ABSTRACTS

American College of Clinical Pharmacy
1999 Annual Meeting
October 24–27 ▪ 1999
H. Roe Bartle Hall Convention Center
Kansas City Marriott Downtown Hotel
Kansas City ▪ Missouri

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Adverse Drug Reactions/Drug Interactions

1. Analysis of adverse drug reactions in hospitalized patients. *Mark A. Malesker, Pharm.D.*, Kay Ryschon, M.S., Patricia J. Lang, Pharm.D., Mike A. Galt, M.S., George W. Benecke, Jr., MBA; Alegent Health Immanuel Medical Center; Creighton University; Omaha, NE.

PURPOSE: The significance of monitoring adverse drug reactions (ADRs) in hospitalized patients is clearly documented. This study used multivariate analysis to evaluate characteristics of reports identified by the hospital's spontaneous ADR reporting system.
METHODS: Data from 954 reports over 5 years were reviewed. All reports met the hospital's definition of an adverse drug reaction. The type of reaction, medication(s) involved, severity scale, probability algorithm, likelihood of preventability, outcome classification, and patient demographics were analyzed for each report.
RESULTS: Adverse reactions occurred in 1.72% of admissions during this period and 19.3% met the criteria for being preventable. Involvement of drug interactions was the most common reason for being preventable (50.3%) and increased in frequency over this time ($p<0.00001$). There was no significant change in the number of reports per year (NS). Fifty-seven percent of the patients were female (NS) and the mean age increased significantly over the study period ($p<0.0001$). Reactions were rated as probably or definite in 54.9% of patients. Sixty-one percent had reactions that required treatment. Reactions for warfarin ($p<0.0001$) and digitalis ($p=0.0011$) increased over the study period, while morphine ($p=0.0026$) and diatrizoate ($p<0.00001$) decreased. The most frequent reaction type was dermatologic in nature (33%). Analgesics and antipyretics were the most prevalent drug category causing the ADR (18.4%). Ninety-one percent of patients recovered without sequelae.
CONCLUSION: These results suggest that ADRs are an important clinical issue. Women and older patients experiencing a drug interaction appear to be at highest risk for the development of an ADR.

2. A comparison of adverse effects of enoxaparin in patients with renal insufficiency versus normal renal function. *Anthony T. Gerlach, Pharm.D.*, Saloni B. Tanna, Pharm.D., Kerry K. Pickworth, Pharm.D., Julie F. Barnes, Shiv Seth, Ph.D.; Ohio State University, Columbus, OH.

PURPOSE: Although enoxaparin is predominately eliminated renally, no guidelines are available for dosing in renal insufficiency. The purpose of this study is to compare the incidence of adverse effects of enoxaparin in patients with normal renal function to patients with renal insufficiency (serum creatinine ≥ 2.0 mg/dl).
METHODS: Data were retrospectively collected on any patient who received two or more doses of enoxaparin between March 1 and December 30, 1998. Charts were reviewed for demographics, renal function, and adverse effects. A major bleed was defined as: a documented cerebrovascular, gastrointestinal or retroperitoneal bleed, use of transfusions, or drop in hemoglobin greater than 2 g/dl with symptoms (i.e., hypotension or hypoxia). Minor bleeds were defined as ecchymosis, epistaxis, hematoma, hematuria, hemoptysis or petechiae without drop of hemoglobin greater than 2 g/dl. Chi squared tests were preformed for statistical analysis.
RESULTS: One hundred three patients were evaluated, 50 with normal renal function and 53 with renal insufficiency.

	Normal Renal Function n=50	Renal Insufficiency n=53	p value
Average age	64	65	NS
Average weight	85 kg	82 kg	NS
Percent male	56%	55%	NS
Minor bleeds	10	11	NS
Major bleeds	1	16	<0.05
Total bleeds	11	27	<0.05
All-cause death	2	9	<0.05

CONCLUSIONS: Patients receiving enoxaparin with renal insufficiency might be at a higher risk for bleeding complications, including death. The use of enoxaparin in patients with renal insufficiency should be discouraged, and heparin should be used.

Cardiology

3. Evidence-based appraisal of randomized, controlled trials in hypertension. *Robin R. Feuge, Pharm.D.*, Elaine Chiquette, Pharm.D., Kelly Montgomery, M.P.H.; University of Texas at Austin; University of Texas Health Science Center at San Antonio; Audie L. Murphy Memorial Veterans Hospital; San Antonio Cochrane Center, San Antonio, TX.

PURPOSE: To index the randomized, controlled trials (RCT) in the Cochrane Hypertension Review Group registry in order to facilitate future use and searches of the database.
METHODS: RCT were found through a comprehensive MEDLINE search (1966 to 1998) using a validated filter and MESH terms/text words to identify RCT related to hypertension. Data recorded from the abstracts included descriptors of intervention (length and type of therapy), setting (e.g., essential, pregnancy, peri-operative), trial design, population, and outcomes.
RESULTS: Of 4300 abstracts found by the search, 3700 have been reviewed to date. From the abstracts we identified 2620 definite randomized trials and 47 systematic reviews. More than half (85%) were of less than 6 months duration and only 5% followed patients for more than 1 year. The vast majority of trials assessed efficacy of drug therapy (80%). Diet, exercise, and salt restriction were utilized in less than 10% of trials. Most trials looked exclusively at blood pressure or physiologic effects (69%); a minority addressed antihypertensive intervention's impact on morbidity and/or mortality (8%) or quality of life (2.4%). Most trials included middle aged men; other specific populations studied included elderly (9%), diabetes (3%), and severe hypertension (3%). Few trials included young adults with hypertension or subjects with multiple comorbidities.
CONCLUSIONS: Few RCT provide evidence to guide practitioners in long-term management of hypertension. Most trials focus on disease-oriented outcomes versus patient-oriented outcomes such as morbidity, mortality, or quality of life. Specific populations such as young adults and subjects with multiple risk factors deserve further study.

4. Platelet activity in vascular disease and the dose of aspirin. *Robert L. Talbert, Pharm.D.*, Anne D. Leonard, B.S.N., Lesly A. Pearce, M.S., Robert G. Hart, M.D.; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX; Axio Research Corporation, Seattle, WA.

Antithrombotic trials with aspirin (ASA) using doses of 75-1500 mg/day have demonstrated a 25% reduction in vascular events in high-risk patients with no apparent relationship to dose (Chest 1998;114 suppl:475S). The national recommendation is ASA 50-325 mg/day for secondary prevention of vascular events.
PURPOSE: To determine if ASA dose differentially affects markers of platelet activity in elderly people with vascular disease.
METHODS: Patients receiving daily ASA for prevention of stroke or myocardial infarction due to atherosclerotic disease of the coronary or cerebral vessels were studied. Participants took buffered ASA 325 mg/day for 1 month, and then were randomly allocated to one of three ASA groups for 1 month: ASA 81 mg/day (n=17); ASA 325 mg/day (n=16); or ASA 1300 mg/day (n=16), following which they returned to 325 mg/day for 1 month. Serum D-dimer (DD), prothrombin activation fragment F1.2 (F1.2), thromboxane-B_2 (TXB2), and urinary 11-dehydro-thromboxane-B_2 (DTXB2) were obtained at weeks 4, 8, and 12.
RESULTS: DD, F1.2, DTXB2, and TXB2 were not different across the three groups at 4 weeks on ASA 325 mg; median values (n=49) for DD, F1.2, DTXB2, and TXB2 were 138 ng/ml, 1.3 nM, 124 pg/mg creatinine, and 0.3 ng/ml, respectively. Comparing values 4 weeks later (ANOVA-ranked differences), DD ($p=0.009$), DTXB2 ($p=0.002$), and TXB2 ($p=0.001$) were significantly affected by change in aspirin dose, while F1.2 ($p=0.3$) was not. Median within patient changes in DD were 5.1, 11, and -14 ng/ml, respectively, for the 325->325, 325->81, and 325->1300 mg ASA groups. Similarly, changes in DTXB2 were 5.0, 45, and -29 pg/mg creatinine, and in TXB2 were -0.03, 1.4, and -0.1 ng/ml, respectively. After 4 weeks more of ASA 325 mg, levels of DD ($p=0.2$), DTXB2 ($p=0.6$), and TXB2 ($p=0.5$) were not significantly different from those following the initial 4 weeks among the

3 groups. Patients > 75 (n=13, median = 181 ng/ml) were more likely to have higher levels of DD (p=0.04, ANOVA of ranks) than < 75 (n=36, median = 104 ng/ml). Patients with hypertension (n=32, median = 0.4 ng/ml) were more likely to have higher levels of TXB2 (p=0.03, ANOVA of ranks) than others (n=17, median = 0.2 ng/ml).
CONCLUSIONS: Higher doses of ASA had a greater effect on indices of platelet activity and in DD activity in elderly patients.

5. β_2-adrenoceptor polymorphisms and hypertension. *Larisa M. Humma, Pharm.D.*, William G. Farmerie, Ph.D., Margaret R. Wallace, Ph.D., Julie A. Johnson, Pharm.D.; University of Florida, Gainesville, FL.

PURPOSE: The β_2-adrenergic receptor (β_2AR) plays a role in blood pressure regulation by mediating peripheral vasodilation and plasma renin release. Polymorphisms of the β_2AR gene commonly occur at codons 16 (Arg or Gly) and 27 (Gln or Glu), with the Gly16 and Gln27 forms displaying increased receptor down-regulation. The objective of this study was to determine if β_2AR polymorphisms at codons 16 and 27 differ significantly between hypertensive subjects and published normotensive controls.
METHODS: Blood samples were collected from 67 hypertensive subjects for genotyping of the β_2AR. Following isolation of genomic DNA, β_2AR genotype was determined by polymerase chain reaction and direct sequencing. β_2AR genotypes and allele frequencies of hypertensive subjects were compared to those of 212 published normotensive controls (Liggett, et al. J Clin Invest 1998;102:1534-9).
RESULTS: The allele frequencies at codon 27 of the β_2AR differed between hypertensives (Gln27 = 77%, Glu27 = 23%) and published normotensive controls (Gln27 = 58%, Glu27 = 42%), $p<0.05$. Hypertensives had a higher frequency of the homozygous Gln27 genotype than normotensives (64.2% versus 31.6%, respectively; $p<0.05$). The frequency of the Gln/Glu genotype at codon 27 was higher in normotensive (52.9%) than hypertensives (25.4%), $p<0.05$. β_2AR genotypes and allele frequencies at codon 16 were not significantly different between hypertensives (Arg16 = 42%, Gly16 = 58%) and normotensives (Arg16 = 38%, Gly16 = 62%).
CONCLUSION: This study suggests an association between β_2AR polymorphisms at codon 27 and HTN. The Gln27 genotype may attenuate β_2AR-mediated vasodilation in the periphery and contribute to the development of HTN.

6. Comparison between the efficacy and safety of simvastatin and atorvastatin. *Kwok-Kin Mah, B.Sc. (Hons)*; Singapore General Hospital, Singapore.

PURPOSE: The study compared atorvastatin 10 mg and simvastatin 20 mg in patients with hypercholesterolemia or combined hyperlipidemia in terms of efficacy and safety.
METHODS: Medical records of 118 patients who had been on simvastatin monotherapy, and later switched to atorvastatin, were reviewed. Lipid profiles and liver function test (LFT) results were documented.
RESULTS: Atorvastatin 10 mg produced a further drop in total cholesterol (-8.75%, $p<0.005$) and low-density lipoprotein cholesterol (LDL-chol; -13.45%, $p<0.005$) when patients were switched from simvastatin 20 mg to atorvastatin 10 mg. High-density lipoprotein cholesterol (HDL-chol) and triglyceride levels were not significantly changed. There was also no statistical difference in alanine aminotransferase (ALT) levels when patients were switched from simvastatin 20 mg to atorvastatin 10 mg. No patients experienced elevation of ALT above 3 times the upper limit.
CONCLUSION: Atorvastatin 10 mg appears to be more potent than simvastatin 20 mg in terms of total cholesterol and LDL-chol lowering. Safety, in terms of ALT elevation, was not significantly different. As such, in clinical practice, atorvastatin 10 mg should not be considered to be equipotent with simvastatin 20 mg.

7E. The effects of controlled-onset extended-release verapamil on early morning rise in blood pressure and forearm vascular resistance. *B. Nhi Nguyen, Pharm.D.*, Mohammad Noujedehi, Pharm.D., Robert B. Parker, Pharm.D., Jay M. Sullivan, M.D., Julie A. Johnson, Pharm.D.; University of Florida, Gainesville, FL; University of Tennessee, Memphis, TN; Trinity Mother Francis Hospital, Tyler, TX.

Controlled-onset extended-release verapamil (COER-V) is designed so that drug concentrations rise sharply in the early morning to coincide with the peak incidence of cardiovascular events. We studied the effects of COER-V on 24-hour ambulatory blood pressure (ABP), in particular the early morning rate of BP rise. We also compared the forearm vascular resistance (FVR) diurnal pattern in hypertensives to normotensives, and studied the effects of COER-V on the FVR diurnal pattern in hypertensives. Baseline 24-hour ABP was recorded and FVR was determined by venous occlusion plethysmography at 7 a.m., 2 p.m., and 9 p.m. in 19 untreated hypertensives. COER-V 180 mg was given at 9 p.m., and doses were titrated to achieve DBP ≤ 90 mm Hg. After ≥ 4 weeks on the final dose, 24-hr ABP and plethysmography studies were repeated and S-verapamil concentrations were determined over 24 hours by HPLC. COER-V reduced ABP throughout a 24-hr period ($p<0.05$). Twenty-four hour, daytime and nighttime ABP (mean ± SD) at baseline was 142/89 ± 11/7, 145/92 ± 11/8, and 134/84 ± 12/9 mm Hg, and on COER-V was 130/81 ± 7/9, 133/84 ± 11/8, and 121/75 ± 7/7 mm Hg, respectively. No significant differences were found in the slopes of the early morning rise in BP, or change in morning trough to peak BP at baseline and on drug (+36/29 ± 9/9 mm Hg vs + 33/25 ± 17/13 mm Hg), respectively. S-verapamil concentrations were highest at 7 a.m.: 41 ± 36 ng/ml. COER-V flattened the FVR curve although there were no significant differences at any single time point (baseline 7 a.m.: 58 ± 24, 2 p.m.: 48 ± 13, and 9 p.m.: 55 ± 19 vs COER-V 7 a.m.: 51 ± 23, 2 p.m.: 51 ± 17, and 9 p.m.: 54 ± 17 mm Hg/ml/min/100 g).
CONCLUSIONS: COER-V is an effective antihypertensive that lowers BP throughout a 24-hr period, but it does not blunt the early morning rate of BP rise despite peak S-verapamil concentrations in the early morning. The FVR diurnal pattern in hypertensives is different from normotensives. COER-V does not significantly alter the FVR diurnal pattern in hypertensives.
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8E. Effect of inhaled β-agonists on outcome in heart failure. *Eric J. Stanek, Pharm.D.*, Mark A. Munger, Pharm.D., Edward M. Gilbert, M.D., David DeNofrio, M.D., Gregory J. Stoddard, Ph.D., Christy M. Evans, Pharm.D., Evan Loh, M.D.; Philadelphia College of Pharmacy, University of the Sciences in Philadelphia; University of Pennsylvania Medical Center, Philadelphia, PA; University of Utah, Salt Lake City, UT.

