ABSTRACTS

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THE IMPACT OF CIRCADIAN RHYTHMS ON FOLATE ABSORPTION.

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INTRODUCTION: In attempts to prevent neural tube defects and treat iron deficiency anaemia, multivitamin supplementation is recommended before and during pregnancy. A new multivitamin product (PregVit®, Duchesnay, Laval, Quebec) has been designed that is taken twice daily. With PregVit®, folate is administered at an unusual time. It has been documented that circadian rhythms can impact pharmacokinetics of a drug or supplement in humans. A previous study demonstrated that circadian rhythms have an effect on serum folate levels in rats. However, there are no known human studies have investigated the role of temporal variations on folate absorption.

OBJECTIVES: To compare folate absorption at various points through the day.

METHODS: In a cross-over design, six healthy, non-pregnant women were randomized to receive 1 tablet of PregVit®, containing folate, in the morning or evening. Serum folate levels were measured over 10 hours. The area under the concentration time curve (AUC) was used to compare absorption between the two time periods. The 2 study days for each woman were 4 weeks apart.

RESULTS: The mean AUC values for serum folate after administration of PregVit® were 334.5 ± 119.6 nM*h and 283.1 ± 64.3 nM*h for day and night, respectively ($P > 0.05$). Comparing the peak concentration, the day and night peak serum folate levels were 135.3 ± 41.7 nM and 130.3 ± 14.2 nM, respectively ($P > 0.05$). Finally, the time to peak for the day arm was at 1 ± 0.5 hour, which was not significantly different from the Tmax at night, which was 1 ± 0.4 hour.

CONCLUSIONS: The time change at which folate is administered does not affect folate absorption. Thus, the folate contained in PregVit® p.m. will be absorbed similarly if it were given in the morning.

KEYWORDS: *Folic Acid, Drug Absorption, Neural Tube Defects*

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PHARMACOKINETICS AND ADVERSE EVENTS OF FERROUS FUMARATE IN TWO PRENATAL MULTIVITAMIN SUPPLEMENTS.

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INTRODUCTION: To maintain maternal health and prevent fetal malformations, multivitamin supplementation is recommended before and during pregnancy. Yet, because iron is associated with gastrointestinal side effects, adherence to supplementation is often difficult. A new multivitamin (PregVit®, Duchesnay, Laval, Quebec) was designed to address this issue by containing lower amounts of iron and is administered twice daily to enhance absorption.

OBJECTIVES: To compare iron pharmacokinetics following a single dose of Materna® and PregVit® a.m and compare the adverse effects of two prenatal multivitamin supplements in a randomised control trial.

METHODS: 1) Twelve healthy, non–pregnant women randomly received 1 tablet of PregVit® a.m. or Materna® in a cross over methodology. Serum iron levels were measured over 8 hours. Subjects were given a standardized meal 4 hours after the study dose. The 2 study days for each woman were conducted 4 weeks apart. 2) To compare adverse effects, one hundred pregnant women were assigned to Materna® and PregVit® for one month each. A pill count was conducted to corroborate their reports of compliance. Patients also kept a diary to record adverse events.

RESULTS: For the iron kinetic analysis, after standardizing iron absorption for dose, the AUC of iron absorbed with PregVit® and Materna® was 2.3µM*h/mg and 1.5 µM*h/mg, respectively ($P=0.021$). In comparing the effectiveness, two fold more patients experienced constipation while on Materna® ($P = 0.008$). Women were also constipated for a longer period of time when they were on Materna® ($P = 0.013$).

CONCLUSION: Calcium inhibits iron absorption in Materna®. By decreasing iron content and giving it without calcium, PregVit® decreases the irritating effects of iron in women with NVP, including constipation, without decreasing iron intake.

KEYWORDS: *Iron, pharmacokinetics, pregnancy*

3

CHRONIC TREATMENT WITH VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) RESTORES VASCULAR RESPONSES TO ACETYLCHOLINE AND NORMALIZES NITRIC OXIDE FUNCTION IN THE STREPTOZOTOCIN (STZ)-INDUCED DIABETIC RAT.

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INTRODUCTION: Objective: We sought to determine what effect chronic treatment with VEGF would have on endothelial dysfunction in diabetes.

METHODS: Twice weekly intravenous injections of VEGF commenced 5 weeks after induction of diabetes in Sprague-Dawley (SD) rats injected with streptozotocin (STZ, 55mg/kg, IP). Inactivated VEGF (iVEGF) treatment of STZ diabetic rats, and untreated SD non-diabetic rats served as controls. After 4 weeks of VEGF treatment, vascular responses to acetylcholine (ACh, 0.1-12.5 μg/kg) and endothelin (ET)-1 (100-1200 pmol/kg) were assessed by recording blood pressure (BP) and superior mesenteric arterial (SMA) flow in anesthetized rats. Aorta were harvested from a separate set of animals in each group for measurement of eNOS protein expression, and superoxide anion.

RESULTS: The vasodilation evoked by ACh was attenuated in iVEGF treated STZ rats ($P<0.05$). Attenuated vascular responses were associated with increased superoxide anion generation (chemiluminescence assay) and elevated nitrotyrosine staining (immunohistochemistry) in the vasculature, and reduced levels of nitrates/nitrites (colorimetric analysis) in the plasma. Endothelial nitric oxide synthase (eNOS) expression (Western blot analysis) was paradoxically increased. Treatment of diabetic STZ rats with VEGF restored vascular responses to those observed in non-diabetic SD rats. The restored vascular responses by VEGF were associated with restoration of superoxide anion generation, nitrotyrosine staining, plasma nitrates/nitrites, and eNOS expression to levels observed in non-diabetic SD rats.

CONCLUSION: Our results suggest that chronic treatment with VEGF is able to restore vasodilator responses to ACh. The restoration of vasodilator responses appears associated with restoration of NO function, likely as a consequence of reduced superoxide anion generation.

KEYWORDS: *Acetycholine, Growth Factor, Nitric Oxide, Diabetes*

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SOLUBLE METAL COMPONENTS OF PARTICULATE MATTER TRIGGER CARDIAC FUNCTION IMPAIRMENT.

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OBJECTIVE & METHODS: Exposure to particulate matter (PM) is associated with increased mortality and morbidity among those subjects with cardiovascular impairment. Since the spontaneous hypertensive rat (SHR) genetically resembles the disease state of mature cardiovascular disease, we hypothesised that PM would affect cardiovascular performance in isolated perfused hearts (Langendorff model) from SHR rats. The experimental protocol included 30 minutes of stabilisation, followed by 130 minutes of perfusion. For treated hearts, zinc sulphate (10 μM), the main water-soluble metal found within the PM (Ottawa dust) used in our previous studies, was perfused over a 10 minute time period. The ability of PM and its soluble metals to modify calcium influx by ATP (100 μM) and KCl (50 mM) was evaluated *in vitro* using H9C2 cardiomyoblast cells. Following loading with Fura-2, cells were stabilised for 10 min before treatment began. Agonists were tested (100s) at two time points with a 30-min interval separating them. $ZnSO_4$ (50 μM) or PM filtrate (100 μM) were applied during the separation time.

RESULTS: In the Langendorff model, $ZnSO_4$ (10 μM) induced more than 70 % decrease in heart rate ($p<0,05$) and 60 % decrease in dP/dt max ($p<0.05$). The left ventricular developing pressure (LVDP) was also affected by approximately a 50 % decrease ($p<0.05$). The depression of all these parameters resulted in a decrease of heart contraction and performance. In the cardiomyoblast cells, both ATP (100 μM) and KCl (50mM) induced calcium influx. No difference was observed for each agonist between the two periods of activation. In the presence of a PM filtrate (100 μM), calcium influx elicited by KCl (50 mM) and ATP (100 μM) was completely abolished ($p<0,001$). The same inhibitory effect has been observed in the presence of ZnSO4 (50 μM), KCl ($p<0.05$) and ATP ($p<0.01$).

CONCLUSION: Our data suggests that the fraction of soluble metals within PM has an acute effect on several cardiovascular parameters measured in the Langendorff model. Soluble metals elicit a decrease of cardiac contraction and performance. These observations were confirmed by inhibition of agonist-induced calcium influx by soluble metals, since calcium is very important for cardiac contraction. In conclusion, our data suggest that particulate air pollution can cause cardiac impairment by interfering with calcium homeostasis within the heart.

KEYWORDS: *Cardiac function, metals*

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SIGNAL TRANDUCTION PATHWAY INVOLVED IN PARTICULATE MATTER INDUCED RELAXATION: SPONTANEOUS HYPERTENSIVE RAT (SHR) VERSUS WISTAR KYOTO.

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Direct application of ambient particulate matter (PM) on rat aorta rings has been shown to induce a dose-dependent vasorelaxation. In the present study, we investigated the intracellular messengers involved in PM (EHC-93) elicited vasodilatation in rat aorta. We evaluated the relative contribution of NO-cGMP and prostanoids by using respective inhibitors of sGC (NS2028, 10 μM) and COX (Diclofenac, 100 μM). The suppression of the response with high extracellular potassium supports the contribution of endothelium derived hyperpolarisation factors (EDHF). We further investigated the effects of cytochrome P450 inhibition (17-ODYA, 10 μM). The role of certain susceptible receptors in response to PM has been verified using specific antagonists. The SHR, used as a model for humans with cardiovascular disease, has been compared to the wild type wistar Kyoto (WKY). Both PM suspension and its water soluble components (PM filtrate) induced a dose-dependent relaxation in both animal type aorta rings. The PM suspension response was consistently higher than that induced by the PM filtrate in both rat aortas (E_{max} = 27% vs 7% PM filtrate, SHR) and (E_{max} = 15% vs 10% PM filtrate, WKY). In endothelium denuded rings, a similar vasorelaxation was observed. However, in contrast to WKY, the response elicited by PM suspension in these rings was higher than in normal rings in SHR (E_{max} = 55% vs 27%, p<0,05). PM induced response was significantly higher in SHR than in WKY (E_{max} = 27% vs 15%, p<0.02 normal rings) and (E_{max} = 55% vs11%, p<0,01 denuded rings). Only sGC inhibition suppressed PM induced vasodilatation in both animals aorta, (E_{max} = 27% vs 5%, p<0.01, SHR) and (E_{max} = 15 % vs 2%, p<0,001, WKY). The same inhibitory responses have been observed in aorta denuded rings but also with PM filtrate. 17-ODYA and high KCl concentration failed to modified PM induced relaxation. Furthermore, Capsazepine (100μM) a capsaicin receptor antagonist, pyrilamine (10 μM) and cimetidine, the histamine H_1 and H_2 receptors antagonist respectively, did not inhibit the PM nor the PM filtrate response. Zinc (2+) and Coppper (2+), in their sulphate salts form (10-100 μM), also induced a relaxation of aortic rings. Similar to PM, these metal responses were significantly higher in SHR than in WKY (E_{max} = 55% vs 23%, p<0,001 for $CuSO_4$) and (E_{max} = 25 vs 11%, p<0,001 for $ZnSO_4$). Our data suggest that SHR are more sensitive to PM effects than WKY, as it has been suggested for humans with cardiovascular diseases. PM induced relaxation by activation of sGC, an effect linked to the ability of PM to induce NO release in combination with the activities of its of soluble metals. Furthermore, the observed PM effects appear to be receptor-independent.

KEYWORDS: *Hypertension, signal transduction, metals*

6

A BASELINE STUDY OF NEONATAL HAIR FATTY ACID ETHYL ESTERS AMONG INFANTS BORN TO NON-DRINKING WOMEN.

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BACKGROUND: Identifying in utero alcohol exposure can be a difficult task due to the lack of a clear and consistent diagnostic marker. Fatty acid ethyl esters (FAEE) are significantly elevated in the hair of adult alcoholics and levels can also be measured in the hair of infants exposed pre-natally to alcohol. The detection of FAEE in neonatal hair holds much promise as a biological marker for in utero alcohol exposure, and may help identify cases of gestational alcohol abuse since maternal history is often unreliable. FAEE are found endogenously in the body at low levels. As such, it is critical to establish a population baseline for FAEE levels found in neonatal hair.

OBJECTIVE: To determine basal FAEE levels in neonatal hair of infants not exposed to alcohol to help define a reliable screening cut-off for in utero alcohol exposure.

METHODS: Hair samples were collected from 106 non-drinking women and their neonates recruited from two study centers. FAEE were extracted from the hair matrix by SPE and analyzed by GC/MS/CI. Six individual FAEE were analyzed and results were expressed in pmol per mg of hair. Detection limits ranged from 0.01 to 0.08 pmol /mg.

RESULTS: Low levels of total FAEE were detected in 46% of our baseline cohort (n = 61). FAEE levels ranged from 0.00 to 2.953 pmol /mg, with ethyl oleate being the most prevalent FAEE. The mean cumulative FAEE was 0.315 ± 0.651 pmol/mg.

CONCLUSION: The low but measurable amounts of certain FAEE found in neonatal hair taken from infants born to non-drinking mothers suggest a need for the standardization of these basal levels. Establishing a baseline for the quantitative analysis of FAEE in neonatal hair will thus help to define a reliable positive screening cut-off for in utero alcohol exposure and will aid in the diagnosis and treatment of fetal alcohol spectrum disorder.

KEYWORDS: *Alcohol, screening in pregnancy, fatty acids*

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INHIBITION OF MITOCHONDRIAL MEMBRANE POTENTIAL BY REACTIVE DRUG METABOLITES.

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BACKGROUND: Treatment with Sulfonamides has been associated with severe hypersensitivity reactions, with a higher incidence observed in HIV-infected patients. The metabolism of Sulfamethoxazole (SMX) to its Hydroxylamine (SMX-HA) metabolite is believed to be key in mediating these reactions. Recent data has shown that SMX-HA induces cell toxicity and suppression of proliferation; the mechanism(s) of cellular dysfunction associated with reactive drug metabolites remains unclear. Exposure of cells to SMX-HA can potentially induce apoptosis, which may involve a decrease in mitochondrial membrane potential as an indication of loss of mitochondrial function.

METHOD: We studied changes in mitochondrial membrane potential associated with incubation with SMX-HA in MOLT-3 lymphoblasts using the dye JC-1 and using K+ ionophor Valinomycin as a positive control.

RESULTS: There was a significant and immediate decline in mitochondrial membrane potential associated with incubation with SMX-HA compared to incubation with SMX alone ($p>0.05$). However, this decline was neither concentration- nor time-dependent (from 0 to 800 μM and from 0 to 6 hours).

CONCLUSIONS: Although these results may suggest a low threshold effect for SMX-HA, it is more likely that this represents a unique drug-dye interaction. This suggests that caution is needed when studying the effect(s) of reactive drug metabolites on organelle function. This is currently under investigation in our laboratory.

KEYWORDS*: Adverse drug reactions, sulphonamides, mitochondria*

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ENDOPLASMIC RETICULUM STRESS AND CYTOCHROME P450 INDUCTION IN CULTURED HUMAN HEPATOCYTES.

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BACKGROUND: Induction of CYP3A4, CYP2C9. and CYP2B6 is regulated primarily through the CAR and PXR nuclear receptors. Accumulation of unfolded proteins in the endoplasmic reticulum (ER) as a result of over-production of proteins or disruption of ER function leads to an ER stress response characterized by induction of GRP78 and GRP94.

OBJECTIVE: To determine in cultured human hepatocytes if there was an interaction between induction of endoplasmic reticulum (ER) stress and induction of cytochrome P450 enzymes.Methods: Cultured human hepatocytes were exposed to known inducers of an ER stress response and activators of CAR/PXR. Induction of ER stress proteins GRP78 *and* GRP94 and the cytochrome P450 enzymes CYP3A4, CYP2C9, and CYP2B6 were assessed by real-time PCR and immunoblotting

RESULTS: Induction of an ER stress response as indicated by a marked increase in GRP78 and GRP94 mRNA and protein was accompanied by a 2- to 10-fold induction of CYP3A4, CYP2C9, and CYP2B6 mRNA. The extent of induction was dependent on the concentration of the stress inducer used and the hepatocyte culture. In cultured hepatocytes exposed to rifampin (10 μM) or phenobarbital (500-1000 μM), there was a concomitant induction of CYP3A4, CYP2C9, and CYP2B6 mRNA, and GRP78 and GRP94 mRNA and protein (2 -3 fold).

CONCLUSION: Although the exact molecular events are unknown, it appears that there is a link between the ER stress response and induction of cytochrome P450. This could reflect an evolutionary advantage to concomitant induction of two defense systems, one to enhance clearance of foreign substances and one to protect against the disruption of ER homeostasis that could occur during that process. As several xenobiotics and disease states are known to induce ER stress, this interaction may contribute to altered drug metabolism during disease.

KEYWORDS: *Stress, cytochrome P450, endoplasmic reticulum*

9

ANDROGENS PLAY AN IMPORTANT ROLE IN THE DEVELOPMENT OF HYPERTENSION AND INSULIN RESISTANCE IN FRUCTOSE-FED RATS.

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BACKGROUND: Hyperinsulinemia and insulin resistance are found to be associated with the development of hypertension both in humans and in animal models. Previous experiments have found that male rats developed hypertension and hypersinsulinemia after 9 weeks of fructose diet while female rats did not. The content of Thromboxane A_2 is significantly increased in the vascular beds of fructose induced hypertensive models. We speculated that androgens may play an essential role in the relationship between hyperinsulinemia/insulin resistance and hypertension.

OBJECTIVE: To clarify whether androgen is required in the development of hyperinsulinemia, insulin resistance and hypertension or whether cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX) which regulate the production of thromboxane A_2 are also increased in the arteries of these rats.

METHODS: Male rats were gonadectomized or sham operated and fed a 60% fructose diet beginning at seven weeks of age. Blood pressure was measured by a tail-cuff method, and an oral glucose tolerance test was performed to assess insulin sensitivity after eight weeks of fructose feeding. Cyclooxygenase-1 and cyclooxygenase-2 mRNA expression was assessed in the thoracic aortae and mesenteric arteries.

RESULTS: Gonadectomy prevented the fructose-fed rats from developing hypertension but not from acquiring hyperinsulinemia and insulin resistance. There was an increase in cyclooxygenase-2 expression both in the thoracic aortae and mesenteric arteries of the fructose-fed sham-operated rats while the expression of cyclooxygenase-1 remained unchanged. Gonadectomy prevented the mRNA over expression of vascular cyclooxygenase-2 in the fructose-fed rats

CONCLUSION: The presence of androgens is necessary for the development of fructose-induced hypertension. Androgens apparently act as a link between hyperinsulinemia/ insulin resistance and hypertension in fructose hypertensive rats. An increase in the expression of cyclooxygenase-2 is implicated in the development of hypertension. The mechanism(s) involved requires further study. (Supported by a grant from the Heart and Stroke Fdn of BC & Yukon)

KEYWORDS: *Insulin resistance, androgens, cyclooxygenase*

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IMPROVED INSULIN SENSITIVITY FOLLOWING INHIBITION OF ACETYLCHOINESTERASE IN RATS WITH EXPERIMENTALLY-INDUCED INSULIN RESISTANCE.

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BACKGROUND: Insulin sensitivity in fed rats decreases acutely (55%) when hepatic parasympathetic nerves are interrupted surgically or pharmacologically using atropine. Intraportal infusions of exogenous acetylcholine (ACh) restore insulin sensitivity. We hypothesised that if parasympathetic nerve impairment is involved in insulin resistance, restoring endogenous levels of ACh with acetylcholinesterase inhibitors would improve insulin sensitivity.

OBJECTIVE: To determine if insulin sensitivity can be restored using the acetylcholinesterase inhibitor, neostigmine, in 2 rodent models of insulin resistance.

METHODS: Models of acute and progressive insulin resistance were used. The acute model (ATROPINE) consisted of normal, anesthetized rats given atropine to produce a submaximal, atropine-induced inhibition of insulin sensitivity (5×10^{-6} mg/kg). The progressive model (SUCROSE) consisted of rats fed a 35% sucrose, liquid diet for 9 weeks which has been shown to produce insulin resistance. Insulin sensitivity was determined using a modified euglycemic clamp in response to a 50 mU/kg dose of insulin in anesthetized rats.

RESULTS: Insulin sensitivity in the ATROPINE group (n=8) was determined before and after atropine and during an infusion of neostigmine (1 ug/kg/min) into the portal vein. Atropine produced 84 ± 9% of the maximal atropine-induced inhibition of insulin sensitivity. Insulin sensitivity during neostigmine infusion was 58 ± 15% higher than that seen after atropine. Neostigmine infusion (2 ug/kg/min) in SUCROSE rats increased insulin sensitivity by 41 ± 17% compared to the control responses (n=4).

CONCLUSION: The effect of neostigmine in the ATROPINE group indicates that the parasympathetic nerves play a significant role in regulating glucose disposal in response to insulin. The SUCROSE group data support our hypothesis that impairment of the hepatic parasympathetic nerves play a role in causing insulin resistance. Enhancing endogenous ACh levels may be a therapeutic approach to treating insulin resistance and diabetes.

KEYWORDS: *Insulin resistance, acetylcholinesterase*

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POST-MARKETING EVALUATION OF ETANERCEPT IN RHEUMATOID ARTHRITIS (RA) PATIENTS: A COMMUNITY BASED COHORT STUDY.

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BACKGROUND: Several randomized clinical trials have shown that etanercept is effective and safe in the treatment of RA.

OBJECTIVE: Evaluation of clinical outcomes in patients with rheumatoid arthritis who are using Enbrel (etanercept) therapy in a community setting.

METHOD: Inclusion criteria: Rheumatoid arthritis patients at least 18 years of age, with 6 painful or tender joints, who called the Enbrel information line were eligible to participate in the study.

DESIGN: Cohort study, patients stratified into control and treatment arms, based upon individual accessibility to the drug. All patients received a baseline interview and interviews at 1, 3, 6, 9 and 12 months after baseline.

RESULTS: Baseline: There were 223 patients in treatment arm (T) and 208 patients in control arm (C) (74% female in each group). Baseline demographic and clinical characteristics data showed no statistical difference between the two groups except for education and income. Mental Component Summary Score (MSC) of SF-36 was significantly higher in treatment group (T=50.4±11.7 vs. C=47.9±12.4, p=0.041). Co-morbid conditions were equally distributed between two groups except cancer (T=1.9% vs. C=5.8%, p=0.031).

TREATMENT RESPONSE: There were significantly larger proportions of patients in the treatment group compared to the control group who achieved the ACR20, ACR50 and ACR70 response at 6 and 12 months. There were significant improvements in all clinical variables (i.e.joint count, pain, stiffness, fatique, QoL) during the first six months in treatment arm compared to the control arm, except MSC. During the second 6 months the magnitude of difference for some variables decreased between the two groups and the difference for some variables became non-significant (i.e. fatigue, social QoL variables). There were 45 patients discontinuing therapy during the 12 months of follow up in the treatment group; 40 were related to the drug therapy (lack of effectiveness=14, toxicity=21 and cost of drug=5).

CONCLUSION: Etanercept treatment in RA patients can rapidly and dramatically improve the disease state, functional class and quality of life during the first 6 months of use. To determine the sustainability of these effects will require studies with more than 12 months duration.

KEYWORDS: *Rheumatoid Arthritis, etanercept*

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CLINICAL DATA GAP BETWEEN PHASE III CLINICAL TRIALS (PRE-MARKETING) AND PHASE IV (POST-MARKETING) STUDIES: EVALUATION OF ETANERCEPT IN RHEUMATOID ARTHRITIS.

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BACKGROUND: Theoretically there are fundamental differences between the design of clinical trials (phase III) and post-marketing studies (phase IV). For example, the patient characteristics, the clinical setting (environment) and the manner of drug use can be quite different between phase III and phase IV studies. As a consequence differences between the results obtained from pre- and post-marketing may stem from the differences in study design.

OBJECTIVE: To determine if the data obtained through phase III (clinical trials) for etanercept (Enbrel) use in the treatment of rheumatoid arthritis would be representative of the effects attainable in community practice.

METHOD: We compared the data from a clinical practice cohort study started in 1999 of etanercept use in rheumatoid arthritis patients with the data from published randomized clinical trials.

RESULTS: At baseline, most clinical and demographic data were significantly different between the treatment groups from the cohort study and the RCTs. Similar differences were noted amongst the control groups of the different studies. In treatment response, the ACR50 rates at 6 month were not statistically different between the cohort study and the RCTs, while the ACR50 rates at 12 month were less for the cohort patients than the RCT patients. At 6 months there were fewer withdrawals in the cohort patients than the RCT patients, the due to less withdrawals arising from a lack of efficacy. At 12 months the drop-out or withdrawal rates due to either lack of efficacy or adverse events were similar between data sets.

CONCLUSION: Data from the Enbrel RCTs may not reflect the characteristics of patients using Enbrel in everyday practice nor the clinical outcomes attainable for RA patients by 12 months. On the other hand, withdrawal rates at 12 months appear comparable between the two types of population.

KEYWORDS: *Rheumatoid Arthritis, etanercept, post-marketing study*

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FETAL OUTCOME AFTER INTRAUTERINE EXPOSURE TO BISPHOSPHONATES.

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BACKGROUND: Bisphosphonates are used for prevention and treatment of osteoporosis, including secondary osteoporosis induced by long-term corticosteroid use. They have long terminal-elimination half lives due to slow release from the bones after administration. To date, only case reports were found in the literature with respect to the use of bisphosphonates in pregnancy in humans. Given the long terminal-elimination half lives, it is important to verify its pregnancy safety for women of child-bearing age.

OBJECTIVES: To characterize pregnancy outcomes of women receiving bisphosphonates.

METHODS: A prospective cohort study based on teratogen information service programs in Ontario.

RESULTS: Twelve patients were followed. Bisphosphonates used were etidronate (5), alendronate (4), risedronate (2), and pamidronate (1). Seven of these women received concurrent systemic corticosteroids. Six patients had stopped the drug 1 to 3 months prior to the last menstrual period and the remaining 6 patients had first-trimester exposure. There were 11 live births, and one spontaneous abortion. The gestational ages were 38 ± 2 weeks, and the birth weight, 2.95 ± 0.38 kg (mean ±SD). Of the 11 infants, one was diagnosed to have Apert syndrome, an autosomal dominant acrocephalosyndactyly. No apparent abnormality was observed in the remaining 10 infants.

CONCLUSION: Although preliminary, our data suggest that preconceptional and first-trimester use of bisphosphonates may not pose serious fetal risks.

KEYWORDS: *Pregnancy, bisphoponates, foetal outcome*

14

EFFECT OF SMOKING CESSATION ON PLASMA CLOZAPINE CONCENTRATIONS AFTER IMPLEMENTATION OF AN INSTITUTIONAL NON-SMOKING POLICY.

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BACKGROUND: Clozapine is an effective atypical neuroleptic agent for the treatment of schizophrenia which is resistant to conventional agents. The dose-concentration relationship of clozapine is variable and TDM is a useful tool for guiding dose changes to maintain concentrations at threshold (400ug/mL) or above. A major pathway of clozapine metabolism is via hepatic CYP1A2 which is inducible by cigarette smoke. It is also polymorphic thus creating metabolic variability between patients and a potential for unpredictable increases in drug concentrations when individuals stop smoking.

OBJECTIVE: To determine the effect of smoking cessation on clozapine levels in institutionalized patients who were changed from a smoking environment to a government - imposed non-smoking environment.

METHODS: Plasma clozapine was routinely monitored in each of 15 patients (chronic smokers) before and after a non-smoking policy was introduced to a regional mental health facility. Concentrations were plotted over time for each patient and pre/post differences determined over the transition period (ie. before any dose adjustments were made).

RESULTS: In most patients (10/15) clozapine concentrations rose immediately after the non-smoking policy was introduced. The increase ranged from 30 to 100% and then declined as dose adjustments were made based on TDM results. Changes were minimal in the remaining 5 patients ranging from -4 to 5%. Metabolic rate was highly induced in 2 patients with concentrations doubling after smoking cessation.

DISCUSSION: Case reports have suggested that smoking cessation by individual patients was responsible for the dramatic increases in their plasma clozapine concentrations. The results of this study on institutionalized patients support this view and suggest that changes in smoking habits by patients on the drug should be accompanied by increased frequency of plasma concentration monitoring to guide appropriate dose adjustments.

KEYWORDS: *Clozapine, pharmaockinetics, smoking*

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ETHICAL FRAMEWORK OF NEONATAL SCREENING FOR IN UTERO ALCOHOL EXPOSURE AND THE POTENTIAL APPLICATION OF MECONIUM ANALYSIS FOR FATTY ACID ETHYL ESTERS.

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BACKGROUND: Fetal alcohol spectrum disorder (FASD) afflicts nearly 1% of children born in North America. The etiology of FASD dictates that poorly understood genetic factors compound the effects of alcohol; mothers of FASD children are 75% more likely to produce another FASD child. The cost FASD is tremendous to both the affected individuals and society as a whole. Only 11% of individuals are diagnosed before age 6, when therapy is most effective. Diagnosis is paramount to implementing childhood treatment and preventing FASD by directing addicted mothers into effective treatment programs.

OBJECTIVE: Assess the ethical implications of applying the FAEE meconium test as an objective neonatal screening tool and create a framework under which it would be most acceptable.

METHODS: Systematic analysis of the ethics of neonatal screening focusing on current screens for prenatal alcohol consumption and screens associated with potential maternal stigmatization, criminalization, and dual treatment of both mother and child.

RESULTS: Maternal self-reporting is often unreliable due to guilt, shame, or fear of punishment. Implementing an objective test, such as FAEE meconium analysis, would improve sensitivity over questionnaire-based perinatal alcohol-use screening tests. Diagnosing intrauterine exposure to alcohol has the potential to create maternal-fetal/neonatal conflict. Approaching the issue from a public health perspective and creating a non-labeling and non-criminalizing system is therefore crucial for such tests to be acceptable.

CONCLUSION: Concurrent establishment of a support system providing access to diagnosis and treatment of both the child and mother is essential to the successful application of FAEE analysis as an objective screen for fetal alcohol exposure. The mother-child relationship should be preserved if possible, as it is crucial to development and indispensable in maximizing the benefits of early intervention. A system which encourages participation and addresses the realities of the addicted lifestyle would see the implementation of this screening test reach its full potential.

KEYWORDS: *Alcohol, screening in pregnancy, fatty acid ethyl esters*

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MOTHERNET: A COMPUTERIZED DATABASE OF CALLS ON THE SAFETY OF DRUGS DURING PREGNANCY AND LACTATION.

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BACKGROUND: Computer technology is quickly becoming an important aid to physicians everywhere. The aggregation of data into one location assists researchers in the quick and simple task of data retrieval. Already the process of a literature search is dramatically simplified into a query on the web using PubMed, Medline or other services.

The Motherisk Program at the Hospital for Sick Children in Toronto has published over 200 scientific papers and over a dozen books. A large portion of the research that goes into these papers comes from primary data collected through the phone help-line for pregnant or lactating mothers.

OBJECTIVE: Currently, counselors collect the data by hand and researchers must search these intake forms at a later time. The purpose of this study was to weigh the benefits of the creation of a computerized intake form storing the caller's data. Researchers will then be able to perform statistical analysis on a large sample of collected data with ease.

METHODS: MotherNET was created to test the validity of this hypothesis. It is a computerized database of calls which allows for simpler access to the data gathered in calls. Each call received is entered into the database and the researchers can then access it to perform queries. The new database will be the largest of its kind worldwide, allowing us to have more efficient research. The equipment required for implementation is a server running Microsoft SQL Server (or related product). As the database grows and the efficacy of the service is determined, the database might be expanded to service other call centres in order to increase the diversity of data entered.

RESULTS: The study is still in progress and there are no results to report yet.

CONCLUSION: e predict that the service will decrease the time required for researchers to gather the data required in their studies.

KEYWORDS: *Pregnancy, drug exposure, lactation*

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TOLL-LIKE 4 RECEPTOR SIGNALLING IS REQUIRED FOR HEPATIC CYTOCHROME P450 3A11 DOWN-REGULATION AFTER THE ADMINISTRATION OF LPS DIRECTLY INTO THE CNS.

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BACKGROUND: Intracranial ventricular injection (i.c.v.) of E.coli LPS produces a loss in cytochrome P450 expression and activity in the liver and the brain. Our understanding of how LPS action in the brain mediates reductions in hepatic P450s is incomplete. Recently, it has been described that toll-like receptor 4 (TLR4) expression in the brain is required for LPS to produce an inflammatory response in that organ.

OBJECTIVE: We have tested the hypothesis that a reduction in cyp3a11 expression in the liver, following i.c.v. injection of LPS is dependent on intact toll-like receptor 4 (TLR4) signalling.

METHODS: Male C3H/HeouJ (TLR4 wild-type) and C3H/HeJ (TLR4 mutant) mice were injected i.c.v. with purified *E. coli* LPS (2.5 μg). Hepatic cyp3a11 mRNA and corresponding enzyme activity (α-hydroxylation of triazolam) was measured at 4 and 24 hours.

RESULTS: Our major finding was that LPS-mediated CNS inflammation caused a reduction in liver cyp3a11 mRNA and microsomal triazolam hydroxylation in the C3H/HeouJ but not the C3H/HeJ mice. Consistent with the LPS responsiveness in those mouse strains, TNFα and IL-1B levels were more highly elevated in the brains of C3H/HeouJ as compared to the C3H/HeJ mice 4 hr after LPS administration i.c.v. However, when challenged with TNFα, only the C3H/HeouJ mice responded with a decrease in cyp3a11 expression and enzyme activity.

CONCLUSIONS: Depression of the major hepatic cytochrome p450 family (CYP3A) by inflammatory responses has consequences for the reduced elimination of many therapeutic agents. Overall, our data support the hypothesis that the down-regulation of hepatic cyp3a11 that occurs after the central administration of LPS is linked to TLR4 receptor signaling pathways.

KEYWORDS: *Toll-like receptors, cytochrome P450, inflammation*

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PATIENT VIEWS ON ELECTRONIC HEALTH INFORMATION PRIVACY.

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BACKGROUND: Health information privacy and security is reported to be a prominent concern of patients but few reports explore the balance of perceived risks and benefits of electronic health data. In previous research, we have detailed patients' concerns about health information privacy. In this study, we sought to systematically study patients perceptions of privacy risks compared to potential benefits of electronic health record systems.

METHODS: Subjects were 496 patients with diabetes participating in a study investigating the effectiveness of a Web-based personal diabetes tracker linked to the physician's electronic medical record. All patients answered telephone questionnaires, one of which was the Health Information Privacy Questionnaire.

RESULTS: While patients had mixed opinions on the ability of computers to keep their health information private (40.1% strongly agree (SA) or agree (A) vs 37.7% strongly disagree (SD) or disagree (D)), there was wide support for the usefulness of computers to share personal health records amongst their health care professionals (89.9% SA/A vs 3.0% SD/D), to inform their physician about their allergies, labs, medications (93.1% SA/A vs 1.8% SD/D), or to advise on how a condition should be treated (91.2% SA/A vs 1.2% SD/D). Although most patients judged the benefits of computers to outweigh the confidentiality risks (57.9% SA/A vs 29.3% SD/D), they were more concerned if their health information was to travel via Internet. Many patients did not want outside organizations access their health information even if personal identifiers were removed (government 40.3% SA/A, private insurers 77.2% SA/A, pharmaceutical industry 45.2% SA/A, university or hospital-based researchers 21.6% SA/A).

CONCLUSIONS: Patients appear to value the potential benefits of electronic health records more than the potential risks, if in the hands of their own providers. They are less inclined to share their health information with other healthcare groups.

KEYWORDS: *Patient perceptions, health policy*

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CYSTEINYL LEUKOTREINES (CYSLT) CONTRIBUTE TO ANGIOTENSIN II (ANG II) EVOKED EXAGGERATED $[CA^{2+}]_I$ RESPONSES IN AORTIC SMOOTH MUSCLE CELLS (ASMC) OF SPONTANEOUSLY HYPERTENSIVE RATS (SHR).

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BACKGROUND & OBJECTIVE: Previously, we have shown that increased CysLT production may contribute to the exaggerated vasoconstrictor responses to Ang II in SHR. We examined whether Ang II evoked Ca^{2+} mobilization is linked to CysLT production and whether this is higher in the primary cultures of ASMC of SHR compared to cells isolated from age-matched Wistar-Kyoto (WKY) strain.

METHODS: Ang II and endothelin-1 (ET-1) evoked increases in $[Ca^{2+}]_i$ level was determined by Fura-2 fluorescence measurement in adherent as well as single ASMC. Total CysLT levels in the culture medium was determined using an ELISA kit. $CysLT_1/CysLT_2$ receptor mRNA levels were quantified by Northern blot analysis.

RESULTS: Ang II and ET-1 evoked $[Ca^{2+}]_i$ responses were higher in the ASMC of SHR. Addition of a $CysLT_1$ selective antagonist MK571, or a dual $CysLT_1/CysLT_2$ antagonist, BAY u9773, reduced the E_{max} values to Ang II (but not to ET-1) in both strains. While BAY u9773 abolished the $[Ca^{2+}]_i$ responses evoked by both LTD_4 and LTC_4, MK571 reduced the responses evoked by LTD_4 but not LTC_4. The basal CysLT levels were higher in the ASMC of SHR. Ang II but not ET-1 evoked time and concentration-dependent increases in CysLT levels in both WKY and SHR cells. The AT_1 antagonist, losartan, but not the AT_2 antagonist, PD123319, attenuated the increases in $[Ca^{2+}]_i$ and CysLT levels evoked by Ang II. The IP_3 antagonist, 2-APB, attenuated the $[Ca^{2+}]_i$ responses to Ang II, LTD_4 and LTC_4.. Both $CysLT_1$ and $CysLT_2$ mRNA were detected in the ASMC of either strain; their levels were significantly higher in SHR.

CONCLUSION: Elevated CysLT production along with increased expression of both $CysLT_1/CysLT_2$ may account for the exaggerated $[Ca^{2+}]_i$ responses to Ang II in SHR due to enhanced mobilization of Ca^{2+} from IP_3 sensitive intracellular stores.

KEYWORDS: *Hypertension, leukotrienes, angiotensin*

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METHYLGLYOXAL-INDUCED STRUCTURAL AND FUNCTIONAL CHANGES OF INSULIN.

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BACKGROUND: Methylglyoxal (MG), a metabolite of glucose, interacts with selective proteins to form irreversible advanced glycoxidated endproducts. The correlation of MG level with different insulin resistance states has been noticed but the direct interaction of MG and insulin molecule is unknown.

OBJECTIVE: To investigate whether MG induces structural and/or functional changes of insulin.

METHODS: MG-induced mass change of insulin was determined by Tricine SDS-PAGE and Mass Spectrometry (MALDI-TOF-MS). 2-deoxy-D-[^{3}H]-glucose was used for glucose uptake experiments in insulin sensitive cell lines 3T3-L1 (mouse adipocyte) and L8 (rat skeletal muscle cell).

RESULTS: Incubation of insulin (0.5 μg/μl or 86 μM) with MG (10 mM) at 37^{o}C for 3 days yielded insulin-MG adducts, evidenced by the appearance of multiple bands with molecular weights greater than native insulin on Tricine SDS-PAGE gels. Native insulin was detected as a molecular ion (MH+) peak of m/z 5808 using MALDI-TOF-MS. Additional peaks appeared in insulin samples incubated with MG, including a significant peak at m/z 5880. The mass difference of 72 Da between m/z 5808 and m/z 5880 matched exactly the molecular weight of MG, indicating that one MG molecule had been added to the insulin molecule, or that insulin had been glycoxidated by MG. Glucose uptake by 3T3-L1 cells was significantly decreased (by 17%, 38%, and 50%, respectively) after treating the cells with MG-insulin adducts generated by incubating insulin (1, 10 or 100 nM) with MG (0.3, 3 or 30 μM), in comparison with the effects of insulin alone at the matched concentrations. A significant decrease in glucose uptake by different MG-insulin adduct preparations was also observed in L8 cells. MG alone (0.3-30 μM) had no effect on glucose uptake by either 3T3-L1 or L8 cells.

CONCLUSION: MG induces structural changes of insulin. The formation of MG-insulin adducts may be responsible for the reduced effect of insulin in stimulating glucose uptake.

Supported by CIHR/RPP

KEYWORDS: *Insulin, glucose metabolism*

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THE TRANSFER OF GLYBURIDE INTO BREAST MILK

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PURPOSE: To determine the extent of transfer of glyburide into breast milk in women with type 2 diabetes. Presently women are advised not to breastfeed while on oral hypoglycemics.

METHODS: Six women were studied following a single 5 mg oral dose of glyburide. Glyburide concentrations in plasma and milk were measured by high performance liquid chromatography with fluorescence detection following liquid-liquid extraction with chloroform and derivatization with NBD-Chloride.

RESULTS: The subjects had a mean age of 38 years (range 33-42 years) and a mean body weight of 91 kg (range 69-123 kg). When normalized to body weight, the median dose of glyburide was 0.06 $mg \cdot kg^{-1} \cdot day^{-1}$ (range 0.04-0.07 $mg \cdot kg^{-1} \cdot day^{-1}$). There was no detectable glyburide in any of the milk samples (limit of detection (LOD) 5ng/ml) over an 8 hour period. In contrast, plasma concentrations were within the normal range for patients taking 5 mg per day of the drug.

CONCLUSIONS: The concentrations of glyburide in breast milk are not detectable above the 5ng/ml LOD. Thus the maximum relative infant exposure is negligible for breastfeeding. We conclude that glyburide use by breastfeeding mothers is safe. Nevertheless, it is still prudent to follow the baby for potential signs of hypoglycemia.

KEYWORDS: *Type II diabetes, glyburide, lactation*

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SIX MONTH FOLLOW-UP OF BREASTFEEDING WOMEN WITH DEPRESSION: HEALTH AND WELL-BEING OF MOTHER AND INFANT.

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BACKGROUND: Exposing an infant to maternal medication through breastmilk is cited as a reason for discontinuing/not commencing medication, or discontinuing breastfeeding. In the case of women with depression, not treating the condition may cause detrimental outcomes to mother and infant.

