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4TH CANADIAN THERAPEUTICS CONGRESS

"The Virtuous Circle: Therapeutics from Molecule to Patient to Population and Back"

MAY 27 - 30, 2007
HALIFAX, NOVA SCOTIA

CSCP SCPC
Canadian Society for Clinical Pharmacology
Société Canadienne de Pharmacologie Clinique

CCCP
Canadian College of Clinical Pharmacy
Collège canadien de pharmacie clinique

CAPT ACTP
Canadian Association for Population Therapeutics
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TABLE OF CONTENTS

CAPT – Canadian Association for Population Therapeutics

CCCP – Canadian College of Clinical Pharmacy

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Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

ABSTRACTS

4th CANADIAN THERAPEUTICS CONGRESS
"THE VIRTUOUS CIRCLE: THERAPEUTICS FROM MOLECULE TO PATIENT TO POPULATION AND BACK"

MAY 27- 30, 2007 - HALIFAX, NOVA SCOTIA

CAPT - ORAL PRESENTATIONS
MONDAY MAY 28, 2007

1

Cost effectiveness of drug eluting stents (DES) compared to bare metal stents (BMS) in Ontario

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Funding Source: Ontario Ministry of Health and Long Term Care

Background: DES has been associated with a lower rate of restenosis compared to BMS in clinical trials. The study objective was to evaluate the cost effectiveness of DES compared to BMS using "real-world" data from a large prospective Ontario cohort.
Methods: Clinical patient-level data from the Cardiac Care Network (CCN) registry of Ontario was used to populate a one-year decision analytic model to estimate the costs and effects (QALYs, revascularizations) associated with DES or BMS, from a Ministry of Health perspective. The costs of revascularizations and the stent costs were obtained from a hospital in southern Ontario and device manufacturers, respectively. Utility values were derived from the ARTS trial. Parameter uncertainty was assessed by means of probabilistic sensitivity analyses. Forty-four groups based on diabetes status, lesion characteristics, and a recent history of acute myocardial infarction, were analyzed.
Results: 16,498 patients from Ontario receiving DES or BMS were followed-up for at least one year (median follow-up: 602 days). Incremental cost-effectiveness ratios per QALY gained ranged from $261,508 (non-post MI patients, diabetes with very long and narrow lesions) to $5,054,811 (non-post MI patients, non-diabetes with long lesions).Incremental cost effectiveness ratios per revascularization avoided ranged from $10,860 to $211,252.
Conclusions: The incremental cost-effectiveness of DES compared to BMS was high in all patient cohorts. Differences from other published economic analyses using clinical trial data may be attributed to improved clinical benefits of current BMS and differences in pharmacotherapy practices in Ontario.
Keywords: *Drug eluting stents, cost-effectiveness, Ontario*

2

Benefit-risk assessment of the use of Zyprexa in the treatment of schizophrenia: Canadian context for the interpretation of CATIE

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Funding Source: Eli Lilly Canada Inc.

Background: The Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) examined the effectiveness of Zyprexa [OLA], perphenazine [PER], Seroquel [QUE], Risperdal [RIS], and Geodon [ZIP] in the treatment of schizophrenia over 18 months. The primary outcome, time to all-cause discontinuation, reflected efficacy, safety and tolerability. Patients started on OLA had the longest time to discontinuation and were hospitalized for psychotic relapse less often, but OLA was associated with significant weight gain. To provide a Canadian context for CATIE, the overall benefit-risk profile, represented by the likelihood of being helped or harmed (LHH), was determined. A US economic evaluation of CATIE provided no resource utilization details so limited Canadian costing was undertaken.
Methods: The LHH was calculated as (1/NNT): (1/NNH). Benefit was defined as prevention of hospitalization (1-year risk ratio). Harm was defined as weight gain >7% or initiation of antidiabetic medication. Canadian costing was based on the NNT for hospitalization and initiation of antidiabetic medication.
Results: A LHH > 1 indicated a risk-benefit in favour of OLA. The LHH for hospitalization: weight gain ranged from 1.01 to 2.66 while the LHH for hospitalization: new antidiabetic medication ranged from 13.13 to 24.79. The prevention of one hospitalization by OLA offset up to 3/4 of the OLA acquisition cost. The initiation of antidiabetic therapy cost $55 to $74 per 100 patients.
Conclusions: In CATIE, the benefit-risk profile for OLA was superior to other antipsychotics. The prevention of one hospitalization substantially offset the cost of OLA while the cost of antidiabetic therapy was minimal.
Keywords: *Schizophrenia, risk-benefit, health technology assessment*

3

The association of obesity and psychiatric disorders and their impact on HRQoL: a Canadian population-based study

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Funding Source: None

Background: Obesity is epidemic in the developed world, and is considered a risk factor for a number of chronic health conditions. Obesity may also be associated with mood and anxiety disorders, as each have been noted to impact mental health domains of Health Related Quality of Life (HRQoL). Our objectives were to examine the association between obesity and psychiatric conditions, and determine their respective and collective effects on HRQoL.

Methods: We analyzed a representative sub-sample of the Canadian Community Health Survey (CCHS 3.1). Logistic regression analysis was used to determine the association between obesity and psychiatric conditions, while multiple linear regression analysis was used to determine the effects of obesity (BMI≥30kg/m2), diagnoses of psychiatric conditions, and their interaction on HRQoL, measured by the Health Utilities Index.

Results: Our study sample consisted of N=27,418 respondents. Obesity was associated with an increased adjusted odds of mood disorders (OR, obese vs. non-obese: 1.70; 95% CI (1.49, 1.94)) and anxiety disorders (1.55(1.34,1.80)). We found obesity (-0.011, p<0.01), mood disorders (-0.178, p<0.01) and anxiety disorders (-0.063, p<0.01) each had significant negative effects on HRQoL. The interaction of obesity and mood disorder was not statistically significant, while the interaction of obesity and anxiety (-0.042, p<0.01), indicated obesity had a modifying effect on the HRQoL of individuals with anxiety disorders.

Conclusions: Obesity has a strong modifying effect on the quality of life of individuals suffering from anxiety disorders. Greater public health efforts are required to detect and prevent psychiatric conditions among the obese at early stages to minimize their substantial impact on HRQoL.

Keywords: *Obesity, psychiatric conditions, health related quality of life*

TUESDAY MAY 29, 2007

4

Canadian national active surveillance network for adverse drug reactions: genotypic adjustment of therapeutics in children (GATC the first year)

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Funding Source: Genome Canada and other unrestricted funding will be disclosed.

Background: Adverse Drug Reactions (ADRs) cause significant morbidity and mortality in children. 95% of ADRs are never reported. Active surveillance may be more effective than voluntary reporting in identifying and collecting comprehensive case information for severe ADRs.

Objectives:1) Establish a network of full-time clinical surveillors in eight major paediatric hospitals across Canada; 2) Document ADR cases with all relevant clinical data; 3) Identify ADR and matched control patients and collect biomaterial to determine the role of genetics in the occurrence of specific ADRs.

Methods: Network surveillors identify children who have suffered ADRs (and matched controls) from inpatient, outpatient and emergency departments at paediatric tertiary care hospitals in Canada. Biological samples are obtained from patients for genotyping. Biomarkers of drug risk are identified via analysis of single nucleotide polymorphisms in genes controlling drug kinetics. Identified biomarkers will be validated by pharmacokinetic studies.

Results: National network development required 18 months and included collaboration at multiple levels: senior administration; department heads; clinicians; support staff. Other activities included; recruiting and hiring of surveillors; addressing privacy concerns; local ethics approvals; protocols for ADR reporting; sample collection processes; remote project orientation and support. In one year, 325 ADRs and 1257 control patients were enrolled. Biomarkers for three serious ADRs have been identified; anthracycline cardiotoxicity, cisplatin ototoxicity, maternal-infant codeine CNS depression.

Conclusions: Active ADR surveillance networks like GATC require extensive planning and ongoing support. GATC is effective for ADR reporting and drug safety biomarker research. Design of the network allows capture of a broad range of ADR cases and targeted surveillance of specific drugs or ADRs of principal concern.

Keywords: *Adverse drug reactions, pharmacovigilance, patient safety*

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5

Montelukast use during pregnancy: a multi-centre, prospective, comparative study of infant outcomes

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Funding Source: None

Background: Montelukast (Singulair)® is a selective leukotriene receptor antagonist indicated for the prophylaxis and long-term treatment of asthma in adults and children between 2-14 years of age. Currently, no studies examining the safety of montelukast use in pregnancy are available.

Objectives: The primary objective of this study was to determine whether exposure to montelukast during pregnancy, increases the rate of major malformations above the 1-3% baseline risk.

Methods: Pregnant women taking montelukast were enrolled in the study from six teratogen information services around the world. They were compared to two other groups of women: 1) disease-matched, who used inhalers for similar indications and 2) women not diagnosed with asthma and not exposed to any known teratogens. The primary outcome was major malformations and secondary endpoints included spontaneous abortion, therapeutic abortion, gestational age at birth and birthweight.

Results: Out of 150 pregnancies, which included three sets of twins, there were 132 live births, 19 miscarriages, two fetal deaths and two major malformations. The mean birth weight was smaller (3197±691g) compared to controls and there was a shorter gestational age (37.7±5.9 wks) among exposed women. About 25% of the newborns had fetal distress, which was greater than controls (p=0.038). However, upon sub-analysis of women who continued montelukast until delivery, only birthweight difference (328g) remained significant between the montelukast and non-asthmatic women.

Conclusions: Montelukast does not appear to increase the baseline rate of major malformations. The lower birthweight in both asthma groups is probably associated with the severity of the maternal condition.

Keywords: *Pregnancy outcome, montelukast, exposure*

WEDNESDAY MAY 30, 2007
8:00AM – 10:00AM

6

Importance of diabetes as a risk factor for fractures after solid organ transplantation

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Funding Source: Aucune

Background: Diabetes has been recently associated with osteoporosis in the general population. Both diabetes and fractures are prevalent among Solid Organ Transplantation (SOT) recipients. It is therefore relevant to clarify the association between post-transplant fractures and pre-transplant diabetes (PTD).

Methods: We conducted a nested case-control study. Cases were 18 years and older, enrolled in the Quebec Health Insurance Plan, who received a first SOT between 01/1986 and 12/2005 and who had sustained an incident fracture between the date of discharge after SOT and the end of the study period. The index date was defined as the date of the fracture. Cases were matched to 1-4 controls on the type of organ transplanted and on the date of the transplantation. Crude and adjusted odds ratios (OR) were obtained with multivariable conditional logistic regression models.

Results: The study included 147 cases and 555 controls. PTD was present in 18% of the cases and 15% of the controls (crude OR 1.96 95% CI:1.33-2.87). After adjusting for age, sex, past fractures, use of narcotics, steroids, immunosuppressants, hormone replacement therapy, osteoporosis treatments, hospitalisation duration and past hyperthyroidism, PTD remained a significant risk factor for fractures (OR 2.1 95 % CI: 1.38-3.24). Use of narcotics in the month preceding the index date was also a significant risk factor for fractures (OR 2.67 95% CI: 1.64-4.37).

Conclusions: PTD is significantly associated with post-transplant fractures among a cohort of adults receiving a SOT. Pre-transplant fracture prophylaxis could be considered in these patients.

Keywords: *Osteoporosis, diabetes, nested case-control study*

7

The impact of pharmacists' interventions: sensitivity on patient outcomes in hypertension management

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Funding Source: Funded by Ontario Ministry of Health and Long Term Care-Health Care Outcomes
Background: Hypertension is a major health concern, which pharmacists can impact positively. Few studies have quantitatively assessed pharmacists' interventions.
Objectives: To identify and quantify outcomes sensitive (clinical benefit + statistical significance) to pharmacists' interventions.
Methods: We searched IPA, Medline, and Embase, from inception to 2006. Two independent reviewers identified articles; results were compared and settled through consensus. Data extracted included intervention type, patient numbers, demographics, study characteristics, instruments used, data compared, and outcomes reported. A random-effects meta-analysis was used to combine appropriate available data. Study quality was assessed using the validated Downs and Black scale.
Results: Initially, 203 potential articles were identified; 98 were selected and abstracts read. From them, 9 were included as full-text and 19 were identified from their references for 28 in total. Research designs were: 18 randomized controlled trials, 6 single-arm clinical trials, 3 non-randomized comparative trials, and 1 database study. Average quality score was 66%±12% ("fair"). Medication management (82%) and hypertension education (68%) were pharmacists' most used interventions. Thirty-nine study results (58%) were 'sensitive' to pharmacists' interventions. Meta-analysis found pharmacists could further reduce systolic blood pressure compared to standard care (6.9±3.5 mm Hg in 2246 patients from 13 studies, P=0.047). Non-sensitive results included further reduction in diastolic blood pressure (3.6±1.9 mm Hg in 2246 patients from 13 studies, P=0.06), quality of life (1/8 significant) and compliance (5/13 significant).
Conclusions: Systolic blood pressure is definitely sensitive to pharmacists' interventions. Other outcomes may also be sensitive however, more high-quality studies are needed for a comprehensive quantitative assessment.
Keywords: *Pharmacist, intervention, diabetes, pharmaceutical care, clinical pharmacy*

8

Does incorporating health-related quality of life into composite outcome analyses improve transparency?

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Funding Source: None
Background: Analyses of composite outcome are typically based on the assumption of equally weighed components. In many cases, however, those components represent a trade-off (for example, death vs. hospitalization). We propose incorporating health-related quality of life (HRQL) into survival analyses to improve the transparency and interpretation of composite outcome analyses.
Methods: Using standard survival analysis, we compared a composite outcome of hospitalization or mortality for users of metformin (n=208) or sulfonylurea (n=773) monotherapy in type-2 diabetes. The composite outcome was partitioned into its component health states and assigned literature-derived utilities: H1 (initial health state, 0.81); H2 (health state after hospitalization until death or censoring, 0.57), H3 (dead, 0.0). Total quality adjusted survival (QAS) time was calculated by multiplying the mean survival time for the health state by the assigned utility. Variance estimates were generated through a bootstrap procedure (n=500).
Results: The composite outcome occurred in 115 (55%) metformin users and 480 (63%) sulfonylurea users [HR 0.83 (95% CI 0.70-0.99)] and conventional survival analysis resulted in a total gain of 0.32 event free years if favour of metformin users. However, the total QAS time was 3.95 years in metformin users versus 3.39 years in sulfonylurea users. Resulting in a mean gain of 0.56 quality adjusted life years for metformin users, which is both clinically and statistically significant (95% CI: 0.54 – 0.56, p<0.001).
Conclusion: QAS analysis incorporates HRQL to "adjust" for the unequal health states used in composite outcomes, providing further insight to traditional approaches of equally weighting each component.
Keywords: *QALY, survival analysis*

9

How do common drug review recommendations compare with that of international heath technology agencies and listing decisions of the Canadian provinces?

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Funding Source: AstraZeneca

Background: This study compares Health Technology Assessments (HTAs) conducted by the Common Drug Review (CDR) in Canada, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, and the Scottish Medicines Consortium (SMC) in Scotland. CDR recommendations were also compared to provincial listings (participating plans).
Methods: HTA websites were searched for guidelines and appraisal documents for common HTAs (Jan 2007). Evidence requirements, recommendations and decision criteria were compared. Brogan Pharmastat and IMAM databases provided provincial reimbursement information.
Results: 12 common appraisals were identified. All had similar evidence requirements but recommendations differed. CDR, PBAC and SMC made the same recommendation for 3 appraisals. CDR made 1 recommendation to list, whereas SMC and PBAC made 3 positive recommendations. The number of rejections was 6 for CDR, 5 for PBAC and 2 for SMC. CDR listed with criteria in 5 cases, PBAC 4 cases and SMC 7. CDR list and do not list recommendations were followed by 44% and 75% of provinces, respectively. CDR list with criteria was followed by 31% of provinces, while 49% made do not list decisions. CDR reasons for rejection/restriction were efficacy (50%), economics (33%) and safety (17%). Stated time from submission to recommendation was 20-26 weeks for CDR with provincial reviews adding on average 27 weeks, 17-19 weeks for PBAC and 7-11 weeks for SMC
Conclusions: Despite the same evidence, different listing recommendations are made internationally by HTAs and between CDR and provinces, resulting in Canadian patients having reduced access to medicines deemed valuable by HTAs in Australia and Scotland.
Keywords: *Health technology assessment, common drug review, access to medicines*

WEDNESDAY MAY 30, 2007
10:30AM – 12:00PM

10

The role of economic evidence in Canadian oncology reimbursement decision-making: to lambda and beyond

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Funding Source: Partially funded by an unrestricted grant from Hoffmann-La Roche Canada Ltd.

Objective: To determine the use of economic evidence and the role of cost-effectiveness thresholds in reimbursement decision-making for oncology drugs in Canada.
Methods: A literature search was conducted to identify public information regarding the use of economic evidence and the existence of a threshold (lambda) for economic value. A one-day key informant round table was held with invited individuals from across Canada to glean further information.
Results: The limited public information suggests that the uptake of structured economic evidence in the decision-making process has been tentative, despite its formal requirement. The failure to systematically consider economic evidence may contribute to inconsistent reimbursement decisions. Implicit economic thresholds have emerged in Australia and the UK, but not in Canada. The key informant round table confirmed the inconsistent uptake of economic evidence: panelists were divided between those who found economic information useful and supportive to decision-making, and those who did not. Panelists generally agreed on the need for publicly defensible and ethical reimbursement restrictions. They suggested process improvements: transparency of processes and decisions, dynamic formularies for adapting to evolving treatment practices and clinical data, broader inclusiveness of review panels, supporting decision-makers by using ethics to resolve inevitable conflicts between programs and individuals, and most importantly, the development of an explicit Canadian weighting system for evidence and values.
Conclusions: Canadian oncology reimbursement decision-makers do not agree about the use of economic evidence, and do not favour cost-effectiveness thresholds, instead offering alternate suggestions for improved decision-making.
Keywords: *Economic, reimbursement, decision-making*

11

Evaluation of a workplace asthma self-management program

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Funding Source: GlaxoSmithKline

Background: Asthma impacts employers in the form of reduced productivity and increased absenteeism and healthcare costs. To address this, a workplace self-management wellness program, Inspire at Work, was developed by a benefits carrier with the objective of improving the health and productivity of patients with asthma.

Methods: A cohort of patients (employees and the family members of employees in seven large companies in New Brunswick) enrolled in the program was followed over 9 months. The intervention consisted two pre-scheduled, private educational sessions, including a complete asthma assessment along with spirometry testing, with a certified asthma educator and two follow-up assessments. The ECHO model was used to capture a range of Economic, Clinical and Humanistic outcomes. Most outcomes were measured at 4 time points and were collected via survey. Changes in continuous variables across the four time points were evaluated using a one-way repeated measures design while changes in dichotomous variables were evaluated using the Cochrane's Q Test.

Results: One hundred and five patients enrolled in the program with 99 patients completing all four sessions. A statistically significant improvement was seen in absenteeism, productivity, public payer costs, and in scores related to quality of life, the 30 Second Asthma test, participant satisfaction and inhaler technique. The Return on Investment was $4.24 for each dollar spent.

Conclusions: An asthma educator, proactively helping patients at the workplace, can discover many gaps in asthma care and improve many asthma-related outcomes. Employer-benefits carrier partnerships, as exemplified by this workplace wellness program, have many potential advantages including increased accessibility to care.

Keywords: *Asthma, workplace wellness, program evaluation*

12

A Canadian net-benefit analysis of the use of clopidogrel in reducing the risk of major cardiac events

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Funding Source: Contract from Sanofi-Aventis Canada

Background: Results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial demonstrated that up to 12 months of clopidogrel in combination with ASA significantly reduced the absolute combined risk of death, MI or stroke post percutaneous coronary intervention (PCI). We sought to determine patients-level costs based on the Canadian Case Mix Group (CMG) system, and then assess cost-effectiveness using a net-benefit approach.

Methods: Canadian hospital case costs and length of stay were obtained from the 2003 Health Funding and Costing Branch of Alberta Health and Wellness Report. These costs were adjusted to reflect average national case costs for Canada and 2004 CAN$. Net-benefit was expressed as net monetary benefit (NMB) defined as the additional cost of implementing the experimental treatment subtracted from the additional effect of the treatment valued in dollars. NMB was estimated by linear regression for "willingness-to-pay" (WTP) thresholds ranging from C$0 to C$100,000. Life expectancy in trial survivors was estimated from Saskatchewan Health database patients undergoing PCI from 1985 to1995 and followed for >1 to 15 years.

Results: Total per patient costs was higher in the clopidogrel arm by C$455 annually. At a WTP threshold of only C$3,000 per life-year gained, NMB equal to C$1,031 was significantly greater than zero (95% CI=C$42-C$2020, p=0.041). Adjusted for age, gender, presence of acute coronary syndromes and diabetes, NMB was C$1,049 (p=0.037).

Conclusions: The results suggest that long-term use of clopidogrel in patients undergoing percutaneous coronary intervention is highly cost effective in the Canadian health care system.

Keywords: *Clopidogrel, net benefit, case mix group*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

13

A qualitative study of physician and pharmacist perspectives on prior authorization policies of the Nova Scotia Pharmacare Programs

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Funding Source: Drug Evaluation Alliance of Nova Scotia

Background: The use of prior authorization policies has grown dramatically as both public and private insurers attempt to control drug use and rising expenditures. However, the impact of these policies has largely been explored through quantitative research using administrative claims data. The purpose of this study is to provide a qualitative perspective on the Nova Scotia Pharmacare Programs prior authorization process and to gain insight on how these policies can be improved.

Methods: Focus groups were conducted with physicians (3 groups) and pharmacists (2 groups). Open-ended questions were used to generate discussion. Transcripts were analyzed using established qualitative methods and with the assistance of the software tool QSR-N6.

Results: Four themes emerged from the discussions:*Working with a Policy Context*, which highlights the effects on daily practice including increased workload and frustration in an often disconnected process; *Support for Prior Authorization Policies*, which reveals that, despite describing negative attributes of these policies, most participants had fairly moderate views; *Strategies to Minimize the Effects of Policies*, which describes the actions that practitioners take to minimize the effects of these policies; and *The Information Gap*, which highlights the need for more information, more practical tools, and more transparency, particularly to engage physicians.

Conclusion (original): Practical insights were gained regarding how prior authorization policies translate into real life practice. Understanding the practitioners' perspective, how they react and adapt to these policies and trigger points for frustration, can assist in ensuring these policies are delivered in the most efficient and acceptable manner possible.

Keywords: *Prior authorization policies, qualitative research, focus groups*

CAPT - POSTER PRESENTATIONS
MONDAY MAY 28, 2007

Therapeutics for Vulnerable Populations

14

Clinical response to a second or third anti-TNF agent after discontinuation of the first in patients with rheumatoid arthritis. Implications for therapeutic decision-making

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Funding Source: Bristol-Myers Squibb Canada

Background: To evaluate the clinical response to a second and eventually a third anti-TNF agent and reasons for discontinuation in patients with rheumatoid arthritis (RA).

Methods: One hundred RA patients treated with either etanercept (ETN, n=50) or infliximab (IFX, n=50) were included. To qualify, patients had to have received ETN or IFX for a minimum of 3 months unless discontinued for an adverse event (AE). Patients were followed prospectively up to four years.

Results: Overall, both groups were comparable. A total of 35 patients discontinued therapy for lack /loss of efficacy (LOE n= 18), adverse events (AE n=14) or other (n=3). The mean time to discontinuation was comparable (ETN=0.8 vs. IFX=1.2 years ns). Twenty-one patients switched to a second anti-TNF (LOE group:15; AE group: 6). Nine patients (60%) from the LOE group discontinued the 2nd anti-TNF for inadequate clinical response while 3 patients (50%) from the AE group discontinued it because of AEs. Only 9/21 (43%) of the total switch population were able to continue the 2nd anti-TNF. Eleven patients received a 3rd anti-TNF and only 4 (37%) are still continuing after a mean of 8 months.

Conclusions: The maintenance rate and the clinical response to a 2nd or 3rd anti-TNF drug are lower than for the 1st one. Patients seem also to follow the same pattern for the reasons of discontinuation. This observation, coupled to other reports raises the issue of the appropriateness of switching to another anti-TNF agent versus starting another class of biologics. Further randomised and ideally head-to-head trials are needed to answer this important question.

Keywords: *Efficacy, anti-TNF agents, rheumatoid arthritis*

15

Relationship between socioeconomic status and psychotropic drug use among the elderly: a review of literature

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Funding Source: None

Background / Objectives: A complete assessment of drug use among the elderly should consider their socioeconomic status (SES) as a means of understanding how socioeconomic factors can affect psychotropic drug use. The purpose of this literature review was to provide an updated review of the empirical evidence of the relationship between psychotropic drug use among the elderly and SES.

Methods: A search of Medline was conducted by utilizing the search terms 'socioeconomic', 'sociodemographic', psychotropics', 'elderly', and 'income'. The search was supplemented with a review of reference lists of each article. Each article was examined for its purpose, methods, measures of SES and medication employed findings, and limitations.

Results: Nine relevant studies were identified. Most studies were conducted in community settings in Canada and USA. There were methodological differences among the reviewed studies such as sources of data, SES and medication measures employed. High use of psychotropic drug among the elderly was associated with certain SES characteristics in the majority of studies: female, white, low education level, being widow in men and divorced in women, having been blue-collar workers before retirement, poor health perception, and low income. Notwithstanding the above-mentioned evidence, some studies demonstrated there were no significant differences by gender, marital status and education.

Conclusions: High psychotropic drug use among the elderly is not only influenced by symptoms but also by low SES among the elderly population. Nonetheless, more research is needed to better identify the relationship between SES and psychotropic drug use among the elderly.

Keywords: *Psychotropics, socioeconomic status, literature review*

16

Access and intensity of use of analgesics among older Manitobans

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Background: Under-treatment of pain is frequently reported, especially among seniors, with chronic non-cancer pain most likely to be under-treated. Legislation regarding the prescribing/dispensing of opioid analgesics (including multiple prescription programs) may impede access to needed analgesics. We describe access and intensity of use of analgesics among older Manitobans.

Methods: A cross-sectional study of non-Aboriginal non-institutionalized Manitoba residents over 65 years of age during April 1, 2002 to March 31, 2003 was conducted using the Pharmaceutical Claims data and the Cancer Registry from the province of Manitoba. Access to analgesics (users/1000/Yr), and four measures of intensity (using defined daily dose [DDD] methodology) were calculated for non-opioid analgesics, opioids, and multiple-prescription-program opioids [MP-opioids]. Usage was categorized by age, gender, and stratified by cancer diagnosis. Age-sex standardized rates of prevalence and intensity are reported for the eleven health regions of Manitoba.

Results: Approximately one-third of older Manitobans accessed analgesics during the study period. Female gender, increasing age, and a cancer diagnosis were associated with greater access and intensity of use of all classes of analgesics. Age-sex standardized access and intensity measures revealed the highest overall analgesic use in the most rural/remote regions of the province. However, these same regions had the lowest use of opioids, and MP-opioids among residents lacking a cancer diagnosis.

Conclusions: This population-based study of analgesic use suggests patients in remote and rural regions of Manitoba have limited access to opioid analgesics. Reasons for lower opioid use require further study.

Keywords: *Analgesics, rural health services, aged*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

17

Retrospective analysis of health care resource utilization and costs associated with methicillin-resistant staphylococcus aureus (MRSA) complicated skin and skin structure infections

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Funding Source: Wyeth Pharmaceuticals, Markham, ON

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major health problem. MRSA infections are commonly found in patients with complicated skin and skin-structure infections (cSSSI). Its incidence increased from 1.0-11.2% during 1995-2004 in Canada.

Objective: To determine health care resources utilized to manage MRSA related cSSSIs and estimate associated costs.

Methods: A chart review was conducted in two Canadian teaching hospitals (Montréal/ Vancouver). Eligible patients must have been hospitalized for MRSA infections associated with cSSSIs. Resources (medications, physician visits, hospitalizations, surgery and laboratory) were quantified, then costed using standard price lists in 2006 CAD$.

Results: Data were extracted from 117 charts (79 males, mean age = 55.7 years & 38 females, mean age = 62.4). The most frequent type of cSSSIs was cellulitis associated with ulcer, abscess, or infected surgical incision (41.5%). Vancomycin was the most utilized drug (96.6%). Ten patients fully recovered during their hospitalization (9%), 81% partially resolved and were discharged, while 10% did not resolve, with half of them dying in hospital (one due to cSSSI). Average hospital stay was 21.0±22.3 days (median =15.0). The total estimated cost per patient hospitalized was $13,102±$13,165 (median = $9,200). Hospitalization costs accounted for 92.2%, diagnostic tests for 4.7%, while medications and physician visits each accounted for 1.5%.

Conclusions: MRSA infections resulted in substantial morbidity, duration of hospital stay and resource utilization. Hospitalization costs represented the greatest proportion of the overall costs. Future studies should focus on how we can optimally manage patients and associated hospital costs related to MRSA in cSSSIs.

Keywords: *Chart review, MRSA, resource utilization*

18

Sulfonylureas and impaired functional recovery following an ischemic event in people with diabetes: an exploratory analysis

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Funding Source: None

Background: Recent insights into sulfonylurea pharmacology suggest that they impair the cardioprotective effects of brief, sub-clinical periods of ischemia. Based on this biologic mechanism, we hypothesized that sulfonylurea use will increase the risk of mortality following an acute ischemic event, and furthermore, that people with pre-existing ischemia (i.e., angina) will be more susceptible to this adverse effect.

Methods: This pilot study used available population-based administrative data from Saskatchewan Health. Our study group consisted of patients with diabetes admitted to hospital for ischemia (ICD-9 codes 410-414) between 1991 and 1999. Study cohorts were established according to dispensations of either glyburide or metformin monotherapy prior to hospital admission. Our primary outcome was all-cause mortality at 30 days following hospital admission. Any dispensation of nitrates prior to hospital admission was used to identify people with angina.

Results: Overall, glyburide use was not associated with an increased risk of mortality (OR: 0.99; 95%CI: 0.57-1.71) compared to metformin monotherapy. However, we observed a significant interaction between nitrate use and oral antidiabetic therapy (p=0.08). Compared to metformin users, glyburide users with prior nitrate use had a much greater risk of 30-day mortality 2.28 (0.72-7.15), while those not using nitrates had a lower risk 0.66 (0.35-1.27).

Conclusions: The divergence of odds ratios between users and non-users of nitrates suggests that pre-existing ischemia alters susceptibility to potential glyburide cardiotoxicity. Based on our findings, we will focus on people with pre-existing ischemia to further explore the relationship between sulfonylurea use and outcomes in people with diabetes.

Keywords: *Type 2 diabetes, functional recovery, retrospective cohort analysis*

19

Community trial of the cardiovascular health awareness program (C-CHAP)

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Funding Source: Canadian Stroke Network/Ministry of Health Promotion (Ontario)
Background: Community-level interventions are a promising strategy to improve the cardiovascular health of populations. Evidence from large-scale pragmatic community-level trials can inform health policy decision-making.
Methods: We conducted a 39-community cluster randomized controlled trial involving 129 community-based pharmacies and 383 family physicians in Ontario, Canada. 1,240 three-hour long CHAP sessions were held in pharmacies over ten weeks in the Fall 2006. Family physicians were encouraged to participate by inviting eligible patients and receiving session results. Intervention community residents aged 65 years and older were invited to attend one or more sessions using multiple strategies, including a letter from their family physician. 577 trained volunteer peer health educators ensured accurate measurement and reporting of blood pressure and self-reported cardiovascular risk factor information to participants, family physicians and regular pharmacists.
Results: A total of 27,359 assessments of 15,883 unique patients were conducted. The study is powered to detect a 21% reduction in the annual mean rate of hospital admission for acute myocardial infarction, congestive heart failure, and stroke (composite primary end-point) for residents 65 years of age and older during the year following implementation of CHAP in program compared to control communities, using routinely-collected, population-based administrative health data.
Conclusions: C-CHAP highlights considerations in design, implementation and evaluation of large-scale, community-wide cardiovascular health promotion initiatives.
Keywords: *Randomized controlled trial, cardiovascular disease, primary care*

20

Family physicians' attitudes and beliefs towards insulin therapy in elderly patients with type 2 diabetes: a qualitative study using the nominal group technique

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Funding Source: Green Shield Canada
Background/Objectives: Tight blood glucose control using insulin can lead to better outcomes and fewer complications. Nonetheless, insulin use in the elderly remains infrequent. This study explored the attitudes and beliefs of family physicians when treating patients over the age of 65 years with type 2 diabetes. This study also sought to validate the findings from a previous study that had developed a model regarding factors influencing insulin prescribing.
Methods: This qualitative study used a grounded theory approach. Data collection occurred through a series of telephone-based nominal group interviews, with physicians completing 3 successive interviews. Between interviews, findings were synthesized and provided in a summative format to physicians for feedback prior to the next interview. As well, a number of single interviews were completed at the end of the study in order to fill in gaps in the analytic picture. Analysis was conducted by at least 2 researchers.
Results: Thirty-three physicians completed interviews. Findings were consistent with the previously developed model. Both doctor-related and patient-related factors mediated physicians' rationale for prescribing (or not prescribing) insulin. Physicians' beliefs about diabetes in general, as well as the capabilities and preferences of the elderly influenced their preference for insulin use. Other influencing factors included the intensity of therapy required, presence of a support system, and physicians' own experience and comfort level. Many physicians acknowledged knowledge gaps and frustration at managing diabetes in the elderly.
Conclusions: Study findings highlight the importance of understanding prescribers' attitudes and perceptions when dealing with populations with complex therapeutic needs.
Keywords: *Insulin, elderly, nominal group*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

21

Cardiovascular outcomes of a pharmaceutical care program integrated into family practices

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Background: Improved management of cardiovascular disease and diabetes has been shown to reduce cardiovascular morbidity and mortality. The IMPACT (Integrating family Medicine and Pharmacy to Advance primary Care Therapeutics) project aimed to improve patient outcomes by optimizing drug therapy through a practice model that integrated pharmacists into family practices.

Methods: This was before-and-after study. Patients from seven family practice sites in Ontario who were diagnosed with hypertension, dyslipidemia or diabetes, and had either uncontrolled blood pressure (BP) (n=395), LDL concentrations (n=142) or A1c levels (n=150) were included. Pharmacists provided individual patient assessments, monitoring and follow-up for patients referred by physicians based on criteria targeting cardiovascular disease. Data were collected using structured chart audits. Mean changes from baseline to 6-month follow-up for BP (systolic and diastolic), LDL values and hemoglobin A1c were calculated using paired t-tests with 95% confidence intervals.

Results: Patients with uncontrolled hypertension had decreases in both systolic and diastolic BP (7.75 mmHg [SD 19.82]; P<0.0001 and 2.04 mmHg [SD 11.42]; P=0.001, respectively). Patients with uncontrolled dyslipidemia showed a decrease of 0.65 mmol/L (SD 0.88) in their LDL concentrations (P<0.0001). Patients with uncontrolled diabetes demonstrated a 0.4% (SD 1.0) decrease in their hemoglobin A1c levels (P<0.0001). In addition, 38.5% of patients with uncontrolled hypertension reached target systolic BP; 37.3% with uncontrolled dyslipidemia reached their target LDL value; and 25.0% with uncontrolled diabetes achieved an A1c ≤ 7.0%.

Conclusions: Pharmacist assessment in family practice was associated with improved patient clinical surrogate health outcomes.