PURPOSE: Decreased lung volumes with mild obstructive symptoms are common in patients with CHF. Inhaled β-agonist (β) therapy may improve these abnormalities. Although chronic oral/IV β therapy decreases CHF survival, the effect of inhaled β therapy on CHF survival is unknown.
METHODS: We retrospectively reviewed the records of 709 CHF patients at two treatment centers. We studied age- and sex-matched β exposed (β+; n=87) and unexposed (β-; n=87) CHF cohorts to determine the effect of β therapy on survival, using a composite endpoint of death, heart transplant, or ventricular assist device implant.
RESULTS: Cohorts were similar upon study entry: age 55 ± 12 years; male 58%; dilated cardiomyopathy 58%; smoking 54%; EF 22 ± 8%; NYHA class III-IV 60%; VO_2 16 ± 6 ml/min/kg; ACE inhibitor 84%; digoxin 83%; β-blocker 18%. β+ patients had greater history of asthma/COPD (72% vs 5%, $p<0.001$), lower FEV_1 (1.9 ± 0.7 L vs 2.6 ± 0.9 L, $p<0.01$), and FEV_1/FVC (64 ± 15% vs 77 ± 7%, $p<0.01$) than β- patients. Four-year event free survival was greater in β+ patients (50.3% vs 39.7%, p=0.068). Significant independent predictors for survival are:

Factor	Adjusted RR (95% CI)	p value
β+	0.60 (0.37, 0.95)	0.03
NYHA class I-II	0.49 (0.26, 0.89)	0.02
Ischemic etiology	2.14 (1.32, 3.49)	0.002
Smoking	1.72 (1.08, 2.78)	0.02
β-blocker	0.47 (0.23, 0.97)	0.04

CONCLUSIONS: Based on this retrospective analysis, β exposure may be safe in CHF patients and may be associated with improved outcome. Prospective studies to validate and determine the mechanism of these effects is needed.
Presented at the 3rd Annual Scientific Meeting of the Heart Failure Society of America, San Francisco, CA, September 23, 1999.

9. Care of hypertensive patients participating in a clinical trial compared with matched non-participating controls. *Rex W. Force, Pharm.D., BCPS*, Mimi Macdonald, L.P.N.; Idaho State University, Pocatello, ID.

PURPOSE: One of the basic tenets in defining the applicability of medical research to clinical practice is to determine whether the patients enrolled in trials are similar to the patients cared for in everyday practice (identifying selection and/or intervention biases). Data from the neonatal ICU and oncology literature indicate better outcomes in patients enrolled in clinical trials as compared with those not participating. We set out to determine if patients enrolled in a trial of antihypertensive medications received similar care as compared with patients not enrolled.
METHODS: In a case-control design, patients participating in a clinical trial of therapy for hypertension (group 1, n=27) were compared with age and disease-state matched controls (group 2, n=27) receiving care in the same clinic. Patients in both groups had significant cardiovascular risks and patients in group 2 met randomization criteria for the trial that group 1 was in. Comparisons were made between the two groups with regard to blood pressure control and number of clinic visits over a 1-year period with one-way ANOVA.
RESULTS: Group 1 patients had lower mean SBP, mean DBP and more clinic visits when compared with group 2 (SBP 133 vs 145 mm Hg; DBP 77 vs 87 mm Hg; clinic visits 6.1 vs 3.6, all $p<0.002$).
CONCLUSIONS: Participation in a clinical trial results in lower BP values and more follow up as compared with usual clinic care. The design of clinical trials should include efforts to improve the generalizability of results since the care provided in trials may not mirror usual clinic care.

10. Comparison of cerivastatin 0.3 mg to pravastatin 20 mg, and cerivastatin 0.4 mg to pravastatin 40 mg in 1030 hypercholesterolemic patients. *Carlos Dujovne, M.D.*, Peter Kwiterovich, M.D., Donald Hunninghake, Marcia Poland; Kansas Foundation for Clinical Pharmacology, Overland Park, KS; Johns

Hopkins University, Baltimore, MD; University of Minnesota, Minneapolis, MN; SmithKline Beecham, Collegeville, PA.

Cerivastatin (CER) is a synthetic HMG-CoA reductase inhibitor effective at microgram range.
PURPOSE: To compare the efficacy and safety of CER 0.3 and 0.4 mg to pravastatin (PRA) 20 and 40 mg.
METHODS: 1030 hypercholesterolemic patients were diet-stabilized for 6-8 weeks prior to randomization to CER 0.3 or 0.4 mg QD, or PRA 20 or 40 mg QD for 8 weeks. 970 patients were evaluated per protocol analysis. The primary comparison was reduction in LDL-C.
RESULTS: CER 0.3 and 0.4 mg reduced serum LDL-C to a statistically significantly greater extent than PRA 20 and 40 mg, respectively. Results are expressed as mean (± SEM) percentage change from baseline (mg/dl) to endpoint.

Variable	CER 0.3 (n=235)	PRA 2 (n=244)	CER 0.4 (n=252)	PRA 40 (n=239)
LDL-C BL	174 ± 2.4	172 ± 1.9	176 ± 2.4	181 ± 2.5
mean %Δ	-29.6 ± 0.8[a]	-26.8 ± 0.7	-34.2 ± 0.8[b]	-30.3 ± 0.8
Total-C BL	259 ± 2.7	258 ± 2.2	261 ± 2.6	268 ± 2.8
mean %Δ	-20.5 ± 0.6[a]	-18.5 ± 0.6	–23.5 ± 0.6	-21.8 ± 0.6
LDL-C/HDL-C BL	3.7 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.8 ± 0.1
mean % Δ	–32.0 ± 0.8	-31.1 ± 0.8	–36.8 ± 0.8[b]	–34.2 ± 0.9
% of patients at NCEP goal	53.0%	44.0%	62.3%	57.4%

[a]p<0.025; CER 0.3 vs PRA 20; [b]p <0.025; CER 0.4 vs PRA 40

Adverse events and discontinuation rates were similar. Myopathy associated with CK elevations >10x upper limits of normal was not observed in either CER- or PRA-treated patients.
CONCLUSION: CER had greater efficacy than PRA in lowering serum LDL-cholesterol levels in hypercholesterolemic patients with no difference in safety.

11. Efficacy and safety of cerivastatin and pravastatin in the treatment of patients with primary hypercholesterolemia. *Elijah Saunders, M.D.,* Keith Ferdinand, M.D., Laurence G. Yellen, Melvin J. Tonkon, M.D., Marcia Poland, M.S.; University of Maryland Medical Center, Baltimore, MD; Heartbeats Life Center, New Orleans, LA; Cardiology Associates Medical Group of East San Diego, San Diego, CA; Cardiology Associates Medical Group, Anaheim, CA; Smith-Kline Beecham, Collegeville, PA for the Cerivastatin Study Group.

PURPOSE: Cerivastatin, a member of the statin class of lipid-lowering agents, is currently available in the U.S. at dosages 0.3 mg, and 0.4 mg daily. This study compares the efficacy and safety of cerivastatin 0.3 mg QD to that of pravastatin 20 mg QD.
METHODS: In this randomized, double-blind, parallel group study across 28 centers, patients with primary hypercholesterolemia with and without documented coronary heart disease underwent 6-8 week dietary run-in prior to randomization to treatment with cerivastatin 0.3 mg or pravastatin 20 mg for 8 weeks. Plasma lipid profiles and safety measures were assessed.
RESULTS: Cerivastatin reduced LDL-C and total-C to a significantly greater extent than pravastatin, presented as percent change (± SEM) from baseline (mg/dl, ± SEM) of plasma lipids in efficacy valid patients.

Lipid variable	Parameter	Cerivastatin 0.3 mg n=202	Pravastatin 20 mg n=200
LDL-C	baseline	179.0 ± 2.0	172.3 ± 2.1
	% Δ	-31.1 ± 0.8*	-26.0 ± 0.8
Total-C	baseline	264.6 ± 2.2	258.2 ± 2.5
	% Δ	-21.1 ± 0.6*	-17.8 ± 0.6
HDL-C	baseline	50.9 ± 0.9	50.9 ± 0.9
	% Δ	6.5 ± 0.8	4.7 ± 0.8
TG	baseline	173.9 ± 4.5	175.2 ± 4.5
	% Δ	-8.5 ± 1.7	-9.1 ± 1.7

*p<0.0001 vs pravastatin

65.1% of patients treated with cerivastatin and 63.3% of patients with pravastatin achieved NCEP-defined LDL-C target goals. Both drugs were well tolerated; the most commonly reported adverse events were headache and sinusitis.
CONCLUSION: Cerivastatin 0.3 mg was better than pravastatin 20 mg in reducing LDL-C, and enables a large proportion of patients with primary hypercholesterolemia to achieve NCEP-target goals.

12E. Pharmacological and non-pharmacological risk factors for hypertensive crisis. *James E. Tisdale, Pharm.D.,* Michael B. Huang, Pharm.D., Steven Borzak, M.D.; Henry Ford Hospital, Detroit, MI.

PURPOSE: To test the hypotheses: 1) risk of hypertensive crisis (HC) is increased in patients with poorly controlled blood pressure (BP), heart failure, or chronic renal failure, and 2) diuretics, β-blockers, ACE inhibitors, or calcium channel blockers reduce the risk of HC.
METHODS: This was a retrospective case-controlled study of 664 urban hypertensive patients. Sources of data were a health system database, a health maintenance organization database, and medical record review. Cases consisted of 164 hypertensive patients who presented to the emergency department (ED) with systolic BP ≥ 180 and/or diastolic ≥ 110 mm Hg and symptoms of HC. Controls consisted of 500 age, sex, and race-matched patients selected from 21,371 outpatients with an ICD-9 code for essential hypertension (401.0) who never had an ED presentation for HC.
RESULTS: Mean BP upon ED presentation in the case group was 198 ± 21/109 ±14 mm Hg. Multivariate odds ratios (95% CI) for HC were:

History of heart failure	3.56 (1.06-11.91)
Prior systolic BP (per mm Hg)*	1.02 (1.01-1.03)
Prior diastolic BP (per mm Hg)*	1.02 (1.00-1.04)
Clonidine	2.11 (1.04-4.29)
Diuretics	0.42 (0.27-0.65)
β-blockers	0.53 (0.29-0.96)
Calcium channel blockers	0.51 (0.34-0.77)

*BP during previous randomly selected outpatient clinic visits

CONCLUSIONS: ED visits for hypertensive crisis are associated with prior heart failure and less well-controlled hypertension. Therapy with β-blockers, diuretics, or calcium channel blockers is associated with a reduced risk of HC, while clonidine therapy is associated with an increased risk.
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13E. Risk factors for QTc interval prolongation induced by intravenous haloperidol. *James E. Tisdale, Pharm.D.,* Neeta B. Amin, Pharm.D., Nagaraja Sharma, M.D., Howard Rosman, M.D.; Henry Ford Hospital, Detroit, MI.

PURPOSE: To determine the incidence of haloperidol (H)-induced QTc interval prolongation in critically ill patients, and to test the hypothesis that H-induced QTc interval prolongation is related to dose, pretreatment QTc interval, female sex, and/or history of ischemic heart disease.
METHODS: This was a retrospective case-controlled study of 215 critically ill patients with pretreatment QTc interval ≤ 450 ms who received intravenous H for agitation. Patients were excluded if they had other metabolic, pharmacological, or neurological risk factors for QTc prolongation, defined as on-treatment QTc > 450 ms. Demographics , comorbid conditions, H dose, and QTc intervals were compared in patients who developed QTc prolongation vs those who did not.
RESULTS: QTc prolongation developed in 107 (49.8%) patients. By univariate analysis, longer pretreatment QTc interval (p=0.03), higher H dose within 24 hours prior to maximum QTc, (p<0.001), higher total H dose (p<0.001), and longer duration of therapy (p=0.03) were risk factors. Multivariate analysis results:

	QTc > 450 ms	QTc < 450 ms	p value
Pretreatment QTc (ms)	409 ± 29	400 ± 28	0.02
Total H dose (mg)	264 ± 539	71 ± 88	0.05
Caucasian race	47%	34%	0.08
Duration of H therapy (hours)	76 ± 74	57 ± 62	0.37
Female sex	34%	39%	0.46
24-hour H dose (mg)	82 ± 129	31 ± 42	0.56

CONCLUSIONS: QTc interval prolongation associated with intravenous H occurs frequently in critically ill patients. Longer pretreatment QTc interval is a risk factor for H-induced QTc interval prolongation.
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14. The 0.4 mg dose of cerivastatin: comparative safety and efficacy of cerivastatin 0.3 mg versus fluvastatin 40 mg. *Donald Hunninghake, M.D.,* Carlos Dujovne, M.D., Evan Stein, M.D., Ph.D., William Insull, M.D., Steven Ripa, M.D., Michael Shan, Ph.D.; University of Minnesota, Minneapolis, MN; Kansas Foundation for Clinical Pharmacology, Overland Park, KS; Metabolic and Atherosclerosis Research Center, Cincinnati, OH; Baylor-Methodist Lipid Research Clinic, Houston, TX; Bayer Corporation, West Haven, CT for the Cerivastatin Study Group.

Cerivastatin (CER) is a synthetic HMG-CoA reductase inhibitor that lowers LDL-cholesterol (LDL-C) by 30% at the 0.3 mg daily dose.
PURPOSE: To determine the safety of CER 0.4 mg when given over 26 weeks; and, to compare the efficacy of CER 0.4 mg to CER 0.3 mg or fluvastatin 40 mg (FLUV).
METHODS: In this double-blind, multicenter trial, 908 hypercholesterolemic patients underwent 10 week lipid stabilization before randomization to treatment with CER (0.3 mg or 0.4 mg) or 8-week treatment with placebo, then FLUV, all given QD.
RESULTS: CER 0.4 mg was more effective than FLUV in reducing LDL-C, total-C, and triglycerides (TRIG), and in elevating HDL-C. Results are expressed as mean percentage change from baseline to endpoint.

	8-weeks			24 weeks		
Variable	CER 0.3 (n=200)	CER 0.4 (n=408)	placebo (n=190)	CER 0.3 (n=194)	CER 0.4 (n=385)	FLUV (n=185)
LDL-C baseline	191.8	187.4	191.7	191.3	187.3	190.1
% change	-30.8*#	-33.6#	-0.2	-30.0*#	-33.4#	-23.0
Total-C	-21.5*#	-23.5#	0.5	-20.3*#	-23.0#	-16.0
Triglyceride	-11.3	-12.0	4.5	-4.1*	-10.4#	-4.9
HDL-C	7.8#	8.1#	0.5	6.6	7.7#	4.6

*p<0.01 from CER 0.4; #p<0.02 from placebo/FLUV

Both drugs were well-tolerated. Myalgia occurred in ≤ 5% of both treatment groups. Discontinuations due to adverse events were similar (≤ 7%). CK elevations >10x upper limits of normal (ULN) occurred in ≤ 3 patients per group. Incidence of elevated plasma transaminase levels (> 3x ULN) were also similar (range 0-2.2%).
CONCLUSION: CER produces greater LDL-C lowering (-33%) than FLUV (-23%) at 1% of daily dose with no added safety concerns.