OBJECTIVE: To determine the health and well-being of depressed, breastfeeding women on antidepressants (Group 1, G1), compared to those forgoing pharmacotherapy (Group 2, G2), and healthy breastfeeding women (Group 3, G3), and their infants.

METHODS: Mother-infant pairs were followed-up at 6 weeks, 3, and 6 months postpartum. Information on medication use, infant feeding, and adverse events were collected. The Edinburgh Postnatal Depression Scale (EPDS), Short Form 36 (SF-36), and Functional Status II-Revised (FS-IIR) were used to measure maternal depression severity, well-being, and infant well-being, respectively.

RESULTS: Six month follow-up data are available for 67, 30, and 72 women in G1, G2, and G3, respectively. No antidepressant related adverse events were noted in infants. EPDS scores at each follow-up differed statistically (median 7, 12, and 4 for G1, G2, and G3, respectively at 6 months, $p<0.01$), indicating significant morbidity in G2. No differences existed in SF-36 physical component scores. G1 and G2 women had lower mental component scores than G3 women (median 48.6, 43.0, and 56.2, respectively). A significant number of women in G1 (42%) and G2 (57%) reported still feeling depressed at the 6 month follow-up. G1 infants scored statistically lower in FS-IIR total and health scores at 6 months, compared to G3.

CONCLUSION: Women with postpartum depression do not benefit from forgoing pharmacotherapy. Even treated women do not attain the same functional status as healthy individuals, suggesting inadequate treatment. Postpartum women with depression should continue to breastfeed and be treated with the adequate dose of the antidepressant.

KEYWORDS: *Lactation, breast-feeding*

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IMPROVEMENT IN CARDIAC FUNCTION OF DIABETIC RATS BY BOSENTAN IS NOT ASSOCIATED WITH CHANGES IN THE ACTIVATION OF PKC ISOFORMS

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BACKGROUND: Previously we demonstrated that chronic treatment with the mixed ET_A and ET_B receptor blocker bosentan improved isolated working heart function in streptozotocin (STZ) diabetic rats, suggesting that an altered ET system may contribute towards the cardiac complications of diabetes. ET-1 peptide levels, ET-1 mRNA and ET_A and ET_B receptor mRN_A were all increased in diabetic hearts, but were unaffected by bosentan treatment. Stimulation of ET-1 receptors leads to increased activation of protein kinase C (PKC), which is associated with it's translocation from the cytosol to the membrane fraction. Persistent activation of specific isoforms of PKC has been proposed to contribute to diabetic cardiomyopathy.

OBJECTIVE: To determine whether chronic treatment with bosentan influences the activation of PKC isoforms in hearts from diabetic rats.

METHODS: Male Wistar rats were divided into 4 groups: control, bosentan-treated control, diabetic, and bosentan-treated diabetic. Diabetes was induced by IV injection of 60mg/kg streptozotocin. One week later, treatment with bosentan (100mg/kg/day) was begun and continued for 10 weeks. The heart was removed, homogenized and separated into soluble (cytosolic) and particulate (membrane) fractions. Aliquots of each fraction were subject to SDS-PAGE and PKC isoform content in each fraction determined by Western blotting.

RESULTS: PKC α, β2, δ, ε and ξ were all detected in hearts from both control and diabetic rats. However, no change in the levels or distribution between the soluble and particulate fractions of any of these isoforms could be detected in diabetic hearts compared to control, whether untreated or treated with bosentan.

CONCLUSION: Bosentan does not improve cardiac performance in STZ-diabetic rats by affecting the activation of PKC isoforms.

KEYWORDS: *Cardiac function, Protein kinase C, bosentan*

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PRENATAL EXPOSURE TO HMG-COA REDUCTASE INHIBITORS: EFFECTS ON FETAL AND NEONATAL OUTCOME.

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BACKGROUND: HMG-CoA reductase inhibitors (statins) have been widely used for the treatment of hyperlipidemia. Although no increase in birth defects was suggested by a study based on post-marketing volunteer reports on lovastatin and simvastatin, no data exists on other commonly used statins. Moreover, detailed outcome data on use of any statins during pregnancy are non-existent.

OBJECTIVE: To determine whether in utero exposure to statins results in adverse fetal/neonatal outcome.

METHODS: This was an observational cohort study of women who contacted Motherisk and were taking statins antenatally. Control subjects, who were not exposed to any known teratogens, were matched for maternal age, gestational age at time of call, smoking and alcohol consumption, and pregnancy history. The primary outcome was the incidence of major birth defects. Secondary outcomes included the rate of live births, spontaneous and therapeutic abortions and fetal/neonatal death; neonatal outcomes included birth weight, gestational age at delivery, as well as general infant health and development.

RESULTS: Thirty women on statins (atorvastatin: 20; pravastatin: 5; and simvastatin: 5), and 30 matched controls were followed. There were 20 and 26 live births in the exposed and the control groups, respectively. There was no difference in the rate of major malformations between cases (0/20) and controls (3/26: p=0.25). There were twice as many spontaneous abortions in the exposed group (8/30) than the control group (4/30), but the difference did not reach statistical significance (p=0.33). Gestational age at delivery, adjusted birth weight, delivery method and neonatal health problems were also not significantly different between the two groups.

CONCLUSION: Our data suggest that statins including atorvastatin are not major human teratogens, providing a framework for a large-scale cohort study.

KEYWORDS: *Pregnancy, HMG-CoA Reductase inhibitors foetal outcome*

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EFFECT OF CHRONIC ENDOTHELIN BLOCKADE ON PKC ISOFORM DISTRIBUTION IN MESENTERIC ARTERIES FROM DIABETIC RATS.

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BACKGROUND: Previously we have demonstrated that superior mesenteric arteries (SMA) from rats with chronic streptozotocin-induced diabetes exhibit increased levels of immunoreactive endothelin-1 (ET-1). Increased protein kinase C (PKC) activity, associated with translocation of specific isoforms from the cytosol to the membrane fraction, has been demonstrated to occur on stimulation of ET receptors. We hypothesized that the increase in ET-1 levels leads to increased activation of specific PKC isoforms, which then contribute to the enhanced contractile response to ET-1 that we have also detected in endothelium-intact SMA from diabetic rats.

OBJECTIVE: To determine whether chronic treatment with bosentan influences the activation of PKC isoforms in SMA from diabetic rats.

METHODS: Male Wistar rats were divided into 4 groups: control, bosentan-treated control, diabetic, and bosentan-treated diabetic. Diabetes was induced by IV injection of 60mg/kg streptozotocin. One week later, treatment with bosentan (100mg/kg/day) was begun and continued for 10 weeks. The SMA was removed, homogenized and separated into soluble (cytosolic) and particulate (membrane) fractions. Aliquots of each fraction were subject to SDS-PAGE and PKC isoform content in each fraction determined by Western blotting.

RESULTS: An increase in PKCβ1 and PKCε in the particulate fraction, with no change in their levels in the cytosolic fraction, was detected in SMA from untreated diabetic rats. However, treatment with bosentan was without effect on the levels or distribution of any isoform of PKC in SMA from either control or diabetic rats.

CONCLUSION: These data suggest that increased activation of PKCβ2 and PKCε occurs in SMA from diabetic rats, but that this does not result from stimulation of ET-1 receptors.

KEYWORDS: *Protein kinase C, diabetes, endothelin*

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COMMUNITY METHODS: DEVELOPING BRIEF ALCOHOL INTERVENTIONS FOR ABORIGINAL MOTHERS TO PREVENT FASD.

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Promoting health among women of childbearing age in Aboriginal Communities is an important national public health challenge. In this population, addressing alcohol abuse, binge drinking and Fetal Alcohol Spectrum Disorder (FASD) is an important issue. Studies have suggested that the prevalence of FASD may be significantly higher in Aboriginal versus to non-aboriginal populations in Canada. Thus, preventing alcohol abuse, the direct cause of FASD, warrants national attention to develop effective, culturally appropriate prevention strategies.

In this methods development project, we utilize a participatory research approach with the expectation that this will increase cultural appropriateness and acceptance within the communities. 'Local Opinion Leaders', identified by women in the community, will form the foundation of the intervention development teams and will have key roles in the 'Community Advisory Panels' that are charged with operationalizing the interventions.

The university-based researchers will work in close collaboration with the community-based research teams. Our goal is to develop a model that could be used by communities interested in developing and implementing community-specific FASD interventions that utilize the strengths and characteristics of the community. The project consists of three methodological phases:

PHASES

1. developing the instruments and interventions through a process of listening and learning from local community people;
2. implementing and evaluating the model; and
3. documenting the process to provide a guide or model for communities interested in developing and implementing culturally appropriate brief alcohol interventions for women at-risk in the postpartum period.

(Note: We are currently in phase #1 of this 3-yr project. We are in a position to report the methods of this project and some of the preliminary lessons learned and experiences to date.)

KEYWORDS: *Alcohol, Aboriginal women, FASD*

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AMIODARONE ACTIVATION OF PPARα TARGET GENES IN MOUSE HEPATOCYTES.

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BACKGROUND: Amiodarone, a potent antiarrhythmic agent, is known to cause hepatotoxicity in some patients and this potential toxicity interferes with its use in some populations.

OBJECTIVE: To elucidate the mechanism by which amiodarone induces unwanted hepatic effects.

Methods: Groups of mice were administered amiodarone intraperitoneally in doses ranging from 10 to 150 mg/kg/day for a 4 day period.

RESULTS: Amiodarone treatment induced the formation of lipid containing vacuoles in hepatocytes in a dose-dependent manner while also inducing a significant decrease in serum triglycerides and glucose. Serum cholesterol, bile acids and AST concentrations were unaltered over the 4 days of exposure to amiodarone. Northern blot analysis of liver RNA revealed a dose-dependent increase in the expression of a number of genes critical for mitochondrial and peroxisomal fatty acid □-oxidation. Because many of these genes are regulated by the peroxisome proliferator activated receptor-□ (PPAR□), a ligand activated nuclear hormone receptor transcription factor, transactivation assays were performed in human HepG2 hepatoma cells to determine if amiodarone was a ligand activator of PPAR□. Amiodarone failed to directly activate either human or transiently expressed mouse PPAR□in these cells.

CONCLUSION: These results indicate that amiodarone only indirectly activates hepatic target genes involved in fatty acid □-oxidation and that the mechanism does not involve direct binding to PPAR□. It is likely that amiodarone causes accumulation of fatty acids in the liver through disruption of the mitochondrial fatty acid □oxidation pathway. Accumulation of these fatty acids would then stimulate a proliferative effect on the peroxisomal □-oxidative pathway. An indirect activation of PPAR□target genes by amiodarone may be an indicator of the mechanisms responsible for the hepatotoxicity seen in some patients undergoing amiodarone treatment.

KEYWORDS: *Amiodarone, hepatotoxicity, fatty acid oxidation*

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20-HYDROXYEICOSATETRAENOIC ACID (20-HETE) EVOKED INCREASE OF SPONTANEOUS TONE IN AORTA OF DEOXYCORTICOSTERONE ACETATE (DOCA)-SALT HYPERTENSIVE RATS IS MEDIATED BY CYCLOOXYGENASE (COX) METABOLITES.

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BACKGROUND: Spontaneous tone increases as a function of preload in aortic rings isolated from DOCA-salt hypertensive rats, but not from SHAM normotensive rats (Ghosh *et al*., Br. J. Pharmacol, 2004, in press), but the role of 20-HETE and its cyclooxygenase (COX) products had not been examined.

OBJECTIVE: We sought to address this issue by recording responses to 20-HETE in the presence and absence of the COX inhibitor, valeroyl salicylate (VAS, 3 mM), or the thromboxane/prostaglandin (TP) receptor antagonist, SQ 29548 (3 μM).

METHODS: Aortic rings were mounted in an organ bath containing Kreb's buffer (37˚C). The preload was increased to an optimal tension of 5 g in the presence of 100 nM sodium nitroprusside (SNP) to ensure passive conditions. Tension was recorded isometrically.

RESULTS: Endogenous 20-HETE levels were higher in aortae from DOCA-salt hypertensive rats (26 ± 2 ng/g tissue) than in those from SHAM normotensive rats (7 ± 5 ng/g). Washout of SNP evoked spontaneous tone. Tone was 35 ± 2% of the maximum contraction evoked by 120 mM KCl in untreated endothelium-intact rings and 55 ± 4% in endothelium-denuded rings. 20-HETE increased spontaneous tone in endothelium-intact aortic rings (54 ± 4%), but not endothelium-denuded rings (62 ± 4%). VAS and SQ 29548 reduced spontaneous tone dramatically in endothelium-intact rings (2 ± 2% and 3 ± 1% respectively), but not in endothelium-denuded rings. Both VAS and SQ 29548 blocked the increases in spontaneous tone evoked by 20-HETE in endothelium-intact rings (6 ± 3% and 5 ± 3% respectively), but not endothelium-denuded rings. The BK_{ca} channel blocker, iberiotoxin (IBT, 10nM) also prevented 20-HETE evoked increases in tone.

CONCLUSION: These results indicate that COX metabolites of 20-HETE mediate the increase in tone evoked by 20-HETE. Those COX metabolites appear to exert their effect through BK_{ca} channels and TP-receptors (Supported by CIHR)

KEYWORDS: *Hypertension, cyclooxygenase*

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EFFECT OF FUNCTIONAL GROUPS ON NADPH: CYTOCHROME P450 REDUCTASE-MEDIATED REDUCTION AND ACTIVATION OF BENZOQUINONE MUSTARDS.

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BACKGROUND: Bioreductive antitumor agents are an important class of anticancer drugs due to their suitability for enzyme-directed tumor targeting. Enzyme-directed tumor targeting refers to the use of drugs that are specifically activated by a particular enzyme that is more active in tumor cells compared to normal cells. Current bioreductive agents are activated by more than one bioreductive enzyme. Determining the effects of structural factors on the activation of bioreductive agents will allow the development of bioreductive agents that are specific for activation by a single enzyme.

OBJECTIVE: To identify functional groups that will confer specificity of activation ofe novel bioreductive benzoquinone mustard (BM) antitumor agents by the reductive enzyme NADPH: cytochrome P450 reductase (P450 Reductase).

METHODS: A series of model BM analogs were utilized that included analogs substituted with electron-donating groups, electron-withdrawing groups, and sterically bulky groups. Cytotoxicity of BM analogs was determined in two human cancer cell lines by means of MTT assays. The effect of the functional groups on the rate of reduction of BM analogs by P450 reductase was determined by: a) electron paramagnetic resonance (EPR), a technique that measures the formation of semiquinone species. b) spectrophotometric assays, which measure changes of the quinone group absorbance maxima. DNA damage subsequent to reduction of the BM analogs was measured gel by electrophoresis assays.

RESULTS & CONCLUSIONS: Cytotoxicity studies demonstrated that functional groups could affect the cytotoxic activity of quinone bioreductive agents in whole cell systems. Analogs substituted with electron donating groups had greater cytotoxic activity compared to other BM analogs including the parent compound. No semiquinone radicals were detected after treatment of the BM analogs with P450 reductase, suggesting that reduction of the semiquinone by this enzyme may be fast compared with reduction of the quinone. Spectrophotometric studies provide evidence that P450 reductase can reduce some of the BM analogs, and that functional groups can affect the rate of reduction of these compounds. Preliminary data suggested that BM analogs can produce DNA damage after reduction by P450 reductase.

KEYWORDS: *Cytochrome P450 reductase, antitumour agents*

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TOXICITY OF MONOCYTES VERSUS PERIPHERAL BLOOD MONONUCLEAR CELLS WITH SULFAMETHOXAZOLE HYDROXOLAMINE.

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BACKGROUND: Sulfamethoxazole is still widely used. Unfortunately, drug hypersensitivity remains a major problem associated with sulfonamide therapy. Activation of the parent sulfamethoxazole to its reactive sulfamethoxazole hydroxylamine (SMX-HA) has been demonstrated to be a critical determinant of drug hypersensitivity. SMX-HA produces cytotoxicity which is exaggerated in cells of patients who have sustained reactions. The precise cellular target(s) of reactive metabolite toxicity remain unclear.

OBJECTIVES: To determine there is differential toxicity between the peripheral blood mononuclear cells (PBMCs) and monocytes.

METHODS: Monocytes from the U937 line and PBMCs from 23 control volunteers were incubated with increased concentrations of sulfamethoxazole and sulfamethoxazole hydroxylamine. After incubation cellular viability was determined using an MTTcytotoxicity assay.

RESULTS: There was no decline in viability associated with incubation with the parent (sulfamethoxazole) with either monocytes or PBMCs. There was concentration-dependent decline in viability with both PBMCs and monocytes over the concentration range from 0 to 800 μM. There was significantly more cell death among PBMCs than among monocytes (at 800 μM, viability of 65.9 ± 6.13% for monocytes, 18.2 ± 12.11% for PBMCs, $p>0.05$).

CONCLUSIONS: Phagocytic cells such as monocytes appear to be more resistant to reactive drug metabolites than the general PBMCs population, suggesting that cellular target(s) for reactive sulfonamide metabolites may be lymphocyte sub-populations.

KEYWORDS: *Sulphonamides, keratinocytes, adverse drug reactions*

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INTER-SPECIES DIFFERENCES IN PHARMACOKINETICS OF VITAMIN B12 (CYANOCOBALAMIN).

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BACKGROUND: Clinical and experimental evidence on the therapeutic benefits of high dose vitamin B12 have been well documented. Sparse data exist on the disposition of this vitamin to support dose requirements. We studied the pharmacokinetics (PK) of vitamin B12 in different animal models as well as in healthy volunteers.
OBJECTIVE: To evaluate the inter-species differences in the PK of high doses of vitamin B12.
METHODS: Vitamin B12 100 mg/kg was administered as a single i.v. bolus dose to Sprague-Dawley rats, to Beagle dogs, and to healthy volunteers. Plasma levels were obtained by means of an HPLC method using UV detector and an external standard. The detection limit was 20 ng/ml and the within- and between-run CV (%) were 3.5 and 10.4, respectively. In all cases, the PK analysis was performed by means of a non-compartmental model.
RESULTS: The elimination rate constant was 0.025 ± 0.005 min-1 in rats, 0.018 ± 0.002 min-1 in dogs, and 0.0085 ± 0.003 min-1 in humans. The half-life was 29.0 ± 6.1 min in rats, 38.8 ± 3.7 min in dogs, and 90 ± 24 min in humans. The volume of distribution was 335.6 ± 46.7 ml in rats, 317.8 ± 85.9 ml in dogs, and 22,900 ± 2,400 ml in humans.
CONCLUSION: The PK of vitamin B12 exhibited similarity between the two animal species, whereas in humans it was substantially different, with much slower elimination. These results confirm a much more rapid elimination in animals. The new human data should allow development of more appropriate dosing guidelines.
KEYWORDS*: Pharmacokinetics, Vitamin B12*

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NEURODEVELOPMENT IN CHILDREN EXPOSED IN UTERO TO CYCLOSPORINE AND AZATHIOPRINE FOLLOWING MATERNAL RENAL TRANSPLANT: PRELIMINARY RESULTS.

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BACKGROUND: Cyclosporine and azathioprine are the most commonly used drugs to prevent rejection of transplanted organs. Pregnancy following renal transplantation can be associated with risks for both the mother and the fetus, therefore it is essential to study the reproductive safety of these drugs.
OBJECTIVES: To evaluate the prenatal effects of cyclosporine and azathioprine on children's neurodevelopment following maternal renal transplant, and to compare to control children.
METHODS: Prospective cohort with matched controls. Exposed children were assessed using the Wechsler Preschool and Primary Scales of Intelligence – Revised, the Wechsler Intelligence Scale for Children-III, the Developmental Neuropsychological Assessment, the Preschool Language Scale-III, and the Clinical Evaluation of Language Fundamentals-III. The preliminary results of the exposed children were compared to standard norms.
RESULTS: Currently, the 20 exposed children (age 3 to13 years) were not significantly different from the norms on Global, Verbal, and Performance IQ (103 + 15; 105 + 16; and 101 + 14 respectively). The exposed children appear to have language scores (Total 112 + 8; Expressive 111 + 10; and Auditory 112 + 7) in the upper range of the norms.
CONCLUSION: These preliminary results are reassuring and may contribute to informed decision making by pregnant women and health professionals.
KEYWORDS: *Cyclosporine, azathioprine, pregnancy*

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TOPICAL 4% AMETHOCAINE FOR REDUCING PAIN OF MEASLES-MUMPS-RUBELLA IMMUNIZATION.

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BACKGROUND: Despite routine immunizations being a common source of iatrogenic pain in infants and children, this pain is not routinely managed. Ametop™ gel is a novel preparation of the local anaesthetic 4% amethocaine; it has the advantage of achieving effective skin anesthesia within 30 - 45 minutes of application.
OBJECTIVE: To determine the efficacy and safety of 4% amethocaine for reducing measles-mumps-rubella vaccination pain.
METHODS: Healthy infants receiving their routine 12-month measles-mumps-rubella (MMR) vaccination participated in a double-blind, randomized placebo-controlled trial. Infants were randomized to receive 1g of amethocaine or a visually identical placebo for 30 minutes prior to vaccination. The vaccination procedure was videotaped and the tape used later for pain assessment; the Modified Behavioural Pain Scale (MBPS) was the primary pain outcome measure. To ensure that amethocaine did not interfere with the immunogenicity of the vaccine, a blood sample was collected from infants 1 month post-vaccination to assess antibody titers. Local skin reactions were also assessed.
RESULTS: One hundred and twenty infants participated in the study; 60 were followed up for assessment of antibody titers. There were no significant differences in demographic characteristics between treatment groups. The amethocaine group (n = 61) had significantly lower MBPS scores than the placebo group (n = 59); 1.51 vs. 2.29 (p=0.029). The rate of vaccination success (antibody titers positive for measles, mumps and rubella) was not different between the amethocaine and placebo groups (p =0.823). The amethocaine group developed significantly more local skin reactions than the placebo group; erythema was the most commonly observed reaction ($p < 0.001$).
CONCLUSION: Amethocaine 4% gel significantly reduced the pain associated with subcutaneous measles-mumps-rubella vaccination in infants when compared to placebo and did not interfere with subsequent development of protective antibody levels. Further investigation of its safety during vaccination is recommended before widespread clinical use.
KEYWORDS: *Pain, Topical anaesthetics, immunization*

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LYSOPHOSPHATIDYLCHOLINE MEDIATED AUGMENTATION OF CARDIAC LUMINAL LPL REQUIRES GENERATION OF LYSOPHOSPHATIDIC ACID.

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BACKGROUND: Coronary lipoprotein lipase (LPL) actively metabolizes the triglyceride (TG) of lipoproteins to fatty acid (FA) for energy production. As endothelial cells (EC) cannot synthesize LPL, myocytes provide LPL that is then translocated across the coronary lumen. Recently, palmitoyl lysophosphatidylcholine (PA-lysoPC) generated following TG breakdown has been shown to augment cardiac luminal LPL.
OBJECTIVE: To examine the mechanisms by which lysoPC augment coronary luminal LPL.
METHODS: Retrograde Langendorff perfusions were carried out with PA-lysoPC, 1 nM for 60 min, and LPL activity measured. Separately, animals were administered cycloheximide (CHX, 2 mg/kg, i.p.) with subsequent in vitro perfusion with PA-lysoPC (1 nM). Cardiac myocytes were also incubated with either PA-lysoPC (1 nM) or lysophospatidic acid (LPA) (1 nM) either in the presence or absence of cytochalasin (1μM).
RESULTS: Perfusing PA-lysoPC for 60 min through control hearts augmented heparin-releasable luminal LPL activity. LPL augmenting property of PA-lysoPC was blocked by the protein synthesis inhibitor, CHX, implying that PA-lysoPC mobilizes LPL from cardiomyocytes. Incubating myocytes with PA-lysoPC did not change total myocyte LPL suggesting that PA-lysoPC probably requires breakdown in the EC, before increasing luminal LPL. Interestingly, LPA can be generated from the hydrolysis of PA-lysoPC in the outer leaflet of the cell membrane. Incubation of control myocytes with LPA significantly enhanced basal and heparin releasable LPL activity an effect that was inhibited effectively by pretreatment with cytochalasin an inhibitor of actin cytoskeleton polymerization.
CONCLUSIONS: PA-lysoPC causes posttranslational augmentation of luminal LPL via LPL mobilization from cardiomyocytes. Metabolism of PA-lysoPC to LPA in the EC is mandatory for luminal LPL augmentation. LPA by modulating actin cytoskeleton reassembly influences myocyte LPL.
KEYWORDS: *Cardiac function, lipoproteins, fatty acids*

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ORAL ADMINISTRATION OF SODIUM TUNGSTATE IMPROVES CARDIAC PERFORMANCE IN STZ DIABETIC RATS.

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BACKGROUND: Diabetic cardiomyopathy, a secondary complication in long-term diabetes is a major cause of morbidity and mortality. Normalization of hyperglycemia and hyperlipidemia is an important therapeutic objective in containing the development of cardiac dysfunction in diabetes. Recent studies have demonstrated the antidiabetic activity of sodium tungstate in several animal models of diabetes though its effects on the ensuing cardiac dysfunction are yet to be investigated.

OBJECTIVE: The present investigation attempts to study the effects of orally administered sodium tungstate on cardiac performance along with glucose and lipid levels in STZ-diabetic rats.

METHODS: Male wistar rats were randomly divided into four groups: Control, Control treated, Diabetic and Diabetic treated. Treatment consisted of sodium tungstate in drinking water for 9 weeks. Bodyweight, food and fluid intake, plasma glucose, insulin, triglyceride and free fatty acid levels were measured. An oral glucose tolerance test was performed before termination, subsequent to which the cardiac performance of isolated hearts was evaluated using a working heart apparatus.

RESULTS: Diabetic rats ingesting sodium tungstate in varying doses over 9 weeks, showed a significant reduction in fluid intake, food intake, plasma glucose, triglycerides, free fatty acids and improved tolerance to oral glucose load. Analysis of the data indicates that the effect of tungstate is more likely due to an enhancement of insulin activity rather than to increase in insulin levels. Assessment of cardiac performance showed that tungstate treatment in diabetic rats significantly improved left ventricular pressure development (LVP), the rate of contraction (+dP/dT) and the rate of relaxation (-dP/dT). While, there were no deaths or hypoglycemic episodes in tungstate treated rats, either control or diabetic, there was a marked decrease in body weight gain.

CONCLUSION: This study extends previous observations on the antidiabetic activities of tungstate and also reports for the first time the salutary effects in preventing diabetic cardiomyopathy.

KEYWORDS: *Diabetes, tungstate, cardiac performance*

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INHIBITION OF INDUCIBLE NITRIC OXIDE SYNTHASE (INOS) INCREASES PRESSOR RESPONSES TO ANGIOTENSIN-2 (AT-2) IN STREPTOZOTOCIN (STZ) DIABETIC RATS

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BACKGROUND: STZ-diabetic rats are found to be either normotensive or slightly hypotensive despite exhibiting endothelial dysfunction. Studies have reported increased plasma nitric oxide (NO) levels and elevated iNOS expression in heart and vascular smooth muscle of STZ diabetic rats. Therefore in the absence of functional endothelium, increased NO might be produced by iNOS and thus help prevent the development of hypertension. We therefore studied the hemodynamic effects of AT-2 following iNOS inhibition in STZ diabetic rats using 1400W, a selective iNOS inhibitor.

OBJECTIVE: To determine if inhibition of iNOS influences the pressor response of angiotensin-2 in STZ diabetic rats.Methods: Eight rats were made diabetic by a single bolus iv injection of STZ (60 mg/kg). Basal body weights, serum glucose and insulin levels were measured. Three weeks following STZ or saline injection, surgical implantation of catheters was done by placing fluid filled catheters in the carotid artery and left jugular vein to record blood pressure and drug administration respectively. Pressor responses to bolus doses of AT-2 (20-320-pmol/kg) were measured before and after the administration of 1400W(3mg/Kg, iv, single bolus).

RESULTS: Induction of diabetes in rats resulted in hyperglycemia, hypoinsulinemia, decreased body weight and depressed basal mean arterial blood pressure (Control: 113 ± 2 vs Diabetic: 89 ± 2 mmHg). Preliminary data demonstrated a dose-dependent pressor response to AT-2 in both control and diabetic rats. The effect of AT-2 on blood pressure was not affected by iNOS inhibition in control rats whereas in diabetic rats there was a greater elevation in blood pressure following 1400W administration.

CONCLUSION: Inhibition of iNOS increases the pressor response to AT-2 in diabetic rats. The data support the hypothesis that increased production of NO through iNOS may play an important role in the prevention of the development of hypertension in STZ diabetic rats.

KEYWORDS: *Diabetes, Nitric Oxide Synthetase, Angiotension II*

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INHIBITION OF HEPATIC COX CAUSES HISS-DEPENDENT INSULIN RESISTANCE.

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BACKGROUND: We have recently proposed that insulin causes the release of a hepatic insulin sensitizing substance (HISS) from the liver. The hepatic parasympathetic nerves play a permissive role in allowing insulin to trigger HISS release. HISS enhances the skeletal muscle response to insulin and accounts for approximately 55% of the glucose disposal resulting from a bolus of insulin. In the absence of HISS, severe HISS-dependent insulin resistance (HDIR) occurs. We have also shown that HISS release depends on the production of nitric oxide (NO) in the liver. Blockade of NO production in the liver, by NO synthase antagonists, results in inhibition of HISS release from the liver and results in HDIR.

OBJECTIVE: Since, in many physiological responses, NO and prostaglandins (PGs) are co-released and/or NO action is mediated through the production of PGs, we hypothesised that the release of HISS from the liver is also mediated through the hepatic production of PGs.

METHODS: In all our experiments a rapid insulin sensitivity test (RIST), developed in our laboratory, was used. RIST index is the amount of glucose infused after injection of a bolus of insulin (50 mU/kg) to maintain the euglycemia during the test.

RESULTS: Intraportal administration of indomethacin, a cyclooxygenase inhibitor, (4.0 mg/kg, RIST index = 82.2 ± 11.8 mg/kg) inhibited the control RIST (RIST index = 227.4 ± 12.2 mg/kg), by 64% and produced HDIR. However, administration of the same dose of indometacin intravenously did not produce significant HDIR (RIST index = 162.1 ± 18.1 mg/kg) and inhibited the control RIST (RIST index = 200.2 ± 10.9 mg/kg) only by 19%.

CONCLUSION: The results are consistent with the hypothesis that the hepatic parasympathetic-dependent release of HISS is mediated through PGs production in the liver.

KEYWORDS: *Insulin resistance, cyclooxygenase*

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NITRIC OXIDE SYNTHASE INHIBITION EXAGGERATES THE HYPOTENSIVE RESPONSE TO GHRELIN: ROLE OF CALCIUM-ACTIVATED POTASSIUM CHANNELS.

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BACKGROUND & OBJECTIVE: Ghrelin, the cognate endogenous ligand for the growth hormone secretagogue (GHS) receptor, promotes growth hormone release and food intake. While ghrelin has been shown to exert a beneficial hemodynamic effect with a fall in mean arterial pressure (MAP) with no change in heart rate (HR), the mechanism that contributes to this effect has not been addressed.

METHODS: The effect of a single bolus infusion of ghrelin (12 nmole/kg, i.v) on the changes in MAP and HR was recorded in 12 week old male anaesthetized Sparague-Dawley rats subjected to either pretreatment with the nitric oxide synthase (NOS) inhibitor, L-NAME (0.7mg/ml p.o. ad libitum for 5 days), or saline (control) group.

RESULTS: Ghrelin evoked a significant fall in mean arterial pressure (MAP) at 20 min ($P<0.05$) after infusion in the control group without any change in HR. The blood pressure returned to basal value at 1 hr. Ghrelin-evoked fall in MAP was much higher ($P<0.01$) and sustained for an hour in rats subjected to NOS inhibition. Pretreatment with the cyclooxygenase inhibitor, indomethacin failed to affect the responses in either group. Pretreatment with apamin (25 μg/kg) and charybdotoxin (ChTx; 25 μg/kg), a combination that is known to selectively block endothelium-dependent hyperpolarization factor (EDHF) attenuated the hypotensive response to ghrelin in both control and NOS inhibited rats. Sodium nitroprusside (SNP) induced fall in MAP was unaffected by preinfusion with apamin and ChTX combination in either group while ACh-evoked hypotension was attenuated in L-NAME treated rats.

CONCLUSION: These data confirm that the NO-independent hypotensive response to ghrelin may be mediated by EDHF that is linked to stimulation of apamin and ChTX sensitive Ca^{2+} activated potassium channels present on the endothelial cells. The ghrelin-evoked fall in MAP may be significant in states of endothelial dysfunction associated with reduced NO availability.

KEYWORDS: *Blood pressure, nitric oxide synthetase; glurelin*

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POST-MORTEM CHLORAL HYDRATE DISPOSITION AND INTERPRETATION OF FORENSIC DATA.

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BACKGROUND: In separate and unrelated incidents, three children with profound developmental delay, treated with routine doses of chloral hydrate as a sedative hypnotic, died unexpectedly. All had post-mortem serum concentrations of its active metabolite, trichloroethanol (TCOH), in the fatal range. Post-mortem tissue redistribution occurs for some drugs and represents a potential explanation for these findings.
OBJECTIVE: We investigated whether post-mortem redistribution of chloral hydrate metabolites occurs in a rat model.
METHODS: Rats were administered 100 mg/kg of chloral hydrate by gavage and euthanized at 1.0 hour after dosing. Multiple tissues (liver, kidney, blood, heart, lung, muscle and brain) were sampled at 0, 6, 24 and 48 hours after death to quantify TCOH and trichloroacetic acid (TCA), two chloral hydrate metabolites. There were six rats in each of these four groups. Metabolite quantitation was by gas chromatography, and statistical analysis employed ANOVA and Tukey's Test.
RESULTS: Significant TCOH redistribution was observed only in liver, with an increase from 30.3 $\pm$ 9.8 μg/g (mean $\pm$ SE) at death to 75.7 $\pm$ 10.9 μg/g at 48 hours post-mortem ($p=0.011$), but not when normalized to blood concentration. In blood, the TCOH concentration increased from 4.4 $\pm$ 0.8 μg/g at death to 10.2 $\pm$ 1.4 μg/g at 48 hours post-mortem ($p=0.078$). For TCA, no tissue redistribution was detected post-mortem excepting lung, where normalization of TCA tissue to blood concentration suggested an increase in lung:blood content from 0.6 $\pm$ 0.2 to 1.2 $\pm$ 0.1 by 6 hours after death ($p=0.017$).
CONCLUSION: Our data suggest modest and tissue-selective post-mortem redistribution of chloral hydrate metabolites. Further studies are necessary to clarify the impact on the interpretation of human post-mortem toxicology data.
KEYWORDS: *Post-mortem redistribution, chloral hydrate*

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SHORT COURSE DIRECTLY OBSERVED THERAPY (DOT) WITH AZITHROMYCIN FOR BACTERIAL INFECTIONS IN HIV-INFECTED INTRAVENOUS DRUG USERS (IVDUS).

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BACKGROUND: A frequent medical problem in IVDUs is intercurrent bacterial infection usually involving the skin & soft tissues or the respiratory tract.
OBJECTIVE: We have evaluated a DOT model for the administration of antibiotics to such patients using a three-day course of azithromycin.
METHODS: We have evaluated 116 HIV and/or HCV-positive IVDUs on methadone maintenance therapy that have been treated with azithromycin as the sole antibiotic for acute bacterial infections between January 1, 2001 and November 30, 2003. Retrospective (n = 40 in 2001-2002) and prospective (n = 76 in 2003) patients treated for respiratory (RTIs, 16 and 40 cases) and skin or soft tissue infections (SSTIs, 24 and 36 cases) received azithromycin at 500mg/day for 3 days. Evaluation of clinical response was done at weeks 1 and 2, and again at week 8. Use of additional antibiotics or a course of azithromycin prolonged beyond 7 days was counted as a failure for the purposes of this analysis. We tabulated the overall rate of response to therapy as well as the correlates of therapeutic success.
RESULTS: At 8 weeks, a complete clinical response to azithromycin therapy was noted in 33/40 (83%) of cases in the retrospective group and 64/76 (84%) of cases in the prospective group. HIV infection, CD4 count, plasma viral load, current HAART, hepatic dysfunction, type of infection (RTI vs. SSTI) and baseline WBC were not correlated with outcome. Intercurrent active serious illnesses, ongoing cocaine use (>60% time) and documented non-adherence to therapy were significantly correlated with a lack of response to azithromycin.
CONCLUSION: The availability of potent, once daily antibiotics such as azithromycin may offer an effective approach to treat intercurrent bacterial infections in IVDUs with a degree of therapeutic success that equals or exceeds that associated with the use of this agent in the general population.
KEYWORDS: *HIV, opportunistic infection, compliance*

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THE EFFECT OF INTRAVENOUS MESNA (SODIUM 2-MERCAPTOETHANESULFONIC ACID) ON PLASMA HOMOCYSTEINE CONCENTRATIONS IN HEMODIALYSIS PATIENTS.

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BACKGROUND: Elevated plasma total homocysteiene (tHcy), termed hyperhomocysteinemia (tHcy > 15 μmol/L) is a graded, independent risk factor for development of atherosclerosis. Over 90% of patients with end-stage renal disease (ESRD) have elevated plasma tHcy despite routine vitamin supplementation. The leading causes of morbidity and mortality in patients with ESRD are cardiovascular pathologies such as myocardial infarction and stroke. Only a small fraction of plasma tHcy is removed by hemodialysis due to its extensive (70-80%), covalent binding to albumin. Mesna is a thiol containing drug used to prevent hemorrhagic cystitis caused by oxazaphosphorine chemotherapeutic drugs such as ifosfamide.

OBJECTIVE: The objective of this pilot study was to determine whether a single intravenous dose of mesna would decrease plasma tHcy during hemodialysis.

METHODS: Mesna's ability to exchange with protein bound Hcy was initially tested in vitro by adding homocysteine to plasma to a final concentration of 30 μmol/L and allowing it to bind to albumin for 72 hours. Mesna (305 μmol/L) was added to the plasma and incubated at 37°C and free Hcy was measured at various time points. In vivo, mesna's activity was tested in 3 patients by administering a 5 mg/kg intravenous dose into the arterial line of the dialysis machine at the beginning of a hemodialysis session. Blood samples were drawn throughout dialysis and plasma tHcy levels compared to those obtained on a previous dialysis session when mesna was not administered.

RESULTS: In vitro, 305 μmol/L mesna liberated 23% of protein bound homocysteine in only 5 minutes. In vivo, a single 5 mg/kg dose of mesna caused a 56% decrease in plasma tHcy post-dialysis compared to a 27% decrease with dialysis alone ($p=0.035$).

CONCLUSION: A single, 5 mg/kg, intravenous dose of mesna causes a rapid decrease of plasma tHcy during hemodialysis due to improved dialytic clearance.

KEYWORDS: *Renal failure, homocysteine, mesna*

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ANTIHYPERGLYCAEMIC ACTIVITY OF CHRONIC COBALT TREATMENT IN STZ-DIABETIC RATS.

Harish Vasudevan, J.H. McNeill

BACKGROUND: Diabetes is a metabolic disorder characterized by elevated blood glucose levels. In hypoinsulinemic states concomitant effects observed include polydipsia, polyphagia and reduced body weight. Though conventional treatments like insulin and other drugs reduce blood glucose, there is still a therapeutic need for effective orally administered drugs. Trace elements like vanadium and tungstate have been successfully demonstrated to reduce blood glucose in experimental diabetes with minimal chronic complications.

OBJECTIVE: To investigate the anti-hyperglycemic effects of cobalt in STZ-diabetic rats

METHODS: Male Wistar rats were made diabetic with a single dose of streptozotocin (STZ) 60 mg/kg i.v. Normal and diabetic rats were provided with drinking water containing 3.5mM cobalt chloride for three weeks followed by 4 mM for 4 weeks. Control rats imbibed 108±7mg/kg/day while diabetic rats drank 267±23 mg/kg/day. Body weights and fluid consumption were monitored on a daily basis, while food intake was recorded biweekly. Plasma was withdrawn from the tail vein for analysis of glucose and insulin. Prior to termination, an oral glucose tolerance test was performed on the animals using 1 gm/kg dose of glucose.

RESULTS: Diabetic rats lost significant body weight (325±9.4gm) compared to controls, which was further reduced by cobalt (274.5±3.6gm). Though difficult to establish a dosing regimen without weight loss, food and fluid consumption in treated diabetic animals improved significantly compared to untreated diabetics. Plasma glucose levels were significantly reduced with reference to diabetic controls (29.3±0.9mM) by the third week to slightly hyperglycemic levels (13.6±3.4mM). Cobalt-treated diabetic rats demonstrated an enhanced ability to clear a glucose load compared to untreated diabetics. Cobalt treatment neither affected the feeding and drinking patterns nor plasma glucose in normoglycemic animals though body weights decreased compared to untreated controls.

CONCLUSIONS: We conclude that chronic cobalt treatment decreases plasma glucose levels in STZ-diabetic rats and improves tolerance to glucose.

KEYWORDS: *Diabetes, cobalt*

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ESTROGEN REDUCES INSULIN RESISTANCE AND SUBSEQUENT HYPERTENSION IN MALE FRUCTOSE HYPERTENSIVE RATS.

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BACKGROUND: Hypertension is an early complication arising out of resistance to insulin. Rats on a high fructose diet develop hypertension within 4-5 weeks subsequent to induction of insulin resistance. Estrogen has been strongly implicated in influencing the hypertensive process by modulating insulin sensitivity and subsequent cardiovascular complications in female rats. However no studies have been reported on the hemodynamic effects of estrogen on insulin resistant males.

OBJECTIVE: To investigate the effects of estrogen treatment on insulin resistance (IR) and hypertension in male insulin resistant rats.

METHODS: Male Wistar rats, maintained on a high (66%) fructose diet were treated with subcutaneous estrogen implants (0.5mg/day) for 7 weeks. Systolic blood pressure was measured and blood samples collected to analyze plasma glucose, insulin, testosterone and 17β-estradiol at the start and end of study. At the end of treatment, insulin sensitivity was assessed by an oral glucose tolerance test using 1 gm/kg dose glucose. Following termination, superior mesenteric arteries were isolated and evaluated for alterations in eNOS and ET-1 using immunohistochemistry.