Keywords: *Pharmaceutical care, cardiovascular, before-and-after study*

22

Clinical and economic effects of a therapeutic substitution policy for proton pump inhibitors for aboriginal patients in northern communities in the Northwest Territories

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Background: Proton pump inhibitors (PPIs) used to treat gastroesophageal symptoms can vary greatly in price but are thought not to differ in clinical benefits. Health Canada's Non-Insured Health Benefits (NIHB) Program instituted a therapeutic substitution policy for PPIs as a cost containment strategy (CCS). The objective of this study was to determine the effect of this CCS on First Nations and Inuit people in northern isolated communities.

Methods: 5 pharmacies in the Northwest Territories identified a sample of patients subjected to the substitution policy. Eligible patients who provided informed consent received a face-to-face or telephone interview with a pharmacist using a standardized questionnaire.

Results: 44 of 66 patients identified consented to be interviewed; 70% female, mean age 57 years. 34 (85%) patients reported problems after the required PPI switch. Frequency for new or recurrent gastroesophageal symptoms varied from 20% (stomach pain) to 58% (heartburn). Problems were severe enough to send 19 (48%) patients to the nursing station, 6 (15%) to the hospital for assessment, with 1 requiring hospital admission. During the initial 15 month period of the program there was a net incremental drug cost of $30.96 per person due to drug wastage, delayed switching and switching back. A conservative estimate of additional healthcare service costs related to perceived health problems from the switch, paid by NIHB or the territorial health program, was $36,624.31 (n=19).

Conclusions: A majority of the patients sampled experienced problems following the PPI switch, possibly associated with diminished efficacy or adverse drug effects. Although causality is not proven, perceptions in this sample of patients influenced resource use resulting in no net savings (average incremental cost $946.57 per patient) during the first 15 months of the policy

Keywords: *Aboriginal, patient interviews, economic effect*

23

Epidemiology of obesity and cardiometabolic risk factors in Canada

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Background: Obesity has become a major public health issue over the last 2 decades, as it is known to be strongly related to hypertension, heart disease, stroke, diabetes, and several cancers. Also, the presence of cardiometabolic risk factors (CMRF) is suspected to further increase the risk of cardiac and metabolic morbidity and mortality.

Objective: To assess the prevalence and incidence of obesity and CMRF in Canada.

Methods: This was done through a literature search and the Canadian Community Health Survey (CCHS) and the Canadian Heart Health Survey (CHHS) analysis.

Results: The prevalence of overweight (BMI 25.0-29.9 kg/m^2) in Canada in 2004 was found to be 42% in males and 30.2% in females while the prevalence of obesity (BMI $\geq$ 30 kg/m^2) was 22.9% in males and 23.2% in females. Among men and women who had a normal weight in 1994/95, 38% and 28%, respectively, became overweight by 2002/03. Of those who were overweight in 1994/95, 20% and 28%, respectively, became obese by 2002/03. The most recent national data on CMRF is the Canadian Heart Health Surveys (1986-92). The overall prevalence of people CMRF was 17.5% in men and 14.7% in women (1986-92 CHHS). Prevalence increases with advancing age, from a low of 3-8% in 20-29 y olds to a high of 30-39% in 70-74 y olds. Among ethnic groups, CMRF appears to be more prevalent among Aboriginal groups. Although temporal trends cannot be established at this point, the age-adjusted prevalence of CMRF increased from 24.1% in 1988-94 to 27.0% in 1999-2000 in the United States.

Conclusions: The combined influence of obesity and metabolic dysregulation remains a public health burden requiring effective prevention and treatments. These prevalences are likely to be underestimated and more recent surveys are required.

Keywords: *Obesity, metabolic syndrome, epidemiology*

24

Antibiotic exposure during infancy leads to increase risk of asthma: a population based analysis

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Background: A number of studies have tested whether antibiotic exposure in early childhood leads to childhood asthma with conflicting results.

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

Methods: Using the BC Linked Health Databases, birth cohorts from 1997 to 2003 were evaluated (N =282,790). Antibiotic exposure was determined for the first year of life (N=116,329). The diagnosis of asthma after the 2nd year of life (determined using a validated algorithm) was then determined for children exposed and not exposed to antibiotics in the first 12 months of life (N=13,539 and 10,068, respectively). Cox proportional hazards models were used to adjust for potential confounders and determine the hazard ratios (HR) associated with antibiotic exposure and the development of asthma.

Results: Antibiotic exposure in the first year of life was associated with an increased risk of developing asthma (HR, 1.46; 95% CI, 1.42-1.51). Adjusting for confounders (gender, socioeconomic status, frequency of physician office visits, and various infections during the first year of life) reduced this risk (adjusted HR, 1.09; 95% CI, 1.05-1.14). The highest risk was in children receiving >4 courses (adjusted HR, 1.20; 95% CI, 1.10-1.30). The risk decreased from an adjusted HR 1.15 95% CI 1.08-1.22 in the 3rd year of life to an adjusted HR of 1.06 95% CI 1.01 - 1.11 after the 5th year of life.

Conclusions: Use of antibiotics in the first year of life is associated with a very small increase in risk of asthma.

Keywords: *Antibiotics, asthma, pharmacoepidemiology*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

25

The monetary value of a genetic test to identify the patients susceptible to develop statin-induced muscular adverse events

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Background: Statins are effective in the treatment of dyslipidemias. Muscular side effects (MSE) associated with statins play an important role in the discontinuation of this therapy. It is of interest to develop a genetic test that would identify a priori the patients who are likely to develop MSE. Our aim is to determine the monetary value of this test.

Methods: Markov model method was used to compare a genetic tested population of new statin users to a similar non tested population. We then compared the costs incurred by these two populations. Assumptions were: 60$ for average monthly cost for lipid lowering therapy; probability to develop mild, moderate or severe myalgia or rhabdomyolysis, 1/100, 1/1000, 1/10000 and 1/100000 with a cost of 50$, 100$, 200$ and 100000$ respectively.

Results: The simulated value of the test is 19.43$. With one-way sensitivity analysis it varies between 11.86$ and 31.42$.

Conclusions: These result suggest a value of 19.43$ per test. However the incidence, hazard functions and costs of the muscular side-effects will have to be determined by a prospective field study since they are not available in the literature. Furthermore by pre-identifying the patients likely to develop muscular side effects the test could avoid the money wasted by the patients who discontinue their statin therapy before they are likely to derive any benefit from this therapy. Since this cannot be estimated with Markov models further studies will be done with discrete event analysis.

Keywords: *Statin, Markov, pharmacoeconomic*

26

Metabolic syndrome is an independent predictor of postoperative renal failure after coronary artery bypass surgery

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Background: Cardiometabolic risk factors such as diabetes and obesity are highly prevalent among patients undergoing coronary artery bypass grafting surgery (CABG). We observed a possible link between CABG and postoperative renal failure, but it remains to be confirmed. Therefore, we assessed if the presence of metabolic syndrome (MS) could negatively impact renal function following CABG surgery.

Methods: We retrospectively analyzed the data of 5304 consecutive patients who underwent CABG surgery between 2000 and 2004 at Laval Hospital, Quebec. 340 (6.4%) with a history of renal failure and/or plasma creatinine≥150 µmol/l were excluded. Of those included, 2411 (49%) had MS according to the criteria of NCEP-ATPIII. The primary end-point was the development of postoperative renal failure defined as an acute elevation of plasma creatinine of more than 50µmol/l above the preoperative value.

Results: Renal failure following CABG surgery occurred in 8.1% of patients with MS and 4.2% of patients without MS ($p<0.0001$). Univariate analysis revealed that age, diabetes, hypertension, peripheral vascular diseases, body mass index (BMI), and metabolic syndrome were predictors of postoperative renal failure. Multivariate analysis confirmed that MS was a predictor of renal failure RR= 1.40 ($p=0.03$) after adjusting for age, gender, BMI, history of diabetes, hypertension, and peripheral vascular diseases. MS is an independent risk factor for postoperative renal failure after cardiac surgery.

Conclusions: Thus, interventions that could contribute to reduce the prevalence of MS in patients with coronary artery disease or at least modify metabolic perturbations of MS at time of CABG may prevent occurrence of renal complications.

Keywords: *Obesity, metabolic syndrome, renal failure*

27

Health service use of Nova Scotians treated for hepatitis C from 1998-2004

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Background: Hepatitis C virus (HCV) causes chronic liver disease, liver failure and death. The prevalence of persons with HCV is increasing worldwide, including within the province of Nova Scotia. Over 5000 individuals are infected with HCV in Nova Scotia, and antiviral treatment costs approximately $20 000/patient. The number of patients requiring treatment is expected to increase in the future.
Methods: For this retrospective cohort study, the study group is all patients that were treated in the Chronic Liver Diseases Clinic at the Capital District Health Authority from January 1, 1998 – December 31, 2004 (n=400). The comparison group are those patients from the Liver Clinic that are HCV+ and untreated from 1998-2004 (n=1000). The objective of this project is to link Liver Clinic with administrative MSI data to characterize the treated and untreated groups, and determine number of physician visits, number of hospital admissions, and mental health outpatient services accessed.
Results: We will investigate if patients with successful treatment will have an increase in health service utilization during the treatment period, and then a subsequent decrease to their baseline level of utilization. Those that are unsuccessfully treated will likely remain at an increased level of utilization over time vs. those that were successfully treated or untreated.
Conclusions: Treatment of HCV impacts on patients' utilization of health services. The results of this project will provide insight into the provincial health burden of HCV, may enhance management of care of HCV individuals, as well as inform policy and program planning for HCV disease.
Keywords: *HCV antiviral treatment, health care utilization, data linkage*

28

Proton pump inhibitors (PPIs) may not be protective against upper gastrointestinal complications in users of non-steroidal anti-inflammatory drugs

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Background: Proton pump inhibitors (PPIs) are commonly recommended for NSAID users at increased risk of upper gastrointestinal (UGI) complications. Do PPIs prevent UGI complications in non-aspirin NSAID users to the same degree as other drug classes?
Methods: Manitoba Health's population-based database was used to perform a matched case-control analysis. All health care contacts and pharmacy dispensations for all Manitobans are available from 1995 to 2004. All subjects using NSAIDs at the time of admission to hospital with a primary diagnosis for an UGI complication were identified and matched to up to 20 age- and sex-matched NSAID-using controls (with no UGI complication on the case's index date). PPI use was the main predictor and conditional logistic regression analysis was used to adjust for history of previous UGI complications, comorbidity, prior hospitalizations, use of corticosteroids, warfarin, and clopidogrel, and socioeconomic status.
Results: NSAID users admitted with UGI complications (n=1010) were matched to 17,911 NSAID-using controls. PPIs were used by 8.0% cases immediately prior to the GI event vs. 3.7% of controls (P<0.001). Cases were also more likely to have severe comorbid illness or a history of UGI complications, and to use medications associated with an increased risk of UGI complications. After adjustment, PPI use was associated with a non-significantly decreased likelihood of developing a UGI complication when compared with non PPI users (OR 0.95, 95% CI 0.71-1.27).
Conclusions: PPIs do not appear to significantly decrease the risk of UGI complications to the same degree as COX-2 inhibitors or misoprostol in prescription NSAID users.
Keywords: *Proton pump inhibitors, gastrointestinal complications, NSAIDs*

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29

Proton pump inhibitor use is associated with an increased risk of severe community acquired infections

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Background: Proton pump inhibitor (PPI) use has been associated with an increased risk of community acquired pneumonia and C. difficile. Are PPIs associated with an increase in the risk of severe community-acquired infections (SCAI)?

Methods: We performed a matched case-control analysis using Manitoba Health's population-based database. All individuals admitted to hospital with severe SCAI and active use of PPIs were identified from October 1995-March 2004. A primary ICD-9 admission code for an infectious disease and a secondary code for organ system dysfunction within 3 days of admission defined a SCAI. Cases were matched to ≤ 10 controls on sex, birth year, index date. Conditional logistic regression was used to estimate the relationship between PPI active use and SCAI and to adjust for the presence of comorbidity, antibiotic and immunosuppressive agent use.

Results: Of the 119,047 PPI users identified, 904 met our diagnostic criteria for SCAI. Persons with SCAI were more likely than controls to be using PPIs (adjusted OR 1.62, 95% CI 1.38-1.90). The association was increased for high dose proton pump inhibitor users, (adjusted OR vs. standard dose PPIs: 1.39, 95% CI: 1.02-1.88). Both respiratory (OR 1.78) and non-respiratory severe infections (OR 1.52) were associated with active PPI use. Mortality in patients with severe community acquired pneumonia was increased among PPI users (OR 1.66 (95% CI:1.21-2.11)

Conclusions: The use of proton pump inhibitors is associated with an increased risk of severe community-acquired infections. This increased risk is seen for respiratory and non-respiratory infections, and is further pronounced in patients using high-doses of PPIs.

Keywords: *Proton pump inhibitors, severe community-acquired infections, pneumonia*

30

Comparing double dose vs. standard dose proton pump inhibitor therapy for initial treatment of upper gastrointestinal symptoms

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Background: Proton pump inhibitors (PPIs) are frequently used in persons presenting with upper gastrointestinal (GI) symptoms. Is the initial prescription (Rx) of a higher dose of PPI associated with improved clinical and economic outcomes?

Methods: Manitoba Health's population-based database identified persons with a new PPI Rx (no PPI Rx in previous 12 months) from 1997-2002. All persons with new double-dose (2x) PPI Rxs were matched to a standard dose control on age, sex, socioeconomic status, severe comorbidity, previous GI/non-GI hospital admissions, Rx date. GI-related in-/out-patient resources were tracked for cases/controls for 12 months.

Results: Double-dose PPI new users (n=2236) were linked to a standard dose control. No significant difference in resource use was found between cases/control in the 12 months before analysis. In the year following initial prescription, there were no differences in overall duration of PPI use between cases and controls (128d vs. 126d, p>0.2), and subjects prescribed 2x-dose PPIs ingested at this dose for a mean of 30 days. Subjects initially prescribed 2x-dose PPIs had an equal number of GI-related ambulatory care visits (2.2 vs. 2.2 visits/yr, p>0.2), were not statistically more likely to undergo endoscopy (21.8% vs. 20.8%, p>0.2), or be admitted to hospital for upper GI disease (1.1% vs. 0.6%, p=0.090). 12-month GI related costs are higher for subjects initially prescribed 2x-dose PPIs ($680.60 vs. $510.52, p<0.001)

Conclusions: Initial therapy with double-dose PPIs does not appear to lead to any reduction in GI-related health care utilization. Prescribing double-dose PPIs as initial therapy for upper gastrointestinal symptoms should be discouraged.

Keywords: *Proton pump inhibitors, healthcare resource use, gastrointestinal symptoms*

31

Evaluation of prescribing adherence to recommended drug therapy for acute myocardial infarction patients discharged from seven Ontario hospitals

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Background: Canadian and American evidence-based guidelines have been published outlining quality indicators for the treatment of patients hospitalized for acute myocardial infarction (AMI). Outlined in these guidelines are the medications that patients should be prescribed upon hospital discharge.
Objective: To assess the percentage of AMI patients receiving recommended drug therapy on the day of discharge from hospital.
Methods: We employed a historical cohort design to analyze data from pharmacy records of seven community hospitals in Ontario contributing data to Brogan MedMap database for the years 2005 and 2006. We included patients whose reason for admission was explicitly stated as "ACS" or "AMI"; we excluded patients whose length of stay was less than 48 hours and who received therapy with IV beta-blockers on the day of discharge as we assumed these patients had expired. We determined what medications patients received on the day of discharge from hospital, and assumed that these would be prescribed upon discharge. Drugs were identified by generic name and categorized as statins, beta-blockers, antiplatelets and angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). The rates of prescribing of these medications on day of discharge were compared to benchmark levels suggested in the Canadian guidelines.
Results: There were 2151 patients included in the analysis. One thousand, eight hundred and sixty-seven (87%) received an antiplatelet medication (aspirin or clopidogrel) on the day of discharge, 1690 (79%) received beta-blockers, 1520 (71%) received ACEIs or ARBs and 1612 (75%) received a statin. Canadian target levels for prescribing of these medications are $\geq$ 90%, $\geq$ 85%, $\geq$ 85% and $\geq$ 70%, respectively. Overall 1062 (49%) received all 4 of the target medications.
Conclusions: Using this database we were able to assess adherence to prescribing benchmarks for patients being discharged from hospital after treatment for AMI. Results indicate that benchmark prescribing rates for antiplatelet medication, beta-blockers, and ACEIs and ARBs are not being met in these patients; the benchmark prescribing rate for statins is being met in this patient population.
Keywords: *Hospital database, AMI, adherence, guidelines, discharge*

32

Patterns and medical resource utilization after generic switching in antiepileptic drugs – a review of the Quebec experience

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Funding Source: GlaxoSmithKline, RTP, NC, USA
Background: 1) To determine the switchback rates in antiepileptic drugs (AEDs) compared to other therapeutic areas; 2) to investigate medical services utilization associated with generic switching of lamotrigine.
Methods: Medical and pharmacy claims data from the Régie de l'assurance maladie du Québec (RAMQ) database from 04/1998 to 07/2006 were used. Patients with epilepsy (ICD-9 345) and treated with lamotrigine for >60 days in the 90 days before generic entry were selected. The proportion of patients switching back to brand were calculated for lamotrigine, and for other AEDs and other non-AEDs chronic-use drugs (clobazam, gabapentin, carbamazepin CR, simvastatin, fosinopril, carvedilol). Medical resource utilization was compared between periods of branded versus generic use of lamotrigine.
Results: Of the 671 patients treated with branded lamotrigine, 187 patients (27.9%) switched to a generic, and 51 of these patients (27.5%) switched back to the brand name medication. Rates of switchback were from 20.8% to 44.1% for AEDs and from 7.7% to 9.1% for non-AEDs. Mean daily dose of lamotrigine increased by 5.1% (239.1 vs. 251.4 mg, p=0.0149). Generic use periods showed higher incidence rates of medical services compared to brand use (9.8 versus 8.7 visits per person-year; rate ratio: 1.12; 95% C.I. 1.08-1.17; p<0.0001). Lengths of hospital stays increased during generic use periods (3.29 days/person-year in brand vs. 4.86 days/person-year in generic period; p<0.0001).
Conclusions: A higher propensity of switchback to branded medications was observed among epilepsy patients. Switch to generic lamotrigine was significantly associated with increased physician visits and hospitalizations.
Keywords: *Lamotrigine, generic switching, medical services utilization*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

33

Statins, NSAIDs, and pancreatic cancer

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Background: Recent epidemiological studies and meta-analyses of randomized controlled trials have suggested that statins and NSAIDs might reduce the incidence of cancers in general as well as some specific cancers such as colon cancer. Since pancreatic cancer is relatively rare, none of these studies specifically looked at the effect of these drugs on the incidence of pancreatic cancer. The object of this study was to study the effect of NSAIDs and statins on the incidence of pancreatic cancer.

Methods: Cases were defined as subjects, aged 70 years or more, who received at least 2 diagnoses of pancreatic cancer between 1993 and 2003. The index date was defined as the date of the first diagnosis. One to 4 controls were matched to each case for age and sex. The exposure to statins and to NSAID was defined as at least 1 prescribed dispensation of the drug within the 5 years preceding the index date.

Results: A total of 2,403 cases and 9,592 controls were included. Statin exposure was present in 20.0% of the cases and 19.2% of controls (p-value=0.4, crude odds ratio (OR)=1.05, 95% confidence interval (CI): 0.94-1.72). NSAIDs exposure was present in 59.6% of the cases and 56.5% of the controls (p-value=0.007, crude OR=1.13, 95% CI: 1.03-1.24).

Conclusion: Our results suggest that the protective effects of statins and NSAIDs, which have been suggested for some cancers, are not present in the case of cancers of the pancreas.

Keywords: *Pancreatic cancer, NSAIDs, statins*

34

Oxybutynin use in the elderly

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Objective: Survey on medication compliance, sleep interference/night-time awakening and intensity of side-effects of immediate-release (IR) oxybutynin therapy in the elderly.

Methods: Urologists collected information from patients ≥65 years who were receiving/had received treatment with IR oxybutynin.

Results: Data were collected for 79 patients. The mean duration of IR oxybutynin use was 16.8 ± 26.3 months. Individuals used incontinence pads more frequently during the day (2.6 ± 2.2) than at night (0.9 ± 1.0). Over one-third of patients indicated they were incontinent while asleep. Mean daily dose was 7.5 ± 4.3mg/day and the mean administration frequency was 1.8 ± 0.6 times/day. Seventy-five percent of patients took a dose of oxybutynin between 6pm and before retiring to bed. Eighty-two percent of patients indicated that they could not sleep all night and had to get up to use the bathroom. Sixteen percent of patients indicated that they did not always take the prescribed number of IR oxybutynin tablets each day. The most commonly adverse effect was dry mouth with a moderate severity rating of 3.5 ± 1.2 (rating of 5 = maximum severity). Forty patients were taking medications that may cause or worsen urinary incontinence.

Conclusions: The data showed that IR oxybutynin dosing does not control night-time micturition in most patients. Fifty-one percent of elderly patients were taking drugs that could adversely affect bladder function and highlighted that concomitant medications should be reviewed for drug interactions and side effects and changed/discontinued or used in lower doses, if possible.

Keywords: *Oxybutynin, elderly, utilization*

35 - ENCORE PRESENTATION

The connections among attention-deficit/hyperactivity disorder (ADHD), medical stimulant use, the diversion of prescribed stimulants and non-medical stimulant use in the general adolescent population of Atlantic Canada

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Background: The increased trend in methylphenidate prescribing has led to concerns about the possible over-diagnosis of ADHD and over-prescribing of stimulants. The purpose of this study was to describe the connections among ADHD, and medical and non-medical methylphenidate and amphetamine use in the general adolescent population.

Methods: This cross-sectional study used self-reported anonymous data from the 2002 *Student Drug Use Survey in the Atlantic Provinces* (SDUSAP). The Ontario Child Health Study Hyperactivity Scale was used to screen for ADHD. A total of 12990 students in junior and senior high

schools, with an average age of 15 years, participated in the 2002 SDUSAP. The self-reported prevalence of prescribed stimulants was validated against data from the NS Prescription Monitoring Program.

Results: The prevalence of a positive ADHD screening test was 6%. The prevalence of medical and non-medical methylphenidate use was 2.0% and 6.6% respectively. The prevalence of medical and non-medical amphetamine use was 1.2% and 8.7% respectively. A positive ADHD screening test was independently predictive of both medical and non-medical stimulant use. Students in a school class where at least one student had given or sold some of their prescribed pills were found to be at increased risk of non-medical methylphenidate use.

Conclusions: Connections were demonstrated at the population level between ADHD, medical methylphenidate use, the diversion of prescribed methylphenidate and the non-medical use of methylphenidate. The appropriate assessment and management of ADHD are essential to minimize both the risk of the diversion of methylphenidate medication and the risk of substance use associated with unrecognized or untreated ADHD.

Keywords: *Attention deficit hyperactivity disorder, stimulants, substance abuse*

36

Association between antidepressant use during pregnancy and infants born small for gestational age

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Funding Source: FRSQ, RQRUM, and the FRSQ network for the wellbeing of children

Background: Studies have suggested a possible association between antidepressant use during pregnancy, low birth weight, and prematurity. Outcome measures combining birth weight and age e.g. 'Small for Gestational Age' (SGA) have rarely been investigated.

Objective: To determine the association between class of antidepressant and the risk of infants being born SGA, according to trimester of exposure.

Methods: A 'Medication and Pregnancy' registry, built by linking three databases (RAMQ, Med-Écho, ISQ) and data from a questionnaire was used. Eligible women had 1) to be 15-45 years of age at the beginning of pregnancy, 2) be insured by the RAMQ drug plan for ≥12 months prior to the first gestational day and during pregnancy, 3) have ≥1 diagnosis of psychiatric disorder before pregnancy, 4) have used antidepressants for ≥30 days in the year prior to pregnancy, and 5) have a pregnancy ending with a live singleton birth. Cases were defined as newborns with birth weight ≤10th percentile for that gestational age. Relative risks were estimated using modified Poisson regression.

Results: Among the 3061 pregnancies meeting inclusion criteria, 419 (7.3%) infants were born SGA. New antidepressants used during the second trimester such as SNRIs were associated with SGA at birth (new antidepressants vs. none: aRR 1.88, 95% CI 1.05, 3.34). However, SSRIs and tricyclics were not associated with an increased risk of infants being born SGA.

Conclusions: These data suggest that the use of new antidepressants during the second trimester of pregnancy is associated with an increased risk of infants being born SGA.

Keywords: *Antidepressant, pregnancy, case-control*

37

Duration of antidepressant use during pregnancy and risk of major congenital malformations

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Funding Source: FRSQ, RQRUM, and the FRSQ network for the wellbeing of children

Background: Antidepressant use during the pregnancy is controversial.

Objective: To determine whether duration of antidepressant use during the first trimester increases the risk of major congenital malformations in women diagnosed with psychiatric disorders.

Methods: The Medication and Pregnancy registry, built by linking three databases (RAMQ, Med-Écho, ISQ) was used. To be included in this study, women had 1) to be 15-45 years of age at the beginning of pregnancy, 2) be insured by the RAMQ drug plan for ≥12 months prior to the first day of gestation and during pregnancy, 3) have ≥1 diagnosis of psychiatric disorder before pregnancy, 4) have used antidepressants for ≥30 days in the year prior to pregnancy, and 5) have a pregnancy ending with a delivery. Cases were defined as any major congenital malformations diagnosed in the first year of life. Odds ratios, adjusted for relevant confounders, were estimated using logistic regression.

Results: Among the 2329 women meeting the inclusion criteria, there were 189 (8.1%) infants with major congenital malformations. Duration of antidepressant use during the first trimester of pregnancy was not associated with an increased risk of major congenital malformations (1–30 days versus 0 days: aOR 1.23, 95% CI 0.77, 1.98; 31–60 days versus

0 days: aOR 1.03, 95% CI 0.63, 1.69; ≥ 61 days versus 0 days: aOR 0.92, 95% CI 0.50, 1.69).

Conclusion: These data do not support an association between duration of antidepressant use during the first trimester of pregnancy and major congenital malformations in women with psychiatric disorders.

Keywords: *Antidepressant, congenital malformations, case-control*

38

Economic evaluation of voriconazole for the treatment of candidemia in Canada

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Funding Source: Pfizer Canada Inc.

Background: Candidemia is a nosocomial bloodstream infection associated with considerable morbidity and mortality. The objective of this study was to assess voriconazole's cost-effectiveness relative to conventional amphotericin B (CAB) followed by fluconazole in the treatment of non-neutropenic patients with candidemia in the Canadian setting.

Methods: A decision-analytic model was designed to reflect the clinical treatment pathways used in clinical practice when comparing voriconazole to CAB/fluconazole for the treatment of non-neutropenic patients with candidemia over a 14-week horizon. The clinical outcome and resource use data were based on the Global Candidemia Study while costs were collected from Canadian sources. Any missing data were obtained from an independent panel of experts.

Results: While the costs of voriconazole exceeded the costs of CAB/fluconazole, these costs were largely offset by lower hospitalization costs. Accounting for both differences in total costs and clinical outcomes, this analysis estimated an incremental cost per patient surviving at day 98 of CDN$ 17,744 and an incremental cost per patient avoiding toxicity of CDN$ 9,300. In the case of cost per patient cured, voriconazole had a higher cost (CDN$ 1,121) than CAB/fluconazole but cure rates were 41% in both arms. Sensitivity analyses demonstrated that results were robust over a range of values for key variables.

Conclusions: Results of the decision-analytic model demonstrated the cost-effectiveness of voriconazole relative to a regimen of CAB followed by fluconazole in the treatment of non-neutropenic patients with candidemia in the Canadian setting.

Keywords: *Cost-effectiveness, candidemia, voriconazole*

39

A meta analysis of the impact of medications on falling in the elderly

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Funding Source: None

Background: The impact of medications on falls in the elderly has not been established for many commonly prescribed drug classes. Our systematic review and meta analysis assessed the association between the use of specific drug classes and falls in the elderly.

Methods: Observational studies were identified through a systematic search of English-Language articles collected from EBM, CINAHL, EMBASE and MEDLINE using the keywords: falls, accidents and accidental falls, aged or age factor, elderly, drug or drug therapy and therapeutic. Studies were limited to those with subjects >60 years who were exposed to one or more drug therapies and had an identified outcome of falling. From the included studies, random effects pooled odds ratios (OR) were estimated for the drug classes: sedatives, antidepressants, benzodiazepines, anti-psychotics, diuretics, and beta blockers.

Results: Sixteen studies, covering 73,793 participants and 23,357 falls, were identified. The risk of falling was significantly increased for those receiving sedatives (6 studies, 18,453 falls) (OR: 1.59; 95% CI: 1.19-2.13), antidepressants, (10 studies, 7,280 falls) (1.71; 1.37-2.14), benzodiazepines (8 studies, 5,112 falls) (1.53; 1.37-1.72), and anti-psychotics (5 studies, 3,800 falls) (1.68; 1.37-2.07). A significantly increased risk of falling was not observed for diuretics (7 studies, 1,685 falls) (OR: 0.91; 95%CI: 0.70-1.19) or beta blockers (5 studies, 1,464 falls) (1.08; 0.85-1.39).

Conclusions: Sedatives, antidepressants, benzodiazepines, and anti-psychotics are associated with increased risk of falls in the elderly. In the elderly, use of these drug classes should be minimized and monitored to lower their impact on individuals' risk of falling.

Keywords: *Meta analysis, medications, falls in the elderly*

Advances in Therapeutics Education

40

A process evaluation of Calgary health region academic detailing initiative

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Background: An academic detailing (AD) initiative was launched for family physicians in the Calgary Health Region (CHR) in 2005. AD was the cornerstone of this multifaceted educational intervention; additional components included continuing education, printed education materials, opinion leader consultation and prescribing feedback reports. The Alberta Drug Utilization Program (ADUP) managed the initiative in collaboration with two established regional programs; Department of Family Medicine and Chronic Disease Management. Two specially trained pharmacists carried out local planning activities, coordinated promotion and bookings, oriented themselves to clinical practice guidelines (CPG), conducted AD visits and assisted in evaluation activities.

Methods: A process evaluation was conducted after delivering the first topic, dyslipidemia. The evaluation framework focused on feasibility, outputs obtained and lessons learned. Qualitative data was collected through document review, physician surveys and from the recollections of the academic detailers and the program director.

Results: The following were selected findings. 1) Partnering locally with established CHR programs increased credibility, built relationships and increased utilization of regional resources (e.g., PADIS, Calgary Lipid Interest Group). 2) Utilizing a variety of marketing and recruitment strategies resulted in 100 physicians participating in the 1st topic. 3) Physicians were highly satisfied with AD visits (responses to survey questions averaged 4.6 or higher on a 5 point scale). 4) Physicians indicated strong intentions to follow the dyslipidemia CPG after the visits (average score of 4 or higher on 5 point scale).

Conclusions: The AD initiative was successfully launched in the CHR. Delivery of the first topic met or exceeded objectives set for physician participation and satisfaction. The evaluation served as an important aid for CHR administrators in their decision to operate a local program after the province discontinued funding for ADUP.

Keywords: *Process evaluation, academic detailing*

41 – ENCORE PRESENTATION

Effect of academic detailing on COX-2 utilisation rates in the Nova Scotia seniors population: a retrospective cohort design using propensity scores to adjust for bias due to unequivalent comparison groups

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Background: The prevalence of osteoarthritis (OA) is estimated at 50 to 80% of the elderly population. Nova Scotia general practitioners (GPs) identified a need for an academic detailing (AD) intervention aimed at optimizing the management of OA. The primary objective was to measure the effect of an OA AD intervention to reduce the utilisation rate of COX-2 inhibitors. Secondary objectives were to examine the intervention effect on the utilisation rates of gastro-protective agents and medical services.

Methods: A retrospective cohort study design employing administrative data was used. Differences in utilisation rates were evaluated using generalized estimating equation (GEE) analysis for longitudinal data. Selection bias was anticipated since the intervention was voluntary. Three methods of propensity score (PS) analysis were evaluated for the ability to adjust for bias on PS model covariates.

Results: A significant difference in the change in COX-2 utilisation rates between groups for the three month period following the intervention ($p = 0.0395$, 95% CI (0.0365, 1.4815)) and a significant decrease in the intervention group's within group utilisation rate between the pre and post intervention periods ($z=-2.34$, $p=0.0191$) were observed. The GP office visit rate was significantly higher ($p=0.0275$, 95% CI (-0.7926, -0.0464)) for the intervention group.

Conclusions: The OA AD intervention was associated with a significant decrease in COX-2 utilisation rates in the three month period immediately following the intervention. The effect of decreased utilisation continued over the post intervention period but was not statistically significant. The GP office visit rate was significantly higher for the intervention group in the second three month post intervention time period.

Keywords: *Academic detailing, prescribing behaviour, propensity scores*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

42

Use of holding chambers in the emergency department: perceptions of evidence

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Background: Published evidence over the last two decades points to the therapeutic equivalence of MDI plus holding chamber compared to nebulization when used for delivery of beta-agonists in children with mild to moderate acute exacerbations of asthma. A recent national survey found that 86% of pediatric Emergency Physicians and 60% of Emergency Nurses believed there was enough evidence to justify switching to MDI plus holding chamber, yet only 21% of physician respondents currently use this treatment strategy. These results attest to the challenge of translating research findings into knowledge and subsequent behavioral or practice change.

Methods: This qualitative study was guided by the principles of grounded theory. Data were collected through focus groups and individual interviews at two sites in Eastern Canada: Hospital A, where inhalers and holding chambers are used routinely; and Hospital B, where prevailing practice is use of nebulization for acute asthma. Focus group and interview questions and probes were prospectively defined and approved by ethics review committees at the respective institutions. Participant encounters were transcribed verbatim and analyzed for emerging themes.

Results: At Hospital A, 6 physicians and 7 nurses participated in separate focus groups. Four interviews were conducted with physician, nurse, respiratory therapy and pharmacy leaders. At Hospital B, 4 physicians and 3 nurses participated in focus groups while 6 leaders were interviewed. Qualitative analysis of the transcripts is in progress and will be completed in April 2007. Main themes and exemplar quotations demonstrating participants' perceptions of evidence in clinical practice will be presented.

Keywords: *Qualitative research, knowledge translation, evidence-based medicine*

43

Safety and efficacy of the top-selling herbal dietary supplements in pregnancy- a systematic review

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Background: There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbal medicines used during pregnancy and lactation.

Objectives: To systematically review the literature for evidence on 1) efficacy, 2) safety/harm during pregnancy and lactation, and 3) pharmacology of the 10 top-selling herbal dietary supplements in the United States.

Methods: We systematically searched and reviewed 7 electronic databases and compiled data according to the grade of evidence found.

Results: We found varying levels of evidence on the clinical efficacy of the herbal medicines reviewed. We found fair to very good levels of evidence of safety in pregnancy for garlic, echinacea, cranberry, Panax ginseng, St John's wort and milk thistle. Due to the absence of data or due to weak evidence based on theoretical or expert opinion, we found inconclusive evidence of safety in pregnancy for black cohosh and ginkgo. We found very good evidence that soy may have weak estrogenic activity and strong evidence that soy may increase the risk of developing hypospadias in boys. Saw palmetto (third top-seller) was excluded as it is predominantly an herbal medicine for men's health.

Conclusions: The herbal medicines reviewed showed evidence of being effective aids for a number of therapeutic conditions. However, some safety concerns are important to highlight for women considering the use of certain herbal medicines during pregnancy.

