES-medication relationship is required.

**Key Words:** Socioeconomic status, medication, systematic review

87

### Is there an association amongst current medication use and quality-of-life scores in elderly patients with type 2 diabetes?

Jurcic J, Gaebel K, Levine MAH

Centre for the Evaluation of Medicines, St. Joseph's Healthcare, Hamilton, Canada

Corresponding Author: [jurcicj@mcmaster.ca](mailto:jurcicj@mcmaster.ca)

**Background:** Several groups of antidiabetic agents are available to manage type 2 diabetes and as the disease progresses patients often use two or more classes of medications to improve glycemic control. The aim of this study is to examine the association amongst current medications and QOL.

**Methods:** Patients 68 years and older, with type 2 diabetes currently taking an antidiabetic medication were recruited from community pharmacies in Ontario. QOL was assessed by telephone interview using the diabetes-39 survey (D-QOL has 5 domains: diabetes control, anxiety/worry, social burden, sexual functioning, energy/mobility). Patients also ranked their overall QOL on a scale of 1-7. Current diabetes medications were retrieved from physician medical records. Spearman's correlation coefficients were used to assess association.

**Results:** Data were available for 344 patients (mean age 77 years, 58% male, diabetes for mean 12 years). Three cohorts of drug use were identified: monotherapy (44%), double-therapy (47%), and triple-therapy (9%). Other cohorts of drug use include patients using a drug that requires provincial approval (20%) and patients using insulin (8%). Diabetes control ( $r=0.158, p=0.003$ ) and energy/mobility ( $r=0.127, p=0.019$ ) were weakly associated with the number of drugs used. Sexual functioning was weakly associated with use of a provincial approval drug ( $r=0.15, p=0.005$ ). Diabetes control ( $r=0.205, p<0.001$ ) anxiety/worry ( $r=0.108, p=0.045$ ), energy/mobility ( $r=0.209, p<0.001$ ) were associated with use of insulin. Overall QOL was not associated with any category of medication use.

**Conclusion:** Correlation between current medication use and some domains of DQOL were positive with more intensive management but were weak or negligible in magnitude. These findings suggest that other factors related to drug regimen or disease may also contribute to DQOL.

**Key Words:** *Diabetes mellitus, quality of life, antidiabetic medications*

88

### LDL-C recommended goal achievement in Canadian patients with hypercholesterolemia

Sénécal M, Davignon J, Fodor G, Gagné C, Gaudet D, Genest J, Lavoie M-A, Leiter L, McPherson R, Marentette M, Sebaldt R, Bourgault C

Merck Frosst Canada, Montreal, Canada

Corresponding Author: [martin\\_senecal@merck.com](mailto:martin_senecal@merck.com)

**Background:** Many patients do not achieve recommended low density lipoprotein-cholesterol (LDL-C) targets despite therapy. The objective of this study is to document the profile of treated patients not at LDL-C goal, and identify factors associated with failure to achieve goal.

**Methods:** CALIPSO (Canadian Lipid Study – Observational) is a cross-sectional study of statin-treated patients in Canada. 3,721 patients with hypercholesterolemia, at least 18 years of age, who had been using a statin for at least eight weeks, and for whom coronary artery disease (CAD) risk factors and LDL-C levels were available were included. From this group, 1,767 were at high CAD risk and had LDL-C levels  $>2.5$  mmol/L prior to treatment initiation. Goal attainment was defined using the most recent (2003) Canadian treatment guidelines. Multivariate logistic regression was used to identify independent correlates of failure to reach goal.

**Results:** CALIPSO results indicate that 35.4% of high risk patients did not achieve recommended LDL-C targets despite therapy. Factors independently associated with failure to achieve goal included younger age, elevated pre-treatment LDL-C levels, multiple CAD risk factors without established CAD or diabetes, current use of higher dose statins, physician's targeting of less aggressive LDL-C levels and no use of antihypertensive drugs.

**Conclusion:** A large proportion of patients at high CAD risk are not achieving recommended LDL-C targets despite statin therapy. Sub-optimal management of dyslipidemia is a major problem in the Canadian clinical setting and strategies should be implemented to promote achievement of lipid treatment goals for high risk patients.

**Key Words:** *Low density lipoprotein cholesterol, goal attainment, observational study*

89

**LOGIC [longitudinal outcomes study of gastrointestinal symptoms in Canada]: recruitment methodology and collection of data using an electronic data capture system**

Keown P,<sup>1</sup> Khorasheh S,<sup>1</sup> Balshaw R,<sup>1</sup> Barbeau M,<sup>2</sup> Garon E,<sup>2</sup> Kelly S,<sup>2</sup> McBurney C<sup>3</sup>

<sup>1</sup>Syreon Corporation, <sup>2</sup>Novartis Pharmaceuticals Canada Inc., <sup>3</sup>Novartis Pharma AG

*Corresponding Author:* [Shideh.Khorasheh@syreon.com](mailto:Shideh.Khorasheh@syreon.com)

**Background:** Irritable bowel syndrome (IBS) is associated with impaired quality of life and increased health care resource utilization. LOGIC is an ongoing prospective, observational, population-based study designed to evaluate treatment patterns and health outcomes from subjects with IBS dysmotility symptoms in routine clinical practice in Canada.

**Methods:** LOGIC aimed to recruit 200 community and specialist sites and 2000 subjects from 5 provinces across Canada. Potential sites were selected based on commitment and experience with clinical research, and asked to recruit and follow 5-25 subjects for 12 months. Physicians reported baseline data in real time using an electronic data capture system, provided subject questionnaires, and contacted subjects prior to the assigned date of completion. Subjects reported data at baseline and months 1, 3, 6, 9 and 12 via business reply mail, and received reminders if questionnaires were not received.

**Results:** Between March and September 2004, over 2800 physicians were invited to participate; 313 sites were recruited; 190 are participating and 131 are actively enrolling. To date, more than 1000 subjects have been recruited and enrollment will continue until March 2005. 80% of expected subject questionnaires have been returned.

**Discussion:** Population-based studies provide critical information for disorders like IBS, but entail unique design, logistical and statistical challenges. The site recruitment ratio is consistent with large population studies. Innovative information systems facilitate communication between the clinical research organization, the sponsor and the investigators as well as distributed data retrieval. Furthermore the information system diminishes the risk of incomplete or erroneous data at baseline.

**Key Words:** IBS, LOGIC, syreon

90

**Mandatory reporting of adverse drug reactions in the Canadian Forces**

Gervais A, Vaillancourt R, Gauthier C  
Canadian Forces Health Services Group, Ottawa, Canada

*Corresponding Author:* [gervais.aa2@forces.gc.ca](mailto:gervais.aa2@forces.gc.ca)

**Background:** In the past, our department has relied heavily upon spontaneous reports of adverse drug reactions (ADRs) to stimulate policy revisions and direct research initiatives. We have since implemented a program to encourage more formal reporting of ADRs.

**Methods:** Health professionals are now required to report ADRs to a central office, the Canadian Forces Drug Exception Centre. This office is can respond proactively (by facilitating access to non-benefit items) when given advance notification that a person has experienced adverse effects with a regular benefit drug. This office also has responsibility to ensure that all ADR reports are forwarded to the Canadian Adverse Drug Reaction Monitoring Program for inclusion in their surveillance programs.

**Results:** Since its implementation in November 2003, the program has noted an increase in the number of ADRs reported to the Drug Exception Centre. Between November 2003 and August 2004, 79 requests for non-benefit medications were approved as a result of an ADR to regularly listed items. An ADR form was completed for each of these cases, and a copy forwarded to the national ADR surveillance program. Two previous studies which were prompted in part by spontaneous ADR reports have also been conducted which resulted in modifications to the benefit list.

**Conclusions:** Allocation of resources to facilitate ADR reporting will provide information on risk assessment beyond that reported in pre-marketing phase trials. Our previous experience with spontaneous ADR reporting has led to policy initiatives which are intended to minimize the impact of adverse effects from medications.

**Key Words:** Adverse effects, program development

91

### An evaluation of the diagnostic accuracy of the osmole gap as a screening test for toxic alcohol poisoning

Lynd LD,<sup>1,2</sup> Richardson K,<sup>2</sup> Brubacher J,<sup>3</sup> Sivlotti MLA,<sup>5</sup> Abu-Laban RB,<sup>2,3</sup> Lepik KJ,<sup>4</sup> Purssell RA<sup>3</sup>

<sup>1</sup>University of British Columbia, <sup>2</sup>Centre for Clinical Epidemiology and Evaluation, <sup>3</sup>Vancouver General Hospital, <sup>4</sup>BC Drug and Poison Information Centre, Vancouver, British Columbia, Canada, <sup>5</sup>Kingston General Hospital, Kingston, ON, Canada

Corresponding Author: [llynd@interchange.ubc.ca](mailto:llynd@interchange.ubc.ca)

**Background:** The osmole gap (OG), the difference between measured (Om) and calculated (Oc) serum osmolality, is routinely used as a screening test for methanol (MeOH) or ethylene glycol (EG) poisoning. A recent literature review revealed no well-designed studies evaluating its diagnostic performance. Our objective was to evaluate the OG as a screening test for toxic alcohol poisoning using gas chromatography as the gold standard.

**Methods:** We examined laboratory records from two tertiary care hospitals from 01/01/1996 to 01/03/2002 and found 163 patients with simultaneous measurements of EG, MeOH, Na, K, urea, glucose, Om and ethanol (EtOH). Oc was calculated using the Smithline-Gardner formula and EtOH coefficients of both 1 and 1.25. The sensitivity and specificity of the OG to detect toxic alcohol levels requiring antidote (EG >3 or MeOH >6 mmol/L) or hemodialysis (EG >8 or MeOH >15 mmol/L) were determined. The results were plotted on ROC curves and the AUC was calculated for each equation and compared.

**Results:** The AUCs for the detection of levels requiring antidote were 0.686 and 0.732 using EtOH coefficients of 1 and 1.25, respectively ( $p=0.070$ ). The AUCs for levels requiring hemodialysis were 0.859 and 0.893, respectively ( $p=0.122$ ). At the conventional OG threshold of 10 mOsm/l, the 1.25\*EtOH equation had a sensitivity of 0.75 and specificity of 0.50 for the detection of levels requiring antidote, resulting in the false-negative diagnosis of 5 patients, none of whom developed clinically significant sequelae.

**Conclusion:** The OG performed relatively well as a screening tool for toxic alcohol poisoning in this population independent of the equation applied.

**Key Words:** Screening test, osmole gap, toxic alcohol poisoning

92

### Methods for evaluating the benefits and risks of drug therapies

Lynd LD,<sup>1,2</sup> Sculpher MJ,<sup>3</sup> Willan AR,<sup>4</sup> Coombes M<sup>2</sup>

<sup>1</sup>University of British Columbia, Vancouver, British Columbia, Canada, <sup>2</sup>Centre for Clinical Epidemiology and Evaluation, Vancouver, British Columbia, Canada, <sup>3</sup>Centre for Health Economics, University of York, York, UK, <sup>4</sup>University of Toronto, Canada

Corresponding Author: [llynd@interchange.ubc.ca](mailto:llynd@interchange.ubc.ca)

**Background:** While new drug therapies offer one or more health benefits to patients, they frequently pose a risk of adverse events. Therefore, an explicit risk-benefit analysis methodology must be employed to aid in the decision to adopt a new therapy. The objectives of this study were to identify criteria for an ideal risk-benefit evaluation methodology, and to assess all currently proposed risk-benefit analysis methods for drug therapy against these criteria.

**Methods:** Published papers pertaining to risk-benefit analysis methodologies were identified by searching all major medical journal electronic databases and through a secondary scan of the reference lists of papers identified in the primary search. The analytic methods were then evaluated against the criteria we identified as essential for a valid, practical, and applicable risk-benefit evaluation methodology.

**Results:** Ten methodologic criteria and fourteen risk-benefit analytic methods were identified from 221 published articles plus additional textbooks and working papers. No method satisfied all criteria, and only two methods permitted the simultaneous consideration of both risks and benefits. Just two methods facilitated the consideration of the duration, intensity, and reversibility of both objective (e.g. mortality) and subjective (e.g. QOL) benefits and risks, and only one method accounted for differences in patient's baseline risk. No method differentiated between the nature of the benefit or risk, i.e. prevention vs cure, acute vs. chronic.

**Conclusions:** No currently available method meets all of the proposed criteria. Therefore, newer methods that facilitate the simultaneous consideration of multiple benefits and risks, and differing risk preferences are needed.

**Key Words:** Risk-benefit analysis, methods, evaluation

93

**NSAID use and the risk of Parkinson's Disease**Etminan M, Suissa S

Clinical Epidemiology, Royal Victoria Hospital and McGill Health Center, Montreal, Canada

*Corresponding Author:* [mahyar.etminan@mail.mcgill.ca](mailto:mahyar.etminan@mail.mcgill.ca)**Background:** Studies have shown that inflammation may play a role in the pathology of Parkinson's Disease (PD). We sought to explore this association using a nested-case control study.**Methods:** We followed a cohort of antihypertensive users in the Province of Saskatchewan, from 1980 to June 1999 using the Saskatchewan prescription drug plan database. Entry to cohort was defined as having at least one prescription of an antihypertensive from 1980 to 1987. A case was defined as having at least three prescriptions for a dopamine agonist during a one year period. For each case, a risk set of all potential controls consisting of all cohort members with the same year and month of cohort entry and followed as long, or longer than the case was formed. Ten controls were randomly selected matched to the cases by age. Conditional logistic regression was used to estimate rate ratios adjusting for gender, use of arthritis and antipsychotic medications. All analyses were done using SAS (version 8).**Results:** 1259 cases and 12,590 controls were included in the analysis. Compared to users of antihypertensives, current users of NSAIDs (use of at least one NSAID prescription within 60 days of index) were at a slightly higher risk of developing PD (RR 1.49 95% CI 1.01-2.01). Users of antipsychotics also had an elevated risk for developing PD (RR 1.90, 95% CI 1.70-2.14).**Conclusion:** Our study is indicative of a slight increase in the risk of PD with use of NSAIDs.**Key Words:** *Parkinson's disease, case-control, NSAIDs*

94

**Use of angiotensin converting enzyme inhibitors and the risk of community acquired pneumonia**Etminan M,<sup>1,4</sup> Zhang B,<sup>1</sup> Brophy JM,<sup>2</sup> Suissa S,<sup>1</sup> Gill S,<sup>3</sup> Fitzgerald JM<sup>4</sup><sup>1</sup>Division of Clinical Epidemiology, Royal Vic, <sup>2</sup>Division of Cardiology, McGill University Health Centre, Montreal, <sup>3</sup>Dept of Medicine, Queen's University, <sup>4</sup>Center for Clinical Epidemiology and Evaluation, Vancouver Hospital, Canada*Corresponding Author:* [mahyar.etminan@mail.mcgill.ca](mailto:mahyar.etminan@mail.mcgill.ca)**Background:** Recent studies have associated the use of angiotensin-converting enzyme inhibitors (ace-inhibitors) to a lower risk of developing community acquired pneumonia (CAP). It is possible that cough produced by ace-inhibitors could limit microaspiration. We decided to explore whether use of ace-inhibitors lowers the risk of CAP**Methods:** We conducted a nested-case-control study using the Quebec Linked Administrative Databases. We first created a cohort of all users of beta-blockers, calcium channel blockers, diuretics, ace-inhibitors and angiotensin-II receptor blockers (AIIRBs) from 1996-2000. Cases were defined as those newly diagnosed with CAP. For each case 20 controls were selected matched to the cases by age and calendar time. All matched controls had to have had a duration of follow up at least as long as the time to CAP diagnosis. We defined current use of ace-inhibitors as having received at least one ace-inhibitor prescription seven days prior to the index date. Conditional logistic regression was used to estimate rate ratios adjusting for gender, comorbidity, number of physician visits and prior history of diabetes, CHF and COPD.**Results:** There were 1666 cases and 33,315 controls in our analysis. Compared to users of other antihypertensive agents (beta-blockers, diuretics and calcium channel blockers) current users of ace-inhibitors did not have a lower risk of developing CAP (RR 0.98, 95% CI, 0.69-1.40). This risk did not change for current users of AIIRBs (RR 1.02, 95% CI 0.70-1.49).**Conclusion:** The results of our study do not indicate that ace-inhibitors have a protective effect in CAP.**Key Words:** *Pharmacoepidemiology, pneumonia, ace-inhibitors*



95

### A model of assessing the cost-effectiveness of atorvastatin and simvastatin in achieving Canadian Working Group Guidelines

Lachaine J,<sup>1</sup> Merikle E,<sup>2</sup> Montpetit M<sup>2</sup>

<sup>1</sup>Faculty of Pharmacy, University of Montreal, Canada,

<sup>2</sup>Outcomes Research, Pfizer Canada Inc., Canada

Corresponding Author: [jean.lachaine@umontreal.ca](mailto:jean.lachaine@umontreal.ca)

**Background:** Statins are the most effective pharmacological treatments for reducing LDL-C cholesterol and achieving treatment targets. The objective of this study was to assess the cost-effectiveness (CE) of the two most widely prescribed statins (atorvastatin and simvastatin) in Canada in achieving the Canadian Working Group (CWG) treatment targets.

**Methods:** A spreadsheet model was developed to: estimate the number of patients achieving CWG LDL-C targets for each dose of atorvastatin and simvastatin, calculate the drug cost and calculate the incremental drug cost per patient achieving the target levels. The population baseline LDL-C levels, stratified by CV risk level, were taken from Canadian Heart Health Survey. Drug efficacy in reducing LDL-C was taken from a recently published meta-analysis. Estimates of the distribution of patients receiving each dose of statin were derived from Canadian IMS data. Drug costs were taken from the 2004 BC Pharmacare program.

**Results:** The estimated annual drug cost per 1000 patients treated with atorvastatin was \$689,050, with simvastatin \$538,144. The percentage of patients achieving targets was 73% for atorvastatin, 57% for simvastatin. The incremental CE ratio per additional patient treated to LDL-C target for atorvastatin was \$932 which is less than the average CE ratio for both atorvastatin and simvastatin (\$942 and \$947, respectively).

**Conclusions:** As a result of its superior efficacy, atorvastatin generates a favourable cost-effectiveness profile as measured by drug cost per patient treated to LDL-C target. For a given drug budget, more patients would achieve CWG LDL-C targets with atorvastatin than with simvastatin.

**Key Words:** *Cost-effectiveness analysis, cholesterol, statins*

96

### Painful neuropathic disorders: an analysis of the regie assurance maladie du Quebec (RAMQ) database

Lachaine J,<sup>1</sup> Tarride J-E<sup>2</sup>

<sup>1</sup>Faculty of Pharmacy, University of Montreal,

Montreal, Canada, <sup>2</sup>Outcomes Research, Pfizer Canada Inc., Canada

Corresponding Author: [jean.lachaine@umontreal.ca](mailto:jean.lachaine@umontreal.ca)

**Background:** Painful Neuropathic Disorders (PND) refers to neurologic disorders involving peripheral nerves where pain is a predominant symptom. Treatment of PND is likely to be associated with a large use of health care resources. However, little is known about the economic burden of PND in Canada.

**Methods:** This study was performed, using data from a 15% random sample of patients covered by the RAMQ drug plan. Subjects were included in the PND cohort if a diagnosis of PND was found at least on two occasions during 2002. Comorbidities, assessed by the VonKorff Chronic Disease Score (CDS), and 2002 resource utilization were compared between PND patients and a control group without PND matched for age and sex in a 1:1 ratio.

**Results:** A total of 4,912 patients with PND were identified (mean age: 57.7). A higher level of comorbidities was found in the PND group (CDS: 3.91 vs. 2.54;  $p < 0.001$ ). For all categories of pain-related medications, the proportion of users was significantly higher in the PND cohort than in the control group ( $f\acute{O}2 < 0.001$ ). The average annual number of physician visits (General practitioners and Specialists) was also significantly higher in the PND group than in the control group (14.7 vs. 6.4;  $p < 0.001$ ). From a health ministry perspective, costs of health care resources were significantly higher in the PND group (\$4,163 vs. \$1,846;  $p < 0.001$ ).

**Conclusions:** PND is associated with higher level of comorbidities, higher medical resources utilization and higher health care costs than non-PND conditions.

**Key Words:** *Painful neuropathic disorders, administrative database analysis, economic burden*

97

### Adherence to therapeutic trial criteria in clinical practice guidelines for gastrointestinal disorders

Lopatka H, Kluchky J

Alberta Drug Utilization Program, Edmonton, Canada

Corresponding Author: [harold.lopatka@ualberta.ca](mailto:harold.lopatka@ualberta.ca)

**Background:** More than 4% of the patients covered by Alberta Health and Wellness drug benefit programs take a proton pump inhibitor on a daily basis. Consumption of these agents is increasing on an annually. Appropriateness criteria were adapted from the Alberta clinical practice guidelines. The results are presented for adherence to therapeutic trial criteria for the conditions GERD and chronic dyspepsia.

**Methods:** The review was limited to the population with drug benefits covered by Alberta Health and Wellness (groups 66, 66A and 1). Data was extracted for three years from April 1, 1999 to March 31, 2002. Three data sources were used that included prescriber payment, patient demographics, and prescription claims data. Patient data for specific ICD9 diagnoses were taken from physician billing claims and matched to prescription claims for gastrointestinal medications. The following additional criteria were studied: (i) received maximum 10 week duration therapeutic trial (excluding antibiotics received a first prescription for either a PPI, H2RA, prokinetic agent), (ii) referral to specialist (gastroenterologist, general surgeon, internal medicine) after failure of therapeutic trial, (iii) investigation with gastroscopy after failure of therapeutic trial.

**Results:** 12347 individuals received first prescriptions for a PPI, H2RA or prokinetic agent. 43.4% of prescriptions were for the maximum 10 week duration (therapeutic trial). Where drug treatment exceeded the therapeutic trial (10 weeks) 15.9% of individuals were referred to a specialist (gastroenterologist, general surgeon or internal medicine), and 44% of individuals had gastroscopies performed.

**Conclusion:** Significant opportunities exist to improve guideline adherence for therapeutic trials in the treatment of the conditions. The research provides a baseline to measure the effectiveness of provincial and local drug use management initiatives (e.g., academic detailing).

**Key Words:** *Utilization review, guideline adherence*

98

### Perceptions and experiences of an academic detailer

Lopatka H, Rees S

Alberta Drug Utilization Program, Edmonton, Canada

Corresponding Author: [harold.lopatka@ualberta.ca](mailto:harold.lopatka@ualberta.ca)

**Background:** The Academic Detailing Initiative has provides evidence-based drug information in the form of a clinical practice guideline (CPG), to physicians in the David Thompson Health Region. The program consists of 4 interventions: CME, academic detailing visit, opinion leader consult, and prescriber feedback reports. The detailing visits involve a one on one visit with a detailer who presents an overview of the CPG.

**Methods:** The detailer completes a visit report outlining perceived success and information provided during the visit. These reports were summarised for 4 topics– Upper respiratory tract infections (URTI), GI conditions (GI), osteoporosis (OP) and COPD. Information documented include: # key messages and written materials; # of requests for follow-up information; perceived interest in the visit and CPG. Interest was rated on a scale of 1-5 with 5 representing strongly agree.

**Results:** 259 visits were provided: 66 for URTI, 84 for GI, 50 for OP, and 59 for COPD. The average visit time ranged from 21.4 minutes (URTI) to 33.3 minutes (COPD) with overall average 27.7 minutes. An average of 3 key messages and 3 written materials were provided. Perceived interest in the visits was high at 4.5/5. The interest in the CPG was lower for URTI at 4.3/5 and higher for the GI and OP at 4.5/5 and COPD at 4.6/5. Requests for follow-up information were high for the GI area at 1.3 requests per visit with the other topic areas at 0.6.

**Conclusion:** Detailer reports show high physician interest. Requests for follow-up information show CPGs may not be complete and program credibility is high. This information will be used in a full program evaluation.

**Key Words:** *Academic detailing, experiences, behavioral change*

99

### Pharmacists attitudes towards INR monitoring reimbursement

Liovas A, Tremblay D, Haiderali A, Kim T  
AstraZeneca Canada Inc., Mississauga, Canada

*Corresponding Author:* [anna.liovas@astrazeneca.com](mailto:anna.liovas@astrazeneca.com)

**Background:** Patients with atrial fibrillation (AF) taking warfarin must be closely monitored and undergo frequent INR testing. This is a critical and time consuming component of anticoagulation. The objective of this analysis is to determine and compare both physician and pharmacists' attitudes toward reimbursement for INR monitoring.

**Methods:** Seventy-two pharmacists attending an Anticoagulation Training course with the OPA completed a questionnaire. The results of it were compared to results from qualitative research done with physicians between Sept. 3rd and Oct. 23, 2003.

**Results:** Pharmacists attending this course saw each of their AF clients a mean of 10 times in one year. Further, a mean of 2.43 hours are spent/week with these patients. The activities include counselling, referrals, blood testing and telephone calls. Pharmacists receive no reimbursement for these services. Similar results were found in research done with physicians who saw their AF patients a mean of 7 times/year, spend 26 hours/week on activities around monitoring and receive a mean of \$23 per visit.

**Conclusion:** Results suggest that both physicians and pharmacists perceive current INR monitoring reimbursement is inadequate and not an accurate reflection of the time and complexity of the task.

**Key Words:** *Atrial fibrillation, anticoagulation, pharmacists*

100

### Warfarin patient segments: GPs vs specialists

Liovas A, Rufino S, Haiderali A, Kim T, Khurram I  
AstraZeneca Canada Inc., Mississauga, Canada

*Corresponding Author:* [anna.liovas@astrazeneca.com](mailto:anna.liovas@astrazeneca.com)

**Background:** There is a documented lack of treatment and undertreatment with warfarin in AF patients. GPs and Specialists (SPs) may take different approaches to anticoagulation for their AF patients. Our objective in this research was to identify, compare and quantify warfarin patient segments for both SPs and GPs.

**Methods:** Physicians from Toronto, Montreal and Vancouver, randomly recruited from lists of high warfarin prescribers, participated in 60 minute qualitative interviews. Thirty-Six physicians were interviewed (14 GPs, 8 Cardiologists, 6 Internists and 3 Haematologists).

**Results:** SPs placed patients in 3 major segments: UNTREATED (5% of their patients), TREATED (90-95%) and UNDERTREATED (5%). GPs had only 2 segments: UNTREATED (10-25%) and TREATED (75-90%). Both physician groups identified UNTREATED patients as those at risk of falling, demented, prone to bleed, immobile or refusing treatment. SPs referred to UNDERTREATED patients as those using ASA. GPs saw ASA users as part of their TREATED group. The other segment within the GP TREATED group was warfarin users. SPs divided their TREATED segment into well-controlled and not well-controlled.

**Conclusions:** SPs and GPs use similar criteria in determining which patients do not receive warfarin. However, views on the value of ASA seem different. Further, GPs in this study did not distinguish between well and not-well controlled warfarin, but rather indicated ASA vs warfarin users are both considered TREATED. Further research is required to further investigate the differences in opinion, lack of treatment and to quantify each segment.

**Key Words:** *Undertreated, warfarin, qualitative*

101

**Physician perceptions and experiences with restrictive policies for patient access to diabetic medications**

Gaebel K, Cosby J, Abushomar H, Levine M  
The Centre for Evaluation of Medicine, Hamilton,  
*Corresponding Author:* [gaebk@mcmaster.ca](mailto:gaebk@mcmaster.ca)

**Background:** Rosiglitazone (Avandia) and pioglitazone (Actos) are two new generation of oral hypoglycemic medications known as thiazolidinediones (TZD). They are available to Ontario Drug Benefit (ODB) eligible patients according to specific reimbursement criteria developed for the Section 8 special authorization policy. This study sought to evaluate physician experiences and perceptions associated with the use of the Section 8 policy as it applied to obtaining reimbursement for TZD therapy through ODB program.

**Methods:** Qualitative methods were used. 12 family physicians and 1 endocrinologist were individually interviewed for 50-75 minutes each. All interviews were taped and fully transcribed. The data were analysed and themes were generated. After the data were analysed the results were presented to two family physicians in a small focus group to assess data validity.

**Results:** Four themes emerged - Efficacy of the medication; lack of confidence in the Section 8 process; effect of Section 8 on prescribing TZDs; managing Section 8 medicines. Some physicians felt there was adequate evidence of benefit for using TZDs while others were still in a wait and see mode. Physicians found the Section 8 process to be punitive, opaque and inconsistent in its adjudication. The goals of the policy were unclear and physicians were resentful of being used as tool of policy implementation. The process generated undesirable tensions amongst patients, physicians, pharmacists, and caused delays in appropriate prescribing. Physicians identified three types of strategies used to deal with the policy – tenacity; circumnavigation; backing down.

**Conclusions:** Physician perceptions regarding the Section 8 controls for TZDs were heterogeneous, and their response would depend upon their experience and their perspective of the evidence. The policy was felt to be more a hassle than a barrier to patient access for TZD therapy, but limitations on the physician's personal experience with using the drug decreased the use of the therapy in general.

**Key Words:** *Prescribing, drug utilization, diabetes*

102

**Physician requirements for improved stabilization in patients prescribed medications for alzheimer's disease**

Oremus M, Wolfson C, Bergman H, Vandal AC  
Centre for Clinical Epidemiology and Community Studies, Jewish General Hospital, Montreal, Quebec,  
*Corresponding Author:* [mark.oremus@mail.mcgill.ca](mailto:mark.oremus@mail.mcgill.ca)

**Background:** One goal for new medications in Alzheimer's disease (AD) is to increase the length of time that patients spend in the mild or moderate stage of disease. Physicians were asked to specify the minimum increases that they would require as a prerequisite to prescribing a hypothetical, new AD medication.

**Methods:** A self-administered postal questionnaire was mailed to all of Quebec's geriatricians (n=49), neurologists (n=215), and psychogeriatricians (n=53), as well as to 191 general practitioners who took courses on elder care, and to a random sample of 295 general practitioners who did not take such courses. Descriptive statistics were used to summarize responses; logistic regression was used to examine the association between physicians' requirements and the proportion of AD patients who were prescribed cholinesterase inhibitors (ChEIs).

**Results:** On average, physicians reported requiring an increase of 15 months for patients in the mild stage (SD=10 months; range=1-60 months) and 11 months for patients in the moderate stage (SD=6 months; range 1-36 months). There was a small, inverse association between increases in length of time and prescribing (OR=0.99; 95% CI=0.97-1.00; p=0.0457).

**Conclusions:** As a prerequisite to prescribing a new AD medication, physicians would require that patients spend an additional 11 or 15 months in the mild or moderate stage of disease. Physicians who required greater lengths of time prescribed ChEIs to fewer AD patients, perhaps because they felt that ChEIs were not meeting their requirements. The results of this study can serve as efficacy benchmarks to help guide drug development and assessment.

**Key Words:** *Alzheimer's disease, drug treatment, efficacy requirements*

103

**Pitfalls in the use of multiple imputation to handle missing data: the case of a physician questionnaire on drug treatments for alzheimer's disease**

Oremus M, Steele R

Centre for Clinical Epidemiology and Community Studies, Jewish General Hospital, Montreal, Quebec

Corresponding Author: [mark.oremus@mail.mcgill.ca](mailto:mark.oremus@mail.mcgill.ca)

**Background:** Multiple imputation is the gold standard for handling missing data. However, researchers should be aware of certain pitfalls. These pitfalls are discussed in the context of a questionnaire on drug treatments for Alzheimer's disease.

**Methods:** The questionnaire was mailed to 803 Quebec physicians. The purpose was to investigate the association between physicians' efficacy requirements for prescribing a hypothetical new Alzheimer's disease medication and the current prescribing of cholinesterase inhibitors. S-Plus software was used to conduct multiple imputation. SAS software was used to build two regression models. The first model included respondents for whom there were no missing data. The second model drew upon the imputed data and included all respondents.

**Results:** There were missing data for at least one respondent on 84% (46/55) of the questions. Crude and adjusted associations between efficacy requirements and current prescribing did not differ across the models. However, the models did differ in terms of the covariates that were independently associated with current prescribing.

**Conclusions:** Two pitfalls are evident in the use of multiple imputation. First, the imputation routines of SAS and S-plus are not flexible enough to adequately handle every missing data problem. Novice users should be careful when using commercial missing data software. Second, researchers must decide a priori whether to fit regression models to imputed data or to develop models first and impute later. The order is important because different strategies may lead to different results. These pitfalls are not readily apparent unless researchers have past experience conducting multiple imputation.