RESULTS: Estrogen treated rats consumed less food and lost body weight significantly compared to controls. Increase in systolic blood pressure was prevented by estrogen (125±1 mmHg) compared to untreated rats (140±2 mmHg). Both plasma testosterone and 17β-estradiol levels decreased significantly compared to basal values. Fructose feeding impaired insulin sensitivity in rats and was improved on treatment with estrogen. Immunohistochemical data suggest reduced ET-1 in estrogen treated rats compared to fructose fed controls, without affecting eNOS activity. Further studies are in progress to confirm this finding.

CONCLUSIONS: Estrogen treatment augments insulin sensitivity in male IR rats resulting in reduced blood pressure; a finding, which merits further investigation.

KEYWORDS: *Insulin resistance, hypertension, Estrogen*

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THE EFFECTS OF ROSIGLITAZONE ON HYPERTENSION DEVELOPMENT IN SPONTANEOUSLY HYPERTENSIVE RATS.

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BACKGROUND: The anti-hypertensive effect of PPARγ agonist rosiglitazone has been reported in patients with diabetes or obesity.

OBJECTIVE: To investigate the correlation of PPARγ expression with blood pressure and the therapeutic application of rosiglitazone in spontaneously hypertensive rats (SHR).

METHOD: In Study 1, SHR at ages of 5, 13, and 21 weeks (n=5-8 for each group) and age-matched WKY were used. In Study 2, SHR of 5 weeks were divided into non-treated (n=7), rosiglitazone (n=5), and Wy14643 (n=5) treated groups. Rosiglitazone (150 mg/kg/day) and Wy14643 (50 mg/kg/day) were used for 8 consecutive weeks. Age-matched WKY (n=7) were used as the control. Blood pressure was monitored and protein levels were evaluated with Western blot. The average thickness of left ventricle wall was determined with a minimum of 10 sites from each ventricle, which was measured and analyzed using an image analysis software.

RESULTS: Systolic blood pressure of 21-week SHR was significantly higher that that of age-matched Wistar-Kyoto rats (WKY) (225±5 vs. 144±2 mmHg, $p<0.05$). Basal expression levels of PPARγ proteins in vascular tissues of 21-week SHR were significantly lower than that of age-matched 21-week WKY ($p<0.05$). This reduced expression of PPARγ was not detected between 5- and 13- week SHR and age-matched WKY. Cardiac PPARγ expression was also not different among different age groups between SHR and WKY. Chronic treatment with rosiglitazone, but not PPARα agonist Wy14643, significantly retarded hypertension development and reversed abnormally faster heart rate in young SHR. An unfavourable effect of rosiglitazone treatment was the increased heart/body weight ratio accompanied by left ventricular hypertrophy.

CONCLUSION: Vascular PPARγ protein expression in adult SHR is decreased secondary to hypertension establishment. Chronic rosiglitazone treatment offers retards hypertension development, but the associated pro-hypertrophy effect calls for a cautious evaluation of the application of this Thiazolidinedindione in the treatment of insulin resistance syndrome. Support by HSFC

KEYWORDS: *Hypertension, rosiglitazone*

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EFFECTS OF INFANT FORMULA AND HUMAN MILK ON CYTOCHROME P450 1A EXPRESSION.

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BACKGROUND: The elimination of caffeine, a CYP1A2 substrate for neonatal apnea treatment, is 3-fold slower in breast-fed infants than in formula-fed infants. Paradoxically, human milk reportedly contains higher levels of environmental pollutants. Many of them are CYP1A inducers and exert toxic effects via aryl hydrocarbon receptor (AhR) activation. In this study, we hypothesized that formula would induce CYP1A expression. We further hypothesized this effect was due to the activation of AhR by formula treatment. We are currently investigating the active component(s) in formula.

OBJECTIVES: To examine the effects of formula and human milk on CYP1A mRNA and protein expression; to examine the role of AhR pathway in the formula-induced CYP1A expression; to evaluate the amount of AhR agonists in formula and human milk; to identify the active component(s) in formula.

METHODS: HepG2 CYP1A mRNA, protein expressions and mouse Cyp1a1 mRNA were measured by RT-PCR and western blotting. Using a luciferase reporter construct containing Cyp1a promoter, we examined HepG2 AhR activity, and determined the toxic equivalents (TEQs) of milk and formula. The active component(s) will be identified by fractionation and chromatography.

RESULTS: Formula but not human milk induced CYP1A mRNA and protein. Formula induced fetal mouse hepatic Cyp1a1 expression. Both cow milk-based and soy formula but not human milk showed AhR activation. Moreover, the co-treatment of 3, 4-dimethoxyflavone, an AhR antagonist, abolished formula's effect on AhR and CYP1A mRNA. Formula milk activated AhR with TEQs up to 6.4 pg TCDD/g, nearly 100-fold higher than the reported values. The structural identification of the active component(s) is currently under way.

CONCLUSION: Formula may increase infant drug metabolism by increasing CYP1A expression via AhR activation. The origin of this effect is likely due to an unknown natural AhR ligand(s). Human milk does not elicit the same effect despite reported higher levels of environmental pollutants.

KEYWORDS: *Lactation, cytochrome P4540 expression*

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THE DOSE-RESPONSE RELATIONSHIP OF CONTROLLED-RELEASE OXYBUTYNIN IN URINARY URGE INCONTINENCE (UUI) – A RANDOMIZED, DOUBLE-BLIND STUDY

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BACKGROUND: Controlled-release (CR) formulations of oxybutynin chloride have been shown to have a more favourable efficacy-side effect ratio than immediate-release formulations. The goal of this study was to compare the efficacy of 5, 10 and 15 mg of a new, once-daily CR formulation of oxybutynin (Uromax®), when used as the initial dose in patients with UUI.

METHODS: Patients attending Canadian urological clinics who reported at least 1 urinary incontinence (UI) episode, and either void frequency (≥ 8 voids/d) or urgency (≥ 1 episode/d), during the 2-wk baseline (BL; no-treatment) period were eligible for randomization. Patients were randomized to 5 mg, 10 mg or 15 mg CR oxybutynin OD for 4 weeks. UI, voids, urgency, and adverse events (AE) were recorded in a 3-day diary at BL, 2 and 4 weeks. Assessments of dry mouth symptoms (DMS), efficacy/AE ratio, and satisfaction (ordinal; 0-4) were also conducted.

RESULTS: 237 patients (15% male) were randomized and evaluated for efficacy and safety. Over the 4 weeks of treatment, there was a significant reduction from BL in daily UI episodes, voids and urgency in all treatment groups ($p \leq 0.0001$, all comparisons). There were significantly fewer daily UI episodes with 15 mg/d vs. 10 mg/d ($p=0.0385$) and 5 mg/d ($p=0.0061$) over the 4-week study period. Dry mouth was the most frequently reported AE and increased with dose (5 mg: 56%, 10 mg: 68%, 15 mg: 70%). Significantly greater DMS were reported with 15 mg/d vs. 5 mg/d ($p=0.0008$) and 10 mg/d vs. 5 mg/d ($p=0.0001$). There was a significant increase from BL in satisfaction in all groups ($p=0.0001$, all comparisons). At Week 4, there was significantly greater patient satisfaction observed with 15 mg/d vs. 5 mg/d ($p=0.0400$) and the proportion of patients reporting "good efficacy/few side effects" was related to dose (5 mg: 35%, 10 mg: 36%, 15 mg: 52%; $p=0.066$).

CONCLUSIONS: This study is the first to demonstrate a significant dose-response relationship with oxybutynin, with maximal reductions in UI at 15 mg/day. Patients also reported highest satisfaction with doses of 15 mg/day, indicating that the greater efficacy at doses of 15 mg/day was achieved without compromising tolerability

KEYWORDS: *Incontinence, RCT, dose-response*

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HIGH VIROLOGIC FAILURE IN PATIENTS RECEIVING TRIPLE-NRTI THERAPY COMPARED TO STANDARD HAART IN REGIMENS CONTAINING TENOFOVIR (TDF) IN SALVAGE THERAPY.

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BACKGROUND: Recent data suggest early virologic failure at a high frequency in patients receiving the combinations of ABC-3TC and DDI-3TC in combination with TDF in first-line therapy. This may be associated with a higher emergence of the mutation K65R in patients receiving triple-NRTI regimens.

OBJECTIVE: In an observational study we have evaluated the virologic efficacy of TDF-based combination therapy received through expanded access programs in our tertiary care referral clinic.

METHODS: All patients enrolled in our TDF program and who received their assigned therapy > 3 mo were included in this retrospective chart review. Baseline information was collected including data on prior therapy and current immunologic and virologic status.

RESULTS: A total of 65 patients were included, 50 on TDF in combination with either a NNRTI or PI, and 15 on a triple NRTI regimen containing TDF. Baseline and follow-up data are shown in the table below (median follow-up 52 weeks in both groups).

CONCLUSION: Virologic response was poorer in triple-NRTI TDF-based regimens vs. other TDF-based regimens, despite similar baseline immunologic disease, prior and ongoing drug exposure, and despite a lower plasma viral load at initiation of therapy. In patients receiving TDF, virologic failure was accompanied by more frequent emergence of K65R, but no other resistance mutations. Therefore, TDF/N/N regimens should be used with great caution (if at all) until the mechanism of emergence of K65R in this setting is better understood.

KEYWORDS: *HIV, HAART, viral load, salvage therapy*

	TDF/N/PI-TDF/N/NNRTI	TDF/N/N
N	50	15
Male/Female	43/7	15/0
Median CD4 Count (baseline)	200	230
Median V_L (baseline)	87,100	21,800
Median V_L (MR)	102	2,850
Prior Rx (Median Total, Median NRTI/NNRTI/PI)	7, 4/1/2	6, 3/0/1
Current Rx (PI/NRTI, NNN/NN)	32/18	13/2
Δ CD4 count	+42	+25
Δ V_L, % < 400 copies/mL	-49,182 (62%)	-18,950 (20%)
K65R (%)	6%	33%
M41L/L210W (%)	6%	7%
Any TAMs (%)	8%	7%

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CLOFIBRATE LOWERS BLOOD PRESSURE IN TWO EXPERIMENTAL MODELS OF HYPERTENSION: ROLE OF 20-HYDROXY EICOSATETRAENOIC ACID (20-HETE).

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BACKGROUND: Clofibrate a peroxisome proliferator-activated receptor α agonist prevents the development of hypertension in Dahl salt sensitive rats by inducing renal cytochrome P-450 fatty acid ω-hydroxylase activity.

OBJECTIVE: To study the effect of clofibrate on blood pressure, urinary 20-HETE excretion, cumulative sodium balance and body weight in Sprague-Dawley (SD) rats treated with tap water, normal saline or normal saline and L-NAME.

METHODS: Six groups (n=5 to 7) of 5 week old male SD rats were treated with vehicle (20mM Na2CO3), normal saline (0.9% NaCl), normal saline + L-NAME (30mg/100ml), clofibrate (80mg/day), normal saline + clofibrate (80mg/day) or normal saline + L-NAME (30mg/100ml) + clofibrate (80mg/day) for three weeks. Systolic blood pressure (SBP) was measured with a rat-tail cuff. Urinary 20-HETE levels were measured using reverse phase HPLC with fluorescence detector. Urine sodium was measured using flame emission spectrophotometry.

RESULTS: The values are Mean ± SEM. Significance was accepted at $P < 0.05$ and determined with ANOVA and a post hoc test.

CONCLUSION: Clofibrate lowers blood pressure in both salt induced and L-NAME induced hypertension likely by increasing urinary 20-HETE excretion and promoting natriuresis. Hence clofibrate might play a role in the treatment of salt induced hypertension and in nitric oxide compromised states.

KEYWORDS: *Hypertension, clofibrate, fatty acids*

Parameter	Control	0.9% NaCl	0.9% NaCl +L-NAME	Tap water +clofibrate	0.9% NaCl +clofibrate	0.9% NaCl + L-NAME +clofibrate
SBP (mmHg)	122±2	129+1**	178+2 ***	124+2	92+2***	125+2
20-HETE (ng/d)	413+10	494+6*	908+22***	552+10***	938+16***	833+2***
Body wt (g)	266+2	277+2	292+4***	264+3	246+2*	260+4
Na+ balance (mmol/d)	3+1	23+3***	35+2***	13+3	8+1**	17+3***

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AZALANSTAT ANALOGUES AS NEW HEME OXYGENASE INHIBITORS.

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BACKGROUND: Heme oxygenase-mediated degradation of heme results in the liberation of iron, biliverdin and approximately 85% of the daily carbon monoxide (CO) production in mammals; two of the three isozymes, namely HO-1 (inducible) and HO-2 (constitutive), have been studied in some detail, while relatively little is known about HO-3. There is much interest in the role of HO/CO in vascular and neuronal function as well as in the survival of transplanted organs. In order to elucidate the role of the HO/CO system in these, a number of metalloporphyrins, such as tin protoporphyrin and chromium mesoporphyrin, have been exploited. A limiting feature of these drugs is their ability to inhibit other heme-dependent enzymes at concentrations close to those that inhibit HO.

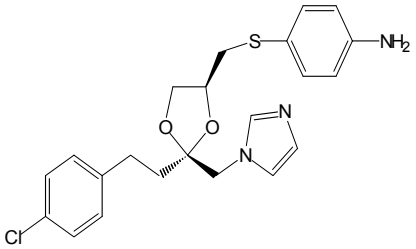
OBJECTIVE: We have embarked on a program to synthesize selective inhibitors of HO-1 and HO–2.

METHODS: In this work, we are pursuing three leads, namely norleucine-based peptides, imidazo-pyridines, and `azalanstat (an analogue of the antifungal agent ketoconazole). We have synthesized a number of analogues of azalanstat (structure below). Their ability to inhibit HO activity was tested in rat spleen (HO-1) and rat brain (HO-2) microsomes. HO activity was determined by the measurement of CO production using gas chromatography with mercuric oxide reduction detection.

RESULTS: In contrast to the metalloporphyrins which show some selectivity for HO-2, azalanstat and its analogs showed selectivity for HO-1. For example, the IC50 values for the 2-aminophenyl analogue of azalanstat are 5 + 1 μM in rat spleen and 63 + 5 μM in rat brain. The effects of a variety of structural modifications to azalanstat on HO activity and selectivity will be discussed.

CONCLUSION: These novel drugs may lead to the development of isozyme selective inhibitors of HO.

KEYWORDS: *Heme oxygenase, azalanstat*



Azalanstat

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CAPT

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A RISK-BENEFIT ANALYSIS OF ENOXAPARIN VS. UNFRACTIONATED HEPARIN FOR DVT PROPHYLAXIS POST-TRAUMA – A BAYESIAN PERSPECTIVE.

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Funding Source: CIHR post doctoral fellowship

BACKGROUND: Using a traditional frequentist approach, the only clinical trial comparing enoxaparin to unfractionated heparin (UH) for the prevention of deep vein thrombosis (DVT) post-major trauma concluded that there is no difference in risk (major bleeds; p=0.12), and that enoxaparin is more effective (p=0.012).The objective of this study was to perform a probabilistic risk-benefit evaluation of enoxaparin vs. UH for this indication using a Bayesian approach.

METHODS: 2nd order Monte Carlo simulation modeling was used to evaluate the joint density of the incremental risk (major bleeding) and incremental benefit (prevention of DVT) of enoxaparin vs UH. Beta distributions for each outcome were derived from the published results of the trial. The incremental risk-benefit ratio was calculated for each iteration of the model, and the joint density of the risks and benefits was plotted on a risk-benefit plane. A risk benefit acceptability curve was used to present the probability that enoxaparin is net-beneficial at different risk thresholds.

RESULTS: Using 3000 replications of the model, the probability that enoxaparin is more beneficial but posed a greater risk than UH is 0.97. At a risk threshold of 1 (willingness to accept 1 bleed to avert 1 DVT), the probability that enoxaparin results in a net benefit is 0.9, with 10% chance that it does not. This exceeds the traditional frequentist threshold of p=0.05.

CONCLUSION: Contrary to the published results, this analysis reveals that enoxaparin actually poses a greater risk in this population. Whether enoxaparin is the treatment of choice should be dependent upon the decision-makers risk threshold.

KEY WORDS: *Risk benefit analysis; enoxaparin; heparin; deep vein thrombosis.*

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ADHERENCE TO ANTIRESORPTIVE AGENTS AND RISK OF OSTEOPOROTIC FRACTURE IN ELDERLY WOMEN: A POPULATION-BASED STUDY.

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Funding Source: CIHR

AIM: Osteoporotic fractures are associated with considerable morbidity, mortality and economic consequences. Scientific evidence for the efficacy of bone-specific drug such as, bisphosphonates (ART) is convincing for the most part in terms of risk reduction of osteoporotic fractures among high-risk postmenopausal women. To date no information is available for the effectiveness.

OBJECTIVE: To determine whether ART or Hormone Replacement (HRT) decrease the risk of fracture in community-dwelling elderly women.

METHODS: A nested case-control design was used. We have selected a cohort of 89,041 elderly women from RAMQ database. The cohort entry was defined as being aged of 70 years old or more between Jan 1995 and Dec 2000. We identified 2,767 cases of fracture. All cases were matched to 10 randomly selected controls based on age, prior fracture and time period. We examined ART or HRT exposure during the period prior the index date: recent exposure (< 1 year), current exposure (>= 1 and < 3 years) and late exposure (>= 3 years). The risk reduction of fracture was estimated based on conditional logistic regression after adjustment.

RESULTS: During an average follow-up of 2.6 years, 2,767 women experienced one incident fracture, giving 38.9% of spine fracture and 61% non-spine fracture. Compared with non-users, women with recent (OR: 0.81, 0.69-0.94), current (OR: 0.49, 0.32-0.75), and late (OR: 0.43, 0.32-0.58) exposure of HRT had a decrease in the risk of fracture. The corresponding figures for elderly women exposed to ART are (OD: 1.39, 1.19-1.64), (OR: 1.32, 0.97-1.83) and (OR: 1.07, 0.51-2.26). Compared to non-users, women having polyarthritis treated with corticosteroids (OR: 1.45, 1.02-2.07), risk of fall (OR: 1.31, 1.13-1.52), osteoporosis-related to drugs (OR: 1.88, 1.52-2.32), antidepressants (OR: 1.50, 1.34-1.68) and narcotics (OR: 2.51, 2.03-3.09) had increases in the risks of osteoporotic fractures.

CONCLUSION: Community-dwelling older women taking HRT have a decreased risk of osteoporotic fracture. On the other hand, ART exposure provided only a trend in the risk reduction of fracture probably due to a lack of statistical power.

KEYWORDS: A*dherence; antiresorptive agents; osteoporotic fracture; risk reduction; effectiveness*

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ADHERENCE TO ANTIRETROVIRAL THERAPY (HAART) IN QUEBEC.

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Funding Source: Bristol-Myers Squibb

BACKGROUND: The use of highly active antiretroviral therapy (HAART) has greatly reduced the morbidity and mortality of HIV infection. However, the benefits of HAART are directly linked to the degree of adherence to treatment. We performed a population based study to estimate adherence to HAART.

METHODS: Subjects (age 18 – 81) were eligible for drug coverage under the RAMQ and were antiretroviral (ARV) users with an index date (initial dispensed prescription) between January, 1997 and June, 2003. Adherence was estimated by: 1) percentage of patients who renewed ARV 2) percentage of days under therapy 3) persistence defined as the time elapsed until therapy discontinuation. We used descriptive statistics, Kaplan-Meier curves and Cox Regression analyses.

RESULTS: There were 3,399 patients in the final cohort. In the year following the index date, 90% of patients renewed the ARV. The median percentage of days under therapy during the year following the index date was 100%. One year after the index date, 58% were persistent to therapy. Men were more persistent (adjusted RR of treatment discontinuation: 0.66; 95% CI: 0.59-0.73). Persistence was also better for the following variables measured in the year prior to the index date: patients who received NRTIs, patients who were hospitalized longer, and patients who visited a specialist. However, patients who visited the emergency room in the year preceding the index date were less persistent.

CONCLUSION: A population-based database may play an important role in anticipating public health problems that could result from the use or misuse of therapeutic drugs.

KEY WORDS: *Antiretroviral therapy; HIV infection; population based study; public health*

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CONFOUNDING BY INDICATION: CAN WE FIND WHAT WE SHOULD FIND? AN EMPIRICAL STUDY.

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Funding Source: Merck & Co.

BACKGROUND: Randomised controlled trials have clearly shown the beneficial effects of statins (RR = 0.69) in the prevention of myocardial infarction (MI) in diabetic patients. In a database study this beneficial effect might be masked by confounding by indication. The appropriate comparison could thus be between the patients who complied to their statin prescriptions and those who did not. Given that we know what the unconfounded result should be (RR =0.69), is it possible to show, using an administrative database, a protective effect of statins on the risk of MI?

METHODS: A nested case-control study in a cohort of diabetics in which patients who had a MI were matched with one control each.

RESULTS: The risk of MI in patients who never used statins was set at one. The adjusted RR of MI for patients who filled one or more statin prescriptions was 1.16 (95%CI: 1.07, 1.26) while the RR of the most compliant group was 1.05 (95% CI: 0.90, 1.21). The RR of MI became 0.66 (95% CI: 0.31, 1.38) when the most compliant group was compared to the least compliant.

CONCLUSION: Using an appropriate comparison group seems to control for confounding by indication. This is due to the fact that both good and bad compliers shared the same indication but only good compliers benefited from the therapeutic effects of the statins.

KEY WORDS: *Randomised controlled trials; statins; myocardial infraction; diabetic patients; nested case-control*

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DEPLETION OF SUSCEPTIBLES: HOW MUCH IS ENOUGH?

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Funding Source: None

BACKGROUND: Depletion of a susceptible pool can be a source of bias in pharmacoepidemiological studies. In the comparison of the incidence of an adverse event between an old and a new drug, the occurrence of this bias requires two conditions: (1) the risk function of the event in the exposed, to both products, has to decline through time and (2) the new product has to be preferentially prescribed to new users. If these two conditions are met, the incidence of the event will appear, in a standard case-control study, to be higher in the new than in the old product even if, in fact, they are the same. We used computer simulations to investigate the conditions that have to be met to significantly distort the results.

METHODS: A user friendly "cohort synthesizer" was constructed. A dynamic cohort of women was used to simulate the entry into the market of a new oral contraceptive (OC). Simulations of 0.1M women were run, with an equal frequency of thromboembolic events (TEs) in the old and the new products but varying the values of the following parameters: the baseline frequency of TEs in non users, the frequency of new users receiving the new OC and the shape and area under the risk function curve.

RESULTS AND CONCLUSION: Very moderate slopes in the risk function curve can produce a distortion of the risk ratio from a real value of 1 to an apparent value of 1.7.

KEY WORDS: *Bias; pharmacoepidemiological studies; adverse event; case-control; cohort synthesizer*

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DIFFUSION OF PRESCRIBING OF A NEW DRUG: THE CASE OF CELEBREX

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Funding Source: Pfizer (formerly Pharmacia)

BACKGROUND: Celebrex enjoyed a rapid uptake in use. Numerous patient and physician factors determine the adoption of newly marketed drugs. This research was undertaken to describe the diffusion of prescribing of Celebrex in Manitoba.

METHODS: Using Manitoba's population-based health care databases, all first prescriptions dispensed for Celebrex during the first year of market availability were selected for individual physicians. The Roger's Diffusion of Innovation model was applied to the prescription data to determine early (first 10%), majority and late prescribers (last 10%) of Celebrex. The odds ratio for being a early or late prescriber (versus majority prescriber) was related to recipient age, gender, income, drug plan status and indication (acute or chronic), and physician factors (eg. specialty, hospital affiliation), using polytomous logistic regression.

RESULTS: 311 physicians (25%) prescribed their first prescriptions for Celebrex within 2 weeks of market availability. Early prescribers were more likely to be GPs and physicians with a hospital affiliation. While early prescribers were less likely to prescribe Celebrex for acute conditions, such as backpain, 36% of Celebrex prescriptions were written for these conditions. The odds ratio for an early prescriber for a acute condition was 2.28 (95% CI: 1.56-3.35) for a GP (vs specialist) and 1.58 (95% CI: 1.07-2.34) for a hospital-affiliated physician. The converse was observed for late prescribers. Findings were similar for early prescribers of Celebrex for chronic conditions. In addition, their patients were more likely to be high income**.**

CONCLUSIONS: Characterization of early and late prescribers of newly-marketed drugs identifies opportunities for intervention.

KEY WORDS: *Celecoxib; newly-marketed drug; diffusion of prescribing; early prescribers; hospital-affiliated physicians*

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EFFECT OF DRUG PLAN ACCESS AND SOCIOECONOMIC STATUS ON QUALITY OF LIFE IN CHILDREN WITH ASTHMA

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Institutions: The Hospital for Sick Children
Funding Source: CIHR

BACKGROUND: Socioeconomic factors such as low income, poor education and lack of a drug plan may lead to poorer health outcomes in children with asthma. The objective was to study asthma-related quality of life in children as a function of drug plan access and socioeconomic factors.

METHODS: The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) was administered by interview to 879 asthmatic children or their parents. The PAQLQ has three domains: Activity Limitations (AL), Symptoms (S) and Emotional Function (EF). Mean domain scores were compared in children from families with different levels of income and drug plan access using analysis of variance.

RESULTS: Children with no drug plan had significantly lower scores for AL ($p<0.04$) and S ($p<0.03$) compared to children with drug plans. Significantly reduced quality of life was observed in the low income group for all 3 domains ($p<0.0001$) compared to high income children. Among children with no drug plan, clinically significant reductions in AL, S and EF domain scores were observed in low income compared to high income children. A similar trend was detected in children with drug plans. Other Socioeconomic factors that significantly influenced PAQLQ domain scores included ethnic background, language spoken at home, parents' marital status, mother's education and mother's employment status.

CONCLUSIONS: Access to a drug plan and income level are significant determinants of a child's asthma-related quality of life. This study emphasizes the important roles that socioeconomic status and drug plan access play in the optimal management of pediatric asthma.

KEY WORDS: *Asthma; pediatrics; quality of life; drug plan; socioeconomic status*

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EVALUATION OF ADHERENCE TO ORAL ANTIDIABETIC DRUG REGIMENS ON MORBIDITY AND MORTALITY

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Funding Source: Institute of Health Economics

BACKGROUND: Patient decisions to take less than the prescribed dose for chronic medications can significantly impact clinical outcomes. Poor adherence has been associated with an increased risk of hospitalization and mortality. We evaluated the impact of poor medication adherence to oral antidiabetic drugs on risk of hospitalization and mortality in people with type 2 diabetes.

METHODS: We used the administrative databases of Saskatchewan Health to identify 12,272 new users of oral antidiabetic drugs between 1991 and 1996. In the absence of information on days supplied, we estimated an expected duration of each dispensation based on the quantity dispensed and most likely daily regimens for glyburide and metformin. Adherence was estimated using the ratio of expected duration to observed interval between consecutive dispensations. Subjects with a use ratio < 0.8 were defined as having poor adherence, which is consistent with other studies. Multivariate Cox proportional hazard models were used, with the poor adherence group as the reference.

RESULTS: Subjects were 64.0 years old, 45.0% females, and were followed for an average of 5.1 (SD 2.2) years. Seventy-two percent of subjects had a use ratio > 0.8. Subjects with poor adherence were significantly younger (62.0 vs 64.7; $p<0.001$) and contained fewer females (42.8% vs 45.8%; $p<0.01$). Good adherence to oral antidiabetic drugs was associated with a lower risk of mortality; however, this relationship was not statistically significant (HR 0.96; 95% CI 0.88-1.05). Good adherence was associated with a lower risk of hospitalization (HR 0.91; 95% CI 0.87-0.95).

CONCLUSIONS: Our observations suggest that patients who are more adherent to prescribed oral antidiabetic regimens have a lower risk of hospitalization, but adherence rate does not appear to be associated with risk of mortality.

KEY WORDS: *Medication adherence; mortality; hospitalizations; oral antidiabetic agents*

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IMPACT OF ADMINISTRATIVE RESTRICTIONS FOR COXIBS IN QUEBEC (PQ), ONTARIO (ON) AND BRITISH COLUMBIA (BC)

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Institutions: McMaster University, Department of Clinical Epidemiology and Biostatistics

Funding Source: CIHR

BACKGROUND: In anticipation of the rapid uptake of selective cyclo-oxygenase-2 inhibitors (coxibs), provincial drug plans in ON and BC implemented restrictive reimbursement policies to limit their use. Reimbursement restrictions in BC were more stringent than in ON. In PQ, no restrictions were placed on these drugs.

OBJECTIVE: To examine the impact of reimbursement rules in PQ, ON and BC on use of coxibs among senior (65+) provincial drug plan beneficiaries, and attendant effects on the use of other anti-inflammatory therapies.

METHODS: Population based retrospective study of drug claims by senior beneficiaries of the PQ, ON and BC provincial drug plans. Monthly consumption rates per 100 seniors for acetaminophen, non-selective non-steroidal anti-inflammatory drugs (NSNSAIDs), and coxibs were estimated. In BC, both provincial-plan and out-of-plan claims were examined.

RESULTS: Coxibs were introduced into the market in Oct 1999 in PQ, Apr 2000 in ON, and Dec 2000 in BC. During the first year after their introduction, the utilization of coxibs (number of claims per 100 beneficiaries) rose to 8.8 in PQ, 5.2 in ON, and 0.2 in BC. Although the uptake of coxibs in the public system was steeper in ON compared to BC, there was substantial out-of-plan (privately paid) use in BC (~2 claims per 100 seniors). Total combined use of NSNSAIDs and coxibs was doubled in ON and PQ during this time.

CONCLUSIONS: The restrictive policies in ON and BC appear to have reduced the growth of coxib prescriptions claimed from drug plans compared to PQ. In BC, there was substantial cost-shifting to patients and other insurers, but still a reduced intensity of coxib prescribing.

KEY WORDS: *Osteoarthritis; administrative restrictions; health policy; NSAIDS; coxibs; diffusion*

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INTERVENTIONS THAT IMPROVE THE APPROPRIATE UTILIZATION OF NSAIDS, EVIDENCE FROM A RANDOMIZED CONTROLLED TRIAL

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BACKGROUND: Exception drug status (EDS) criteria have been implemented in Manitoba, to help manage the escalating pharmaceutical expenditures for NSAIDs. The Manitoba Anti-inflammatory Appropriate Utilization Initiative (MAAUI) determines the extent that primary care physicians adhere to these EDS criteria, and implements interventions to optimize physician behavior, when prescribing NSAIDs. The effectiveness of these educational interventions are reported.

METHODS: Physicians were grouped into twenty-one geographical areas, based on their clinical practice site. After stratifying by urban and rural status, each geographic area was randomly assigned to a control or intervention group. Each physician in the intervention group was mailed a personalized prescribing profile, comparing his/her adherence to the EDS guidelines, to peers. A second self-selected intervention group was formed, by physicians who chose to attend an educational workshop.

RESULTS: Using administrative data from the Manitoba Health Data Repository, an "appropriate use" value has been developed for each participating physician, during the baseline and follow-up study periods. The average rate of appropriate prescribing for NSAIDs in the baseline period was 60.5% (S.D., standard deviation=10.3%). This rate of appropriate prescribing was significantly higher for: i) rural physicians (Mean=61.1%, S.D.=11.5%) versus urban physicians (Mean=58.9%, S.D.=11.9%) (p=.003); and ii) physicians who prescribed NSAIDs to more (Mean=60.5%, S.D.=6.6%) verses fewer (Mean=58.1%, S.D.=17%) patients (p=.02). Using multivariate analysis and controlling for participant demographic and baseline measurements, physicians in the profile and workshop group significantly improved their appropriate prescribing of NSAIDs. This improvement was greater for rural physicians (Mean=15.8%, S.D.=5.8%) versus urban physicians (Mean=10.8%, S.D.=3.4%) (p=.03). Similar results are found, for the different classes of anti-inflammatory medications.

CONCLUSIONS: Interventions that combine personal feedback and education can significantly improve physician adherence to the EDS guidelines for NSAIDs. These findings represent one strategy to help control the escalating cost of NSAIDs in Manitoba.

KEY WORDS:*Randomized, controlled clinical trials; utilization of administrative data;musculoskeletal/rheumatology;clinical practice guideline*

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MEDICATIONS WITH ANTICHOLINERGIC EFFECTS AND ADVERSE HEALTH OUTCOMES AMONG OLDER PERSONS

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Funding Source: Health Canada (NHRDP) - Core CSHA

BACKGROUND: Medications with anticholinergic effects (ACEs) have the potential for a variety of adverse consequences. We examined the association between use of medications with ACEs and the subsequent risk of cognitive decline and dementia among participants in the Canadian Study of Health & Aging (CSHA).The CSHA is a population-based longitudinal study of the epidemiology of dementia among Canadians aged 65+ years. Subjects underwent standardized evaluations in 1991-92 and 1996-97. Global cognition was assessed with the Modified Mini-Mental State (3MS) examination. The diagnosis of dementia was made at a consensus conference using established criteria. Medication use at baseline (1991-92) was assessed during the clinical examination (community subjects) or via health record review (institutional subjects) and coded according to the American Hospital Formulary System Pharmacologic / Therapeutic Classification Scheme. Three different listings of drugs with significant ACEs (Tune, Saskatchewan Health [SH], Roe) were examined. Users and non-users of drugs with ACEs were compared in 1996-97 for the development of cognitive decline (defined as a drop of 10+ points on the 3MS) and incident dementia.

RESULTS: After adjusting for relevant covariates, use of drugs with ACEs, based on the SH or Roe listings, was associated with significantly greater risks for cognitive decline (ORs 1.71 [1.06-2.76] and 1.77 [1.08-2.90], respectively) and incident dementia (ORs 1.81 [1.11-2.95] and 2.04 [1.24-3.36], respectively). The Tune listing failed to show significant associations with cognitive decline or incident dementia.

CONCLUSIONS: The use of medications with ACEs was associated with worse cognitive performance in this prospective cohort study. Our results would justify caution in the use of these medications in older vulnerable patients and further research on the topic.

KEY WORDS: *Anticholinergic effects; medications; cognitive impairment; dementia; cohort; elderly*

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PERSISTENCE AND ADHERENCE TO ANTIHYPERTENSIVE AGENTS

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Funding Source: Pfizer Canada

BACKGROUND: Hypertension practice guidelines recommend the selection of treatment based on efficacy, safety, and cost. Given the need for long-term utilization of these agents, treatment compliance is essential to treatment success. The objective of this study was to estimate persistence and adherence to antihypertensive agents over a 2 year period in a real life setting.

METHODS: This study was performed using data from the Régie de l assurance maladie du Québec (RAMQ). Persistence (proportion of patients who had not abandoned treatment) and adherence (proportion of patients who took > 80% of the required medication) to treatment were estimated separately and an index combining these two measures was calculated. The persistence-adherence index was calculated by multiplying the monthly persistence rates by the monthly adherence rates over a two-year period.

RESULTS: A random sample of patients (N=64,175) who received a new prescription for an antihypertensive agent reimbursed between January 1999 and December 2000 were analysed. Their average age was 45.8 years, 36% were> 60 years and 55% were female. Persistence varied across antihypertensive agents: 71% beta-blockers, 67% amlodipine, 66% angiotensin receptor antagonists (ARAs), 64% other calcium channel blockers (CCBs), 63% ACE inhibitors, 60% other diuretics, 52% hydrochlorothiazide, and 23% chlorthalidone. The persistence-adherence index at two years was 66% ARAs, 63% amlodipine, 62% beta-blockers, 61% other CCBs, 60% ACE inhibitors, 51% hydrochorothiazide, 50% other diuretics and 32% chlorthalidone.

CONCLUSION: Results of this study indicate that, in a real life setting, patients are significantly less compliant to diuretics than to any other antihypertensive agents.

KEY WORDS: *Treatment compliance; antihypertensive drugs; drug databases analyses*

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PROGRESSIVE MANAGEMENT OF GLYCEMIA IN TYPE 2 DIABETES

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Funding Source: Eli Lilly

BACKGROUND: Type 2 diabetes is characterized by a progressive loss of metabolic control, likely due to a continuous decline in beta cell function. It is conceivable that antidiabetic agents may be able to retard the progression of the disease. Some drug classes may have a greater ability to slow this decline than others. We examined the relationship between initiation of metformin monotherapy and the time to starting alternative therapy due to progressive loss of metabolic control.

METHODS: The administrative databases of Saskatchewan Health were used to identify new users of oral antidiabetic drugs between 1991 and 1996. Subject groups were defined by initial antidiabetic drug use within the first 100 days of their index date: metformin monotherapy (n=2,426) or sulphonylurea (SU) monotherapy (n=7,298). Progression of diabetes was defined as: addition of a second agent (either an oral antidiabetic drug or insulin) and switch to alternate oral therapy. The association between initial drug therapy and progression of diabetes was evaluated using multivariate Cox proportional hazard models with SU monotherapy as the reference group.

RESULTS: Initiation with metformin monotherapy was associated with a reduced risk of adding a second oral agent (HR 0.88; 95% CI 0.81-0.95) or starting insulin (HR 0.68; 95% CI 0.59-0.79). In contrast, initiation of metformin monotherapy was associated with an increased risk of switching oral therapy (HR 1.55; 95% CI 1.31-1.82).

CONCLUSION: With the progressive loss of beta cell function, agents that optimize utilization of endogenous insulin (e.g., metformin) appear to be associated with a delay in the need for additional antidiabetic therapy compared to agents that promote insulin secretion (e.g, sulfonylureas). Our observation also suggests that patients initiated on SU monotherapy were less likely to be switched to metformin monotherapy.

KEY WORDS: *Type 2 diabetes, Oral antidiabetic agents, Disease Progression*

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REDUCED INCIDENCE OF BREAST CANCER ASSOCIATED WITH FREQUENT USE OF SELECTIVE AND NONSELECTIVE NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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Funding Source: Canadian Institutes of Health Research, The Arthritis Society

BACKGROUND: The cyclooxygenase (COX)-2 enzyme is expressed more in breast cancers than in normal breast tissue. COX-2 inhibition may have a role in prevention of breast cancer. We examined the association between NSAID use and breast cancer incidence among post-menopausal women.

METHODS: Data were obtained from the RAMQ databases concerning all women > 65 years of age who had undergone a mammogram in Quebec between April 2001 and June 2002. Cases were those women with a diagnosis of breast cancer within six months following their mammogram. Controls included those without a diagnosis of any cancer during the six months following their mammogram. Cases and controls were compared in terms of probability of frequent NSAID use, the exposure of interest. Frequent NSAID use was, defined as use of coxibs and/or NSAIDs for >=90 days in the prior year.

RESULTS: We identified 652 cases and 41,390 controls. Cases were older and more likely to have risk factors for breast cancer. Logistic regression models adjusting for potential confounders showed that frequent use of selective/nonselective NSAIDs was associated with a lower risk of breast cancer (OR: 0.70, 95% confidence interval 0.56-0.88). Results were similar for coxibs (0.78, 0.62-0.98) and NSAIDs (0.39, 0.19-0.79), when assessed separately. Frequent use of aspirin in the year prior to mammogram had no association with breast cancer incidence.

CONCLUSION: NSAID use may prevent breast cancer among post-menopausal women. Both nonselective NSAIDs and coxibs are associated with such a protective effect.

KEY WORDS: *Breast cancer; NSAIDS; coxibs; case-control; mammography*

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THE BURDEN AND MANAGEMENT OF OSTEOPOROSIS: A MISSED OPPORTUNITY

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Funding Source: This project was funded by an unrestricted educational grant by Merck Frosst Canada

BACKGROUND: The difference between 'best care' (use of proven interventions) and 'usual care' is often large. The Maximizing Osteoporosis Management in Manitoba (MOMM) project is a public/private partnership between the U.Manitoba, Merck Frosst Canada Ltd. and Manitoba Health; its sole purpose is to identify gaps in the delivery of osteoporosis care and promote 'best care'.

METHODS: Using administrative claims data, we performed a panel study (1997-2002) of women aged ≥ 50 years who were residents of Manitoba and had experienced a hip or spine or a non-spine/non-hip fracture. Fracture events were used to identify women at high risk of osteoporosis and fracture. To examine the kinds of care women received 1-year post-fracture we used two data sources and calculated rates of bone mineral density (BMD) testing and pharmacological intervention for each panel. BMD testing is indicated after a non-spine/non-hip fracture in women over 50; the availability of a province-wide BMD database allowed us to identify when BMD investigation was done post-fracture. The use of pharmacological treatment post-spine or hip fracture was determined by examining dispensations of recognized osteoporosis therapies.

RESULTS: Among the 1802 women fracturing a hip or spine vertebra in 2001/2002, < 18% (n=317) were dispensed a known pharmacological treatment for osteoporosis and < 5% (n=83) had BMD testing in the year post-fracture. The same low patterns of intervention were found in the 4673 women with a non-spine/non-hip fracture in 2001/2002; 15.5% (n=723) were dispensed pharmacological treatment and only 7.0% (n=328) had BMD testing in the year post-fracture.

CONCLUSION: ps in the treatment and prevention of osteoporosis in Manitoba women ≥ 50 years old have been identified. Data responsive interventions are currently being implemented in a rural health region of Manitoba.

This project was funded by an unrestricted educational grant by Merck Frosst Canada and Co.

KEY WORDS: *Osteoporosis, fracture, administrative data, bone densitometry*

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THE IMPACT OF AN OPEN ACCESS POLICY FOR ATYPICAL ANTIPSYCHOTIC MEDICATIONS IN NEWFOUNDLAND AND LABRADOR

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Funding Source: Funded by an educational grant from PMAC

BACKGROUND: To measure hospital utilization following the implementation of an unrestricted policy for atypical antipsychotic medications for a publicly funded drug program.