Keywords: *Herbal medicines, pregnancy*

44

Minimal clinically important difference in randomized controlled trials of therapies?

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Background: The minimal clinically important difference (MCID) for a study of therapy is the smallest change in an outcome measure that would necessitate a modification of a patient's medical management. Planning of clinical trials and the interpretation of study results rests heavily on the concept of the MCID. The objective of this study is to assess how well the MCID is reported and determined in a sample of therapy RCTs recently published.
Methods: Primary articles describing randomized clinical trials of therapies from five high-impact journals (NEJM, BMJ, JAMA, Annals of Internal Medicine, Lancet), published in 2006 were selected. A random sample of 25 studies from a total of 161 articles identified was appraised. We assessed the use of MCID in the sample size calculation and how it was determined, as well as the discussion of clinical importance or MCID in the report.
Results: The majority of reports (20/25) included an estimated outcome in each group (the clinically important target difference) in their sample size calculation. However, only 2 trials included a justification of how this difference was determined. In the discussion of study results, only 6 of the 25 reports made any direct statement or comment related to the clinical significance and MCID of the observed differences.
Conclusions: Reporting of MCID and discussion about whether the observed differences are clinically meaningful was inadequate in this sample of high profile therapy trials. Further study and possible enhancement of methods of determining the MCID, is warranted.
Keywords: *Minimal clinically important difference, critical review, randomized trials*

45

The impact of pharmacists' interventions: sensitivity on patient outcomes in diabetes management

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Background: Pharmacists participate in managing diabetes therapy; few papers have quantified their impact.
Objectives: To identify and quantify outcomes sensitive (clinical benefit + statistical significance) to pharmacists' interventions.
Methods: Studies describing pharmacists' interventions in diabetics were sought in IPA, Medline, and Embase, from inception to 2006. Two independent reviewers identified articles; results were compared and settled through consensus. Data extracted included type of intervention, patient numbers, demographics, study characteristics, instruments used, data compared, and outcomes. Random-effects meta-analysis combined appropriate/available results. Study quality was assessed using Downs and Black's validated scale.
Results: Of 302 potential articles, 108 involved pharmacists' pharmacotherapeutic interventions, 36 in diabetes (14 in medical clinics, 11 in community pharmacies, 7 in ambulatory clinics, 4 in hospital wards, 1 in physicians' offices and 1 in a prison). Research designs varied (18 randomized controlled trials, 9 non-randomized trials, 2-pre-post observational cohorts, 1 retrospective cohort study, 4 chart reviews, 1 database study). Diabetes education (72%) and medication management (64%) were pharmacists' most used interventions. Average quality was 62%±11% ("fair"). Fifty-one results (69%) were 'sensitive' to the pharmacist's intervention. Meta-analysis found pharmacists further reduced glycosylated hemoglobin compared to standard care (0.62%±0.29% in 2247 patients from 16 studies, P=0.03). Fasting blood glucose levels were sensitive (5/5 studies). Blood pressure and total cholesterol were equivocal (8/14 and 6/10 significant outcomes, respectively).
Conclusions: Glycosylated hemoglobin level is definitely sensitive to pharmacists' interventions. Several additional outcomes that may also be sensitive were identified, but too few studies have been conducted to quantitatively summarize them.
Keywords: *Pharmacist, intervention, diabetes, pharmaceutical care, clinical pharmacy*

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46

Methods for individualizing the benefit and harm of warfarin

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Background: For narrow therapeutic index drugs, probability of drug benefits is balanced by probability of harmful drug side effects. Population-based approaches can be inadequate in tailoring therapies to individual patients. Our objective was to refine methods of creating individual profiles with 4 possible outcomes – benefit/no harm, benefit/harm, harm/no benefit, no benefit/no harm – using warfarin, where benefit = stroke prevention and harm = major bleeding.

Methods: Using the Atrial Fibrillation Investigators database (n=9155), classification and regression tree (CART) modeling and polytomous regression were conducted to identify patient factors predicting an individual's expected benefit/harm outcome. The database contains patient-level data from ten atrial fibrillation RCTs comparing warfarin to a control, including data for previously identified factors for stroke and bleeding. Stratifying patients based on their benefit/harm outcome, we used the two techniques to determine combination of factors predictive of each of the four outcome groups. Criterion for statistical significance was set at alpha = 0.05.

Results: In 3967 patients taking warfarin, there were 175 stroke outcomes, 27 major bleeds and 3 combined strokes and bleeds. With CART modeling, a history of stroke was the factor that most discriminated between the four outcome groups, followed by history of transient ischemic attack and high systolic blood pressure (>175 mmHg). Polytomous regression identified more factors: age, systolic blood pressure, history of stroke or TIA were predictive of an individual's benefit/harm outcome group ($p < 0.05$).

Conclusions: This type of individual patient data analysis may be a useful step forward in the quest for evidence-based individualization of drug therapy.

Keywords: *Regression, tree modeling, individualization*

Information Technology

47

Predictors of failure to keep primary care appointments

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Background: Missing medical visits negatively affects health outcomes, and results in reduced efficiency of the health care system. The study objective is to explore the factors associated with failure to keep clinical appointments among diabetic patients.

Methods: Electronic medical and administrative records of 19 primary care clinics in Hamilton area were used. Only records for diabetic patients were selected. Logistic regression models were used to predict non-adherence to scheduled medical visits using the characteristics of patients and their medical status.

Preliminary Results: 1589 diabetic patients, attending 19 primary care clinics, were identified. Failure to keep scheduled appointments was estimated to be as high as forty percent form all scheduled appointments. The process of data cleaning and logistic regression is still to be completed in March of this year.

Keywords: *Heath care services, office visits, patient compliance*

48

Discontinuation of vascular medications among patients at risk for vascular disease in the primary care setting

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Background: Long-term persistence with vascular medications is necessary for prevention of vascular events, however patients and physicians may prematurely discontinue these important medications. The objective of this study was to provide pharmacosurveillance data on the frequency and reasons for discontinuation of vascular medication among primary care patients with vascular risk, and to determine the effect of a vascular management program on rates of discontinuation.
Methods: Medication information was collected for all patients enrolled in COMPETE III, a large randomized controlled trial of an electronic vascular disease management program on the quality of vascular care. Start and stop dates for each medication and the reason for discontinuation were collected over 12 months by patient telephone interview and a review of electronic medical records in family physicians' offices. Discontinuation rates were calculated as the number of times medications were discontinued over the number of times medications were prescribed during the study.
Results: Of the 15,870 medications prescribed, there were 738 discontinuations among 1104 study patients. The mean (± SD) number of medications discontinued was 0.69 (±1.02) with a mean discontinuation rate of 6.9% (±16.9%). No difference was seen in the rate of medication discontinuation between the intervention and control group (6.7% vs. 7.2%, p = 0.665). The most common reasons for medication discontinuation were intolerance (26.8%), lack of efficacy (12.3%), and stopped by a physician other than the primary prescriber (12.2%). The drug classes with the highest rate of discontinuations were anticoagulants (18.5%), ACE-inhibitors (18.0%), and statins (15.7%).
Conclusions: Discontinuation of vascular medications is not uncommon, even among patients with high vascular risk. Medications were discontinued for both appropriate and inappropriate reasons. The reasons for discontinuation are helpful in explaining why physicians are not able to always adhere to evidence-based guidelines for prescribing vascular medications.
Keywords: *Pharmacosurveillance, vascular, medication discontinuation*

49 – ENCORE PRESENTATION

Survey of North American teratogen information services

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Background: Medication use amongst women of child-bearing age is high. Women and health care providers (HCPs) have few information sources regarding the safety/risk of exposures in pregnancy and lactation. Teratology Information Services (TIS) provide this information via telephone. Maintaining TIS funding is a challenge, limiting access. The objective was to gather data from North American TIS regarding their operations for a future cost-benefit analysis.
Methods: 18 TIS (2 CDN, 16 U.S.) completed a survey regarding services, staffing, operations, research, and knowledge transfer activities. Results summarized using descriptive statistics.
Results: Services: Goals ranked as most important were: correction of risk misperceptions, education of other HCPs on teratology, prevention of malformations caused by teratogen exposure. Inquiries were primarily for medications (median 50%), followed by workplace exposures and drugs of abuse (median 5%). Staffing: Median of four employees per TIS was found. Sixteen TIS train at least one student per year (range 0-55). Operations: Two TIS only counsel HCPs. Main callers to the other 16 TIS are pregnant women (median 40%), physicians (median 10%), nurses (median 10%). Call number per week varies (mean 78, range 4-600). Annual budgets range: USD $28,500-$335,000 (mean $128,281). Research and knowledge transfer: 17 TIS collect patient data for research purposes. All TIS participate in knowledge transfer activities.
Conclusions: This survey is the first to capture the scope of TIS operations in North America, and demonstrated a spectrum of clinical and research activities. The results will be used as inputs for a service model and cost-benefit analysis.
Keywords: *Medications, teratology, cost-benefit*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

50

Factors determining the success of computerized decision support in prescribing: a systematic review

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Background: Computerized decision support systems (CDSS) which can provide intelligent patient-specific recommendations are believed to improve the quality of health care delivery, but recent systematic reviews caution that the evidence is still inconclusive. However, these reviews pool many different types of CDSS and use subjective and variable definitions of success. We conducted a quantitative systematic review to determine factors that can predict success for CDSS devoted to prescribing (RxCDSS).

Methods: We searched Medline, EMBASE, CINAHL and INSPEC databases for randomized controlled trials of electronic RxCDSS reporting outcomes categorized as system implementation, impact on clinical processes, and impact on clinical outcomes. We found data on 29 of 40 factors in 6 domains: general features, user-system interaction features, content features, organizational features, alignment of objectives, and other features. We used logistic regression (LR) to determine their association with CDSS success.

Results: Of 2,117 citations, 26 met the inclusion criteria. Of these, 88.2% reported successful implementation (the system was used), 42.3% reported impact on process (changed clinician behaviour) and 3.8% reported improvement in patient outcomes. No study provided a rigorous analysis of factors predicting success or failure of the RxCDSS and LR was unhelpful. Those factors mentioned in > 75% of successful implementations largely reflect system speed, convenience of use, quality, relevance to the task at hand and integration with workflow.

Conclusions: Very few high quality studies demonstrated improved patient outcomes with RxCDSS. The features associated with a system's success or failures are inadequately studied, thus making it difficult for system design to improve.

Keywords: *Computerized decision support, predictors of success, systematic review*

51

Provider and patient reminders in Ontario: multi-strategy prevention tools (P-PROMPT)– a demonstration project to systematically increase the delivery of four targeted preventive care services to 350,000 Ontarians

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Background: 25-50% of Ontarians eligible for evidence-based preventive care (annual influenza vaccination, completion of childhood immunization, biannual pap screening, biannual screening mammography) are not up-to-date. An underlying opportunistic approach to preventive care in primary care practice may arise from roster status information that may be available to physicians being incomplete, continually degrading as patients fall overdue, and entirely blind to patients who never present.

Methods: To demonstrate a multi-strategy information-based intervention to improve delivery of the above four services, P-PROMPT recruited 249 physicians having 350,000 rostered patients. Ontario Ministry of Health regularly provided participating physicians with electronic files of their patient rosters, including demographics and dates of recent mammograms (50% of total). Ontario Breast Screening Program provided dates of recent mammograms (other 50%). Cytobase provided dates of recent pap tests (90% of total). Physicians and staff used a secure data-enabled P-PROMPT website to display eligible subsets of patients for each service, ordered "by need" (never done and most overdue on top), and to routinely enter updated service dates, ineligibilities and roster changes. Physicians without office internet access used "2-way" paper data forms on a 3-month cycle. P-PROMPT regularly mailed individualized patient reminder/recall letters to all overdue patients on behalf of physicians.

Results: Physicians verifiably achieving Ontario top-tier performance targets rose from 29% to 52% (80% or more of patients up-to-date for pap screening) and from 43% to 61% (75% or more of patients up-to-date for screening mammography).

Conclusions: Information-based interventions can increase preventive care delivery on a large scale.

Keywords: *Knowledge implementation, preventive care service delivery, demonstration project*

52

Parents of asthmatic children were accurate proxy reporters of urgent health services use – a retrospective agreement analysis

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Background: While parents are frequently relied upon to report their children's health services use, the accuracy of parental proxy reports remains unknown. The objective was to assess agreement between parents' proxy reports of children's respiratory-related health service use and administrative data in pediatric asthma patients.

Methods: A retrospective analysis of agreement between clinical and claims data for reports of physician visits, Emergency Department (ED) visits and hospitalizations was conducted for 545 asthmatic children in the greater Toronto area. Health services use data were extracted from Ontario Health Insurance Plan and Canadian Institute for Health Information administrative databases. Agreement was assessed with the kappa statistic. Disease and socioeconomic determinants of agreement were investigated.

Results: Agreement between administrative data and respondent reports was substantial for inpatient admissions (k=0.80, 95% CI 0.74, 0.86) in the past year, moderate for ED visits (k=0.60, 95% CI 0.53, 0.67) in the past year and poor for outpatient physician visits (k=0.13, 95% CI 0.00, 0.27) in the past 6 months. Income, parent's education and child quality of life symptom scores did not affect agreement. Agreement for ED visits was significantly higher ($p<0.05$) for children that had an asthma attack in the past 6 months (k=0.61, 95% CI 0.54, 0.68) compared to children that did not (k=0.25, 95% CI 0.00, 0.59).

Conclusions: Parents of asthmatic children are good proxy reporters of their child's respiratory-related health services utilization for ED visits and inpatient admissions.

Keywords: *Health services utilization, proxy report, agreement*

TUESDAY MAY 29, 2007

Human Resources in Drug Evaluation

53

The importance of patient participation in health policy decision making

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Background: The use of patients and 'lay representatives' in health policy and health decision making is becoming more widespread as decision makers acknowledge the right of the public to have input into how the public purse is spent. Ontario's Bill 102, the Transparent Drug System for Patients Act, which mandates the creation of a Citizens' Council, is just one example of this trend. Specifically, the bill states that "the Minister shall establish a Citizens' Council whose duty shall be to ensure the involvement of patients in the development of pharmaceutical and health policy." The objective of this study is to provide feedback to the Ministry of Health and Long Term Care (MoHLTC) with suggestions for moving forward.

Methods: A succinct literature and jurisdictional review of patient participation in health decision making was followed by key informant interviews (surveys) with representatives of Ontario-based health charities. A consensus conference with key opinion leaders from health charities and MoHLTC representatives was also conducted.

Results: Recommendations are provided based on previous work on related topics published in the literature, lessons gleaned from the jurisdictional review, and responses to the survey. Recommendations for the following topics are included: Council composition, topics for discussion, member recruitment, frequency and duration of meetings, training, resources required, and payment.

Conclusions: The Citizens' Council is an exciting prospect for patients and consumers that will allow them to have direct input into health and pharmaceutical policy in Ontario.

Keywords: *Patient engagement, key informant interviews, health decision making*

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54

Literature review of economic evaluation of multivitamin supplementation during pregnancy and congenital malformations

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Funding Source: None

Background: Prenatal multivitamins have been shown to be associated with protective effects for congenital anomalies. As such, women who are actively planning pregnancy or who discover they are pregnant, are advised by their healthcare provider to supplement with prenatal multivitamins.
Methods: Medline (1950-Jan 2007), EMBASE (1980-Jan 2007), Healthstar (1966-Nov 2006), and PubMed (1950-Jan 2007) were searched for the following terms: vitamins, costs and cost analysis, and abnormalities. Articles were search in all languages without any date restriction. Titles and abstracts were reviewed for articles containing information on economic evaluation of multivitamin use in pregnancy and malformations. Articles discussing economic impacts of folic acid fortification of food, supplementation of folic acid alone, or outcomes other than pregnancy and malformations were rejected. References of articles were searched for additional original articles.
Results: Only one study reported the cost-effectiveness of prenatal multivitamin supplementation in pregnancy. This Californian based study calculated the potential cost-savings were only reported for neural tube defects and cardiovascular defects. There are currently no articles available on Canadian cost-effectiveness.
Conclusions: Prenatal multivitamin supplementation appears to be associated with cost-saving for neural tube defects and cardiovascular defects in California. Given that information regarding the prevalence of congenital malformation and the costs associated with these malformations can be obtained, a study of the potential cost-saving of prenatal multivitamin supplementation versus other modalities such as food fortification with folic acid and the prevention of congenital malformations for the United States and Canada should be undertaken.
Keywords: *Multivitamin, economic analysis*

55 – ENCORE PRESENTATION

Drug evaluation unit: a structure to support evidence-based policy decisions and educational interventions

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Funding Source: None

Background: The Drug Evaluation Unit (DEU) provides support to the Atlantic Common Drug Review formulary decision-making process by providing evidence-based written and oral presentations of a drug's safety, efficacy and cost-effectiveness. The expertise in critical appraisal and knowledge of specialized drug topics are valuable assets that aide in the provision of on-going support to the Atlantic Provinces Pharmacare Programs for the implementation and administration of policy decisions. On a national level, DEU pharmacists have consulted with the Canadian Agency for Drugs and Technology in Health (CADTH) in the developmental stages of the Common Drug Review and have participated as a member on a Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) expert advisory panel. The relationships built between the DEU, policy makers, national bodies, expert opinion leaders and academia have provided a structure to work collaboratively, and share knowledge efficiently with other evidence-based educational interventions designed to influence practice. As examples, the DEU collaborates with the Drug Evaluation Alliance of Nova Scotia (DEANS), the Dalhousie University Continuing Medical Education Academic Detailing Service, the National Academic Detailing Collaboration, Continuing Pharmacy Education, local clinical practice guideline developers and researchers at Dalhousie University.
Conclusions: The knowledge gained in the process of performing drug evaluation reviews is a resource that can contribute to several stages of the "virtuous circle", from informing drug policy to providing evidence-based material to develop educational interventions.
Keywords: *Drug evaluation, knowledge transfer, drug policy*

56

Amiobisphosphonates reduce incident fractures compared to etidronate in postmenopausal women with osteoporosis

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Funding Source: None

Background: Despite the extensive use of etidronate, alendronate and risedronate in postmenopausal osteoporosis, there are no head-to-head studies that compare the effectiveness of these agents in reducing fractures. The purpose of our study was to compare incident fracture rates in women prescribed etidronate (ETD) to those prescribed aminobisphosphonates alendronate or risedronate (ALDRIS).

Methods: This study utilizes prospective data from the Canadian Database of Osteoporosis and Osteopenia (CANDOO) which features approximately 10,000 patients from across Canada. Women over 40 years of age were included in the analysis if they were taking one of the three bisphosphonates for greater than 270 days and were not prescribed another bisphosphonate for more than 60 days. A total of 1300 and 416 women were included in the ETD and ALDRIS groups, respectively. A multivariable logistic regression analysis was performed to compare differences in incident fracture rates between groups. To account for missing data, multiple imputation analysis was conducted. Ten completed data sets were analyzed and combined to construct inferential results.

Results: Patients were on therapy for a mean duration (SD) of 4.4 (2.7) and 3.3 (1.9) years in the ETD and ALDRIS groups, respectively. The annual incident fracture rate (15 fracture sites were combined) for the ETD was 3.9% versus 2.4% for the ALDRIS group. Adjusted results indicated that the ALDRIS group had a 40% risk reduction in new fractures as compare with the ETD group.

Conclusion: In postmenopausal women, alendronate and risedronate, are more effective at reducing incident fractures as compared with etidronate.

Keywords: *Osteoporosis bisphosphonate CANDOO*

Therapeutics Innovations

57

Cost-effectiveness of 80 mg versus 10 mg of atorvastatin in Canada based on the results of the TNT study

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Funding Source: Pfizer Inc

Background: The TNT study demonstrated a 22% reduction in major cardiovascular events with intensive atorvastatin 80 mg (A80) over moderate atorvastatin 10 mg (A10) lipid lowering in patients (N=10,001) with stable coronary heart disease (CHD) over 4.9 years.

Objectives: To assess the cost-effectiveness of lipid-lowering below current guidelines with A80 versus A10 from the perspective of the Canadian Ministries of Health. Methods: A lifetime Markov model was developed to predict cardiovascular events, costs, survival, and quality-adjusted life years (QALYs) for CHD patients receiving A80 versus A10. Treatment-specific event risks were estimated and extrapolated to 10 years. Beyond year 10, equivalent cardiovascular risks were assumed for all patients. Medical-care costs and post-event survival were estimated using Canadian data. Health utility scores were obtained from published studies. Benefits and costs were discounted 5% annually. Probabilistic and deterministic sensitivity analyses were performed.

Results: Treatment with A80 resulted in increased costs ($18,357 vs. $17,341), survival (10.85 vs. 10.74 life years), and QALYs (8.26 vs. 8.14) per patient compared with A10, yielding an incremental cost-effectiveness of $9,313 per life year gained and $8,755 per QALY. The incremental cost per QALY remained below $50,000 in 99% of 1000 simulations. Results were robust to variations in event hazard ratios, costs, health utility scores, and discount rate.

Conclusion: Intensive A80 treatment is estimated to be cost-effective versus A10 in CHD patients in Canada. Prior secondary prevention studies demonstrated cost-effectiveness of statin treatment compared with no treatment. These results demonstrate that treatment intensity should be considered in treatment algorithms.

Keywords: *Cost-effectiveness, lipids, treatment guidelines*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

58

Patient satisfaction with a single pill treatment of hypertension and dyslipidemia

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Background: Poor adherence to treatment contributes to lack of goal attainment in patients with hypertension and dyslipidemia. Patients satisfied with their treatment are more likely to be adherent and behave in ways that improve or maintain their health. This study assessed patients' satisfaction with a single pill amlodipine/atorvastatin to treat hypertension and dyslipidemia.
Methods: Patients were administered the Expectations and Satisfaction with Treatment Questionnaire Short Form (ESTQ-SF) at baseline and follow-up visits as part of the JEWEL trials; two multi-centre, open-label, titration-to-goal studies in patients with hypertension and dyslipidemia (N=2225). Patients were grouped according to their treatment history (hypertension, dyslipidemia, hypertension & dyslipidemia, treatment naïve). Psychometric analyses were performed on the ESTQ-SF satisfaction and expectation subscales. Mixed models were used to assess the significance of changes in satisfaction scores over time and to assess differences based on treatment history.
Results: Internal consistency of the satisfaction scale was high (alpha=0.77). Test-retest reliability ranged from 0.53 to 0.61 across treatment history groups. Patients' level of satisfaction with their pill burden significantly increased when switching or incorporating amlodipine/atorvastatin into their treatment regimen at the first follow-up visit ($p<.0001$) and was maintained throughout follow-up. A significant increase in satisfaction was observed across all groups ($p<.001$).
Conclusions: The ESTQ-SF demonstrates adequate reliability and is sensitive to changes in treatment satisfaction in patients treated with amlodipine/atorvastatin. Further, these findings suggest that a single pill treatment for hypertension and dyslipidemia increases patient satisfaction, an important determinant of adherence with therapy and ultimately blood pressure and LDL-cholesterol control.
Keywords: *Patient satisfaction, hypertension, lipids*

59

Community mobilization, participation, and risk factors in a Cardiovascular Health Awareness Program (CHAP) in Ontario

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Background: Community-based programs linked to primary care have potential to reach a significant portion of the population to enhance detection and management of high blood pressure (BP) and awareness of cardiovascular and stroke risk. We conducted community-wide demonstration projects in Grimsby and Brockville, Ontario, to assess the feasibility of a Cardiovascular Health Awareness Program for older adults.
Methods: Working with local agencies, we mobilized communities to offer a volunteer-led program for assessment of BP and other risk factors, with feedback of results to family physicians, pharmacists and participants. Residents 65+ years of age were invited through their physician or community-wide advertising. At pharmacy sessions, trained peer volunteers assisted with BP measurement, completion of risk profiles, and advice about locally available resources for modifiable risk factors.
Results: Nearly all family physicians (n=56/63) and pharmacies (n=18/19) participated. Over 90 volunteers were recruited. Physicians sent letters to 4394 patients. Over 10 weeks, there were 4165 visits by 2350 older adults, representing around 30% of the total senior population in each community. 40% had elevated BP, and more than half of these were on antihypertensive therapy. Older age, BMI >30, antihypertensive medication, diabetes, and 2+ alcoholic drinks per day predicted elevated BP.
Conclusions: Invitation by physicians was effective in promoting attendance and repeat visits. A large number of attendees had elevated BP, including patients currently taking antihypertensive medication. The community-wide program proved feasible, identified a significant number of seniors with elevated (undiagnosed or uncontrolled) BP, and warrants implementation and evaluation on a larger scale.
Keywords: *Community pharmacy, cardiovascular risk, population health*

Health Technology Assessment

60

Technology Assessment at Sick Kids (TASK): A model for health technology assessment in a pediatric tertiary care and research centre

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Background: At the Hospital for Sick Children (SickKids), there is a growing interest in Health Technology Assessment (HTA) of new technologies, from an institutional perspective, with the hospital increasingly facing challenging purchasing decisions, and from a researcher's perspective, as an opportunity to develop and evaluate new methodologies. The objective was to establish a centre for research in pediatric HTA called TASK (Technology Assessment at Sick Kids).

Methods: The goals of TASK include 1) conducting HTA and health economic methods research, 2) performing HTAs to support allocation decision-making at SickKids, 3) creating educational and training opportunities in HTA, 4) establishing partnerships and linkages locally, nationally and internationally and 5) engaging in knowledge transfer with researchers, health professionals, decision-makers and the public.

Results: In the last 5 years, 10 economic evaluations and 4 methodological investigations of pediatric interventions have been completed or are ongoing, fuelling the need for establishing TASK. Twenty-four trainees have participated in the conduct of these studies. Examples of recent HTA conducted at SickKids include studies of the cost-effectiveness of image-guided therapy versus operating room insertion of port catheters in children with cancer and the cost-effectiveness of omitting a chest radiograph in the diagnosis of bronchiolitis in the Emergency Department.

Conclusions: As a part of the virtuous circle, TASK may benefit SickKids and other Canadian paediatric hospitals and the pediatric population in general. Individual HTA projects completed within TASK may positively impact the health of children by improving the use of evidence and the quality of decision-making.

Keywords: *Children, health technology assessment, economic evaluation*

61

Agreement between parent reports and medical charts for pediatric asthma medication utilization

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Background: Although parents are often asked to report their children's medication use, the accuracy of these reports is unknown. The objective was to assess agreement between parent report and medical record for pediatric asthma patients.

Methods: A retrospective analysis compared parent reports and medical charts for current asthma medication name and strength in 99 asthmatic children recruited from specialist practices.

Results: A total of 279 asthma medications were reported with an average of 2.8±1.2 asthma medications per child. Perfect agreement between reported and charted asthma medication names and strengths was found in 4% of the medical charts and occurred for 33% of reported medications. Medication names were found in the chart for 85% (238/279) of reported medications and a strength was located in the chart for 52% (123/238) of these. Parents reported a medication strength that did not match the chart for 24% (29/123) of the medications for which strengths were found in the chart. Medication strengths were frequently found in the chart for inhaled corticosteroids (90/100), a class for which multiple strengths are available. Short-acting beta agonists are typically available in a single strength which may explain the infrequent recording in the chart for this class (9/95). The difference in recording of strength was significant ($p<0.03$). Of the 90 inhaled corticosteroids for which strengths were recorded in the chart, 70 (78%) matched the parent report.

Conclusions: Parents may be able to provide more detailed information about their child's current asthma medications than the medical chart.

Keywords: *Proxy, medical record, agreement*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

62

Alberta diabetes surveillance system: documenting regional variation in diabetes epidemiology

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Funding Source: Alberta Health and Wellness

Background: Diabetes is a serious and growing public health concern in Canada. The objectives of the Alberta Diabetes Surveillance System (ADSS) are to disseminate information on the incidence, prevalence and mortality of diabetes and its complications and comorbidities among adults in Alberta.

Methods: Administrative databases from Alberta Health and Wellness were used to identify cases of diabetes among Albertans, ages 20 and above. The National Diabetes Surveillance System's (NDSS) algorithm was used to identify cases. Descriptive analyses present trends over time (1995-2005) and variation in diabetes epidemiology across Alberta's nine health regions. Rates were age-adjusted using the 2001 Alberta population as a reference.

Results: There were approximately 130,000 Albertans living with diabetes in 2005, which is a doubling of the number ten years ago. The age-adjusted prevalence was 5.3% in 2005 compared to 3.8% in 1995. The highest prevalence is seen in the older population, with over 14% in ages 65 years and above compared to 1.4% in those 20-30 years old. Approximately 12,000 new cases were identified in 2004; the age-adjusted incidence rate was 5.5 (5.4-5.6) per 1000. Northern Lights Health Region had the highest age-adjusted prevalence of diabetes in 2005, at 6.8% (6.4-7.1). Mortality was 2 to 4 times higher in the diabetes population, depending on the age group.

Conclusions: The ADSS is intended to provide a timely, comprehensive, standardized database for diabetes surveillance in Alberta and provision of population-based diabetes information to systematically evaluate health care utilization, policy and processes.

Keywords: *Diabetes, surveillance, epidemiology*

63

Trends in kidney disease in the diabetes population of Alberta, 1996-2005

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Funding Source: Alberta Health and Wellness

Background: End stage renal disease (ESRD) is one of the most serious complications of diabetes, and requires life-sustaining treatment with chronic dialysis or kidney transplantation. Despite treatment, patients who develop ESRD have increased mortality, poor quality of life, and incur high healthcare costs.

Methods: Administrative databases from Alberta Health and Wellness were used to identify cases of ESRD, based on procedure codes for dialysis and kidney transplantation among Albertans aged 20 and above. Descriptive analyses present trends over time (1996-2005) and average annual growth rates of incident and prevalent ESRD are calculated for people with and without diabetes. Rates were age-standardized using the 2001 Alberta population as the reference.

Results: In 2005, there were 468.4 ESRD patients per 100,000 in the diabetes population, compared to 373.3 per 100,000 in 1996, with an annual growth rate of 13.0%. ESRD rates were over 10 times higher in the diabetes population compared to the non-diabetes population. The average annual growth in ESRD incidence was 3.7% for people without diabetes and 9.4% among people with diabetes.

Conclusions: Growth in incident and prevalent ESRD for persons with diabetes are several times greater than the general population over the past decade. Efforts need to be directed at reducing the complications of diabetes and ensuring that Alberta has adequate resources to meet the future needs of these complex patients.

Keywords: *Kidney disease, diabetes, surveillance epidemiology*

64

Economic evaluation of symbicort® (budesonide/formoterol) maintenance and reliever therapy in asthma (SMART) compared to fixed dose combination strategies

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Funding Source: AstraZeneca Inc

Background: To compare the cost-effectiveness of budesonide/formoterol in a single inhaler used as Maintenance and Reliever Therapy (SMART) versus fixed-dose fluticasone/salmeterol (FD) plus as-needed terbutaline reliever or fixed higher-dose budesonide/formoterol (FHD) plus as-needed terbutaline reliever in controlling asthma in adults and adolescents.

Methods: An economic evaluation was conducted based on the results of a large (N=3,335) RCT in which health resource utilization was prospectively collected. Primary outcome measurements included time to first exacerbation and the number of severe exacerbations. Costs included direct medical costs (physician/emergency room visits, hospitalizations, asthma drug costs) and productivity (absenteeism). The time horizon was six-months which corresponded to the duration of the trial. Prices were obtained from 2006 Canadian sources. Both healthcare (HC) and societal (Soc) perspectives were considered. Deterministic univariate sensitivity analyses were conducted.

Results: In the clinical trial, SMART was superior to FD ($p<0.001$) and FHD ($p=0.0048$). Exacerbation rates (reported as per patient per 6 months) were 0.12 for SMART, 0.19 for FD, and 0.16 for FHD. All treatments provided similar improvements in lung function, asthma control days and asthma-related quality of life. From the HC perspective, the mean cost per patient per 6 months was $583 in the SMART arm versus $867 in the FD arm versus $737 in the FHD arm. From the Soc perspective, it was $633 for SMART, $914 for FD and $799 for FHD. SMART was dominant (more effective, less expensive) in the base case analysis from both the HC and Soc perspectives. The results were robust under sensitivity testing.

Conclusions: The SMART strategy which allows budesonide/formoterol to be used as both maintenance and reliever medication is dominant over a strategy of fixed dose salmeterol and fluticasone plus as-needed terbutaline and fixed higher dose budesonide and formoterol plus as-needed terbutaline.

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

65

Guidelines for budget impact analysis in Canada

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Funding Source: Patented Medicine Prices Review Board / Conflict of Interest: None

Background: Budget impact analyses (BIAs) in Canada assess the financial impact, for a given drug plan, of adopting a new drug. Although most drug plan managers now require BIAs as part of the formal decision process on the pricing and reimbursement of drugs, there is no standardized method of performing and presenting BIAs. Guidelines were developed to facilitate the development and reporting of BIAs in Canada.

Methods: A survey of representatives across Canada and a review of 35 previously submitted BIAs were conducted to assess existing needs for BIA guidelines. Based on these findings, previously published guidelines (ISPOR) and input from the project's Steering Committee, guidelines were developed to provide instructions on how to perform BIAs. An interactive budget impact model template was also designed to facilitate BIA model development.

Results: Five key problem areas were identified for improvement in BIA models: Lack of transparency, inaccurate or misapplied assumptions, generalized analysis (non-specific or inaccurate jurisdiction and/or plan), inappropriate choice of comparators, and overall quality. The guidelines and template address these issues and cover model design, analytic perspective, time horizon, target population, costing, scenarios to be compared, uncertainty analysis, discounting and validation methods that should be used when preparing a BIA, as well as provide detailed guidance on data inputs and data sources.

Conclusions: The BIA guidelines and template address the requirements of each of the participating drug plans in Canada. Their introduction promises to facilitate the decision-making process for reviewing new drugs for listing and reimbursement on drug plan formularies.

Keywords: *Budget impact analysis, guidelines*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

66

Cost-effectiveness of peginterferon alfa 2-a (pegasys®) for the treatment of chronic hepatitis B in Canada

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Funding Source: None

Background: Chronic hepatitis B (CHB) is a serious infectious disease that attacks the liver leading to an increase in both morbidity and mortality in affected patients. The prevalence of hepatitis B in Canada has been estimated between 0.5% and 1.0% of the population. Peginterferon alfa-2a (PEG), has been shown to offer improved efficacy over lamivudine (LMV). The objective of this study was to estimate the cost-effectiveness of 48 weeks of PEG compared to long term LMV treatment (208 weeks) in patients with HBeAg-negative CHB.

Methods: A cost-utility analysis was performed from the payer perspective based on a previously published Markov model simulating the natural course of disease in a hypothetical cohort of 40-year old HBeAg-negative CHB patients. (Veenstra et al. 2006) Clinical inputs were taken from a randomized trial comparing PEG to LMV(Marcellin et al. 2004). Transition probabilities, costs and quality of life were estimated from published sources. Lifetime direct healthcare costs, and incremental cost-utility ratios (ICURs) were estimated. One way sensitivity analyses were performed on various parameters to test the robustness of the model.

Results: Treatment with PEG resulted in an additional 0.7 QALYs at an incremental cost of $10,492 resulting in an ICUR of $15,006/QALY gained when compared to LMV monotherapy. In sensitivity analyses, ICURs ranged from $6,562/QALY to $24,109/QALY.

Conclusions: This cost-effective analysis shows that defined treatment duration of 48 weeks with PEG represents good value for money in the treatment of HBeAg-negative CHB.