15. Reduction in major bleeding and length of hospitalization following percutaneous coronary interventions with abciximab: impact of a targeted clinical pharmacy education program. *Paul P. Dobesh, Pharm.D., BCPS*, Jonathan E. Lakamp, Pharm.D., BCPS; St. Louis College of Pharmacy; St. Luke's Hospital, St. Louis, MO.

PURPOSE: Controlled clinical trials have demonstrated that weight-adjusted heparin dosing, early sheath removal, and avoidance of post-procedure heparin can reduce the incidence of bleeding in patients undergoing percutaneous coronary interventions (PCI) with abciximab. We evaluated the impact of a clinical pharmacy education program on PCI-associated bleeding.
METHODS: In an attempt to reduce PCI-associated bleeding, an educational program focusing on steps to minimize this complication was developed by clinical pharmacists and presented to invasive cardiologists and nursing staff in a 493-bed community hospital. Bleeding rates, adherence to weight-adjusted heparin dosing recommendations, time of sheath removal, post-procedure heparin use, and length of hospitalization (LOH) were compared retrospectively in patients undergoing PCI with abciximab before (5/97-4/98; n=28) and after (6/98-11/98; n=55) presentation of the educational program.
RESULTS: Compared to the pre-education period, patients receiving PCI with abciximab after presentation of the educational program displayed a decreased incidence of major bleeding (1.8% vs 14.3%; p=0.042), shorter median indwelling sheath time (7.5h vs 13h; p=0.011), reduced post-PCI heparin use (20% vs 82%; p<0.001) and reduced median LOH (2.0 vs 4.5 days; p<0.001). Adherence to weight-adjusted heparin recommendations did not improve significantly in the post-education period (29% vs 38%; p=NS).
CONCLUSIONS: A clinical pharmacy education program targeted toward invasive cardiologists and cardiology staff can reduce bleeding complications and LOH in patients undergoing PCI.

16. Outcomes of abciximab use in patients undergoing percutaneous coronary intervention: preliminary results in the community hospital setting. *Paul P. Dobesh, Pharm.D., BCPS*, Jonathan E. Lakamp, Pharm.D. BCPS; St. Louis College of Pharmacy; St. Luke's Hospital, St. Louis, MO.

PURPOSE: Controlled clinical trials have shown significant reductions in the composite of death and myocardial infarction (MI) following the use of abciximab in patients undergoing percutaneous coronary intervention (PCI). It is not known if similar results can be achieved outside of large controlled studies conducted primarily in the tertiary care environment. We evaluated our institution's initial experiences with the use of abciximab in patients undergoing PCI to determine the relative success of this therapy in the community hospital setting.
METHODS: Medical records were reviewed and telephone follow-up was conducted with 83 patients who underwent PCI (48 MI, 26 unstable angina, and 9 stable angina) with abciximab at our facility between May 1997 and November 1998. Occurrence of death/MI at 30 days and 6 months post-PCI were recorded. These data were compared (chi squared analysis) with published results obtained from major controlled trials with abciximab.
RESULTS: Comparison of death/MI at 30 days (p=0.106) and 6 months (p=0.098) post-PCI revealed no significant difference between our community hospital and the published clinical trials.

	Death/MI	
	30 Days	6 Months
Community hospital (n=83)	4.8%	6.0%
EPIC (n=708)	5.8%	6.9%
EPILOG (n=935)	3.8%	5.8%
EPISTENT (n=794)	3.0%	5.6%
RAPPORT (n=241)	4.6%	8.7%

CONCLUSIONS: Initial experiences with the use of abciximab in patients undergoing PCI in our institution suggest that results comparable to those obtained in controlled trials can be achieved in the community hospital setting. Once a larger number of patients have been treated, subsequent re-evaluation of this experience will be necessary to confirm these findings with greater confidence.

17. Combination diuretics: a comparison of sequential versus simultaneous dosing (the CODI study). *T. Kristopher Harrell, Pharm.D.*, Barry K. Rayburn, M.D., John A. Farringer, Pharm.D., Stephen E. Bakir, M.D.; UAB Health System, Morton, MS.

PURPOSE: This study compared sequential versus simultaneous intravenous combination diuretic therapy to determine if sequence of administration is a factor in removing fluid from congestive heart failure patients.
METHODS: The study was an open label, randomized, crossover pilot study. Efficacy was primarily assessed through measurement of urine sodium excretion over 6 hours. Secondary measures included urine potassium excretion over six hours, total inputs and outputs over 6 and 24 hours, changes in weight, and changes in blood urea nitrogen and serum creatinine. Patients were randomized into one of two treatment groups. Each patient served as his or her own control and had to receive both sequential and simultaneous treatments to be evaluated.
RESULTS: Of the nine patients enrolled in the study, seven patients were evaluated. The remaining two were not evaluated because they received only one treatment. With regard to urine sodium excretion over six hours, five of the seven patients demonstrated a better response from simultaneous rather than sequential therapy. Average urine sodium excretion over six hours for simultaneous dosing was 175.3 mEq versus 129.8 mEq for sequential dosing. Net fluid loss at both six and twenty-four hours favored simultaneous dosing. With regard to change in weight and change in blood urea nitrogen and serum creatinine, there appeared to be no difference between simultaneous versus sequential dosing.
CONCLUSIONS: These data suggest it may be more beneficial to administer intravenous combination diuretic therapy simultaneously rather than sequentially. Further data collection is needed with a larger sample size to determine significance.

18E. Cytochrome P450 induction improves endothelial dysfunction in insulin resistance. Prasad V.G. Katakam, M.D., Ph.D., Michael R. Ujhelyi, Pharm.D., *Allison W. Miller, Pharm.D.*; University of Georgia; Medical College of Georgia School of Medicine; Augusta VA Medical Center, Augusta, Georgia.

PURPOSE: Impaired endothelium dependent relaxation in insulin resistant (IR) rats is due to a defect in endothelium derived hyperpolarizing factor (EDHF). EDHF may be a by-product of cytochrome-P450 (CP) metabolism. Hence increased CP activity may correct the IR induced EDHF defect.
METHODS: Rats were randomized to control (C; n=32) and IR (n=32). Each group was further randomized to treatment (n=48) or placebo (n=16). CP inhibition and induction was achieved by miconazole (Mic; 3 day) and phenobarbital (PB; 3 and 14 days). Blood pressure (BP) and in vitro vascular function was assessed. Specifically, in small mesenteric arteries, acetylcholine (ACh) and EDHF mediated relaxation were determined.
RESULTS: Both 3 and 14 day treatment of PB improved ACh induced E_{max} from 44 ± 4% for placebo to 70 ± 7% and 88 ± 3% after 3 and 14 days, respectively (p<0.05). In addition, 3 and 14 day PB improved EDHF mediated relaxation from 12 ± 4% for placebo to 40 ± 4% for day 3 and 59 ± 9% for day 14 (p<0.05). Also, 14 day PB normalized the BP in IR rats. PB did not affect C. Mic reduced maximal relaxation (E_{max}) to ACh in C (67 ± 8 % in Mic vs 92 ± 4 % in placebo, p<0.05). Similarly, EDHF mediated relaxation was reduced in Mic treated C. Mic also induced an elevation of BP in C. Mic did not affect IR.
CONCLUSIONS: Cytochrome P450 induction results in restoration of EDHF mediated relaxation and normalization of BP in IR rats while CP450 inhibition leads to impaired EDHF mediated relaxation and elevation of BP in C rats.
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19. Rate control in post-CABG atrial fibrillation: a comparison of beta-blocker versus calcium channel antagonist with and without digoxin. *Daniel E. Hilleman, Pharm.D.*, Thomas L. Lenz, Pharm.D., Richard L. Wurdeman, Pharm.D.; Creighton University, Omaha, NE.

PURPOSE: Atrial fibrillation (AF) is a common complication following CABG surgery. The outcome of 275 episodes of post-CABG AF ≥ 1 hr duration treated with a beta-blocker (BB) or a calcium channel antagonist (CA) was evaluated.
METHODS: A retrospective chart review of 431 consecutive CABG and 50 valve implant surgeries was conducted. Two hundred seventy-five episodes of AF ≥ 1 hr were treated with a BB or a CA with or without baseline digoxin (DIG) therapy. Success was defined as cardioversion (CV) to sinus rhythm or heart rate control (HRC) < 90 bpm. Time to success was also recorded as a primary outcome parameter.
RESULTS: One hundred sixty episodes of AF were treated with BB (72 = esmolol; 28 = IV metoprolol; 60 = PO metoprolol) and 115 episodes of AF were treated with CA (58 = IV diltiazem; 32 = PO diltiazem; 25 PO = verapamil). Baseline DIG therapy was equally distributed between the BB and CA treatment groups. BB had significantly greater success than CA (81% vs 54%; p=0.03). Baseline DIG therapy did not influence results. Time to CV or HRC was significantly shorter with esmolol than with other BB or any CA. Incidences of hypotension, bradycardia, heart block, and heart failure were not different between BB and CA.
CONCLUSIONS: BB are superior to CA for post-CABG AF management. IV esmolol is associated with the shortest time to successful treatment. BB remain the drugs of choice for prevention and treatment of post-CABG AF.

20. Conversion of recent onset atrial fibrillation with IV amiodarone: a meta-analytic evaluation. *Daniel E. Hilleman, Pharm.D.*, Sarah A. Spinler, Pharm.D.; Creighton University, Omaha, NE; Philadelphia College of Pharmacy, Philadelphia, PA.

PURPOSE: To evaluate the efficacy and safety of IV amiodarone (IVA) in the conversion of recent onset atrial fibrillation (AF) using a meta-analytic technique.
METHODS: MEDLINE literature search identified 23 published articles including IVA in the treatment of recent onset AF. Four trials were placebo-controlled, 15 were active-controlled (propafenone 4; digoxin, 3; flecainide 2; DCC 1; verapamil 1; quinidine 2; procainamide 1), and 8 were observational (no control). Five studies included post-cardiac surgery AF and 18 included spontaneous AF.
RESULTS: Conversion rates from AF to NSR for IVA active-control treatments, and placebo were 72% (465/650), 69% (271/391), and 56% (58/103), respectively. Differences between IVA and active-control were not significantly different. Both IVA and active-controls were statistically superior to placebo. HR reduction with IVA, active-control and placebo were 37%, 29% and 27%, respectively. Overall incidence of adverse events with IVA, active-control and placebo was 12% (62/535), 17% (45/263) and 13% (13/103). Incidence of adverse events requiring drug discontinuance was 3% (16/525), 7% (18/263) and 8% (8/103).
CONCLUSION: IVA is at least as efficacious as class IA, class IC or digoxin therapy in conversion of recent onset AF with less toxicity. This data would suggest that IVA may have a role in conversion of acute AF. Of some concern is that two of the three placebo controlled trials indicate no benefit with IVA. Larger, placebo-controlled trials with IVA in acute AF are needed.

21. The value of lipid levels in patients hospitalized with acute coronary events. *Michele A. Faulkner, Pharm.D.*, Janis M. Taniyama, Pharm.D., Daniel E. Hilleman, Pharm.D.; Creighton University; St. Joseph Hospital, Omaha, NE.

PURPOSE: This study examined low-density lipoprotein (LDL) levels in patients hospitalized with chest pain 1) to determine if the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for lipid analysis after an acute coronary event were being followed, and 2) to evaluate the economic and clinical significance of these findings.
METHODS: Data was collected on patients admitted to the coronary care unit over six months. Patients with evidence of coronary artery disease based on a history of myocardial infarction, percutaneous coronary angioplasty, coronary artery bypass graft, or a 70% vessel occlusion by catheterization were included.
RESULTS: Of the 75 patients who had no documented lipid-lowering therapy, eight (10.7%) had a lipid analysis within 24 hours of presentation as outlined in the ACC/AHA guidelines for the management of patients with acute myocardial infarction. The mean hospital LDL value for these patients was 101.3 mg/dl compared to 141.1 mg/dl based on levels drawn in the ambulatory setting. For patients whose lipid analysis was delayed, the mean hospital and outpatient LDL values were 84.4 mg/dl and 144.9 mg/dl, respectively. According to the National Cholesterol Education Program recommendations, of those patients who did not have their LDL determined according to ACC/AHA guidelines, only 1.5% needed drug therapy using hospital data compared to 79.1% based on outpatient data.
CONCLUSION: In this population, a hospital lipoprotein analysis may result in inappropriate lipid-lowering therapy, and unnecessary laboratory costs. Treatment should be based on outpatient lab results, especially if the analysis can not be done within 24 hours of hospital admission.

22. Cost efficacy of esmolol versus diltiazem for atrial fibrillation/flutter following heart surgery. Aryan N. Mooss, M.D., Syed. M. Mohiuddin, M.D., *Richard L. Wurdeman, Pharm.D.*, Seyed Ali Seyedroudbari, Pharm.D., Daniel E. Hilleman, Pharm.D.; Creighton University, Omaha, NE.

PURPOSE: This study was designed to compare the efficacy and cost of IV esmolol (IVE) versus IV diltiazem (IVD) for the treatment of atrial fibrillation/flutter (AF/F) following coronary artery bypass and or valve replacement surgery (CABG/VRS).
METHODS: Written informed consent was obtained from 182 patients. Subjects received drug if they developed AF/F with a rapid ventricular rate >100 BPM. Subjects were excluded if they had a contraindication to beta blockade. Drug was continuously infused for 24 hours or until the patient converted to normal sinus rhythm (NSR); an alternate drug was added; patient was cardioverted; or death. Variables measured were time to rate control, incidence of drug induced side-effects, length of hospitalization, and percentage of patients that converted to NSR within 1, 2, 5, 6, 8, 10, 12, and 24 hours. A cost analysis was done between the two groups based on AWP (Medispan PC Price Chek™). Significance was defined as $p<0.05$.
RESULTS: Thirty patients received IVE (15) or IVD (15) for AF/F based on study protocol. Both groups had similar pre- and postoperative characteristics. Conversion rate was significantly better for IVE than for IVD during any time point within the first 6 hours ($p<0.05$) after which no differences were observed. The overall conversion rate within 24 hours was higher for IVE than IVD (80% vs 66.6%). Other measured variables were similar for both groups. The cost/successfully treated patient was less for IVE during the first 6 hours and IVD after 6 hours.
CONCLUSIONS: IVE produced a faster rate of conversion and was more cost effective during the initial phase of treatment than IVD for treating AF/F following CABG/VRS .

23. Do alteplase and reteplase differ? *Ruth J. Perkins, Pharm.D.*, Nancy H. Huntington, Pharm.D., Ruth Soule, CNS, Deborah K. VanLoan, B.S.N.; Glens Falls Hospital, Glens Falls, NY.