**Key Words:** *Multiple imputation, questionnaire, alzheimer's disease*

104

**Pointing the way to evidence-based health care: introducing the Canadian optimal medication prescribing and utilization service (COMPUS)**

Wells B, Bai A

Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Ottawa, Canada

Corresponding Author: [barbaraw@ccohta.ca](mailto:barbaraw@ccohta.ca)

**Background:** The Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) is a collaborative cross-Canada service funded by Health Canada and delivered by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA). COMPUS was launched in March 2004 to support the F/P/T jurisdictions in encouraging health care provider and patient/consumer behaviours that will result in improved drug-related health outcomes

**Methods:** COMPUS will provide independent authoritative information to help health care decision makers and patients by identifying, evaluating and promoting best practices in drug prescribing and use. Evaluations of best practices and best practice initiatives will be based on evidence-based information from clinical practice guidelines, systematic reviews and/or primary studies. COMPUS will also consolidate information resources and develop and support networks for best practices in drug prescribing and use.

**Results:** COMPUS' initial outcomes will include: an online database of best practice initiatives, and toolkits for provincial/territorial governments and interested stakeholders to support the uptake of best practices in three initial priority prescribing areas – proton pump inhibitors, diabetes management, and anti-hypertensives.

**Conclusions:** The adoption of evidence-based best practices in drug prescribing and utilization will improve drug-related health outcomes and result in more cost-effective utilization of drugs. A collaborative national service will reduce duplication of effort and improve consistency of approach within individual jurisdictions; create a better understanding of how to achieve optimal drug-related health outcomes; and provide information and resources that will result in shorter start-up time for new best practice initiatives.

**Key Words:** *Evidence-based, guidelines, best practices*

105

**Psychotropic drug utilization in Canada**

Beck CA, Patten SB, Williams JVA, Wang J, El Guebaly N, Currie S, Maxwell C

University of Calgary Departments of Community Health Sciences and Psychiatry, Calgary, Canada

Corresponding Author: [cindy.beck@calgaryhealthregion.ca](mailto:cindy.beck@calgaryhealthregion.ca)

**Background:** Psychotropic drug utilization can be a useful indicator of appropriate treatment for mental disorders. Yet until now, economic evaluation and policy-making in Canada have occurred in an evidence-poor environment. The Canadian Community Health Survey 1.2 (2002) offers the first opportunity to characterize psychotropic medication use nationally in a wide range of mental disorders.

**Methods:** The prevalence of antidepressant, sedative-hypnotic/anxiolytic, mood stabilizer, psychostimulant, and antipsychotic use over two days was assessed overall and in subgroups defined by sociodemographics and Composite International Diagnostic Interview (CIDI) mental disorders. Sampling weights and bootstrap methods were employed.

**Results:** Overall psychotropic drug utilization was 7.2%. Use was higher for women and increasing age. With any lifetime CIDI-diagnosed disorder utilization was 19.3%, while without such disorders it was 4.1%. Selective serotonin reuptake inhibitors (SSRIs) were the most commonly-used antidepressants for those with a past-year major depressive episode (17.8%), followed by venlafaxine (7.4%). Among 15-19 year-olds, antidepressant use was 1.8% overall and 11.7% with past-year depression; SSRIs made up the majority of use. Sedative-hypnotic/anxiolytics were used by 3.1% overall, increasing with age to 11.2% over 75 years.

**Conclusions:** International comparison is complicated by varying evaluation methods, but Canadian antidepressant use may be higher and sedative-hypnotic/anxiolytic use lower than in a recent European report. In light of contemporary evidence suggesting a lack of antidepressant efficacy in adolescents, one hopes that antidepressant use in this group has declined since 2002. The increased use of sedative-hypnotic/anxiolytics with age is disturbing, given the associated risk of adverse effects in the elderly.

**Key Words:** *Drug Utilization, psychotropic drugs, cross-sectional studies*

106

**A population-based study of asthma medication and health services use in Ontario children from social assistance families**

Ungar WJ, Gunraj N, Kozyrskyj A, Paterson M, Mamdani M

The Hospital for Sick Children, Toronto, Canada, Institute for Clinical Evaluative Sciences, Toronto, Canada, Department of Health Policy, Management and Evaluation, Toronto, Canada, Manitoba Centre for Health Policy, Winnipeg, Canada

Corresponding Author: [wendy.ungar@sickkids.ca](mailto:wendy.ungar@sickkids.ca)

**Background:** The highest incidence of asthma occurs in children. According to Canadian prescribing guidelines, proper management to achieve control requires treatment with multiple medications, including inhaled corticosteroids for maintenance and beta-agonist bronchodilators as needed. The primary objective was to examine asthma medication use patterns and health services use in asthmatic children from Ontario families receiving social assistance.

**Methods:** A cohort of 7,150 asthmatic Ontario children with a history of asthma medication and health services use between 1998 and 2001 was followed for 1 year. Rates of use of bronchodilators (BD), inhaled corticosteroids (ICS), leukotriene antagonists (LA), oral corticosteroids (OS) and combinations were determined from the Ontario Drug Benefits population database. Cohort data were linked to CIHI and OHIP claims to determine Emergency Department (ED) and outpatient visits and hospital admissions for asthma (ICD-9CM code 493). Analyses were stratified by age group and sex.

**Results:** Children aged 2 to < 5 years experienced the highest rates of health service use, with higher rates in boys compared to girls. Fifteen percent experienced an ED visit and 5% were admitted. On average, 46% of all children were treated as recommended with concomitant prescriptions for BDs and ICSs. OS use, indicating a severe exacerbation, was prevalent in 17% of children.

**Conclusions:** Use of ICS was below recommended levels. Better asthma control with ICS could avert the need for ED visits and hospital admissions in this vulnerable population. Policies governing public drug plans must ensure adequate access to necessary medications for children with asthma.

**Key Words:** *Asthma medication use, health services use, low-income children*

107

**Public drug plan coverage for children across Canada: a portrait of too many colours**Ungar WJ, Witkos M

The Hospital for Sick Children, Toronto, Canada

*Corresponding Author:* [wendy.ungar@sickkids.ca](mailto:wendy.ungar@sickkids.ca)

**Background:** At a time of critical debate regarding Pharmacare in Canada, there has been little discussion regarding appropriate pharmaceutical policies for vulnerable populations. The primary objective was to determine the extent of medication coverage for children in publicly administered programs in each province across Canada.

**Methods:** Data were collected on provincial, territorial and federal government drug plans and 2003 formulary updates for each region were obtained. Programs were compared descriptively. The inter-provincial variation in 2003 formulary approvals was measured statistically with the coefficient of variation, extremal quotient and chi-square test.

**Results:** With respect to access to medications for children, provincial drug programs vary considerably in terms of whom they cover, what drugs are covered and how much subscribers must pay out-of-pocket. There was 39% variation between provinces with respect to 2003 formulary approvals ( $p < 0.0001$ ) and 48% variation for 2003 pediatric-labeled products ( $p < 0.0001$ ). Across Canada, only 8% of 2003 formulary approvals were indicated primarily for pediatric conditions. Expensive products such as Enbrel<sup>TM</sup> and Neupogen<sup>TM</sup> displayed extreme variation in coverage, including full benefit, limited use and non-coverage.

**Conclusions:** Drug programs for children are often considered a low priority to provincial policy makers. There is no single comprehensive drug plan to address children's needs or pediatric diseases. Canada's vulnerable populations must be protected in policy reforms concerning access to prescription medicines in Canada.

**Key Words:** *Provincial drug plans, area variation, children*

108

**Quantifying warfarin and inr monitoring practices of physicians in Ontario, Canada**Seung, SJ,<sup>1</sup> Mittmann, N,<sup>1</sup> Liovas, A<sup>2</sup><sup>1</sup>HOPE Research Centre, Division of Clinical Pharmacology, Department of Medicine, Sunnybrook & Women's College Health Sciences Centre, Toronto, Canada, <sup>2</sup>AstraZeneca Canada, Mississauga, Canada*Corresponding Author:* [soojin.seung@sw.ca](mailto:soojin.seung@sw.ca)

**Background:** Patients prescribed warfarin require long-term prophylaxis and physicians must manage their anticoagulation with INR testing that can be resource-intensive. The objective of this study was to quantify the facets associated with providing anticoagulation care.

**Methods:** An on-line survey of 49 questions was developed pertaining to warfarin use, time burden and clinical protocols. Clinical input on the questions was provided by members of the Thromboembolism Clinic at Sunnybrook & Women's College Health Sciences Centre and a general practice physician panel (N=11). A total of 3836 Ontario physicians were randomly selected from the Canadian Medical Directory with an 80:20 ratio of general practitioner to specialist. A \$75 honorarium was provided.

**Results:** A total of 179 surveys were completed. Physicians reported seeing a mean (+/- SD) of 161 +/- 63 patients (range 10-350) and wrote 6 +/- 8 (1-60) warfarin prescriptions per week. With warfarin initiation physicians spent 15 +/- 8 (2-60) minutes per patient counseling about warfarin dosing, INR testing, compliance and contraindications. For patients with INR results within therapeutic range (2-3), 25% of respondents reported 10-20 minutes per week being spent providing all aspects of anticoagulation care. For INR results >3, 28% of physicians spent 20-30 minutes.

**Conclusions:** Ontario physicians spend considerable time providing anticoagulation care for warfarin patients, but that they may not be compensated adequately for the time and effort involved. The mean time units collected in this study could be multiplied by the number of warfarin prescribers to estimate the burden of warfarin and INR testing.

**Key Words:** *Physician surveys, multiple diseases*

109

**Recognizing osteoporosis and its consequences in Québec (ROCQ): fragility fracture rate among women who sustained a fracture**

Bessette L,<sup>1</sup> Brown JP,<sup>1</sup> Beaulieu M,<sup>2</sup> Sauriol L,<sup>3</sup> Jean S,<sup>1</sup> Davison SK,<sup>1</sup> Ste-Marie L-G<sup>4</sup>

<sup>1</sup>Univ. Laval, Ste-Foy, Canada, <sup>2</sup>Merck Frosst Canada, Montréal, Canada, <sup>3</sup>Aventis Pharma, Montréal, Canada, <sup>4</sup>Univ. Montréal, Montréal, Canada

*Corresponding Author:* [michele.beaulieu@merck.com](mailto:michele.beaulieu@merck.com)

**Background:** To evaluate the proportion of fragility and traumatic fracture in women 50 years and over participating in a patient health-management programme (ROCQ) aimed at improving diagnosis and treatment of osteoporosis.

**Methods:** ROCQ is prospective cohort study involving 23 centers in three socio-sanitary regions in the province of Quebec (Canada). Women with fragility and traumatic fractures were recruited during their visit at a cast or outpatient clinic and contacted by phone to answer a questionnaire aimed at identifying the specific circumstances of their fracture. Based on this questionnaire, patients were classified as having a fragility or traumatic fracture.

**Results:** After 9 months, 646 women (mean age: 65.3 years) have been recruited of which 514 sustained a fragility fracture (83.7%) and 105 a traumatic fracture (16.3 %). 78% of women recruited with a fragility fracture were 75 years of age or less. The age distribution between fragility and traumatic fractures was similar

**Conclusion:** In ROCQ, 83.7% of fractures were related to osteoporosis while the literature estimates that 70% of the fractures in those over age 45 are attributable to osteoporosis. (P<0.0001) (1).ROCQ is the first prospective study evaluating fragility vs traumatic fracture among women 50 years and over. It is an ongoing study and updated data on a larger population will be presented at the meeting after further collection has been completed.

(See author for reference)

**Key Words:** *Fragility fracture, patient health management, epidemiology*

110

**Review of the use of quality of life instruments for measuring change in pain in MS patients**

Maturi B, Vicente C

Bayer HealthCare, Toronto, Canada

*Corresponding Author:* [colin.vicente.b@bayer.com](mailto:colin.vicente.b@bayer.com)

**Background:** Multiple sclerosis (MS) is a chronic neurological disease associated with a variety of symptomatic conditions. One of which, pain, has been shown to impact patients' quality of life (QoL). The objective of this study was to review clinical trials to identify and assess the value of QoL instruments for measuring change in pain in MS patients.

**Methods:** A literature review of the Medline, EMBASE, and HealthStar databases was conducted by two independent reviewers. Key words included "multiple sclerosis AND (quality of life OR patient reported outcomes)". Included articles were randomized, controlled clinical trials of pharmacologic interventions for MS with QoL outcomes.

**Results:** A total of 12 titles were identified and reviewed. Seven were excluded due to inappropriate research design (5), inappropriate outcomes (1), and duplicate study (1). The five included trials used the Short Form 36 (SF-36), General Health Questionnaire (GHQ), Sickness Impact Profile (SIP), and Multiple Sclerosis Quality of Life Inventory (MSQoLI) QoL instruments. Four of the five studies reported no significant change in overall QoL scores for active treatment versus placebo on generic measures (SIP, SF-36, and GHQ). Of two trials that assessed pain as an outcome measure, patient reported symptom improvement was not associated with a change in overall QoL.

**Conclusion:** Little data is available on the sensitivity of QoL instruments to changes in pain. Further research on QoL of patients with MS pain is warranted.

**Key Words:** *Quality of Life, neuropathic pain, multiple sclerosis*



111

### Canadian cost-effectiveness analysis of eletriptan hydrobromide for the treatment of acute migraine

Lescrauwaet B, Bonnefis-Boyer S, Montpetit M  
Pfizer Canada Inc., Kirkland, Canada

Corresponding Author: [benedicte.lesrauwaet@pfizer.com](mailto:benedicte.lesrauwaet@pfizer.com)

**Background:** Eletriptan hydrobromide is indicated for the acute treatment of migraine with or without aura in adults. An economic evaluation of eletriptan was performed to establish the value of this new molecule.

**Methods:** A model was developed to estimate the incremental cost-effectiveness ratio (ICER) of eletriptan versus sumatriptan. The clinical outcome considered is the number of successfully treated migraineurs defined as 'sustained pain-free (SPF) responders. Direct (drug cost and health care resource use) and indirect (work and non-work time loss) costs per attack were calculated. ICERs are expressed as cost per SPF response. Clinical outcomes were derived from a pooled analysis of 3 double-blind, placebo-controlled eletriptan versus sumatriptan trials. Resource utilization and time loss was derived from a retrospective survey among Canadian migraineurs. Cost data were extracted from a variety of Canadian sources. Analyses applied the societal and provincial health care system perspective.

**Results:** Treatment cost associated with a migraine attack was estimated at \$129 consisting of the cost of drug treatment (\$13.3), other healthcare resource utilization (\$10.0) and paid and unpaid time loss (\$105.7). When treating the migraine attack of a cohort of 100 migraineurs, eletriptan 40 mg generated 7 additional SPF-responders at a direct cost saving of \$354, compared to sumatriptan 100 mg. From a societal perspective, the incremental cost-savings amounted to \$1094.

**Conclusion:** Eletriptan 40 mg represents a cost-effective and cost-saving treatment option in the management of acute migraine attacks in comparison to sumatriptan 100 mg.

**Key Words:** *Cost-effectiveness analysis, triptans, migraine*

112

### Risking health to avoid injections. Stated preferences of Canadians with diabetes

Hauber B,<sup>1</sup> Johnson R,<sup>1</sup> Sauriol L,<sup>2</sup> Lescrauwaet B<sup>3</sup>  
<sup>1</sup>RTI Health Solutions, Research Triangle Park, NC, USA, <sup>2</sup>Aventis Pharma, Quebec, Canada, <sup>3</sup>Pfizer Canada, Quebec, Canada

Corresponding Author: [benedicte.lesrauwaet@pfizer.com](mailto:benedicte.lesrauwaet@pfizer.com)

**Background:** Patients with diabetes may require frequent administration of insulin to achieve adequate glycemic control, but many patients find insulin injections burdensome. This study quantifies diabetes patient preferences for short-term treatment outcomes and the number of daily insulin injections.

**Methods:** 1054 Canadian subjects with diabetes completed a stated-choice questionnaire that included a series of hypothetical treatment choices. Each treatment alternative specified and varied the number of daily insulin injections, fasting plasma glucose and glycosylated hemoglobin levels, and the number of hypoglycemic events per month.

**Results:** Patients placed significant value on reducing the number of daily insulin injections and improving glucose control. On average, patients valued avoiding an increase from 1 injection to 2 injections. Likewise, patients valued improving their current glucose control to the best level. Type 1 patients placed less value decreasing the number of injections than did type 2 patients. Type 1 patients placed greater value on improving glucose control than did type 2 patients. Insulin-using type 2 patients placed no value on reducing the number of injections while insulin-naïve type 2 patients placed significant value on reducing the number of injections. In addition, insulin-using type 2 patients placed greater value on improving glucose control than did insulin-naïve type 2 patients. While all patients were willing to sacrifice glucose control to avoid injections, type 2 patients were more than twice as likely as type 1 patients to do so.

**Conclusion:** The study results indicate that diabetes patients are willing to sacrifice glucose control to reduce the number of daily insulin injections.

**Key Words:** *Conjoint analysis, patient preference, diabetes*

113

### Increased prescribing of gastric acid suppressants among antidepressant users: a retrospective cohort study

Ma J, Vaillancourt R, Auger S, Sampalis J  
Canadian Forces Health Services Group, Ottawa, Canada

*Corresponding Author:* [ma.j@forces.gc.ca](mailto:ma.j@forces.gc.ca)

**Background:** Antidepressants, particularly the serotonin-reuptake inhibitors, have been linked to an increase in gastrointestinal bleeding. This study was undertaken to determine if this increased risk is also present for younger, generally healthy adults.

**Methods:** Cohort subjects were Canadian Forces (CF) members who received an antidepressant between June 1997 and November 2002, excluding those taking bupropion for smoking cessation. The control group consisted of personnel who received salbutamol without antidepressant therapy. Usage rates of gastric acid reducers (GAR) were compared pre- and post-initiation of salbutamol or antidepressant. Multiple logistic regression analysis was used to evaluate the effects of age, sex and concomitant drugs.

**Results:** A total of 8722 antidepressant exposures were identified among 5588 subjects, compared to 4154 salbutamol exposures among 3059 control subjects. Antidepressant users were significantly more likely to receive a new GAR prescription following both short-term and long-term exposure (adjusted OR 4.93, 95% CI 2.66 – 9.21 and 2.83, 95% CI 2.05 – 3.92). Logistic regression analyses identified antiplatelet agents, bisphosphonates, oral corticosteroids, and non-steroidal anti-inflammatory drugs as significant predictors of GAR prescription.

**Conclusions:** The identification of an increased risk in our relatively healthy population strongly suggests that gastric side effects of SSRIs may be more substantial than previously thought. Further study should be directed to quantifying the impact of antidepressants on health costs and quality of life among users of antidepressants.

**Key Words:** *Antidepressants, anti-ulcer agents, gastrointestinal bleeding*

114

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

Ma J, Gervais A, Vaillancourt R  
Canadian Forces Health Services Group, Ottawa, Canada

*Corresponding Author:* [ma.j@forces.gc.ca](mailto:ma.j@forces.gc.ca)

**Background:** Preferential listing of a single drug is undertaken by many drug benefit programs to control costs associated with a therapeutic class of medications. Despite preferential listing, however, our program has continued to sustain significant expenditures for non-benefit proton pump inhibitors (PPIs). An evaluation is being performed to identify reasons for this anomalous usage pattern.

**Methods:** A database analysis using pharmacy records information will be performed to evaluate PPI usage patterns in the Canadian Forces since implementation of the current policy. Descriptive statistics will be used to compare demographic characteristics of PPI users who are receiving treatment with the preferred agent as compared to those who are not. The pharmacy records will also be reviewed to identify reasons for non-use of the preferred PPI. If information gleaned from the database review indicates that side effects are significant with the benefit PPI, or, alternately, that the database contains inconsistencies which would compromise the validity of the review, a telephone survey will be undertaken among subjects who received a non-benefit PPI.

**Results:** We hope to obtain information which will inform future initiatives to rationalize drug use. This study should also provide information on the validity of database records, particularly with respect to override codes, as a reflector of drug tolerability in a population.

**Conclusions:** The results of this study may provide further information regarding the effectiveness of preferred listing as a cost-saving measure. The conclusions drawn from our example may also help to guide policy development in other therapeutic classes.

**Key Words:** *Anti-ulcer agents, drug utilization review, health benefits*

115

### Signaling possible gender effect in a spontaneous reporting system: cardiac effects associated with the use of antibiotics

Ferrarotto F, Moride Y, Bégau B, Lachaine J  
Université de Montréal, Montreal, Canada

*Corresponding Author:* [felicia.ferrarotto@pfizer.com](mailto:felicia.ferrarotto@pfizer.com)

**Background:** Gender differences in cardiac effects associated with the commonly prescribed macrolide antibiotic, erythromycin, have been noted in spontaneous reports. It is not known whether similar effects are present with the newer macrolides: azithromycin and clarithromycin. **Objectives:** i) To assess the association between azithromycin, clarithromycin and the reporting of cardiac events; ii) To determine whether the association is modified by gender; iii) To determine whether gender differences could be confounded by differences in patterns of drug use.

**Method:** The proportional reporting method applied to the FDA spontaneous reporting database was used. The cases were reports of cardiac effects (using Costart terms) and the non-cases were reports of other adverse effects. All reports, excluding consumer reports, from Jan.1st 1992 to Dec.1997 (peak reporting period) were considered.

**Results:** 248,230 reports met the eligibility criteria. Adjusting for age, the proportional reporting ratio was 1.03 (95%CI: 0.80-1.33) for azythromycin and 1.02 (0.90 to 1.15) for clarithromycin. Ratios for men were 0.77 (0.53-1.11) for azythromycin and 0.88 (0.73-1.06) for clarithromycin, and for women they were 1.36 (0.96 -1.92) for azythromycin and 1.17 (0.99 to 1.38) for clarithromycin. A drug utilization study (n=4000) conducted with the RAMQ database revealed no differences across genders in patterns of drug use (duration and dosage).

**Conclusion:** Due to the rarity of exposed events, a statistically significant gender difference in the reporting of cardiac effects could not be found in this study. Advantages and limitations of the method will be discussed.

**Key Words:** *Pharmacovigilance, proportional reporting, gender differences*

116

### Sustainable quality and cost-effectiveness of care: integrating health innovation in the Canadian healthcare delivery system

Cavanaugh S, McLaughlin-Elder F, Donoahue-Walker T, Chow V

Merck Frosst Canada Limited and University of Western Ontario (Ivey), Canada

*Corresponding Author:* [siobhan.cavanaugh@merck.com](mailto:siobhan.cavanaugh@merck.com)

**Background:** Health care resource allocation will increasingly need to be determined by an assessment of cost-effectiveness across the entire health care system. Silo-based management of budgets will not serve patients or lead to a sustainable system for Canadians.

**Methods:** Evidence of provincial listing data of efficacious drug therapies for four chronic diseases (arthritis; migraine; asthma; osteoporosis) was analyzed using data from Brogan Inc., and Provincial formularies.

**Results:** The results show that since 1950's new drug technologies are increasingly restricted from patient access and as such lead to sub-optimal care and inefficient use of available healthcare resources. For some diseases those not benefiting from innovative drug therapy are enduring more costly interventions such as the need for hospitalization, rehospitalization, rehabilitation, chronic care and long-term care facility admission. A most compelling case shown in this analysis is in the bisphosphonate class of therapies used to treat osteoporosis. The average annual cost of treatment using innovative bisphosphonate therapies is about \$468.00 (Fracture Intervention Trial, 1999). Conversely the average cost of one year of hip fractures is \$26,525 (Wiktorowicz, M.E. et al, 2001). Yet, this innovative class of therapies remains highly restrictive to Canadian patients--only two provinces have provided open access to these therapies. About 1.4 million Canadians suffer from osteoporosis: one in four women, and, one in 8 men, over 50 years of age. Historical trends of increasingly restrictive access to innovative drugs, and an aging population, will further exacerbate suboptimal health outcomes and inefficient use of scarce healthcare resources across the Canadian healthcare system.

**Conclusion:** A sustainable health care system must better integrate innovation in care and in the delivery of care.

**Key Words:** *Health innovation*

117

### The caveat study: an observational study of pain management approaches by Ontario primary care physicians in patients with osteoarthritis

Sebaldt RJ,<sup>1,2,7</sup> Faiers A,<sup>3</sup> Morgan D,<sup>1</sup> Kraag G,<sup>4</sup> Lamb S,<sup>1</sup> Thorne C,<sup>5</sup> Thabane L,<sup>1,7</sup> Petrie A,<sup>2</sup> Rochon S<sup>6</sup>

<sup>1</sup>McMaster University, Hamilton, Canada, <sup>2</sup>Clinforma Data Systems & Project Management, Hamilton, Canada, <sup>3</sup>Toronto East General Hospital, Toronto, Canada, <sup>4</sup>University of Ottawa, Ottawa, Canada, <sup>5</sup>Southlake Regional Health Centre, Newmarket, Canada, <sup>6</sup>Pfizer Canada Inc., Kirkland, Canada, <sup>7</sup>Centre for Evaluation of Medicines, St Joseph's Healthcare, Hamilton, Canada

Corresponding Author: [sebaldt@mcmaster.ca](mailto:sebaldt@mcmaster.ca)

**Background:** The primary objective of this study was to evaluate the "care gap" in the treatment of symptomatic osteoarthritis (OA) patients in routine clinical practice in Ontario (care gap defined as proportion of patients not treated consistently with Clinical Practice Guidelines (CPG)).

**Methods:** A random sample of physicians, stratified according to whether a physician is a high traditional NSAID prescriber or high coxib prescriber, were recruited. Over four study cycles, estimates of care gap were obtained for each cycle, expressed as a proportion with corresponding 95% confidence interval (CI). Singh's risk score and the effect of feedback were assessed using generalized estimating equations modeling.

**Results:** 112 physicians recruited 2,860 patients over all four cycles. X-ray findings compatible with OA were reported in more than 80% of the patients. There were significant differences in care gap between traditional NSAID prescribers and coxib prescribers ( $p < 0.001$ ) according to CPG. The pooled estimate of care gap based on CPG was 0.47 (95% CI = 0.43, 0.52) for traditional NSAID prescribers versus 0.33 (0.28, 0.38) for coxib prescribers. Singh's risk score was found to be a strong predictor of care gap ( $p < 0.0012$ ).

**Conclusions:** Care gap based on CPG is significantly higher among high traditional NSAID prescribers than among high coxib prescribers. Singh's risk score was a significant predictor of care gap. Feedback materials about personal and study-wide practice patterns designed for this study and given at the end of each cycle did not have a significant impact on care gap.

**Key Words:** OA, treatment, general practice

118

### Application of lag-time into exposure definitions to avoid protopathic bias

Tamim HM, Tahami Monfared AA, LeLorier J  
CR-CHUM, Montreal, Canada

Corresponding Author: [hani.tamim@elf.mcgill.ca](mailto:hani.tamim@elf.mcgill.ca)

**Background:** Protopathic bias occurs when a pharmaceutical agent is prescribed for an early manifestation of a disease that has not yet been diagnostically detected. To control for protopathic bias, some studies have incorporated the concept of lag-time into their exposure definition (time period before the index date that was not considered in the assessment of exposure). The objective of this study was to introduce a procedure to identify the best lag-time to be applied in different studies.

**Methods:** We used data from a case-control study carried out to assess the association between exposure to PPIs and risk of gastric cancers. Exposure definition was based on the number of PPI pills dispensed to subjects in the study period (divided into 4 quartiles). By applying different lag-times (ranging from 0 to 30 months, based on 3-month intervals), we estimated the rate ratios (RRs) using logistic regression models. For the range of the lag-times, the optimal change-point (where the RRs stabilize) was identified by applying two independent methods: a two-compartmental model and a segmented regression model.

**Results:** For the first, second, third, and fourth quartiles of the number of pills dispensed, the RRs ranged as follows: 3.38-1.12, 3.38-1.16, 3.05-1.07, and 1.52-1.38, respectively. Applying the two-compartmental model for the different lag-times showed that the RRs stabilize at 6 months, indicating the best lag-time to be applied to control for protopathic bias. The same result was obtained with the segmented regression model.

**Conclusion:** For the purpose of controlling for protopathic bias in pharmaco-epidemiologic studies, we have provided a method to assess the most appropriate lag-time that can be applied for the assessment of exposure.

**Key Words:** Protopathic bias, pharmacoepidemiology, case-control

119

### The concept of “brand fidelity” applied to drug use: examples on dyspepsia drugs and COX-2 inhibitors

Tamim HM, Dorais M, LeLorier J  
CR-CHUM, Montreal, Canada

*Corresponding Author:* [hani.tamim@elf.mcgill.ca](mailto:hani.tamim@elf.mcgill.ca)

**Background:** Our objective is to introduce the concept of “brand fidelity”, which serves as a marker for satisfaction with different treatment alternatives.

**Methods:** Data were obtained from the RAMQ. A 10% random sample of all individuals enrolled in the RAMQ databases during 2000 was used. “Brand fidelity” to either of two classes of drugs used to treat the same disease was measured as the percentage of patients who switch back to product A after having switched to product B, and vice versa.

**Results:** After the introduction of PPIs in 1990 the percentage of H2RBs dispensed prescriptions decreased over time (reaching 10% in 2003), whereas that of PPIs increased (reaching 90% in 2003). Among those who started on an H2RB, 53% switched to PPIs, of whom 28% switched back to H2RBs. Among those who started on a PPI, 10% switched to H2RBs, of whom 69% switched back to PPIs. The two selective cox-2 inhibitors (Rofecoxibs and Celecoxibs) equally shared the market between 1999 and 2003, each one representing around 50%. Among those who started on a Celecoxib, 15% switched to a Rofecoxib, of whom 19% switched back to Celecoxibs. As for those who started on a Rofecoxib, 12% switched to a Celecoxib, of whom 23% switched back to Rofecoxibs.

**Conclusion:** The concept of “brand fidelity” greatly favors PPI drugs, relative to H2RBs, whereas it does not favor any of the two cox-2 inhibitors over the other.

**Key Words:** *Drug utilization, brand fidelity, RAMQ*

120

### The cost effectiveness of two-dose versus single-dose vaccination schedules for meningococcal conjugate vaccine

Woolcott JC,<sup>1</sup> Pielak K,<sup>1</sup> Marra F,<sup>1,2</sup> Skowronski D<sup>1</sup>  
<sup>1</sup>British Columbia Centre for Disease Control,  
<sup>2</sup>University of British Columbia, Faculty of  
Pharmaceutical Sciences, Canada

*Corresponding Author:* [john.woolcott@bccdc.ca](mailto:john.woolcott@bccdc.ca)

**Background:** Meningococcal C conjugate (MCC) vaccine is licensed in Canada for vaccination of infants. Vaccination before 12 months requires more than one dose to achieve sustained protection. We assess the incremental cost-effectiveness of two-dose vs. one dose schedules.

**Methods:** A decision analytical model comparing children vaccinated with MCC vaccine at 12 months versus 2 and 12 months was developed. The clinical pathway incorporates the probability of infection due to meningitis or other invasive illness due to meningococcus C for an otherwise healthy population. Health outcomes of interest include death, hospitalizations, and life years gained. Costs included are vaccination, treatment, prophylaxis, hospitalization, and surveillance. The protection afforded by MCC vaccination according to either schedule beyond twelve months of age is assumed identical.

**Results:** The average annual cost of a one dose MMC program is \$1.28M. The average annual cost of a two dose MCC program is \$2.50M. The incremental cost effectiveness of a two dose vs. one dose program is \$1,052,985 per case averted, \$7,019,902.49 per death averted and \$301,420 per life year gained. The high incremental cost-effectiveness is driven by the paucity of cases between two and twelve months of age.

**Conclusion:** Incremental cost-effectiveness is a useful way to highlight value for money achieved with added doses in a given vaccine’s schedule. In this analysis, a two dose MCC schedule is not a cost effective alternative to a single dose regimen. Other considerations such as differential waning of immunity, outbreak activity or public concern must also be incorporated into vaccine program decision-making.

**Key Words:** *Meningitis, cost-effectiveness, immunization*

121

### The cost-effectiveness of maintenance infliximab for chronic active Crohn's disease in Canada including productivity

Wong JB, Loftus EV, Sandborn WJ, Feagan BG  
Tufts-New England Medical Center, Boston, MA, USA, Mayo Clinic, Rochester, MN, USA, Robarts Research Institute, London, Canada

Corresponding Author: [jwong@tufts-nemc.org](mailto:jwong@tufts-nemc.org)

**Background:** Prior cost-effectiveness analyses of infliximab have not accounted for productivity benefits. Aim: To estimate the cost-effectiveness of maintenance infliximab for chronic active Crohn's disease incorporating productivity benefits.