Keywords: *Cost-effectiveness, PEGASYS®, peginterferon, hepatitis B*

67

Canadian economic evaluation of tysabri (natalizumab) in relapsing-remitting multiple sclerosis (RRMS)

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Funding Source: Partially funded by an unrestricted grant from Biogen-Idec Canada

Objective: The objective was to conduct a cost-utility analysis of natalizumab monotherapy, versus no treatment and interferon beta, in three populations of RRMS patients: treatment naive, treatment failure, and those with rapidly-evolving severe disease.

Methodology: The economic model was a memory-free state-transition model, with a one-year cycle length and with health states represented by Expanded Disability Status Scale (EDSS) levels from 0 to 10. Health state transitional probabilities were represented by the annual risk of progression between EDSS levels. Randomized controlled trial data exclusively informed all probabilities for the first two years of the model. Subsequently, disease progression was based on observed rates from a natural history cohort (from London, Ontario). Each health state (EDSS level) was associated with a defined cost and utility score, derived from the Nova Scotia MS clinic. Patients were followed over a twenty year horizon. Extensive sensitivity analyses were conducted.

Results: Compared to both interferon beta and no treatment, natalizumab provided superior clinical outcomes in all patient groups and reduced non-drug health care costs. However, total costs were higher due to the higher cost of natalizumab. Cost-utility ratios from the health care perspective varied from $78K/QALY to $200K/QALY, depending on the comparator, subgroup and perspective (health care or societal).

Conclusion: Economic results for natalizumab were more favourable than economic results generated previously for the existing, widely reimbursed MS therapies, although they did not meet traditional standards for the adoption of new therapies.

Keywords: *Economic, multiple sclerosis, costs*

68

Fulvestrant: economic evaluation for the Canadian setting

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Funding Source: Partially funded by an unrestricted grant from AstraZeneca Canada

Background: Fulvestrant is a new, intramuscular hormonal agent, for use in postmenopausal women with locally advanced or metastatic breast cancer who have disease progression following prior endocrine therapy. An economic evaluation was conducted to compare fulvestrant followed by delayed chemotherapy versus immediate initiation of chemotherapy alone in this setting.

Methods: Data for the expected Canadian setting (the last endocrine agent before cytotoxic chemotherapy) were limited, lacking long-term outcomes. Patient benefit was assigned in the conservative base case by assuming that fulvestrant did not affect overall survival; with an equivalent outcome, the analytic technique was a cost-minimization analysis (CMA). Under an alternative scenario, it was assumed that fulvestrant extended overall survival by an amount commensurate with the duration of fulvestrant therapy. This required a cost-effectiveness analysis (CEA). Costs for the economic model were derived from clinical practice data for fulvestrant, and Canadian-based publications for breast cancer management. Costs were reported in 2006 Canadian dollars. There was a lifetime horizon and a 5% discount rate.

Results: In the base case analysis (the CMA), fulvestrant was associated with a savings of $520 per patient. Under the alternative assumption of maximal survival benefit (the CEA), fulvestrant cost $6,953 per life year gained (or $9,604 per QALY). Univariate sensitivity analyses supported the direction of these results.

Conclusions: Used as a last endocrine agent before chemotherapy for postmenopausal women with metastatic breast cancer, fulvestrant would be a cost-neutral choice if it did not extend survival. Any survival benefit would be obtained with a low cost-effectiveness ratio.

Keywords: *Economic evaluation, costs, breast cancer*

69

Clopidogrel drug use evaluation in a tertiary care setting

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Funding Source: None

Background/Objectives: The Queen Elizabeth II Health Sciences Centre (QEII HSC) reported an increase in clopidogrel expenditures from $71,773 in 2002-03 to $89,872 in 2003-04. Current formulary criteria restricted clopidogrel use to: 1) secondary prevention of MI, stroke or vascular death in patients with history of symptomatic atheroscler otic disease, including severe ASA allergy or recurrent thrombotic event, 2) prevention of thrombosis in patients with post intracoronary stent implantation and 3) treatment of acute coronary syndrome (NSTEMI or UA) in combination with ASA. The objective of this study was to determine whether the increase in clopidogrel utilization was appropriate.

Methods: All patients treated with clopidogrel in 2002-03 (n=1922) and 2003-04 (n=2127) were identified and compared to the number of patients with a documented diagnosis within formulary restriction #2 or #3 or a documented ASA allergy. For remaining patients (n=2083), 100 (50 from each year) were randomly selected for a retrospective chart review.

Results: Overall, clopidogrel was used appropriately in >95% and >92% of cases in 2002-03 and 2003-04 respectively. The major contributor to increased use was a 19% increase in the number of intracoronary stent procedures. The majority of patients (84% in 2002-03 vs. 81% in 2003-04) received clopidogrel according to formulary restrictions #2 or #3. The most common indication for use in the remaining patients was anticipation of cardiac stent. Inappropriate uses of clopidogrel included monotherapy without prior ASA use and combination therapy with ASA for stroke prophylaxis.

Conclusions: Clopidogrel appears to be used appropriately at the QEII HSC. The major contributor to increased clopidogrel usage was intracoronary stent procedures.

Keywords: *Clopidogrel, utilization, stent*

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70

Community-based economic evaluation of lipid lowering drugs (statins) in the Canadian population

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Background: Cost-savings associated with a therapeutic intervention to prevent cardiovascular (CV) morbidity and mortality in the real world is dependant upon the distribution of risk in the population. Using community-based data, we assessed the non-drug related healthcare costs (savings) associated with the use of lipid lowering drugs (statins) in the full Canadian population.

Methods: A population-based estimate of CV risk amongst statin users was derived from a sample of 1103 patients. The benefit of reducing LDL cholesterol was incorporated into an economic analysis through a reduction in CV risk (cardiac and cerebrovascular events). All direct medical costs per CV event from the perspective of the Canadian healthcare system were included in the model.

Results: It was estimated that approximately 3,100,000 patients used lipid-lowering drugs in Canada in 2004 with a distribution of CV risk: 1,612,000 high (HR), 1,054,000 moderate (MR) and 434,000 low (LR). Annual healthcare cost-savings ($CDN) through CV events prevention related to lipid lowering (statins) therapy were estimated (sensitivity analysis): non-fatal myocardial infarction HR $61,160,092 ($8,154,677 to $163,093,579), MR $21,310,804 ($2,636,311 to $53,987,371), LR $2,410,011 ($96,402 to $8,676,041); ischemic stroke HR $237,814,339 ($31,705,760 to $634,171,571). Cost-savings per patient, for HR and MR patients were 6.8 ($p < 0.0001$) and 3.6 ($p < 0.005$) times greater than LR patients, respectively, for non-fatal myocardial infarction.

Conclusions: Based upon the distribution of CV risk amongst Canadian statin users, we conservatively estimate that between 25-35% of drug costs are offset by cost savings from a reduction in health care costs associated with the management of CV events and sequelae.

Keywords: *Economic evaluation, lipid lowering drugs, population based*

71

Preliminary results from a cost–effectiveness analysis for adjuvant therapy with trastuzumab (herceptin®) for early breast cancer in Canada

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Background: Herceptin® (trastuzumab), is a recombinant, humanised, monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2) and is an effective treatment for HER2-positive metastatic breast cancer. This analysis was a Canadian adaptation of a global analysis conducted to determine the cost-effectiveness of adjuvant trastuzumab for 1 year following standard chemotherapy.

Methods: A five-state (disease free survival, recurrence, metastatic, cardiac event, death), lifetime Markov model was developed to evaluate direct costs and disease progression over a lifetime horizon (45 years). The economic evaluation was performed using efficacy and safety data from the HERA (HERceptin Adjuvant) trial. The study population was aligned with the HERA study and included women (age 50 at the start of treatment) with primary invasive breast cancer that over expresses HER2 who completed (neo) adjuvant systemic chemotherapy and radiotherapy, if applicable. Health benefits are expressed in terms of quality adjusted life years (QALYs). The comparator for the economic evaluation is observation, following standard adjuvant chemotherapy. All relevant direct costs were included in the model including drug costs, administration, monitoring and adverse events (UK costs converted to CAD). Costs and benefits were discounted at 5% per annum.

Results: The use of trastuzumab in early breast cancer resulted in increased life expectancy and QALYs compared to observation alone. The incremental cost-effectiveness ratio (ICER) of adjuvant trastuzumab was $7,998 per QALY gained in the preliminary analysis.

Conclusions: Health economic modelling based on available clinical evidence demonstrates that trastuzumab for 1 year following adjuvant chemotherapy is a cost-effective therapeutic innovation.

Keywords: *Cost–effectiveness, Herceptin®, breast cancer*

72

Lower hip fracture rates in the first year of therapy translate into favorable cost-effectiveness ratios for risedronate vs. alendronate: the case of Canada

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Funding Source: Alliance for Better Bone Health
Background: Recently an observational US cohort study (n=33,830) directly comparing risedronate to alendronate showed that patients treated with risedronate had a 43% lower incidence of hip fractures in the first year of treatment (Silverman, 2006). The objective of this analysis was to determine the cost-effectiveness of risedronate compared to alendronate using these effectiveness data.
Methods: A validated Markov model of osteoporosis (Tosteson, 2001) was used to estimate the impact of therapy on hip fractures, costs, and quality-adjusted life years (QALYs). The model simulated a cohort of 1,000 women aged 65+ with BMD≤-2.5 or a previous fracture, treated with once-a-week dosing of risedronate or alendronate over one year, and simulated downstream costs and QALYs for five years. Canadian data included hip fracture and mortality rates, drug (risedronate CDN$9.36/wk; alendronate CDN$4.43/wk) and fracture costs.
Results: For 1,000 women treated with risedronate versus alendronate, the model predicted 7 fewer hip fractures and 3.4 additional QALYs, resulting in a cost per fracture avoided of CDN$3,100 and a cost per QALY gained of CDN$6,436 for patients with BMD≤-2.5 or a previous fracture**.** Extrapolating these results to osteoporotic women aged 65+ in Ontario who initiate therapy suggests that risedronate would prevent an additional 304 hip fractures in the first 12 months of therapy compared to alendronate.
Conclusions: Based on "real world" data this analysis suggests risedronate provides superior fracture protection at favorable cost-effectiveness and cost-utility ratios when compared to alendronate for women in Canada aged 65+ with BMD≤-2.5 or a previous fracture.
Keywords: *Cost-effectiveness, Markov model, bisphosphonates, real world data*

73

Orthogonal experimental designs can disentangle confounding in database studies

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Funding Source: None
Background: To help determine whether factor confounding in database studies can be disentangled using orthogonality principles in factorial designs.
Methods: Complete factorial designs permit the estimation of important or ambiguous interactions as well as main effects, with sampling from the database using bootstrap methods, by selecting balanced replicates of cases needed for the sample size requirements of the study and the design, one can estimate the impact of the factors directly from the analysis of the design. The bootstrapping part permits a large number of iterations of this sampling, say 10,000, and from all these analyses, provide an empirical distribution for the main effects, all estimable interactions as well as their variances, and these results can be combined in a manner like imputation methods to provide an analysis of the factors and interactions that would not be possible with the usual analysis provided of the complete database because of confounding.
Results: Ideas will be illustrated using an osteoporosis database, a complete factorial design with 3 factors at 2 levels replicated 10 times using 10,000 bootstrap samples from the database. A comparison with the usual analysis, feasibility and interpretations of these bootstrapped effects will be shown during the presentation.
Conclusions: Orthogonal experimental designs can help to disentangle important interactions between factors in database studies that are confounded using the usual statistical analysis.
Keywords: *Orthogonal designs, confounding, databases*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

74

Comparative LDL-c effects of rosuvastatin and simvastatin – dose response curves from meta analysis of randomised controlled clinical trials

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Funding Source: AstraZeneca

Background: Meta-analyses of randomised controlled clinical trials (RCT) provide a robust methodological framework for addressing the question of comparative clinical efficacy. The comparative clinical efficacy of rosuvastatin (5, 10, 20 & 40mg) and simvastatin (10, 20, 40 & 80mg) is examined here.

Methods: A systematic literature search was conducted in early 2006 to identify published comparative RCTs of rosuvastatin and atorvastatin or simvastatin. Every available result for mean reduction in LDL-c for rosuvastatin and simvastatin from the studies was aggregated using meta-analytical techniques (random effects), to construct a dose response curve.

Results: 27 RCTs with rosuvastatin (including 7 v simvastatin) were identified. These studies provided 51 results for rosuvastatin (8, 23, 12 and 8 results for 5, 10, 20 and 40mg respectively) and 11 results for simvastatin (1, 7, 2 and 1 results for 10mg, 20mg, 40mg and 80mg respectively). The resulting dose response curves are separate, parallel and demonstrate a sustained (across dose range) improvement in LDL-c reduction of rosuvastatin over simvastatin. The curves suggest a clinical relativity of 1:8, that is, rosuvastatin 5mg is similar to simvastatin 40mg and 10mg is similar to 80 mg. No dose of simvastatin is equivalent to rosuvastatin 20mg or 40mg.

Conclusions: This meta-analysis of data from RCTs suggests that rosuvastatin effectively reduces LDL-c compared to simvastatin and can elicit reductions exceeding those possible with the highest doses of simvastatin. This may help guide physician prescribing for patients with elevated levels of LDL-c.

Keywords: *Meta-analysis, LDL-c, statins*

75

Clopidogrel versus aspirin in patients with peripheral arterial disease: a cost-effectiveness analysis

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Background: Clopidogrel is cost-effective in preventing vascular events in US patients with peripheral arterial disease (PAD). Due to country-to-country variation in healthcare utilization and costs, as well as the framing of cost-effectiveness analyses, it is unclear if clopidogrel is cost-effective for Canadian patients with PAD.

Methods: A Markov model was constructed from a societal perspective based on lifetime treatment of a 63 year-old Canadian. Event probabilities and efficacy estimates were derived from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial. Cost inputs, in 2005 Canadian dollars, were derived from Canadian data and published sources. Outcome measures included costs, life expectancy in quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER). One-way, two-way and probabilistic sensitivity analyses were used to assess the robustness of the results.

Results: PAD patients treated with aspirin lived an average of 7.55 QALYs, incurring costs of $110,000. Clopidogrel increased life expectancy by 0.40 QALYs at an ICER of $16,500 per QALY relative to aspirin. The ICER increased to $67,300 at the lower bound of the efficacy estimate for clopidogrel, an 8.9% relative risk reduction compared to aspirin. Results were robust to probabilistic sensitivity analysis, with clopidogrel preferred to aspirin in over 94% of simulations at cost-effectiveness thresholds greater than $50,000 per QALY.

Conclusions: For Canadian patients with PAD, clopidogrel provides a substantial increase in quality-adjusted life expectancy at an affordable value.

Keywords: *Cost-effectiveness analysis, PAD, anti-platelet therapy*

76

Quantitative risk-benefit analysis of alosetron in irritiable bowel syndrome: a patient-level meta-cohort analysis

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Funding Source: GlaxoSmithKline

Background: Irritable Bowel Syndrome (IBS) is a chronic condition of the gastrointestinal tract. Alosetron (Lotronex) is used in the treatment of IBS however, it is associated with potential risks of complicated adverse events. The objective of this analysis was to estimate the incremental net benefit (INB) of alosetron relative to placebo in IBS patients.

Methods: The INB of alosetron (n=1,810) relative to placebo (n=1,1113) was calculated using a patient-level meta-analysis of 7 randomized, placebo controlled clinical trials. Effectiveness, in terms of improvements in abdominal pain, urgency and diarrhea frequency had been observed on a daily basis. Risk of treatment included constipation, colitis and impacted or perforated bowel. Incremental net benefit was calculated based on quality-adjusted life years (QALYs) using patient's utilities measured by both standard gamble and conjoint analysis. Uncertainty in the outcomes was determined using bootstrapping with replacement.

Results: Alosetron had a small positive net benefit relative to placebo (p-value < 0.001). The net QALY gain was 0.012 (SD 0.011) in alosetron and 0.008 (SD 0.010) in placebo treated patients, respectively, over 12 weeks resulting in an INB of 0.018 QALYs per patient per year. Stratified analysis revealed that the INB was greater in patients with more severe relative mild IBS, and in patients with diarrhea predominant relative to constipation predominant IBS.

Conclusions: This quantitative analysis supports the FDA's subjective determination that the potential benefits of alosetron outweigh the potential risks, and that the INB is greater in patients with more severe, diarrhea predominant disease.

Keywords: *Risk benefit analysis, irritable bowel syndrome, alosetron*

77

How does the cost-utility of therapies to prevent NSAID induced GI complications vary with age?

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Funding Source: Nova Scotia Health Research Foundation (NSHRF)

Background: There is unequivocal evidence that links NSAIDs to GI complications including ulcers, GI bleeding, and death. To prevent GI complications, patients are often co-prescribed gastrointestinal prophylaxis agents (GPA).

Objective: The main objective of this study is to determine the relationship between age and cost-effectiveness of gastrointestinal prophylaxis strategies in Canada.

Methods: A decision tree model was developed using TreeAge. A hypothetical cohort of patients in the general population (age≥18) and patients aged ≥65 and aged ≥75 beginning a 6-month course of NSAIDs entered the model and were treated with either: 1) No Prophylaxis, 2) standard dose Proton Pump Inhibitors (omeprazole 20mg od) 3) misoprostol (200ug bid), 4) misoprostol (200ug qid), 5) ranitidine (150mg bid), 6) ranitidine (300mg bid). Input parameters were obtained from systematic reviews and RCTs. Costs were from the perspective of a provincial payer and outcomes were cost per Quality Adjusted Life Year (QALY) gained. Probabilistic sensitivity analysis was used to generate measures of uncertainty of the results.

Results: Misoprostol (200ug bid) and misoprostol (200ug qid) both had ICERs less than $30,000 per QALY gained in all seniors. Misoprostol (200ug bid) was more effective and less costly than ranitidine (150mg bid) and standard dose PPI dominated ranitidine (300mg bid) in all cohorts. PPI had an ICER of $62,000 in the age ≥65 cohort and an ICER of $19,000 in the age ≥75 cohort.

Conclusions: The cost-utility of alternative gastrointestinal prophylaxis strategies in preventing NSAID associated GI complications increases with age and decision makers' willingness to pay.

Keywords: *Cost-utility analysis, NSAIDs, gastrointestinal complications*

78

Pharmacoeconomic evaluation of avonex®, betaseron®, and best supportive care in MS patients following a clinically isolated syndrome

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Background/Objectives: To perform a cost-utility analysis comparing two beta-interferons (Avonex®, Betaseron®) and best-supportive-care (BSC) to reduce progression to clinically definite multiple sclerosis (CDMS) after having a clinically isolated syndrome (CIS).

Methods: A Markov model defined health states using Expanded Disability Status Scale level 6.5 as absorbing state, to determine incremental cost/QALY, from the perspectives of Ministry of Health (MoH) and society (SOC). Transitional probabilities and utilities were derived from the literature, costs from standard lists in 2006 CAD$. A 15-year time horizon was used with 5% discounting (costs/outcomes). Uncertainties were tested in univariate and Monte Carlo sensitivity analyses.

Results: Total MoH costs/patient were $16,527, $169,610, $228,757, and $234,062 for BSC, BSC followed by Avonex® (BSC→Avonex®), Avonex®, and Betaseron®, respectively; QALYs were 7.13, 7.47, 8.09, and 7.78. The incremental cost/QALY for Avonex® vs. BSC was $221,708; BSC→Avonex® and Betaseron® were dominated. From SOC perspective, incremental cost/QALY for Avonex® was $121,884, with BSC→Avonex® and Betaseron® dominated. The model was sensitive, in magnitude not in direction of results, to variations in CIS group types (monofocal and multifocal), time horizon, discount rate, utilities, and CDMS progression rates, Betaseron® being dominated by Avonex®. With indirect costs removed from the CIS state, the incremental cost/QALY for Avonex® was $96,878. Treating monofocal CIS led to lower incremental costs/QALY, and multifocal CIS to higher incremental costs/QALY.

Conclusions: Avonex® or Betaseron® for CIS delayed CDMS onset, but at a cost (lower for Avonex). When compared against a common comparator (BSC), Avonex® dominated Betaseron® in terms of cost/QALY gained.

Keywords: *Multiple Sclerosis, economics*

79

A cost-neutral threshold price of paliperidone ER compared to standard oral atypical antipsychotic care for schizophrenia in Canada

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Funding Source: Janssen-Ortho Inc.

Background: Schizophrenia affects 1% of most populations in the Western World but consumes a disproportionate share of health care costs. Paliperidone ER is a second-generation oral atypical antipsychotic developed as a new therapeutic agent for the treatment of schizophrenia.

Objective: To assess the threshold daily price at which paliperidone ER would be cost-neutral compared to standard atypical antipsychotic care (i.e., treatment with risperidone, olanzapine and quetiapine) in patients with an acute exacerbation of schizophrenia over one-year from an Ontario Ministry of Health perspective.

Methods: Published medical literature, the Ontario Case Costing Initiative database, and clinical experts were utilized to populate a decision tree model. The model captured rates of discontinuation from published and unpublished clinical trials, response and relapse; frequency and duration of relapse; adverse events; medical resource utilization; and unit costs.

Results: The mean number of days of relapse per patient per year was similar for paliperidone ER (24.8) and olanzapine (24.6) and was slightly higher with risperidone (26.0), and quetiapine (27.0). The price at which paliperidone ER was cost neutral relative to standard oral atypical antipsychotic care was CDN $8.65 per day. Sensitivity analyses around key model input parameter values found that the range of threshold costs at which paliperidone ER was cost neutral was from CDN $7.28 to $9.30.

Conclusions: Predictive modeling of cost-effectiveness is a valuable tool to estimate the threshold price at which paliperidone ER will be cost-neutral for Canadian patients with schizophrenia.

Keywords: *Pharmacoeconomic model, threshold analysis, antipsychotics*

80

Sildenafil for the treatment of pulmonary arterial hypertension (PAH): a Canadian economic evaluation

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Background: Pulmonary arterial hypertension (PAH) is a chronic, progressive disorder that affects patient quality of life, and ultimately, their survival. Patients with PAH are classified into four functional classes [FC], from FC I, mild, to FC IV, severe. Sildenafil is the first approved treatment of FC II PAH patients, and the fourth for FC III PAH patients. The objective of the study is to determine the cost-effectiveness of sildenafil in the management of PAH in FC II and III patients.

Methods: The cost-effectiveness outcome measures for sildenafil treatment for FC II patients compared to no PAH-specific treatment, are expressed in terms of life-year saved, per patient walking 380m or more during the 6 Minute Walk Distance test, and per patient maintaining or improving their FC status. For FC III patients, a cost-consequence analysis is used to compare sildenafil to bosentan.

Results: The incremental cost per life-year saved for sildenafil treatment of FC II patients is $45,904. The 12-week incremental cost-effectiveness ratio is $5,494 per patient walking 380m or more, and it is $53,840 per patient maintaining or improving their FC level. Treatment with sildenafil for FC III patients is cost-saving versus bosentan, the only other oral therapy for PAH, with estimated savings of $8,186 for a 12-week period. Sensitivity analyses support the base case conclusion that sildenafil is cost-effective, despite assumptions being conservative and/or biased against sildenafil.

Conclusion: This study demonstrates that sildenafil is a cost-effective treatment option for PAH in Canada. It is a cost-saving treatment strategy vs. bosentan in FC III patients.

Keywords: *Cost-effectiveness, sildenafil, pulmonary, arterial, hypertension*

81

A systematic review of the cost of cardiovascular disease in Canada and other selected developed countries

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Background/Objective: In Canada, 74,255 deaths (33% of all deaths) were due to cardiovascular disease (CVD) in 2003. CVD was the most costly disease in Canada, representing 12% of the combined cost of all diseases. The purpose of this study was to conduct a systematic literature review to synthesize the literature published on the economic costs of CVD in Canada and other developed countries (United States, Europe, Australia and New Zealand). Included were English articles published from 1998 to 2006.

Methods: A search strategy was developed to identify the economic literature related to the economic cost of CVD, stroke, hypertension, congestive heart failure (CHF), and coronary artery disease (CAD). The search was conducted in the Ovid MEDLINE, EMBASE, CINAHL, OHE HEED and CRD databases. Key information was abstracted using a standardized abstraction form.

Results: 1561 titles and abstracts were screened. Of the 35 included studies, 6 reported cost of illness estimates for Canada, 17 for the US, 1 for Australia, and 11 for Europe. The most common disease categories studied in these articles were CVD in general (n=7), stroke (n=12), hypertension (n=9), and CHF (n=2). Nine studies identified costs associated with various aspects of CAD or coronary heart disease.

Conclusions: A wide variation was observed in the methods used to estimate the cost of CVD. Nonetheless, all the studies indicated that the costs of treating CVD related conditions are significant from both a payer and societal perspective, outlining a convincing case for CVD prevention programs.

Keywords: *Cost of illness, cardiovascular disease, review*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

82

Cost-effectiveness of primary prevention programs for cardiovascular disease in Canada and other selected developed countries: a systematic literature review

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Background: CVD is responsible for an estimated 16.7 million deaths worldwide (30% of all deaths) and represents a major economic burden on health care systems. To alleviate this burden preventive action should be taken against modifiable CVD risk factors. The objective of this study was to review the cost-effectiveness (CE) associated with primary CVD prevention programs (e.g. diet, exercise, smoking cessation) in Canada and other developed countries (United States, Europe, Australia and New Zealand).

Methods: A systematic literature review was undertaken. Computerized searches were conducted in Ovid, MEDLINE, EMBASE, CINAHL, OHE HEED and CRD to identify the English literature published from 1998 to 2006. A standardized abstraction form was used to extract key information.

Results: 2495 titles and abstracts were initially screened and 34 articles were included after the full text review: 2 for Canada, 11 for the US, 3 for Australia, and 18 for Europe. Three studies assessed the CE of CVD screening and management programs, 3 reviewed the CE associated with the primary prevention of stroke, 6 examined the CE associated with diet and exercise programs, 19 evaluated the CE of smoking cessation programs and 3 assessed screening programs for familial hypercholesterolemia. Results indicated that CVD primary prevention programs are generally cost-effective in reducing the burden of CVD.

Conclusions: Only 2 studies, partially assessing the cost-effectiveness of CVD prevention programs in Canada were identified, suggesting that more research is necessary in Canada to assess the cost-effectiveness of CVD primary prevention strategies.

Keywords: *Cost-effectiveness, cardiovascular disease, review*

83

A patient-level economic evaluation of elective endovascular repair (EVAR) of non-ruptured abdominal aortic aneurysms (AAA) compared to open surgical repair (OSR) in high risk patients

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Background: AAA is a prevalent health condition affecting up to 14% of males and 6% of females. Current treatment options for AAA include open surgical repair (OSR), endovascular aneurysm repair (EVAR) and best medical treatment (BMT). The objective of this study was to estimate the cost-effectiveness and cost-utility of elective EVAR compared to OSR in high risk patients.

Methods: Patient-level cost and outcome data from a prospective observational study conducted at London Health Sciences Centre was used to determine the incremental cost per Life Year Gained (LYG) gained and the incremental cost per Quality-Adjusted Life Year (QALY) gained of EVAR compared to OSR. The analysis was taken from the perspective of the Ontario Ministry of Health and the time horizon was 1 year. To measure uncertainty on costs and effects, non-parametric boostrap techniques were applied. Uncertainty results were expressed using cost-effectiveness acceptability curves.

Results: Between August 11, 2003 and April 3, 2005, 342 subjects were enrolled in the study. Based on point estimates, EVAR dominated OSR for high risk patients in terms of incremental cost per LYG and incremental cost per QALYs. However, bootstrap estimates of uncertainty for the 2 cost-effectiveness measures indicated that there were a lot of uncertainty regarding the costs and the QALYs and less uncertainty regarding LYGs. If society is willing to pay $50,000 per LYG or per QALY gained, the probability of EVAR of being cost-effective is 0.76 and 0.55, respectively.

Conclusions: EVAR is a cost-effective strategy compared to OSR for high risk patients.

Keywords: *Non-ruptured abdominal aortic aneurysms, EVAR, economic evaluation*

84

Long-term cost utility analysis of a multifaceted primary care diabetes management program in Ontario

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Background: As diabetes-related complications significantly contribute to healthcare costs, simulation models can be used to evaluate the impact of interventions on the progression of diabetes and the health and economic consequences likely to accrue over a patient's lifetime. The objectives of the current study were to estimate the cost-utility of a multidisciplinary diabetes management program using the Ontario Diabetes Economic Model (ODEM).
Methods: Using the ODEM, we conducted a cost-effectiveness analysis (CEA) based on data from a 1-year DM program involving 404 patients. Changes in intermediate outcomes (e.g. HbA1c, blood pressure) at study end were used to estimate the incidence for 7 DM complications, difference in cost, and quality-adjusted life-years (QALYs). Incremental cost-effectiveness ratios (ICER) were calculated based on the net healthcare costs associated with the program and on effectiveness estimated over a patient's lifetime. A discount rate of 3% and 40-year time horizon were used to calculate the ICER for the base case, assuming a 1 year treatment effect. Sensitivity analyses were conducted by varying the duration of the program and treatment effect.
Results: The program improved risk factors and the ODEM estimated that these improvements prevented 16.2/1,000 deaths, 15.5/1,000 myocardial infarctions and a 50% relative risk reduction in first amputations. The lifetime incremental cost per QALY gained in the base case was $5,992.
Conclusions: Short-term outcomes were improved, translating into avoidance of downstream complications, thus the increased costs of program implementation were partly offset. Overall, the program represents a cost-effective method for managing type 2 diabetes.
Keywords: *Diabetes management, economic evaluation*

85

A systematic review and meta-analysis of rosiglitazone and pioglitazone for the treatment of type 2 diabetes mellitus in adults

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Background: Rosiglitazone and pioglitazone belong to a class of oral anti-diabetic agents, the thiazolidinediones (TZDs), which act to improve insulin sensitivity of peripheral tissues in patients with type 2 diabetes. In Canada, TZDs are approved for use both as monotherapy and in combination with metformin or a sulfonylurea.
Methods: Electronic databases were searched between 1993 and March 2006. Selection criteria were developed and study selection and data extraction were performed by independent reviewers. The main outcomes were HbA1c and fasting plasma glucose (FPG). Included studies were categorized by drug, dosage, patient type, and comparator. Treatment effects were pooled across studies using a weighted mean difference using random-effects models.
Results: The search produced 3,854 unique citations with 26 rosiglitazone and 25 pioglitazone trials met inclusion criteria. Both rosiglitazone and pioglitazone showed the greatest decreases in HbA1c (up to 1.90%) and FPG (up to 4.55 mmol/L) when they were added to failed monotherapy compared with placebo. Combined results indicated that initiating TZD monotherapy in treatment-naïve patients was associated with a smaller decrease from baseline in HbA1c compared with other regimens. Adding a TZD to failed dual therapy was not as effective at reducing HbA1c (-1.90% vs. -2.30%, respectively) and FPG (-2.90 mmol/L vs. -4.30 mmol/L) as adding insulin to the failed therapy. No study directly compared the addition of a TZD to failed dual therapy with switching patients to insulin.
Conclusions: There were a limited number of studies providing efficacy data for specific populations to determine TZDs best place in therapy.
Keywords: *Diabetes, meta-analysis, glitazones*

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86

An assessment of the construct validity of the Health Utilities Index Mark 3 in asthmatics using the population based Canadian Community Health Survey Cycle 3.1

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Background: The Health Utilities Index Mark 3 (HUI3) is often used to evaluate health related quality of life (HRQoL) in chronic disease; however, its validity in asthma has not been established. The objective of this analysis was to evaluate construct validity of HUI3 in asthmatics using the Canadian Community Health Survey (CCHS) Cycle 3.1.
Methods: Participants in the CCHS Cycle 3.1 between 15-49 years were selected, from which those with self-reported asthma were selected. Using the known groups methodology, asthmatics were grouped by HUI3 score as having no (HUI3 ¡Ý0.90), moderate (0.9
Results: As hypothesized, mean HUI3 score was lower in asthmatics (n=1467) than in non-asthmatics (n=14996) (0.85 vs. 0.90, p<0.01). . LR results consistently showed increased HRQoL impairment associated with increasing risk of HRU and asthma symptoms. Relative to asthmatics with mild HRQOL impairment (n=967), those with severe impairment (N=245) were more likely to exceed median number of PV (OR: 1.97, 95% CI: 1.41-2.82), experience an OH (OR: 2.35, 95%CI: 1.57, 3.54) and experience asthma symptoms (OR 1.45, 95% CI 1.01, 2.06) in the previous year.
Conclusions: Our analysis shows the HUI3 could be a valid instrument for measuring HRQoL in asthmatics, with the expected relationship between HUI3 scores and HRU and asthma symptoms.
Keywords: *Health related quality of life, validity, asthma*

87

Description of infliximab costs for the management of crohn's disease in Quebec

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Background: Infliximab is efficacious in Crohn's disease (CD). It is important to use accurate cost data in decision-making. Purpose: Describe the annual costs of infliximab in the management of CD in Quebec.
Methods: Prescription data were obtained from the provincial drug insurance claims of the Regie de l'assurance maladie du Quebec (RAMQ) for patients with CD treated with infliximab between 2002-2005. Number of vials and cost of infliximab since treatment initiation obtained from the RAMQ were analysed.
Results: Number of patients (N), mean cost per patient (M) and total cost for infliximab (T) by calendar year were: 2002: N=54, M=$9,885, T=$533,834; 2003: N=184, M=$13,311, T=$2,449,305; 2004: N=328, M=$15,326, T=$5,026,841; 2005: N=344, M=$18,947, T=$6,517,846. Number of patients (n) and mean annual cost (C) for infliximab by duration of use in years was: ≤1 year: n=497, C=$19,541; 1–2 years: n=259, C=$16,908; 2–3 years: n=127, C=$14,469; and 3–4 years: n=38, C=$10,660. The mean number of vials/prescriptions of infliximab decreased from 17.7/5.5 in the 1st to 15.6/4.7 in 2nd, 13.3/4.0 in 3rd and 10.7/3.2 in 4th year of use.
Conclusion: The data show that annual cost by calendar year for the treatment of CD with infliximab in Quebec increased as expected since 2002. This was likely due to new patient-starts using induction. The data also show that costs by year of treatment decreased. Initial estimated listing costs for infliximab in the management of CD patients overestimated actual costs. These results have important implications for government formulary and third party payer decisions.
Keywords: *Crohn's disease, infliximab, costs*

88

Infliximab decreases corticosteroid use in crohn's disease patients

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Background: Use of corticosteroids is a risk factor for serious infections, osteoporosis, slow growth in children and mortality in patients with Crohn's Disease (CD). In addition to providing effective symptom control for CD infliximab may be beneficial by virtue of its steroid sparing effect. Objective: Determine the change in prednisone use in CD patients after initiating treatment with infliximab.

Methods: Use of prednisone in CD patients prior to and after initiation of treatment with infliximab was ascertained from the drug insurance claims of the Regie de l'assurance maladie du Quebec (RAMQ). The cohort inception began in 2002 and follow-up continued until March31st 2006.

Results: A total of 497 patients with CD were initiated on treatment with infliximab in Quebec during the study period. Of these, 388 (78%) stopped using prednisone after initiating treatment with infliximab. Prednisone was either stopped immediately (n=181, 36%) or after initiation of infliximab (n=207, 42%). There were 27 (5%) patients never stopped using prednisone, 32 (6%) initiated prednisone at the same time or after infliximab and 50 (10%) were censored being lost to follow up. Kaplan Meier estimates of mean (95% CI) time to prednisone termination was 380 (338,422) days with a median of 148 (96,231) days.