PURPOSE: This study was conducted to determine if there was a difference in the commonly accepted clinical indicators of reperfusion (resolution of ST segment elevation and chest pain [CP]) between those patients who received either alteplase or reteplase.
METHODS: This was a retrospective study evaluating patients at our institution who received either alteplase or reteplase in 1998. Data was collected for demographics; comorbidities; aspirin use; specific thrombolytic administered; site of myocardial infarction; time of evidence of reperfusion (resolution of ST segment elevation or partial resolution to a persistent small elevation and/or CP resolution); time of evidence of reocclusion (ECG changes and/or recurrent CP); and emergent interventions (i.e., intra-arterial balloon pump placement or emergent transfer). Logistic regression analysis (STATISTIX™) was performed using a maximum likelihood function. Odds ratios with 95% confidence intervals were calculated.
RESULTS: A total of 90 patients were evaluated (44 received alteplase, 46 received reteplase). There were no differences between the groups ($p>0.05$) regarding age, gender, site of infarct, number of comorbidities, or time to treatment. Logistic regression analysis found all variables to be necessary for a good fitting model, but only the thrombolytic had any predictive value for an adverse event (lack of reperfusion or reocclusion). The odds ratio (95% CI) for reteplase was 3.83 (1.13, 12.95). This increased risk was associated with younger males.
CONCLUSION: Based on the results of this analysis, we are discouraging the use of a single formulary agent for all thrombolytic eligible patients, and encouraging the use of alteplase for younger males.

24. Predictive performance study of two digoxin assays in subjects with various degrees of renal function. *Abdulrazaq S. Al-Jazairi, Pharm.D.*, Judy W.M. Cheng, Pharm.D., Shiv Kapoor, Ph.D., Leslie Shaw, Ph.D., Sidney Kobrin, M.D., Sarah A. Spinler, Pharm.D.; University of the Sciences in Philadelphia; University of Pennsylvania, Philadelphia, PA; Long Island University, Brooklyn, NY.

PURPOSE: To compare the predictive performance of a fluorescence polarization immunoassay (FPIA, Abbott TDx Digoxin II) and radio-immunoassay (RIA, Kallestad Labs) with low-pressure liquid chro-matography/RIA (LPLC/ RIA, Longerich, et al) digoxin assay, which removes digoxin-like immunoreactive substances (DLIS). Previously, older RIAs and FPIAs have been shown to overpredict serum digoxin concentrations (SDC) in patients with renal dysfunction secondary to assay interference with DLIS. Whether this occurs with newer assay versions is unknown.
METHODS: Prospective study designed to determine the predictive performance (Sheiner and Beal) of using TDx and RIA, compared to LPLC/ RIA digoxin assay in 3 age-and gender-matched groups (n=6 in each, group I (CrCl <10 ml/min), group II (CrCl 10-50 ml/minute), and group III (CrCl > 50 ml/minute, n=6). After a single 10 µg/kg intravenous digoxin dose, a total of 15 consecutive samples from each subject were drawn over 7 days. The bias (mean error [ME]) and precision (mean squared error [MSE]) were calculated with 95% confidence intervals (CI). The magnitude of bias was calculated by dividing the mean error of the compared assay by the mean SDC measured by the reference standard, LPLC/RIA.
RESULTS: Bias for each group was determined.

Digoxin Assay	Number of Paired Samples	ME	CI	Magnitude of Bias
Group I				
TDx digoxin II	97	-0.1610	(-0.2484, -0.0735)	13.56%
RIA	96	-0.0638	(-0.1564, 0.0289)	4.98%
Group II				
TDx digoxin II	89	0.3002	(0.1084, 0.4921)	8.41%
RIA	89	-0.2987	(-0.4528, -0.1445)	8.36%
Group III				
TDx digoxin II	90	-0.3892	(-0.5877, -0.1908)	5.74%
RIA	90	-0.4875	(-0.6309, -0.3439)	2.27%

With regard to precision, both assays were imprecise for all groups.
CONCLUSION: Overall, RIA and TDx were biased to overpredict SDC in patients with renal dysfunction; however, the magnitude of bias was low (< 20%) for both assays in all groups. Since both RIA and TDx are easier to perform than LPLC/RIA, either assay may be used to measure SDC in patients with renal dysfunction.

25E. Cost-minimization analysis of milrinone versus dobutamine treatment strategies as a bridge to heart transplant. *Eric J. Stanek, Pharm.D.*, Denise E. Kinky, Pharm.D., Evan Loh, M.D., David DeNofrio, M.D., Gene A. Gibson, Pharm.D.; Philadelphia College of Pharmacy, University of the Sciences in Philadelphia; University of Pennsylvania Medical Center, Philadelphia, PA.

PURPOSE: This study examined the economic impact of inotropic agent selection in patients successfully bridged to heart transplant in 1993 and 1996 at our center.

METHODS: Three treatment groups were identified from itemized billing records: milrinone (n=18), dobutamine (n=16), and combined dobutamine plus amrinone or milrinone (n=6). Costs (1997 U.S. $) were calculated for each billed item using institutional cost:charge ratios, excluding professional fees. Pretransplant (preHT) and posttransplant (postHT) costs were categorized by pharmacy, procedure, lab, bed, blood product, respiratory care, and supply. Per diem costs (cost/day) were calculated to adjust for varying length of stay.
RESULTS: No intergroup baseline demographic or clinical differences were observed. Categorized cost comparisons are:

PreHT Per Diem Cost	Milrinone	Dobutamine	Combined
Total	$2740 ± 623	$2451 ± 464	$2742 ± 838
Pharmacy	425 ± 81[a,c]	48 ± 103[a,b]	188 ± 84[b,c]
Procedure	154 ± 233	282 ± 247	366 ± 484
Lab	228 ± 122	296 ± 156	260 ± 129
Bed	1014 ± 53	978 ± 103	1015 ± 44

[a,b,c] like letters differ; p<0.02

Other preHT costs were minor and did not differ between groups. No differences in categorized costs were observed postHT.
CONCLUSION: Use of a milrinone-based inotropic strategy led to nonsignificant increases in total per diem costs in patients successfully bridged to transplant. Greater pharmacy costs of milrinone appear to be partially offset by reduced procedure and laboratory costs. Formulary decisions on inotropic therapy should not be based solely on drug acquisition costs.
Presented at the 3rd Annual Scientific Meeting of the Heart Failure Society of America, San Francisco, CA, September 23, 1999.

26. Practice patterns versus clinical trial use of the newer glycoprotein IIb/IIIa inhibitors. *Anne Spencer, Pharm.D., BCPS*, Jean Nappi, Pharm.D., BCPS, FCCP; Medical University of South Carolina, Charleston, SC.

PURPOSE: To document the clinical use of eptifibatide (E) and tirofiban (T) in a tertiary care setting.
METHODS: Patients receiving either E or T were identified at the initiation of therapy. Patient demographic information, drug, dose, duration of infusion, incidence of bleeding, thrombocytopenia, heparin administration, emergent revascularization, and cost data were collected prospectively.
RESULTS: Thirty-seven cases of E and T administration between November 1, 1998 and May 31, 1999 were included in this evaluation.

	Eptifibatide (n=23)	Tirofiban (n=14)	Total (n=37)
Age, years (mean ± SD)	61 ± 9	69 ± 12	64 ± 11
% male	70%	71%	70%
Incorrect dosing (over/under)	1/2	0/0	1/2
Transferred on E or T	5	0	5 (14%)
Duration of infusion (hours, mean ± SD)	mean = 26.5 ± 18.1 median = 24 range = 5-68	mean = 30.6 ± 26.8 median = 23 range = 0-94	mean = 28.0 ± 21.5 median = 24 range = 0-94
Complications	8 (35%)	2 (14%)	10 (27%)
Bleeding	3 (13%)	2 (14%)	5 (13%)
Thrombocytopenia	5 (22%)	0 (0%)	5 (13%)
Heparin administered	19 (83%)	14 (100%)	33 (89%)
APTT > 70	10 (53%)	9 (64%)	19 (58%)
Cost, $ (mean ± SD)	$610 ± 422	$630 ± 273	
Emergent revascularization	2 (9%)	1 (7%)	3 (8%)

CONCLUSION: These agents are not utilized at our institution in a similar fashion to the pivotal clinical trials (PURSUIT and PRISM-PLUS). Although the mean duration of infusion is similar between E and T, it is markedly shorter than the length of therapy shown to improve patient outcomes. Some of the bleeding complications may be attributed to over anticoagulation with heparin. Based on these data, targets for educational efforts have been identified.

27. Evaluation of the accuracy of patient-operated blood pressure measuring devices available in community pharmacies. *Cathleen M. Edick*, Diane Parnell, Michael Christensen, Pharm.D., Lawrence Hak, Pharm.D.; University of Tennessee, Memphis, TN.

PURPOSE: This study compared the accuracy of patient-operated blood pressure measuring devices (PBPD) versus a mercury column sphygmomanometer (MCS) and also evaluated immediate measurement versus five minute resting PBPD measurement.
METHODS: PBPD located in 33 pharmacies were evaluated. To replicate usual patient use, one person walked up to the device and immediately measured blood pressure (baseline). Subject rested for five minutes then measured blood pressure in random sequence, two times by device and two times using MCS. Blood pressures were measured in the same subject for each location and MCS measurements were by a single person. The mean ± SD for PBPD and MCS were compared using the paired t-test.
RESULTS: The PBPD baseline systolic (112 ± 6) versus the PBPD resting systolic (104 ± 6) was significantly higher (p<0.01). PBPD baseline diastolic (68 ± 7) versus the PBPD resting diastolic (68 ± 4) showed no difference (p=0.6). Comparison of the PBPD baseline (systolic 112 ± 6, diastolic 68 ± 7) to the MCS resting (systolic 104 ± 3, diastolic 71 ± 4) showed a higher systolic pressure (p<0.01) and a lower diastolic pressure (p=0.02). Comparison of PBPD resting systolic (104 ± 6) versus the MCS resting systolic (104 ± 6) showed no difference (p=0.46), while PBPD resting diastolic (68 ± 4) was lower in comparison to the MCS resting diastolic (71 ± 4; p<0.01).
CONCLUSION: PBPD are more likely to be accurate if at least a five minute resting period is taken. Diastolic blood pressures are significantly lower on the PBPD versus the sphygmomanometer.

28. Safety and efficacy of cerivastatin 0.8 mg daily for 8 weeks; the pivotal placebo-controlled clinical trial. *William Insull, Jr., M.D.*, Evan Stein, M.D., Ph.D., Patrick Ma, M.D., Peter Kwiterovich, M.D., Ronald Brazg, M.D., Carlos Dujovne, M.D., Michael Shan, Ph.D., Elizabeth Shugrue-Crowley, Steven Ripa, M.D.; Baylor-Methodist Lipid Research Clinic, Houston, TX; Metabolic and Atherosclerosis Research Center, Cincinnati, OH; Heart Health Institute, Calgary, AB, Canada; Johns Hopkins University Baltimore, MD; Rainer Clinical Research Center, Renton, WA; Kansas Foundation for Clinical Pharmacology, Overland Park, KS; Bayer Corporation, West Haven, CT for the Cerivastatin Study Group.

An assessment of the safety and efficacy of cerivastatin (CER) in the higher dose range warrants full investigation.
PURPOSE: To compare the efficacy and safety of CER 0.8 mg to CER 0.4 mg or placebo.
METHODS: In this randomized, double-blind trial, 1170 hypercholesterolemic patients underwent 10 week dietary stabilization prior to 8-week treatment with CER 0.8 or 0.4 mg QD, or placebo.
RESULTS: CER 0.8 mg was more effective in reducing LDL-C, total-C, and triglycerides (TG). LDL-C reductions > 45% were reached by 43% of patients given CER 0.8 mg. CER 0.4 and 0.8 mg elevated HDL-C to a similar degree. CER 0.8 mg reduced TG by 28% in 106 patients with basal TG > 250 mg/dl. Results are expressed as mean percentage change (± SEM) from baseline (± SD, mg/dl) to 8-week endpoint.

Lipid Parameters	Placebo (n=177)	CER 0.4 (n=168)	CER 0.8 (n=663)
LDL-C baseline	185 ± 34	191 ± 51	190 ± 40
mean % Δ	+0.3 ± 0.9[a]	-35.8 ± 0.9[a]	-41.7 ± 0.5[a]
Total-C baseline	268 ± 36	277 ± 54	276 ± 42
mean % Δ	+0.9 ± 0.7[a]	-25.1 ± 0.7[a]	-29.8 ± 0.4[a]
TG baseline	175 ± 61	187 ± 65	185 ± 67
median % Δ	-1.9	-15.2	-22.7
HDL-C baseline	48 ± 11	48 ± 12	49 ± 12
mean %Δ	+2.8 ± 0.8[ab]	+7.7 ± 0.8[a]	+8.7 ± 0.5[b]

[a,b] common letters indicate between-treatment differences to be p<0.05

Causes of AE with rates > 5% and discontinuations were similar across groups. CK levels > 10x upper limits of normal with myalgia occurred in 0%, 0.5%, and 0.5% of patients receiving placebo, CER 0.4 or 0.8 mg.
CONCLUSION: CER 0.8 mg produced a significantly greater LDL-C reduction than CER 0.4 mg. The NCEP goal of 130 mg/dl (no CAD, ≥ 2 risk factors) was reached with CER 0.8 mg by 78% of patients.

29. Does misoprostol attenuate NSAID-induced changes in blood pressure and renal hemodynamics?: the MEDIC study. *Mark A. Munger, Pharm.D.*, Stephanie F. Gardner, Pharm.D., Gary M. Rabetoy, M.D., Alfred K. Cheung, M.D., Yousri M. Barri, M.D., Gregory M. Stoddard, M.P.H.; University of Utah, Salt Lake City, UT; University of Arkansas, Little Rock, AK.

PURPOSE: NSAIDs are known to interfere with blood pressure regulation and renal function. Misoprostol (MIS), a synthetic PGE_1 analog causes significant reductions in blood pressure and heart rate (HR), and increases in renal blood flow and glomerular filtration rate.
METHODS: To test the hypothesis of whether MIS (200 µg BID) plus diclofenac (D; 75 mg BID) attenuates D-induced increased BP loads and renal hemodynamic changes we conducted a prospective, double-blind, randomized, 14-day crossover design study in salt-sensitive elderly subjects with stage I-II hypertension. Salt sensitivity was determined by a ≥ 10 mm Hg difference in systolic BP (SBP) or diastolic BP (DBP) between 10-day sodium intake periods of 200 mmol vs 20 mmol. BP was measured by 24-hour ambulatory blood pressure monitoring, ERPF by para-aminohippurate and GFR by cold iothalamate clearances, respectively.
RESULTS: Nineteen subjects (61.8 ± 1.2 years) completed the study. Results are changes from baseline presented as mean ± SEM.

	SBP	DBP	SBT-T	DBP-T	HR	ERPF	GFR
D	11 ± 3	11 ± 3	10 ± 3	12 ± 3	-1 ± 1	-41 ± 27	-14 ± 7
D + MIS	4 ± 4*	-0.3 ± 3*	4 ± 4*	-0.5 ± 3*	-4 ± 1*	16 ± 26	4 ± 8*

*p<0.05 D vs D + MIS; SBP = SBP load (%); DBP = DBP load (%); SBP-T = SBP time load (%); DBP-T = DBP time load (%)

CONCLUSIONS: D plus MIS attenuates the change in BP load and improves the renal vasoconstrictive effects from D.

30. A retrospective evaluation of discharge medications in post-myocardial infarction patients. *Brigitte T. Luong, Pharm.D.*, Wendy C. Cox, Pharm.D., Jean Nappi, Pharm.D., FCCP, BCPS; Medical University of South Carolina, Charleston, SC.