**Methods:** Summary data from ACCENT I trial examining infliximab were adapted and applied to a previously published Markov model for Crohn's disease. Cost-effectiveness analyses were performed for 1) responders censoring for dose escalation and 2) all patients including possible dose escalation. Costs were based on Canadian costs with discounting at 3%. Productivity benefits were based on ACCENT I data for patients in or not in remission that were working full-time or part- or full-time.

**Results:** Patients in remission had a higher likelihood of working (31% full- or part-time versus 16% if not in remission,  $p < 0.05$ ), and infliximab maintenance resulted in a higher likelihood of remission (28% versus 14% with placebo among responders,  $p < 0.01$ ). Among responders, maintenance infliximab (5 mg/kg) compared to placebo had incremental cost-effectiveness ratios of \$41,000 per quality-adjusted life year gained when incorporating part- or full-time work and \$39,600 when incorporating full-time work. When examining all patients and considering possible dose escalation, initial 5 mg/kg maintenance infliximab was cost-saving compared to initial single infliximab dosing and possible reinfusions for responders. Varying the Canadian hourly wage (\$10.44-\$28.62) resulted in cost-effectiveness ratios ranging from \$35,500 to \$43,500 and varying the likelihood of employment over the 95% CIs resulted in ratios ranging from \$37,400 to \$42,900.

**Conclusions:** Our results suggest that maintenance infliximab is likely to be "cost-effective" especially when incorporating productivity benefits.

**Key Words:** Crohn's disease, infliximab, cost-effectiveness

122

### The economic burden of neuropathic pain

Tarride J-E,<sup>1</sup> Gordon A,<sup>2</sup> Choiniere M,<sup>3</sup> Collet J-P<sup>4</sup>  
<sup>1</sup>Pfizer Canada Inc., <sup>2</sup>Mount Sinai Hospital, <sup>3</sup>Montreal Heart Institute, <sup>4</sup>Jewish General Hospital, Canada

Corresponding Author: [jean-eric.tarride@pfizer.com](mailto:jean-eric.tarride@pfizer.com)

**Background:** The management of Neuropathic Pain (NeP) is a major health care consideration, both from a treatment and funding perspective. One of the objectives of this research was to evaluate the economic burden of NeP in Canada.

**Methods:** A cross sectional, non-interventional study was conducted at primary care sites across three provinces (Alberta, Ontario and Quebec) amongst patients with diabetic peripheral neuropathy, post-herpetic neuralgia, cervical radiculopathy and postoperative neuropathy. Economic burden of illness data was collected through a medical chart review and patient self-administered questionnaires.

**Results:** 126 subjects were enrolled. The mean age was 58.7 (+13.5). Over a 3-month period, the mean number of General Practitioner visits related to NeP was reported at 2.2 (+/-1.9) and 25.4% of subjects visited other health care professionals (e.g., physical therapist). In that same recall period, 34.9% of the subjects underwent a diagnostic test and 27.8% consulted a specialist for their NeP. 16.7% were currently waiting for an appointment with a specialist (waiting average time: 3.2 months SD:2.5). The mean number of classes of pain-related medication taken over the last 3 months was 2.3 (SD:1.6). 84.1% had taken a pain-related OTC over the last week. Missed full unpaid days due to NeP (e.g., housework, volunteer work) over the last 4 weeks was 4.7 (SD: 7.8). Among subjects working for pay the mean number of full days of work missed due to NeP over the last 4 weeks was 2.6 (SD:6.4).

**Conclusions:** NeP is a costly disease from a payer, employer and patient perspective.

**Key Words:** Neuropathic pain, economic burden

123

**The humanistic burden of neuropathic pain**Tarride J-E,<sup>1</sup> Gordon A,<sup>2</sup> Choiniere M,<sup>3</sup> Collet J-P<sup>4</sup><sup>1</sup>Pfizer Canada Inc., <sup>2</sup>Mount Sinai Hospital, <sup>3</sup>Montreal Heart Institute, <sup>4</sup>Jewish General Hospital*Corresponding Author:* [jean-eric.tarride@pfizer.com](mailto:jean-eric.tarride@pfizer.com)**Background:** Neuropathic Pain (NeP) is a chronic condition thought to have a significant impact on the quality of life (QoL) of affected individuals. One of the objectives of this research was to evaluate the humanistic burden of NeP in Canada.**Methods:** A cross sectional, non-interventional study was conducted at primary care sites across three provinces (Alberta, Ontario and Quebec) amongst patients with diabetic peripheral neuropathy, post-herpetic neuralgia, cervical radiculopathy and post-operative neuropathy. Patients completed several questionnaires evaluating health status including the modified-Brief Pain Intensity Inventory (m-BPI), the EQ-5D, a generic disease QoL instrument, the Hospital Anxiety and Depression Scale (HADS) and the MOS Sleep Scale (MOS-S).**Results:** 126 subjects were enrolled. The mean age was 58.7 (+13.5) and the mean duration of NeP was 6.6 years (+6.6). On a scale from 0 to 10, mean (+SD) current, average, worst, and least pain over the last week due to NeP were 4.8 (+2.6), 5.4 (+2.0), 6.7 (+2.4), and 3.5 (+2.4) respectively. On a scale from 0 (death) to 1 (perfect health), subjects reported a mean EQ-5D utility score of 0.42 (+0.35). Moderate to severe levels of anxiety (HADS-A scores >10 on 0-21 scale) and depression (HADS-D scores >10 on 0-21 scale) occurred in 31.7% and 19.1% of subjects, respectively. On a scale from 0 to 100, the MOS Sleep Adequacy Scale Score was 43.1 (+26.5).**Conclusions:** Pain intensity due to NeP is substantial, and has a profound impact on health status.**Key Words:** *Neuropathic pain, humanistic burden*

124

**The economic impact of treatment of falls-related injuries**Asche C,<sup>1</sup> Stockdale W,<sup>2</sup> Pepper G,<sup>3</sup> Gallagher E<sup>4</sup><sup>1</sup>Pharmacotherapy, University of Utah, USA, <sup>2</sup>University of Utah, USA, <sup>3</sup>Nursing, University of Utah, USA, <sup>4</sup>Nursing, University of Victoria, Canada*Corresponding Author:* [carl.asche@pharm.utah.edu](mailto:carl.asche@pharm.utah.edu)**Background:** Determining the costs associated with falls among older persons is of interest to health practitioners and planners but has not been widely studied. Such knowledge may lead to enhancing the quality of care, improving patient outcomes and decreasing the economic burden of falls in the healthcare system.**Objective:** To determine the cost associated with the treatment of falls-related injuries.**Methods:** A U.S. national employer database (MedStat Commercial Claims and MedStat Medicare), representing approximately 7 million patient lives, was queried to identify persons having a fall related diagnosis code for the years 2000 to 2002. Cost of care from the date of first incident (fall) forward (average of 286.1 days) were recovered which included medical (inpatient and outpatient) and prescription costs. Medications known to induce falls among older persons were appropriately researched and are referenced. All statistical tests used MS-ACCESS® and STATA® statistical software.**Results:** A total of 15,900 (51% women) persons representing all ages had diagnosis codes associated with falls representing a cost of care of approximately \$91.4 million or \$5,750 per person. Of these, only 5.4% (851) were older persons (> 60 years of age) reflecting 12% (\$ 11 million) of the total costs. Of these, 462 (54.3%) had been taking medications known to induce falls amounting to \$4.9 million dollars or \$10,600 per patient.**Conclusion:** The costs associated with falls in the U.S. are substantial and tend to increase among older persons many (>50%) of whom have taken medications known for inducing falls.**Key Words:** *Economics, falls, injuries*

125

### The Usefulness of the EQ-5D in Differentiating Persons with and without Major Depressive Episode and, by Treatment Adequacy

Supina AL, Maxwell CJ, Johnson JA, Patten SB, Williams J

Community Health Sciences & Institute of Health Economics, University of Calgary, Calgary, Canada

Corresponding Author: [alsupina@ucalgary.ca](mailto:alsupina@ucalgary.ca)

**Background:** Major depressive episodes (MDE) are associated with decreased well-being and health-related quality of life (HRQL). Antidepressant treatments are effective in reducing MDE severity, and increasing well-being and HRQL. Our objective was to examine HRQL between people with and without MDE and between MDE subjects with and without adequate treatment.

**Methods:** Data were collected in 2003 as part of the Alberta Mental Health Survey. Data were obtained through random digit dialing and computer assisted telephone interviews. MDE was defined by DSM-IV using the Mini International Neuropsychiatric Interview. HRQL was measured with the EQ-5D; responses on the anxiety/depression domain were dichotomized to (1) no problem or (2) moderate/extreme problems. Descriptive and multivariate analyses were used to examine associations between EQ-5D scores and MDE according to the presence and adequacy of antidepressant therapy, using American Hospital Formulary System guidelines.

**Results:** The average age of the respondent sample (n=5383) was 40.8 (12.1) years, 61% were female. Approximately 8% (422) of respondents were classified as having MDE, 70% of whom reported having moderate/extreme symptoms on the EQ-5D anxiety/depression domain. Among the 422 MDE subjects, 27% (113) were receiving one or more antidepressants, with 91 (81%) receiving an adequate dose. Both the treated and adequately treated subjects were more likely to report having problems with anxiety-depression (83% vs. 65% for those with and without treatment and 90% vs. 55% for those with and without adequate doses). EQ-Index and EQ-VAS scores were significantly lower for subjects with MDE and those receiving MDE treatment.

**Conclusions:** The EQ-5D performed well in differentiating among persons with MDE; cross-sectional HRQL assessments may be limited in interpreting treatment adequacy.

**Key Words:** Major depression, health-related quality of life, EuroQoL, antidepressant

126

### Productivity and welfare lost of absenteeism for Canadian labour force with diabetes mellitus

Farahati F, Hurley J

McMaster University, Hamilton, Canada

Corresponding Author: [farahf@mcmaster.ca](mailto:farahf@mcmaster.ca)

**Objectives:** This study estimates the productivity and welfare lost of absenteeism for individuals with Diabetes Mellitus (DM) as a whole and with Insulin Dependent Diabetes Mellitus (IDDM) and Non-Insulin Dependent Diabetes Mellitus (NIDDM) and Diabetes-Related Comorbidities/Complications (DRCOM), among respondents to the Canadian Community Health Survey 2001.

**Methods:** Two-part modelling is used, logistic regression to model probability of working and log transformed OLS regression with smearing to estimate the weekly working hours for workers.

**Results:** The results indicate that having IDDM and NIDDM are negatively associated with the probability of working for both men and women. Consistent with the previous studies we find no statistically significant effects of any type of DM on working hours among workers for both women and men. However, DRCOM have statistically negative effect on working hours for women with DM but not for men. The annual productivity and welfare lost were higher for women and men with IDDM and DRCOM; however, due to the higher prevalence rate of NIDDM compared with IDDM, the national productivity and welfare lost were higher for NIDDM and DRCOM.

**Conclusion:** Per capita productivity lost of DM in Canada is estimated similar to the reported studies by American Diabetes Association in 2002. Results of use to health service researchers interested in econometric modeling in identifying and quantifying the economics burden of DM among the labour force.

**Key Words:** Diabetes mellitus, econometric modeling, Canada



127

**Use of selective serotonin reuptake inhibitors and the risk of myocardial infarction: systematic review and meta-analysis of observational studies**

Ganjizadeh SR,<sup>1</sup> Fitzgerald JM,<sup>1</sup> Etminan M<sup>2</sup>

<sup>1</sup>Center for Clinical Epidemiology and Evaluation, Vancouver Hospital, Vancouver, Canada, <sup>2</sup>Division of Clinical Epidemiology, Royal Victoria Hospital, Montreal, Canada

*Corresponding Author: [metminan@shaw.ca](mailto:metminan@shaw.ca)*

**Background:** Several studies have found an association between the use of selective serotonin reuptake inhibitors (SSRIs) and the risk of myocardial infarction (MI). We sought to explore this association by conducting a systematic review and met-analysis of the literature.

**Methods:** We systematically searched Medline and Embase for all potential observational studies. We included studies that had clearly stated diagnostic criteria for the outcome of MI and explicitly described exposure to SSRIs. Studies also had to present data on relative risks or odds ratios or had to at least present enough data to allow these to be calculated. We made two separate analyses where we compared the risk of SSRIs and tricyclic antidepressants (TCAs) with respect to the risk of MI. We used the random effects model to calculate pooled relative risks (or odds ratios) and 95% confidence intervals. Because the tests of heterogeneity are usually underpowered, we also quantified heterogeneity graphically as well as quantitatively using the I<sup>2</sup> statistic.

**Results:** We included five case-control studies and one cohort study in the first analysis. The relative risk of MI with respect to SSRI use was 0.86 (95% CI, 0.74-0.99, P=0.078) for the case-control studies and 0.86 (95% CI, 0.75 - 1.00, P=0.45) for the cohort study. The relative risk of MI with (five case-control studies) with respect to TCAs was 0.94 (95% CI, 0.75 - 1.19, P=0.42).

**Conclusion:** SSRIs may lower the risk MI among depressed patients. More studies are needed to further explore this association.

**Key Words:** *Antidepressants, meta-analysis, SSRIs*

128

**Valuation modeling for evaluating biotechnology/ pharmaceutical developmental opportunities**

Shane LG,<sup>1</sup> Cox F,<sup>1</sup> Vernon J<sup>2</sup>

<sup>1</sup>Worldwide Outcomes Research, Pfizer Inc., New York City, USA, <sup>2</sup>University of Connecticut, National Bureau of Economic Research (NBER), USA

*Corresponding Author: [lesley.shane@pfizer.com](mailto:lesley.shane@pfizer.com)*

**Background:** Reimbursement authorities are faced with significant escalating health care costs, pressured budgets and numerous launches of biotech and pharmaceutical technologies with uncertain “value for money”. At the same time, biotechnology/pharmaceutical companies are assessing their developmental pipeline. An econometric modeling application, based on cost-effective methodology, is illustrated which helps analyze and predict the appropriate patient populations, future product market access value and pricing for product opportunities by considering payers’ use of cost-effectiveness methods and willingness to pay thresholds.

**Method:** A Markov deterministic Excel model compared populations with a chronic disease treated with Drug X to standard care. The US, Canadian, and selected European (Italy, Germany) healthcare system perspectives were evaluated and the methodology followed respective country economic guidelines. Physicians validated disease progression rates, treatment patterns and resource use. The literature provided estimates for disease transitions, utilities, resource utilization and direct costs. Estimated life expectancy, quality-adjusted life expectancy, total lifetime costs and incremental cost-utility ratios between strategies were determined. A unified analysis tested scenarios for various sub-population groups to understand the aggregate weighted incremental cost-utility outcomes and trade-offs. Optimal price for Drug X was solved using Crystal Ball software for various scenarios at selected fixed payer’s willingness to pay thresholds. Stochastic multivariate stochastic sensitivity analyses was performed for an array of parameters.

**Results:** Econometric valuation approaches have been influential in guiding companies on anticipated key market access dynamics; projected cost-effective positioning and target sub-populations; and optimal pricing for product opportunities. This process could also help payers by identifying patient groups that will derive the clinical benefit at a cost-effective price. Furthermore, it is increasingly becoming recognized by biotechnology/pharmaceutical manufacturers that this approach may reduce product development risk by establishing the realistic market potential.

**Key Words:** *Econometric modeling, product development, cost-effectiveness*

129

**Do patients with atrial fibrillation receive appropriate stroke prevention therapy in practice ?**

Folia C,<sup>1</sup> Liovas A,<sup>2</sup> Haiderali A,<sup>2</sup> Kim T<sup>2</sup>

<sup>1</sup>Agro Health Associates Inc., <sup>2</sup>AstraZeneca Canada Inc., Canada

Corresponding Author: [christine.folia@agrohealth.com](mailto:christine.folia@agrohealth.com)

**Background:** Clinical practice guidelines and several clinical trials support the use of warfarin for stroke prevention in most patients with atrial fibrillation (AF). Warfarin should not be used in cases where contraindications exist or the risk of stroke is low. It is not clear what proportion of patients at risk of stroke and without contraindications do not receive warfarin in practice.

**Methods:** A MEDLINE search was conducted (1966-2001) using the MeSH terms anticoagulants, AF, warfarin and cerebrovascular disorder (prevention and control). Practice-based studies reporting the proportion of patients eligible to receive warfarin (i.e., no contraindications to thromboprophylaxis and at moderate or high risk of stroke) who actually received warfarin for stroke prevention in AF were retrieved.

**Results:** Twenty-one practice-based studies were found, of which 3 were excluded because the patient population or centre/setting significantly varied from the other identified studies. Approximately 47-89% of patients enrolled in the remaining 18 studies were eligible for stroke prevention. Only 15-64% of eligible patients received warfarin and 15-56% did not receive any form of stroke prevention therapy at all (i.e., no warfarin or antiplatelet agent).

**Conclusions:** Despite the publication of multiple clinical trials and practice guidelines supporting the use of warfarin for stroke prevention in AF, many eligible patients do not receive appropriate preventive therapy, and therefore remain at increased risk of stroke. Reasons for the sub-optimal use of warfarin for stroke prevention in AF require further research.

**Key Words:** *Atrial fibrillation, stroke prevention, anticoagulants, survey*

130

**Warfarin for stroke prevention in atrial fibrillation: to use, or not to use, that is the question**

Folia C,<sup>1</sup> Liovas A,<sup>2</sup> Haiderali A,<sup>2</sup> Kim T<sup>2</sup>

<sup>1</sup>Agro Health Associates Inc., Ontario, Canada, <sup>2</sup>AstraZeneca Canada Inc., Ontario, Canada

Corresponding Author: [christine.folia@agrohealth.com](mailto:christine.folia@agrohealth.com)

**Background:** Although beneficial in atrial fibrillation (AF), warfarin should not be used when the risk of bleeding outweighs the potential clinical benefit. Professional judgement must be used on a case-by-case basis. Since clinical practice guidelines do not explicitly state warfarin contraindications, clinicians must often rely on personal interpretation and judgement when prescribing warfarin. However, are these perceptions of warfarin contraindications consistent/uniform in clinical practice?

**Methods:** A MEDLINE search (1966-2001) was conducted using the MeSH terms warfarin, anticoagulants, AF and cerebrovascular disorder (prevention and control). Practice-based studies assessing the proportion of AF patients without warfarin contraindications who received warfarin for stroke prevention were gathered. From these, the percentage of studies citing various warfarin contraindications was assessed.

**Results:** Sixteen practice-based studies citing contraindications to warfarin use were identified. Contraindications included: history of bleed (100%), history of falls (75%), alcoholism (69%), confusion/dementia (56%), terminal illness (44%), hepatic impairment (44%), peptic ulcers (44%), noncompliance (44%), coagulation defects (38%), seizure/syncope (38%), renal impairment (38%), allergy (31%), mental illness (12%), uncontrolled hypertension (12%), NSAIDs (12%), iron deficiency (6%), and age (6%).

**Conclusions:** Practice-based studies vary in their interpretation of warfarin contraindications. The impact of this variation on patient outcomes is unknown and requires further research. Previous assessments of practice-based studies have shown warfarin use in AF is sub-optimal. Measures to better clarify warfarin contraindications may improve appropriate utilization for this indication.

**Key Words:** *Atrial fibrillation, stroke prevention, warfarin, survey*

**CCCP- ORIGINAL RESEARCH**

131

**Removal of Benzocaine spray from hospital formulary due to a series of adverse events—one hospital's experience**

Bayliff CD, Anderson S, Gupta A, Ponich T  
London Health Sciences Centre, London Canada

*Corresponding Author:* [Charlie.bayliff@lhsc.on.ca](mailto:Charlie.bayliff@lhsc.on.ca)

**Background:** Benzocaine is commonly employed as a topical anesthetic but has been associated infrequently, with serious adverse events including methemoglobinemia. We summarize our experience with this drug and describe the processes involved to ensure safe medication practices.

**Methods:** Following a case of benzocaine-induced methemoglobinemia staff pharmacists were surveyed to determine if they knew of any additional cases of same. As well, a report was generated using the hospital's medication system for individual prescriptions for methylene blue, the specific treatment for methemoglobinemia. This information was compiled and presented to the Pharmacy & Therapeutics Committee.

**Results:** Over an 18 month period, 7 cases of BIM were identified at our hospital with detailed information available for 6 cases. The mean age of the patients was 62 years with a range of 43 to 71 years. Three patients were undergoing endoscopy for gastroenterology work up and 3 were undergoing transesophageal echocardiography. The mean peak concentration of methemoglobin was 43.8% with a range of 31-60.5% with our laboratory's normal range being 0.2-0.6%. Methylene blue was administered in 5 of the 6 cases. In terms of clinical sequelae both outpatients were admitted to hospital and remained in hospital overnight. Of the 4 inpatients, 2 were transferred to the intensive care area; 1 experienced a symptomatic elevation in troponin level; 3 patients received bronchodilators. All 6 patients received oxygen therapy or had the flow rate of oxygen increased. Following this presentation and after assessing the morbidity associated with the reaction in these cases it was determined that the drug would be withdrawn from general use in our institution.

**Conclusions:** Starting with data collected and compiled in our institution a process was initiated to enhance safe medication practices involving topical benzocaine.

**Key Words:** *Benzocaine, adverse events, patient morbidity, methemoglobinemia, safe medication practices*

132

**Development of a pharmacy seamless care strategy and tool for chronic renal failure patients**

Cesta A, Ong S, Fernandes O, Battistella M, Bajcar J  
Toronto General Hospital–University Health Network,  
Toronto, Canada

*Corresponding Author:* [annemarie.cesta@uhn.on.ca](mailto:annemarie.cesta@uhn.on.ca)

**Background:** Continuity of care is required when patients move from the care of one pharmacist to another. The appropriate transfer of information to pharmacists as well as to patients at these times is essential in order to prevent drug related problems (DRPs) from occurring. There is currently no formal system or tool that is used consistently by various pharmacists at University Health Network to transfer medication-related information.

**Objectives:** To develop a strategy and tool to transfer medication-related information between pharmacists caring for chronic renal failure (CRF) patients.

**Methods:** The project was divided into three phases including data collection, tool design and developmental pilot. The data collection phase consisted of a literature review, collection of patients' drug related problems on admission and a needs assessment of stakeholders. Qualitative research methods were used for data collection and data analysis. Data collected was used in phase 2 to determine the most optimal tool and strategy for medication information transfer in dialysis patients. In phase 3 the developed tool was tested on various pharmacists to assess feasibility.

**Results:** The electronic Dear Pharmacist Letter created communicates pertinent medication-related information to community or clinic pharmacists including an up to date list of the patient's medications. The tool also creates two different formats of a patient medication schedule to be given to the patient when they are discharged from the hospital.

**Conclusions:** A large proportion of DRPs occurring in dialysis patients on admission are a result of the lack of appropriate information transfer between health care professionals, as well as to the patient. A stakeholder needs assessment; collection of DRPs on admission, and a literature review can be used to develop a seamless care strategy and electronic tool for CRF patients.

**Key Words:** *Dialysis, drug related problems, electronic medication scheduler, chronic renal failure*

133

**Establishing a limited sampling strategy for Cyclosporine (Neoral®) for pediatric transplant patients**

Ensom MHH, Lai AA, Lirenman DS, Carter J, Morrison Hurley R, White C, Strong DK  
University of British Columbia Faculty of Pharmaceutical Science, Children's & Women's Health Centre of British Columbia Department of Pharmacy, Vancouver, Canada

Corresponding Author: [ensom@interchange.ubc.ca](mailto:ensom@interchange.ubc.ca)

**Background:** Monitoring of cyclosporine (CSA) Neoral® is crucial in achieving optimal therapeutic outcomes. However, few practical limited sampling strategies (LSSs) have been developed for the pediatric population.

**Objectives:** In pediatric renal transplant patients, 1) to define the optimal LSS for CSA (Neoral®) monitoring and to test its predictive performance, and 2) to characterize the pharmacokinetic parameters of Neoral®.

**Methods:** In Phase I, 18 pediatric renal transplant patients were entered into the study. Upon administration of a steady-state morning Neoral® dose, blood samples were collected at 0,0.5,1,2,4,6, and 8 hours post-dose. The whole blood samples were analyzed for CSA by fluorescence polarization immunoassay using a specific monoclonal antibody kit. Pharmacokinetic parameters were determined via non-compartmental analysis using WinNonlin® software. LSSs were determined by multiple regression analysis with forward stepwise elimination using Statistica® software. In Phase II, 16 patients underwent regular clinical monitoring of Neoral® and had blood collected and analyzed according to the above procedures. These data were used to test the predictive performance [measured by the coefficient of determination ( $r^2$ ), bias, and precision] of LSSs developed in Phase I.

**Results:** The optimal and most clinically feasible LSS for pediatric renal transplant recipients is  $AUC=8.38C_0+3.48C_2+134.53$  ( $r^2=0.816$ ; % bias=0.06; % precision=0.10). For Phase I patients (Phase II patients), mean±SD  $AUC_{0-\tau}$  was  $4407.73\pm1675.41$  ( $5387.56\pm1963.20$ )  $\mu\text{g}\cdot\text{hr}/\text{L}$ ,  $C_{max}$  was  $1059.94\pm381.59$  ( $1162.38\pm414.54$ )  $\mu\text{g}/\text{L}$ ,  $C_{min}$  was  $161.61\pm76.11$  ( $196.81\pm103.88$ )  $\mu\text{g}/\text{L}$ ,  $T_{max}$  was  $1.39\pm0.50$  ( $1.69\pm0.50$ ) hours, and half-life was  $4.08\pm1.10$  ( $5.91\pm2.27$ ) hours.

**Conclusions:** The optimal LSS  $AUC=8.38C_0+3.48C_2+134.53$ , requires 2 blood samples at 0 and 2 hours post-dose. For the two LSSs requiring only one blood sample, using C2 did not yield a significant advantage over the traditional use of C0 (i.e., trough monitoring) in our pediatric patients.

**Key Words:** Cyclosporine, pharmacokinetics, renal transplantation, pediatric, limited sampling strategy

134

**Utility of anti-Xa monitoring in children receiving Enoxaparin for therapeutic anticoagulation**

Ensom MHH, Leung M, Ho S, Hamilton DP, Wu JK, Dix DB, Wadsworth LD  
University of British Columbia Faculty of Pharmaceutical Sciences; Children's & Women's Health Centre of British Columbia Department of Pharmacy, Vancouver, Canada

Corresponding Author: [ensom@interchange.ubc.ca](mailto:ensom@interchange.ubc.ca)

**Background:** Although enoxaparin is commonly used in the treatment of thromboembolism in children, current treatment guidelines are largely extrapolated from adults.

**Objectives:** The objectives of this study were to determine: i) correlation between enoxaparin dose and anti-Xa level; ii) intra-patient variability; and iii) whether dose or anti-Xa level is a predictor of clinical outcomes.

**Methods:** A retrospective chart review was conducted on all hospitalized patients receiving enoxaparin from March 2000 to July 2003 in a tertiary care pediatric institution. Excluded were patients whose enoxaparin was administered intravenously, who were >19 years old, or whose health records were not available for review. Simple linear regression, coefficient of variation (CV), and Student's t-test were used to analyze objectives i, ii, and iii, respectively.

**Results:** Of 148 records reviewed, 80 treatment courses with interpretable anti-Xa levels were analyzed. Mean patient age was  $6.5\pm6.5$  years. Mean enoxaparin dose was  $1.10\pm0.38$  mg/kg q12h. Correlation between empiric dosing and anti-Xa level was poor,  $r^2=0.0453$  and  $0.0005$  (ages  $\leq 2$  or  $> 2$  months, respectively). Fifty-seven percent (4/7) of patients  $\leq 2$  months of age compared to 12.5% (4/32) of patients  $> 2$  months had a CV>40%. Similarly, 33% (4/12) of cardiac patients compared to 15% (4/27) of non-cardiac patients had a CV>40%. Neither dose nor anti-Xa level was a predictor of treatment success or adverse reactions ( $p>0.05$ ).

**Conclusions:** These results suggest a need to reexamine the use of anti-Xa levels for guiding enoxaparin therapy. Further prospective studies are warranted to clarify whether routine or selective anti-Xa monitoring should be recommended in pediatric patients.

**Key Words:** Enoxaparin, low molecular weight heparin, anti-Xa monitoring, pediatrics, anticoagulation

135

**Pharmacokinetics of intravenous immunoglobulin (IVIG) before and during pregnancy**

Ensom MHH, Kinnear ME, Houlihan E, Stephenson MD  
University of British Columbia Faculty of Pharmaceutical Sciences, Children's & Women's Health Centre of British Columbia Department of Pharmacy, Vancouver, Canada

*Corresponding Author:* [ensom@interchange.ubc.ca](mailto:ensom@interchange.ubc.ca)

**Background:** To date, little pharmacokinetic data for intravenous immunoglobulin (IVIG) exist for women before and during pregnancy, despite IVIG's usage in obstetrics, expense, and worldwide shortage.

**Objectives:** The objective of this study is to characterize intravenous immunoglobulin (IVIG) pharmacokinetics in women with recurrent miscarriages.

**Methods:** Of 20 enrolled women (9 in an open-label pharmacokinetic study for treatment of antiphospholipid antibody syndrome and 11 in a randomized placebo-controlled trial for idiopathic secondary recurrent miscarriage), 14 received IVIG (GamimuneN 5%) 500-1000mg/kg and 6 placebo over a 2-10h period q4wks pre-pregnancy until up to 18-20 weeks gestation. Serum IgG concentrations were measured by rate nephelometry before and at 0.5h and 1,2,3, and 4 weeks following the 1<sup>st</sup> dose, and a dose during each of the 1<sup>st</sup> and 2<sup>nd</sup> trimesters.

**Results:** Mean ( $\pm$ SD) age was 34.5 $\pm$ 4.4yr (IVIG) and 34.5 $\pm$ 4.8yr (placebo). History of spontaneous abortions was 4.5 $\pm$ 2.2 (IVIG) and 3.5 $\pm$ 0.8 (placebo). Pharmacokinetic parameters (mean $\pm$ SD) for C<sub>max</sub> (g/L), C<sub>min</sub> (g/L) and AUC<sub>0- $\tau$</sub>  (g\*h/L), respectively, were: IVIG pre-pregnancy: 26.8 $\pm$ 4.2, 12.5 $\pm$ 1.8, 11735.3 $\pm$ 1800.6; IVIG 1<sup>st</sup> trimester: 30.8 $\pm$ 7.5<sup>#</sup>, 12.6 $\pm$ 2.7, 11901.7 $\pm$ 2546.6; IVIG 2<sup>nd</sup> trimester: 27.1 $\pm$ 4.1<sup>#</sup>, 11.6 $\pm$ 2.8, 11365.2 $\pm$ 1781.9; placebo pre-pregnancy: 10.1 $\pm$ 2.6, 8.6 $\pm$ 2.6, 5768.0 $\pm$ 1405.3; placebo 1<sup>st</sup> trimester: 11.4 $\pm$ 3.4, 9.2 $\pm$ 2.6, 6846.2 $\pm$ 2018.0; placebo 2<sup>nd</sup> trimester: 10.5 $\pm$ 0.2, 9.4 $\pm$ 1.2, 6761.2 $\pm$ 321.9. [<sup>#</sup>p=0.05; repeated measures ANOVA (Student-Newman-Keuls) or paired t-test]. Dosages (on mg/kg basis) and AUCs did not differ significantly within the IVIG group between the 3 sampling periods. Roughly-estimated contributions of exogenously-administered IVIG to total AUC<sub>0- $\tau$</sub>  [calculated as mean AUC<sub>0- $\tau$</sub> (IVIG group) minus mean AUC<sub>0- $\tau$</sub> (placebo group)] were 5967.3g\*h/L (pre-pregnancy), 5055.5g\*h/L (1<sup>st</sup> trimester), and 4604.0g\*h/L (2<sup>nd</sup> trimester).

**Conclusions:** Pregnancy did not have a significant effect on exposure to the same mg/kg dosage of exogenously-administered IVIG. The estimated contribution of exogenous IVIG (i.e.~5200g\*h/L) to total AUC<sub>0- $\tau$</sub>  was similar to, albeit slightly lower than, that contributed by endogenous IgG (i.e.~6500g\*h/L). These preliminary data warrant further study in larger groups of patients.