Conclusion: This analysis shows that corticosteroids are completely tapered and discontinued in more than 75% of CD patients after initiation of treatment with infliximab. This significant steroid sparing effect has important implications for the overall risk reduction and clinical management of these patients.

Keywords: *Crohn's disease, infliximab, corticosteroids*

89

Cost-effectiveness of abatacept versus other biologic agents in DMARDS and anti-TNF inadequate responders for the management of moderate to severe rheumatoid arthritis in Canada

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Background: To assess the cost-effectiveness of different treatment strategies for moderate to severe Rheumatoid Arthritis (RA).

Methods: Simulation modeling was used to assess the cost-effectiveness of various biologic therapeutic regimens based on current medical practices in Canada. The model used a simulation decision framework over a 2-year period and two effectiveness endpoints: low disease activity (LDA) and remission. Data sources come from published clinical data and abatacept clinical trials. Probabilistic sensitivity analyses were conducted using 5000 Monte-Carlo simulations.

Results: DMARDs inadequate responders. Abatacept as first biologic agent is cost-effective, providing greater treatment success rate of achieving LDA than anti-TNF therapeutic regimen (29.4% versus 15.6%) with overall cost savings of $730. The mean cost-effectiveness ratio also shows significantly lower cost to achieve LDA ($p<0.0001$). Using remission as effectiveness, abatacept as first biologic agent provides greater treatment success rate compared to anti-TNF therapeutic regimen (14.8% versus 5.2%) with overall cost savings of $504. The mean cost-effectiveness ratio also shows significantly lower cost to achieve remission with abatacept ($p<0.0001$). Anti-TNF inadequate responders Abatacept as second biologic after an inadequate response to one anti-TNF is cost-effective, providing additional effectiveness with 6.9% and 3.5% additional treatment success rate of LDA and remission, respectively, at an incremental cost-effectiveness of $20,377 per additional case of LDA and $26,400 per additional remission.

Conclusions: This modeling is the first assessing the cost-effectiveness of various RA biologic therapeutic regimens according to current medical practices in Canada. This study establishes that abatacept as first biologic agent represents a dominant strategy in DMARDs inadequate responders, and a cost-effective strategy in anti-TNF inadequate responders.

Keywords: *Costs, cost-effectiveness, abatacept*

90

Time horizon considerations in economic evaluations for chronic illness medications: what do patents have to do with it?

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Background: Literature on economic evaluations suggests the most appropriate time horizon should reflect the "period over which costs and benefits are expected to differ between the alternative options". Furthermore, they suggest when possible a lifetime horizon should be used. These strategies seem defendable, but for a number of chronic illness therapies some additional characteristics need to be considered: benefits may be either, equable, increasing, or decreasing with time; and assumptions regarding the treatment options are typically considered based on the currently available therapies. History suggests, and business models predict, that large markets provide sufficient motivation for pharmaceutical companies to undertake research for better medicines. Hence it is plausible that current therapies may not be the best available care following their patent expiration.

Methods: To account for these issues a sensitivity analysis using a "patent time horizon" (PTH) rather than lifetime, or a time horizon with additional time past patent expiration to accommodate market erosion patterns, should be considered.

Results: With therapies where benefits are equable over time the PTH should have little impact compared to lifetime on incremental cost-effectiveness ratios (ICER). However where the benefits are increasing or decreasing over time the PTH would result in less favorable or more favorable ICERs respectively. Some challenges exist with this sensitivity analysis related to assessing whether accumulated benefits of the therapy exist, and require an assessment. If accumulated benefits exist an adjusted PTH could be considered.

Conclusions: This analysis would provide decision makers with a more comprehensive understanding of time horizon assumptions.

Keywords: *Cost-effectiveness analysis, time horizon, patented medications*

91

Diabetic retinopathy progression in type 2 diabetes: a systematic review

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Background: Diabetic retinopathy (DR) is a well-known micro-vascular complication and a leading cause of blindness among individuals with type 2 Diabetics (T2D). Given the potential epidemic of type 2 diabetes, consolidated data on the progression of DR and associated risk factors is needed to facilitate the formulation of screening and management policies.

Methods: Systematic review of MEDLINE (1966-2007) and EMBASE (1980-2007; exploded keywords: "retinopathy" and "diabetes") was conducted to identify studies reporting DR incidence data. Broad screening, full-text reviewing and data abstraction were conducted independently by two reviewers. Observed incidence data were expressed as functions of transition rates and durations in a 4-state Markov model. Progression rates between health states (S0: None, S1: Background, S2: Pre-Proliferative and S4: Proliferative) and future projections were estimated using a Bayesian approach with WinBugs software.

Results: 38 studies (1189 citations screened, 161 articles reviewed) and 22,168 participants (males: 51%, mean T2D-duration: 8 yrs, and mean HbA1C: 9.1%) were included. Annual transition rates were S0->S1: 0.08 (95% credible interval: 0.03-0.21); S1->S2: 0.10 (0.04-0.27); and S2->S3: 0.14 (0.05-0.35). After 10 and 20 years, 9% (7-11%) and 34% (28-41%) of individuals diagnosed with T2D will have proliferative DR.. 80% of these will have some degree of DR after 20 years. Factors that significantly modified this progression included reduction in HbA1C and SBP, among others.

Conclusions: Early diagnosis of DR and better management of hypertension and hyperglycemia in individuals with T2D is important given the aggressive progression to latter stages beyond background levels of DR.

Keywords: *Type 2 diabetes, diabetic retinopathy, systematic review*

92

Dispensing of emergency contraceptives by general practitioners in BC

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Background: In 2002, BC physicians prescribed 7,212 and 3,457 Ovral and Plan B treatments for emergency contraception (EC).[1] Dispensing of EC by physicians has never been quantified. We estimated the magnitude of EC dispensing by general practitioners (GPs) from office supplies in 2001/2002.

Methods: A stratified random sample (365/3517) of GPs in BC were administered a survey on EC prescribing and dispensing from office supplies. Respondent prescription estimates were extrapolated to all GPs, and recall bias was estimated using BC PharmaNet data. GP estimates of EC dispensing were extrapolated and adjusted for recall bias. For validation, total estimated dispensing and documented prescribing of EC was compared to IMS-derived EC sales data.

Results: Based on survey responses (222/365) and PharmaNet data, GPs overestimated their Ovral and Plan B prescribing 2.3- and 2.0-fold, respectively. Extrapolation and adjustment indicated GPs dispensed 25,072 and 3,842 Ovral and Plan B treatments, respectively. Total pharmacy sales of Ovral and Plan B tablets were estimated to be 250,343 and 17,736, respectively. This was consistent with IMS data for Ovral (268,149) and Plan B (17,072).

Conclusions: GPs dispensed Ovral and Plan B 3.5- and 1.1-fold more often than they prescribed these agents. EC dispensing, particularly Ovral, by GPs has been the major source of EC for women in BC. It will be important to determine whether this was altered by the change in Plan B status.

[1]Soon JA et al. CMAJ 2005;172(7):878-83.

Keywords: *Emergency contraception, reproductive health care, physician's practice patterns*

Drug Policy

93

A review of the public perspectives on physician-pharma interaction

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Funding Source: None

Background: Recent publicity has raised concern that close relationships between physicians and the pharmaceutical industry could result in physician conflict of interest (COI). COI is defined as conditions, which cause the physician's primary interest - patient welfare, to be adversely influenced by secondary powers1. While a number of studies and commentaries by health professionals have discussed the various aspects of physician-pharmaceutical company relationship, little is heard on the public's perspective regarding these interactions. Our objective was to review, appraise and summarize the literature on the opinions of the general public on physician-pharmaceutical company interactions and their relationship to COI.

Methods: A review was conducted using MEDLINE (1966 to June 2006) and EMBASE (1980 to January 2007) databases, excluding non-English articles. The keywords "conflict of interest", "drug industry", "public opinion", physicians", "gift giving" and "ethics" were used in various combinations.

Results: 57 studies were identified which examined the effects and opinions of physicians regarding these interactions. However, only 8 studies were found which investigated the opinions of patient populations. Moreover, these studies focused on a limited number of interactions. No studies examined the opinions of the general public on the acceptability of a wide range of interactions.

Conclusions: There is limited information on the public's opinions regarding physician-pharmaceutical company interactions. Since these interactions can influence every stage of therapeutics, and public trust in physicians is vital for therapeutic outcomes, further study is warranted. We have embarked on a study to examine the public's opinions on physician-pharmaceutical company interactions.

Keywords: *Public perspective, drug industry, physician*

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94

Perceived barriers to acetaminophen prescribing, especially following rofecoxib withdrawal from the market

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Background: COX-2 inhibitors were publicly subsidized in Australia for osteoarthritis, with guidelines recommending acetaminophen as first choice therapy. When rofecoxib was withdrawn in 2004, acetaminophen should have been offered as replacement. However, dispensing data indicate no increase in acetaminophen use. The objective of this study was to gain understandings about barriers to acetaminophen use and to identify what choices consumers were offered after rofecoxib withdrawal.

Methods: We conducted 2 focus groups (consumers; pharmacists) and 12 semi-structured interviews (7 consumers receiving rofecoxib when it was withdrawn and 5 pharmacists unable to attend focus groups). Familiarity and use of acetaminophen, perceived strengths and weaknesses of acetaminophen for chronic pain, and choices given about therapy changes were investigated. All interviews and focus groups were recorded, transcribed verbatim and thematically analysed.

Results: Consumers reported that transfer of information on medicines was limited or absent. They perceived that knowledge about COX-2 inhibitor safety and/or appropriate use of acetaminophen were lacking. Pharmacists agreed that several factors were important, including lack of counselling and information for consumers. Not personalizing prescribing to elderly patients was identified as a weakness. Perceptions of efficacy of acetaminophen in consumers receiving rofecoxib at the time of withdrawal were not consistent. It appears that they were not offered opportunities to try acetaminophen.

Conclusions: Informed interventions can now be designed to influence better use of acetaminophen. These can be beneficial on a patient level, and, with Australia's national pharmaceutical reimbursement scheme, can be tracked on a population level using the national administrative database.

Keywords: *Consumers, acetaminophen, COX-2 inhibitors*

95

Patient's attitudes towards lipid lowering therapy

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Background: Many Canadians use lipid-lowering drugs (LLD), however little is known about their attitudes towards these drugs. Objective: To explore the attitudes of LLD users about the importance of reaching target goals and preferences about potential therapy changes.

Methods: A self-complete questionnaire to be completed by the person using LLD in the household was mailed in 2006. 44,308 questionnaires were returned. The raw data was weighted to reflect the gender and age distribution of LLD users and geographical distribution of the Canadian population.

Results: 91.9% reported current use of LLD (n=42,359). 75% (n=38,146) used LLD for 2+ years. 91.5% of LLD users (n=38,071) responded it was extremely (E) / very (V) important to reach cholesterol target levels set by their doctor. When LLD users were asked their opinion about possible therapy changes, if they were not reaching their goals: 22.2% (n=37,916) were E/V concerned about changing drugs (CD); 39.7% (n=37,699) E/V concerned about increasing their dose (ID); 42.1% (n=37,740) were E/V concerned about adding another drug (AD) [CD vs. ID $p<0.001$; CD vs. AD $p<0.001$]. Force ranking of three options yielded the following (n=32,723): 52.1% named CD as 1st choice; 42.7% named ID as 1st choice; 4.3% named AD as 1st choice [CD vs. ID $p<0.001$; CD vs. AD $p<0.001$].

Conclusions: Canadians who use lipid-lowering drugs express a strong preference to switch to a different drug, rather than increase the dose of their current drug, or to add another drug to their existing regimen, if they are not reaching their LDL-c goals.

Keywords: *Statins, LDL-c targets, patient attitudes*

96

Drug insurance prior authorization impact: a Cochrane systematic review

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Background: Pharmaceuticals are patented for particular diagnoses. Likewise insurance coverage for a drug may be conditional upon the drug plan granting prior approval based on patient-specific clinical information from the prescriber. We aimed to evaluate the evidence from impact studies of such policies.

Methods: A Cochrane Effective Practice and Organisation protocol was published and 17 databases searched. Randomized and non-randomized trials, interrupted time series analysis and controlled before-after that contained objective measures of drug use, healthcare utilization, health outcomes or costs were included.

Results: Eighteen rigorous evaluations of prior authorization policies applied to non-steroidal anti-inflammatory drugs, anti-ulcer drugs, and nebulized respiratory therapy were evaluated. Two years after implementation, savings on drug costs ranged from –2% to 34%. Drug costs decreased without increases in the utilization of other health services and by implication without increases in serious adverse effects. Impacts on administrative costs were poorly documented.

Conclusions: When drugs are readily interchangeable, prior authorization policies can save millions of dollars without causing cost-shifting. Prior authorization policies are therefore an acceptable component of a National Pharmaceuticals Strategy that seeks to influence prescribing behaviour so that the right drug is used for the right problem. The use of order entry systems in implementing prior authorization policies would create administrative efficiencies over faxed based systems in current use. The widespread adoption of such policies for less interchangeable drugs and drugs that do not provide immediate relief of symptoms should be accompanied by impact evaluation.

Keywords: *Cost control, insurance, health, reimbursement, health services needs and demand*

97

Statin usage: comparing cost of therapy with achievement of lipid target levels

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Background: Patients receiving treatment for dyslipidemia are commonly prescribed a statin product. Some drug plans reimburse patients for the cost of brand products, while others reimburse to the price level of a generic alternative. Such policies are based upon cost of product rather than cost effectiveness of therapy.

Objectives: To determine an estimate of the relative cost effectiveness and the percentage of patients reaching their lipid target levels, according to real-world utilization of statins.

Methods: National private payer claims data (Brogan Inc.) was used for the two leading statin brand products, and for the two leading generic alternatives. Unit claims were compared according to product strengths utilized in relation to percentage LDL reduction, as derived from the STELLAR study comparing statins. For each one percent reduction in LDL, a cost was derived. Across four product categories, the utilization of different strengths according to claims data were weighted to provide an average cost of therapy for patients.

Results: At an average weighted cost of $11.10, rosuvastatin had the lowest average cost for each percentage reduction in LDL, while at the same time more patients reached target levels. Atorvastatin had the highest average weighted cost at $17.04.

Conclusions: Rosuvastatin is the most cost effective treatment for achieving LDL reductions, while also having the most number of patients reach target levels. The implication for drug plan policies is that statin therapy cost should go beyond list price comparisons by considering the product strengths required to get patients to desired target levels.

Keywords: *Statins, cost effectiveness, drug policy*

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98

The assessing cardiovascular targets (act) program: a practice reflective assessment across Canada

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Funding Source: AstraZeneca Canada Inc

Background: The Assessing Cardiovascular Targets (ACT) program was developed to enable physicians to identify their patients' level of cardiovascular risk including metabolic syndrome and to better understand their practice and how it compared to their peers.

Objective: To examine patients' level of cardiovascular risk including metabolic syndrome in community based clinical practices across Canada.

Methods: This study was conducted from January to April 2006. A convenience sample of 450 general practictioners was recruited from each province in Canada. Physicians administered a case report form to patients during normally scheduled office visits. Aggregated data was available to participating physicians through the ACT program website.

Results: 17,188 patients participated in the study. 40% of the population was 65 years or older. 70.1%, 40.7%, and 40.5% of patients had hypertension, diabetes and a history of coronary artery disease respectively. 70% of patients were on lipid lowering therapy. Physicians' responses indicated that 34.9% and 32.7% of patients were not at their LDL-C or TC/HDL-C lipid target. 71.6% of patients were on blood pressure therapy. 26.7% of patients were not at their blood pressure target. 40% of patients met the criteria for metabolic syndrome. The distribution of metabolic syndrome risk factors for patients included the following: 24.4% (increased waist circumference); 22.4% (elevated BP); 19.7% (elevated triglycerides); 18.8% (elevated FBG); and 14.7% (low HDL).

Conclusion: National aggregate data shows that despite drug treatment many patients are not at lipid or blood pressure target levels. In addition, 40% of patients had 3 or more metabolic syndrome risk factors.

Keywords: *Prospective survey, cardiovascular risk, metabolic syndrome*

99

Characteristics of prescribers and adopters of cyclooxygenase-2 inhibitors (COX-2s) implication for interventions to improve prescribing

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Funding Source: PhD Research

Background: The objective of this research was to determine the relationship between physician characteristics and prescribing behaviour. Specifically, the evolution of prescribing behaviour relative to a new class of drugs cyclooxygenase-2 inhibitors (COX-2s).

Methods: Using Nova Scotia Seniors Pharmacare Administrative Health Claims Data, 3067 Nova Scotia physicians were identified as eligible for the study. This number was reduced to 925 following removal of subjects with incomplete records, no COX-2/NS-NSAID prescribing history, and/or absence for periods during the study time-frame. Prescribing activity of (COX-2s) from their period of introduction in the province (mid 1999) to December 31, 2003 served as a preliminary ranking filter of the study population. The characteristics of volume COX-2 prescribers (profiles based on the absolute number of prescriptions written over a given period) and relative COX-2 prescribers (prescribing of COX-2s relative to COX-2s and Non-Specific Non-Steroidal Anti-Inflammatories(NS-NSAIDs)) were established and quantified, using simple regression to determine univariate relationships and multiple regression to establish broader predictive profiles.

Results: Physicians whose COX-2 prescribing volumes were in the upper or first quartile of the population of physicians during the study period, were more likely to be older than the median age of 49, male, and active prescribers of drugs in other key categories with rural practices. Conversely, individuals whose prescribing volumes of COX-2s relative to total COX-2/NSAID prescribing volumes in the upper or first quartile were more likely to be younger, female, with low levels of prescribing in other drug categories, practicing in an urban environment.

Conclusions: The results suggest that physician characteristics, the nature of their practice and historical prescribing activity will influence both their likelihood of prescribing (trial) and adoption of new drugs into their choice of pharmaceuticals.

Keywords: *Physician prescribing behaviour, cyclooxygenase-2 inhibitors (COX-2s)*

100

How much of psychotropic use in primary care is of proven clinical efficacy? Results of an international epidemiological study and implications for policy

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Funding Source: None

Background: To investigate factors in the prescription of psychotropic drugs in primary care, including herbal drugs and tonics.

Methods: A two-phase stratified sampling strategy in primary care facilities from 14 different countries to assess prescribing patterns

Results: 5447 consecutive GP attenders aged between 16 and 65 years of age were recruited. Almost 80% of prescriptions were of unproven clinical efficacy. Herbal drugs, tonics, analgesics, or other unspecified drugs accounted for 35.6% of prescriptions, while daytime & nighttime tranquillisers accounted for another 41.3%. Although antidepressants were used more for depressive disorders and anxiolytics for patients with anxiety, the differential diagnosis was otherwise not an important factor in prescribing behaviour, particularly for herbal drugs, tonics and hypnotics. Antidepressants and anxiolytics were prescribed twice as frequently in client-centered clinics following a `personal physician model' (e.g. Seattle) as opposed to non-client centered settings, where care was less personalized (e.g. Brazil). The reverse was true of hypnotics (adjusted OR=0.5). Older patients were significantly more likely to be prescribed psychotropic medication. Other patient factors associated with individual classes of medication included the loss of a spouse and the absence of physical ill health in the case of antidepressants, and female sex, fewer years of schooling and unemployment in the case of anxiolytics.

Conclusions: Social and health care factors are at least as important as clinical features in the psychotropic prescription. These non-clinical determinants of prescribing should be considered in international comparisons and in the development of treatment guidelines

Keywords: *Epidemiology, primary care, mental health*

101

Cost-effectiveness of peginterferon alfa-2b vs. peginterferon alfa-2a combination therapy in the treatment of genotype 1 chronic HCV based upon week 12 predictability of response

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Background: The standard of care for chronic hepatitis C virus (HCV) treatment is pegylated interferon and ribavirin. In Canada, two products are available: peginterferon alfa-2b plus ribavirin (Pegetron™; Peg-2b plus RBV) and peginterferon alfa-2a plus ribavirin (Pegasys RBV™; Peg-2a plus RBV). Malone et al., 2005 postulated differences in drug utilization between the two products in the US. This analysis investigated the comparative cost in Canada of treating 100 hypothetical patients with genotype 1 (G1) chronic HCV using week 12 positive predictive value (PPV).

Methods: A decision analysis model for a 100-patient cohort was used to determine costs of treatment. Model inputs included week 12 early viral response (EVR), week 48 end of treatment response, 24 week post-treatment sustained viral response (SVR), and positive predictability of achieving SVR based on EVR. Drug costs were obtained from the Quebec drug formulary list. Patients who do not achieve EVR stop treatment and incur no further drug costs.

Results: For Peg-2b plus RBV, 75% of G1 patients achieve EVR and 71% achieve SVR (PPV=71%). Costs associated with treating the 100-patient cohort were $1,560,737. For Peg-2a plus RBV, 81% of G1 patients achieve EVR; with 57% achieving SVR (PPV=57%) with a drug cost of $1,629,936, nearly $70,000 higher. This expense is attributed to a lower PPV of Peg-2a plus RBV.

Conclusions: Payers incur drug costs for 48 weeks or 12 weeks depending on EVR. Peg-2b plus RBV confers cost savings compared to Peg-2a plus RBV based upon higher predictability of response in genotype 1 patients.

Keywords: *Budget impact analysis, peginterferon, chronic HCV*

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102

Beta-blockers in heart failure: the influence of the specialty of the prescriber on clinical outcomes

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Background: Beta-blockers have been shown to reduce mortality and morbidity in heart failure patients. However, real life experience with their use is not well described. This study sought to investigate the effect of the prescribers' specialty on all cause mortality and hospitalizations in heart failure patients treated with different beta-blockers.

Methods: From July 1997 to October 2005, we studied a cohort of patients aged >65, diagnosed with heart failure and covered by the Quebec Health Insurance Plan. Additional inclusion criteria were treatment with an ACE inhibitor or an angiotensin receptor blocker and initiation of beta-blocker therapy (Metoprolol, Bisoprolol, Carvedilol) by cardiologist or general practitioner (GP). All cause mortality and hospitalizations for heart failure were recorded. Multivariate survival analysis using Cox Hazard models were performed.

Results: A total of 7675 patients were included. Multivariate analysis showed lower mortality and hospitalization rate for heart failure when the prescription and follow up of carvedilol was performed by a cardiologist as compared to a GP with Hazard Ratio of 0.61 (95%CI 0.37 – 0.98) and 0.82 (95%CI 0.67–1.00) respectively. These inter-specialty differences were not found in the metoprolol or bisoprolol group.

Conclusion: Our study suggests that prescription of carvedilol by a cardiologist in heart failure patient leads to lower mortality and hospitalization rate when compared to a GP. This is possibly due to the particular pharmacodynamics of carvedilol. Our results are probably not due to selection bias since they were adjusted for markers of disease severity and because patients followed by cardiologist were sicker than those followed by the GPs.

Keywords: *Heart failure, beta-blockers, clinical outcomes*

103

Pharmacy & therapeutics (P&T) committees in Canadian hospitals: results of a nationwide survey

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Background: P&T committees have traditionally evaluated and developed policies for the clinical use of medications and for ensuring effective drug use and administration. The objective was to determine the current activities of academic and community hospital P&T committees across Canada.

Methods: 856 surveys (693 English, 163 French translations) were mailed to all acute, chronic or rehabilitation hospitals across Canada. Questions consisted of health system, P&T membership, scope and responsibilities. Completed surveys were returned by mail or fax. All data was entered into Excel and analyzed for descriptive statistics. Preliminary data reports on English survey results.

Results: 105 surveys were returned, representing 185 hospitals for an effective response rate of 27%. Four hospitals returned incomplete surveys. Surveys were returned from all areas of Canada, except the territories. On average, P&T committees met seven times per year. The average size of the committees was 12 members, with physicians comprising half the membership. Pharmacists and nurses had equal representation; other members were community representatives, dieticians, quality assurance personnel and/or administrators. The top responsibilities of the P&T committee were inpatient formulary management (99% of respondents), drug-use policy making (95%), patient safety (86%), drug-use monitoring (83%) and adverse drug reactions (83%). Subcommittees were utilized by 51% of P&T committees including antimicrobial (21%), medication safety (16%) and nutrition (10%). Economic evaluations were most frequently completed by a pharmacist who had some previous pharmacoeconomic experience.

Conclusions: This survey reports on the current status and responsibilities, namely formulary management and policy making, of P&T committees in Canada.

Keywords: *Survey, Pharmacy and Therapeutics Committee*

104

Development of a national set of medication-use safety indicators

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Funding Source: This study was funded by a grant from the Canadian Patient Safety Institute. Matching and in-kind support was provided by four health authorities: Annapolis Valley District Health Authority, Capital District Health Authority, Eastern Regional Integrated Health Authority (NL) and IWK Health Centre-and six national organizations: Canadian Council on Health Services Accreditation, Canadian College of Health Service Executives, Canadian Institute for Health Information, Canadian Pharmacists Association, Canadian Society of Hospital Pharmacists and the Institute for Safe Medication Practices Canada.

Background: Reports of preventable illness due to medication errors are widespread in Canada. However, quantifying the magnitude of the problem has been hampered by a lack of measurement tools. Canadian-specific indicators, or performance measures, of the safe medication use do not exist. The aim of this study was to develop a set of Canadian consensus-based indicators for the safe use of medication.
Methods: A panel of 20 national experts was established from a convenience sample of medicine, nursing, pharmacy, researchers and decision-makers in hospitals and community settings across Canada. After creating a list of candidate indicators from the literature, the final consensus set was chosen by the panel using a Delphi survey process over e-mail.
Results: After three rounds, consensus was obtained on 20 medication-use safety indicators: seven related to systems of care, five to prescribing–ordering, three to monitoring and assessment, three to medication administration, one to preparation and dispensing and one to purchasing–inventory management. Seventeen indicators measure a process of care (in contrast to health outcome); at least 10 have application outside the inpatient setting.
Conclusions: The final set of medication-use safety indicators on this tool are diverse in scope and applicable both in-patient and out –patient settings. These indicators provide clinicians and decision-makers with another tool to assess the safety of the medication-use system. The validity of a subgroup of these indicators will be tested in the four partnering health authorities. Due to budgetary limitations only five indicators will be tested.
Keywords: *Medication safety, performance measures, safety indicators, medication-use system, Delphi technique*

105

Lessons for a Canadian national pharmaceuticals strategy from Australia and New Zealand?

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Funding Source: None

Background: The provincial formulary review processes in Canada lead to slow and inequitable availability of new products. In 2004, the exploration of a National Pharmaceuticals Strategy (NPS) was announced. The policies of New Zealand and Australia have been suggested as possible models for the NPS. Our objective was to compare health indices and health care utilization information from Canada, Australia and New Zealand with a focus on cardiovascular and respiratory disorders.
Methods: Organization for Economic Cooperation and Development (OECD) health data were used to compare mortality rates, hospital discharge rates, average length of stay, and drug sales in the three countries.
Results: Although the mortality rate from acute myocardial infarction decreased in each country from 1994, it leveled off in New Zealand in 1997, 1998 and 1999. Between 1994 and 2003, average lengths of hospital stay for any cause and for cardiovascular disorders were stable in Australia and Canada but increased in New Zealand, while the rate of hospital discharges for cardiovascular disorders decreased in Canada and Australia but strongly increased in New Zealand. Over the same period, sales of cardiovascular drugs decreased in New Zealand, while sharply increasing in Canada and Australia.
Conclusions: Although only circumstantial, our results suggest an association between decreasing cardiovascular drug sales and markers of declining cardiovascular health in New Zealand. Careful consideration must be given to the potential consequences of any model for a NPS in Canada and opportunities provided for discussion and input from health care professionals and patients.
Keywords: *Canadian health system, prescription drugs, health policy*

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106

Utilization and cost of blood glucose self-monitoring test strips in the Seniors' Pharmacare Program in Nova Scotia, Canada. a retrospective database analysis

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Funding Source: CHSRF/CIHR co-sponsored by NSHRF

Background: To identify the type, frequency and cost of blood glucose monitoring (BGM) test strips claimed by Nova Scotia Seniors' Pharmacare Program (NSSPP) beneficiaries in the fiscal year 2005/06.

Methods: Retrospective analysis was conducted using pharmacy administrative claims data for NSSPP beneficiaries. Study subjects were ≥ 65 years on October 01, 2004, received test strips in the 110 days prior to April 1, 2005, and were alive throughout the study period. Subjects were categorized into four groups: insulin only, oral antihyperglycemic agents (OAA) only, both OAA and insulin; and no reimbursed diabetes medications. Statistical analysis was performed to identify differences in 1) expenditure by medication group and 2) frequency of test strips claimed by treatment group, age and sex.

Results: Of 13,564 included beneficiaries, 13.2% were categorized as insulin only, 53.5% OAA only, 7.2% both OAA and insulin, and 26.0% no reimbursed diabetes medications. Over half (58.7%) were female. The insulin only category had the highest mean (±SD) number of BGM test strips claimed per day (2±1.5) with a mean annual total cost of $615 ±$441. Beneficiaries aged 80 years and above claimed fewer test strips than beneficiaries below 80 years. Accu-Check Advantage® test strips were claimed most often (29.1%).

Conclusion: Significant between group variations exists in self testing of blood glucose by type of treatment. This study provided insights into the characteristics of these beneficiaries. Further work is needed to understand patients' reasons for testing, ability to accomplish self care and link blood glucose testing with health outcomes.

Keywords: *Test strips, frequency, expenditure*

107

The value of intensive statin treatment

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Funding Source: Pzifer Canada Inc.

Background: Recent trials have compared the clinical benefits of intensive versus standard doses of statins in reducing the risk of cardiovascular events. The objective of this study was to estimate the value of intensive statin treatment from the perspective of the Canadian health care system.

Methods: A systematic review of all clinical trials of intensive versus standard dose statin treatment was conducted. Studies meeting the following criteria were included**:** 1) n in each arm, 2) at least 1 disaggregated cardiovascular endpoint, 3) available statistics (rate, hazard ratio, 95% confidence interval (CI)) on all deaths, coronary heart disease deaths or cardiovascular deaths, 4) dose and duration of treatment for each statin. The incremental costs per cardiovascular event averted (ICEA) and per life-year gained (ICLYG) were estimated using a Monte Carlo model.

Results: Four studies met the inclusion criteria: IDEAL, TNT, AtoZ, and PROVE-IT. Compared to standard doses, patients in the intensive arm had fewer cardiovascular events in all 4 and fewer deaths in 3 (IDEAL, PROVE-IT, AtoZ) trials. In TNT the number of deaths was equivalent in the two arms. Intensive treatment was associated with higher direct costs in IDEAL and TNT. The ICEA was $CA8,155 and $CA19,052 in IDEAL and TNT respectively. In IDEAL, the ICLYG was $CA27,929. In AtoZ and PROVE-IT, intensive treatment was associated with lower direct costs and thus dominated standard treatment.

Conclusions: In the patients whose clinical characteristics are similar to those recruited in these trials, intensive statin therapy ranges from cost-savings to cost-effective in Canada.

Keywords: *Statin, cardiovascular events, health care system*

108

A comparison of benzodiazepine and related drug use in Nova Scotia, Canada and Australia

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Funding Source: Pharmacy Endowment Fund, Nova Scotia

Background: The prescription of benzodiazepines can be a problem if used for long periods, or in at-risk populations (elderly). We compared the use of benzodiazepine and related prescription medicines, in Nova Scotia, Canada and in Australia, in seniors and social security beneficiaries.

Methods: The Nova Scotia Pharmacare Program and Pharmaceutical Benefits Scheme in Australia were used to obtain dispensing data for all publicly subsidized benzodiazepines and related compounds. Utilisation was compared (2000-2003) using the WHO Anatomic Therapeutic Chemical/ Defined Daily Dose (DDD) system.

Results: Use of benzodiazepines increased at steady but comparable rates in both areas. However, the use of benzodiazepines in Nova Scotia was more than double that of Australia from 2000 (123 and 48 DDD/1000 beneficiaries per day) through 2003 (138 and 57 DDD/1000 beneficiaries per day). Eight different benzodiazepines made up 90% of the use in Nova Scotia, with lorazepam most commonly prescribed. By contrast, only four different benzodiazepines made up 90% of the use in Australia, with diazepam most commonly prescribed.

Conclusions: There were large differences between the type and rate of benzodiazepine prescribing. Use in both jurisdictions is increasing. The findings are especially concerning in Canada as use of benzodiazepines in Atlantic provinces has been reported to be less than other parts of Canada. Variations between the jurisdictions may be due to the limited range of benzodiazepines available in Australia, or different initiatives to control benzodiazepine use. Modified formulary policies, as well as education for patients and prescribers may promote more appropriate prescribing of benzodiazepines.

Keywords: *Benzodiazepines, prescribing, international*

CCCP - ORAL PRESENTATIONS
MONDAY MAY 28, 2007

109

Maritime provinces symposium on health technology assessment

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Funding Source: Canadian Agency for Drugs and Technology in Health

Background: Canada's Maritime Provinces have no provincial health technology organizations; there is limited awareness and utilization of health technology assessment (HTA) in healthcare decision-making, especially for devices. We presented a two-day interprofessional symposium to raise awareness of and promote HTA in the Maritimes.

Methods: We developed two cases – assessment of a drug and a medical device. Before the symposium, participants selected one case and received two documents for pre-reading: 1) a technology report and 2) a workbook, including an appraisal worksheet, which guided them through the issues to consider when deciding to adopt the technology. Ninety-minute workshops covered critical appraisal of the reports and frequent discussion periods promoted interaction. Program content included economics, quality of life measures, ethics, national and international examples of HTA, a panel discussion with users and producers of HTA, and other topics.

Results: Fifty-eight people attended including hospital administrators, ministry decision-makers, physicians, pharmacists, biomedical engineers, academics, and graduate students. Participants rated all aspects of the Symposium highly and made several suggestions for promoting HTA: 1) include Newfoundland and Labrador in future initiatives to provide an Atlantic approach; 2) build on existing initiatives such as the Atlantic Common Drug review; 3) present more educational programs including topics such as critical appraisal and statistics; and 4) develop a proposal for an HTA project for submission to deputy ministers. A final report is available at cme.medicine.dal.ca/resources.htm.

Conclusions: Participants supported HTA. However, further promotion and adoption of HTA is needed to ensure optimal utilization of health technologies including pharmacotherapies.