PURPOSE: Discharge medications of post-myocardial infarction (MI) patients at an academic hospital were evaluated for compliance with the American College of Cardiology/American Heart Association's (ACC/AHA) Guidelines for the Management of Patients with Acute MI.
METHODS: The medical records of 90 acute MI survivors discharged between March 1, 1997 and February 28, 1999 were reviewed. Patients' discharge medications (antiplatelet agent, beta-blocker, angiotensin converting enzyme [ACE] inhibitor, lipid-lowering agent, and sublingual nitroglycerin) were recorded, as well as relative or absolute contraindications if the agents were not prescribed.
RESULTS: Antiplatelet agents, beta-blockers, ACE inhibitors, lipid-lowering agents, and sublingual nitroglycerin were prescribed in 93.3%, 60%, 52.2%, 53.3%, and 47.7% of the patients, respectively. Of the patients not prescribed these agents and without relative or absolute contraindications, 3.3%, 10%, 8.8%, 32.2%, and 43.3% were not prescribed an antiplatelet agent, beta-blocker, ACE inhibitor, lipid-lowering agent, or sublingual nitroglycerin, respectively.
CONCLUSION: The percentage of patients prescribed the agents recommended in the ACC/AHA guidelines was above those found in the literature after adjusting for relative or absolute contraindications. Areas for improvement include the prescribing of lipid-lowering agents and sublingual nitroglycerin.

31. Meta-analysis of the antiarrhythmic effects of prophylactic amiodarone following cardiac surgery. *Paul E. Nolan, Jr., Pharm.D.*, James E. Tisdale, Pharm.D., Sarah A. Spinler, Pharm.D., Daniel E. Hilleman, Pharm.D., Marion K. Slack, Ph.D., for the Meta-Analysis Pharmacy Collaborators for Amiodarone and Sotalol Investigators; University of Arizona, Tucson, AZ; Wayne State University, Detroit, MI; Philadelphia College of Pharmacy, Philadelphia, PA; Creighton University, Omaha, NE.

PURPOSE: This study evaluated the efficacy and safety of intravenous (IV) or oral (PO) amiodarone (AM) administered prophylactically to decrease atrial fibrillation (AF) following cardiac surgery (CS).
METHODS: To assess the effects of prophylactic AM, six prospective, randomized, controlled studies comparing either IV or PO AM (n=484) vs placebo (PL; n=414) were aggregated using standard meta-analytic techniques.
RESULTS: There were no significant differences between the AM and PL groups with respect to age, gender, left ventricular ejection fraction, bypass time, aortic cross-clamp time, number of coronary artery bypass grafts or pre-CS use of digoxin or beta-adrenergic blocking drugs. The occurrence of post-CS AF was significantly reduced by AM: 26% vs 36% (OR: 0.61; 95% CI: 0.46-0.81; p=0.001). The impact of prophylactic AM with respect to length of hospital stay (LOS), although significantly decreased in one study and reduced in two others, could not be assessed due to inadequate reporting in the remaining three studies. Any post-CS bradycardia, most of which was asymptomatic, was significantly greater in the AM group: 37% vs 24% (OR: 2.1; 95% CI: 1.28- 3.43; p=0.003). The low incidence of postoperative mortality was unaffected by AM.
CONCLUSION: Prophylactic AM decreases post-CS AF and may shorten length of stay.

32. Efficacy of alternate day dosing versus every day dosing with atorvastatin. *Mahtab Jafari, Pharm.D.*, Ramin Ebrahimi, M.D., Harry Ballian, M.D., Mark Okamoto, Pharm.D., Arasb Ateshkadi, Pharm.D.; Western University of Health Sciences, Pomona, CA; University of California at Irvine, Irvine, CA.

There are some data that support the dosing of HMG-CoA reductase inhibitors every other day as opposed to daily with similar results. Atorvastatin is metabolized to at least two active, long-lasting, metabolites with potencies similar to the parent compound. Due to its active metabolites, the half-life of HMG-CoA reductase inhibition is as long as 20-30 hours, making this agent ideal for possible every-other-day dosing. Although there has been a report on the efficacy of every other day dosing with fluvostatin, to date all investigations of atorvastatin have been conducted using daily dosing. Furthermore, the every other day dosing could potentially result in cost savings.
PURPOSE: The main objective of this study was to compare percent reduction of LDL between alternate day dosing and every day dosing with atorvastatin.
METHODS: This is a randomized, prospective, non-blinded, controlled study. To date 24 patients have been enrolled in the study (expected total = 60 patients). Patients were randomized to either experimental group who received 10 mg of atorvastatin every other day (n=12) or control group who received 10 mg of atorvastatin every day (n=12) for 4 weeks. A lipid profile was obtained at baseline and after four weeks.
RESULTS: At baseline there were no significant differences between the groups. For the control group, after four weeks, the average LDL-cholesterol decreased from 143.5 mg/dl to 105.2 mg/dl. This drop was not statistically significant (p=0.12). For the experimental group, LDL-cholesterol decreased from 158.5 mg/dl to 104.8 mg/dl. This drop was statistically significant (p=0.002).
CONCLUSION: Based on our preliminary results, the percent reduction in LDL is similar in every day and every other day dosing with atorvastatin. Every other day dosing should result in significant drug cost savings without compromising the therapeutic effects.

33. Effect of aspirin dose on clinical outcomes in post-myocardial infarction patients. Lisanne DiTusa, Pharm.D., *Aileen Bown Luzier, Pharm.D.*, Anjana Navsarikar, Pharm.D., Khalid Ashai, M.D., Michael F. Wilson, M.D.; State University of New York at Buffalo; Kaleida Health, Buffalo, NY.

PURPOSE: Although scientific evidence indicates that aspirin significantly impacts the clinical outcomes of post-myocardial infarction (MI) patients, the optimal dose remains controversial. We evaluated the effect of aspirin dose on outcomes in post-MI patients.
METHODS: The records of 534 post-MI patients discharged from our institution from June 1996 to May 1997 were reviewed and demographic, clinical, laboratory and pharmacy data were collected. Aspirin dose on discharge was categorized as low (< 160 mg daily) or standard (≥ 160 mg daily), based on AHA/ACC guidelines. Subsequent cardiovascular events, including reinfarction, unstable angina and cardiac interventions or death, were assessed at 6 months post discharge. The impact of aspirin dose on the likelihood of an event occurring within 6 months was analyzed using univariate and stepwise multiple logistic regression.
RESULTS: Of the 497 patients with complete follow-up data, aspirin was prescribed in 87% of the patients; 79% received the standard dose and 8% received low dose aspirin. Events were documented in 22% of the patients. Compared to no aspirin, treatment with low dose was not associated with a decrease in event rate (OR 1.25; 95% CI 0.53-2.97, p=0.61). Standard dose aspirin was associated with a decrease in event rate (OR 0.50; 95% CI 0.31-0.82, p=0.004) and remained significant in multivariate analysis (OR 0.55; 95% CI 0.33-0.92, p=0.02).
CONCLUSION: Although a small number of patients were treated with low dose aspirin, our data indicate that it had no significant impact on outcomes while standard dose aspirin was associated with improved outcomes. This illustrates the need to increase awareness of optimal aspirin dosing in the medical management of post-MI patients.

34. Post-myocardial medication use and outcomes in patients at a Veterans Affairs medical center. *Margaret E. McGuinness, Pharm.D.*, Madeline Downey, Pharm.D.; Oregon State University; Legacy Health System–Mt. Hood Community Hospital, Gresham, OR.

PURPOSE: Myocardial infarction (MI) remains a leading cause of death. Post-MI therapy with beta blockers (BB), aspirin, and angiotensin converting enzyme inhibitors (ACEI) reduce mortality. The purpose of this study conducted in a Veterans Affairs medical center (VA) was to evaluate medication prescribing of BB, ACEI and aspirin in patients discharged following MI, identify documentation of contraindications for non-drug use, and patient outcomes.
METHODS: Patients identified by ICD-9 codes for MI who were treated and discharged from the VA between January 1995 and December 1996 were evaluated for discharge medications, and reinfarction and mortality rates, during follow up through April 1998. Documentation of contraindications to drug therapy were also recorded. Pharmacy medication records and patient medical records were used as data source.
RESULTS: The average age of the 283 eligible patients was 64 years (99.7% male). At discharge 76% were on BB, 51% on ACEI (60% [35/58]; patients with EF < 40%); and 98% on aspirin. Documented contraindications to therapies were found for 72% BB, 36% ACEI, (46% with EF < 40%); and 98% aspirin. Reasons for non-use of BB were primarily cardiac (44%; 67% CHF); and respiratory (54%; 85% COPD); and for ACEI, renal (54%). Reinfarctions occurred in 32% of patients, and overall mortality was 7% during median follow up of 22 months.
CONCLUSIONS: Post-myocardial medical management with BB and ACEI and documentation of contraindications to therapies is not optimal. Advocating use of recommended therapies and improved documentation of contraindications for non drug use needs to be facilitated.

35. Correlation of ambulatory blood pressure monitoring versus home blood pressure monitoring, and their ability to identify hypertensives requiring therapy. Deborah J. Partsch, Pharm.D., *Kjel A. Johnson, Pharm.D.*, Tracy A. Mascari, Pharm.D., Marcus D. Wilson, Pharm.D., John J. Barron, Pharm.D., Kevin T. McCaffrey; HealthAmerica; UPMC Health Plan, Pittsburgh, PA; Health Core Inc., Newark, DE.

PURPOSE: Ambulatory blood pressure monitoring (ABPM) better represents blood pressure (BP) than an office measure, but is time-intensive and costly. We correlated home blood pressure monitoring (HBPM) to ABPM, and the measured ability of each to identify hypertensives requiring therapy.
METHODS: Patients from two managed care organizations deemed hypertensive or white coat hypertensive by their physician were enrolled.

Patients monitored their home BP 2-3 times daily for 2 weeks at defined intervals using a digital automatic home BP monitor. ABPM was performed within 24 hours of the last HBPM recording. Mean daytime BP and BP loads (% of readings > 140/90 mm Hg) were compared. Percent of patients requiring treatment, defined as a BP load ≥40%, was also compared.
RESULTS: Two hundred eight patients were enrolled and 166 (54 ± 11 years, 43% male) had complete data. The mean systolic/diastolic BP was 132 ± 15 mm Hg/82 ± 9 mm Hg for HBPM, and 138 ± 14 mm Hg/83 ± 10 mm Hg for ABPM ($p<0.03$ for both SBP and DBP). The mean systolic/diastolic load was 31 ± 32%/19 ± 27% for HBPM, and 43 ± 33%/28 ± 27% for ABPM ($p<0.001$ for both SBP and DBP). HBPM identified 40% requiring therapy versus 50% with ABPM. There was no difference in the identification of patients requiring treatment between monitors ($p=0.078$).
CONCLUSIONS: There was a significant BP difference between HBPM and ABPM; however, there was no difference in the percent of patients requiring treatment.

36. Lidocaine widens the window of vulnerability to monophasic, but not biphasic T-wave shocks. *J. Jason Sims, Pharm.D.*, Allison W. Miller, Pharm.D., Michael R. Ujhelyi, Pharm.D.; University of Georgia; Medical College of Georgia; Augusta VA Medical Center, Augusta, GA.

PURPOSE: Implantable defibrillators decrease sudden cardiac death mortality, but are limited by the energy required to defibrillate (i.e., high DER values). Multiple drugs increase DER values and cause failed defibrillation, but the specific mechanisms are unknown. One hypothesis of defibrillation relates to shock proarrhythmia, where the less proarrhythmic a shock the lower the DER value. Since defibrillation shocks induce ventricular fibrillation (VF) when delivered during a vulnerable window of ventricular repolarization (T-wave shocks), our purpose was to determine if lidocaine, a model drug probe, widens the window of myocardial vulnerability to T-wave shocks.
METHODS: Window of myocardial vulnerability was assessed for monophasic (MS) and biphasic (BS) T-wave shocks by determining the shortest and longest coupling intervals (CI) that induced VF. Twenty-four swine were randomized to four groups: MS/lidocaine, MS/placebo, BS/lidocaine, or BS/placebo. Shocks of increasing voltage were delivered during a range of CI (140-320 ms) until 600 volts was reached or VF was induced. Window of vulnerability and DER values were determined at baseline and during lidocaine 7.5 mg/kg/hr or placebo.
RESULTS: The table below shows the window of myocardial vulnerability for the MS/lidocaine and BS/lidocaine groups. Lidocaine did not alter the shortest CI that a MS induced VF, but increased the longest CI by 22 ± 8 ms ($p=0.03$), increasing the MS window of vulnerability by 33% (table). However, lidocaine similarly increased the shortest and longest CI that a BS induced VF by 20 ± 4 ms ($p=0.03$) and 26 ± 8 ms ($p=0.02$), respectively. Thus, the BS window of vulnerability did not change. Also, lidocaine increased DER values for MS from 12 ± 2 J to 16 ± 2 J ($p=0.008$), but did not alter BS DER values. Placebo did not alter any parameter.

	Baseline	Lidocaine
Biphasic (n=7)	49 ± 5.9 ms	54 ± 5.7 ms
Monophasic (n=9)	60 ± 4.7 ms	80 ± 10 ms*

*p=0.04, baseline vs lidocaine

CONCLUSIONS: Lidocaine widens the MS window of vulnerability by prolonging only the longest point of repolarization (CI) where VF is induced. Lidocaine shifts the BS window of vulnerability to longer coupling intervals, but does not widen it. The larger MS vulnerable window produced by lidocaine may impair MS defibrillation because the shock is more likely to be delivered within the vulnerable window during fibrillation.

37E. Myocardial vulnerability to ventricular fibrillation is regulated by dispersion in conduction, but not dispersion in refractoriness. *J. Jason Sims, Pharm.D.,* Allison W. Miller, Pharm.D., Michael R. Ujhelyi, Pharm.D.; University of Georgia; Medical College of Georgia; Augusta VA Medical Center, Augusta, GA.

PURPOSE: Acute myocardial ischemia increases myocardial vulnerability to ventricular fibrillation (VF). Myocardial vulnerability is caused by myocardial electrical heterogeneity. However, it is unclear whether dispersion in conduction velocity or refractoriness is responsible. We determined the effects of dispersion in conduction velocity and refractoriness on VF thresholds (VFT).
METHODS: Swine were instrumented with a LAD perfusion catheter for low-dose regional lidocaine 0.75 mg/kg/hr (Lido, n=6), d-sotalol 5 mg/hr (Sot, n=10) or placebo (n=7) to create dispersion in conduction, refractoriness, or serve as control, respectively. VFT was measured at four myocardial sites: lateral LV endocardium (LV), LV epicardial base (LVB), LV epicardial apex (LVA), and anterior epicardial RV (RV). VFT was determined using a 20 stimuli train (100 Hz) given 50 ms after the last beat of an 18 beat 300 ms cycle length drive train. Effective refractory period dispersion (ERP-D) and conduction velocity dispersion (CV-D) were measured as the maximum difference between the four sites.
RESULTS: The table below reports the mean ± SEM of VFT in mA at baseline (B) and during Lido or Sot (PI). Lido and Sot increased VFT in the perfused area by 133% and 86%, respectively. However, Lido decreased VFT at all non-perfused sites by an average of 55%, while Sot did not change VFT at any non-perfused site. Lido also increased CV-D by 100% ($p=0.01$), but did not affect ERP-D. Conversely, Sot increased ERP-D by 150% ($p=0.002$), but did not affect CV-D. Placebo infusion did not alter any parameter.