METHODS: The inpatient records of schizophrenia patients discharged in 1995/96, 1998 and 2000 were reviewed to determine the factors influencing length of stay (LOS) and readmission rates. Cox proportional hazards models were used to identify factors associated with LOS and logistic regression to determine early readmission.

RESULTS: 645 patients had 1,625 episodes of care totaling 47,098 days. Total days increased by 1,229 days in 1998 and 602 days in 2000 compared to 1995/96. The study populations were similar with respect to sociodemographic factors, psychiatric status and level of care provided. 15% of patients were discharged on an atypical in 1995/96 compared to 71% in 2000 and the average LOS increased from 31 to 39 days. Requiring electroconvulsive therapy (ECT), switching from conventional to atypical during the admission, requiring seclusion, or having thought disorder were independently associated with a significantly longer LOS. Leaving against medical advice (AMA), or being suicidal on admission decreased hospitalization. 50% of the population was readmitted in 215 days in 1995/96, 221 days in 1998, and 223 days in 2000. Independent of the class of antipsychotic prescribed on last discharge, leaving AMA and number of previous admissions significantly increased the risk of readmission within 1 year.

CONCLUSION: The number of schizophrenia patients hospitalized decreased but LOS increased with no change in readmission rates. The higher costs of the drugs were not offset by decreased hospitalization.

KEY WORDS: *Drug policy; drug utilization; atypical antipsychotic medications; Provincial drug program*

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THE IMPACT OF INCREASING CONTINUITY OF CARE FROM A DISEASE MANAGEMENT PROGRAM ON THE COSTS AND UTILIZATION OF DIABETES MEDICATIONS

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Funding Source: Canadian Health Services Research Foundation

BACKGROUND: Increased continuity of care improves the consistency to which diabetes process indicators are met; however, it may also affect drug utilization and drug costs. This study determined the utilization and costs of diabetes-related medications for patients participating in the Health Promotion Initiative in Diabetes (HPID).

METHODS: The HPID is a comprehensive, primary care disease management program that demonstrated a 55% improvement in process and clinical outcomes for patients registered in a multidisciplinary health service organization. 404 diabetic patients from this program were included in this descriptive cohort study. Information on the numbers, types, and costs of diabetes-related medications was collected from community pharmacy prescription records and compared over 6-month intervals during the study.

RESULTS: In total, 14,934 prescriptions were filled by 395 patients with costs of $993,519.33 ($1,677/patient per annum). Diabetes-related medications (DRMs) represented 50.1% of all prescriptions and 61.0% of prescription costs. The most frequently prescribed DRMs were ACE-inhibitors (16.8%), insulin (14.0%), statins (12.7%), and biguanides (8.4%). Numbers of DRMs increased by 12.1% over 18 months, with a resultant cost increase of $58.03/patient per annum. Largest increases in DRM utilization were seen with antihypertensives, lipid-lowering agents and biguanides, due to more patients being prescribed these medications. Increased costs were largely attributed to a 17.3% cost increase from antihypertensive prescriptions and a 30.9% cost increase from lipid-lowering agents. However, this was offset by a corresponding 30% ($641/patient per annum) decrease in hospitalization costs.

CONCLUSIONS: The number and costs of DRMs prescribed increased over time for patients in a primary care disease management program. Greater use of drugs that improve glucose, blood pressure, and cholesterol contributed to the increased costs.

KEY WORDS: *Continuity of care; diabetes; drug utilization*

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THE INFLUENCE OF BONE MINERAL DENSITY TESTING ON PERSISTENCE AND ADHERENCE TO OSTEOPOROSIS PHARMACOTHERAPY

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Funding Source: Manitoba Bone Mineral Density Program

BACKGROUND: The influence of bone mineral density (BMD) assessment on a woman's decision to initiate, persist, and adhere to osteoporosis-related pharmacotherapy has not been analyzed at the population-level through the use of administrative databases. Through linkage of a BMD database (containing the results of nearly all BMD measurements performed in Manitoba since 1990), we measured the influence of such testing on persistence and adherence to osteoporosis-related pharmacotherapy (OSRx) in post-menopausal women.

METHODS: Hospital, physician, pharmaceutical, clinical (bone mineral density results) and demographic data for women continuously residing in Manitoba from 1997 through 2002 were obtained from provincial administrative databases. Cox proportional hazards analysis was used to compare differences in persistence between women with and without a BMD assessment prior to initiating an OSRx, while multivariate regression was used to assess differences in adherence. Explanatory variables and covariates tested in the models included: prior osteoporotic fracture since age 50, age, income quintile, and urban vs. rural region of residence. In women for whom a BMD test was performed, the results of the test (i.e. osteoporotic status) were also included as covariates.

RESULTS: Of the original 112, 464 women included in the analysis, 14, 031 (12.5%) were dispensed at least one OSRx and 7.5% (8443 women) received at least one BMD assessment during the study period. Women who received a BMD assessment prior to initiating an OSRx were more likely to continue on therapy than women for whom no BMD assessment was performed ($p<0.001$).

CONCLUSION: A woman's persistence on an osteoporosis pharmacotherapy may be influenced by a BMD assessment performed prior to treatment initiation or during a prevalent course of therapy. BMD testing results may be valuable in women for whom continuation of therapy is undecided.

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TREATMENT COMPLIANCE OF RHEUMATOID ARTHRITIS PATIENTS RECEIVING INFLIXIMAB AND ETANERCEPT: THE SASKATCHEWAN EXPERIENCE

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Funding Source: Schering Canada Inc.

BACKGROUND: The recent introduction of the anti-TNF agents infliximab and etanercept constituted a therapeutic landmark in the management of rheumatoid arthritis (RA). A major difference between these agents is mode of administration, infliximab being administered intravenously approximately every 8 weeks, while etanercept is administered subcutaneously twice weekly. At this time, no Canadian data exists comparing patient compliance to these two agents.

METHODS: A retrospective analysis of the administrative claims data from the Saskatchewan Drug Plan and Extended Benefits Branch database from September 2001 to September 2003 was performed. Compliance of both patient cohorts was determined, with compliance being defined as the actual number of filled prescriptions divided by the expected number of prescriptions.

RESULTS: Over two years, 355 RA patients received at least one claim for infliximab or etanercept. In order to minimize skew, only data from those patients who had been treated for a minimum of one year continuously were included in the analysis (etanercept, n=91; infliximab, n=98). Only 24% of etanercept patients were 100% compliant compared to 80% of infliximab patients ($P<0.01$). The percentage of patients receiving a minimum of 80% of the number of prescriptions was significantly higher ($P<0.01$) for infliximab patients (91%) than for etanercept patients (71%).

CONCLUSION: Analysis of two years of claims data indicate that compliance is significantly higher with infliximab compared to etanercept. While it is not possible to demonstrate based upon the current data, it is reasonable to speculate that this difference in compliance may have an important

KEY WORDS: *Infliximab; etanercept; rheumatoid arthritis; compliance; utilization*

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USING ELECTRONIC PRESCRIPTIONS TO DOCUMENT TREATMENT INDICATION: EVALUATION OF DATA QUALITY IN THE MOXXI INTEGRATED PRESCRIBING AND DRUG MANAGEMENT SYSTEM

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Funding Source: Health Canada

BACKGROUND: Indications for prescribed medication are rarely documented in the chart, and they are also not generally known to the pharmacist responsible for dispensing the prescription. The development and implementation of a prototype integrated electronic prescribing and drug management prototype (MOXXI) allowed us to evaluate the feasibility of including treatment indication as a required field in the electronic prescription.

METHODOLOGY: The MOXXI drug management system links community-based physicians, retail pharmacies, and the provincial insurance program in a secure network. The electronic prescribing pad was developed to record up to 4 treatment indications for a single prescription. As physicians may not be aware of the original indication for a drug prescribed by a prior physician, we had to add a "renewal" indication to the list for each drug. The MOXXI system was implemented in the practices of 30 primary care physicians, 33 pharmacies, and 14,830 consenting patients in an urban community. All electronic prescriptions written between January and November 2003 were retrieved. The proportion of renewals and the frequency of indications by drug were assessed.

RESULTS: A total of 24,119 electronic prescriptions were written by the 30 study physicians in first 11 months of the pilot project. The "renewal" indication was recorded in 22.1% of all electronic prescriptions. The greatest proportion of "renewal" indications was for ASA (56.0%), likely because the indication list was incomplete. Unique information was generated for drugs where indication has traditionally been difficult to determine. For example, the indications for the most common benzodiazepine were anxiety (41.0%), insomnia (33.8%), renewal (22.1%), panic disorder (1.9%), convulsions (0.6%), nausea (0.3%) and cancer co-analgesia (0.3%).

CONCLUSIONS: Electronic prescribing provides an opportunity to resolve long-standing problems in the documentation of treatment indication.

KEY WORDS: *Electronic prescription; integrated drug management; therapeutic intent*

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VALIDATION OF SCORES OF ASTHMA SEVERITY AND CONTROL BASED ON FILLED PRESCRIPTIONS

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Funding Source: MSSS du Québec and GlaxoSmithKline

BACKGROUND: In clinical and epidemiologic research, it is often necessary to categorize patients in terms of asthma severity and control. We thus developed and validated a score of asthma severity (SAS) and a score of asthma control (SAC) based entirely on filled prescriptions for asthma.

METHODS: The SAS is based on the dose of inhaled corticosteroids, the prescriptions of adjuvant asthma therapy and long-term prescriptions of oral corticosteroids filled over a 12-month period. The SAC is based on the number of short-acting beta2-agonists and short-term prescriptions of oral corticosteroids filled over a 3-month period. Adult asthmatic patients were recruited at the asthma outpatient clinic of the Hospital du Sacré-Coeur de Montréal in 2002. The SAS and SAC were calculated based on pharmacy records. The SAS was validated against the FEV1 and a clinical measure of asthma severity. The SAC was validated against the Asthma Control Questionnaire (ACQ) and the use of health care services. Pearson correlation coefficients were estimated.

RESULTS: The 60 recruited patients were on average 50 years old and had a mean (sd) predicted FEV1 of 77% (17%). We found significant correlations between the SAS and the clinical measure of asthma severity (r=0.613; p=0.0001) and the FEV1 (r= -0,289; p=0,025). The SAC was not found to be correlated with the ACQ, but was significantly correlated with the use of health care services (r= 0,335; p= 0,009).

CONCLUSION: The SAS was found to be valid to measure asthma severity. The absence of association between the SAC and the ACQ could be explained by the fact that the ACQ is measured over a 7-day period (acute control), while the SAC is measured over a 3-month period (long-term control).

KEY WORDS: *Asthma, severity, epidemiology, asthma medications, administrative database*

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VARIABILITY OF BREAST CANCER RISK IN OBSERVATIONAL STUDIES OF HORMONE REPLACEMENT THERAPY: A META-REGRESSION ANALYSIS

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Funding Source: Schering AG

OBJECTIVES: A re-analysis of data from 51 epidemiological studies reported a significant 14% increase in the risk of breast cancer associated with the use of hormone replacement therapy (HRT). Unlike randomized trials, these observational studies varied considerably in design and methods. This study was conducted to explore the impact of study design factors on the rate ratio.

METHODS: Meta-regression analysis of epidemiological studies of HRT and breast cancer was undertaken. Rate ratio (RR) of breast cancer associated with ever use of HRT was evaluated in relation to study design, study period, country, primary study objective, method of exposure measurement, age control, adjustment factors related to reproduction and menopause, and the presence of breast cancer surveillance. We used stepwise multiple linear regression analysis, weighted by the inverse of the variance of the logarithm of the RR, to estimate ratios of rate ratios for these factors.

RESULTS: Exposure measured by personal interview and/or medical record review was associated with a significant 14% lower RR as compared with telephone interview or self-administered questionnaire. Among studies that did not adjust for age at menopause, the RR was 12% lower if the primary objective was the use of HRT than not (p=0.016), while it was 43% higher among studies that adjusted for age at menopause (p=0.042). An index representing desirable design features suggests that studies with the lowest score would lead to a RR estimate of 1.14 (95% CI:1.00-1.29), compared with an estimate of 0.98 (95% CI:0.83-1.15) for studies with the highest quality score.

CONCLUSIONS: Design factors of epidemiological studies could be an alternative explanation for the reported increase in the risk of breast cancer associated with the use of HRT. A similar analysis is currently under way for studies of oral contraceptives and breast cancer.

KEY WORDS: *Hormone replacement therapy; breast cancer; meta-analysis; observational studies; heterogeneity*

POSTER PRESENTATIONS

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A CANADIAN ECONOMIC EVALUATION OF PEGASYS® (PEGINTERFERON-A2A[40KD]) IN TREATMENT-NAÏVE PATIENTS CHRONICALLY INFECTED WITH HEPATITIS C

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Funding Source: Hoffmann-La Roche Limited

BACKGROUND: The hepatitis C virus (HCV) is a major cause of liver-related morbidity and mortality; an estimated 240,000 Canadians are chronically infected. With adequate therapy, there is likely reduced progression to endstage liver disease and a decreased need for transplantation, with resultant health care cost-savings. Interferon-based regimens form the mainstay of therapy, and newer pegylated interferons have recently been evaluated. The objective of the study was to compare the cost-effectiveness of peginterferon (PEG)-α2a-based regimens versus conventional therapies and no treatment in previously untreated patients with chronic HCV.

METHODS: A decision analysis using a previously published Markov model (Zou, Can J Gastro 2000;14:575) was employed comparing standard dosages of PEGα2a versus no treatment, interferon-α2a, and PEGα2b. A separate analysis was conducted including combination therapy with ribavirin. Direct costs (in Canadian dollars for the year 2000) were obtained from the Alberta Health and Wellness database; transition probabilities and utilities were obtained from the literature. In the base-case analysis, a representative cohort of Canadian patients (based on age, gender, disease severity, and genotype) was considered, and a 2% annual treatment rate was assumed. Indirect comparisons between PEGα2a- and PEGα2b-containing regimens were made using clinical trial data including a common comparator.

RESULTS: In patients ineligible for ribavirin, the incremental cost-utility ratios (ICURs) of PEGα2a versus no treatment and interferon-α2a were $11,820/QALY and $16,190/QALY, respectively. In patients eligible for ribavirin, PEGα2a/ribavirin combination therapy was dominant over conventional interferon-α2b/ribavirin, with a lower expected lifetime cost ($548/patient) and improved quality-adjusted life expectancy (0.12 years). PEGα2a/ribavirin also dominated PEGα2b/ribavirin ($229 savings and 0.05 years increased quality-adjusted life expectancy/patient). The ICUR of PEGα2a/ribavirin versus no treatment was $6,573/QALY. A one-way sensitivity analysis revealed that changes in the values of the most relevant parameters (including age, genotype, and disease severity) did not appreciably modify the model results.

CONCLUSIONS: PEGα2a (with or without ribavirin) is a cost-effective therapy in Canadian, treatment-naïve patients with chronic hepatitis C.

KEY WORDS: *Chronic hepatits C; pegylated interferon; cost-effectiveness analysis; cost-utility analysis; Markov Modeling.*

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A COST-EFFECTIVENESS ANALYSIS OF GLYCOPROTEIN IIB/IIIA INHIBITORS AS ADJUNCT THERAPY IN PATIENTS WITH ACUTE CORONARY SYNDROME UNDERGOING PERCUTANEOUS CORONARY INTERVENTIONS WITH STENTING

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Funding Source: Canadian Coordinating Office for Health Technology Assessment (CCOHTA)

OBJECTIVES: Coronary stenting has become the standard of care for patients with acute coronary syndrome. This study examines the cost-effectiveness of the platelet glycoprotein IIb/IIIa inhibitors, abciximab (AB) and eptifibatide (EP), as adjunct therapies in patients undergoing percutaneous coronary intervention (PCI) with stenting.

METHODS: Included patients, undergoing elective or urgent PCI with stenting. AB and EP in combination with stenting were compared to a treatment group of stent only patients. Short-term (one year) and long-term (survival-Markov model) decision analytic models (DATA™ 4.0 by TreeAge) were constructed from a Canadian provincial health system perspective. Results were presented in 2001 Canadian dollars. A 5% discount rate was used. Probabilistic sensitivity analysis was done using Crystal Ball® software.

RESULTS: When compared to the stent only group, EP+stent was dominant in terms of costs (-$59), rates of major adverse cardiac events (MACE) (-5.6%) and mortality (-1.0%) over a one year period. There was in increase in the life years gained (0.22 unadjusted and 0.12 adjusted) for EP. For AB+stent, average expected costs were higher (+$1,171) but clinical outcomes were better (-7.0% MACE and -1.0% mortality) relative to the stent only group. The incremental cost-effectiveness analysis was $16,729 per MACE avoided and $117,100 per death avoided. AB+stent patients had more life years than the stent only group (0.12 unadjusted or 0.07 adjusted). Incremental ratios were $9,758 unadjusted and $16,729 per adjusted life year gained.

CONCLUSIONS: EP and AB were considered cost-effective in the treatment of patients undergoing PCI with stenting.

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A COST-EFFECTIVENESS COMPARISON OF ALTERNATIVE STRATEGIES AT ONE YEAR TO MANAGE PATIENTS WITH UNINVESTIGATED DYSPEPSIA: THE CANDYS APPROACH VERSUS ANTISECRETORY THERAPY VERSUS PROMPT ENDOSCOPY

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Funding Source: Supported in part by AstraZeneca Canada, Inc

BACKGROUND: The optimal cost-effective management of adult patients with uninvestigated dyspepsia (UD) remains unknown.

METHODS: We compared the CanDys approach (acid suppression if heartburn predominant symptoms, and a test-and-treat strategy for others, acid suppression for H. pylori (HP) negative patients and eradication for HP+) to initial empirical anti-secretory therapy (EAS) and prompt endoscopy (PE). Effectiveness was the number of symptom-free (SF) months at 1 year. Probabilities and resource use were from patient specific trial data, and healthcare costs (in 2001 CAN$) from provincial fees. A decision analysis incorporating a 3-month cycle Markov model for each alternative was constructed using DATA Pro. Probabilistic sensitivity analyses were conducted using a Monte Carlo simulation technique. Acceptability curves were used to compare strategies.

RESULTS: The least effective strategy was EAS-ranitidine at 4.11 SF-months (95%CI 3.64-4.62), followed by EAS-omeprazole, 4.14 (3.69-4.61), CanDys ranitidine, 4.40 (3.80-5.02), CanDys omeprazole, 4.73 (4.10-5.36), PE ranitidine, 4.79 (3.68-5.87), and PE omeprazole, 7.43 (6.80-8.02). The least costly strategy was CanDys ranitidine $259 ($157-$572), followed by EAS omeprazole $273 ($146-$829), CanDys omeprazole $277 ($206-$490), EAS ranitidine $283 ($139-$1053), PE ranitidine $878 ($556-$1751), and PE omeprazole $2288 ($465-$10,282). When comparing all approaches to the least costly, CanDys omeprazole appeared to be the strategy of choice with 72% of all simulations satisfying a pre-set willingness-to-pay (WTP) threshold of $175 (CDN) per SF month.

CONCLUSIONS: Based on the model assumptions, the WTP analysis suggests that the CanDys approaches may be the strategies of choice in the approach to patients with UD over the medium term.

KEY WORDS: *Dyspepsia, economic modeling; cost-effectiveness; endoscopy; anti-secretory therapy; helicobacter pylori*

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A COST-UTILITY ANALYSIS OF LOSARTAN VERSUS ATENOLOL IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION

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Funding Source: Funding for this project was provided in part by Merck Frosst Canada Ltd.

OBJECTIVES: The Losartan Intervention for End Point Reduction in Hypertension (LIFE) study demonstrated a 13% relative risk reduction in the primary composite endpoint (myocardial infarction, stroke or death) and a 25% relative risk reduction in stroke for patients treated with losartan compared to patients treated with a first-line antihypertensive agent (atenolol). Incorporating the results found in the LIFE study, an incremental cost-effectiveness analysis was performed to determine the economic feasibility of making losartan a first line anti-hypertensive agent in the prevention of cardiovascular morbidity and mortality.

METHODS: A Markov State Transition model based, in part, on published results of the LIFE trial (mean follow-up of 4.8 years) was utilized to extrapolate observed outcomes to the patients' lifetime. Considering a societal perspective, fully allocated costs were calculated using the St. Paul's Hospital Cost Model. QALY estimates for each of the health states were obtained from a variety of sources within the literature. Sensitivity analysis was performed in order to examine the impact of a broad range of variation in our model parameters.

RESULTS: The incremental cost effectiveness ratio of losartan versus atenolol was CDN$1,337 per QALY gained. Probabilistic sensitivity analysis demonstrated a 95% probability that the cost-effectiveness ratio would be less than CDN$20,000 per QALY gained.

CONCLUSIONS: Losartan appears to be an effective and cost-effective alternative to traditional first-line therapies for hypertension. Results were robust to univariate and probabilistic sensitivity analysis and are well within the accepted ranges of cost-effectiveness ratios deemed to be efficient and cost effective.

KEY WORDS: *Losartan; cost-utility; cost-effectiveness; hypertension; stroke.*

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A NATIONAL LIST OF PROVINCIAL HEALTH CARE COSTS FOR CANADA – 2002 UPDATE

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Funding Source: Canadian Coordinating Office for Health Technology Assessment, Institute of Health Economics

BACKGROUND: In 2000 the Institute of Health Economics formed a working group which developed a 1997 version of a list of standard health care costs for Canadian provinces. The list was very comprehensive in nature. It contained detailed and high quality data from most provinces for inpatient hospital, outpatient pharmaceuticals and physician visits. It contained more limited data from a number of other areas. We have begun an initiative to update the routinely collected costs, and develop methods for improving less routinely collected costs. In this abstract, we describe the 2002 update. **METHODS:** The 2002 Update will contain inpatient hospital costs, physician fees, outpatient hospital costs, and outpatient drugs for all available provinces. Inpatient costs are obtained in two ways: (1) using the cost per weighted case method from the Canadian Institute for Health Information and (2) using aggregated (by case mix) results from Ontario and Alberta. Outpatient hospital costs will be obtained by unit costing from Alberta Health using the Alberta Ambulatory Care Classification System. Outpatient drugs are presented in two ways: (1) according to a special run by province from IMS, Inc. for the 1,000 most used drugs, as well as those most recently introduced; and (2) using provincial formulary lists. An internet interface will be presented for all units, so they can be downloaded.
RESULTS: A descriptive analysis and instructions for access will be included here. Access will be via the internet, with an instruction booklet also available.
KEY WORDS: *Cost; economic evaluation; cost effectiveness*

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A PILOT STUDY ASSESSING AWARENESS OF RISK FACTORS FOR FALLS IN PATIENTS WITH PARKINSON'S DISEASE

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Funding Source: None

BACKGROUND: The purpose of this study was to examine the awareness and perception of risk factors for falling among community dwelling people with Parkinson's Disease (PD). In addition to the usual risks for falling, gait impairment and postural instability greatly increase the risk of falls.
METHODS: A cross-sectional survey of PD patients attending the Glenrose Rehabilitation Hospital in Edmonton, Alberta, Canada, was conducted between January-March, 2003. Behavioural, medication, physical, environmental, and medical risks were included. Participants were asked a series of open-ended and self-administered closed-ended questions, which took approximately 30 minutes. A debriefing took place after completion of the survey to elicit feedback regarding the instrument.
RESULTS: Twenty-eight subjects completed the survey. The mean age was 61 (10.8) years; 54% (n=15) of the sample were women. Only 7% (n=2) of the sample had less than high school education. Seventy-five percent (n=21) of the participants reported a history of fall(s). Twenty nine percent (n=8) reported using sedative hypnotics, and 21% (n=6) reported using a medication for mood. Half of participants (n=14) identified taking more medications as a risk for falling, while 89% (n=25) identified increasing age as a risk factor for falls. Ninety-two percent (n=26) reported that seniors may be able to change their behaviour to prevent falls.
CONCLUSIONS: This well educated sample of patients with PD appeared to have some knowledge of medical, behavioural, and environmental risk factors, but a limited knowledge of medication risk factors. Further education is necessary to increase awareness of fall risks.
KEY WORDS: *Parkinson's disease; elderly; falls; falls awareness; drug therapy; risk factors*

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A POPULATION-BASED STUDY OF OSTEOPOROSIS TESTING AND TREATMENT FOLLOWING INTRODUCTION OF A NEW BONE DENSITOMETRY SERVICE

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Funding Source: Manitoba Bone Mineral Density Program

BACKGROUND: Bone density measurement plays a key role in the intial diagnostic assessment of osteoporosis and for targeting pharmacologic therapies. However, the impact of access to dual x-ray absorptiometry (DXA) on physician prescribing habits remains unclear. The objective of this study was to directly evaluate the change in physician osteoporosis testing and prescribing following the introduction of a DXA testing service in a geographic region that previously had very limited access.

METHODS: Manitoba has a provincially-based bone density testing program and maintains a population-based bone density database that can be linked with other provincial health databases. Manitoba was geographically partitioned into the urban and rural health regions serviced by the new DXA (URBANnew and RURALnew) and compared to health regions which had relatively unchanged DXA access during this period (URBANcontrol and RURALcontrol). Regression models of DXA testing rates and osteoporosis prescription rates were created for all women over 50 years of age in these regions.

RESULTS: There was a statistically significant increase in bone density testing and BMD-guided osteoporosis treatment in the URBANnew and RURALnew regions after introduction of the DXA testing service relative to the control regions. There were no significant changes in overall prescribing rates for any group. When analysis was limited to non-hormonal agents a significant reduction in preventive and empiric post-fracture treatment emerged in some subgroups of women.

CONCLUSION: Access to bone density testing led to an increase in both testing and BMD-guided osteoporosis treatment initiation, with a decrease in the use of newer non-hormonal osteoporosis agents for preventive and empiric treatment in some subgroups. This would be expected to translate into more cost-effective targeting of treatment, particularly for newer, more expensive agents.

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ACADEMIC DETAILING TO PROMOTE OPTIMAL DRUG USE IN THE ELDERLY

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Funding Source: Saskatchewan Health

BACKGROUND: The RxFiles Academic Detailing program was initiated in May, 1997 to promote optimal drug therapy. The program utilizes a newsletter followed with a physician office visit (academic detailing) to discuss specific recommendations and questions. Trends in drug utilization were used to help assess the impact of this intervention.

METHODS: The RxFiles - Psychotropic Drugs in the Elderly newsletter was published and distributed to all family physicians in the province in early May 2001. Academic detailing sessions were offered in select areas. Visits focused on reductions in the overall use of benzodiazepines in general, triazolam specifically and highly anticholinergic drugs such as amitriptyline. Drug utilization data was obtained to compare utilization data for the 7 months prior to and following the publication of the newsletter.

RESULTS: All detailed centers had reductions in the total number of benzodiazepine scripts for beneficiaries age 75 and older. In contrast, benzodiazepine scripts for this age group increased provincially. Detailed centers had consistently greater reductions than the rest of the province. All detailed centers with the exception of Saskatoon had greater reductions than the rest of the province in number of triazolam prescriptions in the elderly. Analysis showed consistent reductions in amitriptyline prescriptions for all detailed centers compared to the rest of the province which had a gain of 1.5%. A subanalysis of higher dosage amitriptyline scripts also showed reductions in number of higher dosage scripts in detailed areas.

CONCLUSIONS: Academic detailing was associated with favorable psychotropic utilization trends in the elderly.

KEY WORDS: *Academic detailing; drug utilization; elderly; psychotropics; anticholinergics; benzodiazepines*

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ACCURACY OF ICD-9 DIAGNOSIS CODE '410' TO IDENTIFY EPISODES OF HOSPITALIZATIONS FOR ACUTE MYOCARDIAL INFARCTION IN RAMQ

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Funding Source: None

BACKGROUND: RAMQ administrative databases are frequently used beyond their primary role in patient care, including epidemiologic and economic studies. Although the quality of RAMQ data directly affects these studies, there has been no previous review of data accuracy in RAMQ medical services database regarding diagnoses codes and inhospital records. The objective of this study was to assess the validity of ICD-9 diagnosis code '410' in the RAMQ claims database to identify episodes of hospitalizations for acute myocardial infarction (AMI).

METHODS: We used 707,916 patients aged >=65 years with medical records between April 1999 and December 2002. Inhospital claims were then identified using diagnosis and institutional codes. The validation process was then implemented through comparison analyses with the "gold standard", MED-ECHO (hospital discharge summary).

RESULTS: From RAMQ, we identified 23,860 patients who were admitted at least once for AMI during the study period. Sensitivity and specificity of the algorithm identifying the first inhospital stay for AMI were 81.09% (95%CI: 80.52-81.64) and 98.78% (95%CI: 98.76-98.81), respectively, with kappa=0.72 that indicates substantial agreement. The efficiency of a claim with ICD-9 code '410' to identify AMI was estimated to be 93.30%. The mean length of stay (LOS) was 8.69 days, with a geometric mean of 7.22 days in RAMQ vs. 11.48 and 8.04 days ($p<0.001$) in MED-ECHO; the average readmission was 1.13 times vs. 1.02 ($p=0.54$) in patients with AMI, respectively.

CONCLUSION: The use of ICD-9 code '410' to identify hospitalized cases of AMI results in a modestly biased overestimate of the number of hospitalizations; however, inhospital LOS is underestimated. Overall, RAMQ medical services database gives an acceptable estimates for AMI; it can be used as a powerful tool to identify episodes of hospitalizations for AMI. Further studies are needed to establish data accuracy for other medical conditions.

KEY WORDS: *Administrative database; record linkage; ICD-9 codes; myocardial infarction; hospitalization; validation*

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ACCURACY OF RAMQ CLAIMS TO IDENTIFY EPISODES OF HOSPITALIZATIONS FOR UPPER GASTROINTESTINAL BLEEDING: A DATA VALIDATION STUDY

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Funding Source: None

BACKGROUND: Administrative information has become an increasingly important source of data for epidemiologic research. However, the validity of such data needs to be assessed. The objective of this study was to evaluate the validity and reliability of ICD-9 codes in RAMQ medical services database for identifying episodes of hospitalizations for upper gastrointestinal bleeding (UGIB).

METHODS: We used medical records of 707,916 patients aged >=65 years between April 1999 and December 2002 provided by the RAMQ. Claims data from inpatients records were then retrieved if the claim was one of the ICD-9 codes (531X-534X, 578X) for UGIB. To identify episodes of hospitalizations for UGIB, 4 algorithms were developed using combinations of different diagnoses and procedural codes for endoscopy. Validity was assessed by calculating sensitivity, specificity, efficiency, and positive and negative predictive values when compared to the "gold standard", MED-ECHO database (hospital discharge summary). Reliability was assessed using kappa statistics.

RESULTS: Overall, 5280 case abstracts were identified using MED-ECHO database. The sensitivity ranged from 61.9-73.7% with the specificity of >99%. The efficiency was found to be >99%. In addition, predictive values ranged from 36.7-56.1% for the positive and above 99% for the negative tests. Overall kappa statistic indicated moderate agreement (0.46-0.60).

CONCLUSION: Comparison of observed data with the gold standard revealed more than 98% accuracy of the RAMQ medical services database for estimating UGIB hospitalizations. The most precise algorithm was found to be highly specific, but inadequately sensitive which underestimated UGIB events. In other words, an individual with diagnosis-defined hospitalization is predicted to be almost certain to have UGIB, but many individuals with UGIB will be labeled as not having this condition. The reliability of RAMQ data for UGIB hospitalizations was acceptable.

KEY WORDS: *Administrative database; record linkage; ICD-9 codes; upper gastrointestinal bleeding; hospitalization; validation.*

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ACHIEVING TARGET INRs WITH WARFARIN: DOES CLINICAL PRACTICE MIRROR CLINICAL TRIALS?

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Funding Source: Unrestricted grant from AstraZeneca Canada Inc.

BACKGROUND: The efficacy and safety of anticoagulation therapy largely depend on meeting target INR values. Target INRs have been established through clinical trials, but are these targets met in practice?

METHODS: A MEDLINE search was conducted (1966-2001) using the MeSH terms anticoagulants, atrial fibrillation, warfarin and guideline adherence. Studies reporting the percentage time in the target INR range for stroke prevention in atrial fibrillation (AF) were retrieved.

RESULTS: RCTs: One pooled analysis and seven clinical trials were found. Patients were in the target INR range 66%, above the range 9% and below the range 25% of the time, according to the pooled analysis of five of the seven major trials (SPAF, SPINAF, BAATAF, AFASAK, CAFA). Patients were in the target range 59-75% of the time in the two trials not in the pooled analysis (SPAF-2, EAFT).

CLINICAL PRACTICE STUDIES: Eight clinical practice studies were found. Across all eight studies, patients were in the target INR range 40-62%, above the range 13-40% and below the range 17-45% of the time. One Canadian cardiology practice study (including non-AF cases) reported patients in the target INR range 62.3%, above the range 20.3% and below the range 17.4% of the time.

CONCLUSION: Target INRs appear to be met less frequently in clinical practice than in RCTs. Clinical, psychological and environmental factors can affect anticoagulation control. Research on clinical risk factors for non-therapeutic INRs is needed to minimize the effects of under- or over-anticoagulation.

KEY WORDS: *Anticoagulation; warfarin; stroke; atrial fibrillation; overview, RCT and clinical practice studies.*

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ADHERENCE TO CLINICAL PRACTICE GUIDELINES FOR GASTROINTESTINAL DISORDERS

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Funding Source: Government

BACKGROUND: The use of PPIs has steadily increased in Alberta with yearly quantity increases of 33.7% and 25.4% from 2000 to 2002. Similar trends have been noted in other provinces and countries. This study was conducted to assess specific "appropriateness" criteria adapted from the Alberta Clinical Practice Guidelines. Three criteria were studied.

METHODS: The review was limited to the population with drug benefits covered by Alberta Health and Wellness (Groups 66, 66A and 1). Data was extracted for three years from April 1, 1999 to March 31, 2002. Three data sources were used that included prescriber payment, patient demographics, and prescription data. Patient data for specific ICD9 diagnoses were taken from the physician billing claims and matched to prescription claims for gastrointestinal medications. The following criteria were studied: (i) concomitant use of a PPI with two antibiotics prescribed for H.Pylori treatment; (ii) for GERD/chronic dyspepsia that within 45 days of initial diagnosis a PPI or H2RA was dispensed; and (iii) duration of treatment with a PPI or H2RA was a maximum of ten weeks.

RESULTS: Over the three years, the total number of matched cases studied was 77,555. 3094 cases were studied for H. Pylori treatment with 86% having concomitant therapy. Of the 77,555 cases, 13.4% were initiated within 45 days of diagnosis, and 42.1% of these cases (4392) had a maximum treatment of 10 weeks with a PPI or H2RA. Further analysis is to be completed with the other cases that did not adhere to the criteria.

CONCLUSIONS: Improvements in adherence specific to all three criteria are possible; however, greater opportunities exist for improving treatment of GERD/chronic dyspepsia.

KEY WORDS: *Drug utilization; review; proton pump inhibitors; appropriateness of prescribing*

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AN ASSESSMENT OF LINEZOLID UTILIZATION IN CANADA

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Funding Source: Pfizer Canada Inc.

BACKGROUND: Linezolid was approved for treatment of designated infections caused by methicillin-resistant and Csusceptible S. aureus (MRSA, MSSA) and vancomycin-resistant E. faecium. The objective of this study was to characterize linezolid utilization since its launch in 2001.
METHODS: Demographics, antimicrobial regimens, clinical and resource utilization data for linezolid-treated patients were collected retrospectively by hospital pharmacists at nine tertiary hospitals in four provinces. Statistics describing linezolid utilization were calculated and the appropriateness of use was assessed according to a treatment algorithm based on recommendations of the Infectious Diseases Pharmacist Specialty Network.
RESULTS: Ninety-nine linezolid courses (continuous administration without interruption > 72 hours) were prescribed for 103 infections in 95 patients (mean age 57.8 years, 52.6% male) with an average length of hospital stay of 40.6 days. Fifty-three percent of patients had ¡Ý1 allergies to antibiotics other than linezolid. The major use of linezolid was for treatment of skin and soft tissue infections (32.0%), followed by bacteremia (15.5%). The most prevalent pathogen was MRSA, identified in 44.7% of infections. Linezolid (average duration 14.4 days) was most commonly prescribed as the oral form following other intravenous anti-infectives (55.6% of courses). The rate of appropriate utilization was 53% (range 25%-75% by site). In 94% of courses deemed inappropriate, recommended first-line therapies were not attempted before linezolid.
CONCLUSIONS: Linezolid was prescribed appropriately in the majority of cases reviewed. The rate of appropriate utilization is similar to rates reported in other Canadian antibiotic reviews.
KEY WORDS: *Linezolid; bacterial infections; drug utilization*

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AN EVALUATION OF PATIENT OUTCOMES IN AN ANTICOAGULATION MANAGEMENT SERVICE (AMS): FROM ADEQUACY OF ANTICOAGULATION TO PATIENT SATISFACTION

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Funding Source: Alberta Health and Wellness

BACKGROUND: Pharmacist-managed anticoagulation services are relatively new in Canada, and comprehensive evaluation is necessary.
OBJECTIVE: To assess the adequacy of anticoagulation, the rate of major bleeding and thromboembolism, as well as patient satisfaction in an AMS.
METHODS: Consecutive outpatients referred managed in ambulatory AMS between April 2001 and December 2002 for a minimum of 90 days. Adequacy of anticoagulation assessed by the Rosendaal method (target INR + 0.5 and excluding the first 30 days of management). Major bleeding (either blood loss > 2g/dL or transfusion of >= 2 units of blood) or thromboembolism (clinical diagnosis given) was adjudicated by an expert panel, and a 34 item self-administered questionnaire, using a 5 point Likert rating scale, was completed by patients to assess opinions of the AMS.
RESULTS: A total of 268 patients were eligible, 64% were male and the mean age was 59 +/- 16 years. The majority had atrial fibrillation (41%) and 27% had venous thromboembolism. Overall, patients are within their desired INR range 69% of the time (median 71%). From a total of 89 events occurring over 130.5 patient years, major bleeding and thromboembolism accounted for 11 events (0.08/patient-year) and 7 events (0.05/patient-year), respectively. Of those responding to the survey (74%), at least 90% agreed or strongly agreed to being satisfied with 16 of the 27 items that assessed promptness, communication, knowledge, etc.
CONCLUSIONS: Accounting for referral bias for hard to manage patients, adequacy of anticoagulation and rates of thrombosis and hemorrhage are reasonable. Patient satisfaction with the service is very high.
KEY WORDS: *Anticoagulant; warfarin; practice evaluation; health outcomes; satisfaction*

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AN INCREMENTAL WILLINGNESS-TO-PAY (WTP) INSTRUMENT TO MEASURE PATIENT PREFERENCE FOR MIGRAINE THERAPY: A VALIDATION STUDY

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Funding Source: Pfizer Canada Inc.

BACKGROUND: Migraine is a recurrent headache disorder incapacitating over 3 million Canadians. Migraine pain and symptoms significantly impact daily functioning, QoL, productivity and use of health resources. Therefore, a comprehensive assessment is warranted to measure the impact of migraine therapies. This study validates a WTP instrument developed to measure patient preference for substitute migraine treatments.

METHODS: Patients were recruited from a Quebec migraine clinic in November 2003. Eligibility included the use of two different migraine therapies within the previous year. The clinic coordinators administered the questionnaire through phone interviews. Subjects were first asked to indicate their preferred therapy. In essence, the maximum incremental WTP was elicited with the following question: "Given that therapy A costs $X, how much more would you be WTP for therapy B", where therapy B was preferred. The incremental WTP responses give a measure of the extent to which patients prefer one drug versus another.

RESULTS: Twenty-nine migraine patients consented to participate and 25 were successfully contacted for interview. All respondents were able to give a preference for one of the two therapies and were willing to pay for their preferred therapy. The mean incremental WTP for the preferred therapy was $5.92 per attack [95% C.I. 3.31, 8.53]. Finally, 96% of respondents found the questionnaire easy to understand.

CONCLUSIONS: The WTP questionnaire performed well in the pilot study. The questionnaire was easy to understand. The open-ended WTP questions were answered by all respondents. All patients were willing to pay a positive amount for their preferred therapy. No outliers were recorded.

KEY WORDS: *Migraine therapy; willingness-to-pay; patient preference; validation; Canada*

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ANTI-DIABETIC DRUG USE AND THE RISK OF MOTOR VEHICLE CRASH IN THE ELDERLY

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Funding Source: NHRDP and CIHR

PURPOSE: Studies of the risk of motor vehicle crash (MVC) associated with diabetes, including type 2, have produced conflicting results. In this study, we assess whether the use of insulin, sulfonylureas and biguanides among the elderly increases this risk.

METHODS: The computerized databases of various universal insurance programs of the province of Québec were linked to form a cohort of all 224,734 elderly drivers that was followed from 1990-1993. A nested case-control approach was used to identify all 5,579 drivers involved in an injurious crash (cases) and a random sample of 13,300 control subjects. Exposure to anti-diabetic drugs was assessed in the year prior to the index date, namely the date of the crash for the cases or a randomly selected date during follow-up for the controls.

RESULTS: The adjusted rate ratio of an injurious MVC was 1.42 (95% CI: 1.01-2.00) for current use of insulin monotherapy relative to non-use. The adjusted rate ratio for current use of sulfonylurea and metformin combined was 1.27 (95% CI: 0.98-1.65). There was a significant dose-response effect in subjects using more than two defined daily doses of the combination of sulfonylurea and metformin (RR 1.42; 95% CI: 1.04-1.95). For users of insulin monotherapy or of high doses of combined oral therapy, the increase corresponds to an excess rate of 34 crashes, for each mode of therapy, per 10,000 elderly drivers per year.

CONCLUSIONS: Elderly drivers treated with insulin monotherapy or a combination of sulfonylurea and metformin, especially at high doses, have a small increased risk of injurious MVC. There is no increased risk associated with any regimen involving sulfonylureas or metformin used alone.

KEY WORDS: *Cohort study; case-control analysis; diabetes; elderly; drugs; injurious motor vehicle crash; pharmacoepidemiology*

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ANTI-ULCER ACTIVITY OF ASPARAGUS RACEMOSUS WILD. IN GASTRIC ULCERATIVE MODEL

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Funding Source: None

OBJECTIVE: To study the anti-ulcer activity of Asparagus racemosus (extract and crude drug) and its action against NSAIDs and stress (Restraint stress) induced gastric ulcer model in rats.