Keywords: *Health technology assessment, interprofessional education, organizational learning*

110 - ENCORE PRESENTATION

Description of a pharmacist - managed toxicology consult service at the Ottawa hospital: evaluation of program and impact from an educational perspective

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Funding Source: None
Background: The Toxicology Service at The Ottawa Hospital is a unique consult service operated by pharmacy residents 24-hours per day. We conducted a formal evaluation of our consults and the impact of the program from an educational perspective.
Methods: In the first part of this study physician opinion was solicited using an informal questionnaire to determine the essential components of an ideal written consult. In the second part of this study consecutive patients (June 2005 - May 2006) for which toxicology consults were sought were prospectively identified. Data pertinent to demographics, overdose etiology, clinical outcome and written consult components were extracted from medical records. The third part was a web-based survey designed to collect self-reported values and skills gained from past pharmacy residents who completed the program during the previous 10 years.
Results: Users of the service identified four essential components of the written consult: medication history, overview of toxidrome, severity of overdose and pharmacological treatment recommendations. Fifty-four toxicology consults were conducted over the one-year period (16% of all overdoses) and represent a wide variety of overdoses. More than 80% of written consults had 3 of 4 essential components. Greater than 90% of past pharmacy residents found participation in the program enhanced their confidence, independence, sense of responsibility, communication skills and ability to work in a stressful environment. While 61% of past pharmacy residents found it a significant source of stress, 88% felt their participation did not compromise their learning experience.
Conclusions: This study describes the diversity of overdoses for which the Toxicology Program is consulted at The Ottawa Hospital and identifies essential components of the written consult. Most past pharmacy residents felt that participation in the program was an important part of the residency and the skills and values developed were useful in subsequent careers.
Keywords: *Toxicology, consult, program*

111

Women in Nova Scotia face knowledge barriers in accessing the emergency contraceptive pill from pharmacists: a qualitative study

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Funding Source: Nova Scotia Health Research Foundation
Background: Emergency contraception pills (ECP), are combinations of estrogens/progestins or levonorgestrel which, taken within 120 hours of unprotected intercourse, are effective in preventing up to 85% of unplanned pregnancies. In April 2005, levonorgestrel (Plan B ®) was approved as a schedule II drug in Canada. The purpose of this qualitative study was to identify issues related to the accessibility and use of ECP in Nova Scotia so as to inform the development of a grant proposal for a larger study aimed at identifying ways to reduce barriers to accessing ECP.
Methods: Two focus groups (n=8 for both) of women aged 17-39, were conducted in one urban and one rural area. Women were asked about knowledge, attitudes, and access barriers concerning ECP. Data analysis involved an interpretive process of describing, organizing, connecting, and corroborating research findings with the literature.
Results: Preliminary findings show that some women are unaware that Plan B® can be obtained from a pharmacist without a prescription. Furthermore, women underestimate the timeframe after intercourse in which ECP can be used. Together, these factors could prevent women from accessing ECP because by the time they get a physician appointment, they might perceive it is too late to take ECP. Women also have concerns regarding potential side effects, which could further deter access to ECPs.
Conclusions: Women in these focus groups have provided valuable information that will help shape further planned quantitative research about ECP. Such findings will support refinement of policy, practice and patient education about ECP.
Keywords: *Focus groups, levonorgestrel, emergency contraception*

112

Initiative to convert patients from nebulized respiratory medications to portable inhalers: analysis of pharmacist claims for a professional fee to optimize therapy in Nova Scotia, Canada

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Background: To determine the involvement of pharmacists from Nova Scotia, Canada in the initial years of the wet nebulization respiratory medication conversion initiative (2000-2004). This policy initiative provided pharmacists with a professional fee for the provision of patient education around the use of spacer devices in combination with metered dose-inhalers (MDIs) for eligible beneficiaries of Nova Scotia Pharmacare Programs.

Methods: A retrospective population-based study was performed using claims from the Nova Scotia Pharmacare Program administrative database for the period between January 1, 2000 and December 31, 2004. The study population consisted of those who received drug benefits through the Seniors' and Family Benefits' Pharmacare Programs. Claims by pharmacists for the professional fee were identified using specified billing codes for spacer devices.

Results: Over the five year evaluation period, 21, 590 spacer device claims were billed to the Pharmacare Programs. Spacer device claims from 2000-2004 were 5299, 4582, 4017, 3946, and 4016, respectively. The proportion of spacer device users per 1000 respiratory medication users in 2000-2004 was 137, 127, 150, 155, and 166, respectively.

Conclusions: The policy initiative of paying pharmacists a professional fee to provide spacer devices has had a significant and sustained uptake in Nova Scotia. However, more beneficiaries of the Pharmacare program could potentially benefit from receiving a spacer device in combination with portable inhalers for their respiratory medications, as well as, the education from pharmacists on the correct use of these devices.

Keywords: *Pharmacist involvement, drug policy, wet nebulization*

CCCP - POSTER PRESENTATIONS
MONDAY MAY 28, 2007

Therapeutics for Vulnerable Populations

113

Monitoring and management of metabolic risk factors in outpatients taking antipsychotic drugs: a controlled study

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Funding Source: None

Background: Patients with bipolar disorder and schizophrenia are at higher risk for metabolic complications yet there are few investigations that have assessed monitoring practices of these risk factors in routine psychiatric care. This study evaluated the screening, monitoring, and management of metabolic risk factors and diseases in long-term antipsychotic users in relation to current practice guidelines and to current standards of care as represented by a control group - a HIV Clinic.

Methods: Retrospective chart review performed for mental health (MH) outpatients taking antipsychotic drugs long-term (cases) and HIV outpatients prescribed HAART (controls).

Results: Ninety-nine mental health patients and 98 HIV patients were included in the analysis. Based on information available in the outpatient clinic chart, the 10-year CAD risk was computable for 28% of mental health patients (mean risk 11.9%) and for 90% of HIV patients (mean risk 9.5%) (fÓ2=77.0, P<0.001). Metabolic risk factors were less frequently documented in MH Clinic charts, though the differences were not significant. All HIV Clinic patients were screened for dyslipidemia, hypertension, and diabetes, whereas this was missing for 65%, 34%, and 41% of MH Clinic patients (p<0.001 for all). Disease monitoring was also more comprehensive in HIV Clinic charts (e.g., lipid monitoring 100% vs. 71%, p=0.001).

Conclusions: Improved efforts are needed in the somatic care of patients with bipolar disorder and schizophrenia taking antipsychotics considering they are typically at moderate-to-high risk for metabolic diseases.

Keywords: *Psychotic disorders, bipolar disorder, antipsychotic agents, drug monitoring*

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114

Equivalence of acetaminophen and ibuprofen combination therapy and acetaminophen monotherapy for the treatment of febrile children: a retrospective chart review

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Funding Source: None

Background: Caregivers are often highly concerned about fevers in children and misinformed about the harmful effects of elevated body temperatures. Alternating acetaminophen and ibuprofen is common practice, although there is limited supporting evidence for its efficacy relative to monotherapy. The objective was to determine whether febrile children receiving a combination of acetaminophen and ibuprofen experience enhanced fever reduction compared to those receiving acetaminophen monotherapy.
Methods: This retrospective chart review included paediatric inpatients that received antipyretic therapy for oral temperatures ≥38ºC. Children who received the combination of ibuprofen and acetaminophen were matched according to date of birth and admission to those who received acetaminophen monotherapy. Antipyretic effect was evaluated by comparing the area under the temperature curve (AUTC) over 24 hours for each group.
Results: 63 patients were recruited for each of the combination and monotherapy groups with a median age of 1.9 and 1.6 years, respectively. The combination group had a higher temperature at baseline (39.1ºC vs. 38.7ºC, p=0.001) and a higher AUTC (909.6 vs. 902.9, p=0.002). No significant temperature differences between the two groups were reported at 1, 2, 4, 24 or 48 hours after the initiation of antipyretic therapy. Combination patients received significantly more antipyretic doses than monotherapy patients (5.6, SD=1.9 vs. 3.3, SD=1.2 doses, p<0.001).
Conclusions: There was no evidence that the combination of acetaminophen and ibuprofen results in greater temperature reduction than acetaminophen monotherapy. A randomized clinical trial is warranted to validate the findings of this retrospective study.
Keywords: *Fever, acetaminophen, ibuprofen*

115 – ENCORE PRESENTATION

Evaluation of clinical pharmacy services provided in the home care setting to patients recently discharged from hospital

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Background: Home care is an increasingly important component of Canada's health care system. Despite the vast array of often-complex medication regimens utilized in home care, pharmacists have not traditionally been members of home care teams. Also, there is a high risk of adverse drug events in the period immediately following hospitalization.
Methods: Clinical pharmacy services were provided to patients recently discharged from hospital that were at high risk of adverse drug events. Services were provided upon consult from a home care nurse for a minimum of 3 weeks. Examples of services included: comprehensive or focused medication regimen assessment, adverse drug event assessment, and adherence assessment. The objectives were to determine (a) the number of medication-related issues identified by the pharmacist, (b) the acceptance rate and significance of pharmacist recommendations, and (c) satisfaction levels of patients and team members.
Results: 30 patients (mean age 81 years) participated in the pilot project. Patients took a mean of 11.9 medications. There was a mean of 3.6 medication-related issues identified and 4.3 recommendations made per patient. 74% of recommendations made to physicians were accepted, 5.5% were rejected, and the response to 20% was unknown. The mean significance of recommendations was 4.1 (scale 1-6), indicating the majority of recommendations were significant. Overall satisfaction scores were 9.6 and 9.9 for nurses and patients respectively (scale 1-10).
Conclusions: A wide variety of medication-related issues were identified and recommendations were made to optimize medication regimens. Both patients and team members were very satisfied with the clinical pharmacy services provided.
Keywords: *Clinical pharmacy, home care*

Advances in Therapeutics Education

116

Interprofessional continuing education for management of chronic non-cancer pain

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Funding Source Health Canada Drug Strategy Community Initiatives Fund, Drug Eval Alliance of NS
Background: Managing chronic non-cancer pain (CNCP) is a challenging clinical problem, particularly when some recommended medications have potential for abuse. This educational program was designed to engage physicians, dentists, and pharmacists in Cape Breton District Health Authority in a collaborative approach to management of CNCP with an emphasis on opioid abuse.
Methods: We first conducted a needs assessment through focus groups with 1) patients; and 2) physicians, dentists, and pharmacists. From the two focus groups we developed a questionnaire that was distributed to the three types of health professionals in the Health Authority. We then developed a 2½ hour educational intervention of case presentations discussed by participants and a panel of pain specialists, addiction specialists, and representatives of the provincial Prescription Monitoring Program. The program was presented twice, once by videoconference, and once in face-to-face format.
Results: Thirteen physicians, 15 dentists, and 26 pharmacists attended the two programs. Overall evaluation was high although physicians rated the following domains higher than dentists and pharmacists: the content was applicable to my practice; there was adequate time for discussion; and I gained new knowledge. Pre and post self-efficacy scores increased for: asking a patient starting opioids to sign a management agreement (2.7/5 vs. 3.6/5); and ask the Prescription Monitoring Program for help in monitoring my practice (3.0/5 vs. 4.2/5). It was difficult to engage pharmacists in discussion.
Conclusions: The overall content and format of the program was well received. However, optimizing therapeutics education requires more complete participation of all health professionals in learning.
Keywords: *Interprofessional learning, pain management, addictions*

117

Response to antidepressant monotherapy in depression preceding the diagnosis of bipolar disorder "C" inherent risk and predictive value

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Funding Source: None
Background: Given that the first episode of Bipolar Disorder is most often Major Depression, the unsuspecting use of antidepressant monotherapy in this group is of significant concern. Antidepressant-induced mania, hypomania and rapid-cycling are recognized as potential, though usually later, consequences. Our hypothesis is that there are other less obvious treatment –emergent effects in the immediate response to antidepressant monotherapy treatment. This study's objective was to retrospectively compare treatment emergent symptoms following antidepressant monotherapy in 'pre-bipolar depression" versus a known Unipolar group.
Methods: Retrospective chart review of depression characteristics and assessment of treatment response to antidepressant monotherapy in patients with depression preceding diagnosis of Bipolar Disorder, compared to a matched Unipolar sample.
Results: Mean time to final diagnosis from the first treated episode in the Bipolar group was 7.2 years ± SD 8.2. Immediate (within 2 weeks) treatment emergent serious symptoms (agitation, anger, rage and ↑suicidality) (p=.02) and treatment emergent "mixed symptoms" (2 symptoms of DSM IV hypomania, lability or anger/rage) occurred more commonly in the pre-bipolar group (p=.007).These symptoms were not attributed to antidepressant treatment at the time.When controlling for other variables in logistic regression, only family history of suicide (p=.001), emergent symptoms of agitation (p=.0001), sleep disturbance (p=.001), and increased talkativeness (p=.02) remained significantly associated with development of bipolar disorder.
Conclusions: Family history of completed suicide is predictive of future Bipolarity. Treatment-emergent mixed symptoms may be predictive of future Bipolarity, and inherently dangerous themselves.
Keywords: *Retrospective chart review, antidepressants, bipolar/unipolar*

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118

Development of an integrated pharmacist's patient care process

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Funding Source: None

Background: The main curricular components of Dalhousie University's College of Pharmacy (problem-based learning courses, critical appraisal series, skills laboratories, and the practice experience program) require improved integration and standardized terminology. This is predicted to improve student and pharmacist ability to use literature appraisal skills to improve patient care abilities. A new process, The Pharmacist's Patient Care Process, was developed to address these challenges.

Methods: A small group of faculty and staff representing different aspects of the curriculum was created to standardize terminology and develop the new patient care process by group consensus. Feedback will be requested from all faculty and staff and once approved the accepted version will be introduced to stakeholders and students and integrated into the curriculum.

Results: The Pharmacist's Patient Care Process overtly integrates critical appraisal skill development and application into the current patient-centered problem-solving pharmaceutical care model and has simplified and standardized related terminology. By May of 2007, the new process, currently a work in progress, will be introduced to faculty members and stakeholders, requesting feedback and recommendations for implementation in September 2007. To date, informal feedback has been favourable.

Conclusions: New and advanced learners and current pharmacists need to develop skills to take advantage of advances in information technology, especially access to reliable and valid evidence related to drug therapies that they can apply in their routine care of patients. Modifications to the undergraduate curriculum based on the new Pharmacist's Patient Care Process will support new pharmacists in translating evidence into practice.

Keywords: *Patient-centered care, evidence-based practice, education models*

TUESDAY MAY 29, 2007

Human Resources in Drug Evaluation

119

Integration of a pharmaceutical care program into family practices: drug-therapy problems identified and recommendations made by participating pharmacists

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Funding Source: Primary Health Care Transition Fund, Health Canada

Background: Suboptimal or inappropriate use of medications in the elderly is associated with increased morbidity and mortality. Pharmacists have the potential to optimize drug therapy through the identification of drug-therapy problems (DTPs) and the provision of associated solution-focused recommendations.

Methods: A cross-sectional descriptive study that was part of a larger project aiming to improve patient outcomes by optimizing drug therapy through a practice model integrating pharmacists into family practices (the IMPACT project). Patients from seven family practice sites were referred for a pharmacist assessment by either the practice site physicians or identified by the research team. Pharmacists provided pharmaceutical care including individual patient assessments, monitoring and follow-up. Pharmacists documented DTPs and made recommendations to the physicians for their resolution. Data were extracted from the Microsoft Access-based IMPACT documentation software. Using predefined, validated coding systems, the DTPs were coded by two independent assessors and the recommendations by one (of seven) assessors.

Results: Of 969 patients referred, 908 patients had at least one DTP and for those patients, the pharmacists identified on average 4.4 DTPs per patient. The most common DTP identified was that a patient required therapy for an indication but was not receiving it (27%). The pharmacists made an average of 5.8 drug-related recommendations per patient. One third of the recommendations were related to hypertension, dyslipidemia and diabetes. Twelve per cent of recommendations were classified as having a potentially marked clinical impact.

Conclusions: Pharmacists identified a large number of DTPs in older adults and generated a substantial number of solution-focused recommendations to address these problems.

Keywords: *Drug-therapy problems, pharmacist, descriptive study*

120

Examining physicians' perspectives during the integration of a pharmacist into family practice

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Funding Source: Ontario Primary Health Care Transition Fund

Background/Objectives: Physicians may have concerns about medical-legal issues, scope of practice, continuity of care, workload and satisfaction as other health disciplines integrate into primary care. The objective of this analysis was to conduct a qualitative evaluation of physicians' perspectives after seven pharmacists had integrated into seven physician-led family practices in the Ontario IMPACT (Integrating family Medicine and Pharmacy to Advance primary Care Therapeutics) project.

Methods: Qualitative design using key informant interviews (N=14) twelve months after integration. Family physicians were purposively selected based on age, sex, and degree of support, and those felt by integrating pharmacists to be unsupportive. Interviews were audiotaped and transcribed. Four researchers used immersion and crystallization to identify codes, and iterative grounded theory to determine themes.

Results: Challenges included finding time to make contact and learn about the pharmacist's role and skills. Insufficient space was the main structural challenge. Facilitating factors in developing inter-professional relationships were mutual respect of time, practical skills and boundaries. Appreciations included having a colleague to provide current, reliable drug information, fresh perspectives, time saving measures, and feeling increased confidence in prescribing. Practice-level benefits included group education, medication-related protocols and liaison with community pharmacy and pharmaceutical representatives. Physicians' initial concerns (e.g. medical legal implications, loss of continuity of care, and scope of practice) decreased markedly as they understood and appreciated the pharmacist role.

Conclusions: Physicians' concerns about working with pharmacists in primary care abated with time, creating an environment in which the skills of both professionals can synergistically improve primary care therapeutics.

Keywords: *Qualitative, physician-pharmacist collaboration, primary care*

Therapeutics Innovations

121

Translating pharmacy knowledge into enhanced glycemic and hypertension control in diabetic primary care: an institutional ethnography of practice changes in Alberta

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Funding Source: CIHR, CDA, AHFMR

Background: The Vascular Intervention Program (VIP) study is a randomized controlled trial investigating the impact of introducing pharmacists into primary care on hypertension control in diabetes. The objective of an ethnographic component of VIP is to reveal how the integration takes place and how outcomes are practically achieved.

Methods: Key informant interviews, nonparticpant observation, related procedures, policies, legislations and regulations were analysed using a framework derived from institutional ethnography to create a map of integrated local practices orchestrated by translocal relations.

Results: Encountering a pharmacist engaged in direct patient care in primary care settings is still novel for patients and other care providers. To facilitate shared care, pre-existing information access, record keeping and communication practices need to be reconfigured. To translate pharmacists' knowledge of pharmacology, medicinal chemistry and therapeutics into tailored and optimized prescribing requires the pharmacist to reconcile research and clinical practice guidelines with physicians' preferred prescribing practices and patient contingencies. The Alberta Trilateral Master Agreement, Health Professions Act, College of Pharmacy standards and Capital Health Chronic Care programming descriptions are part of an emerging map of interconnected and diverse governance and funding practices that mediate practice change. Pharmacy academia contributes through updated curriculum, practice guideline and knowledge creation practices.

Conclusions: This analysis shows how the introduction of pharmacists into local primary care practice settings is institutionally orchestrated through changes in Alberta's clinical governance, funding, administrative and educational practices. How change occurs and its impact in combination provides insights useful to continuing efforts to improve care.

Keywords: *Institutional ethnography, knowledge translation, hypertension*

122

CRESTOR® HealthyChanges®–an intervention to improve adherence

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Funding Source: AstraZeneca Canada Inc.

Background: Despite clinical evidence supporting the benefits of cholesterol-lowering over the past two decades, long-term adherence to therapy remains far from optimal. Only about half of the persons who are prescribed a lipid-lowering drug are still taking it six months later. HealthyChanges was developed to determine if a patient-focused program providing telephone access to a dietitian and encouraging healthy eating, physical activity and compliance with medication improves adherence to a statin.

Methods: A cohort of rosuvastatin patients registered with HealthyChanges and was provided with telephone coaching from Registered Dietitians. An information kit with an emphasis on lifestyle modification (i.e. healthy eating, regular physical exercise) and tools to improve understanding of high cholesterol reinforced the importance of lipid control. The dietitians and newsletters also reinforced compliance with the statin. The dietitian contacted the patient at standardized intervals, reviewed progress towards goals, collected self-reported adherence to medication, and answered questions.

Results: Patient characteristics were 51% female, 49% male, average age of 60 years and 54% were new to statins. On the basis of this program and assessment method, the percentage of patients still on rosuvastatin at 6 months (n=1929) and 12 months (n=1215) after registration into HealthyChanges was 95% and 91% respectively.

Conclusions: Our findings indicate that a support program helping patients understand dyslipidemia and adopt healthy lifestyle changes can successfully improve adherence to a statin. HealthyChanges is linked to a specific statin, however, it circles the patient to positively improve adherence and may improve the health burden associated with cardiovascular disease.

Keywords: *Adherence, statins, telephone*

Drug Policy

123

Use of evidenced-based therapy at discharge for patients with acute myocardial infarction (AMI) - a retrospective chart audit

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Funding Source: Cardiac Program, Eastern Health, St. John's, Canada

Background: Quality indicators for acute myocardial infarction (AMI) patients and use of medications upon discharge in Canada have been published. Assessment of current practice at two hospitals in Newfoundland and Labrador was completed. The study objective was to determine the proportion of discharged AMI patients prescribed acetylsalicylic acid (ASA), beta blockers (BB), angiotensin converting enzyme inhibitors (ACE), and HMG-CoA reductase inhibitors (statins).

Methods: Patients with a most responsible diagnosis of AMI from April/04 to March/05 were identified from the administrative database. A total of 346 eligible charts were obtained and reviewed. Retrieved data included AMI diagnosis, demographics, co-morbidities, discharge service, and medications on admission/discharge. A rate of discharge prescribing for the four classes was calculated for all patients and ideal patients (those without documented contraindications). Rates were compared to published benchmark values.

Results: Mean age was 65.3±13.4 years (65.3% male). AMI coded was 26.3% STEMI, 47.4% NSTEMI, and 26.3% MI not specified. Prescribing rates of ASA, BB, ACE and statins for all patients were 89%, 89.6%, 76.3%, and 80.3% respectively. For ideal patients, rates were 99%, 96%, 90.4%, and 88.8%. Of the 346 patients, 229 were discharged from a cardiac service, and 117 from a non-cardiac service. Rates of prescribing for ideal patients discharged from a cardiac service were 100%, 96.7%, 92.2%, and 92.5%. From a non-cardiac service, rates were 96.9%, 95.3%, 86.9%, and 81.2%.

Conclusions: Rates of prescribing of ASA, ACE, BB, and statins for ideal patients discharged with AMI exceeded the published Canadian benchmarks.

Keywords: *Acute myocardial infarction, drug utilization, retrospective analysis*

124

Medication reconciliation by a pharmacist in the emergency department: a pilot project

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Funding Source: CSHP research grant

Background: Medication reconciliation is a process by which patients' home medications are compared to admission orders and discrepancies brought to the attention of the prescriber. Currently, many of our pharmacists' interventions are made at discharge: A pharmacist working in the emergency department (ED) will identify interventions earlier and prevent medication errors.

Methods: A multidisciplinary team developed a Best Possible Medication History (BPMH) form to document home medications and reconcile admission orders in the ED. To identify home medications, the pharmacist interviewed the patient and contacted the community pharmacy. The list was reconciled with admission orders within 24 hours of admission. The pharmacist identified discrepancies between home and admission medications for the physician and documented interventions. After completion of the trial phase, staff were surveyed on the form and process.

Results: During the 8 week trial, the pharmacist completed medication histories and reconciled orders on 98 patients (35% of patients admitted through the ED). The average number of medications per patient was 7 (range 1 - 15) and the average age was 71 (17 – 98). Of 124 interventions made, the majority (81) were home medications omitted on admission orders. Survey results: 85% of respondents had referred to the BPMH for information; 72% found it accurate and useful; 73% found it saved them time; 69% of ED staff agreed the pharmacist was a valuable resource.

Conclusions: Medication errors occur frequently with admitting orders in our ED. A pharmacist performing medication reconciliation in the ED provided timely interventions to prevent medication errors.

Keywords: *Medication reconciliation, medication errors*

CSCP
ORAL PRESENTATIONS
WEDNESDAY MAY 30, 2007

125

Age-related decrease in catecholamine sensitivity is mediated by both ß1- and ß2-adrenergic receptors in ventricular myocytes isolated from Fischer 344 rats

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Background: The sensitivity of the heart to catecholamines declines with age. The aim of the present study was to determine whether reduced sensitivity to catecholamines in aged myocytes resulted from deficits in signaling via ß1-adrenergic receptors (ARs), ß2-ARs, or both.

Methods: Contraction amplitudes were measured in field-stimulated (2 Hz, 37°C) ventricular myocytes isolated from young adult (3 mos) and aged (24 mos) Fischer 344 rats in the presence and absence of various ß-AR agonists.

Results: Maximal positive inotropic responses to the non-selective ß-AR agonist, isoproterenol were decreased in aged compared to young adult myocytes and aged myocytes were less sensitive to isoproterenol (EC50= 39.4±8.8 vs. 12.6±4.6 nM, respectively). The selective ß1-AR agonist, dobutamine caused smaller increases in maximal contraction amplitudes in aged compared to young adult myocytes (403.3±64.2 vs. 657.7±117.6 % control). Aged myocytes also exhibited smaller maximum positive inotropic responses to the selective ß2-AR agonist, salbutamol compared to young adult myocytes (224.5±38.6 vs. 324.4±49.5 % control). Interestingly, pretreatment of cells with pertussis toxin to inhibit Gi proteins abolished the differences in responses to salbutamol between aged and young adult myocytes.

Conclusions: This study shows that the age-related decrease in catecholamine sensitivity is mediated by both ß1- and ß2-ARs. These results suggest that aged myocytes have higher levels of Gi proteins, which may decrease their sensitivity to ß2-AR agonists. The reduced sensitivity of aged myocytes to ß1-AR stimulation may be related to a decrease in the levels of Gs protein and/or another deficit in the ß1-AR signaling pathway.

Keywords: *Aging, ventricular mycoyte, ß-adrenergic receptors*

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126

N-acetylcysteine attenuates ifosfamide-induced nephrotoxicity in rats

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Funding Source: CIHR

Background: Ifosfamide nephrotoxicity is a serious adverse effect for children undergoing cancer chemotherapy. Our recent in vitro studies have shown that the antioxidant N-acetylcysteine (NAC), which is used extensively as an antidote for acetaminophen poisoning in children, protects renal tubular cells from ifosfamide-induced nephrotoxicity at a clinically relevant concentration. To further validate this observation, an animal model of ifosfamide-induced nephrotoxicity was used to determine the protective effect of NAC. We hypothesized that NAC reduces the ifosfamide induced-nephrotoxicity characterized by Fanconi syndrome (FS).

Methods: Male Wistar albino rats were injected intraperitoneally with saline, ifosfamide (50mg/kg daily for 5 days), NAC (1.2g/kg daily for 6 days), or ifosfamide + NAC (for 6 days). Twenty-four hours after the last injection, rats were euthanized, and serum and urine were collected for biochemical analysis. Liver and kidney tissues were obtained for analysis of glutathione content. Statistical differences were assessed by one-way ANOVA.

Results: NAC markedly reduces the severity of renal dysfunction induced by ifosfamide with a significant ($p<0.05$) decrease in elevations of serum creatinine (57.8+/-2.25 umol/L vs. 45.25+/-2.05 umol/L) and phosphate (4.87+/-0.14 mmol/L vs. 4.24+/-0.25 mmol/L), as well as a reduced elevation of *f*Ò2-microglobulin excretion (25.44+/-3.33 nmol/L vs. 8.83+/-1.30 nmol/L). Moreover, NAC significantly improved the ifosfamide-induced glutathione depletion ($p<0.05$) in the kidney when it was given concurrently with ifosfamide.

Conclusions: These biochemical data demonstrate that NAC reduces the severity of ifosfamide-induced Fanconi syndrome in rats, and suggest a potential therapeutic role for NAC in pediatric patients.

Keywords: *Ifosfamide, nephrotoxicity, Fanconi syndrome*

127

Regulation of hepatic cytochrome P450 in a mouse model of chronic renal failure

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Funding Source: CIHR

Background: We have shown that chronic renal failure (CRF) downregulates cytochrome P450 (CYP450) isoforms in both intestine and liver in the rat. The mechanism remains poorly understood. The purposes of this study were a) to develop a model of CRF in the mouse and b) to study the effect of CRF on liver CYP450 in the mouse.

Methods: Models of CRF were tested and sub-total nephrectomy (Nx 5/6) was selected because of the efficacy and reproducibility to induce CRF. HPLC was used to determine seric and urinary creatinine concentrations. Liver protein expression and mRNA levels of CYP1A1, CYP2C29, CYP3A11 and CYP2E1 were assessed by Western Blot analysis and qPCR, respectively.

Results: Protein expression of CYP3A11 and CYP2C29/37 was decreased in liver microsomes of CRF mice by 50% and 40%, respectively ($p<0.05$). HPLC analysis shows a correlation between creatinine clearance and protein expression of CYP3A11 in CRF mice ($R2 = 0.46$, $p<0.05$). Hepatic mRNA expression of CYP3A11 and CYP2C29 in CRF mice were downregulated by 71% and 80%, respectively ($p< 0.001$).

Conclusions: This study demonstrates that protein expression of liver CYP3A11 and CYP2C29 are downregulated in CRF mice, secondary to reduced gene expression. This will allow the use of knock-out mice to precise the mechanism underlying CRF induced downregulation of CYP450.

Keywords: *Chronic renal failure, cytochrome P450, mouse model*

128 – ENCORE PRESENTATION

Fatty acid ethyl esters and cotinine in meconium are predictors of birth weight in a Uruguay cohort

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Funding Source: CIHR & NSERC

Background: Over 10% of births in the public health system in Uruguay are of low birth weight (LBW) (<2500 g), however minimal information exists on factors affecting LBW in this population. Because LBW predicts morbidity and mortality, characterizing factors affecting LBW will lead to effective public health efforts.

Objective: The aim of this study is to determine if prenatal exposure to alcohol, tobacco, and other illicit drugs are significant predictors of birth weight in a Uruguay cohort.

Methods: Meconium samples (n=900) and infant health data were collected from two public hospitals in Montevideo, Uruguay. Fatty acid ethyl esters (FAEE) were extracted from meconium and analyzed using GC-FID. A sample was considered positive for heavy alcohol exposure if the cumulative concentration of seven FAEEs was ≥ 2 nmol/g. Meconium (n=195) was analyzed for cocaine, benzoylecgonine, amphetamine/MDA, THC, and cotinine by ELISA using positive cutoffs of 80 ng/g, 80 ng/g, 100 ng/g, 50 ng/g, and 25 ng/g respectively. Multiple linear regression was used to determine the association between independent variables and birth weight.

Results: Multiple linear regression determined that birth weight can be predicted by cotinine as a dichotomous variable, FAEE as a continuous variable, infant gender, and lack of prenatal care ($p<0.001$). The significant independent variables accounted for 11.1% of the variability in birth weight. Illicit drug use; maternal age; years of maternal education; and parity were insignificant independent variables.

Conclusions: Prenatal exposure to alcohol and tobacco as measured objectively by meconium analysis are significant predictors of birth weight.

Keywords: *Low birth weight, Uruguay, meconium*

129

Fatty acid ethyl esters in maternal hair: a biomarker for fetal alcohol exposure

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Funding Source: CIHR

Background: Previous studies have shown the FAEE hair test to be highly sensitive/specific in evaluating alcohol exposure in the adult male population; however to date no studies have examined the test's sensitivity/specificity in pregnant women in the context of assessing risk for Fetal Alcohol Spectrum Disorders.

Objective: To evaluate the sensitivity/specificity of the FAEE hair test using maternal hair.

Methods: Maternal hair samples (n=78) from Barcelona, Spain, were tested for FAEE using GC-MS. Sensitivity and specificity were evaluated using 0.2 ng FAEE/mg hair of the maternal hair as a cut-off value for positive test indicating exposure to alcohol.

Results: No mothers reported excessive alcohol use. Nine mothers reported drinking 8-10 g of ethanol in a given day mostly on sporadic occasion, and 3 mothers reported drinking 12-15 g in a given day mostly regularly. Sensitivity and specificity of the maternal FAEE hair test using a 0.2 ng/mg cut-off was 25%, and 91%, respectively, based on reported maternal drinking.

Conclusions: Given the relatively low rate of reported maternal drinking during pregnancy in this cohort, and the known tendency to underreport gestational drinking, we believe the maternal FAEE hair test is remarkably specific for prenatal alcohol exposure even at this low range. The lack of sensitivity in this low range is not surprising and may not be clinically relevant in assessing the risk for Fetal Alcohol Spectrum Disorders. It remains imperative to assess the FAEE hair test in heavier drinking women.

Keywords: *FAEE, fetal alcohol, hair test, FASD*

130

Development and validation of the look-alike labelling and packaging score (LAPSE)

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Funding Source: None

Objectives: Medication errors are an important cause of morbidity and mortality. Modifiable system factors including similarities in packaging and labeling contribute to preventable adverse drug events. We developed and tested a method to systematically and proactively identify look-alike medications, the Look-Alike labelling and Packaging Score (LAPSE).

Methods: LAPSE items and weighting were determined by expert opinion and synthesized using a modified Delphi technique. Initial validation was performed on a group of controlled drugs containing similar pairs. The LAPSE was then evaluated on a second group of drugs readily available in the PICU. Physical characteristics, including features of the container, the label and the drug, were abstracted. The LAPSE was calculated for each medication pair.

Results: The final LAPSE contained 19 items. The maximum score was 19, the minimum score was 0. All controlled drugs (n=13, 156 pairs) and all drugs on the ward-stock medication cart (n=95, 4371 pairs) of a large (36 bed) PICU were studied. 70% of all medications were in liquid form, 64% were intravenous preparations. Text was generally black (47%) or white (16%), with a white label background (63%). Medications were most often in glass containers (64%), as either vials (38%) or ampoules (15%). Known look-alike pairs attained high scores (>16), and the LAPSE discriminated between similar and dissimilar drug pairs. In the second data set, twenty-four (0.54%) drug pairs had high LAPSE scores. Confusion of 12 (50%) of these pairs may result in serious injury or death.

Conclusions: The LAPSE is a feasible and valid method to proactively and systematically identify physically similar drug pairs with an increased risk for serious medication administration errors in the PICU and other hospital environments.

Keywords: *Look-alike medications, medication errors*

131

Human breast milk and formulas differentially modulate OATP1B1 transporter

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Background: Neonatal hyperbilirubinemia is a commonly occurring sequelae of imbalance in bilirubin production, metabolism and excretion. Currently, bilirubin clearance is thought to be mediated via OATP1B1 (hepatic entry), UGT1A1 (glucoronidation) and ABCC2 (biliary excretion). Since breast-fed infants have higher risk of developing neonatal hyperbilirubinemia in comparison to those who are formula-fed, we hypothesized that differences in the composition and amounts of specific constituents in various forms of infant diet would account for altered bilirubin disposition.

Methods: Hydrophobic components from mature human breast milk, cow milk, dairy and soy-based formulas were isolated by solid-phase extraction and reconstituted in DMSO (0.1-5%). Uptake transport of the prototypical OATP1B1 substrate, estradiol 17-beta-glucuronide was determined in HeLa cells transiently expressing OATP1B1.

Results: Diluted fractions of various forms of milks (reconstituted in 0.1% DMSO) did not affect OATP1B1 transport function. However, human breast milk extract reconstituted in 1% DMSO significantly inhibited (~18% control activity) OATP1B1-mediated uptake of estradiol 17- beta-glucuronide relative to extracts derived from soy- and milk-based formula (~67% control activity).

Conclusions: Inhibition of hepatic OATP1B1 byconstituents of human breast milk may be one reason to account for the greater propensity for neonatal jaundice among infants receiving human breast milk relative to soy-based formulas. More detailed studies are needed to more fully delineate the specific constituent(s) responsible for this effect.

Keywords: *Bilirubin, breast milk, OATP1B1*

132

The role of CYP2C9 and VKORC1 polymorphisms combined to CYP2C9 phenotypic assessments to explain intersubject variability in warfarin dose requirements in a hospitalized, heavily medicated patient population

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Funding Source: CIHR

Background: Factors such as *CYP2C9* and *VKORC1* polymorphisms have been used to explain intersubject variability in warfarin pharmacokinetic and effects. Most studies have been performed with patients with multiple exclusion criteria.