	Base	Lido	Base	Sot
LVA	9 ± 3	22 ± 4*	9 ± 2	17 ± 2*
LV	12 ± 2	5 ± 2*	14 ± 1	15 ± 2
LVB	10 ± 2	6 ± 2*	12 ± 2	14 ± 3
RV	11 ± 2	4 ± 1*	9 ± 1	12 ± 1

*p<0.05; baseline vs PI

CONCLUSIONS: Both agents had antifibrillatory actions in the perfused area (LVA); however, regional lidocaine had profibrillatory effects when arrhythmic stimuli were delivered outside the perfused region, while regional d-sotalol did not. Hence, dispersion in conduction is a more likely regulator of myocardial vulnerability to VF than dispersion in refractoriness.
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Critical Care

38. Preservation of intestinal transcellular drug transport and P-glycoprotein following thermal injury in rats despite alterations in intestinal cytokines. *Brien L. Neudeck, Pharm.D.*, Jeffrey P. Gonzales, Pharm.D., Richard D. Klein, M.D., Stewart C. Wang, M.D., Lilian Y. Li, M.S., Lynda S. Welage, Pharm.D.; University of Michigan, Ann Arbor, MI.

PURPOSE: This study was designed to assess intestinal drug transport via transcellular absorption and efflux pathways following thermal injury in rats using the marker propranolol.
METHODS: Male Sprague Dawley rats were assigned to burn (n=10) or sham (n=10) groups, anesthetized, and underwent laparotomy during which the proximal jejunum was cannulated. The segment was perfused with buffer containing ^{3}H-propranolol. The burn group underwent a 30% TBSA full thickness burn 24 hours prior to the intestinal perfusion. Perfusate samples were assayed for TNF-α, IL-6, IL-10 and ^{3}H-propranolol. Following euthanasia, the intestinal villi were harvested for Western immunoblotting of P-glycoprotein.
RESULTS: There was no significant difference in the intestinal wall membrane permeability of propranolol between the burn and sham groups ($2.05 \pm 1.39 \times 10^4$ vs $1.75 \pm 1.02 \times 10^4$ cm/sec). Burned rats had significantly lower TNF-α and IL-6 concentrations at the beginning of steady state, 60 minutes, as compared to sham animals (TNF-α: 6.15 ± 10.7 vs 59.9 ± 59.5, IL-6: 0.659 ± 1.39 vs 9.85 ± 12.5 pg/ml). TNF-α and IL-6 concentrations were also depressed at 80, 100 and 120 minutes. In contrast, IL-10 concentrations were not significantly different between the groups. No significant differences in the amounts of intestinal P-glycoprotein were detected.
CONCLUSIONS: Despite alterations in luminal TNF-α and IL-6 concentrations, the transcellular transport of propranolol is unaffected 24 hours following thermal injury in rats. This suggests that a major pathway for drug absorption is preserved following thermal injury. Moreover, the amount of the efflux protein, P-glycoprotein, appears preserved.

39. A review of albumin usage in the neurosurgical patient at the University of Kentucky Medical Center. *Kimberly Varney, Pharm.D.*, Terry Cheak, B.S.N., Byron Young, M.D., Jimmi Hatton-Kolpek, Pharm.D., BCNSP; University of Kentucky Medical Center, Lexington, KY.

PURPOSE: Controversy remains regarding the use of albumin in the neurosurgical (NS) population. Particular concern involves its use for prevention/treatment of subarachnoid hemorrhage (SAH)-induced vasospasm. Our purpose is to determine why and how much albumin we use in this population, thereby facilitating the establishment of guidelines.
METHODS: All neurosurgical patients receiving albumin between October 1, 1998 and May 31, 1999 were reviewed. A data form was utilized for collecting pertinent labs, pressures, fluids, doses, and attending physicians. In addition, a survey was mailed to members of the American Brain Injury Consortium (ABIC) in the U.S., Canada, and Europe. Included were questions regarding their patterns of albumin usage to which we could compare.
RESULTS: Overall, the neurosurgical service was found to be the second highest user of albumin in our hospital. Albumin was prescribed in 35 cases: vasospasm (49%), volume-expansion (40%), and organ preservation (11%). Approximately 1/3 of all SAH patients received albumin. One specific physician (out of five) used albumin in 65% of the SAH patients. Method of administration included continuous infusion (SAH), and bolus dosing. ABIC survey responses found similar inconsistencies in albumin use compared with ours.
CONCLUSIONS: Use in SAH patients constituted the majority of albumin prescribing, and their continuous infusion methods created high usage numbers. Our data demonstrated a lack of consensus and confirms the need for guidelines. The ABIC survey also indicated inconsistencies and the need

for review outside our institution. Our data has provided the basis for establishing guidelines, as well as for an up-coming study comparing colloids and crystalloids in our SAH patients.

40. Empiric versus protocol-based neuromuscular blockade in critically ill patients. *Robert MacLaren, Pharm.D.*, L. Kent Toombs, B.Sc. (Pharm), Johanna M. Plamondon, B.Sc. (Pharm), Graeme M. Rocker, M.A., D.M., FRCP, FRCPC, Richard I. Hall, M.D., FRCPC, FCCP.; The Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: To compare empiric therapy (ET) to protocol-based therapy (PT) of neuromuscular blockade (NMB) in terms of cost, control of paralysis, and blood pressure variations.
METHODS: Thirty ET patients and 17 PT patients requiring NMB for at least six hours were prospectively studied for 8 months before and 4 months after an evidence-based NMB protocol was implemented as a medication order form in the medical/surgical/neurologic intensive care unit (ICU). The protocol promotes the use of pancuronium with vecuronium as an alternative if renal failure, hepatic failure, or hemodynamic failure is present. Comparisons between ET and PT included demographic data, hours of ICU stay, hours of NMB, hourly doses and acquisition costs of neuromuscular blocking agents, fraction of hourly train of four measurements between one and three, and the occurrence of hypertension or hypotension within six hours of initiating NMB. Statistical analyses used the Student's t-test or Mann-Whitney U test for continuous data and chi squared test or Fisher's exact test for dichotomous data.
RESULTS: Demographic data, hours of ICU stay, and hours of NMB were similar between ET and PT groups. Protocol adherence was 88.2%. The mean hourly dose of pancuronium increased from 0.035 ± 0.13 mg during ET to 0.29 ± 0.37 mg during PT ($p<0.005$). The use of vecuronium was similar during ET and PT. Rocuronium and atracurium were not used after protocol implementation. The mean hourly acquisition cost of neuromuscular blocking agents decreased from $8.75 ± 7.08 CDN during ET to $5.11 ± 4.76 CDN during PT ($p<0.005$). Protocol use increased the fraction of train of four measurements between one and three from 32.5% to 52.3% ($p<0.05$) and reduced the occurrence of hypertension or hypotension from 56.7% to 23.5% ($p<0.05$).
CONCLUSIONS: Compliance with an evidence-based neuromuscular blocking protocol that promotes pancuronium use reduces drug costs, improves control of neuromuscular blockade, and may reduce blood pressure variations associated with NMB.

41E. Pharmacokinetics of intravenous levofloxacin in adult critically ill patients. *Jill A. Rebuck, Pharm.D.*, Edward Abraham, M.D., Douglas N. Fish, Pharm.D.; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: Critically ill patients may display alterations in the pharmacokinetics of many drugs. Levofloxacin disposition has not been studied in this population. This study evaluated the pharmacokinetics of intravenous levofloxacin in adult medical and surgical ICU patients.
METHODS: All subjects were studied for one dosing interval after estimated steady state was achieved. Blood samples were collected at predetermined intervals from 0 to 24 hours following levofloxacin administration. Plasma levofloxacin concentrations were determined by validated HPLC assay. Data were analyzed using a noncompartmental pharmacokinetic model.
RESULTS: Eleven critically ill patients (7 male, 4 female); mean ± SD age: 57 ± 9 years; mean creatinine clearance: 69 ± 15 ml/min; mean weight 76.0 ± 7.6 kg) were enrolled after obtaining informed consent. One patient was excluded from analysis due to acute renal failure. Seven patients were treated for pneumonia, 2 for bacteremia, and 1 each for UTI and sinusitis; mean APACHE II scores were 21 ± 4. Eight patients received 500 mg, while 2 patients received 250 mg every 24 hours. The calculated (mean ± SD) $t_{1/2}$, Cl_{ss}, and V_d in all patients were 8.1 ± 2.5 hours, 147 ± 69 ml/min, and 1.3 ± 0.4 L/kg, respectively. In patients receiving 500 mg, calculated C_{max}, C_{min}, and AUC_{0-24} were 7.8 ± 1.0 mg/L, 1.1 ± 0.7 mg/L, 75.1 ± 21.3 mg•hr/L, respectively. In patients receiving 250 mg, calculated C_{max}, C_{min}, and AUC_{0-24} were 3.2 ± 1.0 mg/L, 0.6 ± 0.5 mg/L, and 34.5 ± 8.3 mg•hr/L, respectively.
CONCLUSION: The results of our study are consistent with published values in other patient populations, indicating the pharmacokinetics of intravenous levofloxacin are not substantially altered in critically ill patients with normal or mildly impaired renal function.
Presented at the 28th Educational and Scientific Symposium of the Society of Critical Care Medicine, San Francisco, CA, January 23-28, 1999.

42. Implementation and evaluation of guidelines for the use of enoxaparin as deep vein thrombosis prophylaxis after major trauma. *John W. Devlin, Pharm.D., BCPS*, James Tyburski, M.D., Berton Moed, M.D.; Detroit Receiving Hospital; Wayne State University, Detroit, MI.

PURPOSE: While enoxaparin is more efficacious than many other post-trauma deep vein thrombosis (DVT) prophylactic therapies, its routine use in low risk patients is unlikely to be cost-effective and may be deleterious if risk factors for bleeding are present. Through trauma surgeon consensus, we developed, implemented, and evaluated trauma DVT prophylaxis guidelines incorporating enoxaparin.
METHODS: Fifty patients with major orthopedic or spinal trauma (the approved criteria for enoxaparin use) were followed throughout hospitalization. Routine DVT screening was not performed. Enoxaparin use and incidence of DVT, pulmonary embolus (PE), and enoxaparin-related major bleeding (overt bleeding associated with a hemoglobin decrease ≥ 2g/dl, need for ≥ 2 units PRBC or need for surgery) and thrombocytopenia were recorded. All pharmacist interventions pertaining to enoxaparin were collected.
RESULTS: Average age, injury severity score and length of stay were 45.6 ± 19.5 years, 19.0 ± 11.2, 14.3 ± 10.0 days, respectively. Most injuries (pelvic/acetabular [32%], hip [20%], femur/tibial [52%], and spinal [12%]) were related to motor vehicles (52%) and falls (30%). Two-thirds (68%) of patients received enoxaparin, but only for 53%, on average, of their hospital stay. Vena caval filters were prophylactically inserted in 5 patients. Duplex-proven DVT occurred in 2 patients and angiography-proven PE in one patient. Enoxaparin-related major bleeding and thrombocytopenia occurred in 3 and 1 patients, respectively. Pharmacists recommended enoxaparin in 11 cases and enoxaparin discontinuation in 7 cases (2 for bleeding; 5 for lack of indication). Most recommendations (78%) were accepted.
CONCLUSIONS: Pharmacist-led implementation of enoxaparin DVT prophylaxis guidelines were associated with fewer thrombotic complications but more bleeding than the incidence seen in controlled studies. It is unclear whether the significant number of days patients did not receive enoxaparin, when indicated, was due to fears of enoxaparin-related bleeding or other concomitant factors.

42A. Documenting therapeutic services in a Saudi Arabian military hospital emergency department: what do non-emergency ambulatory patients' prescriptions represent? *Ahmed M. Moussa, M.S.*, Ahmed N. Al-Attar, B.S., Hossam H. Hassan, M.B.B.S., Nancy Hashim, B.S.N., Linda Dugdale, B.S.N., Terisita S. Voctorino, B.S.N.; Armed Forces Hospital, Jabail, Saudi Arabia.

PURPOSE: This study documented therapeutic services in the emergency department (ED) of a Saudi Arabian military hospital in order to 1) determine the urgency of ED patients' prescriptions for their illness; 2) evaluate ambulatory prescriptions; and 3) consider pharmacoeconomics.
METHODS: Nine thousand one hundred forty-four patient data retrieval forms and 6619 prescriptions were reviewed between February 1 and April 30, 1999. In accordance with type of service, ED patients were classified into four groups: emergencies (groups 1 and 2) and ambulatory (groups 3 and 4). The Transition Systems Incorporation was used to evaluate both direct and indirect ED cost items. Data were expressed as means ± SD and ANOVA was used in statistical analysis; a priori below 0.05 was significant.
RESULTS: Emergency patients were 27.61% of the 9144 ED patients and non-emergency ambulatory patients were 72.39%. ED patients formed 15% of total hospital patients; patients who had investigations (i.e., laboratory, radiology, and ECG) were 22.90%, cardiopulmonary resuscitation 0.03%, oxygen therapy 0.59%, admissions 4.68%, nebulization 9.76%, dressing/suturing 16.62%, referral to clinics 6.82%, injections 12.57%, and on-call consultant/specialist services 3.48%. Daily direct costs were 7091 ± 1810 Saudi riyals, while indirect costs were 989 ± 280 Saudi riyals.
CONCLUSIONS: ED patients seen, including, all who were ambulatory, were excessive. Because refusing treatment to ED patients may jeopardize some patients' health, it is recommended we dispense stat dose only and not more than 24-hour doses and discontinue investigations for non-emergency care as a way to cut down the costs of pharmacy and investigations by 50%. This will result in a reduction of 22.35% in direct costs and 19.60% in the overall ED budget. It is recommended that a central committee on emergency medicine be established to set nationwide practice standards, as well as implement a triage system and educational programs to guide both patients and the public.

Dermatology

43. Absorption of acetone across pig skin. Martin Javors, Ph.D., Leo Delallo, *Robert Talbert, Pharm.D.*; University of Texas Health Science Center, San Antonio, TX; University of Texas, Austin, TX.

A number of topical products contain acetone as a solubilizing or drying agent. No systematic study to evaluate the absorption of acetone across the skin has been done. Also, the normal, basal level of acetone in whole blood has never been reported for pigs.
PURPOSE: The purpose of this study was to quantify acetone levels in whole blood of pigs after the application of an acetone-polymer mixture (APM) to the skin of the pigs using acute and chronic dosing.
METHODS: APM was applied to a defined area of skin on the side of the animals that was 25 x 25 cm. In some of the animals, the skin was abraded. Blood samples were collected at 12 time points during a 4 hour experiment. Acetone was quantified with gas chromatography and flame ionization detection.
RESULTS: The baseline acetone levels were 0.575 ± 0.303 µg/ml (mean ± SD) for 16 samples in 9 pigs. The samples measured were the first samples for the pigs in the acute and the chronic study. The levels we observed are about one

fourth the level of 2.9 µg/ml reported for humans (Brega, et al. *J Chromatog* 553;1991:249-54). For the acute pig study, in which pigs were exposed to a single treatment of APM, there was no perceptible, time dependent elevation of blood acetone levels for 5 out of 8 pigs. However, in 3 of the pigs, acetone levels rose above baseline levels; 19.4 µg/ml at 118 min,
8.9 µg/ml at 237 min, and 6.3 µg/ml at 271 min. For the chronic study (50 days of APM), there was evidence in some animals that minimal elevations in acetone levels occurred. The acetone level did not exceed 6 µg/ml in any pig.
CONCLUSIONS: There was no evidence for elevated blood acetone levels over time with chronic treatment. The results of this study indicate that neither the acute nor chronic application of APM to the skin of pigs produces levels of acetone in the blood which would be considered toxic. The results of this study indicate that only a minimal amount of acetone was absorbed systemically due to the external application of APM.