METHOD: Effect of Asparagus racemosus (Shatavari) crude extract in gastric ulcer model was studied. Asparagus racemosus crude extract (100 mg/ Kg/ day p.o.) was given for six days. Drug treatment gives significantly reduced in stress induced gastric lesions as compared to a standard anti-ulcer drug Ranitidine (30 mg/ Kg/ day p.o.).

RESULT: Asparagus racemosus produced significant reduction in volume of gastric secretion, free acidity, total acidity, ulcer index and significant increase in total carbohydrate and total protein ratio and pH of gastric juice in indomethacin and stress induced gastric ulcerative model. Other then above parameters antioxidant enzymes such as catalase, malone di-aldehyde (MDA), ascorbic acid, super oxide dismutase (SOD) were also estimated in various organs of the animal and it showed that all these marker enzymes were significantly increased after the treatment of asparagus racemosus treatment.

CONCLUSION: Asparagus racemosus proved to be an effective antiulcerogenic agent, whose activity can well be compared with that of Ranitidine hydrochloride (Commonly used drug prescribed in allopathic medicine) in NSAID, S and stress induced gastric ulcerative model. There is possibility that shatavari causes inhibitory effect on release of gastric hydrochloric acid in gastric ulcerative model and it protects gastric mucosal damage. Such protective action may because of their antioxidant properties or may be due to increase of the release of gastro protective prostaglandin's (PG).

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APPROPRIATE PRESCRIBING FOR PERSONS AT HIGH RISK OF GI COMPLICATIONS: CURRENT FINDINGS FROM GENERAL PRACTICE

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BACKGROUND: Across Canada, limited use criteria have been implemented to restrain burgeoning pharmaceutical expenditures particularly in the area of anti-inflammatory use. The Manitoba Appropriate Anti-Inflammatory Utilization (MAAUI) Project aimed to (1) determine how primary health care physicians prescribe NSAIDs, gastroprotective agents [GPA] and the newest class, cyclooxygenase-2 inhibitors or COXIBs, (2) using limited use criteria, assess the appropriateness of long-term prescribing of anti-inflammatories for persons at risk for a GI event, and (3) develop educational interventions for physicians to help them prescribe anti-inflammatories to high-risk patients. We report on objective #2.

METHODS: Using administrative claims data, we performed a panel study of Manitoba residents aged ≥ 20 years who received at least one prescription for NSAIDs including NSAIDs/GPA combinations during 1996-2000 and, for NSAIDs, NSAID/GPAs and COXIBs during 1999-2000. For NSAIDs, NSAID/GPAs and COXIBS, a rate of general practice physicians' appropriate prescribing was determined. The appropriate use criteria applied to all chronic-use antiiflammatory dispensations were based on those factors that put individuals at increased risk of gastrointestinal complications (age over 65 years, previous peptic ulcer, bleeding disorder, concurrent prednisone and/or anticoagulant use and serious concomitant disease).

RESULTS: Of those persons prescribed chronic use COXIBs or NSAID/GPAs in 1999/2000, 82.9% (n=11005) and 81.6% (n=3042), respectively, met at least one high-risk criteria. Conversely, 80.8% (n=15,824) of those prescribed an older NSAID alone met at least one high-risk criteria. Additionally, 53% (n=15824) of patients at increased risk for gastrointestinal complications are not receiving gastroprotective therapy.

KEY WORDS: *Pharmaceuticals;health care technologies;utilization administrative data; gastrointestinal;musculoskeletal/rheumatology;epidemiologic/population based.*

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APPROPRIATENESS OF UTILIZATION OF ANTIRETROVIRALS FOR HIV IN ONTARIO: 2003

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Funding Source: Ontario HIV Treatment Network

BACKGROUND: This study was conducted to measure the extent to which the antiretroviral medications prescribed by Ontario physicians in 2003 when initiating patients on treatment for HIV were aligned with practice guidelines.

METHODS: The drugs specified in the first report of antiretroviral therapy noted in the viral load testing histories of all individuals who received a viral load test administered by the Ontario HIV Laboratory in 2003 were analyzed to determine their consistency with drug combinations recommended by the February 4, 2002 version of the US Department of Health and Human Services' *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.*

RESULTS: Of 538 initiations in 2003, 51.5% (277) were Strongly Recommended and an additional 20.4% (110) were Recommended as an Alternative. Outlier regimens that could not be matched with any DHHS category represented 27.0% (145) of all initiations. Of these 145 outlier regimens, 56.6% (82) fell outside DHHS guidelines because of their use of abacavir (51.7%) or tenofovir (4.8%) in the 2-nucleoside analog backbones of three-drug combinations completed by either a non-nucleoside analog or a protease inihibitor. Quad therapy regimens comprised of 3 nucleoside analogs in combination with either a non-nucleoside or a protease inhibitor represented an additional 17.9% (26) of outlier regimens.

CONCLUSIONS: For 2003, a large majority (71.9%) of initiating antiretroviral regimens may be deemed appropriate, as they were either Strongly Recommended or Recommended as an Alternative by DHHS guidelines. Also, a majority of outlier regimens appear consistent with emerging evidence and current debate.

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ASSOCIATION OF INCOME-LEVEL WITH INITIAL HOSPITALIZATION FOR TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA (CAP) IN MANITOBA

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Funding Source: Institute of Health Economics, University of Alberta

BACKGROUND: Reimbursement restrictions on broad-spectrum antibiotics, common to many provincially administered drug plans, may result in unnecessary hospitalization when patients are unable to pay "out of pocket" for recommended antibiotics. CAP is a common severe respiratory tract infection for which broad-spectrum antibiotics are recommended, but often not covered by provincial plans, for subjects with relevant comorbidities. We examined the influence of income-level on the probability of initial hospitalization for CAP.

METHODS: Physician claims from the province of Manitoba, Canada for the period May 1996 to March 2002 were examined to identify episodes of CAP among adults covered by provincially administered drug plans. The probability of hospitalization was related to patient socio-demographic and disease variables defined from healthcare and census data.

RESULTS: Of 36,969 subjects having a diagnosis of CAP, 5,029 (13.6%) were initially hospitalized, while 31,940 (86.4%) were treated as outpatients. Multivariate analysis revealed a number of independent predictors of initial hospitalization, including: age (10-year increase)[OR=1.43 (1.41-1.46)], male gender [OR=1.20 (1.12-1.28)], urban residence [OR=0.53 (0.50-0.57)], presentation to emergency room [OR=5.14 (4.77-5.53)], and increased level of comorbidity [OR=1.66 (1.38-2.01)]. The effect of income-level on hospitalization was modified by comorbidity status, with the greater effect observed among subjects with no CAP-relevant comorbidities; the lowest income-level subjects having a higher likelihood of hospitalization compared to highest income-level subjects [OR=1.92 (1.66-2.22)].

CONCLUSION: The probability of initial hospitalization for treatment of CAP increased as income-level decreased, despite having controlled for patient demographics, site of care, and level of comorbidity.

KEY WORDS: *Community-acquired pneumonia; patient care management; health services research; income*

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AUGMENTATION INQUIÉTANTE DES HÉMORRAGIES ET PERFORATIONS DIGESTIVES (H&PD) SURVENUES CHEZ DES UTILISATEURS D'AINS

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Funding Source: Gouvernement du Québec

PROBLÉMATIQUE: Controverses quant à l'innocuité relative des AINS sélectifs et non sélectifs quant aux risques gastro-intestinaux. Inquiétudes quant à l'impact de la hausse de la prévalence de l'utilisation d'AINS sur les H&PD. L'objectif est de documenter la prévalence de l'utilisation d'AINS et décrire les utilisateurs d'AINS avec une H&PD.

MÉTHODOLOGIE: Étude de cohorte rétrospective descriptive portant sur 2052231 personnes de 18 ans ou plus le 1er janvier 1999 inscrites au régime d'assurance médicaments administré par la RAMQ en 1999, 2000 et 2001. Les médicaments à l'étude sont les AINS sélectifs, non sélectifs et les gastro-protecteurs. Les personnes hospitalisées en raison d'une H&PD sont repérées. Chez celles ayant utilisé un AINS au moins 1 des 30 jours précédant l'H&PD (dites en présence d'AINS), sont examinés la présence de cinq facteurs de risque de complications gastro-intestinales, le type de l'AINS précédant l'H&PD et l'utilisation concomitante de gastro-protection.

RÉSULTATS: De 1999 à 2001, le nombre d'utilisateurs d'AINS augmente de 27,9 % et le nombre d'H&PD en présence d'AINS de 78,8 %. En 2001, parmi les 195 personnes avec H&PD en présence d'AINS, 74,9 % présentent au moins un facteur de risque de complications gastro-intestinales; 51,3 % ont 75 ans ou plus; 75,9 % ont reçu un AINS sélectif comme dernière ordonnance avant l'H&PD dont le tiers avec de la gastro-protection.

CONCLUSION: La prudence quant à l'utilisation d'AINS sélectifs et non sélectifs s'impose particulièrement chez les personnes âgées.

KEY WORDS: *AINS; prevalence; haemorrhage*

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BETTER BREATHING OR BETTER LIVING? A QUALITATIVE STUDY OF HOUSEHOLD AND MEDICATION PURCHASING BEHAVIOUR AND QUALITY OF LIFE IN LOW INCOME FAMILIES WITH ASTHMATIC CHILDREN

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Funding Source: CIHR

OBJECTIVES: Families with asthmatic children with no drug insurance face a significant financial burden. This study aimed to explore how the need to purchase children's asthma medications influenced household purchasing behaviour and quality of life.

METHODS: Low income participants from a study of drug plan access and health outcomes in children with asthma were approached to participate in an in-home qualitative interview. Seventeen parents with no drug plan and whose household incomes were below Cdn $60,000 consented. Interviews were conducted emphasizing the themes of Prescription Drugs Used and Cost versus Effectiveness; Purchasing Behaviour and Drug Administration; Effects of Medication Purchasing on the Family; and Payment Assistance. Transcribed narratives were coded and analyzed thematically. All respondents completed the Pediatric Asthma Quality of Life Questionnaire (PAQLQ).

RESULTS: Annual out-of-pocket expenditures for asthma drugs were $500 to $4,000 per family. As their children's asthma management was a high priority, foregone expenditures included paying for other family members' health problems, purchasing essentials (clothing, food, housing) and purchasing non-essentials (recreation, vacations, outings). Respondents were unable to afford long term investments, such as saving for their child's education or retirement. Respondents believed that their quality of life was negatively affected by the need to purchase asthma medications for their children.

CONCLUSION: Not addressing the health concerns of other family members, making household sacrifices and modifying investment decisions created sustained anxiety in families of asthmatic children. Access to medication benefits would have a profound and positive impact upon the quality of life of family members.

KEY WORDS: *Asthma; pediatrics; qualitative; household purchasing; quality of life*

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BRINGING THE BENEFITS OF AN ANTICOAGULATION MANAGEMENT SERVICE TO THE COMMUNITY

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Funding Source: Alberta Health and Wellness

BACKGROUND: Warfarin is indicated for a variety of thromboembolic diseases, but must be maintained within a narrow therapeutic range. Studies have consistently shown <50% of patients that could benefit from warfarin actually receive it, and once it is prescribed <50% are within their desired range. Strategies directed toward improving both the use and control of this therapy are needed.

OBJECTIVES: To improve anticoagulation management through the implementation of pharmacist-managed anticoagulation management services (AMSs) across Alberta in rural/urban community and hospital pharmacies.

METHODS: Implementation of AMSs was carried out in three stages. Stage 1 was the establishment of a central (core) hospital-based AMS at a tertiary care medical facility. In stage 2 an educational program was developed and pharmacists were trained to initiate and operate an AMS. This program consisted of an interactive, web-based module (PHARMALearn Anticoagulation), a 4 week experiential component of direct patient care, and a self-directed learning component. Stage 3 was the implementation of clinics at the pharmacists' practice site ('satellite' AMSs). The core AMS serves as an ongoing resource for the satellites. An extensive evaluation of the Program is underway, assessing project-specific (i.e., adequacy of anticoagulation, etc.) and system-specific (i.e., integration within the current healthcare infrastructure) parameters.

DISCUSSION: Using a step-wise approach, we have aimed to integrate AMSs into an existing healthcare infrastructure in Alberta by empowering pharmacists to apply their knowledge and skills in their practice within a collaborative environment. The methodology of this Program may be useful for other diseases in both urban and rural settings.

KEY WORDS: *Anticoagulant; warfarin; program overview; health outcomes; practice innovation*

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CANADIAN COST-EFFECTIVENESS ANALYSIS OF TIOTROPIUM BROMIDE FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Funding Source: Boehringer Ingelheim (Canada) Ltd.

BACKGROUND: Tiotropium bromide (TIO) is indicated for the long-term, once daily maintenance treatment of bronchospasm associated with COPD. COPD is a chronic disease with progressive impairment in lung function and health-related quality of life. The economic burden of COPD in Canada is considerable. An economic evaluation of TIO was performed to establish the value of this new molecule.

METHODS: A Markov Model was developed to estimate the incremental cost-effectiveness ratio (ICER) of TIO versus Atrovent and Serevent over 1 and 5 years. Outcomes included number of exacerbations, costs and life years per patient. ICERs are expressed as cost per exacerbation avoided, exacerbation free months, and life years saved. Markov cycles and treatment costs were driven by the probability of transitioning between disease states and the probability of experiencing an exacerbation. Probabilities related to clinical outcomes were derived from clinical trials. Resource utilization was derived from a 1-year Canadian prospective observational study including 594 patients with moderate to severe COPD. The perspective of provincial health care system was selected.

RESULTS: 1-Year analysis: Mean annual results per patient per year for TIO, Atrovent and Serevent respectively were: Number of exacerbations: 0.87, 1.19 and 1.04; Total cost: $2,444, $2,573 and $2,447. 5-Year analysis: Number of exacerbations: 3.93, 5.22 and 4.75; Total cost: $10,957, $11,206 and $11,374; Life years: 4.23, 4.21 and 4.22. TIO dominated Atrovent and Serevent in all ICER analyses.

CONCLUSIONS: TIO provides better health outcomes at potentially lower costs. Savings in tiotropium are mainly due to reductions in exacerbation rate and hospital days.

KEY WORDS: *COPD treatment; Cost effectiveness; Tiotropium; Exacerbations; Life Years Saved; Canada*

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CANADIAN ECONOMIC EVALUATION OF ENFUVIRTIDE (FUZEON®)

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Funding Source: Hoffmann-La Roche Canada Ltd.

BACKGROUND: Enfuvirtide (Fuzeon®, Hoffmann-La Roche), the first fusion inhibitor, is indicated for use in combination with other antiretroviral agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. An economic evaluation was conducted, comparing optimized background therapy (OB) alone versus OB plus enfuvirtide, in treatment-experienced HIV patients from the Ontario public health care system perspective.

METHODS: An economic model was developed as a state-transition (Markov) model which extrapolated the 48-week results of pivotal trials over the lifetime of an HIV patient. Published mathematical models of disease progression were used to predict clinical events. Costs (from a Canadian expert panel) and utility values (from the literature) were applied to each state of disease progression. A lifetime horizon and a 5% discount rate were chosen.

RESULTS: The mean time to virological failure was 0.6 years for OB alone, versus 1.5 years for OB plus enfuvirtide. Overall, life expectancy was 7.2 years for OB patients, and 9.2 years for OB plus enfuvirtide patients (discounted, a 1.4 year gain for patients on OB plus enfuvirtide). Enfuvirtide patients incurred additional costs totaling approximately CDN$86,000 per patient, composed of enfuvirtide therapy (CDN$44,000) and costs of prolonged survival (approximately CDN$42,000). This generated an incremental cost-effectiveness ratio of approximately CDN$62,000 per life year gained, and CDN$66,000 per QALY gained.

CONCLUSION: Enfuvirtide was predicted to prolong a patient's time at higher CD4 counts, which eventually would generate a survival benefit of more than one year (1.3 QALYs), at an incremental cost of CDN$66,000 per QALY.

KEY WORDS: *Enfuvirtide; economic costs; antiretroviral therapy*

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CARDIOVASCULAR MORBIDITY ASSOCIATED WITH STATIN NON-ADHERENCE

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Funding Source: Saskatchewan Health Research Foundation (formerly HSURC)

BACKGROUND: Although non-adherence to statin medications is assumed to result in an increased risk for cardiovascular events, no reports have compared cardiovascular morbidity between adherent and non-adherent individuals. We intended to measure the cardiovascular morbidity associated with statin non-adherence.

METHODS: A retrospective cohort study using linked administrative databases in the province of Saskatchewan, Canada. Eligible patients were between 30 and 70 years who received a new prescription for a statin medication between 1994 and 2001, within one year of their first cardiovascular event [MI, unstable angina, ischemic stroke, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft (CABG)]. The primary endpoint included a composite of MI, unstable angina, PTCA, CABG, or death.

RESULTS: Out of 1221 patients analyzed, adherence to statin medications did not reduce the occurrence of the primary endpoint. However, in the subgroup of patients under 65 years of age (n=884), statin adherence provided significant protection against cardiovascular morbidity. Patients exhibiting adherence rates of over 80% were half as likely to experience MI, unstable angina, stroke, or cardiovascular death compared to patients exhibiting adherence ≤60% (HR 0.47, 95% CI 0.25-0.88, p=0.019). Protection against the composite of MI, UA, or stroke could be demonstrated at adherence levels as low as 40%. As expected, increasing levels of adherence appeared to confer additional cardioprotection.

CONCLUSIONS: There is significant cardiovascular morbidity associated with non-adherence to statin medications. Our findings suggest protection against cardiovascular morbidity may be achieved at levels of adherence lower than previously considered acceptable.

KEYWORDS: *Statins; HMG CoA-reductase inhibitors; adherence; compliance; outcomes*

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CELECOXIB ASSOCIATED WITH REDUCED RISK OF SUPERFICIAL BLADDER CANCER (SBC) RECURRENCE

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Funding Source: Pharmacia & UpJohn

BACKGROUND: Cyclooxyenase (COX)-2 is over-expressed in tumor cells including urinary bladder tumor cells. NSAIDs and aspirin can block the development of many types of cancer.

OBJECTIVE: To determine if celecoxib reduces the risk of SBC recurrence.

MATERIAL AND METHODS: Data were obtained from RAMQ databases in Quebec, Canada, containing prescription and physician service claims. Study patients were newly diagnosed with SBC (ICD-9=188.X, 223.3, 233.7, and 239.4) and had surgical endoscopic treatment for bladder malignancies or cystectomy between 07/01/1999 and 01/01/2002. Patients must have had 1 follow-up visit for diagnostic and therapeutic urethro-cystoscopy after initial procedure (index date). Eligible patients were grouped into cohorts of celecoxib, NSAIDs, acetaminophen, and non-users. SBC recurrence (receipt of another surgical procedure to remove bladder tumor) was compared among study cohorts.

RESULTS: Patients per cohort were: 55 for celecoxib, 382 for NSAIDs, 208 for acetaminophen, and 527 for non-users. There was no significant difference among cohorts exept that patients in the celecoxib and NSAID cohorts had significantly higher chronic disease scores. After adjusting for pertinent variables, the Cox-regression model indicated that celecoxib and NSAIDs users had a significantly lower risk of SBC recurrence (HR = 0.39, 95% CI=0.26-0.61, $p<0.01$ for celecoxib and HR = 0.34, 95% CI=0.28-0.42, $P<0.01$ for other NSAIDs) than non-users.

CONCLUSION: Celecoxib and NSAIDs are associated with a significantly reduced risk of SBC recurrence.

KEY WORDS: *Bladder cancer; celecoxib; Cox-2, NSAIDs; acetaminophen*

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CHANGING THE CULTURE OF MEDICATION ERROR REPORTING

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Funding Source: None

BACKGROUND: The Institute for Safe Medication Practices (ISMP) has identified a strategic need to place less emphasis on comparing error rates, and more emphasis on open reporting, full disclosure and identifying areas for system improvement and safeguards. Reasons for underreporting medication errors include fear of negative repercussions, such as job loss and loss of peer support. Our objective was to assess the culture of safety among hospitals in the Winnipeg Regional Health Authority (WRHA) and to propose strategies to promote more open reporting of medication errors.

METHODS: In 2003, the ISMP Medication Safety Self Assessment was administered to ten WRHA hospitals. Element 10 asked about quality processes and risk management in error prevention. A score ranging from 0 to 100 was assigned to hospitals based on having a non-punitive, system-based approach to error reduction in place for the purpose of improving clinical outcomes.

RESULTS: The average score for WRHA hospitals was 55, with hospital specific scores ranging from 40 to 60. Long-term care hospitals typically scored highest on this measure, followed by community hospitals, with teaching hospitals scoring the lowest.

DISCUSSION: The ISMP survey indicates a need for improvement. An additional survey is planned to better understand the limitations of current medication error reporting practices, followed by the introduction of daily routines to enhance awareness of medication errors, including Patient Safety Briefings, Leadership WalkRounds, and non-punitive medication occurrence reporting systems.

CONCLUSION: Change in the culture of patient safety at the WRHA should lead to a reduction in medication errors and improvement in quality of care.

KEY WORDS: *Patient safety; cultural change; medication error*

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CHARACTERISTICS OF PATIENTS PRESCRIBED ALZHEIMERS' DISEASE MEDICATIONS IN QUEBEC: A TREND ANALYSIS

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Funding Source: Pfizer Canada

BACKGROUND: Three cholinesterase inhibitors (ChEI) are available for the treatment of alzheimers' disease (AD) [donepezil (DPZ), rivastigmine (RIV), galantamine (GAL)]. Limited "real life" evidence is available on the characteristics of users of these AD drug therapies. Therefore, the objective of this study was to characterize the patients prescribed ChEIs.
METHODS: Subjects (age: 40 - 101) were eligible for drug coverage under the RAMQ and were ChEI users with an initial prescription (index date) dispensed between January, 2000 and June, 2003. For each ChEI, we compared patients with an index date within the 3 months post formulary inclusion to those with an index date within a similar period of 3 months, but 1 year later.
RESULTS: The cohort included 18,748 patients. Compared to patients initiated in the 3 months following ChEI formulary inclusion, patients initiated 1 year later had more drug dispensations in the year prior to the index date ($p<0.05$). Relative to patients initiated within the first 3 months post formulary inclusion, patients initiated on DPZ and RIV 1 year post formulary inclusion were hospitalized more often, were hospitalized longer, and visited a general practitioner more frequently in the year prior to the index date ($p<0.05$). No significant difference was observed in GAL patients.
CONCLUSION: The health risks of patients initiated on DPZ and RIV 1 year post formulary inclusion appeared to be more severe compared to patients initiated within the first 3 months post formulary inclusion.
KEY WORDS: *Alzheimers disease; cholinesterase inhibitors*

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CHIROPRACTORS & IMMUNIZATION: BELIEFS AND BEHAVIOURS

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Institutions: University of Calgary
Funding Source: Alberta Childrens' Hospital Foundation

BACKGROUND: Concerns have been raised about the beliefs and behaviors of chiropractors related to immunization; however data that systematically examine the relationships between their beliefs and behaviors have been lacking.
PURPOSE: We examine the immunization related behaviors and beliefs of Alberta chiropractors and explore the relationship of beliefs to immunization related behaviors with patients
METHODS: A 2002 postal survey of Alberta chiropractors inquired about 6 behaviors in the 6 months prior to survey as well as behavioural and normative beliefs. An index of pro/antivaccination behaviour (VACINDEX) was constructed from items on advising people against being immunized, providing information on risks of immunization vs. advising people in favour of immunization, providing information on benefits of immunization. We explored for associations between beliefs and VACINDEX score.
RESULTS: The response rate was 78.2% (503/643). Immunization arose with patients at least monthly for 36.5% of respondents, and at least weekly for 9.2%. Similar proportions advised on freedom of choice (70.3%) and directed patients to information sources (69.9%). A larger proportion gave information on risks (67.8%) than benefits (49.6%). Similar proportions advised in favour (25.1%) and against (27.2%) immunization. VACINDEX was predicted by beliefs about efficacy and safety; chiropractic philosophy, perceptions of individual vs. societal rights, and normative beliefs related to both conventional practitioners and to other chiropractors and their patients.
CONCLUSIONS: A substantial proportion of Alberta chiropractors are providing negatively oriented immunization advice and information to patients. These behaviours can be understood in the context of the chiropractors' beliefs, chiropractic philosophy and perceptions of social norms.
KEY WORDS: *Chiropractic; vaccination; Cross-sectional Studies; Questionnaire; knowledge; attitudes; practice; immunization; attitude*

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CLINICAL AND ECONOMIC IMPACT OF HERD IMMUNITY ON PNEUMOCOCCAL DISEASE IN CANADA

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Funding Source: Wyeth

BACKGROUND: Since mid-2001 a heptavalent pneumococcal conjugate vaccine (PCV-7) against 7 common pneumococcal serotypes has been available in Canada. The purpose of this study is to build upon existing economic evaluations and use recent herd immunity evidence to estimate the real-world clinical and economic effectiveness of PCV-7 in Canada.

METHODS: A systematic literature review was completed using Medline and Canadian healthcare publications including: Canadian Journal of Infectious Disease and Canadian Communicable Disease Report. The search terms included: pneumococcal, costs, cost-effectiveness, herd immunity, and incidence. Clinical and economic impacts of adult pneumococcal disease were determined based on epidemiologic and cost data available from the United States and Canada.

RESULTS: Three pharmacoeconomic evaluations of PCV-7 in Canada have each found that routine immunization would help Canada avoid substantial morbidity and mortality, and associated healthcare costs and productivity losses. Using recent effectiveness data, the reduction in adult pneumococcal disease is estimated to save an additional $40 million from a Canadian healthcare perspective; suggesting the vaccine is cost-saving.

CONCLUSIONS: Herd immunity resulting from a universal childhood PCV-7 program will have a substantial clinical and economic impact on populations ≥ 20 years of age, thereby making PCV-7 a cost-saving intervention for the Canadian healthcare system.

KEY WORDS: *Pneumococcal conjugate vaccine; herd immunity; cost-effectiveness*

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CLINICIANS VS. PATIENTS AT RISK? INFORMING POLICIES FOR RESOURCE ALLOCATION DURING INFLUENZA PANDEMICS

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Institutions: University of Calgary
Funding Source: Health Surveillance, Alberta Health & Wellness

BACKGROUND: Health care providers can transmit influenza and influenza-like illnesses (ILI) to patients and vice-versa. However, the relative magnitudes of these problems at the population level are not known. This might be important for priorizing distribution of drugs and vaccines during national shortages (e.g., influenza pandemic).

METHODS: We used Alberta's Fee-for-Service Administrative Claims Database to test for temporal associations for ILI diagnoses among clinicians and their patients. The database captures information on clinicians eligible to submit a fee-for-service claim in any setting under the publicly funded health care insurance plan. The data include unique identifiers for patients and clinicians and diagnostic codes for encounters. Claims having one or more ICD-9 codes of 487, 480-486 466 or 490 were defined as ILI. Both clinicians & patients were classified as case-exposed or control-exposed on the basis of a visit to a person for whom ILI diagnosis coded visit was made in the 7 days prior to the encounter.

RESULTS: The mean number of exposures to case-patients was higher for case- than for control-clinicians. Case-clinician exposure did not significantly increase the risk of ILI diagnosis among patients (OR 1.11, 95% CI 0.85 - 1.35).

CONCLUSION: The results are consistent with a higher risk for ILI among clinicians from exposures to patients than for patients from clinicians at the population level. The data support promotion of basic infection control and perhaps influenza vaccination for both clinicians and patients, but suggest that during shortages, clinicians should be given a higher priority than patients for prophylaxis.

KEY WORDS: *Influenza; respiratory tract diseases; health services research; disease transmission; Canada*

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COMORBIDITY DECREASES WARFARIN USE IN HIGH RISK PERSONS WITH ATRIAL FIBRILLATION

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Funding Source: Canadian Stroke Network

BACKGROUND: Warfarin is an effective therapy to prevent stroke in persons with atrial fibrillation. However, a gap exists between best practice and real world use. We undertook a population-based study of warfarin use in persons at risk for recurrent stroke.

METHODS: Using Manitoba's health care and prescription records, warfarin prescription use post-discharge was evaluated in a cohort of persons hospitalized for stroke with a history of atrial fibrillation. The likelihood of receiving a warfarin prescription was related to age, gender, income, residence, previous warfarin use, hospital teaching status and presence of dementia, multiple morbidity and contraindications.

RESULTS: During 1996 and 1997, 3797 persons were hospitalized for stroke in Manitoba. 28% had a history of atrial fibrillation. 29% received a prescription for warfarin within 7 days following hospital discharge. Among persons without previous warfarin therapy, the proportion receiving a new warfarin prescription was lower in the low income groups (20%), those with multiple morbidities (12%), and in those with contraindications (22%). Only one patient with dementia received a new warfarin prescription within 7 days post-discharge. The presence of multiple morbidities decreased the likelihood of a warfarin prescription (OR= 0.35, 95% CI: 0.14 - 0.86) in a multivariate model.

CONCLUSION: Less than one third of persons with atrial fibrillation at risk for recurrent stroke received a warfarin prescription. Dementia, other disease and sociodemographic factors may influence physician prescribing of appropriate preventative therapy in high risk patients.

KEY WORDS: *Stroke; warfarin; atrial fibrillation; anticoagulation*

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COMPARISON OF THE CHARACTERISTICS OF PATIENTS WHO ARE PRESCRIBED COXIBS AND TRADITIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN QUEBEC (YEAR 2002)

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Funding Source: Pfizer Canada Inc.

BACKGROUND: When coxibs were introduced on the formulary, they were prescribed to patients at risk of gastropathy. Since then, prescription patterns may have changed given the revised prescription guidelines and further experience with coxibs.

OBJECTIVE: To compare the socio-demographic characteristics, medical history, and past use of NSAIDs among users of coxibs and traditional non-selective NSAIDs.

METHODS: A retrospective study was conducted in a random sample of adult members of the Quebec drug plan (age 18+) who received at least one dispensing of celecoxib (n=49,932), rofecoxib (n=49,793), traditional NSAIDs at low doses (n=14,130), or anti-inflammatory doses or higher (n=34,839) between January 1st and December 31st 2002. All medical services and prescriptions received during the year prior were obtained through linkage with the Quebec health services databases. The effect of individual characteristics on prescribing practices was assessed through multivariate logistic regression. Due to unavailability of data on indication, traditional NSAIDs at anti-inflammatory doses or higher was the reference category.

RESULTS: The prescription of coxibs over NSAIDs at anti-inflammatory doses was greatly influenced by: age 75+ (OR celecoxib= 4.16; 95% CI: 3.97-4.36; OR rofecoxib= 1.89; 1.81-1.97); chronic disease score (for CDS 10+ OR celecoxib = 3.28; 3.04-3.59; OR rofecoxib =2.38; 2.22-2.56); history of acetaminophen use (ORcelecoxib=1.29; 1.24-1.33, OR rofecoxib=1.35 1.31-1.40, history of gastroprotective agents use (OR celecoxib=1.28 ;1.23-1.34; OR rofecoxib=1.35; 1.29-1.41). Hypertension, concomitant use of corticosteroids or diuretics or anticoagulants had no significant effect on prescription practices.

CONCLUSION: Advanced age and high chronic disease scores mainly account for the prescription channelling towards coxibs.

KEY WORDS: *Drug utilization; Pharmacoepidemiology; Cox-2 inhibitors; Non-steroidal anti-inflammatory drugs; Prescription guidelines*

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COST-EFFECTIVENESS ANALYSIS OF LATANOPROST IN THE FIRST-LINE TREATMENT OF OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION IN CANADA

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Funding Source: Pfizer Canada Inc.

BACKGROUND: Glaucoma is a group of ocular diseases characterized by progressive optic nerve damage resulting in visual field defects, often in association with elevated intra-ocular pressure (IOP). First-line therapy includes beta-blockers and more recently latanoprost, a prostaglandin F2á analog. Clinical trials have shown that latanoprost achieves better IOP control than beta-blockers. The objective of the present study was to assess the cost-effectiveness of latanoprost, versus beta-blockers, in the first-line treatment of glaucoma and ocular hypertension (OH) in Canada.

METHODS: A model was developed to simulate the management of a patient, and estimate the days of IOP control and total health care costs incurred over a two-year time period. Variability in time to therapy failure was captured by utilizing Monte Carlo (stochastic) simulation methodology. Clinical outcomes and resource utilization were obtained from a Canadian retrospective, observational study of patients with untreated glaucoma and OH.

RESULTS: The treatment strategy that included latanoprost as the preferred first-line therapy, resulted in more days of IOP control, compared to the beta-blocker strategy (664.20 versus 643.84 days), fewer therapy switches, fewer ophthalmologist visits, and fewer surgical procedures. The incremental cost per IOP controlled day gained was $3.84 (Ministry of Health perspective). The incremental cost per surgery averted was $2,435. Sensitivity analyses showed that the primary drivers of cost-effectiveness were estimates of survival on therapy and assumptions regarding bottle durations

CONCLUSIONS: Under normal clinical practice, as observed in Canada, the treatment strategy that included latanoprost as the first-line treatment for ocular hypertension is cost-effective.

KEY WORDS: *Cost-effectiveness analysis; decision analysis; glaucoma; ocular hypertension; latanoprost*

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COST-EFFECTIVENESS OF VORICONAZOLE FOR THE TREATMENT OF INVASIVE ASPERGILLOSIS IN CANADA

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Funding Source: Pfizer Canada Inc.

BACKGROUND: Immunocompromised patients are at risk of invasive aspergillosis (IA) infection. Voriconazole has been demonstrated to have better efficacy and improved survival compared to conventional amphotericin B deoxycholate (CAB) for the treatment of IA in the Global Comparative Aspergillosis (GCA) study. The objective of this study was to compare cost and outcomes of voriconazole and CAB for the treatment of definite/probableIA.

METHODS: A decision analytic model was designed to reflect the treatment pathways used in clinical practice when using voriconazole or CAB as primary therapy for IA over 12-weeks. Therapy included initial treatment with either voriconazole or CAB and switching to OLAT in the event of an inadequate response, severe toxicity or intolerance. The resource use data was based on the GCA study while implicated costs were obtained from Canadian sources.

RESULTS: The total average cost per patient of voriconazole as initial therapy for IA was $4,176 lower compared to CAB. The cost per successfully treated patient was $72,604 and $134,569 for voriconazole and CAB, respectively, while the cost per life saved was $54,123 and $73,395 for voriconazole and CAB, respectively. Thus, voriconazole dominated CAB as a treatment option. The number of patients needed to be treated with voriconazole instead of CAB to save one additional life was 8. Sensitivity analyses demonstrated that results were robust over a range of values for key variables.

CONCLUSIONS: Voriconazole for primary treatment of IA increased the chances of successful treatment, improved survival, and may be expected to be a cost saving strategy in Canada.

KEY WORDS: *Voriconazole; aspergillosis; costs; cost-effectiveness; amphotericin B*

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COSTS OF COXIBS, NONSELECTIVE NSAIDS AND CONCOMITANT GASTROPROTECTIVE AGENTS AMONG PATIENTS COVERED BY THE RÉGIME GÉNÉRAL D'ASSURANCE-MÉDICAMENTS (RGAM) IN QUEBEC

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Funding Source: Merck Frosst Canada Ltd.

BACKGROUND: Guidelines for nonsteroidal antiinflammatory drugs (NSAIDs) recommend preventive strategies such as a gastroprotective agent (GPA) with nonselective NSAIDs or a selective cyclooxygenase-2 inhibitor (Coxib) in patients with one or more gastrointestinal (GI) risk factors. Some authors also recommend GPAs with Coxibs for patients with prior GI bleed. The objective of this study was to estimate the acquisition costs of Coxibs, NSAIDs and concomitant GPAs from utilization patterns observed in the RGAM population and to project changes in acquisition costs should the treatment guidelines had been followed.

METHODS: We conducted a cross sectional study from the RAMQ databases. All Coxibs, NSAIDs and concomitant GPAs dispensed to patients aged 18 years and over in 2002 were assessed. Coxibs and NSAIDs dispensations were categorized by patients' level of risk (low to very high). Acquisition costs were projected under two hypothetical scenarios of utilization. Scenario 1 considered: NSAIDs alone in the low-risk, Coxibs alone in the medium and high risk and Coxibs+GPA in the very high risk groups; scenario 2 considered: NSAIDs alone in the low-risk, NSAIDs+GPA in the medium and high risk and Coxibs+GPA in the very high risk groups.

RESULTS: In total, 4,462,731 Coxibs and NSAIDs prescriptions were assessed. Acquisition cost of Coxibs, NSAIDs and concomitant GPAs based on observed utilization patterns reached $93.7MM. Acquisition costs were projected at $77.1MM and $128.8MM under scenarios 1 and 2 respectively.

CONCLUSIONS: Should treatment guidelines had been followed, the observed acquisition costs could have been reduced by 16.6MM if Coxibs were prescribed to all patients at risk and increased by 35.1MM if NSAIDs+GPAs were prescribed instead.

KEY WORDS: *Coxibs; NSAIDS; cost; gastrointestinal risk; public drug reimbursement program; antiinflammatory drug, gastroprotective agent, administrative database, cost*

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CURRENT PREVALENCE AND CONTROL OF HYPERTENSION IN THE PRIMARY CARE SETTING

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Funding Source: Pfizer Canada

BACKGROUND: The burden of cardiovascular disease and associated risk factors are seen in primary care settings. The most recent prevalence and control estimates of hypertension in Canada (1986-1992) may not be reflective of more recent clinical evidence and practice guidelines. The objective of this study was to estimate the prevalence, treatment and control of hypertension among recommended classes of anti-hypertensive medication in a large cohort (SWO) of primary care clinics including > 150,000 patients.

METHODS: Patients with at least 4 quarters of data were included in the present analysis (N=42,496). Hypertension was defined as follows: usage of antihypertensive medication OR chart entry of a diagnosis of hypertension OR recorded blood pressure exceeding target values on at least 2 visits in 6 months.

RESULTS: The prevalence of hypertension was 16% (68.6% untreated, 12.8% treated but uncontrolled, 15.0% treated and controlled). The majority of patients (63%) were receiving monotherapy: 34% ACEs, 20% Beta blockers, 19% CCBs, 14% ARBs and 8% diuretics. For patients whose blood pressure was treated and controlled the frequency of monotherapy by class was as follows: 37% ACEs, 22% CCBs, 21% Beta-blockers, 13% ARBs, 7% Diuretics.

CONCLUSIONS: Despite new pivotal clinical evidence and new treatment guidelines, hypertension is largely untreated in primary care. The majority of treated patients receive monotherapy. Patients receiving diuretics in monotherapy have the least likelihood of reaching treatment targets. Educational supports to improve awareness, detection, diagnosis and treatment to recommended targets is needed.

KEY WORDS: *Prevalence; treatment; hypertension; primary care; retrospective database*

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DEPRESSION DURING BREASTFEEDING: HEALTH CARE USE AND WELL BEING OF THE MOTHER AND INFANT

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Funding Source: Physicians' Services Incorporated Foundation

BACKGROUND: The perception of infant harm by exposure to maternal antidepressants through breastmilk is one reason why women do not take their medications as prescribed. Untreated depression may be detrimental to both mother and infant, resulting in increased health care utilization. Adequately treated depression should have minimal impact on infant health and resource use, compared to infants of healthy women.

METHODS: Three groups of breastfeeding mother-infant pairs were followed-up to 6 months postpartum: depressed women on antidepressants (G1), women with untreated depression (G2), and healthy controls (G3). Medical and demographic data, infant feeding method, maternal and infant well-being, depression status, and health care utilization were recorded.

RESULTS: Data are available for 67, 30, and 72 women in G1, G2, and G3, respectively. Although G2 women had significantly impaired mental health, there were no differences in the number of maternal physician visits or costs, or medication costs (excluding antidepressants) among groups. The median antidepressant cost in G1 was $276.86 (including $26.94 in out-of-pocket expenses). More physician visits occurred for G3 infants (median 5.5 (G1), 6.5 (G2), and 7.0 (G3), p=0.02), with most being routine well-baby care. More was spent on infant medication, supplements, and vaccinations in G3 (median $43.00 (G1), $38.00 (G2), and $141.25 (G3), p<0.01).

CONCLUSION: Although G2 women sought physician care as often as G1 and G3 women, they experienced more depression, suggesting inefficient use of health care. Infants of healthy mothers may be receiving better health care than those of depressed mothers, treated and untreated.

KEY WORDS: *Depression; breastfeeding; health care utilization*

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DRUG CLASS UTILIZATION IN GERD THERAPY: BEFORE AND AFTER THE MARKET WITHDRAWAL OF CISAPRIDE IN CANADA

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Funding Source: None

BACKGROUND: Gastroeseophageal reflux disease (GERD) is a common disorder affecting nearly 45% of North Americans. Cisapride, an effective treatment for GERD, was withdrawn from the Canadian market in August 2000. The purpose of this study was to investigate the effect of cisapride withdrawal on utilization of other gastrointestinal agents and hospitalizations associated with GERD.

METHODS: Prescription counts for various classes of GERD pharmacotherapies (H2-antagonists, proton-pump inhibitors, and prokinetic agents) from January 1998 to December 2002 were retrieved from the IMS Canada Inc. database. Total hospital admissions from January 1998 to December 2000 for GERD associated ICD-9 diagnosis codes were retrieved from the Canadian Institute for Health Information Hospital Morbidity Database. Interrupted time-series analyses of slopes and intercepts were used to compare drug utilization rates and hospitalizations before and after cisapride withdrawal.

RESULTS: The rate of utilization of GERD pharmacotherapies appeared to be increasing over the entire study period. The slope of both metoclopramide ($p < 0.05$) and pantoloc ($p < 0.001$) increased significantly following the withdrawal of cisapride. In general, the hospitalization curves were decreasing before and after the withdrawal. However, ICD-9 code 530.4 (perforation of esophagus) was increasing prior to and after the withdrawal of cisapride, but the difference in rates was not significant ($p > 0.05$).