Objective: To determine using an innovative combined phenotypic and genotypic approach the relative contribution of *CYP2C9* and *VKORC1* polymorphisms to warfarin dose requirements in a hospitalized, heavily medicated patient population requiring initiation of warfarin therapy.

Methods: Warfarin doses corresponding to INR at day 14 were recorded in 132 patients. Phenotypic measures were determined by the urinary losartan metabolic ratio prior to the first dose of warfarin and by warfarin enantiomer plasma levels measured on day 1. *CYP2C9* and *VKORC1* genotypes were determined by gene chip analyses.

Results: A major determinant of warfarin dose requirement was plasma ratios of warfarin enantiomers (S:R-warfarin) determined at 14 hours after first dose. Patients carrying at least one *CYP2C9*3* allele needed significant lower doses. Patients with two wild-type alleles of *VKORC1 3673, 6484, 6853* and *7566* required significantly higher mean doses than carriers of two variant alleles. In contrast, *VKORC1 9041 G/G* genotype was associated with lower dose requirements. Our results indicated that the best predictors of warfarin requirement were patient's age, BSA, phenotype determined by ratio of warfarin enantiomers (S:R-warfarin) and *VKORC1 9041*. Best model obtained explained up to 51% of intersubject variability in warfarin dose.

Conclusions: *VKORC1* genotype combined to warfarin phenotype are main determinants of warfarin dose requirements in patients receiving polypharmacy (11±4 drugs/day).

Keywords: *Warfarin, pharmacogenetics, genetic polymorphisms, CYP2C9, VKOR clinical trial and multivariate analysis*

CSCP - POSTER PRESENTATIONS
MONDAY MAY 28, 2007

Therapeutics for Vulnerable Populations

133

Paroxetine use in pregnancy: is there an association with congenital cardiovascular defects?

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Background: Paroxetine (Paxil) is an SSRI, used for the treatment of depression, obsessive compulsive disorder, anxiety disorders and premenstrual dysphoria. Until recently, no studies had associated SSRIs as a group with an increased risk for major malformations above the 1% - 3% baseline rate. However, in the past year, several studies noted specifically, an increase risk of cardiovascular defects associated with paroxetine, compared to other antidepressants within its class.

Objective: To determine whether paroxetine increases the risk of cardiovascular defects in infants of women exposed during the first trimester of pregnancy.

Methods: We collected prospectively ascertained cases of infants from Teratogen Information Services throughout the world, exposed to paroxetine in the first trimester of pregnancy and compared them to a non-exposed Motherisk cohort. We also contacted the authors of data base studies that had been published on antidepressants as a class, to determine how many of these women had been exposed to paroxetine and the rates of cardiovascular defects in their infants.

Results: We were able to ascertain the outcomes of (1013) infants from 8 services. The rate of heart defects in the paroxetine group was 0.7% versus 0.7% non-exposed group. The combined rate in the data base studies was 1.5%.

Conclusion: Paroxetine does not appear to be associated with an increase risk for cardiovascular defects following use in pregnancy, as the incidence in more than 3000 infants were well within the population incidence of 0.7% to 1.2%.

Keywords: *Paroxetine, birth defects, pregnancy*

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134

The association of cardiovascular risk factors clustering with the effectiveness of pharmacotherapeutic interventions for global cardiovascular protection in the Canadian population

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Background: The multiplicity of risk factors for atherosclerosis is prevalent among patients with risk for cardiovascular diseases (CVD).

Objective: To investigate the association between multiplicity of cardiovascular risk factors in patients with dyslipidemia or metabolic syndrome and the effectiveness of pharmacotherapeutic interventions for the global cardiovascular risk reduction (hypertension, diabetes, and dyslipidemia) in community-based clinical practice, in four geographic regions across Canada.

Methods: In a cross-sectional study, patients filling a prescription for any anti-hyperlipidemia therapy in selected pharmacies in Ontario, Quebec, British Columbia and Nova Scotia were recruited. Physicians of the participating patients were requested to provide information from the patient's medical record.

Results: 1103 patients participated in the study. The mean (standard deviation) age was 64 (11) years old. Cardiovascular risk factors were identified: LDL hyperlipidemia (97%), hypertension (50%), family history of premature cardiovascular disease (55%) and peripheral vascular disease (14%). High-risk patients, including diabetics (13%) and patients with previous cardiovascular events (39%), comprised 52% of the patient population; 34% were moderate risk and 14% were low risk. On average, each patient encompassed 2.8 risk factors [high-risk (3.7), moderate risk (2.3) and low risk (1.2), $p < 0.05$]. Almost half of high-risk patients (48%) had metabolic syndrome as well as 19% and 7% of moderate and low risk patients, respectively ($p<0.05$). patients' age, gender, duration of disease and BMI were similarly distributed among risk strata. LDL-C goal attainment was observed in 62%, 79% and 96% of patients in high-risk, moderate risk and low risk strata, respectively. Also, complete global cardiovascular risk reduction was achieved in only 21%, 50% and 73% of high-risk, moderate risk and low risk patients, respectively.

Conclusions: Despite success in reducing LDL-C, there are still considerable cardiovascular risks (hypertension and diabetes) that are inadequately managed to obtain global cardiovascular protection in patients with moderate to high risk for cardiovascular events.

Keywords: *Metabolic syndrome, global cardiovascular protection, effectivness*

135

A lesson in history - clinical history predicts acetaminophen toxicity in children

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Background: Acetaminophen is frequently reported as an agent of toxic ingestions - both accidental and non-accidental. We aimed to determine the diagnostic test properties of history in the diagnosis of acetaminophen toxicity in children.

Methods: This is a retrospective chart review in a tertiary pediatric emergency department (ED) in Canada. We included all children that had acetaminophen levels drawn in the ED. The main outcome measures were sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). We included 1989 acetaminophen levels drawn during 1905 unique patient visits.

Results: Of 1886 analyzed tests, 13 children were considered "toxic" and 55 children were considered "possibly toxic". All but 2 had a clear history of ingestion on arrival to the Emergency Department. There was a statistically significant association between a positive history of ingestion and toxicity ($p<.0001$). This association did not change with re-classification of the "possible-toxicity" group. The overall odds ratio for toxicity when a history of overdose was given was 71.9 (95% CI 17.5 – 294.5). If all children with a "possibly toxic" acetaminophen levels were considered "toxic" the Sensitivity, Specificity, PPV and NPV (95% CI) for history was 0.97 (0.90 – 1.0), 0.69 (0.66-0.71), 0.10 (0.08-0.13), 0.998 (0.994 -1.0) respectively.

Conclusions: Unalike in adults, in children a history of ingestion is an excellent predictor for possibly toxic acetaminophen plasma levels. This may result in a significant reduction of number of acetaminophen levels drawn in the ED.

Keywords: *Acetaminophen, toxicity, children*

136

Fetal risks of radiotherapy for cancer in unintended pregnancies: case series

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Background: Physicians faced with a woman who has become unintentionally pregnant during cancer radiotherapy appear inclined to advocate termination of pregnancy for fear of adverse fetal outcome. Our Motherisk clinic is incidentally contacted by these women for advice. The aim of these case series is to describe the risks of fetal exposure to radiotherapy during early, unintended, pregnancy.

Methods: Our Motherisk clinic in Toronto offers teratogenic advice to women and health professionals. Recently, three women contacted us who received radiotherapy for lymphoma in the first trimester of an unintended pregnancy. The risk for adverse fetal outcome in these women was assessed.

Results: Although all women received 40 Gy radiation for lymphoma during the first trimester, estimated fetal radiation exposure varied considerably consequent to differences in radiation site and women's anatomy: <10cGy=negligible risk, 10-20cGy=small risk and >20cGy=moderate/high risk, respectively. The first newborn with <10 cGy exposure appears normal at 7 months of age, the second woman was lost to follow-up. The third woman terminated pregnancy, but not only for the risks associated with the radiotherapy. No woman received abdominal shielding to minimize fetal radiation exposure, as the pregnancies were unknown at the time of therapy. This could have reduced fetal exposure by 50%.

Conclusion: Fetal exposure to radiotherapy for cancer in unintended pregnancy varies largely in the women described. Hence, to advocate termination of pregnancy in all women who become unintentionally pregnant during radiotherapy is not warranted without knowing estimated fetal radiation exposure and its consequent risks.

Keywords: *Pregnancy, fetal outcome, radiotherapy*

137

Emergency department treatment of childhood migraine

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Background: Migraine is a common presentation to Paediatric Emergency Departments, but data on the burden of illness and treatmentstherapies used are scant. In order to assess the current therapeutic practice, in Paediatric Emergency Departments, our objective was to define the current practice of treating therapy for childhood migraine in a Paediatric Emergency Department.

Methods: A retrospective chart review of all patients aged 1 to 18 years presenting to PED at CHWO with a diagnosis of migraine from 2002 to 2005 was conducted. Data was analyzed using SPSS.]

Results: There were 451 children diagnosed with migraine at CHWO between January 2002 and December 2005. Fifty-one percent of these patients were male. The mean age was 11.4 years (SD=4.7). The most common treatments for migraines were ibuprofen (38.8%), normal saline (36.3%), acetaminophen (15.3%), and either ketorolac, prochloroperazine, or Tylenol 3™ (9.6%). A single dose was most apt to be sufficient with ibuprofen (91.6%), and least likely with normal saline (58.8%), $p<0.0001$. The mean length of stay in the ED was shortest for children receiving ibuprofen (2.0 hrs, SD=1.5), and longest for children receiving normal saline (4.6 hrs, SD=1.7).

Conclusions: In contrast to adult migraine, childhood migraine is most commonly treated with conventional NSAIDs or normal saline. Tryptans were not used. Average length of stay was relatively brief (hrs2.6 hrs, SD=1.9) and) and therapy was not commonly aggressive. This supports the concept that adult and childhood migraine are fundamentally different and that this should be considered when developing therapeutic guidelines for childhood migraine. As well, it suggests that the diagnosis of childhood migraine includes a much broader group of patients then adult migraine.

Keywords: *Migraines, children, therapy*

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138

Rural women and pharmaceutical use: issues, challenges and solutions

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Background: Due to transportation, health care provider issues and cultural attitudes and behaviors, women living in rural settings may be at risk of using drugs inappropriately or not be able to obtain medications and drug-related information. Limited information exists regarding the use of pharmaceuticals by rural women. The objectives of this study were to explore: i) pharmaceuticals that rural women are using/not using and why they are using/not using them, ii) barriers and facilitators to rural women's use of pharmaceuticals, and iii) rural women's needs and solutions regarding pharmaceutical use.
Methods: In-depth face-to-face interviews of 20 rural women, aged 17-88 years, were conducted using a feminist qualitative research methodology that respects women as legitimate knowers.
Results: Key study findings relate to prevalent use of herbal medications, prescription drugs, and illicit drugs, and to rural factors that affect drug use such as cultural expectations regarding women, lack of privacy and anonymity, and lack of access to appropriate health care providers. Suggestions for ways to improve rural women's access to pharmaceuticals and knowledgeable drug decision-making were also revealed.
Conclusions: These results suggest that rural women experience significant barriers and some facilitators to accessing appropriate pharmaceutical knowledge and drugs, and that rural women use various strategies to facilitate what they deem to be appropriate pharmaceutical knowledge and treatment. As a result, this study provides important information about women in rural populations and their place within the circle of pharmaceutical therapeutics.
Keywords: *Rural women, pharmaceuticals, qualitative research*

139

Association between the C3435T polymorphism in the human multidrug resistance gene (*MDR1*) with acute lymphoblastic leukemia

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Introduction: The P-glycoprotein (P-gp), a product of multidrug resistant gene 1 (*MDR1*) is a membrane efflux pump involved in protection against xenobiotics and is associated with multidrug resistance in cancer. The single nucleotide polymorphism C3435 of the *MDR1* gene has been found to be associated with altered tissue expression and function of P-gp. To determine whether there is association between genotypes of drug transporter gene *MDR1* and the occurrence of acute lymphoblastic leukemia (ALL) this study was undertaken.
Methods: To evaluate whether C3435T *MDR1* polymorphism is associated with the occurrence of ALL, 130 patients with ALL and 139 healthy individuals of Iranian origin (Khorasan Province) were studied by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. The patients and healthy controls were divided into three genotype groups; i.e., with T/T allele, C/C and C/T.
Results: We found a relatively higher frequency of the T/T genotype in ALL patients compared to healthy subjects (P=0.026), while the heterozygous TC genotype was associated with reduced occurrence of ALL (P = 0.017).
Conclusions: Our results provide evidence that C3435T *MDR1* polymorphism may be involved in the susceptibility to ALL. Carriers of the TT genotype are more at risk of developing ALL.
Keywords: *ALL, MDR1, polymorphism*

140

Comparing the incidence of letrozole-induced congenital malformations to age- and disease-matched controls

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Background: Infertility can often be caused by ovulatory disorders. Effective treatment options usually include drugs such as clomiphene citrate (CC) or letrozole. Recently, an abstract was published claiming that the use of letrozole to induce ovulation causes increased malformations in offspring. The present controlled study was conducted to determine if letrozole increases the incidence of congenital malformations, and affects other pregnancy outcomes.

Objective: The primary objective was to compare the malformations rates in the offspring of women who conceived using letrozole to women who did not require fertility treatment (age-matched controls), and to women who conceived using CC (disease-matched controls). The secondary objective was to compare other pregnancy outcomes (birthweight and gestational age at birth)

Methods: Data was collected from women who successfully used either letrozole (n=94) or CC (n=242) to induce ovulation. Each woman in the letrozole group was age-matched to a control obtained from the Motherisk database not suffering from an ovulation disorder. Data was analyzed, and differences were considered to be statistically significant when $p<0.05$.

Results: There was no increase in the number of offspring born with malformations when the letrozole group (0%) was compared to disease-matched (2.6%) and age-matched controls (3.2%). There was decreased birthweight in the CC group (3.240 kg) as compared to Motherisk controls (3.320kg). Additionally, birthweight adjusted for gestational age in the CC group (centile=37.2), but not the letrozole group (centile=54.8), was significantly decreased as compared to control (centile=61.7), suggesting that CC and not letrozole, are associated with intrauterine growth restriction.

Conclusions: Letrozole does not appear to increase the risk of congenital malformations, and does not affect intrauterine growth restriction; however, CC appears to cause intrauterine growth restriction.

Keywords: *Letrozole, congenital malformations, clomiphene citrate, ovulatory disorder*

141

Providing health care professionals with evidence-based answers: an online question and answer cancer in pregnancy forum

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Background: Cancer is the second most common cause of death in women of reproductive age, complicating between 0.02 and 0.1% of all pregnancies. This incidence will likely rise as women are delaying pregnancy until later in life when the risk of developing cancer increases. The Motherisk program supports an online forum for health care professionals (HCPs) who require information about treating women with cancer or women who have recovered from cancer and need counseling about risks related to breastfeeding or future conception.

Objective: The main objectives of this forum are providing HCPs with evidence-based information so they can help women make informed decisions about the effects of a cancer or cancer treatment on fertility, conception, or breastfeeding; and promoting discussion among HCPs to increase knowledge of cancer in pregnancy.

Methods: HCPs submit questions to the online forum, such as conception after chemotherapy or pregnancy exacerbating a previous cancer. This is researched and answered by members of the Consortium of Cancer in Pregnancy Evidence (CCoPE) and posted so other HCPs can access it. We typically answer 75 questions yearly from various HCPs.

Results: This forum is a tool for HCPs, giving them access to expert guidance and providing a place for them to share their clinical experiences while at the same time promoting more knowledge and awareness in this area.

Conclusion: This forum provides a vital service for HCPs dealing with women with cancer that are concerned about the risks involved to a fetus or a future conception with cancer treatment.

Keywords: *Cancer in pregnancy, online forum*

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142

Improving the tolerability of prenatal multivitamins for pregnant women: reduced tablet size

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Background: Many pregnant women struggle with taking prenatal multivitamins because they can aggravate gastrointestinal symptoms (i.e. nausea) due to iron dose or large tablet. PregVit® is a 2-tablet prenatal multivitamin with low iron dose and small tablet size. Our objective was to document compliance and adverse events between pregnant women who supplemented with either PregVit® or Orifer F®, a standard prenatal multivitamin.

Methods: Pregnant women who called Motherisk and did not start or discontinued any multivitamin due to adverse events were included in this prospective, 2-arm study. Upon oral consent, women were enrolled and randomized to commence supplementing with either PregVit® or Orifer F®. Monthly telephone interviews documented pill intake and adverse events. Analysis involved chi-square tests and Peto-Prentice survival curve.

Preliminary Results: Since October 2004, 91 women were randomized to PregVit® and 73 were randomized to Orifer F®. No statistical difference was detected in the proportion of subjects who started taking either multivitamin. Among those who started, no difference was detected in the proportion of subjects who were at least 80% compliant with either multivitamin. Survival curve analysis showed no statistical difference in the compliance pattern; the curve for PregVit® suggested that subjects were compliant longer in time.

Conclusion: Preliminary results suggested that low iron dose did not improve compliance. Reported adverse events are pending analysis. Despite PregVit® being taken as 2 daily tablets, compliance was not different compared to Orifer F® - a small tablet taken once a day, suggesting that small tablet size can improve multivitamin tolerability.

Keywords: *Multivitamin, tolerability, PregVit*

143

Beneficial effects of ischemic preconditioning are attenuated with age in rat ventricular myocytes

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Background: Cardioprotective effects of ischemic preconditioning (IPC) are thought to decrease with age. We compared the impact of age on contraction, Ca2+ homeostasis and cell survival in cardiac myocytes exposed to IPC prior to prolonged ischemia and reperfusion.

Methods: Myocytes from young adult (3 mos) and aged (24 mos) male Fischer 344 rats were field stimulated at 4 Hz (37°C). Contraction and intracellular Ca2+ were measured with an edge detector and fura 2. Cells were preconditioned with 5 mins of simulated ischemia prior to prolonged ischemia (30 mins) and were then reperfused with Tyrode's solution.

Results: IPC abolished post-ischemic contractile dysfunction and increased Ca2+ transient amplitudes throughout reperfusion in young adult cells. In contrast, IPC did not improve contractile function and Ca2+ transients until late reperfusion in aged cells. Further, IPC improved cell survival in reperfusion in young adult but not aged myocytes. Despite these protective effects, IPC had little effect on the brief rise in diastolic Ca2+ during ischemia in young adult cells, although IPC attenuated the marked increase in diastolic Ca2+ in ischemia in aged cells.

Conclusions: IPC improves contractile function and cell survival in young adult myocytes, but is much less effective in aged myocytes. These protective effects are not mediated by a decrease in diastolic Ca2+ in ischemia, at least in young adult myocytes. This decrease in effectiveness of IPC at the level of the myocyte may increase sensitivity of aging heart to ischemic heart disease.

Keywords: *Aging, ischemia/reperfusion, intracellular calcium*

144

Susceptibility to ischemia-reperfusion injury is similar in ventricular myocytes from male and female rats

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Background: Studies have shown that male rat hearts are more sensitive to ischemia-reperfusion (I/R) injury than female hearts. As elevated intracellular calcium has been implicated in I/R injury, these differences may reflect changes in calcium homeostasis at the level of the cardiomyocyte. The objective of this study was to investigate sex differences in contraction, calcium homeostasis and cell viability in ventricular myocytes exposed to I/R.

Methods: Male and female rat (3 mos) myocytes were exposed to simulated ischemia (hypoxia, hyperkalemia, hypercapnia acidosis, 0 glucose, lactate) for 20 min (370C) and reperfused with Tyrode's solution for 30 min. Contractions and calcium transients (Fura-2) were simultaneously recorded in field stimulated cells (4 Hz). Cell viabilty was measured with Trypan Blue.

Results: Contraction amplitudes decreased during ischemia in male and female cells. However, contractions recovered during reperfusion in female myocytes, but remained markedly depressed in male myocytes throughout reperfusion. In contrast, amplitudes of calcium transients were similar in male and female myocytes throughout I/R. Furthermore, the increase in diastolic calcium caused by exposure to ischemia was similar in cells from male and female rats. There was no difference in cell viability throughout I/R between male and female myocytes. Thus, although cell viability following I/R injury was similar in male and female myocytes, myocytes from male rats showed less recovery of contractile function in reperfusion compared to female cells.

Conclusions: The sex differences in recovery of contractile function in reperfusion are not due to differences in intracellular calcium homeostasis during I/R.

Keywords: *Ischemia-reperfusion, cardiomyocyte, calcium homeostasis*

145

Adenosine preconditioning attenuates ischemia and reperfusion injury and improves cell survival in young adult but not aged rat cardiomyocytes

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Background: Adenosine preconditioning is thought to be compromised with age. However, whether this is due to a decrease in the ability of adenosine to precondition individual cardiomyocytes has not been investigated. This study determined whether adenosine pre-treatment could improve contractile function and cell survival in young adult and aged rat ventricular myocytes exposed to ischemia and reperfusion.

Methods: Myocytes from young adult (3 mos) and aged (24 mos) male Fischer 344 rats were field stimulated at 4 Hz (37°C). Contraction and cell survival were measured with an edge detector and Trypan blue exclusion. Cells were pre-treated with adenosine (50 µM) for 5 min prior to 30 min of simulated ischemia (hypoxia, acidosis, hyperkalemia, hypercapnia, lactate, no glucose) and cells were then reperfused with Tyrode's solution.

Results: Adenosine pre-treatment abolished post-ichemic contractile depression (called stunning) during reperfusion in young adult myocytes. In contrast, adenosine did not prevent stunning in aged myocytes. Furthermore, adenosine pre-treatment improved cell survival in young adult myocytes but not in aged myocytes.

Conclusions: These results show that adenosine preconditioning improves post-ischemic contractile function and cell survival in young adult myocytes, but not in aged myocytes. These results suggest that a decrease in the efficacy of adenosine preconditioning at the level of the cardiac myocyte may contribute to the increased sensitivity of the aging heart to ischemic heart disease.

Keywords: *Adenosine, aging, cardiomyocyte*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

146

Folate fortification and supplementation – are we there yet?

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Background: Folic acid supplementation and fortification decreased significantly the incidence of Neural Tube Defects (NTD) however; the effect has been less than projected. Since it is eight years into folate fortification in Canada we aimed at reviewing the distribution of RBC folic acid levels in women of child bearing age, in order to assess the percentage of women who are still at risk for NTD.

Methods: Laboratory data on RBC folic acid were available to us for the following years: 1995, 1997, 1998, 2000, 2002 and 2004 through 2006. The data included age, gender, RBC folic acid, serum folate, hemoglobin, mean cell volume, B12, pregnancy test (βHCG) and ferritin. As women of child bearing age we used 14 to 45 year old who were also non anemic and normocytic. For each data set we calculated RBC folic acid mean, median, percent of population below 900nmol/L the accepted protection level for NTD and percent of population below 700nmol/L. The same calculation was performed on a sub-set of women who had positive pregnancy test.

Results: In 2006 about 40% of the women of child bearing age and 36% of women who were also pregnant had RBC folic acid levels below 900nmol/L, rendering them sub-optimally protected for NTD.

Conclusion: The goal of optimal prevention of NTD has not yet been achieved, and there are considerable proportions of pregnant women at risk of having a baby with NTD. An urgent action in increasing awareness, education, fortification, and supplementation needs to be undertaken.

Keywords: *Folic acid, fortification, neutral tube defect*

147

Effects of diphenhydramine and domperidone on human milk production: differences revealed by a medication error

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Funding Source: None

Background: A 28-year-old woman with chorioamnionitis was treated with ampicillin, metronidazole and a hydromorphone infusion following a successful Caesarean delivery. Shortly after delivery a rash on her lower limbs began. On day 1 post delivery the hydromorphone infusion was discontinued. By day 3 post delivery an extremely itchy, erythematous, raised, macular, papular rash covered most of her body. She was able to speak well and able to swallow without difficulty. Seven doses of parenteral diphenhydramine were administered on days 3 and 4 post delivery. She continued to receive antibiotics until day 5 post delivery.

Methods: Her milk production rapidly increased to a maximum of 385 mL / day by day 5, then fell steadily to a low of 76 mL on day 13. A serum prolactin at this time was 9 mcg/L. On day 13 domperidone 10 mg po tid was begun.

Results: Milk production immediately began to increase. By day 17 the 24 hour volume was 545 mL ; serum prolactin was 112 mcg/L. The daily milk production was greater than 1000 mL by day 33. Subsequent investigation revealed a documented history of an allergic reaction (rash) to morphine.

Conclusion: This case illustrates the effect of a histamine (H1) antagonist on serum prolactin and subsequent decrease in milk production in addition to the failure of health professionals to detect a documented medication allergy.

Keywords: *Domperidone, lactation, drug interaction*

148

Morphine and acute chest syndrome in children with sickle cell disease: a case-crossover study

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Background: Recurrent painful vaso-occlusive crises (VOC) are a hallmark of Sickle Cell Disease (SCD), and narcotic analgesics are a common element of therapy. However, narcotic agents have been suggested to contribute to the development of acute chest syndrome (ACS). This may lead to under-treatment of pain associated with VOC. We explore the association between intravenous morphine administration and the development of ACS in children with SCD who present with VOC.
Methods: Using a case-crossover design, we studied all children with SCD who were treated with intravenous morphine for VOC and subsequently developed ACS at a tertiary pediatric hospital from 2000 to 2006. For each child, we identified a comparison admission for VOC, during which ACS did not develop, so that each child could serve as his/her own control for the analysis. Cumulative dose of morphine administered from initiation of infusion to development of ACS during the index admission, compared to the cumulative amount of morphine administered during the same time interval during the reference admission.
Results: 17 children with SCD were included. The mean cumulative morphine dose until development of ACS was 1.24 ± 0.60 mg/kg during the index admissions, compared with 1.44 ± 0.84 mg/kg during the reference admissions (p = 0.21).
Conclusions: Among children with SCD hospitalized for VOC, the administration of morphine was not associated with development of ACS. These data do not support withholding narcotic analgesics in children with painful crises.
Keywords: *Sickle cell disease, vaso-occlusive crisis, acute chest syndrome*

149

The effect of MDR1 polymorphism C3435T on the response to anti-epileptic drugs: a meta-analysis

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Background: One third of patients with epilepsy suffer from recurrent seizures despite appropriate antiepileptic therapy. Reasons for therapeutic failure in some patients are unclear. It has been proposed that antiepileptic drugs may not reach the biophase due to active efflux from the brain by MDR1. The ABCB1 C3435T polymorphism has been suggested to decrease the expression of MDR1. Individuals with the 3435TT genotype may have reduced MDR1 activity, theoretically leading to higher CNS concentrations of antiepileptic drugs, and enhanced therapeutic response. One study reported higher prevalence of the ABCB1 3435CC polymorphism in drug resistant epilepsy. However, these findings could not be replicated. We have conducted a meta-analysis of all published studies to clarify this issue
Methods: MEDLINE and EMBASE were searched for studies comparing patients with epilepsy responsive and refractory to treatment that underwent genotyping for ABCB1 C3435T polymorphism. Data was analyzed by the Mantel-Haenszel method, with random effects modelling. Results are expressed as Odds ratios (OR). Studies were tested for heterogeneity using chi-square.
Results: Eight studies were identified as relevant, all case-control studies. Even though a small trend could be observed towards a higher prevalence of the ABCB1 3435CC genotype in patients resistant to antiepileptic treatment, this difference was not statistically significant (OR 1.67, 95% CI 0.90 – 3.11; p=0.1). Studies included in the metaanalysis were heterogeneous (chi square, p<0.001; I square = 81.5%).
Conclusions: We did not find a significant difference in prevalence of the ABCB1 3435CC genotype among patients with drug resistant and drug responsive epilepsy.
Keywords: *MDR1 polymorphisms, epilepsy, metaanalysis*

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150

Monoclonal antibodies for children with steroid-resistant graft-versus-host disease

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Funding Source: ST is supported by a Research Training Grant, The Hospital for Sick Children
Background: Acute graft-versus-host disease (aGVHD) carries a high risk of mortality in hematopoietic stem cell transplantation (HSCT) patients. The prognosis is poor if aGVHD does not respond to corticosteroid treatment. Recently, monoclonal antibodies (MAbs) have shown promising results in the treatment of corticosteroid-resistant aGVHD in adults.
Methods: We evaluated the efficacy of MAbs in children diagnosed with corticosteroid-resistant aGVHD at The Hospital for Sick Children, Toronto, from 2002 to 2006. Complete response (CR) was defined as full recovery; partial response (PR) was defined as improvement of aGVHD symptoms in at least one organ.
Results: Eighteen children with aGVHD were treated with MAbs; 13 of them had aGVHD grade 3 or 4. The organs involved were gut (n=5), skin (n=4), liver (n=2) and multi-organ involvement (n=7). Fourteen children were given daclizumab; one was treated with infliximab and 3 with their combination. Sixteen children received a full course of MAbs for aGVHD; one child died after the first dose and one child developed arthritis following daclizumab. Ten of the 16 children who completed treatment (62%) responded; 5 had CR and 5 had PR. Three children developed fatal fungal infection and one had fatal adenovirus infection during or shortly after MAbs treatment. Ten children died: 9 due to Transplant Related Mortality and one due to relapse. Median follow up in the remaining 8 patients was 32 months.
Conclusions: MAbs were effective in the treatment of children with corticosteroid-resistant aGVHD, especially in patients with gut involvement. The incidence of infection, mainly fungal, was high.
Keywords: *Monoclonal antibodies, children, graft-versus-host disease*

151

Population pharmacokinetics of doxorubicin in infants and children with malignant diseases: any clue to identify children at risk of cardiac toxicity?

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Funding Source: None
Background: Doxorubicin is an anthracycline glycoside, commonly used in the treatment of pediatric malignancies, which has significant cardiac toxicity.
Methods: We performed a population pharmacokinetic (PK) analysis of doxorubicin, in eleven children receiving intravenous doxorubicin. Blood samples were drawn before the initiation of the doxorubicin infusion and at 0, 4, 18, 36 and 48 hours after the end of the infusion. Plasma drug concentrations of doxorubicin were measured by solid-phase extraction and high performance liquid chromatography (HPLC) with fluorescent detection. Data were analyzed by the compartmental module of SAAM II.
Results: Of 11 patients, plasma doxorubicin concentration-time courses of 9 children best fitted a 2-compartment intravenous PK model and were included in the population PK analysis. The resulting population parameters were k12 0.78 ± 0.46 1/h, k21 0.17 ± 0.088 1/h, kel 0.22 ± 0.10 1/h, Vd 9.6 ± 6.8 ml/kg, Cl 1,297.5 ± 893.1 ml/kg/h, and half-life of 7.7 ± 11.3 h (ranging from 2.1 to 39.8 h).
Conclusions: A 2-compartment PK model was successfully used to describe the plasma levels of doxorubicin in pediatric cancer patients.
Keywords: *Doxorubicin, population pharmacokinetics, children*

152

Mesna for the treatment of hyperhomocysteinemia in hemodialysis patients

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Background: Increased plasma total homocysteine (tHcy) is a graded, independent risk factor for the development of atherosclerosis and thrombosis. Over 90% of patients with end-stage renal disease (ESRD) have hyperhomocysteinemia (plasma tHcy >15 umol/L). Current therapies of vitamin supplementation and hemodialysis fail to normalize plasma homocysteine levels. We have shown that mesna, a thiol containing drug, can exchange with albumin-bound Hcy thereby enhancing dialytic clearance of plasma tHcy. However, low doses of mesna (2.5 & 5 mg/kg) failed to normalize plasma tHcy. We hypothesized that 12 mg/kg intravenous mesna administered pre-dialysis for one week would cause a significant decrease in plasma Hcy compared to placebo.

Methods: This pilot study was a placebo-controlled, double-blind, randomized trial in eight hemodialysis patients with ESRD. Patients were given either an IV bolus of 12 mg/kg mesna or placebo thrice weekly pre-dialysis during the first week of study and then crossed-over to receive the alternate treatment following a washout period of one week. Plasma tHcy concentrations of pre-dialysis samples drawn following mesna and placebo arms were compared by paired t-test.

Results: Following one week of 12 mg/kg IV mesna, pre-dialysis plasma tHcy was significantly decreased by 12.8+/-7.8% compared to placebo (23.4+/-8.0 umol/L vs. 20.5+/-7.6 umol/L, P = 0.0044).

Conclusions: Thrice weekly 12 mg/kg intravenous mesna causes a significant decrease in pre-dialysis plasma tHcy after one week of treatment. However, plasma tHcy failed to reach normal levels. Mesna's ability to further lower plasma tHcy over a longer treatment period is currently being investigated.
Keywords: *Homocysteine, end-stage renal disease, mesna*

153

Timolol concentrations in breast milk of a woman treated for glaucoma: calculation of neonatal exposure

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Background: There is very little information on the excretion of topical anti-glaucoma drugs in breast milk. Substantial data describing serious systemic effects with the use of ocular medication exists. The Ivey Consortium of Drugs in Breast Milk co-ordinates measurements of drugs in milk by international experts who have such tests available. We present a 32 year old lactating woman with open-angle glaucoma who received timolol maleate twice daily to her right eye for six months. Four breast milk samples were collected over a span of one week for analysis.

Methods: Timolol maleate breast milk levels were measured using liquid chromatography tandem mass spectrometry (LC-MS-MS) equipped with an electrospray interface (ESI.). The assay had a 91% recovery and an optimal response over a range of 0.4 ng/ml to 50.0 ng/ml

Results: Timolol concentrations in the four breast milk samples were at or near the limit of detection. The mean timolol level was 0.12 ng/ml; range 0–0.37 ng/ml. Maximum infant dose of timolol through breast milk was 123 ng/kg/day. The weight-adjusted oral maternal dose of timolol was 1 mg/kg/day. Therefore the maximum theoretical relative infant dose after adjusting for maternal weight would be 0.12 %, which is clinically insignificant.

Conclusion: Our study suggests that timolol breast milk levels found in our patient were too low to be of concern to a breastfed infant. It would be prudent though to monitor the suckling infant for signs of beta blockade.
Keywords: *Breast milk, timolol*

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154

Sulphamethoxazole induced cellular toxicity in HIV-1 Tat expressing cell lines is not dependent on the full-length protein

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Background: HIV patients have a high incidence of adverse drug reactions (ADRs) to drugs including antiretrovirals and antimicrobials such as AZT and sulphamethoxazole (SMX) respectively. In combination with trimethoprim, SMX is the first line therapy for Pneumocystis pneumonia, a common AIDS-defining disease. Our previous studies have implicated the HIV regulatory protein Tat together with SMX-HA (sulphamethoxazole-hydroxylamine), a reactive metabolite of sulphamethoxazole, in the pathogenesis of these adverse drug reactions. The objective of this analysis is to map the region of Tat responsible for these ADRs.

Methods: A model was created to differentially express full length Tat (Tat101) and Tat deletion mutants (Tat86, Tat48) that had been fused to green fluorescent protein. These expression cassettes were subsequently introduced into an inducible vector where their expression can be differentially expressed and directly monitored. Next, the recombinant vectors were used to establish stably transfected Jurkat T cell lines that were characterized by flow cytometry and western blots. These cell lines were then incubated with SMX or SMX-HA followed by an assessment of cellular toxicity by the MTT assay of cell viability.

Results: Differential induction of TatGFP expression was both dose and time dependent. Concentration-dependent toxicity was demonstrated with SMX-HA ($p<0.01$). There was no significant difference in toxicity in the cell lines tested (Tat101, Tat86 and Tat48).