**Key Words:** *Pharmacokinetics, IVIG, pregnancy, immunology, immunoglobulin*

136

**Measurement of the effect of discontinuing Baclofen and Dantrelene therapy in long-term institutionalized patients with spasticity**

Farrell B, Pora N, Neutel I, Babcock K  
SCO Health Service, Ottawa, Ontario, Canada

*Corresponding Author:* [bfarrell@scohs.on.ca](mailto:bfarrell@scohs.on.ca)

**Background:** Despite lack of valid trials documenting efficacy, baclofen and dantrolene are widely used to treat spasticity. There is a clinical impression that these drugs are useful, however, their side effects are often overlooked.

**Objectives:** The purpose of this project was to evaluate the effects of planned withdrawal of baclofen and dantrolene in consenting complex continuing care patients.

**Methods:** This descriptive study design collected data before, during and after the withdrawal intervention. A withdrawal protocol was used in which the clinical team made withdrawal decisions and did individualized monitoring. Proportions were used to describe the results.

**Results:** Of 69 patients taking either baclofen or dantrolene, 29 were excluded from the withdrawal protocol primarily due to physicians' decisions. Of the 40 eligible patients, 26 (65%) participated in the tapering protocol. Of these 26, 15 (58%) were able to have baclofen or dantrolene discontinued, 6 (23%) were maintained on a lower dose, 4 (15%) were maintained at the same dose and one patient died during tapering. Six (23%) had other changes made to their spasticity treatment, and 4 (15%) had improvements in other symptoms which could have been adverse effects of the antispasticity agents.

**Conclusions:** Over half of the patients participating in a tapering protocol were able to have baclofen or dantrolene either discontinued or the dose lowered; a few had adjustments in other medications or therapy made. Targeted Medication Withdrawal programs can be a successful approach to reducing unnecessary medication in long-term institutionalized patients.

**Key Words:** *Baclofen, dantrolene, complex continuing care, medication withdrawal, spasticity*

137

**Development of the family medicine medication use processes matrix**

Farrell B,<sup>1,2</sup> Pottie K,<sup>1,3</sup> Woodend K,<sup>3</sup> Haydt S,<sup>1</sup> Kennie, N<sup>4</sup> Dolovich L,<sup>5</sup> Martin C, Sellors C<sup>5</sup> on behalf of the IMPACT investigators

<sup>1</sup>Elizabeth Bruyere Research Institute—C.T. Lamont Centre, <sup>2</sup>SCO Health Service, <sup>3</sup>University of Ottawa, <sup>4</sup>St. Michael's Hospital, University of Toronto, <sup>5</sup>McMaster University, Hamilton, Canada

*Corresponding Author:* [bfarrell@scohs.on.ca](mailto:bfarrell@scohs.on.ca)

**Background:** Successful integration of pharmacists into family medicine practice requires the development of a shared understanding of team members' expertise and roles.

**Objectives:** To design and validate a tool to assist health professionals in assessing how they view their own and other's roles in carrying out family practice medication related processes.

**Methods:** Pharmacist and physician investigators developed a list of medication related processes occurring in primary care and team members who may play a role in each process. Research team members assessed the clinical appropriateness of the resulting matrix using a sensibility questionnaire and provided feedback in a consensus team meeting. Practising pharmacists and physicians reviewed a revised version and completed the sensibility questionnaire. Data from the completed matrices were analyzed and mean scores calculated for each task and associated occupation. Practising physicians and pharmacists completed a third version of the matrix and provided feedback. Investigators participated in a simulated exercise to generate a principle components factor analysis to group tasks in order to simplify scoring and interpretation.

**Results:** Eight research team members completed the matrix and sensibility questionnaire, agreeing the matrix was feasible to complete in 10-20 minutes. Several main changes were made: scale descriptors changed to reflect 'contribution' rather than 'responsibility', items reworded for clarity and missing items added. Seven pharmacists and physicians assessed the second version (6 sensibility questionnaires completed) and four assessed the third version. Minor changes were made. The final matrix is composed of 22 rows of medication processes that occur in family practice with 5 columns of team members who may contribute. Results of sensibility questionnaire assessments and the ongoing factor analysis will be presented.

**Conclusions:** Explicit description of medication related processes in primary care can delineate the pharmacist's and other's contribution and encourage discussion of improvements in these processes.

**Key Words:** *Pharmacists (or pharmacy), family medicine, medication, primary care, questionnaire validation*

138

**What interventions should pharmacist employ to impact physician-prescribing practices?**

Grindrod K, Patel P, Martin J

London Health Sciences Centre, London, Canada

*Corresponding Author:* [Kellygrindrod@yahoo.com](mailto:Kellygrindrod@yahoo.com)

**Background:** Multiple gaps exist between evidence and clinical practice. Many interventions have been developed to reduce these gaps. It is incumbent upon pharmacists to understand which interventions work in order to focus their efforts for impacting change.

**Objectives:** To determine which interventions work to influence physician-prescribing practices. Secondly, to explore differences in: a) effectiveness of multifaceted versus single interventions, b) effectiveness of interventions in the community versus the institutional setting, c) sustainability of various interventions, d) cost-effectiveness of alternative strategies, and e) impact on patient outcomes.

**Methods:** A systematic search for English systematic reviews was performed in MEDLINE, CINAHL, EMBASE and the Cochrane Library from the date of inception to May 2004 using search terms in accordance with Cochrane recommendations. Included reviews were required to clearly report a search strategy, inclusion and exclusion criteria, literature assessment criteria, methods for synthesizing information, and references. Two reviewers independently identified abstracts and studies for inclusion, assessed study quality, and extracted relevant information. Interventions were defined as consistently effective, inconsistently effective, and ineffective.

**Results:** Thirty-two of 4225 titles reviewed met the inclusion criteria and were included in our systematic review. Quality scores ranged from 70% to 100%. Consistently effective interventions included reminders (manual and computerized), audit and feedback, educational outreach visits, and patient mediated interventions. Inconsistently effective interventions included passive dissemination of information and didactic lectures. Simple multi-faceted interventions were consistently shown to be more efficacious than single interventions. Most interventions were delivered in the community setting, and no comparison of relative impact across different settings was possible. Similarly, a paucity of data informed the sustainability, cost-effectiveness, and impact on patient outcomes. Limited data precluded exploration of the effects of interventions in different settings, sustainability of effect, cost-effectiveness, and patient outcomes.

**Conclusions:** Interventions that effectively impact prescribing practice include: audit and feedback, reminders, educational outreach visits, and patient mediated interventions. Pharmacists should focus on these interventions, rather than on didactic sessions and passive dissemination of information. The low quantity of relevant and valid studies in this field suggest that more resources should be devoted to research in this area.

**Key Words:** *Systematic review, prescribing practice, pharmacists, audit and feedback, knowledge translation*

139

**Ciprofloxacin: the impact of a pharmacist-managed dosage form conversion service at a major Canadian teaching hospital**

Ho BP, Lau TTY, Balen RM, Naumann TL, Jewesson PJ  
Pharmaceutical Sciences Clinical Services Unit,  
Vancouver General Hospital, Vancouver Coastal  
Health Authority, Vancouver, BC, and Faculty of  
Pharmaceutical Sciences, University of British  
Columbia, Vancouver, Canada

*Corresponding Author:* [pjj@interchange.ubc.ca](mailto:pjj@interchange.ubc.ca)

**Background:** Despite cost containment efforts, parenteral (IV) ciprofloxacin appears to be overutilized at Vancouver Hospital. In November 2003, the Pharmacist-managed IV-PO Dosage Form Conversion Service was implemented, enabling autonomous pharmacist-initiated dosage form conversion for ciprofloxacin.

**Objectives:** To evaluate the characteristics of ciprofloxacin use prior to and following implementation of a Pharmacist-managed IV-PO Dosage Form Conversion Service.

**Methods:** This was a single-centre, pre/post, unblinded study. Phase I occurred between November 12, 2002 and November 11, 2003 (365 days), and Phase II between November 12, 2003 and March 11, 2004 (120 days). All patients who received ciprofloxacin IV were included. The primary endpoint was IV:PO ciprofloxacin use ratio. The secondary endpoints were total number of ciprofloxacin doses, number of inappropriate IV ciprofloxacin doses, duration of hospital stay, and cost of therapy between phases.

**Results:** Two hundred ciprofloxacin IV treatment courses were included (100/phase). The IV:PO ciprofloxacin use ratio was 3.03 (Phase I) vs. 3.48 (Phase II). Total number of doses and ratio of IV to total doses across phases were similar ( $p=0.2830$ ). There was a significant decrease in the inappropriate ciprofloxacin IV doses between Phases I and II (244/521 (47%) vs. 201/554 (36%) ( $p=0.0005$ ), respectively). Furthermore, there was a reduction in the number of pharmacist-preventable ciprofloxacin IV doses in Phase I and Phase II (114/244 (47%) vs. 65/201 (32%) ( $p=0.0026$ ). The extrapolated cost avoidance of inappropriate IV use was \$7,172 (43%) (Phase I) and \$6,012 (34%) (Phase II) ( $p=0.001$ ). The cost savings from inappropriate pharmacist-preventable doses were reduced from \$3,367 (20%) to \$1,975 (11%) ( $p=0.001$ ).

**Conclusions:** While utilization of ciprofloxacin remained unchanged and the proportion of IV to total doses is stable, the incidence of inappropriate IV doses and its associated costs appear to have declined subsequent to implementation of a Pharmacist-managed IV-PO Dosage Form Conversion Service.

**Key Words:** *Ciprofloxacin, iV-PO stepdown, pharmacist-managed, hospital, cost-savings*

140

**Implementation of a personal digital assistant-based drug-related problem documentation tool for pharmacy practice in a multi-site healthcare organization setting**

Balen RM, Raybardhan S, Loewen P, Partovi N, Liu G, Jewesson PJ

Pharmaceutical Sciences Clinical Services Unit,  
Vancouver General Hospital, Vancouver Coastal  
Health Authority, Vancouver, BC, and Faculty of  
Pharmaceutical Sciences, University of British  
Columbia, Vancouver, BC

*Corresponding Author:* [pjj@interchange.ubc.ca](mailto:pjj@interchange.ubc.ca)

**Background:** Documentation of patient care interventions is an essential component of the pharmaceutical care process. Personal digital assistants (PDAs) can facilitate this documentation process.

**Objectives:** To develop, implement and evaluate the utility of a scaleable, multi-user PDA-based documentation tool designed to facilitate the documentation of pharmacist-identified drug-related problems (DRP) in a multi-site, acute care hospital environment.

**Methods:** A PDA-based documentation tool was developed using Pendragon® Forms database development software. Pharmacists were trained and PDA synchronization stations were configured to transmit encrypted data to a central server. Analysis of data was undertaken using commercially available software. User opinion survey data was solicited to assess utility.

**Results:** Twenty-eight PDAs containing a 15-field database were deployed to 39 pharmacists in 31 service areas across 3 hospital sites. Over a 2-month period, 5,084 DRPs were documented with 90% considered resolved at data entry. The most frequent DRP types were 'need to add drug' (31%) and 'unnecessary drug' (15%). Most pharmacists found the tool easy to use, integrated well with workflow, and spent less than 30 minutes/day documenting DRPs.

**Conclusions:** A PDA-based documentation tool to collect DRP data was successfully implemented across a multi-site health-care organization. Initial experience with this process suggests that PDAs can be used for efficient collection analysis of pharmacist intervention documentation.

**Key Words:** *Personal data assistant (PDA), drug-related problem (DRP), documentation, database, hospital*

141

**Doubling calcium and phosphate concentrations in neonatal parenteral nutrition solutions using monobasic potassium phosphate**

Wong JC, McDougal AR, Tofan M, Aulakh A, Pineault M, Chessex P

Department of Pharmacy, Children's and Women's Health Centre of BC, Vancouver, Canada

*Corresponding Author:* [amcdougal@cw.bc.ca](mailto:amcdougal@cw.bc.ca)**Background:** Premature infants require high intakes of Ca and P to mimic fetal accretion rates. With the current phosphate salt used, adequate amounts cannot be provided due to the precipitation of Ca and P in TPN solutions.**Objectives:** To compare monobasic potassium phosphate (monobasic regimen) and monobasic plus dibasic potassium phosphate (dibasic regimen) on calcium phosphate solubility in 5 amino acid products, and to determine whether solubility differences observed in these products can be explained by buffering capacity.**Methods:** TPN solutions were prepared according to standard clinical practice. The following amino acid products were used at 3% concentrations: Primene, Vamin N, TrophAmine, Aminosyn-PF, and Travasol. Dextrose 10%, standard electrolytes, heparin, vitamins and trace elements were added. Calcium (as gluconate) and phosphate (as monobasic or dibasic regimen) were added in one-to-one molar ratios from 0 – 45 mmol/L. Solutions were inspected macroscopically and microscopically for precipitation under three conditions: immediately, 24 h after preparation at room temperature, and 3 h later in a 37°C water bath. Buffering capacity was determined for each amino acid product by titrating with standardized 0.1 M NaOH.**Results:** No macroscopic or microscopic precipitation was detected up to 45 mmol/L using monobasic regimen, compared to 20 mmol/L using dibasic regimen. Buffering capacity did not account for the solubility differences observed between the five amino acid products, which were related to the pH of the final solution.**Conclusions:** These data will allow clinicians to double the current concentrations of calcium and phosphate in neonatal TPN solutions using monobasic regimen. Although this is particularly relevant to situations when fluid intake is restricted, the effect of the acid load needs to be investigated in extremely low birth weight infants.**Key Words:** Neonatal, potassium phosphate, TPN solution, calcium, fetal accretion rates

142

**Pharmacokinetics of mycophenolate and its glucuronidated metabolites in stable lung transplant recipients**Ting LSL, Partovi N, Riggs KW, Levy RD, Ensom MHH  
University of British Columbia Faculty of Pharmaceutical Sciences, Children's & Women's Health Centre of British Columbia Department of Pharmacy, Vancouver, Canada*Corresponding Author:* [ensom@interchange.ubc.ca](mailto:ensom@interchange.ubc.ca)**Background:** Mycophenolate mofetil (MMF) is commonly used in solid organ transplantation. Mycophenolic acid (MPA) is the active metabolite of MMF, and is metabolized by the UDP-glucuronosyltransferase enzymes via glucuronidation. The two main metabolites of MPA are mycophenolic acid glucuronide (MPAG) and mycophenolic acid acyl glucuronide (AcMPAG). Little information is available regarding the pharmacokinetics of MPA and its glucuronidated metabolites in stable lung transplant recipients.**Objectives:** The objective of this study is to characterize the pharmacokinetics of mycophenolic acid (MPA) and its glucuronidated metabolites, MPAG (phenolic-glucuronide) and AcMPAG (acyl-glucuronide), in stable lung transplant recipients.**Methods:** Eight patients were entered into this open-label study, following written informed consent. Upon administration of a steady-state morning MMF dose, blood samples were collected at 0,0.3,0.6,1,1.5,2,4,6,8,10, and 12 hours post-dose. Total MPA, MPAG, and AcMPAG concentrations were measured by a validated HPLC method with ultraviolet detection and pharmacokinetic parameters analyzed by non-compartmental modeling using WinNonlin 4.1.**Results:** Patient characteristics included: 3 males and 5 females, on average 5.2 years post-transplant (range:2.1-9.2yr), mean( $\pm$ SD) age of 46.9 $\pm$ 14.0yr and weight 69.8 $\pm$ 22.2kg. Mean albumin concentration was 3.7 $\pm$ 0.6g/dL and serum creatinine was 1.3 $\pm$ 0.5mg%. All patients also were on prednisone, with 6 on tacrolimus and 2 on cyclosporine. MMF dosage ranged from 1.5 to 3 grams daily (34.2 $\pm$ 10.5 mg/kg/day; range:18.3-54.0 mg/kg/day). Mean ( $\pm$ SD) for MPA were: area-under-the-curve [AUC(0-12h)] 42.33 $\pm$ 19.49  $\mu$ g\*hr/mL; dose-normalized AUC(0-12h) 39.63 $\pm$ 20.99 $\mu$ g\*hr/mL; maximal concentration (C<sub>max</sub>) 7.80 $\pm$ 3.32 $\mu$ g/mL; time to C<sub>max</sub> (T<sub>max</sub>) 2.25 $\pm$ 3.15h; and minimum concentration (C<sub>min</sub>) 1.10 $\pm$ 0.64 $\mu$ g/mL. AUC ratios of MPAG: MPA and AcMPAG: MPA were 18.68 $\pm$ 6.60 and 0.17 $\pm$ 0.11, respectively.**Conclusions:** This is the first study to determine the pharmacokinetics of MPA and its glucuronidated metabolites in the lung transplant population. Further studies should focus on determining if genetic variability in UDP-glucuronosyltransferase enzymes can explain the observed wide interpatient variability and on identifying MMF dosing strategies that optimize immunosuppressive efficacy and minimize toxicity.**Key Words:** Pharmacokinetics, lung transplantation, mycophenolate, glucuronidation, metabolism



143

### Clinically significant inter-patient variability in Lopinavir pharmacokinetics in HIV-infected patients on salvage therapies

Ting LSL, Alexander CS, Harrigan PR, Montaner J, Ensom MHH

University of British Columbia Faculty of Pharmaceutical Sciences, Children's & Women's Health Centre of British Columbia Department of Pharmacy, Vancouver, Canada

Corresponding Author: [ensom@interchange.ubc.ca](mailto:ensom@interchange.ubc.ca)

**Background:** Lopinavir (LPV) is an antiretroviral agent commonly used in salvage therapies for HIV-infection. Therapeutic drug monitoring (TDM) of LPV has been advocated to ensure adequate drug exposure for optimal clinical outcomes. However, interpretation of TDM results for patients on salvage therapies is often challenging due to inter-patient variability and a lack of pharmacokinetic (PK) information on LPV in this patient subgroup.

**Objectives:** This retrospective study aims to characterize pharmacokinetic parameters of lopinavir (LPV) in HIV-infected individuals.

**Methods:** Study patients were on steady-state twice-daily Kaletra® (LPV+ritonavir; 400/100 mg or 533/133 mg) plus  $\geq 2$  other antiretrovirals. Plasma samples were collected at pre-dose and at 1, 2, 4, 6, 8, 10 and 12 h post-dose. Lopinavir concentrations were determined by a validated HPLC-MS/MS assay. Eighty-eight lopinavir pharmacokinetic profiles (with at least 6 concentrations each), from 73 patients who were mostly on salvage antiretroviral therapy, were analyzed by non-compartmental modeling using WinNonlin 4.1. Sixty-two patients were taking at least one interacting antiretroviral. Apparent oral clearance (Cl<sub>ss</sub>/F), apparent volume of distribution (V<sub>ss</sub>/F), mean residence time (MRT), elimination rate constant ( $\lambda$ ) and absorption rate constant (K<sub>a</sub>) were calculated. Patients were stratified by Kaletra® dosage due to potential alteration in pharmacokinetic parameters caused by different doses of ritonavir (a potent CYP450 inhibitor; LPV-boosting agent).

**Results:** The Cl<sub>ss</sub>/F (L/h), V<sub>ss</sub>/F (L), MRT (h),  $\lambda$  (1/h) and K<sub>a</sub> (1/h) for LPV 400mg dose were: [mean(%CV)] 8.51(95.31%), 61.52(60.60%), 13.29(72.89%), 0.172(73.70%) and 0.378(43.95%). Similarly, the corresponding results for LPV 533mg dose were: 9.82(92.90%), 85.04(67.52%), 13.40(50.33%), 0.146(73.30%) and 0.467(78.85%).

**Conclusions:** Wide inter-patient variability exists in lopinavir pharmacokinetic parameters of patients on salvage antiretroviral therapy. Therapeutic drug monitoring is recommended and studies of TDM strategies are underway to ensure optimal clinical outcome.

**Key Words:** Lopinavir, anti-retrovirals, pharmacokinetics, AIDS, HIV

144

### A pharmacist-run, collaborative awareness campaign to assess and educate patients in low-income countries about cardiovascular disease risk

Zolezzi M,<sup>1</sup> Obregon R<sup>2</sup>

<sup>1</sup>Lecturer, School of Pharmacy, The University of Auckland. Auckland, New Zealand, President,

<sup>2</sup>College of Pharmaceutical Chemists of Arequipa, Peru

Corresponding Author: [m.zolezzi@auckland.ac.nz](mailto:m.zolezzi@auckland.ac.nz)

**Background:** Cardiovascular disease (CVD) is a leading cause of global morbidity and mortality. The majority of individuals who develop heart attacks and strokes every year have one or more cardiovascular risk factors. Most of these cardiovascular (CV) events are preventable if meaningful action is taken against these risk factors. A significant contribution to this global burden derives from developing countries. The accessibility of pharmacists as health care professionals place them in a very suitable position to promote healthy life styles, reduce CVD risk factors and improve CV care through low-cost and easily accessible community based programs.

**Objectives:** 1) To provide increased opportunities to patients in low-income countries for CVD risk evaluation while gaining a global perspective in CVD risk assessment. 2) To collaborate with pharmacists in developing countries in their efforts to establish pharmacy-based CVD risk assessment programs in their countries.

**Methods:** A modified competency course on CVD risk assessment and management developed at the School of Pharmacy, The University of Auckland, was translated into Spanish and used to train pharmacists in CVD risk management. Pharmacists who completed the training program participated in a CVD risk awareness campaign for patients in Arequipa, Peru. A survey to participating pharmacists was conducted at the end of the campaign to gain understanding of their perceptions on the value of the training program and of the awareness campaign.

**Results:** Ten pharmacists completed the training program and participated in the two-day CV risk awareness campaign. A total of eighty patients were screened during the campaign. Descriptive statistics of the data collected on the participating patients provided useful information on levels of risk and contributing risk factors for the population studied.

**Conclusions:** Collaborative awareness campaigns to assess and educate at risk patients in low-income countries may contribute in reducing the worldwide burden of cardiovascular disease.

**Key Words:** Cardiovascular disease, risk factors, pharmacists, awareness, developing countries

**CLINICAL PHARMACY FORUM**

145

**Evaluation model for the integrating family medicine and pharmacy to advance primary care therapeutics (IMPACT) project**Dolovich L,<sup>1,2,3</sup> Sellors C,<sup>1,2</sup> Woodward C,<sup>2</sup> Farrell B,<sup>4</sup> Kaczorowski J,<sup>1,2</sup> Gaebel K,<sup>1</sup> Pottie K<sup>4</sup><sup>1</sup>Centre for Evaluation of Medicines and <sup>2</sup>McMaster University, <sup>3</sup>Faculty of Pharmacy University of Toronto, <sup>4</sup>Elizabeth Bruyère Research Institute, University of Ottawa, Canada*Corresponding Author:* [ldolovic@mcmaster.ca](mailto:ldolovic@mcmaster.ca)**Background:** A program logic model (PLM) is a systematic, visual way to present a planned program with its underlying assumptions and theoretical framework. IMPACT is a multi-faceted multi-site demonstration project that involves 7 pharmacists working with 7 family health networks in Ontario.**Objectives:** To develop an evaluation tool that captures the important aspects of the intervention and its intended effects, and that facilitates effective evaluation planning and good communication within the large multi-institution project team, Advisory Committee and external stakeholders.**Methods:** The research team from three academic centres planned the integrated pharmacist intervention including specification of pharmacist and practice site supports before, during and after the intervention. Research questions were generated and appropriate research methods were proposed. Three investigators drafted the initial PLM based on the intervention, research questions and methods proposed. The PLM was discussed by larger team, project Advisory Committee and external stakeholders to further clarify the IMPACT Program Theory and Implementation Theory.**Results:** The research team sought conceptual clarity to spell out expectations of the integrated pharmacist and family practice site members. The main PLM components identified were: transitional training and mentorship program, individual patient assessments, practice level innovations, integration, physician engagement, drug information support, economics, and oversight / buy-in from stakeholders. Three major tasks of the pharmacist were specified: patient identification and referral, assessment, recommendations to physician and monitoring. The activities involved were translated into implementation objectives. The outputs that each activity would create were specified. The model indicated how activities would lead to expected short and long term outcomes if the intervention was successful.**Conclusions:** Logic models are useful tools for designing evaluations of programs. The IMPACT PLM will ensure that strategies are available to measure the contribution of each program component so that a better understanding of how to interpret overall effectiveness of the program can be achieved.**Key Words:** *Pharmacist, physician, integration, primary care, logic model*

146

**An assessment of drug classification and funding source for clinical drug trials published over 20 years**

Buchkowsky SS, Jewesson PJ

Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada

*Corresponding Author:* [pjj@interchange.ubc.ca](mailto:pjj@interchange.ubc.ca)**Background:** The pharmaceutical industry has become a major source of funding for biomedical research and this prompted an examination of the relationships between sponsors and published clinical trials. In Phase I of this study, we investigated reported clinical drug trial funding sources, author–industry affiliations; and clinical outcome trends over time. We found that industry was responsible for a significant and increasing proportion of trial sponsorship during a 20-year period. Reported author affiliation with industry increased to 66% of clinical trials sponsored by industry in the five journals reviewed. In Phase II of this study, we decided to expand our investigations to include other characteristics of published trials over the same study period.**Objectives:** To characterize published clinical trials according to drug classification investigated and funding over time.**Methods:** We assessed 500 randomly selected clinical drug trial publications (5 per journal-year) extracted from five influential journals (AIM, BMI, JAMA, Lancet, NEJM) for a 20-year publication period (1981–2000). Only published studies involving prospective, comparative, clinical drug trials were included. A “drug” was defined as any chemical used for the prevention, treatment, or cure of disease. The “study sponsor” was defined as an organization declared as being responsible for funding to support the study. Clinical trials were classified according to funding source using a previously published scheme. For each trial, we documented journal, publication date, AHFS pharmacological-therapeutic classifications (first level), funding source and other variables.**Results:** Twenty drug classes were represented in the 500 publications extracted from the 20-year study period. A combination of two or more drug classes was studied in 48 (10%) of the trials investigated. Five drug classes were the focus of clinical investigation for 333 (67%) of the published trials, and this trend was stable across the five 4-year intervals. These were anti-infectives (96 (19%)), cardiovascular drugs (79 (16%)), hormones and synthetic substitutes (53 (13%)), central nervous system agents (53 (13%)) and blood formation/coagulation products (52 (11%)). One hundred and eight-one (36%) of all published trials were funded by industry (alone or in combination with a non-profit sponsor), 180 (36%) were independently sponsored by a non-profit sponsor, while the balance had no declared source of study funding. For the top 5 drug classes, there was an overall difference in funding source by class ( $p=0.004$ ). In particular, industry funded more published anti-infective trials (42 (32%)) than trials involving any of the four remaining drug classes ( $p=0.009$ ).**Conclusions:** This study has given us further insight into drug class and funding characteristics for clinical drug trials over a two-decade period. While many drug classes were under investigation, anti-infectives were the most common focus of published clinical drug trials. Industry funded more anti-infective drug trials than any other drug class identified.**Key Words:** *Clinical drug trials, funding, industry, anti-infectives*

147

**Medication safety huddles – teaming up to improve patient safety**Wilbur K,<sup>1,2</sup> Scarborough K<sup>1</sup><sup>1</sup>Vancouver General Hospital, Vancouver, Canada<sup>2</sup>Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada*Corresponding Author:* [kwilbur@interchange.ubc.ca](mailto:kwilbur@interchange.ubc.ca)

**Background:** Drug-related morbidity and mortality is significant and a focus of efforts to enhance patient safety. Medication errors are considered preventable events that may cause or lead to inappropriate medication use or patient harm. Activities that foster a 'culture of safety' are acknowledged as fundamental in enhancing patient safety in any organization.

**Objectives:** We describe our experience initiating medication safety huddles on an acute adult medicine unit.

**Methods:** Medication safety huddles are short, spontaneous gatherings where nurses and pharmacists regularly share information about actual or potential medication safety problems and concerns. Brainstorming takes place and identified interventions are implemented in a timely fashion. These safety briefings endeavour to identify and address factors contributing to medication errors and promote a collaborative culture among participants. Ultimately, the goal is to reduce medication error and improve quality of patient care.

**Results:** Important safety issues not captured in medication incident documentation processes were identified during medication safety huddle discussions. Nursing input played a critical role in elucidating factors contributing to medication error and near misses that may not have been previously considered. Pharmacists have found participation professionally satisfying, as they share medication knowledge and advocate safe medication use during these briefings.

**Conclusions:** Medication safety huddles are an opportunity for pharmacists to exhibit leadership in enhancing patient safety in the hospital setting. These safety briefings form an element of a broader safety initiative launched by our organization and plans are in place to introduce medication safety huddles to other patient units and hospitals within Vancouver Coastal Health authority.

**Key Words:** *Patient safety, medication error, nursing, pharmacist, collaboration*

**ENCORE PRESENTATIONS**

148

**An assessment of published pediatric dosage guidelines for Enoxaparin: a retrospective review**Ho SH, Wu JK, Hamilton DP, Dix DB, Wadsworth LD  
Children's & Women's Health Centre of BC, Pharmacy Department, Vancouver, Canada*Corresponding Author:* [sho@cw.bc.ca](mailto:sho@cw.bc.ca)

149

**Implementation of a self-administered questionnaire to identify patients at risk for medication-related problems in a family medicine clinic**Langford BJ, Jorgenson D, Kwan D, Papoushek C  
Department of Pharmacy, Toronto Western Hospital, University Health Network, Toronto, Canada*Corresponding Author:* [debbie.kwan@uhn.on.ca](mailto:debbie.kwan@uhn.on.ca)

150

**Impact of antiretroviral therapy on quality of life**Park-Wyllie LY,<sup>1</sup> Antoniou T,<sup>2</sup> Strike CJ,<sup>3</sup> Bayoumi AM<sup>1</sup><sup>1</sup>St. Michael's Hospital, Centre for Research on Inner City Health, <sup>2</sup>St. Michael's Hospital, Inner City Health, <sup>3</sup>Centre for Addiction and Mental Health, Health Systems Research and Consulting Unit, Toronto, Canada*Corresponding Author:* [parkwylliel@smh.toronto.on.ca](mailto:parkwylliel@smh.toronto.on.ca)

151

**Adherence to sulfonylureas may increase risk of mortality**Simpson SH<sup>1,2</sup> Eurich DT,<sup>1,3</sup> Majumdar SR,<sup>1,3,4</sup> Johnson JA<sup>1,3</sup><sup>1</sup>Institute of Health Economics, <sup>2</sup>Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, <sup>3</sup>Department of Public Health Sciences, Faculty of Medicine & Dentistry, University of Alberta, <sup>4</sup>Department of Medicine, Faculty of Medicine & Dentistry, University of Alberta, Alberta, Canada*Corresponding Author:* [ssimpson@pharmacy.ualberta.ca](mailto:ssimpson@pharmacy.ualberta.ca)

152

**Beta blocker prophylaxis for patients with variceal hemorrhage**Wilbur K,<sup>1,2</sup> Sidhu K<sup>1,2</sup><sup>1</sup>Vancouver General Hospital, Vancouver, Canada, <sup>2</sup>Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada*Corresponding Author:* [kwilbur@interchange.ubc.ca](mailto:kwilbur@interchange.ubc.ca)

153

### Examining the appropriateness of HK-2 cells as an in vitro model for ifosfamide-induced nephrotoxicity—Are they more appropriate than LLCPK-1 cells?

Aleksa K, Ito S, Koren G

Hospital for Sick Children, Toronto, University of Toronto, Canada

Corresponding Author: [katarina.aleksa@sickkids.ca](mailto:katarina.aleksa@sickkids.ca)

**Background:** The choice of an appropriate in vitro cell model is important when attempting to validate the ability of a drug to cause toxicity. Although a drug can be metabolized to the same metabolite in different species, the enzymes involved may differ as may the detoxification pathways. One such example is ifosfamide.

**Objectives:** To determine if the HK-2 cells would be a suitable tubular cell model for IF-induced nephrotoxicity.

**Methods:** This chemotherapeutic is oxidized by the cytochrome P450 (CYP) enzymes, specifically CYP 3A and 2B. Recent work from our laboratory has shown that localized renal metabolism of ifosfamide results in the production of the nephrotoxic chloroacetaldehyde. The conventional in vitro cell model used to examine ifosfamide-induced nephrotoxicity are the LLCPK-1 cells. These cells are derived from porcine renal proximal tubule cells, and although they do possess the necessary CYPs and are capable of metabolizing ifosfamide a human derived renal cell line would be more appropriate. Presently, there is no human cell model for ifosfamide-induced nephrotoxicity.