CONCLUSION: The use of various GERD pharmacotherapies has altered since the withdrawal of cisapride. However, an association to the withdrawal event cannot be made. There does not appear to be an association between cisapride withdrawal and hospitalizations of GERD associated disorders.

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DRUG UTILIZATION REVIEW (DUR) FOR THE TREATMENT OF ASTHMA

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Funding Source: Ministry of Health & Social Services, Québec

BACKGROUND: The appropriateness of inhaled β_2 agonists nd leukotriene receptor antagonists (LRAs) for the treatment of asthma in Québec was assessed and compared with the results of a first DUR. The use of Advair® Diskus® was also documented.

METHODS: This retrospective study using provincial database included subjects, aged 5 to 45, enrolled in the public drug insurance plan who received, in 2001, at least one prescription of short acting inhaled β2 agonists (SA) or long acting inhaled β2 agonists (LA) or LRA. Appropriateness of use was assessed according to criteria developed in consultation with an experts' panel.

RESULTS: Although there was a significant improvement in the percentages of appropriate utilization for SA in 2001compared to 1997-1998 (appropriate frequency of use : 41 % vs 8 %; $p<0.01$) and in the continued use of corticosteroids with LA (35 % vs 15 %; $p<0.01$) , SA are still overused and inhaled corticosteroids (i.c.) are still underused. Use of LA and LRAs was not optimal. Advair® Diskus® was often used improperly : In the subjects who received this product for the first time, 68 % had not received an i.c. and 42 % had received neither an i.c. or a SA for a period of at least 7 months prior to the first prescription.

CONCLUSION: Although an improvement was noted in some respects, utilization of main drugs for treating asthma is not optimal. The *Conseil du médicament*, in collaboration with many healthcare stakeholders, will suggest various strategies to promote better use of asthma therapy.

KEY WORDS: *Drug utilization review (DUR); asthma; optimal drug use*

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ECONOMIC IMPACT OF IMPROVED ADHERENCE IN THE TREATMENT OF DYSLIPIDEMIA IN CANADA

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Funding Source: Pfizer Canada Inc.

BACKGROUND: Dyslipidemia is a major risk factor for cardiovascular disease (CVD). Because dyslipidemia is an asymptomatic condition patients often do not take their medication as prescribed, preventing medications from achieving their full beneficial effects. The objective of this study was to determine the clinical and economic impact of a 1% increase in patient adherence to dyslipidemia medications.

METHODS: A decision analytic spreadsheet model was constructed to follow a treated patient cohort of 100,000 for 5 years. We quantified the clinical and economic impact of a 1% increase in the proportion of patients compliant to prescribed drug regimens. Resources included drugs, physician visits, hospitalization, and time off work. Standard costs from government and societal viewpoints were used, discounted at 3%.

RESULTS: For each 1% increase in adherence, average societal savings were $30,693, $43,877, $42,827, $41,615, and $40,205 for each of the 5 years, respectively. Government savings (expenses) per 1% adherence improvement for each year were ($3,319), $11,076, 11,195, $11,110, and $10,788, respectively. For the 5 years, there were a total of 24 avoided cardiovascular hospitalizations for each 1% improvement in adherence, of which 14, 4, and 3 were for Ischemic Heart Disease, Acute Myocardial Infarction, and Stroke, respectively.

CONCLUSIONS: Improved adherence to prescribed drug regimens in the treatment of hypertension results in cost savings from both societal and government perspectives.

KEY WORDS: *Patient adherence; compliance; economics; dyslipidemia; Canada*

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ECONOMIC IMPACT OF IMPROVED ADHERENCE IN THE TREATMENT OF HYPERTENSION IN CANADA

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Funding Source: Pfizer Canada Inc.

BACKGROUND: High blood pressure is a major risk factor for cardiovascular disease (CVD). Many patients diagnosed with hypertension do not take their medication as prescribed, and therefore do not receive the full beneficial effects of these medications on CVD. The objective of this study was to determine the clinical and economic impact of a 1% increase in patient adherence to antihypertensive medications.

METHODS: A decision analytic spreadsheet model was constructed to follow a cohort of 100,000 treated hypertensive patients for 5 years. We quantified the clinical and economic impact of a 1% increase in the proportion of patients compliant to prescribed drug regimens. Resources included drugs, physician visits, hospitalization, and time off work. Standard costs from government and societal viewpoints were used discounted at 3%.

RESULTS: For each 1% increase in adherence, societal savings were $45,677, $57,931, $58,157, $59,419, and $59,631 for each of the 5 years, respectively. Government savings (expenses) per 1% adherence improvement were ($3,099), $10,893, $12,797, $15,675, and $17,447 for each year, respectively. For the 5 years, there were a total of 35 avoided cardiovascular hospitalizations for each 1% improvement in adherence, of which 20, 6, and 5 were for Ischemic Heart Disease, Acute Myocardial Infarction, and Stroke, respectively.

CONCLUSIONS: Improved adherence to prescribed drug regimens in the treatment of hypertension results in cost savings from both societal and government perspectives.

KEY WORDS: *Patient adherence; compliance; economics; hypertension; Canada*

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EFFECT OF A PRIOR AUTHORIZATION PROCESS ON PATIENT COMPLIANCE AND OUTCOMES IN PATIENTS PRESCRIBED CLOPIDOGREL FOLLOWING CORONARY STENTING

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Funding Source: Institute of Health Economics (partial funding)

BACKGROUND: Alberta Blue Cross (ABC) provides co-payment based coverage for residents over 65 years. A prior authorization (PA) process for patients prescribed clopidogrel post-stent insertion was changed to an authorized prescriber (AP) list in March 2002. We sought to evaluate the impact of this change.

METHODS: The effect of this policy change on patients' filling of clopidogrel prescriptions post-stent insertion was determined over the 6 month periods before and after the change to AP in patients receiving a coronary stent and prescription for clopidogrel who were eligible for coverage by ABC. Data were obtained from the APPROACH and ABC databases.

RESULTS: During this period, 113 patients (45 in PA group and 68 in AP group) were evaluated. Baseline variables were similar in the two groups. Fewer patients in the PA group had their prescription filled upon the day of discharge (31% vs 53%; p=0.02) and the median time to fill was 4 days versus 0 days in the PA and AP groups respectively (Wilcoxon p=0.04). There was no significant difference in the proportion of patients filling their prescriptions after 28 days from discharge (67% vs 75%, NS) or in the overall comparison of time to fill (log rank p=0.21). Two repeat revascularization procedures were necessary within 6 weeks after stent placement; both were in the PA group in patients who delayed or failed to fill the prescription.

CONCLUSIONS: The PA process delayed patients filling clopidogrel prescriptions following hospital discharge and may have contributed to negative clinical consequences.

KEY WORDS: *Compliance; drugs; stents*

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EFFECT OF ETANERCEPT ON WORK DISABILITY IN RHEUMATOID ARTHRITIS (RA) PATIENTS TREATED IN A COMMUNITY SETTING

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Funding Source: Wyeth Pharmaceutical

BACKGROUND: Several studies have demonstrated that work disability is common among patients with RA and lost wages through RA are estimated to be 2.5 billion dollars annually in the United States. RCT data have shown that etanercept treatment in RA patients can improve ACR and quality of life.

OBJECTIVES: To evaluate if there are differences in amelioration of work disability between etanercept treated and control patients at 6 and 12 months in a phase IV (community based) cohort study.

METHOD: Patients requesting access to etanercept were stratified into control and treatment arms, based upon individual accessibility to the drug. Interviews were conducted at baseline and at 1, 3, 6, 9 and 12 months after baseline. Inclusion criteria: Rheumatoid arthritis patients at least 18 years of age, with 6 painful or tender joints, calling the Enbrel (etanercept) information & access line were eligible to participate in the study.

RESULTS: There were 223 patients in the treatment group and 208 patients in the control group. 'Down days' in the treatment group were significantly less than the control group at 6 and 12 months ($p = 0.02$). Amongst employed patients there were fewer mean down days for etanercept users (11.8 days) than non users (28.0 days) over a 6 month period, $p<0.002$.

CONCLUSION: Etanercept therapy in RA patients can reduce work disability.

KEY WORDS: *Quality of life; rheumatology; etanercept; cohort study*

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ERYTHROPOIETIN DOSAGE REQUIREMENTS IN A PROVINCIAL HEMODIALYSIS POPULATION: EFFECT OF SWITCHING FROM SUBCUTANEOUS TO INTRAVENOUS ADMINISTRATION

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Institutions: Winnipeg Regional Health Authority
Funding Source: Winnipeg Regional Health Authority

BACKGROUND: The purpose of this initiative was to compare erythropoietin doses in hemodialysis patients who changed from subcutaneous to intravenous administration. The Manitoba Renal Program switched routes due to concern about erythropoietin-associated pure red cell aplasia.

METHODS: We compared erythropoietin dosage requirements during subcutaneous administration (3 months pre-switch) and intravenous administration (months 4-6 post-switch). We also compared: hemoglobin, transferrin saturation (Tsat%), ferritin, and % of patients receiving intravenous iron. The same erythropoietin regimen was initially used when patients were switched.

RESULTS: Of 628 patients receiving erythropoietin, 400 had complete data available. The dose increased 26% (mean [± SD] 10425 ± 7330 vs. 13125 ± 8638 IU/week; $p<0.0001$), despite similar hemoglobin, (mean [± SD] 114.9 ± 11.2g/L vs. 113.5 ± 10.4 g/L; $p=0.0450$) and iron parameters (Tsat 30.9%, ferritin 464 mcg/L vs. Tsat 28.7%, ferritin 538 mcg/L. For the subgroup of 84 patients who maintained target hemoglobin (110-120 g/L) for both periods, the dose increased 26% (mean [± SD] 8393 ± 6242 vs. 10589 ± 7049 IU/week; $p<0.0001$) without a change in hemoglobin, (mean [± SD] 115.2 ± 3.0 g/L vs. 114.9 ± 3.3 g/L; $p=0.5789$). When stratified by subcutaneous dose, patients with the lowest dose (<5000 IU/wk) demonstrated the greatest increase (89%), and those with the highest dose (>20000 IU/wk) experienced no increase (-3%).

CONCLUSION: Overall, erythropoietin doses increased by 26% when patients were converted from subcutaneous to intravenous administration.

KEY WORDS: *Erythropoietin alpha administration; subcutaneous; intravenous*

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EVALUATION OF A PATIENT DECISION AID FOR LOWERING THE RISK OF CARDIOVASCULAR DISEASE IN COMMUNITY PHARMACY: OPTION PILOT STUDY

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Funding Source: Canadian Stroke Network

BACKGROUND: We assessed the feasibility of using a decision aid (DA) for patients at high risk of cardiovascular disease (CVD) or a simpler educational tool, a personalized risk profile (PRP), to assist pharmaceutical care in community pharmacies.

METHODS: A pilot randomized trial was conducted in 10 community pharmacies. Patients on lipid-lowering or antihypertensive pharmacotherapy for less than 12 months were randomly assigned to 1) DA or 2) PRP. Patients meet their pharmacists. Telephone interviews were conducted before and after the pharmacist visit.

RESULTS: Twenty-six middle-aged patients were recruited. All patients received their educational tool and 24 met their pharmacist. We combined patients in the two study groups. Patients were very satisfy with the way the information was presented (19/24), the amount of information presented (21/24), and the usefulness of the tool (24/24). A small proportion of patients were able to correctly estimate their CVD risk category (before-after: 31%-39%; p=0.33), their absolute 10-year CVD risk (19%-34%; p=0.63) and the benefits of modifying all their CVD risk factors (0%-42%; p=0.20). The proportion of patients with a decision conflict score >2.5 (indicating relative discomfort with the decision to take medication) decreased (58%-25%; p=0.02). Patients reported to be satisfied with their role in decision process (median score: 3.3), amount of information provided (4.0), and satisfaction with how pharmacist treated them during the intervention (4.0).

CONCLUSION: There is a need for additional pharmaceutical care among patients at high risk of CVD. Formal pharmacist training and follow-up visits may improve the effectiveness of the intervention.

KEY WORDS: *Cardiovascular disease prevention; hypertension; hypercholesterolemia; pharmaceutical care; community pharmacy; decision aid*

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FLUOROQUINOLONES ARE NOT ASSOCIATED WITH A HIGHER NUMBER OF ADVERSE EVENTS WHEN USED FOR THE TREATMENT OF ACTIVE TUBERCULOSIS COMPARED TO A STANDARD TREATMENT REGIMEN: A BRITISH COLUMBIA POPULATION STUDY

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Institutions: BC Centre for Disease Control, Vancouver Coastal Health Authority and University of British Columbia
Funding Source: None

BACKGROUND: Fluoroquinolones such as ciprofloxacin and levofloxacin are used in the treatment of Mycobacterium tuberculosis. Despite increasing use of these agents, there is little information on their tolerance except for a recent case series that suggested a high incidence of adverse reactions to a combination of levofloxacin and pyrazinamide for treatment of latent tuberculosis (TB) infection. Design: Case-control, population-based study.

OBJECTIVES: To compare the intolerance of fluoroquinolones/pyrazinamide to standard treatment of ethambutol /pyrazinamide in active cases.

METHODS: Between 2000 and 2002, all patients who had received levofloxacin/ pyrazinamide (N=25), ciprofloxacin/pyrazinamide (N=21), or ethambutol/pyrazianmide (N=169) for treatment of TB were identified from the provincial TB database. Drug safety was assessed by evaluation of the nature of the adverse event, likelihood of association with the study medications and severity. Only those side effects that resulted in modification or discontinuation of therapy, or hospitalization were considered for the analysis.

RESULTS: The number of major adverse events was similar for levofloxacin (adjusted log risk ratio, -0.84; 95% CI, -1.7 to 0.03) and for ciprofloxacin (adjusted log risk ratio, 0.23; 95% CI, -0.52 to 0.98) compared to standard treatment. As well, the time to first event was also similar between the fluoroquinolones and standard treatment (levofloxacin odds ratio 1.05; 95% CI, 0.45 to 2.46 and ciprofloxacin odds ratio, 1.18; 95% CI, 0.48 to 2.90). There were no differences between the fluoroquinolones and standard treatment in occurrence of any major adverse event (levofloxacin odds ratio 1.12; 95% CI, 0.42 to 2.95 and ciprofloxacin odds ratio, 1.38; 95% CI, 0.43 to 4.45), central nervous system (levofloxacin odds ratio 2.02; 95% CI, 0.55 to 7.36 and ciprofloxacin odds ratio, 1.79; 95% CI, 0.45 to 7.16), gastrointestinal (levofloxacin odds ratio 2.47; 95% CI, 0.81 to 7.47 and ciprofloxacin odds ratio, 0.92; 95% CI, 0.26 to 3.30), or skin (levofloxacin odds ratio 0.62; 95% CI, 0.07 to 5.44 and ciprofloxacin odds ratio, 2.25; 95% CI, 0.49 to 10.4) events.

CONCLUSIONS: Concomitant treatment with fluoroquinolones/pyrazinamide resulted in similar number of adverse events compared to the control arm when used for treatment of active TB.

KEY WORDS: *Levofloxacin; Ciprofloxacin; Tuberculosis; adverse events*

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FORMULARY IMPACT OF LISTING NEXIUM IN QUEBEC

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Funding Source: AstraZeneca Canada

BACKGROUND: In Quebec, PPI use in greater than standard daily doses (SDD) is prevalent and ranges from 4-13% suggesting the need for more potent PPIs. Reduction of greater than SDD utilization would result in significant cost savings. NEXIUM® produces the greatest level of acid suppression compared to all PPIs at standard daily doses. The objective of this study was to estimate the cost impact from listing NEXIUM on the provincial formulary since January 2001.

METHODS: A random sample of patients with a claim for at least one PPI from RAMQ from January 2001 to June 2003 was obtained. All NEXIUM patients were classified as new to PPI therapy or switched from PPI therapy based on their drug use history within the drug plan. For new patients, it was assumed that they would have used another PPI if NEXIUM were not available. A weighted average daily cost was calculated based on the distribution of PPI prescribing prior to NEXIUM market entry as a reference cost. Actual NEXIUM daily cost was then compared to the reference cost. For patients switching, the difference in the actual daily cost was calculated. All cost differences were applied to the number of days of therapy.

RESULTS: NEXIUM has saved $2.7M in its first 18 months of listing. The majority was from patients switching from LOSEC greater than SDD utilization to NEXIUM once daily. Daily cost decreased by 24% in patients switching from LOSEC to NEXIUM.

CONCLUSION: NEXIUM produced savings by reducing greater than SDD use of LOSEC. When evaluating the financial impact of medicines, decision makers need to give adequate consideration to utilization patterns, which have a major impact on costs.

KEY WORDS: *Drug utilization; Nexium; esomeprazole; PPI; formulary; cost*

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GASTROINTESTINAL EFFECTS OF ROFECOXIB AND CELECOXIB VERSUS NSAIDS AMONG PATIENTS ON LOW DOSE ASPIRIN

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Funding Source: Canadian Institutes of Health Research, The Arthritis Society

BACKGROUND: The GI safety profile of a concomitant use of non-selective NSAID with ASA (NSAIDs & ASA) versus coxib & ASA is unclear.

OBJECTIVE: To compare the rates of GI hospitalization (perforation or hemorrhage in the upper GI tract) among elderly patients taking NSAID & ASA versus those taking coxib & ASA.

METHODS: Elderly patients who filled a prescription for a coxib or non-selective NSAID between April 1999 and March 2002 were identified through the RAMQ database. The index date was defined as the date of the first filled prescription of either coxib or NSAID. Patients were classified into 4 categories: (i) NSAID only (ii) NSAID&ASA (iii) coxib only (iv) coxib &ASA. ASA exposure was assessed at the index date. Cox regression models with time dependent variables were used to compare the rates of GI hospitalization among the 4 treatment categories. Models were adjusted for potential confounders and variations in medication exposure.

RESULTS: A total of 100,283 prescription episodes were for coxibs&ASA; 515,773 for coxibs only; 24,600 for NSAIDs&ASA; and 151,553 for NSAIDs only. Compared to NSAID alone, the adjusted Hazard ratios of GI hospitalization were: Coxibs&ASA 0.86 (0.63, 1.17), coxibs 0.62 (0.45, 0.81) and NSAIDs&ASA 1.61 (1.02, 2.56). In adjusted models, the coxib & ASA combination conferred almost a 50% risk reduction for GI hospitalization compared to NSAID & ASA treatment [HR 0.53 (0.34, 0.83)].

CONCLUSION: Among elderly patients requiring cardiovascular protection with ASA, coxibs may be a safer anti-inflammatory choice than nonselective NSAIDs.

KEY WORDS: *Coxibs; NSAIDS; aspirin; gastrointestinal bleeding; elderly*

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GENERIC REPLACEMENT OF CLOZAPINE: A SIMPLE DECISION MODEL FROM A CANADIAN PERSPECTIVE

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Funding Source: Novartis Pharmaceuticals Canada Inc.

BACKGROUND: Increased relapse incidence has been reported upon switching patients with schizophrenia from brand name to generic clozapine. The cost of treating relapsed patients could offset the reduced drug acquisition cost associated with switching. A decision model was designed to predict the relapse incidence at which switching to generic clozapine is cost-neutral.

METHODS: A hypothetical cohort of 100 patients with schizophrenia stabilized on brand name clozapine was considered either to remain on the brand name product, or to switch to the generic version. Relapse incidences were taken from two reports following patients who underwent generic replacement of clozapine. Direct costs associated with each treatment were projected from a Canadian Ministry of Health perspective, considering drug acquisition and treatment of relapse.

RESULTS: Switching a patient to generic clozapine would save Cdn$1241 annually if the patient did not relapse, and would cost Cdn$9823 if the patient relapsed. Assuming an 11% difference in relapse for patients taking brand name and generic clozapine, respectively, switching 100 patients to generic clozapine would save Cdn$24 per patient. If the relapse difference for patients taking generic clozapine is 28%, the switch to the generic medication would cost Cdn$1857 per patient. Switching patients from brand name to generic clozapine was predicted to be neutral to direct costs when the absolute difference in relapse incidence was 11.2%.

CONCLUSIONS: Switching to a generic medication may not always reduce direct costs. Physicians, patients and third party payers should consider the potential consequences before instituting generic replacement of clozapine for economic reasons.

KEY WORDS: *Clozapine; cost; generic drugs; relapse; schizophrenia; therapeutic equivalency*

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HEALTH PREFERENCE EVALUATION OF ERECTILE DYSFUNCTION IN SPINAL CORD INJURY PATIENTS AND THEIR PARTNERS

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Funding Source: Pfizer Canada Inc.

BACKGROUND: The majority of men with spinal cord injury (SCI) suffer from erectile dysfunction (ED) a secondary complication of their impairment. ED can have a profound effect on a man's and his partner's quality of life. The treatment of ED after SCI is complex. The objective of this analysis was to examine the utilities (u) associated with ED and different ED treatments from the patient (SCI male) and partner perspective.

METHODS: Subjects with spinal cord injury (N=59) and partners (N=19) were interviewed about health preference for different erectile treatments. Standard gamble was used to evaluate the health preference. Clinical scenarios used to determine health preference were approved by clinical experts. Health preference for ED and the following ED treatment comparators was examined in this analysis: oral therapy (sildenafil citrate; SILD), injections, suppositories, vacuum erection device (VED) and penile prothesis surgery (PPS).

RESULTS: A total of 59 male subjects were evaluated. The average age was 40.25 (SD 10.43); range 23-65. The time since injury was 10.30 years (SD 9.35); range 1-36. Men with spinal cord injury reported a higher health preference for oral therapy (u=0.91± 0.16) than for VED (u=0.87± 0.17), injectable (u=0.86±0.19), suppository (u=0.86±0.17) and PPS (u=0.83±0.19). Partners reported a higher health preference for oral therapy (u=0.92± 0.12) than for VED (u=0.90±0.14), suppository (u=0.87± 0.15), injectable (u=0.85± 0.17) and PPS (u=0.85± 0.13).

CONCLUSIONS: Oral SILD is associated with increased health preference when compared to non-oral treatment strategies. The choice of utility instrument is critical to the outcome and may influence economic analyses.

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HOW DOCTORS EVALUATE SERVICES FROM REGIONAL PUBLIC HEALTH INFLUENZA CONTROL PROGRAMS

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Institutions: University of Calgary
Funding Source: Alberta Heritage Foundation for Medical Research, Adult Research Committee Calgary

BACKGROUND: In Alberta vaccine doctors can request supplies of publicly funded vaccine to administer to their patients. Physician assessment of this process may identify areas for improvement, which, if implemented, might increase the number of patients vaccinated.

PURPOSE: We describe Alberta doctors' evaluation of public health influenza vaccination program components involving primary care physicians.

METHODS: 2003 Postal survey of Alberta family doctors. Physicians rated 5 items: 1) efficiency of vaccine ordering system, 2) timeliness of vaccine delivery to office, 3) availability of vaccine for entire season, 4) provision of information to doctors about vaccine and 5) provision of information for distribution to patients.

RESULTS: The survey response rate was 49.2%. 819/981 respondents had ordered vaccine from a regional health authority in the fall of 2002. Three of the 5 items were rated as poor/fair by many respondents: 1) provision of information for distribution to patients (37%), 2) timeliness of vaccine delivery to offices (16%) and 3) vaccine availability over the entire influenza season (18%). While there was regional variation in item ratings provision of information for distribution to patients was consistently a problem.

CONCLUSION: A high priority should be placed on improving: provision of information for distribution to patients, timeliness of vaccine deliveries to doctors' offices and vaccine availability over the entire season.

KEY WORDS: *Program evaluation; influenza/pc; primary health care; vaccination*

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HYPERTENSION CONTROL: RESULTS FROM THE DIABETES CARE PROGRAM OF NOVA SCOTIA REGISTRY AND IMPACT OF CHANGING CLINICAL PRACTICE GUIDELINES (CPGS).

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Funding Source: None

OBJECTIVE: To examine the effect of changing CPGs on the diagnosis and control of hypertension among persons with diabetes (DM).

METHODS: The study population is comprised of 1132 randomly selected records from the Diabetes Care Program of Nova Scotia provincial registry of those who access Diabetes Centers (DCs). Selection criteria: non-pregnant adults ≥ age 19, type 1 or 2 DM, and at least 15 months of current follow-up. Data collected: age, gender, years since diagnosis, weight, renal status (Cockcroft-Gault estimate), mean blood pressure (BP) and type of antihypertensive. Rates of BP above target for people with DM were analyzed according to 4 different sets of CPGs(1992-2003).

RESULTS: Of the 1132 patients included in the study, 418 (36%) were recorded as being treated for hypertension. Using 1992 guidelines, 226 (54%) of those on treatment did not meet target, while an additional 293 (41%) of the not treated were considered hypertensive (BP > 140/90 mmHg). Using 2003 guidelines, 347 (83%) of those on treatment did not meet target, while 528 (74%) of the not treated were above target (> 130/80 mmHg).

CONCLUSION: Using either the 1992 or 2003 CPGs, many with DM had inadequately controlled blood pressure even though taking antihypertensives. The newer 2003 CPGs classify more as treatment candidates. Further work is needed to examine the implications of changing GPGs and reasons for failure to achieve target BPs.

KEY WORDS: *Diabetes; hypertension; clinical practice guidelines*

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IMPACT OF FORMULARY RESTRICTION ON PRESCRIBING OF CELECOXIB IN MANITOBA

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Funding Source: Pharmacia

BACKGROUND: Celecoxib (Celebrex®) received NOC from the Therapeutic Product Directorate in April 1999 for the treatment of osteo/rheumatoid arthritis in adults. It was listed as an unrestricted benefit by the Manitoba Pharmacare program in December 1999; in August 2000 its reimbursement was restricted according to specified criteria in osteo/rheumatoid arthritis.

METHODS: All prescription records for celecoxib (Pharmacare reimbursed and self-pay) during December 1999-March 2001 were identified in Manitoba's population-based health care databases and related to the policy period. The likelihood of unrestrictive vs restrictive use for celecoxib prescriptions was determined for various recipient and physician factors from logistic regression analysis at a 95% level of confidence.

RESULTS: During unrestricted coverage, celecoxib prescriptions were dispensed at a rate of 208 per day; this decreased to 189 per day during the period of restriction. 12% of prescriptions in the later period were not reimbursed by Pharmacare. 53% of unrestricted use prescriptions were for acute conditions, such as backpain, and 49% were for acute use during restriction. In addition to the increased likelihood of use in acute conditions, celecoxib prescriptions were significantly more likely to be dispensed to females and high income persons during unrestricted coverage. Controlling for patient factors, specialists, non hospital-affiliated physicians and group practitioners were more likely to prescribe celecoxib when it was an unrestricted benefit.

CONCLUSION: Restriction of celecoxib reimbursement by a provincial drug program appeared to have influenced the characteristics of its prescribing and use.

KEY WORDS: *Celecoxib; provincial drug program; restricted reimbursement; acute pain; hospital-affiliated physicians*

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IMPACT OF RECEIVING GUIDELINE CONCORDANT PHARMACOTHERAPY FOR MAJOR DEPRESSION ON HEALTH SERVICES USE

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Institutions: McGill University
Funding Source: CIHR

BACKGROUND: Antidepressant treatment is lacking or suboptimal for many patients with major depression.

OBJECTIVE: To determine the impact of receiving guideline concordant pharmacotherapy on use of ambulatory health services.

METHODS: The data source for this population-based, retrospective cohort study was the Quebec universal health insurance plan (1999-2002). Patients were aged 18 to 64, with a new diagnosis of depressive disorder given between October 1, 2000 and March 31, 2001, from primary care physicians or psychiatrists. Medication use was defined as having at least one psychotropic pharmacy claim within 31 days of diagnosis. Guideline concordant care was defined as correctness of starting drug, dose, and duration according to the 1999 Canadian guidelines. Health services use was defined as numbers of visits to prescribing physicians, other physicians, and emergency departments in the year after diagnosis.

RESULTS: 7,191 adults were identified of whom 3,804 (52.9%) received psychotropic medication. Of these, 2,585 (68.0%) received appropriate starting drug, 1,682 (44.2%) received appropriate starting dose, and 386 (10.2%) received drug for the appropriate duration. Three multivariate generalized estimating equations models (poisson) indicated that: 1) number of prescribing physician visits was 53% (95%CI=[39%, 67%]) higher in patients given correct vs incorrect drug and 43% (95%CI=[32%, 56%]) higher in those with correct vs incorrect duration; 2) number of other physician visits was 22% lower in patients with correct vs incorrect drug (95%CI=6%, 35%]); and 3) number of emergency department visits was 25% (95%CI=[8%, 38%]) lower in patients given correct vs incorrect drug.

CONCLUSION: Guideline concordant pharmacotherapy was associated with ambulatory health services use.

KEY WORDS: *Depression; health services utilization; population-based; adherence to guidelines*

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IMPLEMENTATION OF AN ALGORITHM FOR INTRAVENOUS PANTOPRAZOLE: IMPACT ON PRESCRIPTION COMPLIANCE IN UNIVERSITY HOSPITALS

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Funding Source: Centre Hospitalier de l'Université de Montréal (CHUM)

BACKGROUND: Intravenous (IV) pantoprazole is used at CHUM in the adjuvant treatment of nonvariceal upper gastrointestinal bleeding (UGB) and to inhibit acid secretion among nil per os (NPO) patients.

OBJECTIVE: This project consisted of describing the utilization profile of IV pantoprazole and assessing the impact of a use algorithm on prescription compliance.

METHODS: Using a pre-post intervention specification, the use of pantoprazole and prescription compliance were assessed on a retrospective basis (January 1, 2002 to April 30, 2002) and on a prospective basis (January 1, 2003 to April 30, 2003). The intervention consisted of conferences held for pharmacists and physicians working in the intensive care units and emergency services. A pocket size of the algorithm was also distributed to pharmacists and physicians. We reviewed the medical records of all patients having received IV pantoprazole during these periods, assessing the compliance of prescriptions with indication, dose and length of treatment. Cost and the standby treatment were also assessed.

RESULTS: In total, 158 patients were recruited in the retrospective phase and 118 patients in the prospective phase. The subjects were organized into two groups: UGB and NPO. In the UGB group, rates of compliance with indication, dose and length of treatment in the retrospective phase were 8.8%, 76.5% and 58.8%, respectively; the estimated rates for the prospective phase were 26.5%, 80.9% and 69.1%. The total rates of compliance (including indication, dose and duration) were 4.4% in the retrospective phase and 11.8% in the prospective phase ($p = 0.116$). In the NPO group, the rate of compliance for the first dose administered was 42.7% in the retrospective phase and 36.6% in the prospective phase. The cost of non-compliance with the indication in the UGB group was estimated at $12,270 (in the retrospective phase) and $7,829 (in the prospective phase). In the NPO group, the cost figures were $8,047 (retrospective phase) and $5,929 (prospective phase).

CONCLUSIONS: Despite explicit criteria for use, in the prospective phase we observed only 11.8% total compliance in the UGB group and 36.6% compliance with the first dose administered for the NPO group. A review of the training strategy and a subsequent re-evaluation of the algorithm would allow us to determine if compliance is improved.

KEY WORDS: *Pantoprazole; compliance; algorithm; Centre Hospitalier de l'Université de Montréal*

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IMPROVING PRIMARY CARE PHYSICIAN KNOWLEDGE OF THE ASTHMA CONSENSUS GUIDELINES IN QUEBEC WITH A STAMP

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Funding Source: TEAM Project (Towards Excellence in Asthma Management) of the QAEN (Quebec Asthma Education Network)

BACKGROUND: Canadian clinical practice guidelines (CPG)'s on asthma management were published in 1999 and updated in 2001. Efforts were made to disseminate the content of the guidelines but the specific knowledge of these guidelines has not been assessed. We designed a prospective randomized-controlled study in primary care physicians from 5 regions of Quebec.

METHODS: We assessed their knowledge of the criteria for asthma control and therapy while implementing an intervention aimed at supporting their decision-making process at the point of care. The intervention was based on a stamp, to be employed at each visit that summarizes the criteria for control and therapeutic interventions. At the time of enrollment and 6 months later every physician filled in a questionnaire to assess their knowledge of the CPGs.

RESULTS: 104 primary care physicians were recruited between August 2002 and November 2002. The analysis of questionnaires showed average scores of 1.9/8 and 2.5/8 points for control and education/therapy, respectively (4.4/16). There were no differences between regions. At 6 months there was a significant improvement only in those receiving the stamp: controls 0.6/16 (CPG by mail); stamp and instructions by mail: 3.3/16; stamp and evening education event 3.8/16; stamp, evening education event and try to enroll 6 patients 4.6/16.

CONCLUSIONS: We show that although physicians have an up-to-date knowledge of the fundamentals of asthma, certain areas of management still remain to be improved. The use of a stamp improves physician knowledge of CPGs.

KEY WORDS: *Asthma; education tools; Canadian guidelines; physicians*

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INAPPROPRIATE MEDICATION PRESCRIBING IN COMMUNITY-DWELLING ELDERLY PEOPLE LIVING IN ISFAHAN

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Funding Source: Iranian Ministry of Health
Background: Inappropriate medication use is a major safety concern among the elderly. The magnitude of this problem has been documented in North America and Europe. To date however, no such studies have been conducted in the Middle East.
OBJECTIVES: To determine the prevalence of inappropriate medication prescribing in community-dwelling elderly persons, and to determine factors associated with inappropriate prescribing.
METHODS: Prescriptions of 3000 elderly patients (>=65 years) from Isfahan, Iran were extracted from a computerized database. Inappropriate medications were defined according to Beers (1997). The presence of at least one drug-drug interaction (DDI) and at least one drug class duplication within a given prescription were also determined. Multivariate logistic regression models were built to determine factors associated with inappropriate prescribing; age, gender, DDIs, duplications, number of drugs prescribed, and physician years of experience were considered.
RESULTS: The mean age of our cohort was 73 years (SD=6), where 1735 (58%) were females. A total of 829 (28%) patients had received at least one inappropriate medication, 746 (25%) had at least one duplication, and 285 (10%) had at least one DDI. The three most inappropriately prescribed medication classes were antihistamines (29%), non-steroidal anti-inflammatory agents (23%) and benzodiazepines (16%). The number of drugs prescribed was the only factor significantly associated with receiving at least one inappropriate medication (OR 1.24; 95%CI: 1.16-1.32) in multivariate analyses.
CONCLUSION: Our findings indicate a high prevalence of elderly patients with inappropriate medications. Given the potential severity of this problem, further steps need to be implemented to prevent this occurrence.
KEY WORDS: *Inappropriate prescribing; Beers criteria; elderly people; community-dwelling; Isfahan*

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INNOVATIVE PROSPECTIVE APPROACH TO CAPTURE PATIENT REPORTED FUNCTIONAL OUTCOME MEASURES IN PATIENTS USING INJECTABLE BIOLOGIC AGENTS, ETANERCEPT (ENBREL®) OR ANAKINRA (KINERET®)

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Institutions: Institute for Work and Health, Mount Sinai Hospital-Advanced Therapeutics, Institut de Rhumatologie, Royal Victoria Hospital, St. Clare's Hospital, Amgen Canada Inc., Ottawa, Ontario, University Health Network respectively for each author mentioned above…Funding Source: Amgen Canada Inc.
OBJECTIVE: To capture prospective patient-reported outcome measures in Canadian patients with rheumatoid arthritis (RA) who started etanercept or anakinra as part of their standard therapy in usual clinical practice.
METHOD: The primary endpoint of the study was to evaluate response to treatment using the health assessment questionnaire disability index (HAQ-DI) and secondary endpoints included change of work productivity, patient and physician global assessments and patient disease activity index between baseline and each scheduled visit. An improvement in the HAQ-DI of 0.19-0.22 has been shown to correspond to a clinically important change for the typical patient. Trained interviewers used validated measures and conducted computer-assisted telephone interviews in either French or English, allowing for real-time data being made available to Rheumatologists for treatment-based decision-making. A total of 500 patients will be enrolled over a 30-month period from more than 50 Canadian centres. Eligible patients were over 18 years of age with active RA not concurrently on biologics and were candidates for initiation of either etanercept or anakinra therapy. All patients receive commercially available drug and had to qualify for private or public reimbursement. All patients will be followed for a 24-month period.
RESULTS: This interim analysis includes baseline data for the first 100 patients enrolled and 42 patients treated for at least 3 months; 75 % were female and 87 % were Caucasian, the mean age at baseline was 52.4 years +/- 13.4. Sixty-three patients were treated with anakinra, and 37 patients with etanercept. The baseline HAQ-DI score was 1.73 +/- 0.6, and the pain scale reported 2.14 +/- 0.6. The patient global scale at baseline was 3.55 +/- 0.7. Changes between baseline and 3 months (n=42) were -0.27 ($p<0.05$) in the HAQ-DI, -0.61 ($p<0.01$) in the pain scale and -0.43 ($p<0.01$) on the patient global scale. The results for all 100 patients completing 3 months of therapy will be presented at the time of presentation. This innovative real-time approach to providing patient reported outcome measures to the Rheumatologists allows for more robust therapeutic decision-making at regular scheduled clinic visits.
CONCLUSIONS: Baseline demographics are consistent and representative of the general rheumatology clinical practice. The change in the HAQ-DI from baseline to 3 months of therapy shows clinically important improvements. Results will be updated at the time of presentation and will include the changes in the HAQ-DI, pain scale and patient global assessment for the 100 patients treated with etanercept or anakinra.
KEY WORDS: *Outcome studies safety, efficacy, and/or effectiveness; use of pharmaceuticals and other health care technologies; dissemination of research results; rapid assessments*

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IS THERE AN ASSOCIATION AMONGST CURRENT MEDICATION USE, CLINICAL LAB VALUES AND PATIENT-REPORTED QUALITY-OF-LIFE IN PATIENTS WITH TYPE 2 DIABETES?

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Funding Source: GlaxoSmithKline

BACKGROUND: Several groups of antidiabetic agents are available to manage type 2 diabetes: first line agents (sulphonylureas, meglitinides, biguanides, alpha-glucosidase inhibitors), second line agents (thiazolidinediones), and insulin. The aim of this study is to examine the association amongst current medications, clinical lab values and QOL.

METHODS: Patients 68 years and older, with type 2 diabetes currently taking an antidiabetic medication were recruited from community pharmacies in Ontario. QOL was assessed by telephone interview using the diabetes-39 survey. Glycosylated hemoglobin A1c (HbA1c) and fasting glucose (FG) were used as measures of glycemic control. HbA1c, FG and current diabetes medications were retrieved from physician medical records.

RESULTS: Complete data were available for 77 patients. Three cohorts of drug use groups were identified: first line agents (N=51), second line + first line agents (N=17), and insulin in combination with first and/or second line agents (N=9). Mean (95%CI) QOL scores for the three groups were 75 (65-85), 83 (57-109) and 94 (67-121) respectively. Mean HbA1c for the groups were 0.068, 0.070, 0.074 respectively. Mean FG for the three groups were 7.6, 8.2, 7.2 respectively. There was no difference in QOL scores, HbA1c, and FG between the three groups. Correlation between QOL and HbA1c (-0.15), and QOL and FG (0.03) was not statistically significant.

CONCLUSION: QOL scores, HbA1c and FG do not seem to be associated with current medication usage. Whether this reflects a lack of incremental benefit associated with more complicated regimens or confounding-by-indication remains to be explored.

KEY WORDS: *Diabetes; quality of life; HbA1c; telephone interviews; pharmacy*

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LESSONS LEARNED ON THE DIFFUSION OF A COMMUNITY PHARMACY INNOVATION – ALBERTA TRIAL PRESCRIPTION (CHECKPOINT) PROGRAM - 2000-2003

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Funding Source: Alberta Health and Wellness

BACKGROUND: Experience from a provincial trial prescription initiative showed a high rate of adoption by pharmacists initially, however, adoption was only temporary and it was followed by a significant decline. The purpose of this research was to examine this pattern through an assessment of pharmacists' perceptions within the context of Rogers five attributes (relative advantage, compatability, complexity, trialability, observability).

METHODS: Data was examined from the internal management information system reports, and reports from previously conducted surveys and focus groups. Analysis consisted of data tabulations and content analyses.

RESULTS: A high percentage of pharmacists perceived the initiative had a relative advantage over the normal practice (over 50% of all community pharmacists attended training sessions and approximately 75% of eligible pharmacies performed at least one trial). This perception changed after the first year of operation (number of trials initiated monthly dropped by 90% from the highest month). The time and effort required for the initiative was poorly compatible with pharmacists' current beliefs or values (pharmacists indicated performing a trial took too long yet the average time of 7 minutes to complete a trial was the same as the average time to dispense a prescription). The initiative was simple for pharmacists to understand, but difficult to perform. Trialability was less than optimal because the modified pharmacy software was not easy to use and could not be experimented with. Demand for trials was low because the initiative was poorly observable to the patient and physician (90% of patients heard about the program through the pharmacist, day to day physician-pharmacist communications about trials were rare). **CONCLUSIONS:** Continuous attention must be paid to the perceptions of pharmacists when introducing innovative programs in the community pharmacy.

KEY WORDS: *Diffusion; innovations; pharmacy; practice*

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MEDICATION USE DURING THE FIRST TRIMESTER OF PREGNANCY

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Funding Source: Foundation of Hôpital Ste-Justine

BACKGROUND: Gestational exposure to medications has a great impact on the well-being of the mother and the fetus. As of now, no data are available on the use of medications in pregnancy among the population of women calling IMAGe, a teratology information service.

OBJECTIVES: To characterize the population of pregnant women calling IMAGe, and to estimate the prevalence of medication termination during the first trimester.

METHODS: Women were eligible if they were pregnant within 16 weeks of the first day of their last menses, >18 years old, and exposed to a medication at the time of the call to IMAGe. Recruitment period was between July and August 2002. Once eligibility was established, women were called by a research assistant (RA) who collected demographic, socio-economic and lifestyle data; data on medication use, pregnancy history, and co-morbidity were also collected. The RA was calling subjects again 1 month later to collect information on medication changes since baseline.