Conclusion: Tat associated toxicity appears to be present with expression of a minimally active Tat construct. This suggests the mechanism(s) of toxicity are related to very basic Tat functions.

Keywords: *Adverse drug reactions, HIV, sulphamethaxazole*

155

Evolving patterns in management of HIV sero-positive pregnant women

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Background: About 18 million women of child bearing potential are HIV positive today. An increasingly large number of pregnant women are being put on antiretroviral (ARV) therapy, with a view to maintaining the health of the mother and curtailing vertical transmission of the virus to the child. The current Canadian guidelines recommend the use of combinational therapy containing at least 3 different ARVs. This study looks at the prescribing trends of physicians handling HIV positive pregnancies over a span of about 7 years in order to shed light on the evolving prescribing patterns with regards to sero-positive pregnant women.

Methods: The data regarding ARV use in HIV positive mothers was collected by carrying out a retrospective longitudinal and cross-sectional patient chart review. Charts were obtained from the Motherisk program at the HIV clinic, The Hospital for Sick Children. The data ranges from Jan 1998 to May 2005.

Results: Trends in the prescribing pattern seem to shadow the guidelines. A continuous change in the prescription practices can be seen over this period with increasingly more women being put on combinational therapy containing NRTIs with NNRTIs and/or PIs. Moreover an increasing number of women take ARV medication throughout the course of pregnancy.

Conclusions: The data suggests that prescribing patterns in Ontario, while dynamic, are in line with the issued guidelines. While there is room for improvement, the strategy seems to be working, with only one case of vertical transmission seen in all the cases available.

Keywords: *Antiretroviral drug usage, pregnancy, patient chart review*

156

The placental ABC transporter family: a role in fetal-maternal drug transfer

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Background: ABC- transporters such as P-glycoprotein (P-GP), breast Cancer resistant protein (BCRP) and the multi drug resistance proteins (MRP 1, 2 and 3) are expressed in human placenta and may be involved in the transport of drugs from the fetus to the mother. Glyburide, a drug used to treat diabetes, has been shown, to be actively pumped out of the fetal and into maternal circulation. Furthermore, cellular uptake studies in over-expressing cell lines have shown that glyburide is likely transported by BCRP and MRP3.

Objective: To determine which placental ABC efflux transporter(s) are involved in the active transport of glyburide.

Methods: The transport of glyburide in the presence of MRP inhibitor indomethacin was investigated in the dual perfused human placenta. Furthermore, the transport of 3H-glyburide was measured in the presence and absence of specific inhibitors for P-GP, MRP1, 2, 3 and BCRP, across the placental membranes, by measuring uptake and efflux in purified placental membrane vesicles.

Results: Placental perfusion data has shown no significant difference in the rate of transfer of glyburide in the presence or absence of inhibitor. Preliminary vesicular uptake studies indicate that glyburide is possibly transported by placental BCRP and not MRP1, 2, or 3. RT-PCR indicates a relatively low level of MRP 1, 2 and 3 in human placenta.

Conclusions: Glyburide's active transport from the placenta is mediated by the interplay of transport and inhibition of placental ABC transporters. Glyburide is poised to be a likely model drug for future drugs designed for use in pregnancy.

Keywords: *Placenta, ABC transporters, uptake*

157

Effectiveness of trastuzumab (Herceptin®) in stage IV breast cancer in Ontarian women: a comparison to clinical trial outcome

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Funding Source: Brogan Inc.

Background: Trastuzumab, a humanized monoclonal antibody for HER2-positive breast cancer, achieves better response rates and increases in median survival in stage 4 disease. To date, no published reports have reported actual effectiveness.

Objective: To determine if Trastuzumab in combination with chemotherapy is associated with rates of clinical effectiveness in clinical practice comparable to rates in clinical trial.

Methods: A cohort of Trastuzumab patients was selected from 7 community hospital corporations in Ontario from January 2005 to December 2006 (provided by Brogan Inc MedMap database). Only patients receiving combinations of Docetaxel, Paclitaxel or Vinorelbine with Trastuzumab were included for analysis. Adjuvant patients, recognized as AC-Taxol-Trastuzumab, or AC-Taxotere-Trastuzumab or Trastuzumab alone were excluded from the analysis. Outcomes of measure included overall patient response rate (continued treatment after 20 weeks), duration of response (in months) and overall duration of therapy (in months). Assuming discontinuation for non-response or progression, we measured duration and response rates.

Results: 220 women with metastatic breast cancer who received Trastuzumab treatment were included. Preliminary analysis of the cohort indicates an overall response rate of 70% (vs. 50%), an average duration of use in responders of 10.4 months (vs. 9.1 months in RCT) and an overall duration of use in all recipients of 9.0 months (vs. 7.4 months in RCT).

Conclusions: The apparent effectiveness of Trastuzumab, when used in combination with Docetaxel, Paclitaxel, or Vinorelbine, is associated with improved clinical outcomes for HER2 positive women in stage 4 breast cancer in Ontario.

Keywords: *Trastuzumab, stage 4 breast cancer, survival*

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158

Regulation of brain xenobiotic transporters in a rat model of chronic renal failure

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Funding Source: CIHR

Background: We have proven that chronic renal failure (CRF) is responsible for a downregulation of liver and intestine cytochrome P450 (CYP450) in the rat. We have also shown that intestinal drug transporters, such as P-glycoprotein (Pgp) and multi-drug-resistance-related protein (MRP2), are decreased in CRF. The present study aimed to determine the effect of CRF on the expression of drug efflux transporters (Pgp and MRP2) in the brain of CRF rats.
Methods: The entire brain of CRF rats (induced by 5/6th nephrectomy) and control rats (Sham laparotomy) was dissected into 4 parts (cortex, cerebellum, hippocampus, and rest of brain parenchyma). Protein and mRNA expression of Pgp and MRP2 were assessed by Western Blot assay and Real Time PCR, respectively.
Results: In CRF rats, mRNA levels of Pgp and MRP2 were decreased significantly by at least 40% and 50% ($p < 0.05$) respectively in the cerebellum and brain parenchyma. The mRNA levels in other structures remained unchanged. Moreover, a significant 45% decrease ($p < 0.05$) in protein expression of Pgp was observed in cortex and brain parenchyma.
Conclusions: CRF is associated with a decrease in some major drug transporters, which could explain an increase in bioavailability of drugs in the brain.
Keywords: *Chronic renal failure, brain transporters, drug metabolism*

159

Does central nervous system inflammation alter drug handling in adult critically ill patients?

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Background: Following subarachnoid hemorrhage or head trauma, an inflammatory response ensues within the central nervous system (CNS). In this setting, morphine is commonly employed for analgesia and sedation. In healthy patients, morphine undergoes hepatic glucuronidation to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is a ì-opioid receptor agonist more potent than morphine whereas M3G has been shown to be a CNS irritant. In animals, morphine, M3G, and M6G are largely excluded from the brain by P-glycoprotein. Inflammatory responses in the CNS have been shown in vivo to decrease P-glycoprotein concentration and functionality. Our working hypothesis is that the CNS irritant M3G permeates the brain in increased amounts because Pgp in the blood brain barrier (BBB) is diminished during the central inflammatory response.
Methods: 20 patients with subarachnoid hemorrhage or closed head injury that were admitted to the intensive care unit and fitted with cerebrospinal fluid (CSF) drainage catheters and peripheral intravenous (IV) lines were administered intermittent IV boli or continuous infusions of morphine. Blood and CSF samples were collected at multiple time points between time zero and 96 hours. Morphine, M3G, M6G, IL-6, and albumin were then measured in both serum and CSF.
Results: Elevated levels of CSF IL-6 were present, indicating the presence of CNS inflammation. A similar increase in serum IL-6 levels was not observed, indicating inflammation restricted to the CNS. Levels of CSF M3G and M6G were above those in plasma, indicating disruption of the biochemical BBB.
Conclusions: The preliminary observations suggest that our hypothesis may have merit. We are in the process of further analysis to determine if this is a true observation.
Keywords: *Drug transport, critically ill patients, inflammation*

160

Prenatal alcohol and parental psychopathology predict childhood behaviours: preliminary results

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Objective: To identify behavioural patterns of children with psychiatric disorders exposed to in-utero substance/alcohol or parental psychopathology.

Methods: Retrospective cohort study of children aged 6 to 15 assessed with the Child Behaviour Checklist. First comparison: Children exposed to alcohol and other drugs in utero (n=25) versus not exposed to teratogens (n=46). Second comparison: Children of parents with a psychiatric disorder (n=37) versus without one (n=34).

Results: First comparison: Children exposed to alcohol/substances scored significantly lower on school competency than unexposed children (p=0.02) due to the fact that they were more likely to attended special classes (p=0.04) or repeat a grade (p=0.01). Exposed children also had higher "disobedience in school" (p=0.03) and "vandalism" (p=0.03) scores. A regression analysis revealed that gender predicted "special classes" and "disobedience in school". Alcohol/substance use predicted "vandalism" and "repeated grades". Second comparison: Children with parental psychopathology scored higher in the Anxious/Depressed (p=0.04), Social Problems (p=0.004) and Attention Problems (p=0.04) subscales. Within these subscales, items which were significantly different between groups were "nervous" (p=0.002), "self conscious" (p=0.02), "worthless" (p=0.04), "lonely" (p=0.005), and "difficulty concentrating" (p=0.02). Regression analysis revealed that parental psychopathology predicted of all 5 items. Age and gender also predicted "difficulty concentrating". In summary, parental psychopathology, but not substance use in pregnancy, was a significant predictor of child attention, anxiety/depression and social problems. However, school competency scores were predicted by maternal alcohol/substance use in pregnancy.

Conclusion: Both parental psychiatric history and prenatal alcohol exposure are predictors of child behaviour.

Keywords: *Child behavior checklist, prenatal alcohol, child mental health*

161

Fatty acid ethyl esters and cotinine in meconium are predictors of birth weight in a Uruguay cohort

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Background: Over 10% of births in the public health system in Uruguay are of low birth weight (LBW) (<2500g), however minimal information exists on factors affecting LBW in this population. Because LBW predicts morbidity and mortality, characterizing factors affecting LBW will lead to effective public health efforts. The aim of this study is to determine if prenatal exposure to alcohol, tobacco, and other illicit drugs are significant predictors of birth weight in a Uruguay cohort.

Methods: Meconium samples (n=900) and infant health data were collected from two public hospitals in Montevideo, Uruguay. Fatty acid ethyl esters (FAEE) were extracted from meconium and analyzed using GC-FID. A sample was considered positive for heavy alcohol exposure if the cumulative concentration of seven FAEEs was ≥ 2 nmol/g. Meconium (n=195) was analyzed for cocaine, benzoylecgonine, amphetamine/MDA, THC, and cotinine by ELISA using positive cutoffs of 80 ng/g, 80 ng/g, 100 ng/g, 50 ng/g, and 25 ng/g respectively. Multiple linear regression was used to determine the association between independent variables and birth weight.

Results: Multiple linear regression determined that birth weight can be predicted by cotinine as a dichotomous variable, FAEE as a continuous variable, infant gender, and lack of prenatal care (p<0.001). The significant independent variables accounted for 11.1% of the variability in birth weight. Illicit drug use, maternal age, years of maternal education, and parity were insignificant independent variables.

Conclusions: Prenatal exposure to alcohol and tobacco as measured objectively by meconium analysis are significant predictors of birth weight.

Keywords: *Low birth weight, Uruguay, meconium*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

162

The safety of commonly used anti-hemorrhoidal preparations in pregnancy

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Funding Source: Duchesnay Inc.

Background: Up to 24% of women suffer from hemorrhoids during the third trimester of pregnancy. Pregnant women are more prone to hemorrhoids because of increased circulating blood volume, constipation due to high progesterone levels and increased pressure by the growing uterus; all resulting in venous engorgement. Typically, management during pregnancy is conservative in nature.

Objective: The objective of this study was to evaluate the safety of commonly used local treatments by Motherisk callers.

Methods: The Motherisk database was searched (2006-2007) and a list of commonly used local antihemorrhoidal preparations was generated. Medline (1950-2007) and PubMed (1950-2007) were searched for clinical studies evaluating the safety of any of the above treatments. Title and abstracts were reviewed. Only articles written in the English language were included.

Results: The eight most frequently used local treatments by Motherisk callers include Anusol®, Anuzinc® , Anugesic-HC®, Preparation H®, Proctofoam-HC®, Proctosedyl®, Witch hazel (Hamamelis Virginiana) and Tea tree oil (Oleum Melaleuca). Pubmed and Medline search did not yield even a single eligible study on the safety or efficacy of the above preparations during pregnancy.

Conclusions: Hemorrhoids are a common concern during pregnancy and can potentially affect quality of life. No evaluation of the maternal and fetal safety of currently used local antihemorrhoidal treatments is available. It is critical to study the safety and efficacy of antihemorrhoidal treatments used by over 100,000 pregnant Canadian women every year.

Keywords: *Hemorrhoids, pregnancy*

163

Calls to a support center for pregnant and planning women regarding exposures: the Motherisk Program

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Funding Source: Department of Clinical Pharmacology

Background: The Motherisk Program at The Hospital for Sick Children in Toronto, Ontario provides evidence-based information regarding drug, chemical, and disease risk to planning and pregnant women. This program receives over 30,000 calls per year. The aim of this analysis was to characterize the nature of these calls.

Methods: A systematic review of reason for call among Motherisk callers between 6 November 2006 and 3 January 2007 was performed. The nature of the call by pregnancy status (planning or pregnant), non-occupational or occupational, and exposure type were recorded. Exposure categories were broad and included 29 for non-occupational and 5 for occupational.

Results: There were 3474 calls to Motherisk for women planning (17.4%, N=604) or pregnant (82.6%, N=2870) during the period 6 November 2006 and 3 January 2007. The majority (98.5%, N=3422) were for non-occupational exposures, while 1.5% (N=52) were for occupational exposures. Of the non-occupational calls, the most common exposures were psychiatric medications (11.7%,N=400), topical medications (10.8%,N=322), cold/allergy medications (9.2%, N=313),antibiotics(8.4%,N=288),immunizations/vaccinations (8.0%, N=252), and herbal medications (5.4%, N=186). The number of calls regarding multiple exposures was 11.7% (N=400). Of the occupational calls, 26.9% (N=14) were for exposures to organic solvents, 9.6% (N=5) were for gas (methane, propane) exposure, 13.5% (N=7) were for exposure to non-organic paints, while the majority (50%, N=26) were classified as other occupational exposure.

Conclusions: This data provides a breakdown of call reason to a helpline for pregnant and planning women.

Keywords: *Teratogens, pregnancy*

Advances in Therapeutics Education

164

Variablity in the production of dechloroethylifosfamide enantiomers in pediatric oncology patients

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Background: Ifosfamide (IF) is used to treat pediatric solid tumors. It is associated with renal toxicity, which is due to the production of the nephrotoxic agent chloroacetaldehyde following side-chain oxidation. Previous cell culture work showed that the amount of chloroacetaldehyde produced is sufficient to cause kidney damage.

Hypothesis: There is great intra-patient variability in the amount of chloroacetaldehyde due to variability in CYP3A4, 3A5 and 2B6 enzymes which are necessary for the metabolism of IF. It is our hope that a less nephrotoxic IF-enantiomer may be given singly, thus improving the risk benefit ratio.

Methods: The variability in the production of IF dechloroethylifosfamide (DCEIF) metabolites, specifically R-2-DCIEF, S-2-DCEIF, R-3-DCEIF and R-2-DCEIF in pediatric oncology patients (n=22) receiving IF (50:50 mix of R- and S-IF) treatment at The Hospital for Sick Children was examined.

Results: DCEIF variability was lowest with R-2-DCEIF (9.9–238.7 ng/mL) and much greater for R-3-DCEIF (20.8–852.8 ng/mL), S-2-DCEIF (15.0–663.0 ng/mL), and S-3-DCEIF (25.8–862.1 ng/mL). The low variability for R-2-DCEIF may be due to the fact that it is only produced via CYP3A4 while R-3-DCEIF is produced via CYP3A4 and 3A5, the latter enzyme being much more polymorphic. The S-2-DCEIF and S-3-DCEIF enantiomers are metabolized via CYP2B6 which is also highly polymorphic.

Conclusions: Since R-2-DCEIF is produced from the R-IF enentiomer these preliminary findings seem to suggest that administration of a single IF enantiomer may decrease the level of chloroacetaldehyde produced within the kidney thus reducing the incidence of kidney damage in children.

Keywords: *Ifosfamide, pediatric, enantioselective, liquid chromatography-mass spectrometry*

TUESDAY MAY 29, 2007

Human Resources in Drug Evaluation

165

The incidence of poor neonatal adaptation syndrome after intrauterine exposure to venlafaxine

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Background: Venlafaxine, an antidepressant and a serotonin and norepinephrine reuptake inhibitor (SNRI), has mechanisms of action similar to those of selective serotonin reuptake inhibitors (SSRIs). SSRIs are known to cause poor neonatal adaptation syndrome (PNAS) in neonates after intrauterine exposure; however, data on venlafaxine is lacking. Due to the suspected higher incidence of withdrawal syndrome in adults and its shorter half-life, we hypothesized that the incidence of PNAS associated with intrauterine exposure to venlafaxine would be higher than the SSRI-induced PNAS.

Methods: This retrospective cohort study was conducted to obtain data on the frequency of PNAS in neonates exposed to venlafaxine in utero, and to compare the incidence with that of neonates exposed to paroxetine, an SSRI, in utero. Pregnant women who took venlafaxine or paroxetine were identified in the Motherisk records of 2005 and interviewed via telephone. Information regarding perinatal incidents including PNAS was collected. Differences in proportion of PNAS between the groups were analyzed using Fisher's exact test.

Results: To date, we called 81/166 subjects in the venlafaxine group and 38/80 in the paroxetine group. Of which, 27 and 18 mothers took the medications throughout the third trimester, and four (14.8%, 95% C.I.: 4.1-33.2) and two (11.1%, 95% C.I.: 1.3-34.7) cases of PNAS were identified in each group, respectively. No statistically significant difference was observed.

Conclusions: This preliminary result suggests that the incidence of PNAS associated with intrauterine exposure to venlafaxine is similar to the paroxetine-induced PNAS.

Keywords: *Venlafaxine, SSRIs, poor neonatal adaptation syndrome*

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Therapeutics Innovations

166

Single nucleotide polymorphism (SNP) of BCRP/ABCG2 significantly alters the pharmacokinetics of sulfasalazine: implications for interindividual variability during drug therapy

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Funding Source: National Institutes of Health

Background: Breast cancer resistance protein (BCRP) is an efflux transporter expressed in tissues that represent barriers to drug entry. BCRP mediates the efflux transport of a wide variety of substrate drugs and has been implicated in multi-drug resistance during chemotherapy, secretion of drugs into breast milk and limiting the oral bioavailability of drugs. SNPs in BCRP are not only common, but may also be functionally relevant in vivo as a determinant of interindividual variability in drug response. The objective of this study was to evaluate the role of SNPs in BCRP to drug disposition in humans using sulfasalazine as an in vivo probe.

Methods: Fifteen healthy subjects were recruited to the study. Subjects were given one gram of sulfasalazine PO and blood samples were drawn at selected intervals over 24 hours. DNA was extracted and BCRP genotype determined. Plasma sulfasalazine was analyzed using HPLC-MS.

Results: Plasma sulfasalazine concentration varied 20.5 fold between subjects. Four of the 15 volunteers were heterozygous for a common BCRP SNP (BCRP*3). In BCRP*3 heterozygotes, sulfasalazine AUC was increased 2.5 fold compared with wild-type ($P<0.01$). Similarly, Cmax was 22.8 µg/mL in BCRP*3 vs. 9.7 µg/mL in wild-type, $P<0.01$.

Conclusions: Our findings suggest BCRP is a major determinant of variability in response to drugs. This is the first study to link commonly occurring SNPs in BCRP with reduced capacity for sulfasalazine disposition in humans. Accordingly, sulfasalazine may prove to be an important in vivo probe for assessing the clinical impact of BCRP to the disposition and efficacy of many drugs in clinical use.

Keywords: *Drug transport, breast cancer resistance protein (BCRP), pharmacogenetics*

167

Agonist-specific CB1 receptor signaling in human trabecular meshwork cells

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Background: Systemic or topical administration of cannabinoids decreases intraocular pressure, however the mechanisms responsible for the reduction remains unknown. CB1 cannabinoid receptors (CB1) are expressed in cells of the trabecular meshwork (TM), a tissue that is the rate-limiting step in the conventional aqueous humour outflow pathway.

Methods: We used ratiometric calcium imaging, western blot, and infrared In-Cell Western™ (ICW) analysis to determine the pharmacology of CB1 in human TM cells.

Results: WIN55212-2 (WIN), a cannabinoid receptor agonist, evoked a gradual increase in [Ca2+]i in TM cells. These responses were mediated by CB1 and were dependant upon PLC activation and mobilization of intracellular Ca2+ stores. The CB1-induced [Ca2+]i increase was pertussis toxin (PTX)-insensitive and, therefore, independent of Gi/o coupling, but was attenuated in cells expressing a dominant negative Gq/11 á subunit, implicating a CB1-Gq/11 signaling pathway. Western and ICW analysis demonstrated that WIN also increased phosphorylation of the extracellular signal-regulated kinase (ERK). ERK phosphorylation was mediated by CB1 and was sensitive to PTX, implying CB1-Gi/o coupling.

Conclusions: This study suggests that WIN activation of CB1 receptors in TM cells activates both Gi/o and Gq/11 signal transduction pathways. The coupling of CB1 to Gq/11 and PLC-dependent increases in Ca2+ were specific to WIN and were not observed with other CB1 agonists, including anandamide and CP55940, although these compounds were able to activate Gi/o-dependent increases in ERK phosphorylation. Ligand-specific CB1-induced alterations in TM cell signaling may lead to changes in trabecular tone that modulate aqueous outflow and intraocular pressure.

Keywords: *Cannabinoid CB1 receptor, trabecular meshwork, aqueous outflow*

168

Therapeutic potential of cannabigerol-dimethyl-heptyl as an ocular hypotensive

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Background: In humans, intraocular pressure (IOP) is determined by the secretion of aqueous humor and outflow resistance via the trabecular and uveoscleral routes. Cannabinoid receptors are present on tissues of both the inflow and outflow pathways and cannabinoid ligands have been shown to decrease IOP in humans. Cannabigerol-dimethyl heptyl (CBG-DMH) is a synthetic non-psychoactive cannabinoid with hypotensive and vassorelaxative properties (Maor, et al., 2005). This study investigated the ocular pharmacology of CBG-DMH.
Methods: IOP was measured with a tonometer in brown Norway rats at 15 minute intervals for 2 hours. All drugs were administered by intraperitoneal injections. Ratiometric calcium imaging was used to observe the effect of CBG-DMH on human cell lines derived from trabecular meshwork (TM) and ciliary muscle (CM).
Results: 2.5 and 10 mg/kg of CBG-DMH reduced IOP in rat eyes (20.9±0.16 to 19.8±0.31 mmHg and 20.8±0.25 to 19.45±0.15 mmHg, respectively) (mean ± SEM). The IOP-lowering effect of CBG-DMH was significantly reduced by pre-administration of 2.5 mg/kg of O-1918, a selective antagonist of non-CB1/CB2 novel endothelial cannabinoid receptor, and SR141716A, a CB1 specific receptor antagonist. In vitro, exposure to 10 µM CBG-DMH evoked a gradual increase in [Ca2+]i in both TM and CM cells.
Conclusions: This study suggests that administration of CBG-DMH effectively decreases IOP in the rat eye. CBG-DMH has activity at CM and TM cells to increase [Ca2+]i, which may be associated with, altered contractility and outflow resistance. CBG-DMH has the potential to function as a novel ocular hypotensive cannabinoid devoid of psychotropic activity.
Keywords: *Intraocular pressure, cannabinoids, cannabigerol-dimethyl heptyl*

169

Pediatric neurodevelopment following in-utero exposure to labetalol

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Background: Hypertensive disorders require pharmacotherapy to prevent target organ damage. Selection of anti-hypertensive drugs for pregnant women is limited due to risk of teratogenicity. Methyldopa (MET) and labetalol (LBT) are the most commonly used medications in pregnant women. Long-term neurodevelopment of children following exposure to MET or LBT in utero has not been studied.
Objectives: To determine whether in-utero LBT exposure is associated with impaired child neurodevelopment (at age 3-7) when compared to children exposed to MET or non-teratogenic substances.
Methods: A controlled cohort study assessing 3 groups of mother-child pairs from the prospectively-created Motherisk database and patients of the Women's College Hospital. The groups were: (a) exposed to LBT (n=32), (b) exposed to MET (n=25) and (c) healthy controls (n=53). The primary outcome measure was child Full Scale IQ (FIQ).
Results: Children exposed to LBT were no different from controls in FIQ (109vs111, p=.406). Children exposed to MET achieved significantly lower FIQ and Performance IQ (PIQ) scores than control children (112vs105, P =0.037 and 109vs99, P=0.003, respectively). Linear regression models were used to determine the predictors of child FIQ and PIQ. Maternal IQ and being in the MET group were significant predictors of child FIQ (p¨T0.022 and p=0.042, respectively). Being in the MET was the only significant predictor of child PIQ (p=0.03).
Conclusions: In-utero exposure to LBT was not associated with adverse cognitive development of preschool children.
Keywords: *Labetalol, pregnancy, child development*

170

Measurement of cortisol in the hair of ancient mummies by immunoassay

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Background: Cortisol is a vital corticosteroid playing a key role in many systems, and is used to treat various pathological conditions. A technique developed by us allows the measurement of cortisol in hair, yielding long term assessment of cortisol concentrations in individuals compared to the short time window of traditional specimens like blood, saliva and urine. We applied this technique to mummies from the Americas, and hypothesized that the mummies will have a cortisol concentration that is stable for many years and, due to the stresses associated with life during this period, that the levels will be higher than currently seen in normal individuals.

Methods: Hair was obtained from several mummies. Samples were incubated overnight in methanol to extract steroid. Methanol was evaporated and residue reconstituted in PBS. Samples were analyzed using a commercially available salivary ELISA (Alpco Diagnostics).

Results: All mummies analyzed showed detectable cortisol concentrations which were higher (234±131 ng/g) than found in normal present day individuals (49±33 ng/g, $P<0.001$). Concentrations in one individual are suggestive of an endocrine disorder.

Conclusions: These results suggest that hair analysis provides a new method of measuring patho-physiological markers in mummies, in whom hair is well preserved. Hair analysis is now widely used in anthropology, and this technique broadens the range of tools available to piece together our history. This technique could also be used to for monitoring long term concentrations of endogenous and exogenous steroids in relation to diagnosis and treatment of various hormonally-related conditions.

Keywords: *Cortisol, hair, ELISA*

171

The effect of common antioxidants found in traditional Chinese medicine on sulfamethoxazole-induced toxicity

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Funding Source: Work supported by the Canadian Institutes of Health Research and the CIHR-GSK Chair in Paediatric Clinical Pharmacology

Background: Variation in formation and disposition of the N-hydroxylamine (SMX-NHOH) metabolite of sulfamethoxazole (SMX) and non-enzymatic oxidation to the N-nitroso derivative (SMX-NO) is thought to be important in the pathogenesis of SMX-induced idiosyncratic adverse drug reactions. Bioactivation of SMX is thought to produce reactive metabolite-protein haptens that can be processed as an immunogen, and produce reactive oxygen and nitrogen species (ROS/RNS). This suggests a potential role for antioxidants in reducing SMX toxicity. Baicalein, a flavonoid from *Scutellaria baicalensis*, and crocetin, a carotenoid from *Gardenia jaminoides* Ellis, are two antioxidant compounds used in Traditional Chinese Medicine (TCM). Studies have suggested they exert their effect by chelating iron, and trapping and scavenging free radicals, respectively.

Objective: To determine whether baicalein and crocetin would attenuate the toxicity of electrophilic metabolites of sulfamethoxazole (SMX-NHOH and/or SMX-NO) in Jurkat E6.1 cells by decreasing the amount of reactive oxygen species (ROS) formed and maintaining redox status.

Methods: Cells were incubated with 400µM of SMX-NHOH, and baicalein or crocetin at 5 or 50µM for two hours prior to removal of drug, and overnight incubation. Cell death was assayed by flow cytometry after treatment using phycoerythrin (PE)-conjugated Annexin V and 7-amino-actinomycin (7-AAD).

Results: Baicalein or crocetin attenuated SMX-NHOH induced cell death at 5µM, but failed to do so at 50µM.

Conclusion: It is known that many antioxidants are protective in low concentrations but toxic in high concentrations. Baicalein or crocetin treatment, at relatively low µM concentrations, can decrease the toxicity of SMX-NHOH in Jurkat E6.1 cells in culture.

Keywords: *Sulfamethoxazole, idiosyncratic adverse drug reactions, oxidative stress, antioxidant, flow cytometry*

Health Technology Assessment

172

Economic evaluation of intensive atorvastatin compared to standard simvastatin treatment in Canada based on the IDEAL trial

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Background: The IDEAL trial demonstrated an 11% reduction major cardiovascular events with intensive-therapy (atorvastatin 80mg) versus standard therapy simvastatin (20-40mg) in northern European patients (n=8,888) with a previous MI and who were eligible for statin therapy.
Objectives: To assess the within-trial cost-effectiveness of intensive atorvastatin therapy versus generic standard simvastatin therapy in patients with existing coronary heart disease over 4.8 years from a Canadian societal perspective.
Methods: All cardiovascular events and procedures events (includes stroke, transient ischemic attack, non-fatal MI, heart failure, cardiac arrest, angina, coronary bypass surgery, percutaneous coronary intervention, and other cardiothoracic or vascular procedures) occurring during the IDEAL trial (median follow-up 4.8 years) were aggregated by treatment arm on an intention-to-treat basis. Resource use (includes endpoint-related hospitalization and study drug dose and duration) and productivity losses were aggregated and multiplied with the respective Canadian costs. Cost-effectiveness was calculated as the total incremental cost per event avoided.
Results: Over 4.8 years of treatment, patients in the atorvastatin arm experienced on average 0.1 fewer events per patient than patients in the simvastatin arm while incurring Can$968 higher study drug costs. Reduced endpoint-related hospitalization and lower productivity losses led to a net cost savings of Can$663 per patient in the atorvastatin arm.
Conclusions: Intensive atorvastatin therapy is cost-saving compared with standard simvastatin therapy in patients with a previous MI from a Canadian societal perspective based on a within-trial analysis.
Keywords: *Cost-effectiveness analysis, statin treatment, coronary heart disease*

Drug Policy

173

Estimating the economic costs of antidepressant discontinuation during pregnancy

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Background: Depression is a major public health concern that results in a wide range of economic costs to individuals, their families and the health care system. This study sought to determine the direct medical costs incurred by Ontario's government due to cessation of antidepressant therapy during pregnancy.
Methods: An economic evaluation was conducted using assumptions based on data obtained from Statistics Canada, federal and provincial government reports and relevant depression literature.
Results: It was estimated that annually, 1444 depressed and pregnant women in Ontario discontinued antidepressant therapy and subsequently had a depressive relapse. The cost of physician services provided to these women was estimated at $714,347. It was also estimated that $11,136 would be spent on hospitalizations due to untreated depression during pregnancy. Preterm birth and low birth weight (LBW) are two adverse outcomes associated with untreated depression during pregnancy. The total cost of caring for preterm infants born to depressed mothers in the first year of life was determined to be $5,092,544 while the cost of caring for their LBW infants for the first year of life was estimated at $7,637,355. Therefore, the total annual cost to the Ontario government was $11,113,939, after subtracting the cost of risks associated with treated depression during pregnancy ($2,341,443).
Conclusions: An estimated $11,113,939 is spent annually in Ontario on untreated maternal depression during pregnancy. Safe treatment options for the management of depression during pregnancy should be actively explored as treated depression translates into cost savings for the Ontario government.
Keywords: *Depression, pregnancy, economics*

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

174

External contamination of hair with mdma (ecstasy) determined by hair analysis in two young girls from a "meth lab"

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Background: It is not uncommon to find children residing in home laboratories illegally producing methamphetamine, and their environmental exposure to illicit drugs has not been systematically evaluated. We describe the use of hair test to detect MDMA (Ecstasy) exposure in two girls residing in a household where such a laboratory operated.

Methods: In mid 2006, police found evidence in a family house in Ontario suggesting that it had been used to manufacture MDMA. The family living in the house included 2 girls, 14 months and 8 years old. The girls appeared in good health, and were apparently well cared for. Physical examination by a pediatrician revealed no major health problems. As part of the consultation, a hair sample for drug testing was obtained from each girl.

Results: Hair from both children was positive for either MDMA (ELISA method) at relatively high levels (8.63 and 1.35 ng/mg of hair, respectively). Other drugs were negative, as well as the MDMA metabolite, MDA. Presence of MDMA in hair was qualitatively confimed by HPLC with diode array ultraviolet detection (REMEDi HStm system).

Conclusion: We report the case of two young sisters who had positive ecstasy in hair, which was determined to be from external contamination of their hair on the basis of absence of the MDMA metabolite, MDA, and the clinical evaluation of the patients. This is among the first reports, to the best of our knowledge, of a case of external exposure to MDMA leading to a positive hair result in children.

Keywords: *Hair detection, MDMA, drug endangered children*

Author Index by Abstract

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

Ying A	5
Yip CS	171
Young SW	123
Zaher H	166
Zwicker B	116

Keyword Index by Abstract

KEYWORDS	ABSTRACT #
abatacept	89
ABC transporters	156
Aboriginal	22
academic detailing	40
access to medicines	9
acetaminophen	94,114,135
acute chest syndrome	148
acute myocardial infarction	123
addictions	116
adenosine	145
adherence	31
adherence	122
adverse drug reactions	4,154
aged	16
aging	125,143,145
agreement	52,61
ALL	139
alosetron	76
AMI	31
analgesics	16
antibiotics	24
antidepressant	36,37,117
antioxidant	171
anti-platelet therapy	75
antipsychotic agents	113
antipsychotics	79
antiretro viral drug usage	155
anti-TNF agents	14
aqueous outflow	167
arterial	80
asthma	11,24,64,86
attention deficit hyperactivity disorder	35
before-and-after study	21
benzodiazepines	108
beta-blockers	102
Bilirubin	131
bipolar disorder	113
bipolar/unipolar	117
birth defects	133
bisphosphonates	72
brain transporters	158
breast cancer	68,71
breast cancer resistance protein (BCRP)	166
breast milk	131,153
budesonide/formoterol	64
budget impact analysis	65,101
calcium homeostasis	144
Canadian health system	105
cancer in pregnancy	141
candidemia	38
cannabigerol-dimethyl heptyl	168
cannabinoid CB1 receptor	167
cannabinoids	168
cardiomyocyte	144,145
cardiovascular	21
cardiovascular disease	19,81,82
cardiovascular events	107
cardiovascular risk	59, 98
case mix group	12
case-control	36,37
chart review	17
child behavior checklist	160
child development	169
child mental health	160
children	60,135,137,150,151
chronic HCV	101
chronic renal failure	127,158
clinical outcomes	102
clinical pharmacy	7,45,115
clomiphene citrate	140
clopidogrel	12,69
common drug review	9
community pharmacy	59

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007

Can J Clin Pharmacol Vol 14(2) Summer 2007:e104-e204; May 10, 2007