**Results:** Preliminary data show that these cells possess CYP 3A5 and are capable of stereoselective metabolism of ifosfamide to its 2-dechloroethylifosfamide (2-DCEIF) and 3-dechloroethylifosfamide (3-DCEIF) metabolites, by products of chloroacetaldehyde formation.

**Conclusions:** The presence of the relevant CYP enzymes in human renal tubular cells along with their ability to metabolize ifosfamide to its 2- and 3-DCEIF metabolites strengthens the hypothesis that nephrotoxic damage in humans may result from the localized production of chloroacetaldehyde.

**Key Words:** *Ifosfamide, HK-2 cells, renal, CYP3A, CYP2B*

154

### Oseltamivir pharmacokinetics in renal transplant patients

Aoki FY, Lam H, Jeffery JR, Dutkowski R, Sitar DS  
Sections of Clinical Pharmacology & Nephrology, Departments of Medicine and Pharmacology & Therapeutics, University of Manitoba, Winnipeg Canada, and Hoffmann-La Roche Ltd., Nutley, New Jersey, United States;

Corresponding Author: [nelsonak@ms.umanitoba.ca](mailto:nelsonak@ms.umanitoba.ca)

**Background:** Oseltamivir (OS) is a new drug to prevent and treat influenza A and B infection that is metabolized to the antiviral molecule, OS-carboxylate (OS-c).

**Methods:** We studied OS and OS-c comparative pharmacokinetics (PK) after a 75 mg dose of OS-phosphate in 19 stable transplant patients receiving cyclosporine (CyA), azathioprine and prednisone (Pr) (12 pts [group A]) or CyA, mycophenolate mofetil (MMF) and Pr (7 pts [group B]).

**Results:** In groups A and B, respectively: 6/12 and 6/7 were men, ages (mean + SD) were 47 + 10 and 47 + 15 yr, weights were 79.5 + 10.7 and 88.3 + 28.4 kg, and Cl<sub>cr</sub> were 69 + 27 and 75 + 30 ml/min. Time to C<sub>max</sub> was 1.6 + 1.0 vs 1.2 + 0.3 h (OS) and 4.4 + 0.9 vs 5.1 + 1.1 h (OS-c). C<sub>max</sub> was 94.5 + 53.6 vs 68.0 + 39.5 ng/ml (OS) and 579 + 177 vs 532 + 329 ng/ml (OS-c). AUC<sub>0-∞</sub> was 172 + 63 vs 131 + 42 ng/ml.h (OS) and 8041 + 3016 vs 7976 + 4869 ng/ml.h (OS-c). T<sub>1/2λ</sub> was 1.0 + 0.4 vs 1.1 + 0.4 h (OS), and 7.1 + 1.7 vs 8.2 + 2.4 h (OS-c). Renal clearance was 186 + 104 vs 162 + 149 ml/min (OS), and 136 + 47 vs 137 + 83 ml/min (OS-c). These PK characteristics of OS and OS-c appear to be not different from published data in non-transplant individuals with comparable creatinine clearance. Creatinine clearance was not affected by OS.

**Conclusion:** OS and OS-c PK are not altered by concurrent CyA, MMF-HCl, Pr or azathioprine, and creatinine clearance was stable. An effect of OS on CyA and MMF PK is being evaluated. OS-phosphate doses likely can be the same in renal transplant as in non-transplant patients with similar kidney function.

**Key Words:** *Oseltamivir, pharmacokinetics, influenza, drug interaction, renal transplant*

155

### Characteristics of cases that fail the Accutane pregnancy prevention program (PPP) in Canada

Avner M, Koren G

The Motherisk Program, The Hospital for Sick Children, University of Toronto, and the Ivey Chair in Molecular Toxicology, The University of Western Ontario, Canada

Corresponding Author: [marina\\_av2003@yahoo.com](mailto:marina_av2003@yahoo.com)

**Background:** Isotretinoin (Accutane) has been identified as one of the most potent human teratogens, causing birth defects in more than 35% of babies exposed during pregnancy. The manufacturer, Hoffmann-La Roche was aware of significant fetal risk and voluntarily instituted the Pregnancy Prevention Program (PPP). Over the past several years, however, Teratology Information Services (TIS) noted an increase in the number of pregnant women exposed to isotretinoin who contacted their centers. As part of a CDC- funded North American follow-up program, organized by the Organization of Teratology Information Services (OTIS), we prospectively collected 15 cases of Canadian women who became pregnant while on Accutane from April 2002-August 2004.

**Objectives:** To identify causes of failure to prevent pregnancy while on Accutane

**Methods:** Three phone interviews following verbal informed consent. The information was collected during intake interview following interim (1 month later) and outcome interviews (after expected delivery date)

**Results:** We enrolled 15 women, age of 17-39 y.o. Only 28% of them had cystic or nodular acne, for which the drug is indicated. Only 24 % of women had two negative pregnancy tests before receiving a prescription. Only 8% of women used two forms of birth control simultaneously, starting one month before receiving a prescription, as instructed by the PPP. Only 36% of women received a pregnancy test each month before refilling their prescriptions. Only 26 % signed a consent form, and no one saw all the components of PPP, although all participants knew that Accutane was dangerous to the fetus. Pregnancy outcome: Out of 7 live births (1 had isotretinoin embryopathy and 6- no structural abnormalities). There were 4 therapeutic abortions, 1 miscarriage, and 3 are still pregnant.

**Conclusions:** Preventable exposures continue to occur due to non- compliance with current requirements of the PPP. These data suggest that stronger means must be implemented to prevent fetal exposure to isotretinoin. We suggest mandatory certification program for physician before they can prescribe isotretinoin. Mandatory registration of prescribing physicians, patients, and dispensing pharmacies should be also considered.

**Key Words:** *Isotretinoin, teratogens, pregnancy, telephone interview, fetal exposure*

156

### The reproductive effects of beta interferon therapy for multiple sclerosis

Boskovic R, Wade R, Wolpin J, Koren G

The Hospital for Sick Children, Toronto, Canada

Corresponding Author: [radinka.boskovic@sickkids.ca](mailto:radinka.boskovic@sickkids.ca)

**Background:** Beta interferon is an effective therapy for multiple sclerosis (MS). Studies in primate suggest increased rates of miscarriage by this therapeutic agent. The effect of human pregnancy is not known.

**Objectives:** To determine whether interferon therapy during human pregnancy increases reproductive risks in women with MS.

**Methods:** This prospective, observational, controlled study consists of three groups of women: an exposed group, a disease matched unexposed group, and a healthy comparative group. Subjects were selected from women contacting the Motherisk Program regarding maternal beta interferon exposure or MS during pregnancy, from 1997 and 2004. After delivery all of the women were re-contacted for a follow-up interview regarding maternal health, pregnancy outcome, and neonatal health.

**Results:** The study group (n=16, 23 pregnancies) were exposed to interferon beta at doses ranging from 22µg-144 µg/week. There was a decrease in mean birth weight in the exposed group ( 3231 ± 423 g ) as compare to controls (3504 ± 581, 3812 ± 425 g, p=0.003). Women exposed to beta interferon had a significantly higher rate of miscarriages and stillbirths (39.1%) as compared to disease matched (22.7%) or healthy controls (5%) (p=0.03), even after correction for potential confounders. There were 2 major malformations (abnormality in the X chromosome, Down's Syndrome) among exposed fetuses.

**Conclusions:** Beta interferon therapy in the first trimester of pregnancy appears to be associated with an increase risk for fetal loss. It appears prudent to discontinue it in pregnancy.

**Key Words:** *Beta, interferon, pregnancy, multiple sclerosis, reproductive risk*

157

**Formulation of long acting nifedipine tablets influences the heart rate and sympathetic nervous response in hypertensive patients**

Brown MJ, Watts M, Mackenzie IS, Toal CB  
Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK and Bayer Inc, Toronto, Ontario

*Corresponding Author:* [corey.toal.b@bayer.com](mailto:corey.toal.b@bayer.com)

**Background:** Nifedipine is available in a number of once daily formulations. Previous studies suggested that gradual release of drug blunts the baroreceptor response to vasodilatation. However, the osmotic control of nifedipine release from the GITS tablet is not used by other once-daily formulations, whose less gradual release of nifedipine we expected to cause greater increase in plasma norepinephrine (NE) and heart rate.

**Objectives:** To compare the effects of a once daily capsule formulation (Nifedicon-Coracten) with Nifedipine GITS (N-GITS) on plasma NE, BP, and Heart Rate (HR) in mild to moderate previously diagnosed essential hypertensive patients.

**Methods:** The study was a randomized three way crossover in 44 patients aged 18-75, with two treatment periods of 2-week duration. At days 0, 14, 15, 29 & 30, patients came to the clinic, where they were fed, dosed and monitored continuously for 6 hours.

**Results:** Peak nifedipine concentrations were at four and six hours, respectively, after the first dose of Nifedicon and N-GITS. Systolic BP decreased rapidly after the first dose of Nifedicon, achieving nadir at 5 hours post dose, accompanied by a rise in HR of  $1.2 \pm 8.8$  b/min. After N-GITS, by contrast, HR fell by  $2.4 \pm 7.7$  b/min ( $p=0.045$ ). At the time of peak drug concentration, plasma NE was higher in the Nifedicon ( $430 \pm 167$  pg/ml) than N-GITS treated patients ( $320 \pm 131$  pg/ml) and their change from baseline are significantly ( $p=0.0046$ ) different. A similar difference between the drugs was seen again at days 15 and 29, at 5 hours after switching formulations.

**Conclusions:** This study suggests that two different formulations of once daily nifedipine after food result in different BP and plasma NE responses, and that switching between formulations causes opposite effects upon the sympathetic nervous response to falling BP. These acute differences are unlikely to be apparent on single time-point clinic visits, but may lead to clinically important differences in risk for patients.

**Key Words:** *Nifedipine, norepinephrine, baroreceptor response, Nifedicon, hypertension*

158

**Traumatic brain injury and depression: assessing the role of the serotonin transporter promoter polymorphism**

Chan F, Lanctôt KL, Rapoport M, Herrmann N, McCullagh S

Sunnybrook & Women's College Health Sciences Centre, Department of Psychiatry, University of Toronto, Faculty of Medicine, Department of Pharmacology and Department of Psychiatry

*Corresponding Author:* [florance.chan@sw.ca](mailto:florance.chan@sw.ca)

**Background:** Depression is a leading cause of disability following traumatic brain injury (TBI). Among different proposed risk factors, little is known regarding the role of genetics in depression post TBI.

**Objective:** This study investigated whether the serotonin transporter promoter polymorphism (5-HTTLPR), which is characterized by either long (L) or short (S) alleles, is associated with the presence of depression in TBI, as well as with selective serotonin reuptake inhibitor (SSRI) treatment response.

**Methods:** Patients with mild to moderate TBI (American Congress of Rehabilitation Medicine criteria) were genotyped (S/S, S/L, or L/L) and assessed for Major Depressive Disorder (MDD) according to the DSM-IV criteria. Those with MDD were treated with open-label citalopram (20 mg/day p.o.). Drug response was measured after 6 weeks using the Hamilton Depression Scale (HAMD) by an investigator blinded to polymorphism status, and a  $\geq 50\%$  decrease in scores compared to baseline was the criterion for response.

**Results:** Of the patients recruited thus far ( $n=141$ , 96 males, mean age  $38 \pm 18$ ), 27 met criteria for MDD, and 19 were treated with citalopram. While 41% of the depressed patients carried the S/S genotype, only 24% of the controls were S/S ( $p=0.063$ ). Moreover, depressed patients with the S allele had higher baseline HAMD scores ( $23.0 \pm 6.3$ ) than L/L patients ( $16.1 \pm 8.2$ ) ( $p=0.025$ ). Five patients responded to treatment (S/S:2, S/L:2, L/L:1) and 14 did not (S/S:7, S/L:3, L/L:2) (S/S vs S/L, L/L,  $p=0.437$ ).

**Conclusions:** TBI patients with depression carrying the S allele of the 5-HTTLPR suffer from a greater severity of depression. The S allele may also confer a higher risk of MDD following TBI. These preliminary results suggest that genetic risk factors are important contributors to depression post-TBI, and upcoming results may also help identify patients who are more likely to benefit from SSRIs.

**Key Words:** *Traumatic brain injury (TBI), depression, serotonin transporter promoter polymorphism (5-HTTLPR), selective serotonin reuptake inhibitor (SSRI), predictors*

159

**Sulfamethoxazole hydroxylamine- induce in vitro toxicity**Chau K,<sup>2</sup> Tucker J,<sup>4</sup> Rieder M<sup>1,2,3,4</sup><sup>1</sup>Departments Paediatrics, <sup>2</sup>Physiology & Pharmacology, <sup>3</sup>Schulich School of Medicine, University of Western Ontario, <sup>4</sup>John P. Robarts Research Institute, London, Canada*Corresponding Author* [mkchau@uwo.ca](mailto:mkchau@uwo.ca)**Background:** ADRs are common and important adverse consequences of therapy that complicate the course of 5% of courses of therapy. Hypersensitivity ADRs are serious ADRs the mechanism of which is poorly understood. It has been demonstrated that reactive metabolites of Sulfamethoxazole (SMX) are important determinants of sulfonamide hypersensitivity. The mechanism(s) for this remain unclear.**Objectives:** To study the mechanism of cytotoxicity induced by SMX metabolites and to determine the role of apoptosis in reactive-metabolite mediated cell death.**Methods:** Jurkat E6.1 cells were incubated with increasing concentrations (0-800µM) of sulfamethoxazole hydroxylamine (SMX-HA) and 200µM parent compound sulfamethoxazole (SMX) over increasing incubation times (0-2 hours). After incubation, cell viability was determined using a tetrazolium-based assay (MTT). Annexin V, a phospholipid-binding protein, is an assay that we used to detect early signs of apoptosis. Annexin V has a high affinity to bind phosphatidylserine (PS) in the presence of physiological concentrations of Ca<sup>2+</sup> and the labeled annexin V was measured using FACS analysis. A non-permanent dye, 7-Amino Actinomycin D (7-AAD), is used concurrently with annexin V to assess the membrane integrity of cells.**Results:** An immediate concentration- and time- dependent toxicity was demonstrated at all time points, 47.8 ± 4.5% viability at 400 µM and 9.5 ± 3.5% viability at 800 µM SMX- HA at 2 hrs (p<0.01). Additionally, Jurkat cells treated with SMX-HA show a time- and concentration-dependent increase in the percentage of cells staining positive for annexin V and 7AAD.**Conclusions:** The demonstration of concentration-dependent toxicity is consistent with the potential role of reactive drug metabolites in hypersensitivity ADRs. This suggests that caution is needed when studying the effect(s) of reactive drug metabolites on organelle function. The molecular determinant(s) of this effect are under study in our laboratory.**Key Words:** *Sulfamethoxazole hydroxylamine, pediatric, Annexin V, Jurkat, adverse drug reaction*

160

**The effect of supplementation of antioxidants on LLC-PK1 cells exhibiting ifosfamide-induced nephrotoxicity**

Chen N, Aleksa K, Rieder M, Koren G

Ivey Chair in Molecular Toxicology and Department of Pharmacology &amp; Physiology, University of Western Ontario, Division of Clinical Pharmacology/Toxicology, Hospital for Sick Children, Toronto, Canada

*Corresponding Author:* [nchen4@uwo.ca](mailto:nchen4@uwo.ca)**Background:** Ifosfamide (IF) is a chemotherapeutic drug that is commonly used as first-line treatment in a variety of pediatric solid tumours. Although routine concurrent administration of MESNA has greatly diminished urotoxicity caused by its toxic metabolite, acrolein. IF nephrotoxicity remains to be a potential adverse effect that occurs in approximately 30-60% of pediatric patients. As a result, pediatric patients may survive the debilitating cancer but have to endure the rest of their lives with dysfunctional kidneys. The mechanism of increased toxicity of ifosfamide in young children is not known. Studies have indicated that lower level of glutathione (GSH) may predispose the kidney to damage by the locally produced IF metabolite chloroacetaldehyde.**Objectives:** The overall objective for this study is to reverse ifosfamide-induced nephrotoxicity through the administering of various antioxidants (e.g. N-acetylcysteine, dimesna and melatonin).**Methods:** The experimental model is LLC-PK1, a porcine renal tubular proximal cell line, which demonstrates many similarities of physiological characteristics as those of humans. To monitor cellular viability, alamarBlue reduction assay is used. LLC-PK1 cells were treated with 250µM buthionine sufoximine (BSO) alone to deplete intracellular glutathione prior to the addition of 100µM IF and 250µM BSO. GSH levels are monitored in parallel. Cellular cytotoxicity was assessed at 24, 48, 72 and 96 hours.**Results:** Preliminary results showed no significant decrease in cellular viability when LLC-PK1 cells were initially treated with 250µM BSO for 24 hours, then with 250µM BSO and IF for 24 hours. In contrast, there was a significant decrease of cellular viability when cells were treated daily for 96 hours with 100µM IF plus 250µM BSO. Under these conditions, the LLC-PK1 cells metabolize IF to the nephrotoxic chloroacetaldehyde.**Conclusions:** IF nephrotoxicity demands the combination of metabolism to chloroacetaldehyde plus reduced glutathione. Since glutathione or other sulfhydryl antioxidants have the ability to prevent oxidative stress-induced cell death, by supplementing with these compounds, the degree of cellular cytotoxicity may be reduced or prevented.**Key Words:** *Ifosfamide, pediatric, chloroacetaldehyde, nephrotoxicity, LLC-PK1 cells*

161

**Pressure-distention in comparison to pharmacological relaxation in vein grafting upregulates matrix metalloproteinases and smooth muscle proliferation**

Chung A,<sup>1</sup> Okon E,<sup>1</sup> Rauniyar P,<sup>1</sup> Luo H,<sup>1</sup> Hsiang Y,<sup>2</sup> van Breemen C<sup>1</sup>

<sup>1</sup>The James Hogg iCAPTURE Center for Cardiovascular and Pulmonary Research, Vancouver, Canada, <sup>2</sup>Department of Surgery, University of British Columbia, Vancouver, Canada.

Corresponding Author: [achung@mrl.ubc.ca](mailto:achung@mrl.ubc.ca)

**Background:** Pressure-distention of the saphenous vein, a common preparatory procedure during bypass surgery, promotes vascular remodeling and contributes to decreased graft patency. Pharmacological relaxation with a combination of vasodilators ( $\alpha$ -adrenergic antagonist, phenoxybenzamine; Rho-kinase inhibitor, fasudil; calcium blocker, nicardipine) has been suggested as an alternative to distention.

**Objective:** The major causes of graft wall thickening and neointima formation are the proliferation and migration of smooth muscle cells (SMCs). These processes require degradation of extracellular matrix (ECM) by matrix metalloproteinases (MMPs). We studied the effects of distention comparing to pharmacological relaxation on graft remodeling, MMP regulation, and SMC proliferation in porcine vein grafts.

**Methods:** In pigs, either side of external jugular veins were randomized to receive distention or vasodilators, then grafted into the carotid arteries. Two weeks after surgery, vessel morphology, ECM composition and SMC population were measured on Movat stained histological sections. Vein graft extracts were analyzed for the regulations of MMP-2 and MMP-9, tissue inhibitors of MMP (TIMP)-1 and TIMP-2, and cyclin D1.

**Results:** Pressure-distention instantly increased MMP-2 and MMP-9 activity in veins by 40% and 77%, respectively. Arterial grafting induced wall thickening, ECM modification and neointima formation, which were more pronounced in the distended grafts and accompanied by upregulation of MMPs. Distended grafts demonstrated higher expression of active MMP-9, and higher activities of latent and active MMP-2, than the pharmacologically-treated grafts. TIMP-1 and TIMP-2 were downregulated after grafting. Cyclin D1 expression and SMC population were elevated in distended grafts, while those in the pharmacologically-treated ones remained in the pre-grafted levels.

**Conclusions:** Pressure-distention of the vein, in comparison to pharmacological relaxation, upregulates MMPs and cyclin D1, which could account for the pronounced proliferation and migration of SMCs in the distended grafts and contribute to graft failure. Pharmacological relaxation may be clinically superior to distention in improving saphenous vein graft patency.

**Key Words:** *Matrix metalloproteinase, arteriovenous grafting, smooth muscle proliferation, vascular remodeling, intimal hyperplasia*

162

{ WITHDRAWN }

**A pilot study. The risks of hospitalization caused by adverse drug reactions: examining drug interactions, dose, duration, stability and co-morbid conditions**

Connelly S, Zarnke K, Dresser G, Rieder M, Martin J, Bayliff C, Speechly M

The University of Western Ontario, London Health Sciences Centre, London, Canada

Corresponding Author: [sconnel@uwo.ca](mailto:sconnel@uwo.ca)



163

### Non-steroidal anti-inflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis

Costei A,<sup>1</sup> Florescu A,<sup>2</sup> Boskovic R,<sup>1</sup> Koren G<sup>1</sup>

<sup>1</sup>Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Ontario, Canada, <sup>2</sup>Department of Public Health Sciences, University of Toronto, Toronto, Ontario, Canada

Corresponding Author: [adriana.costei@sickkids.ca](mailto:adriana.costei@sickkids.ca)

**Background:** Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs in medicine, and their administration in pregnancy is increasingly popular. NSAIDs are frequently utilized in the prevention of preterm labour. Although not generally recommended for use in the third trimester, the most frequently prescribed NSAIDs in pregnant women are aspirin, ibuprofen, indomethacin and sulindac. The risks associated with NSAIDs use in third trimester have been described. Premature constriction of the *ductus arteriosus* has been previously linked to NSAIDs use in the third trimester. The current literature is inconclusive with respect to the safety of NSAIDs in late pregnancy. In particular, many studies report conflicting results about the closure of the *ductus arteriosus* in response to NSAID treatment.

**Objectives:** The purpose of this study was to determine whether non-steroidal anti-inflammatory drug use during the third trimester of pregnancy is associated with an increased risk of premature constriction of the *ductus arteriosus*. Study design: A meta-analysis based on MEDLINE and EMBASE searches assessing *ductus arteriosus* constriction in fetuses exposed to NSAIDs. Summary estimates of the odds ratios comparing ductal outcomes in exposed and unexposed fetuses and their 95% confidence intervals were calculated.

**Results:** The risk of ductal closure was fifteen fold higher in the group of women exposed to NSAIDs compared to those treated with either placebo or other non-NSAIDs (8 studies; OR= 15.04, 95% CI [3.29-68.68]). There was no significant increased risk of ductal closure in women treated with indomethacin compared to those treated with other drugs (4 studies; OR= 2.12, 95% CI [0.48-9.25]).

**Conclusions:** Chronic use of NSAIDs in late pregnancy is associated with a significant increase in the risk of ductal closure.

**Key Words:** NSAIDs, pregnancy, third trimester, ductus arteriosus, drug safety

164

### Selective cytotoxic effect of *haplophyllum tuberculatum* extract on ER+ and ER- breast cancer cell lines

Doroudchi M, Varamini P, Mohaghegh-Zadeh A, Soltani M, Ghaderi A

Shiraz Institute for Cancer Research, Shiraz University of Medical Sciences, Shiraz, Iran

Corresponding Author: [mdoroud@sums.ac.ir](mailto:mdoroud@sums.ac.ir)

**Background:** There are reports on the presence of cytotoxic compounds in different species of Rutaceae family, however, the cytotoxic effect of *Haplophyllum tuberculatum* on cancer cell lines is not well established.

**Objectives:** In this study, the cytotoxic effect of two members of Rutaceae family on breast, ovary and cervical cancer cell lines was investigated.

**Methods:** Ethanolic extract of *Ruta graveolens* and *Haplophyllum tuberculatum*, prepared by sonication method, was in vitro tested on MDA-MB-453 (ER-), MCF-7 (ER<sup>+</sup>), SK-OV-3 and HeLa cancer cell lines, using WST-1 method.

**Conclusion:** A significant cytotoxic effect of *H. tuberculatum* extract ( $P < 0.05$ ) on MCF-7 cell line was observed, while *R. graveolens* showed no cytotoxic effect on any of the cancer cell lines ( $IC_{50} > 125\mu\text{g/ml}$ ). The cytotoxic effect of *H. tuberculatum* extract on the ER<sup>-</sup> Breast cancer cell line, MDA-MB-453, was significantly ( $P < 0.05$ ) less than the ER<sup>+</sup> Breast cancer cell line, MCF-7 ( $IC_{50} = 65.65\mu\text{g/ml}$  and  $IC_{50} = 129.31\mu\text{g/ml}$ , respectively).

**Conclusions:** Our results suggest that *H. tuberculatum* is a good candidate for further activity-monitored fractionation to identify its active compounds.

**Key Words:** Breast cancer, cytotoxicity, haplophyllum,  $IC_{50}$ , *Ruta*

165

**Antidepressant use during pregnancy and potential neonatal adverse effects: impact of a Health Canada advisory and subsequent reports in the news media**

Einarson A, Schachtschneider AK, Halil R, Bollano E, Koren G

The Motherisk Program, Division of Clinical Pharmacology, The Hospital for Sick Children

*Corresponding Author:* [enarson@sickkids.on.ca](mailto:enarson@sickkids.on.ca)

**Background:** On Aug 9<sup>th</sup> 2004 Health Canada released an advisory regarding the use of SSRI's and other antidepressants during pregnancy and potential adverse effects on newborns. Nowhere in this advisory was it stated that women should discontinue their antidepressant. In the seven days following the release of this advisory, The Motherisk Program received 65 calls from anxious women (49) and health care providers (16) in response to the media reporting of this advisory

**Objectives:** To examine the impact of the advisory and media reporting, on the decision -making of women regarding the use of antidepressants during pregnancy.

**Methods:** We attempted to follow up all the women who had called us who were alarmed by this advisory and asked them to complete a specially designed questionnaire.

**Results:** We were able to complete 43/49 (87.7%) follow-ups of the women who contacted us. All of the callers reported that the messages in the media caused a great deal of anxiety. Seven misunderstood the advisory, i.e, their child was more than 1 year old, five had discontinued their antidepressant (3 abruptly (2 later restarted after speaking with Motherisk counsellors) and 2 with some form of tapering off) and 6) were considering discontinuation, but decided to continue following reassurance from Motherisk.

**Conclusions:** Medical information disseminated in the public domain,(in this instance regarding fetal safety), should be predicated upon on evidence-based knowledge and transferred in a way that does not influence a pregnant woman to make decisions that may not be in the best interest of hers or her child's health.

**Key Words:** *Pregnancy, antidepressants, neonate, media, knowledge transfer*

166

**Pharmacoevidemiogenomics – mixed or dynamic trial design requirements**

Farahani P, Levine M

Centre for Evaluation of Medicines, St. Joseph's Healthcare-McMaster University, Canada

*Corresponding Author:* [farahap@mcmaster.ca](mailto:farahap@mcmaster.ca)

**Background:** Pharmacogenomics and pharmacogenetics trial studies for complex diseases are sophisticated because multiple dynamic factors such as age of the patient, stages of disease, internal and external stressors can influence the drugs behavior in individuals.

**Objectives:** 1) To explore and discuss the necessity of modifying the traditional paradigm for evaluating risk and benefit associated with therapeutic interventions where pharmacogenomics and pharmacogenetics advances have been applied. 2) To propose new methodology of research, which can be applied to pharmacogenomics and pharmacogenetics studies.

**Methods:** An extensive search was conducted using medical information resources regarding the evaluation of pharmacogenetics and pharmacogenomics applications in the clinical trial setting.

**Results:** Published pharmacogenetics and pharmacogenomics trials on cardiovascular and rheumatology drugs demonstrate that the traditional methodology of clinical trials involving selection criteria, randomization, blinding and constant dose are inadequate for assessing risks and benefits in these fields.

**Conclusion:** Traditional clinical trial methodologies are not readily applicable to pharmacogenetics and pharmacogenomics trials and alternatives methods need to be developed incorporating principles of epidemiology. This will be discussed in detail.

**Key Words:** *Pharmacogenomics, cardiovascular, epidemiology, pharmacogenomics, rheumatology*

167

**Clopidogrel use in children with complex heart disease**

Finkelstein Y, Nurmohamed L, Avner M, Benson LN, Koren G

Division of Clinical Pharmacology and Toxicology and the Division of Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada

*Corresponding Author:* [yfinkel@yahoo.com](mailto:yfinkel@yahoo.com)

**Background:** Children with congenital heart problems have an increased incidence (up to 4%) of thrombotic vascular complications, particularly after interventional catheterization procedures that include device implantation. Clopidogrel, a thienopyridine derivative, is a specific platelet aggregation inhibitor. The preferred anti-thrombotic therapy after percutaneous coronary intervention (PCI) with stent placement in adults has evolved from aspirin and systemic anticoagulation with warfarin to dual antiplatelet therapy with aspirin and clopidogrel. Presently, no published data exists on clopidogrel use in children.

**Objectives:** The aim of the present study was to report the first experience with clopidogrel therapy for primary and secondary prevention of thrombotic phenomena in children with complex heart disease after interventional cardiac catheterization, and to suggest a dose regimen for a paediatric population.

**Methods:** A retrospective chart review of all infants and children with complex heart disease treated with clopidogrel in the Hospital for Sick Children, Toronto between January 2001 and April 2004. Clopidogrel dosages, duration of therapy, complications and adverse effects in a paediatric population were explored.

**Results:** Fifteen infants and children with congenital and acquired heart disease were treated with clopidogrel (median age 3.5 years; range 6 weeks- 16 years). In 10 of them endovascular stents were inserted. Dosages ranged from 1 to 6 mg/kg/day, for periods ranging between 1 to 6 months. No thrombotic events were reported in these patients during clopidogrel therapy. One child had a bleeding complication (gastrointestinal) while on triple antithrombotic therapy. Other complications reported in adults, such as rash, were not noted in this paediatric series.

**Conclusions:** Clopidogrel was well tolerated, and there were no thrombotic events during treatment. We suggest a dose of 1mg/kg/day for children to be started.

**Key Words:** *Busulfan, stem cell transplantation, pharmacokinetics, children, veno-occlusive disease*

168

**The effect of oral mesna (sodium 2-mercaptoethanesulfonic acid) on homocysteine clearance in subjects with normal renal function**Freeman DJ,<sup>1</sup> Urquhart BL,<sup>1</sup> House A,<sup>1</sup> Spence DJ<sup>1</sup><sup>1</sup>Departments of Medicine and Physiology/Pharmacology, University of Western Ontario and Robarts Research Institute, London, Ontario, Canada.*Corresponding Author:* [dfreeman@uwo.ca](mailto:dfreeman@uwo.ca)

**Background:** Numerous studies have implicated elevated plasma total homocysteine (tHcy) as an independent risk factor for atherosclerosis. Regimens of folic acid, vitamin B6 and vitamin B12 effectively normalize tHcy in most patients. However, certain patient groups (i.e. with renal failure or enzymatic defects) are resistant to this treatment and remain at increased risk. Mesna is a thiol-containing drug indicated for prevention of ifosfamide-induced hemorrhagic cystitis during chemotherapy. An incidental side effect of intravenous mesna is enhanced clearance of plasma thiols including homocysteine. The effect of oral mesna on plasma thiols has not been evaluated.

**Objectives:** To determine the effect of a single oral dose of mesna on the clearance of homocysteine.

**Methods:** Subjects were water loaded the morning of the study day and an indwelling catheter inserted into an appropriate arm vein upon arrival at the clinic. After voiding their bladders of urine, 2 X 5 mL blood samples were drawn for baseline tHcy and serum creatinine. Spot tHcy and creatinine clearances were performed over the next 2 hours by collecting plasma/serum and urine. For the treatment phase subjects voided urine and a single, oral 10 mg/kg dose of mesna were given. Spot tHcy, mesna and creatinine clearances were repeated at selected intervals post-mesna.

**Results:** Plasma tHcy decreased by 16.6 % following oral mesna and was accompanied by recovery of Hcy and mesna in urine. The fractional excretion of Hcy  $[(\text{CL}_{\text{Hcy}}/\text{CL}_{\text{Creat}})*100]$  increased 60 fold from 0.1 % to 6.0 % after mesna treatment. C<sub>max</sub> and T<sub>max</sub> for mesna were 85.6 µM and 138 minutes respectively.

**Discussion:** We have demonstrated that oral mesna causes an increase in the renal clearance of Hcy. Although oral mesna decreased plasma tHcy minimally, it is likely that a higher dose of mesna is required due to its low oral bioavailability.