RESULTS: 79 women were recruited; women were on average 30 years old (SD: 5), were 10 weeks gestational age (SD: 4), were married (83%), had post-secondary education (69%), and were working (86%). At baseline, women were on 3 medications concomitantly on average; drug discontinuation was the most frequently reported medication change at 1-month follow-up (52%). Antihistamines (17%), antidepressants (16%), anxiolytics (13%), antiemetics (11%), asthma drugs (9%), and antihypertensives (6%) were the most frequently used; at the end of the first trimester, 75% of antihistamines were stopped, 67% of asthma drugs, 56% of anxiolitics, 50% of antiemetics, 27% of antidepressants, and 25% of antihypertensives were also terminated. Although not significant, women with more education and those followed by a family physician (when compared to OB/GYN) were more likely to stop.

CONCLUSIONS: The majority of medications are stopped during the first trimester when the pregnancy is diagnosed, and the phenomenon is more prevalent in educated women and in women with family physician antenatal care.

KEY WORDS: *Pregnancy; medication utilization; first trimester; drug discontinuation rate; teratology information service*

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OUTPATIENT TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN MANITOBA, CANADA

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Funding Source: Institute of Health Economics, University of Alberta

BACKGROUND: The majority of patients with community-acquired pneumonia (CAP) may be treated with antibiotics on an outpatient basis. Dependent upon comorbidity status, Canadian treatment guidelines may recommend costly newer and/or broad-spectrum antibiotics which are subject to reimbursement restrictions in Manitoba (e.g., fluoroquinolones, new macrolides [clarithromycin/azithromycin], and 2nd/3rd generation cephalosporins). We describe current treatment patterns in CAP and identify predictors of receipt of "restricted status" antibiotics.

METHODS: Physician and pharmacy claims from the province of Manitoba, Canada for the period May 1996 to March 2002 were examined to identify adults, covered by provincially administered drug plans, having an episode of CAP initially treated with outpatient antibiotics. Receipt of restricted antibiotics was examined based on temporal, socio-demographic and disease variables.

RESULTS: A total of 31,940 subjects met inclusion criteria: of which approximately 54% received a restricted antibiotic. Of those receiving restricted antibiotics the most common agents included new macrolides (59.2%), fluoroquinolones (23.2%), and 2nd/3rd generation cephalosporins (15.3%). The proportion of subjects receiving a restricted antibiotic increased in each fiscal year from 35% in 1996/97 to 75% in 2001/02. Multivariate analysis identified a number of independent predictors of receipt of restricted antibiotics, including: study year [OR=1.46 (1.44-1.48)], urban residence [OR=1.43 (1.37-1.50)], increased level of comorbidity [OR=1.27 (1.02-1.57)] and income-level (high versus low) [OR=1.36 (1.26-1.47)].

CONCLUSIONS: The use of restricted antibiotics for treatment of CAP increased significantly from 1996 to 2002. In addition, higher income-level, increased level of comorbidity, and urban residence were associated with an increased probability of receipt of restricted antibiotics.

KEY WORDS: *Community-acquired pneumonia; drug utilization; antibiotics*

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PAIN MANAGEMENT AMONG OLDER HOME CARE CLIENTS

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Funding Source: Merck Company Foundation Program / AHFMR

BACKGROUND: Inadequate pain pharmacotherapy remains a concern among seniors receiving formal care services.

METHODS: Baseline data for 216 older (65+) home care clients reporting pain (regardless of intensity or frequency) and participating in a longitudinal study of the correlates and health outcomes of medication-related quality indicators were employed in our analyses. Clients' sociodemographic, functional and clinical characteristics were obtained from the administration of a standardized and comprehensive assessment/care screening instrument (the Minimum Data Set for Home Care~MDS-HC) among a random sample of urban and rural clients residing in Southern Alberta. A comprehensive in-home medication inventory/pill count was administered along with the MDS-HC by trained home care nurses. Descriptive and multivariate logistic regression analyses were employed to estimate the adequacy of medications in controlling pain as well as the relative importance of clients' age, sex, medication adherence, use of alternative therapies, and medication management by physicians as correlates of inadequate treatment.

RESULTS: Approximately 27% of clients reported that their medications did not adequately control pain. Clients exhibiting general medication nonadherence (adj OR 2.08, 95%CI 1.00-4.29) and those with severe/excruciating pain (adj OR 5.97, 95%CI 2.75-12.98) were significantly more likely to report inadequate pain pharmacotherapy. Male clients and those without a recent medication review by their physician were also more likely to report inadequate pain management. Clients reporting inadequate pain control had significantly lower health-related quality of life scores.

CONCLUSION: Although cross-sectional, our findings highlight potential high-risk groups of older clients (e.g., those nonadherent with medications and lacking appropriate medication oversight by a physician) in need of further investigation and intervention to improve their pain management and quality of life.

KEY WORDS: *Pain management; older adults; pharmacotherapy; adherence; Minimum Data Set (MDS)*

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PERSISTENCE AND DETERMINANTS OF STATINS AMONG MIDDLE AGED PATIENTS FOR PRIMARY AND SECONDARY PREVENTION

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Funding Source: CRSH

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

OBJECTIVE: To evaluate the persistence of patients newly treated statin and its relation to age, sex, CVD risk factors and use of health care in middle aged patients for primary and secondary prevention.

METHODS: A cohort was reconstructed using RAMQ databases. All patients aged 50 to 64 years old who received at least 1 statin prescription between Jan 1st, 1998 and Dec 31th, 2000 who had to be newly treated for hyperlipidemia were followed up until June 31th, 2001. The date of the first prescription of statin was defined as the index date. There were 5,694 in the secondary prevention and 11,962 in primary prevention cohorts. The cumulative persistence rate was estimated using Kaplan-Meier. Cox regression models using time dependent variables were used to estimate the probability of ceasing statins after adjustment.

RESULTS: We found that persistence with statins had fallen to 78% after 6 months of treatment, and had declined to 56% in the secondary prevention cohort after 3.5 years; these corresponding figures were 69% and 41% in the primary prevention cohort. Our results suggest that patients with dyslipimia compared to those in secondary prevention (HR:1.77; 1.62-1.94) are less likely to be persistent. Patients with other CVD risk factors such as age, (HR:0.98; 0.97-0.98), diabetes (HR:0.77; 0.72-0.83), hypertension (HR:0.58; 0.55-0.62) were most likely to be persistent to statins. We observed lower persistence in patients who used the greatest number of pharmacists and prescribing physicians.

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

KEY WORDS: *Cardiovascular; primary prevention; secondary prevention; compliance; statin*

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PHARMACISTS PARTICIPATION IN THE WET NEBULIZATION RESPIRATORY CONVERSION INITIATIVE

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Institutions: Dalhousie University, Halifax, Nova Scotia
Funding Source: Funding of P. Flanagan & A. Murphy by Chair of I. Sketris (CHSRF/CIHR/NSHRF)

BACKGROUND: The Nova Scotia Department of Health initiated an intervention to facilitate converting beneficiaries from wet nebulization to dry inhaled delivery devices in August 2000. Community pharmacists provided education and could bill a professional fee in selected circumstances. We conducted a survey of Nova Scotia pharmacists to determine their self-reported rate of participation and identify facilitators or barriers to participation.

METHODS: A survey was developed, pilot-tested and mailed to pharmacists in Nova Scotia during the spring of 2003. Information collected included self-reported billing experiences in the previous 3 months, demographics, work environment, professional experience, financial aspects and opinion regarding the billing process. Quantitative data was evaluated using bivariate and multivariate analyses. Qualitative data was examined using thematic analysis.

RESULTS: Response rate was 39% (297/766). Self-reported billing rates for the professional fee were 34% (switching delivery devices), 58% (optimizing Aerochamber use) and 37% (providing follow-up when replacing Aerochambers). Quantitative analyses demonstrated that pharmacists more likely to bill the professional fee were licensed prior to 1995, practiced greater than 20 years and were owners/managers ($p<0.05$). Thematic analysis identified a cumbersome and time consuming billing process; inadequate fees; and lack of awareness of the initiative; as potential barriers. **CONCLUSIONS:** Pharmacists provided the professional service most often for optimizing Aerochamber use. Barriers to billing frequently identified were inadequate professional fee and difficulty with billing procedures. Factors positively influencing billing included length of practice and job title. Further work is needed to determine the impact of education on patient health outcomes. These results will be used to plan future continuing education and pharmacist intervention initiatives.

KEY WORDS: *Asthma; community pharmacist; cognitive services; reimbursement*

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PHYSICIANS DEFINE INR CONTROL IN AF PATIENTS ANTICOAGULATED WITH WARFARIN

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Funding Source: AstraZeneca Canada

BACKGROUND: INR treatment goals are between 2-3 for prevention of stroke in AF patients. It is accepted that INRs vary greatly within and between patients and control is difficult to achieve. This study explored Canadian physicians attitudes, perceptions and behaviours related to anticoagulation in atrial fibrillation (AF) patients

METHODS: Physicians from B.C, the Prairies, Ontario and Quebec were randomly recruited from lists of high Warfarin (WA) prescribers to participate in a 30 minute, quantitative, telephone interview. One hundred and forty six (146) physicians were interviewed (80 family practitioners (FPs), 43 Cardiologists, 17 Internists and 6 Haematologists).

RESULTS: Participating physicians had a mean 114 AF patients in their practice (FPs 45, Cardiologists 262, Internists 103, Haematologists 32). When asked how they define control, 38% of physicians considered patients well controlled on WA when INR levels are 2-3 100% of the time, 45% said INR should be 2-3 90% of the time, 13% said 80% of the time and 4% said 70% of the time. Physicians estimated that a mean 34% of their AF patients are not well controlled due to unexplained INR variability while a mean 20% are not well controlled due to lack of compliance. MDs cited varied methods of differentiating between the two.

CONCLUSION: Physicians estimate that a substantial percentage of AF patients are not well controlled on WA. Unexplained INR variability seems to be a greater contributor to poor control than lack of compliance.

KEY WORDS: *INR control; real life warfarin; anticoagulation; atrial fibrillation*

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PHYSICIANS' ATTITUDES TOWARD REIMBURSEMENT OF INR MONITORING

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Funding Source: AstraZeneca Canada

BACKGROUND: INR monitoring of atrial fibrillation (AF) patients is a critical, but time consuming, component of anti-coagulation therapy. This study explored Canadian physicians' attitudes, perceptions and behaviours related to anticoagulation in AF patients.

METHODS: Physicians from B.C, the Prairies, Ontario and Quebec were randomly recruited from lists of high Warfarin (WA) prescribers to participate in a 30 minute, quantitative, telephone interview. One hundred and forty six (146) physicians were interviewed (80 family practitioners (FPs), 43 Cardiologists, 17 Internists and 6 Haematologists).

RESULTS: Participating physicians had a mean 114 AF patients in their practice (FPs 45, Cardiologists 262, Internists 103, Haematologists 32). Physicians estimated that they spend a mean 156 minutes per week with all their AF patients (including counseling, referrals, blood testing and phone calls). The mean number of visits per AF patient taking WA was estimated at 7 times per year. Physicians reported they receive a mean $32 for each regular office patient visit. Forty-two percent indicated they are not reimbursed for INR monitoring. Those reimbursed, estimated that they receive a mean $9 per patient. Eighty-four percent of all physicians (77% in B.C., 76% Prairies, 90% in Ontario and 83% in PQ) felt INR reimbursement was insufficient. They felt reimbursement should be a mean $24 per patient.

CONCLUSION: Physicians treating AF patients spend, on average, 2.5 hours/week on activities related to anticoagulation of AF patients. Results suggest that the majority of physicians do not feel they are sufficiently reimbursed for these services.

KEY WORDS: *Reimbursement; INR monitoring; warfarin; atrial fibrillation; anticoagulation*

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PLAVIX® SECTION 8 SURVEILLANCE STUDY

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Institutions: Phase 4 Health Inc.
Funding Source: Bristol Myers Squibb & Sanofi Synthelabo

BACKGROUND: Payer-driven cost containment strategies affect prompt access to evidence-based care. The purpose of this study was to quantify the delays in accessing medications through a special authorization process and to investigate the impact of these delays on health outcomes and healthcare utilization.

METHODS: This study prospectively followed 124 patients in Ontario prescribed Plavix® (clopidogrel). Approval times were collected for each patient along with health outcomes/utilizations during the waiting period.

RESULTS: 121 patients (98%) had their request approved. The mean time duration between the Plavix® request and approval, approval to prescription fill, and Plavix® request to prescription fill was 23 (range 0 to 84), 8 (range 0 to 49) and 28 (range 1 to 92) days respectively (n=108). 79 health outcomes/utilizations, attributed directly to the waiting period, were reported by physicians (n=112): 4 (3.6%) emergency room visits, 7 (6.3%) hospitalizations, 61 (54.5%) physician follow-ups, 7 (6.3%) deterioration of medical condition. 39 patients did not get Plavix® during the waiting period and 72 patients acquired the drug through other means (40% paid out-of-pocket, 44% received samples/drug in advance). Health outcomes/utilization were more common in the group that did not get Plavix®. 9 patients never filled their Plavix® prescription even after approval.

CONCLUSIONS: Special authorization mechanisms aimed solely at controlling utilization can affect access/health outcomes and are not suitable for all products. In this study, all outcomes/delays were associated with the special authorization process and not inappropriate use. Payers should carefully evaluate the impact of cost-containment measures before making formulary decisions.

KEY WORDS: *Outcomes; reimbursement; clopidogrel; health care utilization; special authorization; cost containment; formulary management*

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POST-TRANSPLANT DIABETES MELLITUS IN ELDERLY KIDNEY RECIPIENTS

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Funding Source: Post-transplant diabetes mellitus in elderly kidney recipients

BACKGROUND: The aim of this study was to determine the incidence of post-transplant diabetes mellitus (PTDM) and to define the risk associated with the use of tacrolimus (Tacro) versus cyclosporin (Csa) in elderly kidney transplant (KT) recipients.

METHODS: This retrospective cohort study analyzed data from all elderly (>=60) non-diabetic patients who received a KT between 1985 and 2000 in Quebec. The primary outcome was PTDM. The calcineurin-inhibitor (Tacro vs Csa) used was the main exposure. Recipient age, sex, body mass index (BMI), rejection episodes were measured. Logistic regression was used to identify predictive factors for PTDM at 3 years. The risk in time was defined with a hazard function curve.

RESULTS: There were 221 patients in the cohort (mean age 63, 35% women, mean BMI 24,7). Patients all received Csa (85%) or Tacro (15%). Overall, 21% of patients developed PTDM during follow-up. On multivariate analysis, only the use of Tacro(OR:2,9;p=0.02)was associated with PTDM. There was a trend for an association between a BMI >= 30 and PTDM (OR:2,6;p=0.08. The risk for PTDM is higher in patients treated with Tacro than in Csa only in the first year post transplant as afterwards, the hazard function curves for PTDM in users of Csa and Tacro merge.

CONCLUSIONS: The incidence of PTDM was thus high in this cohort of elderly recipients, and the risk for this complication was greater in users of Tacro mostly in the first post-transplant year.

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POSTMARKETING SURVEILLANCE CAN BE EFFECTIVE IN CLINICAL PRACTICE AND RESEARCH

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Institutions: Toronto General Research Institute
Funding Source: Amgen Canada Inc. and CIHR

OBJECTIVES: To improve the methods of the postmarketing surveillance and apply the results to clinical practice and research

METHODS: Two projects are ongoing to collect longitudinal surveillance data on the efficacy and safety of 2 biologic drugs in a Canadian rheumatoid arthritis (RA) population. We developed databases online to collect the data through either Computer Assisted Telephone Interviewing (CATI) or via patient data collection on a computer in a clinic setting. A report is produced with patient outcomes displayed with graphs and tables. The report records both the current and the previous data, to show change over time, which facilitates physician clinical decision-making within a given time period. The graphics are easily understood and visually attractive. A technology questionnaire was developed to determine ease of use by patients with RA and recommendations for future technology. Questions were asked about ways to improve the program or facilities such as ergonomic keyboards, touch screens to make the technology accessible to patients with RA. Physicians preferred the computer-generated data reports, which showed changes in health status and/or the disease process of both individuals and the overall study group.

CONCLUSIONS: Postmarketing surveillance can be a useful tool in both research and clinical progress notes. Practicing physicians receive information from the data reports, which will save visit time and provide a comprehensive overview visually to enhance decision-making. Pharmaceutical Companies and researchers continue to monitor, evaluate and report results that are based on outcome data to advance clinical practice and improve the quality of care.

KEY WORDS: *Postmarketing surveillance; rheumatoid arthritis (RA); computer assisted telephone interviewing (CATT); patient outcomes*

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PRESCRIBED DAILY DOSES AND DAILY COSTS OF ROFECOXIB AND CELECOXIB FOR ELDERLY BENEFICIARIES OF THE RÉGIME GÉNÉRAL D'ASSURANCE-MÉDICAMENTS IN QUEBEC

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Funding Source: Merck & Co. Inc.

BACKGROUND: At doses recommended for osteoarthritis (OA), rofecoxib and celecoxib have similar daily prices. However, celecoxib is twice more costly than rofecoxib at maximum doses recommended for rheumatoid arthritis (RA) ($1.25 for rofecoxib 25mg once daily vs. $2.50 for celecoxib 200mg twice daily). The objective of this study was to describe the utilization of Coxibs (rofecoxib and celecoxib) in chronic pain (OA or RA) in terms of average daily doses, average number of pills per day, average cost per patient per day and concomitant gastroprotective agent (GPA) utilization in Quebec.

METHODS: Data for all seniors (65 years and over) with OA or RA who received at least three consecutive dispensations of either rofecoxib or celecoxib in 2001 were extracted from the RAMQ databases. Dispensing date of the first of the three dispensations defined the index date; average doses, numbers of pills and costs per day were estimated between the index date and the third dispensing date. Linear regression models were used to compare the average daily cost and logistic regression models to compare concomitant gastroprotective agents (GPAs) utilization between rofecoxib and celecoxib adjusting for patients' characteristics at index date. **RESULTS:** A total of 12,722 and 13,119 patients were included in the rofecoxib and celecoxib groups respectively. Average daily doses used were 20.8mg for rofecoxib vs. 231.6mg for celecoxib. Rofecoxib users received an average of 0.95 pill per day in comparison with 1.34 for celecoxib. Unadjusted daily costs were $1.18 for rofecoxib and $1.45 for celecoxib. When adjusting for patient characteristics, including OA vs. RA diagnosis, the daily cost of rofecoxib was lower than that of celecoxib by $0.35 (95% CI: $0.34-$0.37. Rofecoxib was associated with less concomitant GPA utilization (adjusted odds ratio 0.88; 95% CI 0.82, 0.95).

CONCLUSION: In this study, rofecoxib was significantly less expensive than celecoxib and was associated with less concomitant GPA utilization.

KEY WORDS: *Coxibs; NSAIDS; daily dose; costs; elderly; rofecoxib; celecoxib, administrative database*

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PRESCRIPTION DRUG TREATMENT OF ASTHMA IN YOUNG CHILDREN IN QUEBEC, 1999-2001, AN ANALYSIS USING ADMINISTRATIVE DATABASES

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Funding Source: Vespa

BACKGROUND: Monitoring of asthma medications at the population level can lead to estimates of prevalence and track the evolution of treatment practices. Young children (aged 1 to 4 years) are a unique group of users deserving separate focus.

METHODS: We studied the use of asthma medications in two groups of young children insured by the Quebec public prescription drug plan: those admissible for social assistance (PSRs) and those who do not have access to employee/employer drug plans (adherents) (together these groups comprised 36% of the 2001 Quebec population under 65 years). For each of the years 1999, 2000 and 2001, we obtained a 50% sample of beneficiaries aged 1-4 years for whom ≥1 prescription for an asthma medication were filled during the year. Asthma medications included short- and long-acting ß2 agonists, inhaled corticosteroids (ICS), antileucotriens, theophyllines, ipratropium, ketotifen and cromoglycate. Using population counts, we estimated the 1-year prevalence of asthma medication use (at least 1 prescription for an asthma medication during the year). Regional differences and proportions who used various types of asthma medications were calculated.

RESULTS: In the PSR group, from 1999 to 2001, the 1-year prevalence increased (not significantly) from 17.8% (95% CI from 17.5-18.2) to 18.4% (18.0-18.8), and in the adherents group it increased slighty (but significantly) from 15.0% (14.7-15.2) to 16.0% (15.8-16.3). In both groups, prevalences were significantly higher use in boys than girls. Regional differences were considerable. In 2000 in the adherent sample, 67.4% (66.2-68.6%) of those who received a prescription for an asthma drug received at least one prescription of short-acting ß2 agonists, 69.9% (68.7-71.0) at least one of ICS, and 20.1% (19.1-21.1) at least one of oral steroids. Proportions are similar in the PSR group. Significant increase in the proportion of users who received at least one prescription of ICS was seen in both groups from 1999 to 2001.

CONCLUSION: Prevalence of use of asthma medications in young children is stable or increasing slightly. In line with treatment guidelines, significantly more users rely on ICS. Administrative databanks can highlight regions to focus interventions or further study.

KEY WORDS: *Asthma; medication use; children*

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PREVALENCE OF USE OF GASTROINTESTINAL PREVENTIVE STRATEGIES IN PATIENTS AGED 65 YEARS AND OVER WHO RECEIVE ANTIINFLAMMATORY THERAPIES IN NOVA SCOTIA AND QUEBEC

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Funding Source: Merck Frosst Canada Ltd.

BACKGROUND: Two preventive strategies are recommended for patients with one or more risk factors for NSAID-associated gastrointestinal complications: the use of cyclooxygenase-2-selective inhibitors (Coxibs) or the use of gastroprotective agents (GPAs) with the nonselective NSAIDs. In Nova Scotia Pharmacare program, access to proton pump inhibitors (PPIs) is restricted by limited use criteria and Coxibs are reimbursed under the maximum allowable cost (MAC) policy. In Quebec, no formulary restrictions are imposed on both PPIs and Coxibs. The objective of this study was to estimate the proportion of seniors using antiinflammatory drugs who receive preventive strategies in Nova Scotia and Quebec.

METHODS: We conducted two cross sectional studies: one from the Quebec and the other from the Nova Scotia health services administrative databases. Patients studied were ≥ 65 years and filled a prescription for a Coxib or a nonselective NSAID in 2002 in Quebec or from January 2001 to August 2002 in Nova Scotia. Use of preventive strategies with either a Coxib or a GPA along with the nonselective NSAIDs was assessed at the dispensing date (index date) of the first Coxib or NSAID prescription over the study periods. GPAs considered were misoprostol, PPIs and histamine-2 receptor antagonists dispensed at the index date of an NSAID.

RESULTS: In Nova Scotia, of the 14,587 study patients, 37% received a preventive strategy (26.5% a Coxib; 10.5% a GPA+NSAID). In Quebec, 82% of the 225,851 study patients received a preventive strategy (79% a Coxib; 3% a GPA+NSAID).

CONCLUSION: Utilization of preventive strategies in seniors who are particularly at risk for NSAID-associated gastrointestinal complications is much less common in Nova Scotia compared to Quebec. Further studies would identify factors that contribute to this difference.

KEY WORDS: A*ntiinflammatory drug; Coxib; gastroprotective agent; gastrointestinal risk; administrative database*

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PRODUCTION AND USE OF EVIDENCE IN DRUG BENEFIT DECISION MAKING: DECISION MAKERS' VIEWS ON IMPEDIMENTS TO USING AND PRODUCING EVIDENCE OF DRUG EFFECTIVENESS

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Funding Source: Health Canada

BACKGROUND: Public drug plan managers in Canada often lack 'real world' evidence of drug effectiveness when making coverage decisions. Increasingly, they will need to employ innovative policy designs such as drug benefit 'trials' to help establish 'real world' drug effectiveness data.

METHODS: Structured interviews with 30 Provincial, National and Territorial drug plan managers and drug plan evaluators were carried out, transcribed, coded and analyzed. Answers fell into three thematic areas: drug coverage decision making and reassessment, the use of evidence in decision making and the barriers to using more rigorous methods of drug policy evaluation, such as randomized policy trials. Participants read and responded to a "Mock Notice" describing a hypothetical randomized drug benefit coverage trial. **RESULTS:** The major impediments cited to making coverage decisions more evidence-based were political considerations, lack of staff and resources, and difficulties in accessing trusted expertise to carry out proper evaluation. Standard cost-control techniques such as prior authorization, restricted listings or pricing restrictions were preferred over other policy innovations which could assess drug effectiveness and budgetary impacts. While policy makers and drug plan evaluators in Canada agree that more rigorous policy designs are needed to improve the cost effectiveness of drug budgets, there was little agreement on who should carry out these studies.

CONCLUSION: While most plan managers recognize that drug benefit policy making is an intensely political activity, creating better means of gathering crucial impact information through "decision-based evidence-making" represents a rational way to manage conflict arising from drug benefit decision making.

KEY WORDS: *Drug decision making; Organizational decision making; formulary decision making; prescription drug coverage; drug insurance decision making; insurance, pharmaceutical services; formularies*

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RESOURCE UTILIZATION IN DIABETIC PAINFUL NEUROPATHY PATIENTS

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Funding Source: Pfizer Canada Inc.

BACKGROUND: Diabetic painful neuropathy (DPN) is a prevalent problem in patients with Diabetes Mellitus (DM). Diabetic peripheral neuropathy is documented in approximately 30% of people with DM. Despite its high prevalence, little is known about the medical economic burden of DPN in Canada.

METHOD: This study was performed using data from the Régie de l'assurance maladie du Québec (RAMQ) using a random sample representing 15% of the patients covered by the provincial drug plan. Patients with DPN were identified with the ICD-9 codes (250.6 and 357.2). Resource utilization over a one-year period was compared between DPN patients and a control group without DPN matched for age and sex in a 1:1 ratio.

RESULTS: A total of 343 patients with a diagnosis of DPN were identified. For most therapeutic drug categories, the number of patients reporting use was significantly higher in the DPN group than in the control group ($c2 < 0.001$). The average annual number of physician visits (General practitioners and Specialists) was significantly higher in the DPN group (26.7 vs. 9.9; ANOVA < 0.001). The annual average cost of physician services was also significantly higher in the DPN group ($1,295 vs. $562; ANOVA < 0.001).

CONCLUSIONS: Our results indicate that the burden associated with DPN is substantial. This is the first attempt to identify resource utilization associated with DPN in Canada. More research is warranted to evaluate the direct and indirect costs associated with DPN in Canada as well as the impact of DPN on patients' quality of life.

KEY WORDS: *Diabetic painful neuropathy; economic analysis; economic burden; drug utilization*

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SECURITY SYSTEM OF THE REKINDLE WEB APPLICATION

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Institutions: University Health Network, Toronto, Ontario
Funding Source: Amgen Canada Inc. Mississauga, Canada

OBJECTIVE: to improve patient data security and confidentiality using a web application computer-assisted telephone interview (CATI) data collection tool.

METHODS: To describe the security system of the REKinDLE web application created as a data collection tool for a post marketing surveillance study. This security system is used to protect patient health information from unauthorized users. Our application includes standard health measures. It was developed using PHP programming language with Oracle database as backend. The security system uses PHP's session facilities. The initial access to any parts of the system is restricted by an assigned user name and password entered via a form. This name and password pair is then checked against the corresponding pair in the database. Upon successful authentication, session tokens are assigned to the user's browser environment that is used for subsequent access. These session tokens are set to expire after a fixed amount of time.

RESULTS: When using session variables for authentication, data collected through the web application is stored on the server and therefore has additional protection from unauthorized access. It is easier to program; makes code more readable and organized. In addition in the client browser only unique identification number of the sessions is stored.

CONCLUSIONS: Using session variables increases security of the data as well as simplifies the programming process. It creates the opportunity not to pass user name and password from page to page and protects against hackers. This makes application performance more efficient and faster.

KEY WORDS: *Electronic data capture; patient data security; post marketing surveillance study; web application; rheumatology*

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TELITHROMYCIN RESULTS IN FEWER HOSPITALIZATIONS AMONG PATIENTS WITH ACUTE EXACERBATED CHRONIC BRONCHITIS AND COMMUNITY ACQUIRED PNEUMONIA: HEALTH CARE UTILIZATION DATA FROM 4 DOUBLE-BLIND RCTS VS CLARITHROMYCIN AND AMOXICILLIN/CLAVULANIC ACID

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Funding Source: Aventis Pharma

BACKGROUND & METHODS: Community-acquired pneumonia (CAP) and acute exacerbated chronic bronchitis (AECB) requiring hospitalization is a major health concern and cost-driver in the management of these conditions. Health care utilization data have been collected in four randomized double-blind controlled equivalency trials of telithromycin: two in CAP versus clarithromycin, two in AECB versus amoxicillin/clavulanic acid and clarithromycin. Sample sizes in the four trials ranged from 320 to 575 patients. Treatment groups were similar in size and baseline characteristics. Health care utilization data included hospitalizations, outpatient visits, laboratory tests, and antibiotic use. Health care utilization trends across the four studies were compared. Pooled analyses on hospitalization rates were performed.

RESULTS: Health care utilization trends in the four trials indicate fewer hospitalizations, outpatient visits, laboratory tests, and intra-venous antibiotic use among patients randomized to receive telithromycin. Pooled analyses of all four studies showed the rate of hospitalization/100 patients to be 1.4 for telithromycin and 3.2 for its comparators (p=0.0071). Hospital days/100 patients were 10.3 days and 28.1 days for telithromycin and its comparators, respectively (p=0.0099). Pooled analyses on the two CAP studies alone showed similar relative hospitalization rates, also statistically significant.

CONCLUSION: While clinical cure rates are comparable to other antibiotics, resource use among patients taking telithromycin appears to be consistently lower, particularly hospitalizations. Given that hospital costs account for a major portion of direct costs of AECB and CAP in Canada, use of telithromycin in the treatment of AECB and CAP may significantly reduce the total costs of care of these conditions.

KEY WORDS: *Telithromycin; Antibiotics; Community acquired pneumonia; Acute Exacerbated Chronic Bronchitis; Economics; Health Care Resources*

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THE ASSOCIATION BETWEEN PHYSICIAN SPECIALTY AND THE PRESCRIBING OF CHOLINESTERASE INHIBITORS FOR ALZHEIMER'S DISEASE

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Funding Source: CIHR Institute of Aging Doctoral Training Award

BACKGROUND: To examine whether physician specialty is associated with the prescribing of cholinesterase inhibitors for Alzheimer's disease.

METHODS: A self-administered postal questionnaire was mailed to 803 Quebec physicians, including all of the province's geriatricians (n=49), neurologists (n=215), and psychogeriatricians (n=53). The questionnaire was also mailed to 191 general practitioners who took courses on caring for older persons, as well as to a randomly selected sample of 295 general practitioners who did not take such courses. A regression model, formed using a binomial distribution and a Bernoulli variance function, was employed to examine the relation between physician specialty and the proportion of Alzheimer's disease patients who were prescribed cholinesterase inhibitors in physicians' practices. The impact of potential effect modifiers and confounders was assessed using bivariate analyses and stepwise regression.

RESULTS: Compared to general practitioners, other specialist physicians were more likely to prescribe cholinesterase inhibitors to Alzheimer's disease patients. Adjusted odds ratios were 1.90 (95% confidence interval: 1.06, 3.41) for psychogeriatricians, 2.24 (1.12, 4.49) for geriatricians, and 2.31 (1.41, 3.81) for neurologists. Odds ratios were adjusted for the percentage of patients in physicians' practices who had mild Alzheimer's disease or adverse effects from the cholinesterase inhibitor rivastigmine. Other variables, including the total number of Alzheimer's disease patients in physicians' practices and the level of physicians' knowledge regarding cholinesterase inhibitors, did not modify the relation between specialty and prescribing.

CONCLUSIONS: Physician specialty was positively associated with the prescribing of cholinesterase inhibitors for Alzheimer's disease. The association was maintained after adjusting for several covariates.

KEY WORDS: *Alzheimer's disease; physician; prescribing; cholinesterase inhibitor*

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THE CHALLENGES OF ELECTRONIC HEALTH CARE: A RANDOMIZED TRIAL IN DIABETES

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Institutions: McMaster University, Centre for Evaluation of Medicines
Funding Source: Canada Health Infostructure, Partnership Program

BACKGROUND: Physicians and patients frequently miss opportunities to improve the quality of care of diabetes, primarily because of the complexity of managing many (> 14) risk factors over many years with many other providers. Electronic decision support is a potential way to improve prescribing and quality of care.

METHODS: Consenting patients were randomized to shared provider and patient access to a Web-based personal Diabetes Tracker, health profile and medication cost-effectiveness advisory combined with automated telephone reminder system (ATRS), or usual care. Outcomes included diabetes processes and outcomes, access and continuity of care, health information privacy concerns, ease of use and usability.

RESULTS: 503 patients (mean age 61 yr, 50% female, 78% at least completed high school; 19% living alone) were randomized. 54% of patients used computers regularly. While 89.9% endorsed the usefulness of computers to communicate information among their providers or to provide advice to their doctor, 40.1% felt that computers made it harder to keep their health information private. Baseline usefulness scores were high (4.0, 0.6 SD, maximum 5.0). Interim follow-up analyses of 347 patients showed: a high degree of satisfaction (75.9%) with their diabetes care after the use of the tracker system; a slight increase in continuity of care, physician visits, perceived diabetes control but no statistically significant differences between groups.

CONCLUSIONS: There is a high degree of interest in, expectation and acceptance of electronic decision support systems to assist in managing complex diseases such as diabetes. Since many older patients do not use computers or the Internet, flexibility re: paper versions and telephone support appear to be important.

KEY WORDS: *Diabetes; electronic systems; decision support; health information privacy; usability; internet*

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THE CONCEPT OF THE PERCENT WASTED PATIENTS (PWP)

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Institutions: Centre Hospitalier de l'Universite de Montreal
Funding Source: None

BACKGROUND: The aim of this study was to illustrate the waste in health resources due to low drug persistence when preventive strategies with antihypertensive agents, statins and once a day bisphosphonates are initiated.

METHODS: We used the RAMQ database and published literature to determine the number of patients (out of a hundred patients initiating treatment) who have discontinued therapy before one full year for antihypertensive agents, six months for statins and four months for bisphosphonates. These time points were chosen since in RCTs of treatment versus placebo, beneficial effects of treatment usually become apparent on the event-free survival curves after one year for hypertension, six months for statins and four months for bisphosphonates. Patients who discontinue therapy earlier represent a treatment failure in terms of outcomes prevention and from a public health perspective. Their number is expressed as percent wasted patients (PWP).

RESULTS: Using the most conservative estimates, when patients are started on thiazides, the PWP is 37 %. This figure is 26% for CCBs and 25% for ACE inhibitors. For preventive therapy with statins, the PWP is 50%. This figure is 30% for bisphosphonates.

CONCLUSIONS: The concept of the percent wasted patients provides an intuitively understandable representation of waste in resources and opportunity due to poor persistence.

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THE COST OF LUNG CANCER IN ALBERTA

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Funding Source: Partial support: Amersham Health, Cross Cancer Institute, & University of Alberta Dept of Radiology
BACKGROUND: Lung cancer is the leading cause of cancer death and the second most common cancer in Canada. The economic impact of lung cancer is estimated to be over $3 billion dollars per year. To date there have been relatively few Canadian publications on the cost of lung cancer and these publications are largely based on hypothetical modeling. This study is a descriptive analysis of the cost of lung cancer in a 1998 Canadian cohort relative to actual care received.
METHODS: Health care utilization was determined by a chart review of Alberta Cancer Registry identified patients (n=553). Cost estimates were derived from multiple sources and categorized into ambulatory visits, diagnostic imaging, laboratory tests, hospital admissions, and therapy (e.g. surgery, radiation and numerous chemotherapy protocols).
RESULTS: A total of 10,041 health service events were captured totaling an estimated $8.4 million. In descending order the largest proportion of costs were attributed to therapy, hospital admissions and diagnostic imaging. The median case costs for lung cancer ranged $10,028 to $15,350 depending on the type of lung cancer. Costs varied considerably relative to stage of disease and time from diagnosis. The vast majority (i.e. > 90%) of costs were accrued within the first three months after diagnosis. Our estimated case costs are lower than those quoted in the literature and this is expected as we took an institutional economic prospective.
CONCLUSION: This research provides actual care cost estimates and will allow us to verify published estimates that were developed through modeling and opinion.
KEY WORDS: *Health economics; lung cancer; cohort study*

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THE COST OF STAGES OF HEPATITIS C IN CANADA

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Funding Source: Hoffman - LaRoche Canada
BACKGROUND: Previous estimates for the cost of hepatitis C were based on U.S. practice patterns and costs. When developing economic models of hepatitis C treatments, data which reflects Canadian practice are preferred.
METHODS: Using a services list prepared by Bennett (Ann Int Med 127:855 65, 1997) and revised by Nextractor Inc., we revised the list to reflect Canadian practice using clinical information provided by two hepatologists. Cost per service was added using year 2000 provincial unit costs and fees from Alberta. Pre and post transplant services were obtained from published literature.
RESULTS: Results are presented in terms of costs for specific stages and complications of chronic hepatitis C (CHC). Costs include physician, hospital, laboratory tests and outpatient services. Episodic costs, expressed in annual terms are as follows: Mild CHC, $299; Moderate CHC, $503; Compensated cirrhosis, $1,331; Hepatocellular cancer (established), $14,334; Ascites, $3,006 for the first year and $10,463 for subsequent years; Portal hypertensive bleeding, $8,755 first year, $2,293 subsequent years; Hepatic encephalopathy, $17,300 first year, $3,110 subsequent years. Liver transplant costs are $78,017 for first year (includes pre transplant costs) and $6,267 for subsequent years (based partly on Taylor MC, Can J Surg 45:424 34, 2002).
CONCLUSIONS: The cost of managing patients with chronic hepatitis C in Canada depends to a large extent on the stage of infection, clinical path (duration and transition probabilities), form of hepatic decompensation and whether liver transplantation is undertaken. Outpatient drugs should be added to these estimates if a treatment model is undertaken.
KEY WORDS: *Cost, hepatitis, cost effectiveness*

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THE EFFECT OF FORMULARY INCLUSION ON ANTIMICROBIAL EXPENDITURES IN BRITISH COLUMBIA

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Institutions: BC Centre for Disease Control
Funding Source: BC Centre for Disease Control

BACKGROUND: Prescription drug formularies attempt to control drug expenditures. Our objective was to analyze the change in expenditures resulting from changes in formulary status of various antimicrobials, in British Columbia, Canada.

METHODS: The PharmaNet database collects information on all community prescriptions dispensed in the province of British Columbia. Data on the antimicrobial prescriptions dispensed for macrolides: erythromycin, clarithromycin, and antivirals: acyclovir, famciclovir and valacyclovir from September 1995 to December 2000 was collected from PharmaNet's database. Listing status changes during the analytical horizon provided before and after periods of analysis. Cost analysis was completed using manufacturer's list prices. The mean cost/1000 population/day (MC) was calculated from usage levels and unit cost.

RESULTS: During the period of analysis $74,032,538 was spent on the antimicrobial agents identified. Cost was predominantly from erythromycin and clarithromycin expenditures of $24,390,783 and $21,232,404 respectively. The delisting of clarithromycin resulted in MC decreasing from $2.79 to $1.84, a 34% decline. In contrast, the MC of the macrolide comparator, erythromycin, increased slightly from $3.67 to $3.69. The relisting of clarithromycin increased MC by 13% to $2.51. With respect to the antivirals, the listing of valacyclovir resulted in the MC increasing from $0.17 to $0.73, representing a 433% increase; famciclovir had a similar response with the MC increasing from $0.31 to $0.71. Linear regression analysis showed listing status had significant impact on MC.

CONCLUSIONS: Placing antimicrobials on provincial formularies causes increased usage and expenditure. There exists potential for further research on the long term effects on antimicrobial resistance and resulting increased costs.

KEY WORDS: *Formulary expenditures; health economics; antimicrobials; cost*

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THE IMPACT OF DONEPEZIL (DPZ) ON THE COST OF ALZHEIMER'S DISEASE (AD)

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Institutions: Pfizer Canada Inc.
Funding Source: Pfizer Canada Inc.

BACKGROUND: In Canada, the social and economic impact of AD is considerable. Caregiver time (CGT) accounts for over 50% of costs in mild-to-moderate cases, and institutionalization for up to 84% in advanced disease stages. DPZ may reduce symptomatic progression in AD. The objective of this study is to model, over 1 year, the effect of DPZ observed in a European trial on the resource use among Canadian patients.

METHODS: The ACCORD study, an observational cohort study, was used to derive annual resource utilization and cost for 385 mild-to-moderate AD patients. Cost data included resources used by patient and caregiver, excluding CGT and drug expenditures. A cross-sectional regression linked cost of resources with MMSE score, age and gender from the Canadian study. Regression coefficients were used to impute a Canadian cost given each European patient's MMSE score, age and gender, at baseline, weeks 12, 24, 36, and 52. Incremental costs were calculated by comparing the average costs of DPZ and placebo groups.

RESULTS: Accommodation represents 79% of overall costs (excluding CGT and drug costs) and drove the cost difference between groups. Overall costs are associated with MMSE scores. Imputed costs are significantly different between groups after 1 year, with savings of $190 per treated patient over placebo, representing 12% of the DPZ cost.

CONCLUSION: This study demonstrates an economic benefit with a partial offset of DPZ cost, even though a conservative definition of costs was used. Longer term studies beyond 1 year may assist in evaluating the impact of DPZ on disease milestones including institutionalization.

KEY WORDS: *Alzheimer's disease; cost consequence analysis; resource utilization; donepezil, Canada*

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THE LIFETIME COST OF IRESSA (GEFITINIB) IN TREATING PATIENTS WITH NON SMALL CELL LUNG CANCER

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Funding Source: AstraZeneca Canada Inc.