Drug Delivery

44. The stability of total nutrient admixtures. *Kwang Hyun Namgung, M.S.*, Sukhynag Lee, Pharm.D., M.S.; Sookmyung Women's University, Seoul, Korea.

PURPOSE: The objective is to study the stability of total nutrient admixtures (TNAs) containing lipid emulsions, amino acids and dextrose.
METHODS: The admixtures were prepared as 6 combinations in which 10% Intralipid® or Intralipose® were mixed with 3 different 10% amino acid solutions (Freeamine®, Intrafusin® or Topanusol®) in a glass bottle container. The mixing sequence involved transfer of amino acid solutions to the partial filled 1 liter glass bottle of 20% dextrose, followed by addition of fat emulsion. Electrolytes and heparin were added to the amino acid solution before compounding. The TNAs were tested initially and daily for 7 days at storage condition of 4°C in refrigerator or room temperature. Visual inspection was done first and measured for pH, osmolality, particle size of emulsion, peroxide value and the concentrations of amino acids, dextrose and fatty acids.
RESULTS: The apparent change of creaming has shown from 2 to 7 days according to the different TNA combinations and storage conditions. The measured parameters remained unchanged throughout the study except tryptophan.
CONCLUSIONS: The TNAs were stable at least 2 days at room temperature and 4 days in refrigerator. The TNAs can be stored for a limited period in refrigerator.

Education

45. Characterization of writing tasks required of clinical pharmacists. *Jeffrey Kennicutt, Pharm.D. candidate*, Laurie L. Briceland, Pharm.D., FCCP, Eric H. Hobson, Ph.D., Nancy M. Waite, Pharm.D.; Albany College of Pharmacy, Albany, NY.

PURPOSE: This study characterizes the types, frequencies and value of writing tasks found in clinical pharmacy practice. A secondary purpose was to explore any correlation between specific tasks and clinical practice types.
METHODS: A survey was developed, piloted and mailed to 129 clinical clerkship preceptors who practice in diverse settings representative of contemporary clinical pharmacy practitioners. The survey queried how often the practitioner wrote specific documents (e.g., formulary review), time on task and value to clinical practice for each document.
RESULTS: Sixty-six (51%) questionnaires were returned and sorted by clinical practice site. The majority of respondents were inpatient clinical practitioners (56%) or faculty/researchers (18%). Respondents reported writing 25 distinct documents in varying degrees of frequency. Respondents rated clinical reports and in-services as requiring the most time on task and also indicated they were the most valuable to their professional practices.
CONCLUSIONS: Because clinical pharmacy is a writing intensive professional practice, incorporation of specific didactic instruction into the pharmacy curriculum, based on the most frequent and important writing tasks, should be considered. In addition to pharmacy students, contemporary practitioners may benefit from continuing education instruction in professional writing. The results of this survey will assist the development of writing instruction curricula within the context of contemporary clinical pharmacy practice.

46. A comparison of telephone versus face-to-face interviews as methods for providing warfarin therapy education. Debra M. Offricht, Pharm.D., *Debra J. Barnette, Pharm.D.*, Thad Koppenhafer, B.S.; Kaiser Permanente Rocky Mountain Division; University of Colorado Health Sciences Center; Denver, CO.

Centralized anticoagulation services often utilize telephone contact as the primary mode of interaction with patients. However, little is known about the ability to educate patients regarding warfarin therapy via telephone.
PURPOSE: This pilot study compared telephone versus face-to-face interviews as methods for providing anticoagulation medication education.
METHODS: Two pharmacist-managed clinics were compared, one using primarily telephone education (Clinical Pharmacy Anticoagulation Service [CPAS]) and the other using in-person education (University Group [UG]). Patient anticoagulation knowledge was assessed using a 24-item scripted questionnaire administered via telephone by a neutral research assistant. Study patients were randomly selected from both services.
RESULTS: Ninety patients were surveyed (60 CPAS, 30 UG). The mean age for each group was 66.1 and 63.6 years old, respectively. All patients verbalized their current warfarin dose correctly and nearly all (58/60 CPAS, 30/30 UG) recognized bleeding as the worst possible complication. On average, CPAS patients stated fewer signs of bleeding (2) compared to UG patients (3), p=0.009. Significantly more UG patients (24/30, 80%) compared to CPAS patients (29/60, 48%) indicated they would call or go to the emergency department (ED) for uncontrolled bleeding (bloody stools), p=0.003.
CONCLUSIONS: Results of this study suggest that patients on warfarin therapy who receive in-person education are more likely to recognize signs of bleeding and go to the ED for uncontrolled bleeding. Further prospective research is needed to assure quality and satisfactory educational outcomes for anticoagulation programs via the telephone and in-person.

47. The impact of an active learning, case-based therapeutics course on clerkship case write-ups. *Nancy M. Waite, Pharm.D.*, Eric H. Hobson, Ph.D.; Albany College of Pharmacy, Albany, NY.

PURPOSE: Active learning, case-based instruction is often used by clinical practitioners in their teaching and is purported to improve higher-order abilities. This study was designed to determine the effect of instructional change on performance of professional practice duties as demonstrated by students' patient case write-ups.
METHODS: This study examined patient cases written by undergraduate students while on clerkship. Samples were randomly selected from cases submitted from community versus institutional clerkships and written before and after initiation of the active learning approach in the therapeutics sequence. A 4-point scoring rubric, validated by six clinical, science and humanities faculty, was developed to assess organization, tone, clinical accuracy, readability and persuasiveness. Each case was scored by two reviewers.
RESULTS: Ninety-two case write-ups were randomly selected from 372 cases (71% return rate). This included 10 pre-scored control cases. Cases written after the active-learning approach had significantly higher overall scores, with the shift occurring in the low-range scores (p=0.015). There was no difference in scores with pharmacist or non-pharmacist raters or with clerkship type. Active-learning participants were more likely to use a professional tone, be better organized and demonstrate better readability. Clinical accuracy and persuasiveness were similar in both groups.
CONCLUSIONS: An active learning, case-based approach in therapeutics improves the low to average student's ability to write case summaries in a more organized, professional and readable manner. This method of teaching did not decrease their mastery of clinical knowledge. Continued efforts to implement active learning approaches are warranted to improve the performance for a large percentage of students.

Endocrinology

48. The influence of cigarette smoking on Circadian rhythm of DHEA and DHEA-S. *Patricia D. Kroboth, Ph.D.*, Maggie Folan, B.S.N., Roslyn A. Stone, Ph.D., Janet A. Amico, M.D.; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: During abstinence from smoking, withdrawal symptoms occur despite existing therapeutic strategies, including nicotine supplementation. To date, little attention has been focused on differences in Circadian secretion patterns of adrenal hormones between habitual smokers and never smokers and changes with acute smoking cessation. Smoking stimulates the release of arginine vasopressin, which increases ACTH and in turn, stimulates release of adrenal hormones. Epidemiological data indicate that relative to nonsmokers, habitual smokers have higher concentrations of DHEA-S. This study was designed to characterize the Circadian rhythm of DHEA and DHEA-S in habitual smokers and nonsmokers.
METHODS AND RESULTS: Data from four men (two smokers) and two women (one smoker) show that relative to nonsmokers, smokers have a Circadian rhythm characterized by spikes during the daytime hours. DHEA-S concentrations were 2-fold higher in male smokers than in nonsmokers. In a second component of the study (evening), when one young male smoker abstained from smoking for 3 hours, then smoked three cigarettes within 30 minutes, a greater than 2-fold increase in DHEA concentrations was observed.
CONCLUSIONS: There are no previous reports of the influence of acute smoking on DHEA concentrations, nor of habitual smoking on Circadian pattern. These findings in a small number of subjects have potentially important implications for management of the rate of decline of DHEA and DHEA-S concentrations during smoking cessation. There are also mechanistic implications because of the blunted DHEA Circadian pattern in depression,

and the well-known association between smoking and depression. Continued and more intensive study in additional subjects is warranted.

49. An evidence-based medicine approach for assessing the appropriateness of thyroid hormone suppression in multinodular thyroid disease. *Grace Kuo, Pharm.D.*, Frank Pucino, Pharm.D., Nicholas Sarlis, M.D., Ph.D., Debbie Byrd, Pharm.D., Robert Wesley, Ph.D., Monica C. Skarulis, M.D., Lynnette Nieman, M.D., Gyorgy Csako, M.D.; Clinical Center, National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; Auburn University.

PURPOSE: To evaluate the effectiveness of thyroid hormone suppression on multinodular thyroid disease with systematic review of the literature, survey of endocrinology practitioners, and analysis of patient data.
METHODS: Relevant articles were identified through manual and on-line (MEDLINE) computer searches (1950-1999). Data were extracted from controlled studies, and the likelihood of reduction in nodule size by thyroid hormone suppression therapy (benefit ratio), 95% confidence intervals (CI), and statistical significance were determined. Meta-analysis was used for assessing combined benefit ratios. Published opinions (editorials, reviews, book chapters) and survey results from 22 NIH endocrinology practitioners were also analyzed. An automated database of 969 NIH patients receiving levothyroxine therapy was used for retrospective analysis of therapeutic outcomes in 30 patients with multinodular thyroid disease. Hill's criteria were applied to further assess the causal association between thyroid suppression and nodule reduction.
RESULTS: The combined benefit ratios determined by the random effects model and Mantel-Haenszel approaches were 5.09 (CI 2.46-10.55, $p<0.001$) and 5.62 (CI 2.74-11.53, $p<0.001$), respectively. Most published opinions (20/23) favored or accepted levothyroxine suppression therapy either optionally or routinely. An initial trial of mild-to-definite thyroid suppression therapy (TSH $\leq$ 1.00 mU/L) was suggested by 22 NIH endocrinology practitioners. Furthermore, 79% (23/29) of patients with multinodular thyroid disease managed by 24 NIH endocrinology practitioners had laboratory evidence of mild to moderate thyroid suppression (TSH $\leq$ 1.00 mU/L). Evaluation by Hill's criteria suggested a "possible-to-probable" causal association between thyroid suppression and nodule reduction.
CONCLUSIONS: Thyroid hormone suppression therapy increases the likelihood of nodule reduction in multinodular thyroid disease.

50. An assessment of type-2 diabetic patients' knowledge in a general medicine and an endocrine clinic. Mario M. Zeolla, Pharm.D., *Nancy M. Waite, Pharm.D.*, Michael P. Kane, Pharm.D.; Albany College of Pharmacy, Albany, NY.

PURPOSE: This study compared diabetes knowledge in type-2 patients managed in general and specialized ambulatory settings. The objectives were to examine how patient demographics, previous diabetes education and treatment setting relate to diabetes knowledge, and examine the correlation between diabetes knowledge and glycemic control.
METHODS: A written multiple-choice questionnaire was developed and pilot-tested to assess patients' perceived and actual diabetes knowledge regarding medication, diet and general disease management. Questionnaires were randomly distributed during office visits or by mail at a general medicine and endocrinology clinic. HgA_{1c} values were gathered via chart review. Diabetes knowledge was quantified by perceived and actual knowledge scores.
RESULTS: Eighty questionnaires were included in the analysis (36 general, 44 specialized). There were no significant differences in patient demographics between sites. Endocrine clinic patients attended more diabetes education classes ($p=0.014$) and received more live education ($p=0.01$) than general medicine patients. Total perceived knowledge scores were higher at the endocrine site ($p=0.003$). However, mean HgA_{1c} and actual knowledge scores were not significantly different between sites. Linear regression revealed a significant correlation between perceived and actual knowledge for patients at the general medicine site ($r^2=0.51$, $p=0.001$). No correlation was found between knowledge scores and HgA_{1c} values at either site.
CONCLUSIONS: Similar patient populations treated at general and specialized ambulatory practices demonstrated comparable actual diabetes knowledge and glycemic control. Greater previous diabetes education appears to increase perception of knowledge. However, perception may not correlate with actual diabetes knowledge. Glycemic control does not correlate with perceived or actual diabetes knowledge.

51. Clinical outcomes of a multidisciplinary diabetes education and management program at a Veterans Administration Outpatient Clinic. *Mary G. Amato, Pharm.D., M.P.H.*, Dora Santiago, M.S.N., Anita Moore, R.D.; University of Texas at San Antonio, San Antonio, TX.

PURPOSE: To assess effects of a diabetes education and management program on glycemic control and hyperlipidemia in type-2 diabetics with elevated HgA_{1C} levels.
METHODS: Expansion of an existing diabetes education program to include ongoing monitoring and optimization of treatment regimens was initiated in August 1998. The impact of this program in patients with HgA_{1C} values over 9% was evaluated by comparing glycemic and lipid control in patients enrolled in this program (DMP) versus those followed by their primary care provider only (PCO). Patients with at least two HgA_{1C} values and two primary care visits between April 1998 and March 1999 were included.
RESULTS: Of approximately 1700 diabetics at the clinic, 180 had HgA_{1C} values over 9%, and 86 of these had at least two HgA_{1C} values and two primary care visits during the study period. 50 were in the PCO group and 36 were in the DMP group. Most patients had longstanding diabetes. The mean change in HgA1C was -2.1% in the DMP group versus -0.2% in the PCO group ($p=0.000004$). Forty-seven percent of the DMP patients had over a 2% drop in HgA_{1C} versus 12% in the PCO group. Eighty-two percent of patients in the DMP had low density lipoprotein levels under 130 (1998 goal) versus 57% in the PCO group. No difference in triglyceride levels was seen.
CONCLUSIONS: The DMP has demonstrated improvements in glycemic control. Further analysis of data will include a comparison blood pressure control, compliance with clinical practice guidelines, and utilization of acute care.

52. Diabetogenesis and ketoacidosis with atypical antipsychotics. *Daniel R. Wilson, M.D.*, Leo D'Souza, M.D., Nibar Sarkar, M.D.; The Lewis Center, Cincinnati, OH.

PURPOSE: With the advent of novel antipsychotic compounds that are relatively free of extrapyramidal symptoms, clinicians have shown increased interest in side effects that have previously not been the focus of attention. Recent case reports have suggested that some atypical antipsychotics may induce clinically significant alterations in glucose metabolism. The authors evaluated the risk of diabetogenesis in a large state hospital cohort.
METHODS: The computerized records of all adult patients in an academically affiliated state hospital were retrospectively reviewed over a 48-month period (May 1995 to May 1999). Patients treated with novel antipsychotics were identified as were persons evaluated for diabetes management. The rosters were collated and full charts of patients on both lists were reviewed with respect to age, sex, psychiatric diagnosis, drug treatment history, diabetic risk factors, and clinical association between glucose intolerance and treatment with atypical antipsychotics.
RESULTS: Results of preliminary data analysis revealed acute and marked glucose intolerance in 11 patients. Changes were not related to significant weight gain and typically occurred in the first 6 weeks. Six patients were treated with insulin at least transiently and four experienced diabetic ketoacidosis with referral to a tertiary care facility for intensive and life-saving medical care.
CONCLUSION: It is of considerable concern that at least some anti-psychotics may be dangerously diabetogenic. A more extensive analysis of the larger statewide Ohio Department of Mental Health database is now underway to ascertain whether 1) all or specific medications are diabetogenic, 2) more assertive treatment monitoring is warranted, and 3) atypical antipsychotics are contraindicated in patients at high risk for new-onset diabetes.