**Key Words:** *Homocysteine, mesna, creatinine clearance, atherosclerosis, serum creatinine*

169

**Use of two or more antihypertensive drugs to treat hypertension in elderly Ontarians**

Gardner L,<sup>1</sup> Tu K,<sup>2</sup> McAlister A,<sup>3</sup> Campbell NRC<sup>3</sup>

<sup>1</sup>Departments of Medicine and of Pharmacology and Therapeutics, University of Calgary, Calgary Alberta,

<sup>2</sup>Institute for Clinical Evaluative Sciences and Department of Family Medicine University of Toronto Ontario, <sup>3</sup>Department of Medicine, University of Alberta, Edmonton Canada

*Corresponding Author:* [ncampbel@ucalgary.ca](mailto:ncampbel@ucalgary.ca)

**Background:** The Canadian Hypertension Education program was initiated in 1999 to improve the treatment and control of hypertension in Canada. We used linked administrative data sets from Ontario to define a cohort of newly diagnosed hypertensive patients over age 65 and examined prescriptions for these patients.

**Objectives:** To track the use of two or more antihypertensive medications in elderly Ontarians as a proxy for aggressiveness of antihypertensive management and to determine the appropriateness of the drug combinations.

**Methods:** Linked administrative databases and a province-wide clinical database in Ontario were used to derive a cohort of patients aged 66 years or older who were newly started on an antihypertensive agent between July 1, 1994 and March 31, 2002 without another indication for the agent. Prescribing rates were adjusted for changes in population over time.

**Results:** In 1994, twenty one percent of patients were prescribed 2 or more antihypertensive drugs concurrently within 2 years of diagnosis. This proportion had increased to 40% by 2002 ( $p < 0.0001$ ). The use of three or more antihypertensive drugs increased from 1.5% to 6.0%. Approximately 75% of the drugs used in two drug combinations had been proven to result in additive antihypertensive effect.

**Conclusions:** There is an increasing use of 2 or more drugs to control hypertension in elderly Ontarians in the past decade. This increase may be associated with a better understanding of the need to use multiple drugs in combination to control hypertension. Most of the two drug combinations are consistent with current Canadian recommendations and evidence of effectiveness at reducing blood pressure.

**Key Words:** *Hypertension, high blood pressure, antihypertensive therapy, elderly, pharmacotherapy*

170

**Fatty Acid Ethyl Esters in meconium as a novel method of mass screening for fetal alcohol exposure**

Gareri J, Koren G, Lynn H

Motherisk Program, Hospital for Sick Children, University of Toronto, Canada

*Corresponding Author:* [joey.gareri@utoronto.ca](mailto:joey.gareri@utoronto.ca)

**Background:** Fetal Alcohol Spectrum Disorder (FASD) constitutes a major public health concern in North America affecting nearly 1% of the general neonatal population. Diagnosis of FASD in the absence of pathognomonic craniofacial features requires an accurate in utero alcohol exposure history. High disease prevalence, diagnostic difficulties, and sensitivity issues with maternal self-reporting have resulted in the need for a reliable biomarker of gestational alcohol consumption. Fatty acid ethyl esters (FAEE) in meconium have been established as a novel biomarker for fetal alcohol exposure.

**Objectives:** This study is the first application of the FAEE test as a neonatal screening tool. A positive cut-off value was established by our laboratory in a baseline study of 183 non-drinking women. We aim to apply this positive cut-off value to the meconium FAEE levels of a regional neonatal population in southwestern Ontario in order to establish a fetal alcohol exposure prevalence value for the area.

**Methods:** The study is anonymous and no additional patient information is collected. One meconium sample is collected from each subject. Samples are obtained from five regional birthing hospitals (one tertiary care) and a local midwives collective. FAEE content is determined by gas chromatography following liquid-liquid and solid-phase extraction. Palmitic, palmitoleic, stearic, oleic, linoleic, linolenic, and arachidonic acid ethyl esters are measured.

**Results:** 707 samples were collected between January 1st and November 15th, 2004 with no reported refusals. The coverage rate for the study to date is 78.70%. 223 samples have been analyzed: 8 samples have measured above the positive cut-off of 2.0 nmol total FAEE/g meconium.

**Conclusions:** These preliminary results demonstrate a fetal alcohol exposure rate of 3.59%, a 10-fold increase over the surveyed rate of heavy drinking in pregnancy (>14 drinks/week) established by the CDC in both 1997 and 2002. This suggests that our method exhibits increased sensitivity over maternal self-reporting.

**Key Words:** *Meconium, fatty acid ethyl esters, biomarker, FASD (fetal alcohol spectrum disorder)*

171

### Transplacental transport of glyburide and its implication for treatment of gestational diabetes

Gedeon C, Behravan J, Piquette-Miller M, Koren G  
Hospital for Sick Children, CIHR, University of Toronto, Faculty of Medicine and Faculty of Pharmacy, Canada

Corresponding Author: [douknowwhoiam13@hotmail.com](mailto:douknowwhoiam13@hotmail.com)

**Background:** Hyperglycemia is associated with adverse outcomes of pregnancy in women with gestational diabetes. While the primary approach to glycemic control in pregnant women is insulin therapy, glyburide has proven to be an effective alternative. Unlike other sulfonylureas, glyburide is not detected in cord serum and hence is likely to be actively secreted from fetal tissues. Several ABC- drug efflux transporters such as P-glycoprotein (P-GP), BCRP and the multidrug resistance-associated proteins (particularly MRPs 1, 2 and 3) are expressed in human placenta and thus one or more of these transporters could be involved in the placental extrusion of glyburide.

**Objectives:** To determine whether the ABC efflux transporter(s) are involved in the active transport of glyburide in human placenta.

**Methods:** Efflux assays for 5-CFDA (MRP activity) and rhodamine-123 (PGP) were measured in MRP1, MRP2, MRP3 or P-GP over expressing cells. Indomethacin and verapamil were used as inhibitors of MRP and PGP, respectively. Subsequently, transport of H<sup>3</sup>-Glyburide was measured in the presence and absence of specific inhibitors in P-GP, MRP1, MRP2, MRP3 and BCRP cell lines. Additionally, characterization of glyburide transport is underway using the dual perfused human term placenta method to confirm *in vitro* data.

**Results:** Glyburide was found to significantly increase the intracellular accumulation of 5-CFDA in MRP1, MRP2 and MRP3 over expressing cell lines. Inhibition of MRP-mediated efflux of 5-CFDA was four fold greater than indomethacin for MRP3, two fold greater for MRP2 and comparable to indomethacin in MRP1. Glyburide also increased intracellular accumulation of Rhodamine-123 in the PGP expressing cells. Inhibition with glyburide was two fold greater than that seen with verapamil. Transport data of <sup>3</sup>H-glyburide in each cell line will be presented.

**Conclusions:** Glyburide's active transport from the placenta is possibly mediated by several systems including PGP, MRP1, MRP2 and MRP3 transporters.

**Key Words:** Gestational diabetes, glyburide, ABC-transporters, placenta

172

### Relationship between prenatal tobacco exposure and later uptake of smoking

George A,<sup>1</sup> Barnes G,<sup>2</sup> Patton D<sup>3</sup>

<sup>1</sup>University of British Columbia, Vancouver, BC

<sup>2</sup>University of Victoria, Victoria, BC, <sup>3</sup>Addictions Foundation of Manitoba, Winnipeg, Manitoba

Corresponding Author: [ageorge@cw.bc.ca](mailto:ageorge@cw.bc.ca)

**Background:** In both Canada and the U.S.A., current smoking rates of young adults rose *steadily* until the late 1990's and has dropped in subsequent years (2003, 21.9% in U.S.A., 24% in Canada), with higher rates for females than males. Studies (Kandel, Wu, & Davies, 1994; Buka, Shenassa, Niaura, 2003) have observed a relationship between mothers' smoking during pregnancy and subsequent smoking adolescent female offspring.

**Methods:** We identified through Random Digit Dialing a sample of English-speaking families living in a large Canadian urban centre, with 2 parents and at least 1 adolescent offspring living at home. Our sample of 473 families was subsequently interviewed at home, with self-administrated questionnaires completed independently and privately by each of the 3 family members (mother, father and 1 child). The questionnaires included self-report questions about tobacco use. Both mothers and fathers reported retrospectively on mother's use of tobacco during her pregnancy.

**Results:** There was high agreement between mother's report of smoking and father's report of her smoking, both for the amount smoked during pregnancy ( $r=.80$ ,  $p<.001$ ,  $n=451$ ) and for frequency ( $r=.87$ ,  $p<.001$ ,  $n=452$ ). An association was observed between adolescent girls' smoking and prenatal tobacco exposure through their mothers' smoking (Wald=5.5;  $df=1$ ;  $p<.05$ ), controlling for age of child, mothers' education, and mothers' current smoking. The odds ratio of 3.8 indicates that girls are considerably more likely to smoke if they were prenatally exposure to tobacco. The association was found when mothers smoked  $\frac{1}{2}$  a pack of cigarettes or more daily. A similar relationship between prenatal exposure and adolescent boys' smoking was not found.

**Conclusions:** Our study confirms the relationship between prenatal tobacco exposure and subsequent uptake of smoking by girls during adolescent; however, we observed the outcome at lower rates of tobacco use during pregnancy ( $\frac{1}{2}$  pack of cigarettes) than previous studies (1 pack per day).

**Key Words:** Tobacco exposure, prenatal effects, longitudinal, adolescents

173

**Pregnancy outcome following first-trimester exposure to metformin: a meta-analysis**Gilbert C,<sup>1,2</sup> Koren G<sup>1</sup><sup>1</sup>Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Canada<sup>2</sup>Graduate Student, Institute of Medical Science, University of Toronto*Corresponding Author:* [cameron.gilbert@utoronto.ca](mailto:cameron.gilbert@utoronto.ca)

**Background:** Metformin's efficacy has been proven in the treatment of infertility caused by polycystic ovary syndrome (PCOS). Recently, studies have also looked at the efficacy of Metformin in the reduction of the rate of first trimester spontaneous abortions and the rate of gestational diabetes in women with PCOS. Metformin's safety in pregnancy, however, has not been established. Insulin is currently the drug of choice in the treatment of type I or type II diabetes during pregnancy because it is known not to cross the placenta. The strict dosing regimen of insulin and the high cost of the drug and paraphernalia, however, make it a hard routine to maintain.

**Objectives:** To assess the safety of metformin during pregnancy.

**Methods:** A systematic review was conducted with all pertinent studies in MEDLINE and EMBASE studying metformin and pregnancy outcome. Papers were excluded from the analysis if they did not have adequate control groups, data on the outcome of the pregnancy with respect to major malformations and exposure to the drug in at least the 1st trimester. Meta-analysis was conducted using Review Manager 4.2 software.

**Results:** Metformin therapy in the first-trimester of pregnancy did not increase the rate of major malformations. Eight studies were included in the meta-analysis with an additional five uncontrolled studies included in the calculation of the overall malformation rate. The odds ratio in the meta-analysis (including all studies with disease controls) was 0.48 (95% confidence interval (CI) 0.15, 1.56). The overall malformation rate of exposed pregnancies (including studies without relevant controls) was 1.07% (5 malformations in 467 1st trimester exposures).

**Conclusions:** Based on eight small studies available now, metformin does not appear to be unsafe for use during pregnancy. While more studies are needed, these data are reassuring.

**Key Words:** *Metformin, pregnancy, meta-analysis, diabetes, safety*

174

**Preliminary results of a clinical trial of the neuromuscular blocker advisory system**

Gilhuly T, MacLeod B, Schwarz S, Dumont G

Department of Pharmacology and Therapeutics, University of British Columbia, Canada

*Corresponding Author:* [terenceg@ece.ubc.ca](mailto:terenceg@ece.ubc.ca)

**Background:** The Neuromuscular Blocker Advisory System (NMBAS) is a computer program developed to provide advisory guidance to anesthesiologists on the timing and dose of drug (rocuronium) used to paralyze patients during surgery. It is believed that the use of such a system will administer the minimal effective neuromuscular blocking drug, and will thereby improve patient safety and result in more efficient use of medical resources.

**Objectives:** The objective of this work is to test the NMBAS in a clinical setting, under the hypothesis that the use of this system will result in improved control of muscle paralysis during surgery.

**Methods:** After obtaining informed consent, patients undergoing surgery requiring paralysis, were randomly divided into two groups. One group received standard doses of rocuronium at the discretion of the anesthetist. The second group received rocuronium at the times and doses suggested by NMBAS. The degree of neuromuscular block was assessed using the electromyography response. A computer monitored and recorded each patient's response and suggested the next dose to the anesthetist. The two groups were compared for error (deviation from the ideal condition), incidents of overdosing and inadequate paralysis, time from the last required paralysis to spontaneous recovery of normal function will be recorded, time to return to drug induced reversability of paralysis (for those cases where spontaneous recovery does not occur within accepted clinical time period), and amount of drug used.

**Results:** TBD

**Conclusions:** TBD

**Key Words:** *Computer-control, drug administration, rocuronium, neuromuscular blockers*

175

**In vitro toxicity of the polysaccharide extract of ganoderma lucidum**Gill SK,<sup>2</sup> Tucker J,<sup>4</sup> Man R,<sup>5</sup> Rieder M<sup>1,2,3,4</sup><sup>1</sup>Departments of Paediatrics, <sup>2</sup>Physiology & Pharmacology, <sup>3</sup>Schulich School of Medicine, <sup>4</sup>University of Western Ontario, Robarts Research Institute, <sup>5</sup>Department of Pharmacology, University of Hong Kong, China*Corresponding Author:* [ssgill2@uwo.ca](mailto:ssgill2@uwo.ca)**Background:** Ganoderma lucidum (Ling-zhi, Reishi mushroom) has been used in Traditional Chinese Medicine for over 5000 years for a wide array of ailments. Recently, it has been suggested that the polysaccharide extract of Ganoderma lucidum (PS-GL) possesses anti-tumor properties due to immunostimulation. It has been suggested that PS-GL can be used as an adjunctive to chemotherapy in paediatric patients undergoing chemotherapy to enhance the immune system and decrease the risk of infections. However, the toxicity of PS-GL for this condition remains unknown.**Objectives:** The objective of these experiments was to determine the toxicity of PS-GL in cells of the lymphoreticular lineage (Jurkat E6.1 cells and LG2 cells).**Methods:** Cells were incubated with concentrations of PS-GL ranging from 50 µg/ml to 350 µg/ml for 24 hours and 48 hours. After incubation, 25 µL of MTT was added to each well and then 4 hours later 100 µL of SDS stop solution was added. Plates were incubated overnight, and cell viability was assessed the next day using a spectrophotometer at 590 nm. A thiazolyl blue tetrazolium bromide (MTT) toxicity assay was used to measure percent cell viability as compared to control. Two different cell types were used: Jurkat E6.1 cells, T cell lymphoblasts, and LG2 cells, B cell lymphoblasts.**Results:** There were significant time and concentration dependent decreases in cell viability in both Jurkat E6.1 cells and LG2 cells. For E6.1 cells at 24 hours, a significant decrease in cell viability was observed starting at concentrations of 100 µg/ml and greater ( $p < 0.001$ ); at 48 hours, a significant decrease was observed at 50 µg/ml ( $p < 0.001$ ). Similarly, for LG2 cells, significant concentration-dependent decreases in cell viability were observed in concentrations greater than 50 µg/ml ( $p < 0.001$ ).**Conclusions:** PS-GL produces time and concentration dependent toxicity in both Jurkat E6.1 cells and LG2 cells in low micromolar concentrations. The extent to which toxicity is seen in primary cells such as peripheral mononuclear cells needs to be determined.**Key Words:** *Pediatric, ganoderma lucidum, immunostimulation, toxicity, lymphoreticular lineage*

176

**Counseling regarding drugs in pregnancy by family physicians in Ontario**

Goodwin J, Rieder S, Rieder MJ, Matsui D

Department of Paediatrics, Children's Health Research Institute, University of Western Ontario, Canada

*Corresponding Author:* [dmatsui@uwo.ca](mailto:dmatsui@uwo.ca)**Background:** Providing information to their patients on the effects of medication exposure during pregnancy is a common challenge for family physicians. Women must receive accurate information as unrealistic perception of teratogenic risk may lead to inadequate treatment of maternal disease or termination of otherwise wanted pregnancies.**Objectives:** To collect data on the current practices of family physicians in Ontario in providing information regarding pregnancy-related drug exposures.**Methods:** A mailed survey was sent to a random sample of family physicians in Ontario in 2003.**Results:** Of the 756 surveys, 400 (53%) were returned, 265 (66%) of which were completed by practicing family physicians caring for women of childbearing age. Most (80.3%) felt confident in providing counseling, though a majority (56%) stated that the available sources of information are not adequate. The most commonly cited source consulted for obtaining information on drug use during pregnancy was Motherisk (62%), followed by the Compendium of Pharmaceuticals and Specialties (CPS) (25%), textbooks (13%), electronic sources (7%), obstetricians (4%), pharmacists (4%) and peer-reviewed journals (1%). Lack of evidence-based information was cited as the major barrier to providing effective counselling in this area. Most respondents indicated that they had received "a little" teaching on the effects of drugs in pregnancy during their undergraduate (69%) and postgraduate (65%) medical education. With regards to future development of educational programs in this field many indicated a preference for electronic means.**Conclusions:** Although family physicians were confident in providing counseling to pregnant patients with regards to drug use, more than one-half thought that the available sources of information are not adequate. The dissemination of more evidence-based information in this field is needed, as is the development of electronic educational resources.**Key Words:** *Family physicians, information, drugs, medications, pregnancy, counseling*

177

**Do steroids during delivery alter relations between neonatal pain and stress reactivity in preterm infants?**

Haley DW,<sup>1,2</sup> Grunau RE,<sup>1,2</sup> Weinberg J,<sup>1,3</sup> Solimano A<sup>2</sup>  
<sup>1</sup>Centre for Community Child Health Research, BC Research Institute for Children's & Women's Health, University of Vancouver, Canada, <sup>2</sup>Dept of Pediatrics, University of British Columbia, Canada, <sup>3</sup>Dept of Anatomy and Cell Biology, University of British Columbia, Canada

*Corresponding Author:* [dhaley@cw.bc.ca](mailto:dhaley@cw.bc.ca)

**Background:** Corticosteroids affect multiple aspects of physiology. Previously we reported that cumulative neonatal pain predicted dampened cortisol response to stress at 32 weeks gestation in infants born extremely preterm, who were free of postnatal steroid exposure. However, another lab recently reported that prenatal steroids given to the mother suppressed infants cortisol response to heel-lance.

**Objectives:** To examine whether exposure to prenatal steroids, rather than prior pain, might account for down-regulation of infant cortisol to stress.

**Methods:** N=30 preterm infants born extremely low gestational age  $\leq 28$  weeks (16 boys, 14 girls) participated in the study at 32 weeks post-conceptual age. Infants who had received analgesia or sedation in the 72 hours prior to study, or received any post-natal dexamethasone were excluded. Plasma cortisol was obtained 20 min following a standard series of nursing procedures (diaper change, girth measurement, temperature, mouth care). Medical chart review included number of prenatal dexamethasone courses administered to the mother during delivery, and cumulative neonatal procedural pain exposure (defined as the number of skin breaking procedures since birth), in addition to neonatal characteristics.

**Results:** Hierarchical regression analysis showed that higher cumulative neonatal procedural pain exposure predicted lower cortisol responses to stress ( $t=-2.22$ ,  $p=.05$ ), after controlling for prenatal dexamethasone, postnatal illness severity and morphine exposure since birth.

**Conclusions:** Pain-related alterations in infant cortisol response to stress were not accounted for by prenatal steroids.

**Key Words:** *Steroids, stress, neonates, prematurity, HPA-axis*

178

**Selective scavenging of nitric oxide increases cardiovascular responsiveness to noradrenaline in a rat model of diabetes**

Hutchings SR, Song D, Fricker SP, Pang CCY  
 University of British Columbia, Vancouver, Canada

*Corresponding Author:* [hutchy@interchange.ubc.ca](mailto:hutchy@interchange.ubc.ca)

**Background:** Excess nitric oxide (NO) production by inducible nitric oxide synthase (iNOS) has been implicated in cardiovascular dysfunction associated with the acute phase of diabetes mellitus.

**Objectives:** To examine if the selective NO scavenger, AMD6221 (potassium chlorohydrogen (ethylenedinitrilo) tetraacetato]ruthenate) increases cardiovascular function in rats with streptozotocin-induced diabetes.

**Methods:** Diabetes was induced in male Wistar rats (300-400 g) by injection of streptozotocin (60 mg/kg i.v.). The effects of noradrenaline infusion (16.5nmol/kg/min) on several cardiovascular variables were measured in pentobarbital-anaesthetised diabetic and control rats before and after acute administration of AMD6221 (80 mg/kg).

**Results:** Rats in the acute phase of streptozotocin-induced diabetes had impaired mean arterial pressure (MAP), peak left ventricular systolic pressure (LVSP) and maximum rate of increase (+dP/dt) and decrease (-dP/dt) of left ventricular pressure responses to noradrenaline compared with control rats. Acute treatment with AMD6221 significantly augmented the LVSP, +dP/dt and -dP/dt responses to noradrenaline in diabetic but not control rats.

**Conclusions:** Selective scavenging of nitric oxide by AMD6221 increased the cardiovascular responsiveness to noradrenaline in rats with streptozotocin-induced diabetes.

**Key Words:** *Streptozotocin-induced diabetes, rats, noradrenaline, cardiovascular dysfunction*



179

**Hair cortisol as a biological marker for chronic stress during pregnancy**

Kalra S, Klein J, Woodland C, Karskova T, Einarson A, Koren G

Department of Pharmacology, University of Toronto, The Motherisk Program, Division of Clinical Pharmacology, Toronto, Canada

*Corresponding Author:* [sanjog.kalra@utoronto.ca](mailto:sanjog.kalra@utoronto.ca)

**Background:** Chronic stress during pregnancy is associated with deleterious maternal and fetal health effects and is known to contribute to negative pregnancy outcomes. Women suffering from depression during pregnancy exhibit high levels of acute stress, as measured by validated biological markers. However, given that stress associated with depression is thought to be chronic, there exists a need for a biological marker capable of accurately measuring chronic stress. Hair is in current use as a biological marker for chronic xenobiotic exposure. Previous studies have shown drug levels in hair to accurately reflect the integral of (chronic) free-plasma levels of these substances. Recently, various endogenous substances (including cortisol) have become measurable in human hair.

**Objectives:** To investigate differences in hair cortisol levels between depressed and non-depressed women in pregnancy, to examine the relationship between chronic stress and depression in pregnancy; and to explore the potential of hair cortisol as a biomarker for chronic stress in pregnancy.

**Methods:** In this pilot study, we prospectively enrolled 50 women (25 pregnant/depressed, 25 pregnant/non-depressed), each of whom provided a scalp hair sample and completed two validated questionnaires to measure their levels of depression (CES-D) and chronic stress (PSS). Hair samples were analyzed for cortisol levels using ELISA.

**Results:** Chronic stress correlated strongly with depressive symptoms in all patients ( $r_s=0.86$ ,  $p<0.000001$ ). In depressed patients, both PSS and CES-D scores were significantly negatively correlated with hair cortisol levels ( $r_s=-0.40$ ,  $p<0.05$  and  $r_s=-0.39$ ,  $p<0.05$  respectively). In contrast PSS scores of non-depressed patients were significantly positively correlated with hair cortisol measurements ( $r_s=0.36$ ;  $p<0.05$ ).

**Conclusions:** Stress and depression were highly correlated, suggesting that women who were depressed were also chronically stressed. However, women who were most depressed and most stressed appeared to have the lowest levels of hair cortisol, suggesting that different mechanisms modulate stress in depressed and non-depressed pregnant women.

**Key Words:** *Pregnancy, stress, cortisol, hair testing, depression*

180

**Prenatal blockade of estradiol synthesis alters the functional and morphological development of carotid bodies in newborn rats.**Kerth R, Doan VD, Bairam A, Joseph V  
Centre de Recherche de l'Hopital St François d'Assise, Université Laval, Dpt Pédiatrie, Québec, Canada.*Corresponding Author:* [aida.bairam@crsfa.ulaval.ca](mailto:aida.bairam@crsfa.ulaval.ca)

**Background:** The effects of ovarian steroids on carotid bodies (CB—involved in cardio-respiratory responses to hypoxia) have been described in adult mammals. Since premature newborn are chronically deprived from placental-derived hormones (including estradiol) and are at high risk for respiratory disorders, we tested the hypothesis that prenatal estradiol affects CB development.

**Methods:** We performed i) respiratory studies using whole body plethysmography, before and 2 hours after i.p. injection of domperidone, (peripheral dopaminergic antagonist acting on CB, 10 mg/kg), and ii) morphological analysis of the CB (immunohistochemical staining with tyrosine hydroxylase, TH, a chemosensitive cells marker) on rat pups born to estradiol-deprived or control mothers. Pregnant female rats received 4androst-4-ol-3,17dioneacetate (ATD-5mg/day) to block estradiol synthesis, or vehicle (Veh) during the last week of gestation. Male rat pups were studied 4-5 days after birth.

**Results:** ATD pups ( $n=15$ ) had higher resting respiratory frequency than Veh ( $n=18$ - $160\pm4$  vs.  $146\pm4$  breaths/min,  $p=0.02$ ). Minute ventilation was not affected by domperidone injection in Veh ( $-4\pm6\%$ ), but decreased in ATD pups ( $-23\pm4\%$ ,  $p=0.01$  vs. Veh). Tidal volume increased ( $8\pm7\%$ ) in Veh and decreased in ATD pups ( $-14\pm4\%$ ,  $p=0.01$  vs. Veh). Respiratory frequency decreased in Veh ( $-11\pm2\%$ ) and ATD ( $-10\pm2\%$ ). CB morphological analysis show similar mean area in ATD and Veh pups, but TH positive tissue occupied  $38\pm3\%$  of the CB in ATD ( $n=9$ ) vs.  $25\pm1\%$  in Veh pups ( $n=8$ - $p=0.001$  ATD vs. Veh).

**Conclusion:** In conclusion, our results show that prenatal blockade of estradiol synthesis enhances the dopaminergic contribution to baseline ventilation and leads to a specific hypertrophy of glomic tissue in the carotid body. As in adults, exposure to endogenous estradiol in neonates appears as a major determinant of respiratory homeostasis.

**Key Words:** *Carotid body hypoxia, dopamine, estradiol, preterm birth, rat*

181

**Incorporation of fatty acid ethyl esters in hair as a marker of alcohol exposure in guinea pigs and humans**

Kulaga V, Koren G

Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Ontario

*Corresponding Author:* [viviankulaga@rogers.com](mailto:viviankulaga@rogers.com)

**Background:** Previous investigations into the use of fatty acid ethyl esters (FAEE) as a biomarker for in-utero alcohol exposure have used guinea pigs as the preferred animal model. To use this model, it is essential to compare the incorporation of FAEE in hair to that in humans. To date no investigation has compared the ratio of FAEE concentrations in hair to the systemic exposure to ethanol in either guinea pig or human.

**Objectives:** To compare FAEE concentrations in guinea pig hair to those in humans, correcting for the differences in systemic exposure to ethanol.

**Methods:** Data from 9 pregnant guinea pigs, where maximum blood ethanol concentration, dosage regimen, and total hair FAEE concentration are known, were compared to data from 18 alcohol detoxification patients, where dose of ethanol consumed, and total hair FAEE concentration are known. Ethanol Vmax for pregnant guinea pigs was obtained from Litvin and Switzer, 1988. Vmax in humans was set at the accepted mean of 15 mg/dl/hr.

**Results:** After standardization for AUC of ethanol in humans versus guinea pigs, hair levels of total FAEE were 8 fold higher in humans than in pigs. This may reflect a higher rate of FAEE production in humans versus that in guinea pigs, or a higher FAEE incorporation rate, or both.

**Conclusions:** When extrapolating FAEE concentrations in hair from experimental guinea pigs to humans, a factor of 8 fold difference should be considered.

**Key Words:** *In-utero alcohol exposure, fatty acid ethyl esters, guinea pigs, humans*

182

**Antidepressant use during lactation: clinical and economic consequences**

Lee A, Ungar W, Wang B, Romach M, Ito S

Division of Clinical Pharmacology, Hospital for Sick Children, Department of Pharmacology, University of Toronto, Canada

*Corresponding Author:* [amy.lee.a@utoronto.ca](mailto:amy.lee.a@utoronto.ca)

**Background:** Untreated depression can be detrimental to both mother and infant. Because 13% of postpartum women are depressed, this issue is of societal relevance.

**Objectives:** To examine the well-being and health care costs of depressed, breastfeeding women treated with antidepressants (AD+), and their infants, for the first year postpartum, compared to those forgoing pharmacotherapy (AD-), and to healthy, breastfeeding women (COMP).

**Methods:** Women-infant pairs were followed-up for detailed interviews at 3, 6, 9, and 12 months postpartum. Data collection included medical and demographic data, infant feeding method, adverse events, and health care use. The Edinburgh Postnatal Depression Scale (EPDS), Short Form 36 (SF-36), and the Functional Status II Revised (FS-II(R)) were used to assess maternal depression, maternal well-being, and infant well-being, respectively.

**Results:** Fifty-five, 34, and 60 women in AD+, AD-, and COMP, respectively were followed to 12 months. Although EPDS scores improved over time, all pairwise comparisons between the 3 groups were statistically significant (AD+: 6.5, AD-:10.5, COMP: 3.7), suggesting more depressive symptomatology in AD-. AD+ scores were higher than COMP, suggesting inadequate treatment. SF-36 mental component scores indicated more functional impairment in AD-. Health care utilization was significantly more frequent for AD- mother/infant, thereby making the total annual average health care costs per pair from the provincial ministry of health perspective significantly different between AD+, AD-, and COMP (\$1189.50, \$1676.55, and \$883.31, respectively, p<0.05).

**Conclusions:** Women with untreated depression in the postpartum period experienced more depressive symptomatology and functional impairment compared to those who were treated. Moreover, their health care utilization for themselves and their infants is significantly higher. Our findings further suggest inadequacy of the treatment if provided.

**Key Words:** *Depression, breastfeeding, postpartum, economic, antidepressants*

183

**Placebo equal to nalbuphine for pruritus in pediatrics**

Lim J,<sup>1</sup> Nakatsuka N,<sup>1</sup> Minogue SC,<sup>1</sup> Montgomery CJ,<sup>1</sup> Court CA,<sup>1</sup> Ansermino JM,<sup>1</sup> Malherbe S,<sup>2</sup> Csanyi-Fritz Y,<sup>1</sup> Kearney RA,<sup>2</sup> Phillips L,<sup>2</sup> Reid K<sup>2</sup>

<sup>1</sup>BC Children's Hospital, Vancouver, BC, <sup>2</sup>University of Alberta Hospital Edmonton, Alberta

*Corresponding Author:* [njlim2@cw.bc.ca](mailto:njlim2@cw.bc.ca)

**Background:** The purpose of this investigation was to evaluate the efficacy of nalbuphine, a partial opioid agonist-antagonist, to treat post-operative opioid-induced pruritus (Pr) in a pediatric population.

**Methods:** After approval by the University Research Ethics Boards, the dual centre study planned to recruit 268 subjects, age  $\geq 7$ , receiving continuous opioid analgesia post-operatively who understood the self-report Colour Analogue Scale (CAS) to score pruritus intensity (PrI). Sample size was estimated to demonstrate a 25% improvement compared to placebo ( $\alpha=0.05$  and  $1-\beta=0.8$ ). Subjects who reported PrI score  $\geq 5/10$  were randomized to treatment with nalbuphine 50 mcg/kg IV (max 5mg) or saline placebo. PrI, analgesia (VAS), sedation (5 point score), and side effects of headache, vomiting, and dizziness (yes/no) were recorded at 30 and 60 min. A Pruritus Intensity Difference (PrID) of  $\geq 50\%$  was considered a positive outcome.

**Results:** Of 259 subjects, 212 consented to the study and of these 184 received opioids. The median age was 13 yr (range 7-19) and median weight was 51 kg (range 19.6-134.8). PrI  $\geq 5/10$  occurred in 37 (20.1%) subjects. The CAS was well accepted by all subjects. The incidence of Pr was highest in the PCA group (46%), versus continuous opioid infusion (27%) and epidural (27%). Pr occurred over a wide range of opioid doses (9.4-63.2 mcg/kg/hour IV morphine). Epidural hydromorphone resulted in a lower incidence of Pr than intravenous morphine (29.7% vs. 67.6%). PrID of  $\geq 50\%$  was achieved in 21 (56.8%) subjects. There was no benefit of nalbuphine (55.6%) compared to saline (57.9%). No increased sedation or reversal of analgesia was noted.