BACKGROUND: Lung cancer is the leading cause of cancer death. Non-small cell lung cancer (NSCLC) tends to be extremely lethal and responds poorly to chemotherapy. Patients who have failed treatment with platinum-based therapies and second-line docetaxel are managed with best supportive care (BSC). IRESSA (gefitinib) is the first selective epidermal growth factor receptor tyrosine kinase inhibitor approved for the treatment of patients with advanced NSCLC who have failed two or more chemotherapy regimens. The objective was to determine the lifetime cost for treating NSCLC patients with IRESSA.

METHODS: The duration of IRESSA treatment was estimated by the time to progression in the IDEAL-2, a phase II clinical trial involving patients with NSCLC who failed at least two chemotherapy regimens that contained platinum and docetaxel. Post progression, patients were assumed to be managed with BSC for the remaining time of survival. Resource utilization during treatment was estimated from the clinical trial. The cost of BSC following chemotherapy was provided by CancerCare Manitoba. Costs were expressed in 2003 Canadian dollars.

RESULTS: In 102 patients treated with IRESSA 250 mg/day there were significant improvements in disease-related symptoms associated with improved objective tumour response. The median time to progression was 59 days and the median time of survival was 185 days. The tolerability profile of IRESSA was mild in comparison with other oncology medicines and there were few serious adverse events. The lifetime cost of treating a patient with IRESSA plus BSC was estimated at $14,496. In sensitivity analyses, that lifetime cost ranged from $13,822 up to $24,915.

CONCLUSIONS: The lifetime cost to treat a patient with IRESSA plus BSC was comparable to other chemotherapies for NSCLC. For example, the lifetime cost of second-line docetaxel was $17,739 (1999 dollars) and for other chemotherapies, lifetime costs ranged from $24,828 up to $41,178 (1995 dollars).

KEY WORDS: *IRESSA, gefitinib, oncology, advanced lung cancer, economic evaluation*

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THYROID DISEASE AND ITS TREATMENT IN RELATION TO MAJOR DEPRESSION IN CANADA

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Funding Source: Alberta Heritage Foundation for Medical Research Clinical Fellowship

BACKGROUND: The Canadian Community Health Survey (CCHS) provided an opportunity to examine the relationship of thyroid disease and its treatment with major depression at the population level.

METHODS: The 2000/2001 CCHS gathered self-reported data on presence of thyroid disease. Current treatment was assessed in 29 of 136 regions with the question "In the past month did you take thyroid medication such as Synthroid or levothyroxine?" Three groups were defined: those without thyroid disease (noTHY), with treated thyroid disease (THY+), and with untreated thyroid disease (THY-). Past-year major depression was assessed with the Composite International Diagnostic Interview Short Form. Analysis included subjects ≥ 18 years who provided depression, thyroid, and treatment data (N=27,707). Proportions with depression were calculated in the three groups. Logistic regression was used to examine depression as a function of age, sex, and thyroid disease/treatment group. Sampling weights and bootstrapping were used.

RESULTS: The overall weighted prevalence of thyroid disease was 5.1%(95%CI:4.8-5.5), while that of depression was 7.3%(95%CI:6.8-7.7). The depression prevalence was 7.1%(95%CI:6.7-7.6) for noTHY, 8.4%(95%CI:6.3-10.5) for THY+, and 17.7%(95%CI:10.7-24.7) for THY-. Logistic regression did not demonstrate a significant difference between the odds of depression for THY+ versus noTHY, adjusted for age and sex (odds ratio 1.2, 95%CI:0.9-1.6, Wald p=0.2). However, THY- had significantly higher adjusted odds of depression than noTHY (odds ratio 2.4, 95%CI:1.4-4.0, Wald p<0.002).

CONCLUSIONS: Results suggest that only untreated thyroid disease is associated with major depression. Limitations include the cross-sectional study design (precluding conclusions regarding causality), and assessment of thyroid disease and treatment by self-report.

KEY WORDS: *Thyroid disease, depression, Canada, prevalence epidemiology*

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USE OF NATURAL MEDICINES IN AN OLDER HOME CARE POPULATION: COMPLEMENTARY OR ALTERNATIVE THERAPY?

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Funding Source: Merck Company Foundation / AHFMR

BACKGROUND: Few researchers have examined the use of complementary or alternative medicines (CAM) in older populations, or evaluated concurrent conventional drug treatment among patients using natural therapies.

METHODS: Subjects included 330 home care clients, aged 65+, participating in a longitudinal study of medication adherence and health-related outcomes. Data on clients' demographic, health and functional status and service utilization patterns were collected using the Minimum Data Set for Home Care. A medication review included all substances used for therapeutic purposes in the past 7 days. Natural medicines were identified based on the Anatomic Therapeutic Classification (ATC) system. Multivariate logistic regression models were employed to examine correlates of natural medicine use including; use of prescribed and over-the-counter (OTC) drugs; use of non-prescribed vitamin & mineral supplements; self-administration of prescription drugs; having a recent physician review of medications; and drug adherence.

RESULTS: Seventy-six subjects (23%) were currently using at least one natural medicine. After adjusting for relevant confounding variables, prescription [OR=0.47; 95% CI=0.24-0.90] and OTC [OR=2.24; 95% CI=1.07-4.68] drug use, and use of non-prescribed vitamin and mineral supplements [OR=6.27; 95% CI=3.36-11.7] remained significant predictors of natural medicine use. Intentional nonadherence with prescribed drugs was also positively associated with the use of natural medicines [OR=1.82; 95% CI=0.97-3.40].

CONCLUSIONS: Lower prescription drug use and higher rates of intentional drug nonadherence suggest that older persons using natural medicines may be seeking alternative, rather than complementary therapies to conventional drug treatment. The higher rates of OTC and non-prescribed supplement use may also be indicative of a propensity for self-treatment among this group.

KEY WORDS: *Complementary medicine; elderly; compliance*

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USE OF PHYSICIAN PRESCRIBING PROFILES TO PROMOTE APPROPRIATE, COST-EFFECTIVE PRESCRIBING OF TOPICAL CORTICOSTEROIDS IN NOVA SCOTIA

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Institutions: Dalhousie University
Funding Source: Drug Evaluation Alliance of Nova Scotia (DEANS), Nova Scotia Dept of Health

BACKGROUND: The objective of this project was to evaluate a Drug Evaluation Alliance of Nova Scotia (DEANS) initiative using physician profiling to promote appropriate and cost-effective prescribing of topical corticosteroids.

METHODS: Administrative claims from the Nova Scotia Seniors' Pharmacare program (NSSPP) were utilized to identify all topical corticosteroids dispensed to Nova Scotia seniors. Prescriptions were summarized at the physician level, and aggregated by Anatomical Therapeutic Classification (ATC). Individual-level physician profiles were mailed in June 2001 for the period April 01, 2000 to March 31, 2001. Re-profiles were mailed in June 2002 containing the original profile and the profile for the period April 01, 2001 to March 31, 2002. The number of prescriptions was compared for the twelve-month period before and after mailing of the profiles.

RESULTS: There were 44.0 prescriptions for topical corticosteroids per physician profiled in 2000/2001 compared to 42.8 prescriptions in 2001/2002 (p=0.10). The costs to the NSSPP were $839 per physician profiled in 2000/2001 and $827 in 2001/2002 (p=0.44). There was a small decrease in the number of prescriptions for potent topical products (23.1 prescriptions/physician 2000/2001 versus 22.1 prescriptions/physician in 2001/2002, p=0.03). Otherwise, changes in utilization and expenditures for topical corticosteroids were not statistically different over the study period.

CONCLUSIONS: An evaluation of the project showed that mailing of unsolicited individual-level profiles did not have meaningful impact on overall prescribing or expenditures for topical corticosteroids over a two-year period. Further work is needed to determine physician attitudes towards such interventions and to examine individual-level changes in prescribing.

KEY WORDS: *Prescribing profiles, topical corticosteroids*

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USING THE WHO ANATOMICAL THERAPEUTIC CHEMICAL/ DEFINE DAILY DOES (ATC/DDD) DRUG CLASSIFICATION SYSTEM (ATC/DDD) TO COMPARE NON-STEROIDAL ANTI-ANFLAMMATORY DRUGS AVAILABLE IN ATLANTIC CANADA

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Institutions: Dalhousie University, Halifax, NS
Funding Source: Canadian Institutes of Health Research Undergraduate Pharmacy Studentship

BACKGROUND: Many Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are on the Canadian market, each with different characteristics, indications and prices. We compared NSAIDs by ATC class, indication and price/DDD.

METHODS: NSAIDs on the Canadian market were identified from the Health Canada Drug Product Database. Indications for each chemical entity were obtained from product monographs in the 2002 CPS. The 2002 Atlantic Pharmaceutical Services Incorporated Pricing Guide was used to obtain prices. Drugs were grouped based on the 2002 WHO ATC/DDD classification system and the price/DDD was determined. Price/DDD was classified as low price (median <$0.50); medium price (median >$0.50 <$1); high price (median >$1).

RESULTS: Twenty-one chemical entities were identified, representing 350 individual NSAID products (DINs). Indications for therapy varied with ATC groups B, C, E, X and H indicated for rheumatoid arthritis and osteoarthritis with other specific groups indicated for conditions such as dysmenorrhea and dental surgery. Fourteen NSAIDs were multisource products. Piroxicam and diclofenac were available from the greatest number of manufacturers (12 and 10 respectively). Using the metric price/DDD, the least expensive NSAIDs for arthritic, musculoskeletal conditions and pain were ibuprofen, naproxen and indomethacin.

CONCLUSION: NSAIDs use by drug class, indication, price/DDD and manufacturer were compared. When used in conjunction with appropriate clinical decision-making, these results can assist clinicians and policy makers in selecting NSAIDs.

KEY WORDS: *Defined daily dose; anatomical therapeutic chemical classification; non-steroidal anti-inflammatory drugs; pricing*

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UTILITY VALUES FOR ERECTILE DYSFUNCTION: AN EVOLVING PARADIGM

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Institutions: Nexus Research Solutions
Funding Source: Pfizer Canada Inc.

BACKGROUND: The socioeconomic impact of erectile dysfunction (ED) has changed with the introduction of oral therapies. Improved public awareness and education have resulted in significant growth in the ED population presenting for treatment. Evidence demonstrates that ED patients and the general public consider ED to be an important aspect of wellbeing. From a policy and funding perspective then it is important to understand patient reported utility for ED.

METHODS: We developed a disease specific utility assessment for use in ED, the Erectile Function Visual Analog Scale (EF-VAS) validated using 164 ED patients. A conversion curve was calculated for the EF-VAS, allowing us to capture the aggregate relationship between study specific VAS values and standard gamble results for known health states, therefore, allowing the calculation of von Neumann-Morgenstern (vNM) utilities.

RESULTS: The resulting conversion curve was comparable to those for other disease states. The calculated vNM utilities were validated against corresponding Health Utility Index (HUI) values. The vNM utilities ranged between 0 and 1.0, with a mean of 0.812 (SD=0.203). The HUI utilities ranged between -0.00457 and 1.0 (mean = 0.798). The value of 0.812 is consistent with other states that have a similar impact on quality of life (QOL), such as benign prostatic hypertrophy (0.90), or a minor stroke (0.81).

CONCLUSIONS: Our study demonstrates that the utility associated with ED is an important consideration, consistent with other disabling conditions. As the impact of ED increases with the growth and aging of the male population a better understanding of the utility of ED is necessary.

KEY WORDS: *Disease-specific utility; erectile dysfunction; quality of life*

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UTILIZATION OF INHALED Â2-AGONIST AND CORTICOSTEROID MEDICATIONS IN 2001/2002: A NOVA SCOTIA AND NEW BRUNSWICK COMPARISON FOR SENIORS 65 YEARS AND OVER IN RELATION TO PHARMACARE FORMULARY POLICY

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Institutions: Dalhousie University
Funding Source: DEANS

BACKGROUND: Inhaled â2-agonist and corticosteroid medications are used for a variety of respiratory illnesses. Long-acting inhaled â2-agonists are costly in comparison to short-acting bronchodilators and they are reimbursed under specific criteria in both the Nova Scotia (NS) and New Brunswick (NB) seniors' pharmacare programs. In addition, reimbursement for NS beneficiaries over the age of 45 was limited to those with reversible airway disease confirmed by spirometry or pulmonary function tests. The objective was to compare utilization for inhaled â2-agonists and corticosteroid medications for beneficiaries of the NS and NB seniors' pharmacare programs.

METHODS: Pharmacy administrative claims databases were accessed for beneficiaries who received at least 2 prescriptions for an inhaled â2-agonist in 2001/2002. Patients were stratified by the number of canisters of inhaled short or long-acting â2-agonist received per year, and the average daily dose of inhaled corticosteroids was determined.

RESULTS: Most seniors using an inhaled short-acting â2-agonist received #4 canisters per year (63% of users in NS and 60% in NB), with few seniors receiving >20 canisters per year (4% in NS, 5% in NB). Most seniors on an inhaled short-acting â2-agonist also received an inhaled corticosteroid (55% in NS, 60% in NB). Prescribing of inhaled long-acting â2-agonists was approximately three times higher in NB than in NS (11.6% of users in NB versus 4.1% in NS).

CONCLUSION: Prescribing of inhaled long-acting â2-agonist medications was higher in NB seniors' pharmacare beneficiaries than in NS beneficiaries. Further work is needed to determine the impact of policies on cost-effectiveness and patient health outcomes.

KEY WORDS: *Drug utilization; formulary policy; respiratory disease*

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UTILIZATION OF TEGASEROD IN CANADA

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Funding Source: Novartis Pharmaceuticals Canada Inc.

BACKGROUND: Irritable bowel syndrome remains a poorly understood condition. Recent research suggests that symptoms may be related to levels of serotonin in the GI tract. Tegaserod has shown efficacy in treating the primary symptoms of IBS-C, namely abdominal discomfort/pain, bloating and constipation. Tegaserod is presently indicated for 12 weeks of treatment per episode. However, some reimbursement authorities fear more frequent or even continuous use of tegaserod. The aim of this study was to determine the use and utilization pattern of patients using tegaserod.

METHODS: Data for first-time users of tegaserod between July and December 2002 were extracted from the Brogan Inc. private payer database. Users were followed for a period of 12 months provided that they were still in the database at the end of this period. Information on the number of claims, tablets and days that tegaserod was supplied was obtained. In addition, the province of residence, age group and sex of the patient was gathered.

RESULTS: A total of 3,357 patients (88% women) with a median age of 40 to 49 years were identified. Their average use of tegaserod was 78 days per patient per year. More than 75% of patients used it for less than 90 days and only 1.2% used it for the entire period of follow-up.

CONCLUSIONS: These results fall within the estimate (98 days) the manufacturer provided at the time of submissions to reimbursement authorities. These results should reassure reimbursement authorities that this product is not used more frequently than expected.

KEY WORDS: *Tegaserod; cost; utilization; budget impact; irritable bowel syndrome*

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A PRELIMINARY DESCRIPTION OF THE ROLE OF THE PRIMARY CARE PHARMACIST: AN ANALYSIS OF DRUG-RELATED PROBLEMS

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BACKGROUND: There is a need to better understand and describe a primary care pharmacist role so that this can be communicated to other team members.

OBJECTIVE: To enhance our understanding of the features of the direct patient care role by analyzing pharmacist's initial medication assessments for patients referred by the team members.

METHODS: Initial pharmacist assessment was reviewed for patients who were referred to the pharmacist for comprehensive medication management. Data was gathered from the pharmacy chart, pharmacist consult notes, and medical chart. Drug-related problems (DRP) were described and characterized in terms of the type of DRP, nature of the pharmacist's role and the nature of pharmacist-physician collaboration.

RESULTS: A total of 105 initial patient medication assessments were reviewed that identified a total of 202 DRPs (average of 1.9 DRPs/patient, range: 0 to 9). The most common issues included: patient's gaps in medication knowledge (29.7%), need for additional therapy (22.3%), adverse drug reactions (16.8%), and drug interactions (6.4%). There were two types of approaches used by the pharmacist (a) proactive role (68.2%), (b) problem-solving (31.7%). The nature of the collaboration between the pharmacist and the patient was either shared care mode for 48.5% of the DRPs or more independent care role (51.5%).

CONCLUSIONS: Four features of pharmacist role: (a) need to define the functions; (b) need for accessibility for patients of all ages; (c) integration within the team to allow for proactive role; and (d) flexibility of pharmacist's involvement to allow for either shared care or independent patient care.

KEY WORDS: *Primary care; pharmacy; drug-related problems*

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A COMPREHENSIVE EVALUATION OF AN ANTICOAGULATION MANAGEMENT SERVICE (AMS): ADEQUACY OF ANTICOAGULATION AND PATIENT OUTCOMES

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BACKGROUND: To minimize the risk of bleeding and thrombosis, it is crucial that patients prescribed warfarin are appropriately anticoagulated.

OBJECTIVE: To assess the adequacy of anticoagulation in an AMS, and quantify major bleeds and thromboembolic events.

Methods: Consecutive patients managed in ambulatory AMS over 18 months. The primary endpoint was adequacy of anticoagulation assessed by the Rosendaal method, using the target INR + 0.5 and excluding the first 30 days of management. All major bleeds and thromboembolic events were adjudicated by an expert panel of physicians that defined the event, and then determined the contribution of the AMS by using a 5-point Likert-type scale ranging from highly unlikely to highly likely.

RESULTS: A total of 268 patients were eligible, 64% were male and the mean age was 59 $\pm$ 16 years. The majority had atrial fibrillation (41%), 27% had venous thromboembolism, and 19% had valve replacements. Overall, patients are within their desired INR range 69% of the time (median 71%). From a total of 89 events occurring over 130.5 patient years, major bleeding and thromboembolism accounted for 11 (0.08/patient year followed) and 7 (0.05/patient year followed) events, respectively. Panelists classified the AMS's role in the majority of major bleeds to be highly unlikely (8), and 1 was highly likely. For thromboembolic events, six were classified as highly unlikely and one was neutral.

CONCLUSIONS: Given the referral biases for more difficult to manage patients of this population, the AMS is achieving reasonable INR control, with little contribution to adverse events.

KEY WORDS: *Anticoagulation or Warfarin; INR; Practice Evaluation; Patient Outcomes*

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ENSURING ACCESS AND SPEEDY EVALUATION: THE CARDIAC EASE PROGRAM IN REVIEW

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BACKGROUND: Cardiologist consultation is the entry point for patients to receive applicable testing/procedures and optimal medical management. For non-urgent consultations access to these services is delayed for individual physicians. Current systems in tertiary care are cumbersome due to the lack of a formalized process to triage and book patients, while ensuring appropriate testing prior to the consultation.

OBJECTIVE: To improve access and efficiency of tertiary care cardiology consultative services for non-urgent referrals by establishing a multidisciplinary program.

METHODS: A programmatic approach with two distinct components was implemented – an intake team and multidisciplinary rapid response clinic. The intake team offers a single point of entry for referring physicians via telephone. A Nurse Practitioner (NP) or Doctor of Pharmacy (PharmD) and secretary, in consult with a cardiologist when necessary, arrange appointments based on patient acuity, availability and booking of critical tests, and cardiologists. Also, a new multidisciplinary consult process was created. The EASE clinic was structured to have the PharmD/NP complete the initial history and physical exam, present the case and recommendations to the cardiologist, have the cardiologist see the patient, discuss the plan, and complete documentation while the plan is implemented and coordinated. A detailed program evaluation is underway, and will evaluate clinic processes.

DISCUSSION: This team approach aims to improve access/efficiency of cardiology consultation by employing qualified non-physician advanced practitioners to triage patients, coordinate appropriate testing, undertake patient assessments, and develop the treatment plan within a collaborative practice. Resultantly, we anticipate a reduction in both waiting lists and time.

KEY WORDS: *Program Development or Program implementation; Health outcomes; Interdisciplinary or Multidisciplinary Care; Cardiology Consultation*

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A COMPREHENSIVE EDUCATIONAL PROGRAM FOR PHARMACISTS IN ANTICOAGULATION MANAGEMENT

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BACKGROUND: To reach our goal of optimizing anticoagulation management at the level of the community, we capitalized on existing infrastructure (namely pharmacists) to proactively deliver this care.

OBJECTIVE: To describe a program developed to prepare pharmacists to independently manage anticoagulation therapy.

METHODS: The educational program consisted of three components. Firstly, an interactive, web-based module (PHARMALearn-Anticoagulation) was created to provide the learner with an overview of anticoagulation management. This case-based, stand-alone educational tool provided a foundation for anticoagulation management upon which subsequent components could build. Secondly, a four week experiential component was implemented. Here, the learner gained hands-on experience under the direct supervision of experienced clinicians in managing a diverse group of patients. Thirdly, a self-directed component required completion of objectives with reading materials to prepare learners for therapeutic discussions with the clinicians, ensuring that the didactic material was directly applicable by learners to patient care. These covered the following topics: an antithrombotic overview, venous thromboembolism, atrial fibrillation/stroke, valvular heart disease/replacement, warfarin initiation, managing critical INRs, LMWH bridging therapy, and logistics of initiating/operating an AMS. Formal evaluation of the educational program involves interviews with pharmacists at the completion of the learning program and at 3-6 months following implementation of anticoagulation management at their practice site. Eleven pharmacists with varying backgrounds and practice sites have completed the program to date, and the evaluation is underway.

DISCUSSION: This comprehensive training program aims to provide a diverse group of pharmacists with the knowledge and confidence to independently prescribe anticoagulant therapy within a collaborative environment.

KEY WORDS: *Program Description or Program Implementation; Educational Delivery; Anticoagulation Management*

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PHARMACIST INTEGRATION WITHIN COMMUNITY FAMILY PHYSICIAN GROUP PRACTICES: A QUALITATIVE STUDY

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BACKGROUND: Pharmacists have not been commonly providing care within community family physician practices in Canada.

OBJECTIVE: To conduct a qualitative analysis from multiple perspectives to obtain information about feasibility, implementation issues, generalizability, and sustainability of a practice model for pharmacists integrated into community family physician group practices.

METHODS: This was a qualitative study that used phenomenological approaches. Data were gathered during individual interviews with a purposeful sample of physicians, pharmacists, funders, and decision makers. A semi-structured interview guide was used and included questions on pharmacist role, processes of implementation and collaboration, and barriers to practice. Transcripts from taped interviews were transcribed and cleaned. Verbatim statements were coded independently by at least two people to identify common significant statements and themes. Interviews continued until saturation.

RESULTS: There were sixteen participants. Findings were categorized into four areas: compensation, confidentiality, working in a collaborative environment, and implementation. Few participants looked beyond the government for funding. Concern for patient confidentiality and privacy were universal among the interviewees. Pharmacist accessing patient information in a family practice setting (vs a community pharmacy) was felt to be acceptable with patient consent. The practice model was cautiously acceptable to physicians, funders, and decision makers. Implementation barriers included lack of an effective working model and physicians and pharmacists not knowing enough about the others skills or how to communicate well in a collaborative environment.

CONCLUSIONS: Pharmacist integration into family physician practice was cautiously accepted if funding was available however there are numerous issues to address to facilitate successful implementation.

KEY WORDS: *Pharmacist; primary care; collaboration*

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THE FOLIC ACID COMMUNITY PHARMACIST EDUCATION TRIAL (FACT): A PILOT STUDY

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BACKGROUND: Lack of knowledge about or use of peri-conceptual folic acid has been associated with an increased incidence of neural tube defects. Despite many recent educational efforts a substantial proportion of women in Canada are still unaware of the recommendation for folic acid in pregnancy or did not take them prior to conception.

OBJECTIVE: To determine the effects of a folic acid training workshop pilot for pharmacists on Pharmacist Self-Reported Knowledge And Skills.

METHODS: This was a pre-post pilot study. Included pharmacists were volunteers who responded to advertisements in pharmacy journals or to mailed invitations. Participants attended a five-hour workshop that contained the following elements: needs assessment and immediate post workshop evaluation, didactic presentations, patient simulations, interactive case discussions, and feedback/debriefing. A questionnaire was administered to ascertain the self-reported knowledge (10 point scale pre and post) and skills (post only). A paired t-test was used to test differences in knowledge before and after the workshop.

RESULTS: Seventeen pharmacists participated in the workshop. Knowledge scores changed from 4.7 ± (SD, 2.3) before the workshop to 7.5 (SD, 1.4) after the workshop ($p<0.0001$). Sixteen learning needs were identified as addressed by the workshop. Twelve participants (71%) reported that they felt more confident in applying the information to practice. Simulated patient role play was most commonly identified as the most useful workshop component.

CONCLUSIONS: The workshop improved pharmacists' short term self-reported knowledge and met numerous learning needs. The effect on the use of folic acid by patients requires evaluation in a larger study.

KEY WORDS: *Folic acid; pharmacist training; education*

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PATIENT SATISFACTION WITH PHARMACIST-MANAGED ANTICOAGULATION MANAGEMENT SERVICES

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BACKGROUND: Comprehensive evaluation of pharmacist-managed anticoagulation management services should include not only clinical and economic outcomes, but also patient satisfaction.

OBJECTIVE: To assess patient satisfaction with pharmacist-managed, university hospital based anticoagulation management services (AMS).

METHODS: A 34 item questionnaire, using a 5 point Likert-type rating scale, was mailed between April 2001 and June 2003 to 174 AMS patients who had at least 4 months of services.

RESULTS: Response rate was 74%. Respondents were similar to non-respondents, mean age of 61 years, with 62% being male. More respondents were still receiving services from AMS. Their major diagnoses were: atrial fibrillation (36%) and DVT/PE (16%). At least 90% were very satisfied with the AMS in 16 of the 27 items that assessed promptness, communication, knowledge, etc. In 4 of 6 items comparing patients' expectations to the actual service they received, practice exceeded expectations. Importantly, 73% of respondents perceived that AMS improved their health. Most of these respondents have complex medical conditions that are not expected to improve. Given a choice for the future, 87% of those still receiving AMS would choose to continue to be managed by AMS, 5% would choose to be managed by their family doctor and 8% expressed no preference.

CONCLUSIONS: Patients in a pharmacist-managed, university hospital based AMS reported high levels of satisfaction with the services provided, perceived improvement in their health, and preferred this model over anticoagulation management by their family doctor. Further study will examine patient satisfaction with pharmacist-managed AMS in satellite clinics throughout the province.

KEY WORDS: *Patient satisfaction; Anticoagulation; Pharmacy*

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VALIDITY OF A PRESCRIPTION CLAIMS DATABASE TO ESTIMATE REFILL MEDICATION ADHERENCE IN OLDER PERSONS.

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BACKGROUND: Prescription claims data have been used to estimate refill medication adherence through calculations of continuous medication availability (CMA) and continuous medication gap (CMG) values. Few studies compare these calculated rates against other measures of medication adherence.

OBJECTIVE: The primary objective of this study was to assess the validity of CMA and CMG calculated from the Manitoba prescription claims database (DPIN) against pill count medication adherence, targeting overall medications and Angiotensin Converting Enzyme Inhibitors (ACEIs).

METHODS: Subjects, recruited through community pharmacies, were eligible for study if they were 65+ years old; noninstitutionalized; taking 2 or more 'discrete' prescribed medications, including an ACEI; and willing to provide informed consent. During 3 home interviews spaced 2 months apart, pill counts on all prescribed medicines were conducted. Twenty months of DPIN data were also collected on each subject.

RESULTS: Using 10 months post-interview DPIN data, 714 drugs dispensed to 142 subjects met our criteria for CMA/CMG calculations. Pill count adherence was calculated for 653 drugs used by 148 subjects. Using 5 adherence categories (poor, partial, excellent, partial high, poor high), the concordance between CMA and pill count for overall medications was [411/522 (78.7%)] and for ACEIs [89/101 (88.1%)] with no systematic differences (McNemar's p=0.6837; McNemar's p=0.097, respectively). Using 3 categories of adherence, CMG and pill count showed even better concordance of 438/522 (83.9%) for overall medications and 96/101 (95.0%) for ACEIs, although systematic differences were noted for overall medications (McNemar's p=0.012).

CONCLUSIONS: There was good agreement between DPIN and pill count derived measures of medication adherence for overall medications and ACEIs.

KEY WORDS: *Refill; Medication; Adherence*

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RETROSPECTIVE CHART REVIEW OF CURRENT PRACTICES IN THE TREATMENT OF COPD EXACERBATIONS

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BACKGROUND: Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) are a common cause of hospital admission. While guidelines exist, limited information is available on the management of hospitalized COPD patients.

OBJECTIVE: To review the management of COPD exacerbations in our facility, to determine our compliance with the guidelines and to assess management where no specific guidelines exist. Specifically reviewed were the utilization of long-acting beta-agonists (LABAs), antibiotics, optimal ipratropium dosages, inhaled and systemic steroids, and systemic steroid use in COPD patients with pneumonia.

METHODS: A list was generated of patients who received ipratropium in 2002. Charts were then reviewed for patients admitted for the treatment of a COPD exacerbation.

RESULTS: 61 patients with a mean age of 73 +/-10.5 and a 50.1 +/-28.5 pack year smoking history were studied. LABA use was associated with an increase in Troponin/CK compared with non-use (56% vs. 29%, p = 0.03). 90% of patients received systemic steroids with similar distribution among low, moderate and high cumulative doses received. Concomitant inhaled and systemic steroids were administered to 11% of patients. 92% of patients diagnosed with pneumonia received systemic corticosteroids. Excluding pneumonia patients, antibiotics were used by 83% of patients who met Anthonisen's criteria versus 68% who did not (NS). 40% of antibiotic courses were given parenterally. There were no differences in duration of stay regardless of drug use in our review.

CONCLUSIONS: Substantial variation in the management of COPD exacerbations in patients who require hospitalization was observed. Compliance with the current guidelines could be improved.

KEY WORDS: *COPD; Exacerbation; Inpatient management*

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AN EXPLANATORY MODEL OF PRACTICE THAT DESCRIBES THE PATIENT CARE ROLE OF A PRIMARY CARE PHARMACIST IN AN INTERDISCIPLINARY FAMILY PRACTICE SETTING

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BACKGROUND: To achieve effective collaborative medication management primary care practitioners need to better understand the role of various health care providers.

OBJECTIVE: The purpose is to describe and characterize components of a patient care pharmacy practice model in a team-based interdisciplinary family practice setting.

METHODS: An existing prototype of a pharmacist practice in interdisciplinary family practice was examined using a modified action research approach. Data was gathered through (a) an initial retrospective reflection; (b) retrospective chart review of 105 patient assessments; and (c) patient case studies that were chosen by purposeful and theoretical sampling until theoretical saturation was achieved. Grounded Theory qualitative method was used to gather and analyze the data. The emergent categories were brought back to the primary care pharmacist (member checking) for validation and then reviewed by other two other pharmacists who provide care in the same family practice setting. Theoretical validity was addressed through the use of constant comparison method.

RESULTS: The practice model consists of three key components: (a) seven key principles that guide the pharmacist's practice, (b) a repertoire of nine primary care pharmacist functions that support medication-prescribing practice, patient's medication-taking practice, and medication-dispensing practice; and (c) a process to define the nature of pharmacist's involvement and level of pharmacist's responsibility.

CONCLUSIONS: The explanatory model developed extends our understanding of potential innovative pharmacists' roles in collaborative medication management in primary care and offers a framework that can be used to further define and develop pharmacists; roles and functions in interdisciplinary primary care team-based practices.

KEY WORDS: *Primary care; pharmacy; collaborative medication management*

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TRENDS IN FLUOROQUINOLONE USE IN NOVA SCOTIA HOSPITALS FROM 1997-2002

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BACKGROUND: Antimicrobial resistance results in increased morbidity, mortality, and costs to the health care system. Evidence suggests an association between antimicrobial use in hospitals and antimicrobial resistance. Fluoroquinolones are useful against a variety of bacterial infections; however, overuse and inappropriate use may occur.

OBJECTIVE: To describe the use of fluoroquinolones in the provincial hospital system and to develop a benchmark system to provide a means of comparison among the district health authorities.

METHODS: Purchasing Data expressed as drug volume and expenditures were obtained from the Provincial Drug Distribution Program (PDDP) and aggregated using the World Health Organization (WHO)/ Anatomical Therapeutic Chemical (ATC) Defined Daily Dose (DDD) system for the fiscal years of 1997-2002. Fluoroquinolone drug utilization was expressed as DDD/ occupied acute care bed day/ year.

RESULTS: All provincial hospitals administering the study drugs were included (n= 31). Total fluoroquinolone use increased over the five years studied; mean DDD/1000 bed days 48 in 1997 vs. 163 in 2002. Variations in usage existed between districts, and between hospitals according to size (small, medium, large). Norfloxacin use decreased 78%, while use of oral and IV ciprofloxacin increased by 52% and 240% from 1997 -2002. Levofloxacin use also increased in this time period.

CONCLUSION: The WHO ATC/ DDD system combined with hospital drug purchasing and administrative information is a simple, descriptive tool to aid drug utilization. Comparing the utilization of fluoroquinolones is a practical instrument for benchmarking to examine the impact of policies and interventions to improve prescribing.

KEY WORDS: *Drug Utilization; Fluoroquinolones; Antimicrobials*

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DETERMINING THE PREVALENCE AND PREDICTORS OF SENIORS' BLOOD PRESSURE AWARENESS AND MONITORING PRACTICES

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BACKGROUND: Awareness of blood pressure (BP) status and engagement in self-monitoring can help patients become more involved in their therapeutic management. Although seniors are perceived as passive recipients of healthcare, predictors of BP awareness and self-monitoring are unknown.

OBJECTIVES: To determine the extent to which seniors are aware of their BP status and targets and to determine predictors of BP self-awareness and self-monitoring.

METHODS: In this cross-sectional sub-study of the Community Hypertension Assessment Trial (CHAT), consecutive patients, aged 65 years and older, completed a 32-item written survey as part of their involvement in BP monitoring clinics. Information was collected on sociodemographics, general health, knowledge of current BP readings, and type of treatment and follow-up received in the previous year.

RESULTS: Of 582 respondents, 232 (40%) recalled their most recent BP reading. Of 196 (33.7%) patients who were told their target BP by their physician, 71 (12.2%) reported values consistent with guideline recommendations. Multivariate logistic regression analysis revealed that older patients (>80 years) were significantly less likely to know their BP values than younger patients (OR = 0.54; 0.34-0.87), while patients with a post-secondary education (OR = 1.74; 1.12-2.69), who were diagnosed with hypertension (OR = 2.48; 1.53-4.01), and who were told their target BP (OR = 2.74; 1.72-4.35) were more likely to know their BP. Independent predictors of patient self-monitoring were age >80 years (OR = 0.49;0.30-0.78), living with someone (OR = 2.05; 1.32-3.17), having been diagnosed with hypertension (OR = 2.27; 1.42-3.63), and being told their target BP (OR = 2.50; 1.53-4.07). Taking antihypertensive medication was a positive predictor of awareness and self-monitoring on univariate, but not multivariate analysis.

CONCLUSIONS: Seniors had a relatively poor understanding of their BP readings and targets, but a subset were knowledgeable and potentially suited to be more actively involved in therapeutic management.

KEY WORDS: *Blood pressure; awareness; monitoring*

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THE USE OF DROTRECOGIN IN THE MANAGEMENT OF SEPSIS IN FRASER HEALTH, BC.

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BACKGROUND: Formulary approval for drotrecogin was based on a single randomised, controlled trial. Concerns were raised about its safety and benefit in a large and diverse community setting. A multidisciplinary team defined the usage criteria and appropriate controls were put in place to ensure compliance.

OBJECTIVES: To determine if patients met the usage criteria and to evaluate outcomes such as bleeding complications, mortality and length of stay.

METHODS: A prospective, observational evaluation.

RESULTS: In a period of 8 months, drotrecogin use was considered in 10 patients. Eight patients received the drug and 2 were unsuitable for therapy due to contraindications. In the group that received the drug (n=8), the mean age was 53.3 years and the mean APACHE II score just prior to therapy was 28.7. Three patients (37.5%) had a defined source of infection and the rest were culture negative. However, all patients were deemed to have suspected infections. Four patients completed the full 96-hour infusion. Reasons for not completing therapy included bleeding (n=1), death prior to completion (n=1) and change in diagnosis (n=2) to vasculitis and severe cardiomyopathy. The mortality rate within seven days of treatment was 50% and major bleeding rate (during infusion) was 37.5%.

CONCLUSION: All of our patients met the approved criteria for drotrecogin at the beginning of the infusion. However, only 4 patients completed the therapy. Both the mortality and major bleeding rates in our patients were high. Further experience is required to delineate benefits of this drug in a community setting.

KEY WORDS: *Drotrecogin; Activated Protein C; Sepsis*

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DOES RESTRICTING ACCESS OF CIGARETTES TO INPATIENTS WITH SCHIZOPHRENIA PRECIPITATE NICOTINE WITHDRAWAL? EXAMINING SMOKING MOTIVES.

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BACKGROUND: With a prevalence of smoking as high as 90%, individuals with schizophrenia not only consume more nicotine that the general population but also more than individuals with other psychiatric diagnoses. Although psychosocial motives have been offered to explain this phenomenon, it is the neurobiological determinants of nicotine that have provided the strongest evidence associating cigarette smoking with schizophrenia.

OBJECTIVE: The objective of this study is to determine if differences exist in smoking motives between patients having restricted access to their cigarettes and those patients that have free access to their cigarettes.

METHODS: This cross sectional study recruited patients with schizophrenia or schizoaffective disorder from Riverview Hospital, British Columbia. Eligibility for the study required that the subjects be in good physical health and be current smokers. Smoking behavior was evaluated using the Fagerstrom Test for Nicotine Dependence along with a validated questionnaire that assesses and identifies both pharmacological and non-pharmacological smoking motives.

RESULTS: Subjects that had restricted access to cigarettes scored significantly higher on the motive representing addictive smoking compared to subjects that have free access to their cigarettes (10.6 ± 3.1 vs. 9.4 ± 3.2 respectively, $\chi 2=4.54$, df=1, p=0.03). Addictive smokers have been described as those individuals that are dependent on nicotine to avoid unpleasant withdrawal symptoms. In addition, addictive motive scores have also been shown to correlate with anxiety- a core symptom of nicotine withdrawal. On this note, the subjects in our study that had restricted access to cigarettes were prescribed significantly more anxiolytics compared to subjects that had free access to cigarettes (67.9% vs. 32.4% respectively, $\chi 2=7.75$, df=1, p=0.005).

CONCLUSION: Restricting the access of cigarettes to individuals with schizophrenia may result in a greater degree of nicotine dependency, withdrawal and perhaps increased anxiety.

KEY WORDS: *Schizophrenia; Smoking; Withdrawal*

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EVALUATING THE IMPACT OF PHARMACARE POLICIES AND EDUCATIONAL STRATEGIES ON THE REIMBURSEMENT OF RESPIRATORY MEDICATIONS IN THE NOVA SCOTIA SENIOR POPULATION

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BACKGROUND: In February 2000, the Nova Scotia Seniors' Pharmacare Program (NSSPP) announced changes to wet nebulization respiratory therapy reimbursement criteria. To facilitate the transition, the Drug Evaluation Alliance of Nova Scotia coordinated a multifaceted intervention to educate patients, and health care providers.

OBJECTIVE: To assess the impact of the reimbursement policy and educational interventions on utilization of respiratory medications for Nova Scotia seniors.

METHODS: Interrupted time-series analysis was used to identify changes in the utilization of respiratory medications. The administrative claims database from the NSSPP identified all beneficiaries who received at least 1 respiratory medication in the 12 months prior to the study (reference year). These individuals were then grouped into the wet nebulization cohort (received at least one prescription for wet nebulization therapy in the reference year) or the control cohort (received at least one prescription for inhaled respiratory medications without wet nebulization therapy in the reference year).

RESULTS: Before policy implementation, 21,864 NSSPP beneficiaries were identified as respiratory medication users. 5,129 had at least 1 prescription for wet nebulization therapy. There was a sharp decrease in the use of wet nebulization immediately following the announcement. Increases in the use of short-acting beta2-agonists and anticholinergic agents were also identified in the wet nebulization cohort. These patterns were not observed in the control cohort.

CONCLUSIONS: The lack of change in other respiratory medications in the control cohort supports the effect of the policy and interventions. Further work is needed to determine the impact on cost-effectiveness and patient health outcomes.

KEY WORDS: *Respiratory medications; formulary policy; drug evaluation*

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USING TRANSLATIONAL RESEARCH TO ASSIST THERAPEUTIC DECISIONS IN THE MANAGEMENT OF AN EMERGING PATHOGEN.

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BACKGROUND: Over the past decade, Stenotrophonas.maltophilia has emerged as a high-risk pathogen and important cause of opportunistic infections in hospitalized patients. However, treatment is complicated by high rates of resistance to multiple antibiotics except trimethoprim/sulfamethoxazole (T/S), which is often the drug of choice.

OBJECTIVE: Information regarding antibiotic pharmacodynamics is limited, and therefore our goal was to study T/S, ceftazidime, ciprofloxacin, gentamicin and tobramycin alone and in combination against S.maltophilia in an in vitro pharmacodynamic infection model.

METHODS: Clinical S.maltophilia isolates were used to simulate bacteremia in an immunocompromised host. All isolates were susceptible to T/S and susceptible or intermediately susceptible to at least one other agent. Antibiotics alone and in combination were studied with doses administered Q12h for 48h. Individual antibiotic t½s were used in the model to simulate unbound antibiotic serum concentrations achieved with recommended doses in humans.

RESULTS: T/S alone was bacteriostatic at best against all isolates despite susceptible MICs. Only ceftazidime alone was active against one isolate. Antibiotic combinations were significantly more active producing bacterial reductions of 1.3 to 4.0 log10 colony forming units (CFU)/ml at 24 h and 0.6 to 2.2 log10 CFU/ml at 48 h ($P < 0.0001$). Intra-experimental changes in MIC were not detected.

CONCLUSIONS: In conclusion, antibiotic combinations are significantly more active against S. maltophilia in vitro even if the individual agents are inactive alone or only intermediately susceptible based on MIC. These pre-clinical data support the use and further study of antibiotic combinations in the management of serious S. maltophilia infections.

KEY WORDS: *Antibiotics; in vitro model; pharmacodynamics*

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