**Conclusion:** Saline placebo was as effective as nalbuphine 50 mcg/kg in treating pruritus. The CAS score and PrID proved to be robust instruments for measuring PrI and warrant further investigation with alternate doses, agents or pruritus models.

**Key Words:** Pruritus, nalbuphine, pediatrics, postoperative, opioid

184

**Clinical pharmacology in support of the coroner system**

MacLeod, SM

British Columbia Research Institute for Children's & Women's Health and University of British Columbia, Vancouver, British Columbia

*Corresponding Author:* [smacleod@cw.bc.ca](mailto:smacleod@cw.bc.ca)

**Background:** Clinical pharmacology was conceived as a discipline supporting optimal choice among therapeutic drugs usually based on assessment of efficacy. However, as medical decisions have focused increasingly on safety concerns a parallel responsibility has developed in toxicology from both clinical and forensic perspectives. Pharmaceutical misadventures make up a surprisingly large proportion of cases coming under the scrutiny of Canada's coroners and leading to inquest or extended formal enquiry.

**Methods:** As a clinical pharmacologist practising in Ontario between 1973 and 2002 the author was consulted by regional and provincial coroners on a random case series of 37 fatalities involving drugs, chemicals, and anesthetic gases requiring full investigation, usually culminating in inquests.

**Results:** The five most commonly encountered etiologic groupings were analgesics, anaesthetic, neuroleptic, prokinetic and inotropic agents. Of the series, 9 deaths were judged to have no relationship to drug therapy, 8 were clinically unpredictable but in keeping with known drug actions, 7 were the result of exposure to toxicologic doses through overdose or prescribing error, and 7 were the result of outright error (wrong drug, wrong patient). Of the remaining 6 cases, 3 deaths resulted from an extension of the drug's normal action, 2 deaths were due to drug hypersensitivity, and only these and one other were completely unpredictable and consequently unpreventable.

**Conclusions:** While the cases in this series were unselected, they underscore three important observations. (1) The majority of drug-associated fatalities could be predicted, prevented, or mitigated through prudent therapeutic choices or timely interventions. (2) Therapeutic and other chemical agents are an important factor in many coroners' investigations and expert input of a clinical pharmacologist may be invaluable in resolving causality. (3) In view of the frequency of requests for consultation to coroners, clinical and forensic toxicology should be viewed as an essential component of clinical pharmacology training programs.

**Key Words:** Coroner cases, drug safety, drug fatality, toxicology, clinical pharmacology training

185

**Antidepressant prescribing for Canadian children and youth**MacLeod SM,<sup>1</sup> Rieder MJ,<sup>2</sup> Khaled LA,<sup>3</sup> Fearnley J,<sup>3</sup> Brogan T,<sup>3</sup> Graham J,<sup>4</sup> McCormick J<sup>3</sup><sup>1</sup>British Columbia Research Institute for Children's and Women's Health, Vancouver, <sup>2</sup>University of Western Ontario, London; <sup>3</sup>Brogan Inc, Ottawa, <sup>4</sup>William Osler Health Centre, Brampton, Canada*Corresponding Author:* [smacleod@cw.bc.ca](mailto:smacleod@cw.bc.ca)**Background:** It has been reported that 20% of Canadian children will experience a major depressive illness before 18 years. In 2004 Health Canada warned of psychiatric or behavioural adverse reactions encountered by children/youth taking selective serotonin reuptake inhibitors (SSRIs) or venlafaxine. It was recommended that therapeutic effects of antidepressants, which are often marginal beyond those seen with placebo, should be weighed against risks of possible toxicity and suicide. Fluoxetine and fluvoxamine were excluded from the warning. The warning focused attention on a lack of evidence-based child/youth psychopharmacologic labeling.**Methods:** A pediatric drug use study was conducted based on 1999-2000 private drug plan data covering 2 million beneficiaries (birth – 18 years). Claimants were surveyed for 12 months following their 1999 birthday. Subjects were selected based on any antidepressant use and, for substudy, based on receipt of a prescription for an SSRI or venlafaxine.**Results:** There were 1.032 million child/youth claimants who met overall study criteria and 16,731 received at least one antidepressant prescription. Of these, 10,322 received SSRIs and 972 received venlafaxine. The rate of antidepressant use consistently increased with age, reaching 52 per 1000 active claimants followed after their 17 birthday. In the age group 13-17y, 11,730 claimants received antidepressants and approximately 75% of these received SSRIs or venlafaxine (paroxetine 29%, sertraline 20%, fluoxetine 13%, venlafaxine 7%, fluvoxamine 6%).**Conclusions:** At 1.6% of claimants below the age of 18, Canadian use of antidepressants in 1999-2000 was much lower than anticipated from the burden of depressive illness in children and youth. Either the condition is underdiagnosed or most cases are being treated as recommended with counseling and behavioural therapy. When antidepressant drugs were used, 75% of adolescent patients received an SSRI or venlafaxine. Of this group only 1 in 4 received fluoxetine or fluvoxamine, the agents exempted from the 2004 warning.**Key Words:** *Antidepressants, depression, children, SSRIs, venlafaxine*

186

**Long-term effects of neonatal caffeine administration on hypercapnic chemoreflex development in rats.**

Montandon G, Bairam A, Kinkead R

Centre de Recherche de l'Hopital St François d'Assise, Université Laval, Dpt Pédiatrie, Québec, Canada.

*Corresponding Author:* [aida.bairam@crsfa.ulaval.ca](mailto:aida.bairam@crsfa.ulaval.ca)**Background:** Caffeine is an adenosine receptor antagonist commonly used as a respiratory stimulant to treat neonatal apnoeas of premature newborn. Neonatal caffeine treatment (NCT) has long-term effects on adenosine receptor expression and distribution; however the potential effects on respiratory control are unknown.**Methods:** To determine whether NCT alters respiratory control development in rats, pups received 15mg/kg of caffeine orally each day from postnatal days 3 to 12. Half of the litter was given caffeine (NCT), whereas the other half received vehicle (sham). Measurements of ventilatory response to moderate hypercapnia (FICO<sub>2</sub>=0.05) were made using whole-body plethysmography at postnatal day 20 (before puberty and weaning) and at adulthood (9-12 week-old).**Results:** At day 20, juvenile NCT male rats showed higher tidal volume (11%, P=0.001, n=12), minute ventilation (12%, P=0.025, n=12), and inspiratory flow (22%, P=0.024, n=12) responses to hypercapnia than shams. These effects were not observed in juvenile NCT females. In adult, NCT male rats showed stronger tidal volume (17%, P<0.001, n=12) and inspiratory time (11%, P=0.015, n=12) responses to hypercapnia than shams, but a smaller breathing frequency response (19%, P=0.002, n=12) with no net change in minute ventilation. At normoxia, male rats demonstrated a higher breathing frequency (14%, P=0.002, n=12) in NCT than in shams. No difference was observed in adult females.**Conclusion:** These results show that NCT has a gender-specific influence on respiratory control during early life that persists until adulthood.**Key Words:** *Apnea, caffeine, development, respiratory control, rat*

187

### Exercise improves diabetes-related endothelial dysfunction in db/db mouse model of type II diabetes

Moien-Afshari F,<sup>1</sup> Khazaei M,<sup>2</sup> Merchant S,<sup>1</sup> Laher I<sup>1</sup>  
<sup>1</sup>Department of Pharmacology and Therapeutics, University of British Columbia, Canada, <sup>2</sup>Department of Physiology, Isfahan University, Iran

Corresponding Author: [moien@interchange.ubc.ca](mailto:moien@interchange.ubc.ca)

**Background:** Diabetes mellitus is the leading cardiovascular risk factor in developed countries. Management of patients with type 2 diabetes requires combined life-style modifications (diet, exercise) and pharmacological treatment. While the vascular benefits of pharmacological management of type 2 diabetes are well documented, relatively little is known regarding the effects of life-style modifications on the vascular complications of the disease. We will address this by examining arteries from the db/db mouse, an accepted model of obesity related diabetes.

**Objectives:** We examined arteries from the db/db mouse model of type II diabetes to determine whether exercise improves arterial endothelial function.

**Methods:** Two groups of diabetic and matched control (WT) mice were used and divided into sedentary and exercised. Mice were trained to exercise for 1 hr (212m)/day, 5 days/week for 8 weeks. Vasodilation to acetylcholine (ACh) and sodium nitroprusside (SNP) was measured in precontracted aortic rings and septal coronary arteries. Phenylephrine (PE)-induced constriction was also measured in the presence and absence of L-NAME or bosentan.

**Results:** Responses to ACh were severely impaired in sedentary db/db mice (in aorta and septal arteries) compared to WT animals. The EC<sub>50</sub> to ACh was not changed, while the maximal response (E<sub>max</sub>) was significantly decreased in db/db mice. SNP-induced relaxation was similar in both groups. Exercise significantly improved ACh-induced relaxation in db/db arteries compared to sedentary db/db animals (E<sub>max</sub> in the septal artery: 49.9±4.1% vs 29.5±2.1%; in aorta: 28.8±3.1% vs 5.6±0.7%). PE-induced constriction in aortic rings was significantly higher in db/db compared to WT mice; this response was not altered by exercise. Pretreatment of aortic rings with L-NAME and bosentan did not change the E<sub>max</sub> in db/db mice.

**Conclusions:** We conclude that exercise improves impaired endothelium-dependent vasorelaxation in diabetes with little effect on smooth muscle constriction.

**Key Words:** Diabetes, exercise, endothelium-dependent vasorelaxation, mice

188

### Role of keratinocyte in cutaneous drug reactions with sulfamethoxazole: toxicity and metabolism

Nadeau C, Rieder MJ  
 Biotherapeutic group, RRI, Child Health Research Institute, Departments of Paediatrics, Physiology & Pharmacology and Paediatrics, University of Western Ontario

Corresponding Author: [cnadeau@uwo.ca](mailto:cnadeau@uwo.ca)

**Background:** Cutaneous drug reactions (CDRs) are the most prevalent event in adverse drug reactions (ADRs), occurring in up to 30% of all documented cases. Of all drug regimes, the anti-microbial agents with the highest reported CDRs contain trimethoprim-sulfamethoxazole (TMP-SMX). 4% of immunocompetent patients receiving sulfamethoxazole (SMX) have CDRs, a rate which rises in HIV positive patients (40% to 60%). The role of keratinocytes (Kcs) in CDRs is poorly understood.

**Objectives:** To determine the toxicity of SMX and its metabolite sulfamethoxazole-hydroxylamine (SMX-HA) in Kcs as well the SMX metabolism capacity in Kcs.

**Methods:** Kcs from the HaCaT line were incubated with increased concentration of SMX (50-3200 µM) and SMX-HA (25-1600 µM) and with different incubation time (2-24 hours). After incubation, cellular viability was determined by using a MTT cytotoxicity assay. Also, HaCaT cells were incubated with SMX (0-1500µM) with different incubation time (0-24). Then, SMX metabolite production, acetyl-sulfamethoxazole (AC-SMX), was measured by using HPLC analysis.

**Results:** There is a concentration-dependent and time-dependent decline in cell viability of HaCaT with SMX-HA. At 800 µM at all incubation times the maximum cell viability is 30.02% ± 3.05%. With SMX, there is a very small decline of cell viability only found at high SMX concentration (3200µM). As early as after 2 hours of SMX incubation, HaCaT cell started to produce AC-SMX (0.2703µM ± 0.0076µM with 500µM of SMX). The production of this metabolite was in the range of 1%.

**Conclusions:** The time-course MTT assay in HaCaT cell line with SMX and SMX-HA suggests that keratinocytes are sensitive to reactive-metabolite mediated cytotoxicity. This may be important in the pathogenesis of CDRs. This data also suggests that keratinocytes metabolize SMX to AC-SMX metabolites in time and concentration-dependant manner.

**Key Words:** Sulfamethoxazole, keratinocytes, cutaneous drug reactions

189

### Child neurodevelopment following treatment for nausea and vomiting of pregnancy with Diclectin: a prospective controlled study

Nulman I, Ilios H, Knittel-Keren D, Barrera M, Koren G  
The Motherisk Program, Division of Clinical Pharmacology/Toxicology, Department of Psychology, The Hospital for Sick Children, The University of Toronto, Canada

Corresponding Author: [inulman@sickkids.ca](mailto:inulman@sickkids.ca)

**Background:** Nausea and vomiting of pregnancy (NVP) occurs in 70-80% of women, may lead to Hyperemesis Gravidarum (HG) and severely affect women's life style. The only antiemetic approved by Health Canada for NVP is Diclectin (doxylamine 10 mg, and vitamin B6 10 mg). Thousands of women are being prescribed this drug. While Diclectin has been shown to cause no fetal dysmorphism, its effects on the developing central nervous system (CNS) remain to be established. Potential adverse effects of the drug on fetal CNS may constitute a serious public health issue.

**Objectives:** To assess whether children prospectively collected exposed in utero to NVP and Diclectin and tested with formal psychological tests are different from children exposed only to NVP, and from children not exposed to NVP, Diclectin, and other teratogens.

**Methods:** A prospective, controlled, blinded assessment 3 groups of mother-child pairs exposed to NVP and Diclectin (n=41), exposed to NVP (n=37) and unexposed to NVP or teratogens (n=30). We compared the neuro-cognitive outcomes, language, and measures of child behavior among the 3 groups.

**Results:** There were no significant differences between the groups in Global IQ percentile (79.4+20.5; 73.1+23.1; 73.4+27.3), total percentile of PLS-4 (80.4+28.5; 73.9+19.3; 76.5+24.1) and CPRS-R-L scores (48.4+7.7; 50.3+9.1; 49.2+8.5).

**Conclusions:** Exposure to Diclectin does not adversely affect neuro-cognitive development of preschool and early school children. When indicated, Diclectin therapy should be instituted to prevent HG, and improve pregnant women life style.

**Key Words:** *Diclectin, pregnancy, child development*

190

### Characterizing the molecular events leading to bilirubin mediated apoptosis: lack of aryl hydrocarbon receptor signaling in formation of reactive oxygen species

Oakes GH, Bend JR

Department of Physiology and Pharmacology, University of Western Ontario, Canada

Corresponding Author: [garth.oakes@fmd.uwo.ca](mailto:garth.oakes@fmd.uwo.ca)

**Background:** Unconjugated bilirubin (BR), the potentially toxic, end product of heme catabolism, causes encephalopathy in severely jaundiced neonates. BR has been shown to induce apoptosis in numerous cell types; however, the molecular mechanisms that contribute to BR cytotoxicity remain unclear.

**Objectives:** To characterize the sequence of molecular events leading to BR-induced cytotoxicity in murine hepatoma (Hepa 1c1c7) cells.

**Methods:** Hepa 1c1c7 cells were exposed to elevated concentrations (5-50  $\mu$ M) of BR and assayed for markers of toxicity. Reactive oxygen species (ROS) production was measured using the fluorescent probe, 2,7-dichlorofluorescein diacetate. Changes in mitochondrial membrane potential were assayed with the dye JC-1. Caspase activation was detected by immunoblot analysis. Intracellular glutathione (GSH) concentration was measured using monobromobimane, a compound that reacts non-enzymatically with thiols to form a fluorescent adduct.

**Results:** In the present study, elevated concentrations of BR markedly increased the intracellular generation of ROS in a concentration-dependent manner. ROS production was significantly increased as early as 15 min. The observed increase in ROS was not dependent on aryl hydrocarbon receptor (AhR) signaling, as cell lines (C4 and C12) deficient in the AhR signaling pathway were not protected from BR-mediated oxidative stress. Mitochondrial membrane depolarization was observed 2h after treatment with 50 $\mu$ M BR. A significant decrease in intracellular GSH was observed 6h after exposure to BR. Active caspase-3 was detected 4.5 h post-treatment. Finally, approximately 12 h after BR treatment, procaspase-2 was detected in the cytosol, presumably released from the nucleus. No active caspase-2 was detected.

**Conclusions:** These results demonstrate that the increased production of ROS was the earliest detected event in BR-mediated apoptosis and that AhR signaling did not contribute to this early event. The observed mitochondrial membrane depolarization indicates the mitochondria may be a major source of ROS. Finally, these data clearly demonstrate that caspase-2 is not the initiator caspase in BR-mediated apoptosis.

**Key Words:** *Cytotoxicity, bilirubin, caspase, apoptosis, mitochondrion*

191

**Agreement between real time visual analogue scores & videotaped visual analogue scores**

O'Brien L, Ipp M, Goldbach M, Koren G, Taddio A  
The Hospital for Sick Children, Division of Clinical Pharmacology and Toxicology, Toronto, Canada

*Corresponding Author:* [lisa.obrien@sympatico.ca](mailto:lisa.obrien@sympatico.ca)

**Background:** Assessing pain in a pediatric population that is unable to self-report is a challenging task. Visual Analogue Scales (VAS) are commonly used and well validated pain assessment tools. To date, no one has compared the results of real time assessment using this scale to results from video recordings.

**Objectives:** To determine whether real time assessment of vaccination pain using VAS is consistent with VAS scores obtained from video recordings of the same procedure.

**Methods:** A double-blind, randomized study was conducted to determine whether 4% amethocaine decreases measles-mumps-rubella (MMR) vaccination pain. Infants receiving their routine 12-month MMR vaccination were randomized to receive amethocaine or placebo 30 minutes prior to vaccination. A 100 mm VAS was completed just prior to and within 15 seconds of vaccination by one of two pediatricians that performed the vaccination; a blinded observer also completed a VAS. The procedure was video recorded by the blinded observer. The two pediatricians and the observer independently rated pain of the procedure from the video recording viewed with sound at a later time.

**Results:** A reliability analysis was conducted using the observer's real time and video recorded scores ( $n = 160$ ), an intraclass correlation coefficient (ICC) of 0.889 was produced ( $p < 0.001$ ). The mean pre score was  $9.15 \text{ mm} \pm 15.87$  in real time and  $10.08 \text{ mm} \pm 21.13$  from video recording ( $p = 0.391$ ); post scores were  $26.18 \text{ mm} \pm 26.54$  in real time and  $27.46 \text{ mm} \pm 30.63$  from video recording ( $p = 0.421$ ). Pediatricians had ICC's of 0.912 ( $n = 97$ ) and 0.927 ( $n = 134$ ) respectively ( $p < 0.001$ ). No significant differences between real time and video recorded scores existed for either pediatrician.

**Conclusions:** Real time application of VAS is consistent with assessment from video recordings, thus increasing the utility of this scale for bedside application in pediatric populations.

**Key Words:** *Visual analogue scales, pain assessment, vaccination, infant, video*

192

**Evidence for divided dosing of oral furosemide**

Pollak PT, Tam EV

University of Calgary and Dalhousie University

*Corresponding Author:* [Pollak@dal.ca](mailto:Pollak@dal.ca)

**Background:** Furosemide is a high-ceiling diuretic widely used in the treatment of edematous states, such as congestive heart failure. Increasingly, clinicians are encountering divided dosing regimens in its administration. We found little benefit when moving to divided dosing in one of our patients and questioned what evidence was available to support this treatment strategy.

**Objectives:** Our goal was to conduct a review of the literature, examining the current body of evidence for optimal oral dosing frequency of furosemide.

**Methods:** Pubmed was searched using MeSH terms "Furosemide/administration and dosage" AND "Drug Administration Schedule" (OR the free text entry "divided dose"). To further increase the chances of finding evidence in favour of higher frequency administration the search was widened from studies applicable to the oral use of furosemide, to look for evidence of superiority of continuous intravenous infusion (the equivalent of infinitely divided dosing) over bolus dosing.

**Results:** The number of studies addressing the question of the optimal oral dosing regimen of furosemide was extremely limited. Available studies comparing once daily vs. divided dosing involved very small sample sizes, and presented inconsistent findings. Data involving continuous infusion, while more plentiful, were conflicting as well. There was little discussion of the potential adverse effects associated with long-term treatment with either oral dosing regimen.

**Conclusions:** No high grade evidence to support the use of divided dosing of furosemide could be found. Currently, there is no consistent evidence to suggest any theoretical advantage in terms of increased efficacy or decreased toxicity. Before wide spread use of divided dose administration of furosemide is adopted, a well controlled head-to-head comparison of single vs. divided dosing should be carried out in a sufficient number of patients to determine if any superiority of divided over single daily dosing exists.

**Key Words:** *Furosemide, dosing schedule, effectiveness, evidence*

193

**What factors influence breastfeeding choices and adherence to antidepressant therapy in post-partum women with depression?**

Rubin E, Vohra S, Taguchi N, Lee A, Ito S  
Division of Clinical Pharmacology & Toxicology, Hospital for Sick Children, Departments of Pediatrics and Pharmacology, University of Toronto

*Corresponding Author:* [shinya.ito@sickkids.ca](mailto:shinya.ito@sickkids.ca)

**Background:** Breastfeeding is the ideal method of infant nutrition, but many women will take some form of medication (e.g. antidepressants) while breastfeeding. The decision to breastfeed or not may be affected by the fear of an infant becoming exposed to mother's medication. On the other hand, non-adherence to drug therapy such as antidepressants may have serious consequences.

**Objectives:** The objective of this study was to determine what factors influence breastfeeding choices and adherence to antidepressant therapy in post-partum women with depression.

**Methods:** The study population was women who were prescribed selective serotonin reuptake inhibitors (SSRIs) in pregnancy or the puerperium. Subjects meeting inclusion criteria were identified in our reproductive toxicology program (Motherisk) and surveyed via telephone regarding two outcomes: 1) adherence to antidepressant treatment and 2) breastfeeding choices during this treatment. Based on the woman's medication and breastfeeding history, she was classified as either adherent to both the drug and breastfeeding or non-adherent. All outcomes were compared between the adherent and non-adherent groups. The primary outcome was mother's perception of the toxicity risk in the infants during the maternal antidepressant therapy during breastfeeding.

**Results:** Of 60 women surveyed, 2/3 was classified as adherent. There was no statistical difference in their risk perceptions. However, the internet was often a source of misinformation. The most women reported that their physicians told them to continue breastfeeding during the drug therapy. The survey also showed that women's risk perception changed in favor of breastfeeding during the therapy after counseling by Motherisk.

**Conclusions:** About 2/3 of the women who seek advice from our service about SSRI and breastfeeding are adherent to the therapy during breastfeeding. Internet sources for safety of SSRIs during breastfeeding may pose misinformation risks.

**Key Words:** *Breastfeeding, antidepressants, pregnancy, telephone interview*

194

**Validation of a new hair test for cortisol and progesterone**

Sauvé B,<sup>1</sup> Karaskov T,<sup>1</sup> Klein J,<sup>1</sup> Koren G<sup>1</sup>

<sup>1</sup>Motherisk Program, Hospital for Sick Children and Department of Pharmacology, University of Toronto, Toronto

*Corresponding Author:* [brittany\\_sauve@yahoo.ca](mailto:brittany_sauve@yahoo.ca)

**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 urinary analysis since it provides a long-term perspective, hair growing 1 cm/month. Cortisol is an important hormone in stress response and acute responses to stress are currently measured only in plasma and saliva, reflecting a short time window. Hair cortisol would assess long-term cortisol associated with chronic stress and disease state.

**Objectives:** To validate an enzyme-linked immunoassay for cortisol and progesterone hair testing and to assess sensitivity, specificity and reproducibility.

**Methods:** Hair samples were obtained from 12 healthy individuals (males=5, females=7) to give a total of 122 sections which were analyzed for cortisol and/or progesterone. The hormones from all the samples were extracted and measured using ELISA with a limit of detection of 20pg/mg of hair and 3pg/mg of hair for cortisol and progesterone respectively.

**Results:** The mean cortisol levels in males was 47.2pg/mg (SD=33.6) and in females was 48.4pg/mg (SD=20.3). The cortisol levels ranged between 7.8-106.1pg/mg. Progesterone concentrations ranged from 4.3-27.5pg/mg (mean=17.6) in females and 2.2-14.1pg/mg (mean=9.6) in males, providing evidence that hair concentrations are a reflection of what is seen in plasma for progesterone. Results were reproducible.

**Conclusions:** This is a first attempt to measure the female reproductive hormone progesterone in hair. Levels of cortisol were also measurable and can be used as a long-term biomarker for stress.

**Key Words:** *Hair, cortisol, progesterone, ELISA, analysis*



195

### Intravenous busulfan pharmacokinetics and their relation to toxicity and efficacy in children receiving hematopoietic stem cell transplant: preliminary results

Schechter T, Finkelstein Y, Doyle J, Verjee Z, Koren G, Dupuis LL

Division of Clinical Pharmacology and Toxicology, Division of Haematology/Oncology, Department of Clinical Biochemistry, and Department of Pharmacy, The Hospital for Sick Children, Toronto, ON, Canada

Corresponding Author: [yfinkel@yahoo.com](mailto:yfinkel@yahoo.com)

**Background:** Conditioning regimens preceding hematopoietic stem cell transplantation (HSCT) in children often include busulfan. Recently, intravenous busulfan (IVBu) has been introduced. The use of first dose IVBu area under the curve (AUC) in children undergoing HSCT as a predictor of efficacy and toxicity is under investigation.

**Objectives:** To describe the pharmacokinetics of IVBu in infants and children, and to correlate IVBu AUC with the development of veno-occlusive disease (VOD) and engraftment of neutrophils.

**Methods:** Eighteen children who underwent HSCT at The Hospital for Sick Children, Toronto between April 2003 and September 2004 and received IVBu as part of their conditioning regimen were included in this retrospective study. Diagnoses included malignant (9), metabolic (5) and immunologic (4) diseases. Initial IVBu doses were based on patients' weight. Seven blood samples were drawn from each patient after the first IVBu dose. Pharmacokinetic parameters were calculated using 1-compartment analysis (WinNonLin 4.1). Subsequent IVBu doses were adjusted to achieve an AUC of 900-1500 $\mu$ mol $\cdot$ min.

**Results:** The median patient age was 3.5 years (range 3mo-16.9 years), including 6 infants. Mean IVBu pharmacokinetic parameters were as follows:  $C_{max}$ =4.9 $\mu$ Mol;  $V_{ss}$ =0.64 L/kg; AUC=1323 $\mu$ Mol $\cdot$ min. Dose adjustment was required in 10 patients (55%). Two patients needed dose escalation by 27-50%; 8 patients needed dose reduction by 10-26%. There were no infusion-related or neurologic toxicities. Seventeen patients (94.4%) engrafted between day +10 to +27. VOD was diagnosed in 4 patients with no previous exposure to antineoplastic agents, including 3/6 infants (50%). Three of these had moderate VOD and one had fatal VOD. Median IVBu AUC were 1378 $\mu$ Mol $\cdot$ min (IQR 399) and 982 $\mu$ Mol $\cdot$ min (IQR 485) for the non-VOD group vs. the VOD group, respectively ( $p$ =0.24).

**Conclusions:** There was no significant difference in any busulfan pharmacokinetic parameter measured between children who developed VOD and those who did not. IVBu AUC did not correlate with the occurrence of hepatic VOD in children.

**Key Words:** Busulfan, stem cell transplantation, pharmacokinetics, children, veno-occlusive disease

196

### Views of paediatricians and researchers on the ethics of paediatric research and using children as volunteers – a Canadian perspective

Sitar DS,<sup>1</sup> Malhotra D<sup>2</sup>, Sammons H<sup>3</sup>, Matsui D,<sup>2</sup> Rieder MJ<sup>2</sup>

<sup>1</sup>Section of Clinical Pharmacology, Department of Medicine, Department of Pharmacology and Therapeutics, Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Canada, <sup>2</sup>Child Health Institute, Department of Paediatrics, University of Western Ontario, London, Canada, and <sup>3</sup>Department of Paediatrics and Child health, University of Nottingham, Nottingham, UK

Corresponding Author: [sitar@cc.umanitoba.ca](mailto:sitar@cc.umanitoba.ca)

**Background:** Many medicines for treating childhood diseases are not licensed for this purpose. There is a perceived disparity among jurisdictions concerning acceptability of children as research subjects.

**Objective:** This pilot survey assessed views of paediatricians and researchers regarding the use of children in drug studies, and the possible existence of regional differences within Canada.

**Methods:** An anonymous survey was distributed among paediatricians and researchers in four Canadian academic centres to evaluate their views concerning use of children in clinical research. Response by participants allowed for comparisons between Manitoba and the other Canadian centres. All data were analyzed by nonparametric statistics (Fisher's Exact Test).

**Results:** Fifty completed surveys contributed to the assessed outcomes. Most respondents (94%) were experienced in paediatric research, but only a minority had been members of ethics boards (24%) or had submitted a protocol to one (31%). Very few had training in ethical review (8%), and all positive responses were from Manitoba ( $P$ =0.112). Respondents proposed a median age of assent (10 yr) and consent (15 yr). The majority (60%) disagreed with the use of healthy children for age-specific dosing studies, with financial incentives to parents (61%) and with using teenage magazines for recruitment (67%). The majority favored child participation only when there was potential for direct benefit (59%). Among the six hypothetical clinical trials considered, only two had majority consensus for admission of children, but only one was believed to gain acceptance from their ethics committee by the majority of respondents. A variety of problems was identified for each of the protocols.

**Conclusions:** These data indicate the need for a formal training program in ethics of paediatric clinical trials, both for investigators and for members of ethics committees. This initial survey was unable to discriminate substantial regional disparities between investigators in Manitoba and other academic centres in Canada.

**Key Words:** Clinical research, drug studies, ethics, paediatrics, survey

197

**Chronic n-acetylcysteine treatment protects against insulin resistance and hypertension in fructose-fed rats**

Song D, Hutchings S, Pang CY

Department of Pharmacology &amp; Therapeutics, Faculty of Medicine, The University of British Columbia

*Corresponding Author:* [ssddzz@interchange.ubc.ca](mailto:ssddzz@interchange.ubc.ca)

**Background:** Reactive oxygen species are involved in the pathogenesis of endothelial dysfunction, insulin resistance and hypertension. Free radical scavengers, such as vitamin E, glutathione and superoxide dismutase are depressed in patients and experimental animals with hypertension and/or insulin resistance. It is not known whether N-acetylcysteine, a free radical scavenger and glutathione donor, can prevent the development of insulin resistance and hypertension in metabolic syndrome.

**Objectives:** The purpose of the present study was to examine if chronic treatment of fructose-fed rats with N-acetylcysteine, has a protective action against the progression of insulin resistance and hypertension in a rat model of metabolic syndrome.

**Methods:** Male rats were assigned randomly into four groups, and treated for 12 weeks with normal chow, normal chow plus N-acetylcysteine (1.5 g/day per kg), fructose (60% of diet), and fructose plus N-acetylcysteine. After 10 weeks, plasma triglyceride and 15-F2t-isoprostane, and insulin sensitivity were measured, and after 12 weeks, blood pressure were measured and pressor response to methoxamine (15-60 µg/kg min) was assessed in unstrained conscious rats.

**Results:** Relative to normal chow-fed controls, the fructose-fed rats had increased blood pressure, plasma insulin, triglyceride and 15-F2t-isoprostane, and decreased insulin sensitivity; these changes were inhibited by N-acetylcysteine. Maximal pressor response to methoxamine was attenuated in the fructose-fed rats given N-acetylcysteine relative to the other three groups.

**Conclusions:** Chronic treatment with N-acetylcysteine improves insulin sensitivity and prevents the blood pressure increase associated with fructose feeding in rats, the mechanism may involve the decrease of oxidative stress and  $\alpha$ -adrenoceptor-mediated vasoconstriction.

**Key Words:** *Insulin resistance, hypertension, rats, N-acetylcysteine,  $\alpha$ -adrenoceptor-mediated vasoconstriction*

198

**Methodologic challenges in assessing cost effectiveness of a once daily treatment for attention deficit hyperactivity disorder (ADHD) in children aged 6-18 years**

Stewart D

Brogan Inc, Ottawa, Canada and the Canadian Academic ADHD Pharmacoeconomic Modeling Group

*Corresponding Author:* [dstewart@broganinc.com](mailto:dstewart@broganinc.com)

**Background:** ADHD affects at least 4% of Canadian children aged 6-18. Most traditional approaches to treatment require complex multiple dosing schedules which detract from compliance and effectiveness and also confound pharmacoeconomic analysis. A recently developed hypothetical model derived from Ontario Drug Benefit Plan (ODBP) experience suggests that once daily treatment with mixed salt amphetamine extended release capsules (Adderall XR™) would result in significant cost saving over treatment initiated with dextroamphetamine sulphate (DAS) or methylphenidate hydrochloride (MPH). The computed weighted average annual cost for treatment with DAS was \$6320, with MPH was \$5957, and with AXR was \$3635.

**Methods:** A multidisciplinary panel of Canadian academic clinicians interested in ADHD reviewed the model and agreed on priority requirements for data to be collected prospectively to populate an expanded and strengthened model.

**Results:** The following initiatives will support the development of an improved decision aid for ADHD therapy: (1) tracking social, health, and educational outcomes in ADHD children receiving stimulant therapy. Data recorded will include assessment of the use of health services by patients and families. (2) objective, long term monitoring of adherence to daily multiple dose and single dose therapies among ADHD children to include evaluation of compliance with short, intermediate, and long acting stimulant agents (3) evaluating the impact of adherence to stimulant therapy on utilization of educational resources and on classroom effectiveness and productivity (4) comparison of outcomes among primary and secondary school populations, (5) expanding the definition of ADHD associated costs to include indirect effects such as substance abuse, traffic accidents, traumatic injury, premature school leaving, and subsequent poor employment opportunity.

**Conclusions:** ADHD is an important public health challenge and therapeutic decision-making would be improved by the availability of a validated pharmacoeconomic model populated by prospectively gathered data in keeping with suggestions of the ADHD expert panel.

**Key Words:** *ADHD, pharmacoeconomic modeling, dosing regimen, compliance, stimulants*

199

**Cost effectiveness of mixed salt amphetamine extended release capsules (Adderall AR™) for treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6-18 years**

Stewart D

Brogan Inc, Ottawa, Canada and the Canadian Academic ADHD Pharmacoeconomic Modeling Group

Corresponding Author: [dstewart@broganinc.com](mailto:dstewart@broganinc.com)

**Background:** Once daily therapy with Adderall XR (AXR) for children (6-18y) with ADHD will yield more satisfactory social and health outcomes than will complex multiple dosing with short acting agents dextroamphetamine sulphate (DAS) and methylphenidate hydrochloride (MPH).

**Objective:** To evaluate the cost effectiveness of once daily AXR treatment compared to DAS and MPH based on actual utilization of the latter drugs by qualifying Ontario Drug Benefit Plan (ODBP) beneficiaries in the 2002-2003 school year.

**Methods:** Actual ODBP utilization data from 800 children (DAS: 137; MPH: 663) was used to populate a decision tree and outcome projections were made based on physician and educator expert opinion. Only claimants who were naïve to stimulant therapy for at least 6 months before August 2002 were included. Adequacy of control was defined on the basis of physician consensus as adherence to the therapeutic regimen greater than 80%.

**Results:** Adequate control was achieved in 38.6% of DAS recipients, 42.7% of MPH recipients, and 80.7% (predicted) of AXR recipients. The expected cost of annual therapy from a societal perspective, including educational impact, was computed as \$6320 for DAS, \$5597 for MPH, and \$3635 for AXR recipients. Health care costs inclusive of drug purchase were calculated as \$1653 for DAS, \$1584 for MPH, and \$2172 for AXR.

**Conclusions:** While drug costs are higher for AXR treatment, reduced expenditures and increased productivity in the classroom are likely to mitigate the incremental increase in treatment costs and prove beneficial from a societal perspective. This projection should be validated in a prospective study design.

**Key Words:** *Cost effectiveness, ADHD, stimulants, pharmacoeconomic modeling, dosing regimen*

200

**An in vitro model for human mammary drug transport**

Takahashi S, Yamauchi A, Yeger H, Ito S

Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, and the Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada

Corresponding Author: [Shinya.ito@sickkids.ca](mailto:Shinya.ito@sickkids.ca)

**Background:** Drug excretion into breast milk is mediated not only by passive diffusion, but also by carrier-mediated processes, precluding theoretical prediction. Due to ethical constraints, however, human in vivo studies are difficult, and animal experiments suffer from substantial species difference. A valid in vitro human mammary gland model, which can be used as a pre-clinical testing modality, is of significant importance.

**Objectives:** To develop an in vitro model of human mammary gland for drug excretion studies. To this end, we compared 2 representative human mammary gland cell lines for their suitability as a model.

**Methods:** The non-tumorigenic human mammary gland epithelial cell lines, MCF10A and MCF12A, were cultured. mRNA expression of organic cation transporters was examined using RT-PCR. To examine integrity of the cell monolayer grown on permeable membranes, efflux of labeled mannitol as an extracellular marker was monitored (functional integrity), and tight-junction formation (morphological integrity) was determined by visualizing expression of the tight-junction protein, ZO-1, using confocal immunofluorescence. Using carnitine as a probe compound, vectorial preference of its uptake across the cell monolayer was examined.

**Results:** In both MCF10A and MCF12A cells, the expression profiles of organic cation transporters are similar to that of the in vivo human mammary gland epithelia. After 3 weeks of culture, the MCF10A formed a functionally tight monolayer, which was consistent with ZO-1 expression, whereas the MCF12A failed to form a tight monolayer. Carnitine uptake in the MCF10A monolayer was >10-fold higher from the basal (maternal) side than from the apical (milk) side.

**Conclusions:** The MCF10A cells appear suitable for further development as an in vitro human mammary gland model for drug transport. Supported by CIHR

**Key Words:** *Transporter, Carnitine, MCF10A, ZO-1, breastfeeding*

201

**Establishing a limited sampling strategy for mycophenolic acid in lung transplant recipients**

Ting LSL, Partovi N, Levy RD, Riggs KW, Ensom MHH

University of British Columbia Faculty of Pharmaceutical Sciences, Children's & Women's Health Centre of British Columbia Department of Pharmacy, Canada

Corresponding Author: [ensom@interchange.ubc.ca](mailto:ensom@interchange.ubc.ca)

**Background:** Mycophenolic acid (MPA) is an immunosuppressive agent used in solid organ transplantation. The area-under-the-curve (AUC) pharmacokinetic monitoring of MPA has been advocated to improve treatment outcomes; however, it is impractical and costly. A limited sampling strategy (LSS) provides a reliable alternative, yet no LSSs have been developed for the lung transplant population.

**Objectives:** To define the optimal limited sampling strategy for mycophenolic acid monitoring and to test its predictive performance in lung transplant recipients.

**Methods:** In phase I, 8 lung transplant recipients were entered into the study. Upon administration of a steady-state morning MPA dose, blood samples were collected at 0,0.3,0.6,1,1.5,2,4,6,8,10, and 12 hours post-dose. Total plasma MPA concentrations were measured by a validated HPLC method with ultraviolet detection and pharmacokinetic parameters analyzed by non-compartmental modeling using WinNonlin 4.1. LSSs were determined by multiple regression analysis with forward stepwise elimination using Statistica® software. Potential LSSs were restricted to 3 or fewer time points within the first 2 hours post-dose. In phase II, 6 additional lung transplant recipients underwent serial blood sampling and the samples were analyzed according to the above procedures. These data were used to test the predictive performance of LSSs [measured by the coefficient of determination ( $r^2$ ), bias and precision] developed in Phase I. All concentrations and AUC values were log-transformed to normalize the data.

**Results:** The correlation between AUC and single concentrations was poor (e.g.  $r^2=0.353$  for C0;  $r^2=0.742$  for C2). The optimal LSSs for 2- and 3-concentrations (and their predictive performance) are as follows: Equation 1:  $\text{LogAUC}=0.9957\text{LogC1.5}+1.7125\text{LogC2}+1.2860$ ; precision=13.15%; bias=0.248%;  $r^2=0.917$  Equation 2:  $\text{LogAUC}=0.1402\text{LogC0.8302LogC1.5}+1.4580\text{LogC2}+1.2304$ ; precision=11.50%; bias=-3.82%;  $r^2=0.970$ .

**Conclusions:** The optimal and most clinically feasible LSSs (2- and 3-conc) for lung transplant recipients in this pilot study are Equations 1 and 2, respectively. These are based collectively on number of blood samples required,  $r^2$ , bias and precision.

**Key Words:** Cyclosporine, pharmacokinetics, renal transplantation, pediatric, limited sampling strategy

202

**HIV-infected injection drug users (IDUs) on lopinavir- or atazanavir-based HAART do not require changes in methadone dose when starting or changing regimens in a directly observed therapy (DOT) program**

Tossonian H,<sup>1</sup> Raffa J,<sup>1</sup> Grebely J,<sup>1</sup> DeVlaming S,<sup>2</sup> Conway B<sup>1</sup>

<sup>1</sup>Dept. of Pharmacology and Therapeutics, University of British Columbia, <sup>2</sup>PCHC, Vancouver Coastal Health Authority, Vancouver

Corresponding Author: [hkt@interchange.ubc.ca](mailto:hkt@interchange.ubc.ca)

**Background:** Pharmacokinetic data suggest that changes in methadone levels following the initiation of HAART in IDUs may represent a major barrier to its use in this population. However, little clinical data are available to support this statement.

**Objectives:** Within a prospective observational study, we have measured the adjustment of methadone doses after lopinavir/ritonavir (Kaletra®) or atazanavir (ATV, with and without ritonavir boosting) were prescribed, as well as clinical outcomes and patient adherence to treatment.

**Methods:** We identified 25 HIV-infected IDUs on methadone attending the Pender Community Health Centre requiring HAART, who were prescribed either, Kaletra® and 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs), or ATV and 2 NRTIs. A community pharmacist gave HAART along with methadone under DOT once daily. Follow-up was according to clinical standards, with changes in methadone dose being made as required to achieve clinical stabilization within the first 3 months HAART.

**Results:** Twelve (5 Females, 7 Males) and 13 patients (4 Females, 9 Males) were observed taking Kaletra- or ATV-based HAART, respectively. Of those patients receiving ATV, 10/13 received ritonavir boosting. Mean changes were -5 mg/day on Kaletra ( $p=0.058$ ) and 0 mg/day on ATV ( $p < 0.0001$ ). In patients on Kaletra, 8/12 (67%) patients achieved virological suppression (Viral Load  $< 400$  copies/mL) as compared to 7/13 (54%) patients on ATV. However, no statistically significant difference was observed between the virologic efficacies of the two approaches ( $p = 0.69$ ).

**Conclusions:** While pharmacokinetic data are available to suggest that atazanavir and Kaletra® do not effect serum methadone, this data provides clinical evidence for these observations. These may be viable alternatives to nevirapine in patients demonstrating decreased adherence due to methadone withdrawal in a DOT program.

**Key Words:** HIV, methadone, antiretrovirals, Kaletra, atazanavir

203

**In vitro thiol exchange: a novel assay to predict the efficacy of homocysteine-lowering therapies**

Urquhart B, House A, Cutler M, Spence JD, Freeman DJ  
Departments of Medicine and Physiology/Pharmacology, University of Western Ontario and Robarts Research Institute, London, Ontario, Canada

Corresponding Author: [burquhar@uwo.ca](mailto:burquhar@uwo.ca)

**Background:** Homocysteine (Hcy) is thiol amino acid structurally related to methionine. Elevated total plasma homocysteine (tHcy) is a graded, independent risk factor for development of atherosclerosis. Elevated tHcy can be safely normalized in most patients with folic acid, vitamin B6 and vitamin B12. Unfortunately many patient groups are resistant to this treatment and thus remain at increased risk. Hcy is 70–80 % covalently bound to albumin as a disulfide, limiting its clearance. There have been a number of recent trials evaluating the ability of thiol-containing drugs to exchange with protein bound Hcy to increase its renal or dialytic clearance.

**Objectives:** To validate an in vitro thiol exchange assay to predict the in vivo efficacy of thiol containing drugs to lower tHcy. N-acetylcysteine (NAC), mesna, captopril, dimercaptosuccinic acid (DMSA) and penicillamine were tested in this assay.

**Methods:** DL homocysteine was added to plasma of healthy subjects (n=6) to a final concentration of 30  $\mu$ M and incubated at 40C for 72 hours to allow covalent binding to albumin. Various concentrations of potential thiol exchange agents were added and incubated at 37C for 30 minutes. Aliquots were removed at selected intervals and free Hcy determined by HPLC-FD following protein precipitation.

**Results:** Mesna, captopril and NAC caused a rapid, sustained, concentration dependent increase in free Hcy. At therapeutic concentration, mesna had a greater effect than captopril and NAC. AUC for mesna (1022.9 +/- 35.1) was significantly greater than captopril (854.4 +/-31.0, P<0.01) and NAC (642.5 +/- 20.3, P<0.001). DMSA and penicillamine had minimal effect.

**Conclusions:** Our in vitro results indicate that mesna, captopril and NAC effectively exchange with covalently bound Hcy. Mesna appears to be the most appropriate candidate for decreasing tHcy in resistant populations. This assay can act as screening tool for novel tHcy lowering therapies and should prevent investigators from performing expensive and time-consuming negative trials.

**Key Words:** *Homocysteine, atherosclerosis, mesna, captopril, creatinine clearance*

204

**Comparing in vitro cytotoxicity of Haplophyllum tuberculatum and Ruta graveolens extracts**

Varamini P, Doroudchi M, Mohaghegh-Zadeh A, Soltani M, Ghaderi A  
Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

Corresponding Author: [pegah\\_varamini@yahoo.com](mailto:pegah_varamini@yahoo.com)

**Background:** Despite a vast amount of investigations performed for the development of new synthetic chemotherapeutic agents, only a little improvement is achieved so far. However, plants can be considered as valuable sources of new potential anticancer prototypes.

**Objectives:** To investigate the cytotoxicity of two members of Rutaceae family, Haplophyllum tuberculatum and Ruta graveolens, on cancer cells the in vitro effect of their extracts was studied on three human tumor cell lines.

**Methods:** Ethanolic extracts of the whole plants, prepared by sonication method, were tested on A549 lung carcinoma, 5637 bladder carcinoma and LNCap-FGC-10 prostate adenocarcinoma using WST-1 assay.

**Results:** Inhibitory Concentrations 50% (IC50) of H. tuberculatum showed a significant cytotoxic effect (P < 0.05) of this extract on 5637 (IC50 = 33.01  $\mu$ g/ml) and LNCap-FGC-10 (IC50 < 7.8  $\mu$ g/ml) cell lines. The effect was much higher than the observed activity of R. graveolens on the studied cell lines (IC50 > 125  $\mu$ g/ml and IC50 = 29.98  $\mu$ g/ml, respectively). No effect of either extract was observed on A549 cell line.

**Conclusions:** Higher activity of H. tuberculatum extract compared to R. graveolens, a species with known cytotoxic constituents, gives promises of finding new potent anticancer compounds in this species.

**Key Words:** *Ruta graveolens, Haplophyllum tuberculatum, tumor cell line, cytotoxicity, WST-1*

205

**Possible role of relaxing prostaglandins in blood flow and blood pressure regulation in diabetic patients**

Wong J, Rombach S, Rauniyar P, van Breemen C, Okon E

iCAPTURE Centre, University of British Columbia, Vancouver, Canada

*Corresponding Author:* [eokon@mrl.ubc.ca](mailto:eokon@mrl.ubc.ca)

**Background:** Given that people with diabetes are more prone to vascular complications such as hypertension and arteriosclerosis, understanding the mechanisms underlying vascular disorders could lead to improved treatment for this population. Alterations in prostaglandin metabolism, important regulators of vascular function, could be one of these mechanisms.

**Objectives:** The participation of relaxing prostaglandins in vasomotor function of the internal mammary artery (IMA) in diabetes was studied.

**Methods:** Human IMA were acquired from 30 patients with and without diabetes undergoing coronary artery bypass graft surgery. We measured isometric force generated by the isolated arteries due to application of vasoactive drugs. Application of indomethacin, a COX inhibitor, was used to show the participation of prostaglandins in relaxation.

**Results:** Indomethacin induced contraction in some of the phenylephrine precontracted arteries from the diabetic patients. Capacitative Ca<sup>2+</sup> entry in endothelial cells induced by inhibition of the sarcoplasmic / endoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA) with cyclopiazonic acid (CPA) resulted in arterial relaxation. L-NAME, a nitric oxide synthase inhibitor almost completely inhibited the relaxation in the non-diabetic IMA. However, in the diabetic arteries, there was a 30% L-NAME resistant component of the relaxation that was eliminated by indomethacin.

**Conclusions:** Contribution of relaxing prostaglandins in vasomotion is more pronounced in the arteries of diabetic patients. Therefore relaxing prostaglandins is expected to be more important in the regulation of blood flow and blood pressure for diabetic patients than non-diabetic patients. Based on this data we can expect that NSAIDs, which are COX inhibitors, may be more detrimental to the high blood pressure and other vascular complications for people with diabetes.

**Key Words:** *Diabetes, vascular function, intracellular calcium, prostaglandins*

**ENCORE PRESENTATION**

206

**A comparison of Canadian general paediatric dosing publications**

Dayneka N

Children's Hospital of Eastern Ontario, Ottawa, Canada

*Corresponding Author:* [dayneka@cheo.on.ca](mailto:dayneka@cheo.on.ca)

207

**Measurement of body nitric oxide synthesis in healthy children using L-[<sup>15</sup>N]<sub>2</sub>-guanidino arginine**

Forte P,<sup>1,2</sup> Ogborn M,<sup>2</sup> Lilley T,<sup>2</sup> Nie J<sup>1</sup>

<sup>1</sup>Department of Pharmacology and Therapeutics, University of Manitoba, <sup>2</sup>The Manitoba Institute of Child Health, Winnipeg, Manitoba, Canada

*Corresponding Author:* [pforte@ms.umanitoba.ca](mailto:pforte@ms.umanitoba.ca)

**AUTHOR INDEX (by abstract number)**

**A**

Abu-Laban RB	91
Abushomar H	72, 101
Adachi J	62
Adams J	25
Ahmad F	2,12
Aleksa K	153, 160
Alexander CS	143
Allen M	55, 56
Amin M	1, 52
Anderson G	82
Anderson S	131
Andlin-Sobocki P	51
Anis AH	50, 53
Ansermino JM	183
Antoniou T	150
Aoki FY	154
Asche C	124
Auger S	113
Aulakh A	141
Avner M	155, 167

**B**

Babcock K	136
Bai A	104
Bairam A	180, 186
Bajcar J	132
Balen RM	139, 140
Ballantyne P	16
Balshaw R	89
Bansback N	53
Barbeau M	43, 89
Barkun AN	8
Barnard L	83
Barnes G	172
Barrera M	189
Base C	54
Bassett K	82
Battistella M	132
Bayliff CD	131
Bayoumi AM	150

Beaucage K	76
Beaulieu M	109
Beck CA	105
Bégaud B	115
Behravan J	171
Bell M	54
Bend JR	190
Benson LN	167
Bergman H	102
Bessett L	109
Blackhouse G	18, 45
Blais L	80
Blais N	14
Blais R	85
Boivin JF	10, 44
Bollano E	165
Bonnefis-Boyer S	111
Boskovic R	156, 163
Bouchard M-H	79, 80
Bouin O	1
Bourgault C	88
Bowker S	84
Boyd M	53
Brassard J	14, 76
Brazier N	59
Brogan T	185
Brophy J	23,60,94
Brown JP	109
Brown MJ	157
Brubacher J	91
Buchkowsky SS	146
Burns S	62

**C**

Caetano CA	11
Callum J	37
Campbell NRC	169
Carleton B	15
Carney G	38, 82
Caro JJ	67
Carter C	20

Carter J	133	DeVlaming S	202
Cassels A	82	Dix DB	134, 148
Cavanaugh S	116	Doan VD	180
Cesta A	132	Dolovich L	39,40,41,45,61,62,137,145
Chambers LW	40, 41	Donoahue-Walker T	116
Champoux N	44	Dorais M	64, 65, 119
Chan F	158	Dorkalam M	69
Chandra K	78	Dormuth CR	38
Charbonneau C	22	Doroudchi M	164, 204
Chau D	54	Doyle J	195
Chau K	159	Dragomir A	79, 80, 81
Chen L-Q	5	Ducruet T	10, 44
Chen N	160	Dumont G	174
Chen R	52	Dupont D	52
Chessex P	141	Dupuis LL	168, 195
Cheung S	4	Duranceau A	5
Choiniere M	122, 123	Dutkowski R	154
Chow V	116	Dvorak M	53
Chung A	161		
Cividino AA	42	<b>E</b>	
Clark C	19	Einarson A	165, 179
Collet J-P	122, 123	Einarson TR	48, 49, 69
Collin C	80	El Guebaly N	105
Conway B	202	El-Hadi S	67
Coombes M	29, 92	Ensom MHH	133,134,135,142,143,201
Cosby J	101	Esdaile JM	50
Costei A	163	Etminan M	93, 94,127
Court CA	183	Eurich DT	13,151
Cox F	128		
Coyle D	52	<b>F</b>	
Crott R	10, 44	Faiers A	117
Csanyi-Fritz Y	183	Farahani P	31,32,166
Currie S	105	Farahati F	126
Cutler	203	Farrell B	136,145,137
		Feagan BG	121
<b>D</b>		Fearnley J	185
Dahl ME	74, 75	Fenwick E	18, 24
Davignon J	88	Fernandes O	132
Davison SK	109	Ferrarotto F	115
Daws DE	68	Ferrier S	56
Dayneka N	206	Finkelstein Y	167,195
Desjardins B	70		
Desjardins O	69		
Desroches D	76		



Fisher CG	53
Fisher J	16
Fishman R	77
Fitzgerald JM	26,27,29,94,127
Fleming I	55, 56
Florescu A	163
Fodor G	88
Folia C	129, 130
Forte L	52
Forte P	207
Fournier M	14, 63
Freeman DJ	168, 203
Fricker SP	178
Fung A	20

Gordon A	122, 123
Goudreau J	63
Graham J	185
Grebely J	202
Grindrod K	138
Grootendorst P	3
Groves S	46, 47
Grunau RE	177
Guay MP	81
Guerette B	42
Guévin J-F	76
Guh D	50, 53
Gunraj N	2, 106
Gupta A	131
Gustafson P	23, 60

**G**

Gaebel K	3,31,39,72,87,101,145
Gagné C	88
Galbaud du Fort G	10, 44
Gallagher E	124
Ganjizadeh SR	127
Gardner L	169
Gareri J	170
Garon E	43, 89
Gaudet D	88
Gauthier C	90
Gedeon C	171
Gelin M	15
Genest J	88
George A	172
Gervais A	90, 114
Ghaderi A	164, 204
Gilbert C	173
Gilhuly T	174
Gill S	94
Gill SK	175
Gillis J	31
Gin K	20
Goeree R	45
Goldbach M	191
Goldsmith C	73
Goldsmith G	3
Goodwin J	176

**H**

Haiderali A	66,67,99,100,129,130
Haley DW	177
Halil R	165
Hall H	40
Hamilton DP	134, 148
Han D	33
Hanley D	6
Harrigan PR	143
Hauber B	112
Haydt S	137
Heathcote S	15
Hemels ME	9
Hendriks A	41
Hernandez P	55
Herrmann N	158
Hirdes JP	6
Ho BP	139
Ho S	134
Ho SH	148
Hogan DB	6
Hogg W	41
Holbrook A	3
Hollowell J	67
Houlihan E	135
House A	168, 203
Howard M	39, 45

Hsiang Y	161	Keown P	89
Hurley J	126	Kerth R	180
Hutchings S	197	Keshavjee K	3
Hutchings SR	178	Khaled LA	185
<b>I</b>			
Ignaszewski A	19	Khazaei M	187
Ilios H	189	Khorasheh S	89
Ipp M	191	Khurram I	100
Ishak I	67	Kim T	99,100,129,130
Iskedjian M	49, 69	Kinhead R	186
Ito S	153,182,193,200	Kinnear ME	135
<b>J</b>			
Jackson J	1	Klein J	179, 194
Jacobs P	25	Kluchky J	97
Jang L	19	Knittel-Keren D	189
Jean S	109	Kobelt G	51
Jeffery JR	154	Kolm P	1
Jewesson PJ	139,140,146	Koren G	48,153,156,160,163,167, 170,171,173, 179, 181, 189, 191, 194,195
Johnson J	84	Kozyrskyj A	12,74,75,86,106
Johnson JA	13,125,151	Kozyrskyj K	2
Johnson R	112	Kraag G	117
Johnston KM	23, 60	Kulaga V	181
Jones J	57	Kulin N	17
Jönsson B	7	Kwan D	149
Jorgenson D	149	Kwon B	53
Joseph V	180	<b>L</b>	
Jung L	19	Lablaw D	50, 53
Jurcic J	39, 87	Lachaine J	21,22,85,95,96,115
<b>K</b>			
Kaczorowski J	39,40,41,45,61,145	Lachance-Demers H	76
Kalra S	179	Laher I	187
Karaskov T	179, 194	Lai AA	133
Karwalajtys T	40,41,61	Lalonde L	14,63,76,80
Kearney RA	183	Lam H	154
Kelly S	89	Lamarre D	76
Kennedy C	62	Lamb S	117
Kennedy S	9	Lamy A	1
Kennedy W	21	Lanctôt KL	158
Kennie N	137	Langford BJ	149
		Lau E	39,61,62

Lau J	19	MacLeod S	59
Lau TTY	139	MacLeod SM	184, 185
Laupacis A	82	Maclure M	38
Laurier C	10,44,80	Majumdar SR	13,84,151
Lavoie M-A	88	Maksymowych WP	51
Lee A	182, 193	Malherbe S	183
Legal M	29	Malhotra D	196
Leiter L	88	Mamdani M	2,12,82,106
LeLorier J	5,8,31,33,59,64,65,118,119	Man R	175
Lepik KJ	68, 91	Marentette M	88
Lescrauwaet B	111, 112	Marotta PJ	5
Lesk M	21	Marra CA	20,26,27,29
Leslie WD	11	Marra F	120
Leung M	3, 134	Marshall D	17,24,59
Levin A	52	Marshall DA	18
Levine M	31,32,61,72,101,166	Martin C	137
Levine MAH	87	Martin J	138
Levitt C	41	Martineau A	76
Levy A	24	Martineau J	14
Levy AR	18,23,60,68	Matsui D	176, 196
Levy RD	142, 201	Maturi B	110
Li X	50	Maxwell C	105
Lilley T	207	Maxwell CJ	6, 125
Lim J	183	McAlister A	169
Lindgren P	7	McAlister FA	13
Liovas A	78, 99,100,108,129,130	McBurney C	89
Lirenman DS	133	McCormick J	185
Liu G	140	McCullagh S	158
Lix LM	74, 75	McDonough B	40
Loewen P	140	McDougal AR	141
Loftus EV	121	McGrail K	23, 60
Lopatka H	97, 98	McIvor RA	55
Lordan N	67	McLachlin DT	70
Luo H	161	Mclaughlin-Elder F	116
Lynd L	29	Mclean-Veysey P	55
Lynd LD	91, 92	McMahon M	28
Lynn H	170	McPherson R	88
		Mehta S	1
<b>M</b>		Merchant S	187
Ma J	34,35,46,13,114	Merikle E	7,57,58,95
Mackenzie IS	157	Metge CJ	11
MacLeod B	174	Mignone J	86
		Mihai A	77
		Minogue SC	183

Mittmann N	37,54,66,108
Mohaghegh-Zadeh A	164, 204
Moien-Afshari F	187
Monette J	10, 44
Montandon G	186
Montaner J	143
Montgomery CJ	183
Montpetit M	58,95,111
Mooney D	28
Moran-Mendoza O	26, 27
Morgan D	117
Morgan S	28
Moride Y	10,21,44,81,115
Morrison Hurley R	133
Moubazbaz T	43
Muirhead N	52
Myers RP	25

**N**

Nadeau C	188
Naglie G	82
Nair K	62
Nakatsuka N	183
Naumann TL	139
Neutel CN	35
Neutel I	136
Ngo TTT	76
Nguyen A	38
Nichol G	24
Nie J	207
Nosyk B	53
Nulman I	189
Nurmohamed L	167

**O**

O'Brien L	191
Oakes GH	190
Obregon R	144
Ogborn M	207
Okon E	161, 205
Ong S	132
Oremus M	102, 103

**P**

Palepu A	23, 60
Palmer A	52
Pang CCY	178
Pang CY	197
Papaioannou A	62
Papoushek C	149
Park-Wyllie LY	150
Partlova H	85
Partovi N	140,142,201
Patchell R	53
Patel P	138
Paterson M	2,12,82,106
Pathak A	62
Patten SB	105, 125
Patton D	172
Payne KA	67
Pepper G	124
Perreault L	14
Perreault S	10,21,31,44,79,80,81
Petrella RJ	57
Petrie A	117
Pham B	71
Phillips L	183
Pielak K	120
Pilette D	21
Pilon D	81
Pineault M	141
Piquette-Miller M	171
Pisani N	37
Piwko C	48,49,69
Polk G	77
Pollak PT	192
Polygenis D	77, 78
Ponich T	131
Pora N	136
Poss J	6
Pottie K	39,137,145
Proskorovsky I	67
Pursell RA	68, 91

**R**

Raffa J	202
Rahim-Jamal S	28

Rahme E	8	Schwarz S	174
Rapoport M	158	Sculpher MJ	92
Rauniyar P	161	Sebaldt R	3,40,88,117
Rauniyar P	205	Sellors C	45,137,145
Rawson NSB	30, 71	Sénécal M	88
Raybardhan S	140	Seung SJ	37,66,108
Raymond C	86	Sewitch M	85
Rees S	98	Shalansky S	19
Regier D	20	Shane LG	128
Regine W	53	Shear N	69
Reid K	183	Sheehy O	33, 59
Reid R	23 60	Shemanski L	18
Rene de Cotret P	52	Sidhu K	152
Richardson K	29, 91	Simpson SH	151
Rieder M	159,160,175,176,185, 188,196	Sitar DS	154, 196
Riggs KW	142, 201	Sivlotti MLA	91
Rindress D	70	Skowronski D	120
Rinfret S	7	Slee A	18
Roberts M	6	Smith A	15
Robson RC	71	Smith T	37
Rocchi A	4, 9	Sobolev B	68
Rochon S	8, 117	Solimano A	177
Rodby R	52	Soltani M	164, 204
Rodrigues I	63	Song D	178,197
Roelants HWM	38	Soodeen RA	74, 75
Romach M	182	Soon J	31
Rombach S	205	Soroka S,	52
Rousseau M	9	Soule J	43
Roy M	47	Spence DJ	168
Rubin E	193	Spence JD	203
Rufino S	100	Steele R	103
		Ste-Marie L-G	109
		Stephenson MD	135
		Stewart D	198, 199
		Stockdale W	124
		Strike CJ	150
		Strong DK	133
		Suissa S	93, 94
		Sun H	53
		Sunderji R	20
		Supina AL	125
		<b>T</b>	
		Taddio A	191
<b>S</b>			
Sadri H	54		
Sammons H	196		
Sampalis J	34,35,47,113		
Sandborn WJ	121		
Sauriol L	109, 112		
Sauvé B	194		
Sawka A	62		
Scarborough K	147		
Schachtschneider AK	165		
Schaub P	28		
Schechter T	195		

Taguchi N	193
Tahami Monfared AA	33, 118
Takahashi S	200
Tam EV	192
Tamim HM	5,118,119
Tan J	69
Tan M	26, 27
Tardif J-C	70
Tarride J-E	57,58,96,122,123
Thabane L	117
Thomas KC	53
Thorne C	117
Ting LSL	142,143,201
Toal CB	157
Tofan M	141
Tossonian H	202
Toubouti Y	8
Tremblay D	99
Tricco AC	71
Tsuyuki RT	13
Tu K	169
Tucker J	159, 175

## U

Ungar W	182
Ungar WJ	2,12,48,106,107
Uppaluri A	39
Urquhart B	203
Urquhart BL	168

## V

Vachon C	76
Vaillancourt R	34,35,46,47,90,113,114
van Breemen C	161, 205
Vandal AC	102
Vanier M-C	14
Varamini P	164, 204
Veledar E	1
Verjee Z	195
Verma S	4
Vernon J	128
Veugelers P	84
Vicente C	110
Vik SA	6
Vohra S	193

## W

Wade R	156
Wadsworth LD	134, 148
Wang B	182
Wang J	105
Warren L	82
Watts M	157
Weinberg J	177
Weinstock D	21
Weintraub W	1
Wells B	104
White C	133
Wilbur K	147, 152
Willan AR	92
Williams J	125
Williams JVA	105
Willison D	3, 17
Witkos M	107
Wolfson C	102
Wolpin J	156
Wong J	205
Wong JB	121
Wong JC	141
Woodend K	137
Woodland C	179
Woodward C	145
Woolcott JC	120
Wright J	82
Wu JK	134, 148

## Y

Yamauchi A	200
Yan L	28
Yeger H	200
Yim J	19
Yuan Y	1

## Z

Zdanowicz Y	43
Zhang B	94
Zlateva G	22
Zolezzi M	144