53. Drug utilization review of acarbose in the Saint Louis Veterans Affairs medical center. *Carrie F. Lee, Pharm.D.*, Carla Zeilmann, Pharm.D., BCPS; St. Louis Veterans Affairs Medical Center; St. Louis College of Pharmacy, St. Louis, MO.

PURPOSE: Determine the effectiveness of acarbose in lowering HgA_{1c} in the veteran population at the St. Louis Veterans Affairs Medical Center (VAMC).
METHODS: A list of all outpatients currently receiving acarbose at the St. Louis VAMC was obtained from the electronic pharmacy files. Data on current diabetic agents received and HgA_{1c} prior to and after addition of acarbose was gathered. Patients were excluded if HgA_{1c} data was unavailable up to one year prior or six months after addition of acarbose. Statistical values were determined using the Sigma Stat™ program.
RESULTS: One hundred forty-nine veterans were included and evaluated. The change in HgA_{1c} was non-significant with the exception of the sub-group of veterans on a sulfonylurea and/or metformin with a $HgA_{1c} > 9$ prior to acarbose addition. HgA_{1c} was reduced by 0.6% (NS) in patients taking either a sulfonylurea or metformin prior to acarbose addition. Between group differences were non-significant with the exception of HgA_{1c} reduction being greater in patients receiving one oral therapy prior to acarbose than in those receiving two oral therapies prior to acarbose.
CONCLUSIONS: Acarbose had little effect on HgA_{1c} overall. In this population, acarbose may be useful as an adjunct in patients on oral therapy who have not achieved adequate HgA_{1c} reduction. Though not statistically significant, the reduction in HgA_{1c} noted in patients on one oral therapy prior to acarbose may be clinically significant. Thus, acarbose may be an adequate adjunctive agent in this patient population.

54. Effects of flutamide and testolactone on cortisol clearance in children with congenital adrenal hyperplasia. *Maryam R. Mohassel, Pharm.D.*, Karim A. Calis, Pharm.D., M.P.H., Deborah P. Merke, M.D., Meg Keil, PNP., Alan T. Remaley, M.D., Ph.D.; National Institutes of Health, Bethesda, MD.

PURPOSE: The objective of this study was to determine if flutamide and testolactone decrease the total body clearance of cortisol in children with

congenital adrenal hyperplasia (CAH).
METHODS: Cortisol clearance studies were performed twice in eight children with CAH. The first study was conducted at the time of admission in patients who had received flutamide and testolactone for at least three months. The second study was performed after a washout period of at least 48 hours. All patients received a continuous infusion of hydrocortisone (0.6 $mg/m^2/h$) from 6:00 p.m. to 2:00 a.m. Blood samples for cortisol determination were collected hourly from 6:00 p.m. (baseline) to 3:00 a.m. Serum cortisol concentrations were determined using a fluorescence polarization immunoassay. Total body clearance (CL_{TB}) was calculated using the equation $CL_{TB} = R_0/C_{ss}$ (where R_0 is the hydrocortisone infusion rate and C_{ss} is the steady state serum cortisol concentration).
RESULTS: The mean total body clearance of cortisol during treatment with flutamide and testolactone was 154 ± 76 ml/min. Cortisol clearance after the medication washout period increased to 355 ± 186 ml/min. The difference in cortisol clearance was significant (p=0.0117, Wilcoxon signed rank test).
CONCLUSION: The combination of flutamide and testolactone substantially decreases the total body clearance of cortisol in children with CAH. The mechanism and clinical significance of this effect have yet to be elucidated.

55. Glycemic control in medical inpatients receiving sliding scale insulin regimens versus routine antidiabetic medications: a pilot study. *Lori M. Dickerson, Pharm.D., BCPS*, Jonathon L. Sack, M.D., William J. Hueston, M.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: Patients with diabetes are traditionally converted from their routine antidiabetic medication to a sliding scale insulin (SSI) during hospitalization. However, the benefits of SSI regimens versus routine medications are unclear. The purpose of this study is to compare the effects of routine antidiabetic medications alone versus the combination of SSI and routine antidiabetic medications on the frequency/severity of glycemic excursions and length of stay in diabetic patients hospitalized for other comorbid conditions.
METHODS: Patients with diabetes hospitalized for other co-morbid conditions but not meeting criteria for hyperosmolar nonketotic coma, diabetic ketoacidosis, hyperglycemia (> 400 mg/dl) or hypoglycemia (< 50 mg/day) are enrolled and randomized to receive either their routine antidiabetic medications alone or the combination of SSI and routine antidiabetic medications. Finger stick blood glucose (FSBG) are measured four times daily, and management of all medical conditions is instituted as part of usual care.
RESULTS: Comparisons of the groups of patients randomized to SSI alone or the combination with SSI show no differences in age, gender, admitting diagnosis or average initial glucose on admission. Length of stay (days) for the two groups did not differ (3.67 versus 4.25, p=0.58). One episode of hyperglycemia occurred in the routine antidiabetic medication group and one episode of hypoglycemia occurred in the combination SSI group.
CONCLUSION: Preliminary results indicate that glycemic excursions occur in both groups but length of stay does not differ with the addition of SSI to routine antidiabetic medications in this population. Patient enrollment continues and additional results will be presented.

Gastroenterology

56. Clinical and economic outcomes of treating *Helicobacter pylori* in patients taking chronic acid suppression therapy. *Patrick M. Klem, Pharm.D.*, Julie Himstreet, Pharm.D., Katie Bohnert, Pharm.D., Barry Carter, Pharm.D., Joel Levine, M.D.; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: To compare symptoms, medical costs and quality of life in primary care patients with ulcer-like dyspepsia who are tested and treated for *H. pylori* with a control group treated with chronic antisecretory therapy alone.
METHODS: Historical controls (n=100) were identified by a pharmacy data base and chart review of patients with documented or suspected PUD or ulcer-like dyspepsia taking chronic antisecretory therapy. Study patients were identified by a pharmacy database and treated by clinical pharmacists via a protocol with a gastroenterologist. Patients taking chronic antisecretory therapy for > 3 consecutive months were recruited. Patients with predominant symptoms of GERD or chronic NSAID use were excluded. Patients who tested positive by serology were treated with lansoprazole, amoxicillin, and clarithromycin all dosed twice daily for 14 days. Treatment follow-up was scheduled at day 3, completion of treatment, 2 months post treatment, and 6 months post treatment to assess adverse events, compliance, antisecretory agent use, symptom recurrence, and quality of life. Outcomes measured included total cost (cost of treatment, clinician charges, procedure charges, hospital charges, quality of life).
RESULTS: Historical control patients with *H. pylori* showed only 14% discontinued antisecretory therapy after one year, resulting in a cost of $1136/pt/year. To date, 16 study patients have been enrolled and 2-month follow up has been completed for 14 patients. Seventy percent discontinued all antisecretory medications, 1/14 restarted less aggressive antisecretory therapy, and 3 patients have not changed their antisecretory therapy.
CONCLUSION: Data for additional patients (n=60) and pharmacoeconomic analysis will be presented.

57. A quantitative systematic review of 5-HT_3 receptor antagonists versus conventional agents for the prophylaxis of postoperative nausea and vomiting. *Peter S. Loewen, Pharm.D.*, Carlo A. Marra, Pharm.D., Peter J. Zed, Pharm.D.; Vancouver Hospital and Health Sciences Center; University of British Columbia, Vancouver, BC, Canada.

PURPOSE: Numerous antiemetics have been studied for the prevention of postoperative nausea and vomiting (PONV) including conventional agents (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol) and the 5-HT_3 receptor antagonists (ondansetron, dolasetron, granisetron and tropisetron). The results of these trials have been divergent and inconsistent. The purpose of this quantitative systematic review was to evaluate the effectiveness of $5HT_3$ receptor antagonists compared to conventional antiemetics for the prevention of PONV in all types of surgery.
METHODS: A systematic search of the English language literature using computerized MEDLINE, EMBASE, and Pre-MEDLINE databases from 1966 to March 1999 and a manual search of references from retrieved articles were performed. Individual efficacy and adverse effect data was extracted from each of the studies according to a predefined protocol. The summary odds ratios were calculated using the Dersimonian and Laird method under a random effects model.
RESULTS: A total of 43 trials met our pre-defined inclusion criteria and were included in our analysis. The summary of results of the 32 studies examining PONV indicated a 46% reduction in the odds of PONV in the 5-HT_3-treated group (0.54 [95% CI 0.42-0.71], p<0.001). Evaluation of PONV by conventional antiemetic agent demonstrated a 39% reduction compared to droperidol (0.61 [95% CI
0.42-0.89], p<0.001) and a 56% reduction compared to metoclopramide (0.44 [95% CI 0.31-0.62], p<0.001). The summary of results of the 34 studies examining vomiting indicated a significant 38% reduction in the odds of vomiting in the 5-HT_3-treated group (0.62 [95% CI 0.48-0.81], p<0.001).
CONCLUSIONS: The findings of this quantitative systematic review indicate that 5-HT_3 receptor antagonists are superior to conventional antiemetic agents for the prevention of PONV and vomiting. The reduction in the odds of PONV and vomiting is significant in the overall analysis and the subgroup analyses comparing 5-HT_3 receptor antagonists to droperidol and metoclopramide.

58E. Rabeprazole: safety profile of a new proton pump inhibitor. David A. Johnson, M.D., Dennis Riff, M.D., Carlos Perdomo, Ph.D., John Jaskir, Ed.D., Robert Niecestro, Ph.D., *Jay Barth, M.D.*; Eastern Virginia Medical School, Norfolk, VA; Associated Gastroenterology Medical Group, Anaheim, CA; Eisai Inc., Teaneck, NJ; Covance Inc., Princeton, NJ.

PURPOSE: Rabeprazole shows considerable promise across a range of indications – healing and healing maintenance of erosive or ulcerative gastroesophageal reflux disease (GERD), and healing of duodenal and gastric ulcers – provided that its clinical efficacy is supported by a favorable safety profile.
METHODS: To determine the safety profile of rabeprazole, an integrated summary was compiled using safety data from 3,556 subjects in 63 international clinical trials receiving rabeprazole for up to 1 year.
RESULTS: In short- and long-term controlled international studies, adverse events (AE) probably related to treatment, in at least 1% of treated patients, were headache (2.4% vs 1.6%) and diarrhea (2.4% vs 3.1%) for rabeprazole vs placebo. Rabeprazole 20 mg daily conferred no additional risk compared to the 10 mg dose for all indications. Hematologic parameters, liver and kidney function, cardiac enzymes, systolic/diastolic blood pressure, and ECG measurements showed no apparent dose-related effects. None of the AE suggested that rabeprazole affected any H^+/K^+-ATPase other than the gastric proton pump. Rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin, theophylline, or phenytoin, although, like with all acid suppressants, individual patients may need monitoring and dosage adjustment when digoxin or ketoconazole is coadministered with rabeprazole. There was no increase in AE in elderly patients. No dosage adjustment was required in elderly patients, patients with renal disease, or patients with mild-to-moderate hepatic impairment.
CONCLUSIONS: The present results indicate that rabeprazole is accompanied by a favorable safety profile, for both short- and long-term use.
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59E. Gastric acid suppression by rabeprazole: how much is enough to normalize esophageal acid exposure in gastroesophageal reflux disease? Malcolm Robinson, M.D., Sheldon Sloan, M.D., Jerry D. Gardner, M.D., *Jay Barth, M.D.*; Oklahoma Foundation for Digestive Research; University of Oklahoma Health Sciences Center, Oklahoma City, OK; Janssen Research Foundation, Titusville, NJ; Science for Organizations, Inc., Chatham, NJ; Eisai Inc., Teaneck, NJ; Eisai Ltd., London, United Kingdom.

PURPOSE: To determine the extent of gastric acid suppression (GS) needed to normalize esophageal acid exposure (EAE) in gastroesophageal reflux

disease (GERD) patients treated with rabeprazole, a new proton pump inhibitor.
METHODS: In a randomized, double-blind, two-way crossover study, 20 patients with GERD and abnormal EAE received 20 mg or 40 mg rabeprazole once-daily for 7 days. Intragastric/esophageal pH were measured for 24 hours at baseline, at days 1 and 7 of therapy, and on day 1 post-therapy. EAE and GS times were calculated as percentages of each 24-hour period for each patient for both doses.
RESULTS: Baseline mean GS and EAE times were 9.1% and 24.6% for 20 mg/d and 12.2% and 23.7% for 40 mg/d, respectively. Both doses suppressed gastric acid ≥ 65% of the time (GS time at day 7, 65.6% for 20 mg/d and 75.2% for 40 mg/d) and normalized EAE (EAE time at day 7, 5.1% for 20 mg/d and 2.0% for 40 mg/d). EAE normalized at day 7 in 85% of patients with 20 mg/d and in 90% with 40 mg/d. The relationship between GS and EAE showed that GS for 35% to 40% of a 24-hour period was sufficient to normalize EAE.
CONCLUSIONS: The appropriate dose of antisecretory medication for GERD patients may be determined based on extent and duration of GS. GS for 35% to 40% of a 24-hour period was sufficient to normalize EAE for this group. Both 20 mg and 40 mg doses of rabeprazole produced normal EAE.
Published in Gastroenterol 1999;116:A292-3.

60E. Rabeprazole consistently effective for acid-related diseases based on worldwide studies. Karna Dev Bardhan, M.D., Norman Gitlin, M.D., *Jay Barth, M.D.*, Carlos Perdomo, Ph.D., Robert Niecestro, Ph.D.; Rotheram General Hospital, South Yorkshire, United Kingdom; Emory University, Atlanta, GA; Eisai Ltd., London, United Kingdom; Eisai Inc., Teaneck, NJ.

PURPOSE: Rabeprazole, a new proton pump inhibitor, has been undergoing clinical investigation for gastroesophageal reflux disease (GERD) healing, long-term GERD healing maintenance, and healing of duodenal and gastric ulcers. To evaluate the efficacy of rabeprazole 20 mg for these indications, we compiled a summary of results from worldwide clinical trials.
METHODS: Results of placebo-controlled trials comparing rabeprazole 20 mg once-daily to omeprazole 20 mg or ranitidine 150 mg BID or QID for endoscopically determined GERD healing (≤ 8 wk), GERD maintenance (≤ 1 year), duodenal ulcer healing (≤ 4 wk), and gastric ulcer healing (≤ 6 wk) were compiled and summarized.
RESULTS: Efficacy data for 3 adequately controlled trials for each indication are presented. GERD healing rates for rabeprazole were 88% vs 15% for placebo (n=44; p<0.001), 92% vs 71% for ranitidine (n=316; p<0.001), and 95% vs 96% for omeprazole (n=197). GERD maintenance rates for rabeprazole were 88% vs 21% for placebo (n=122; p<0.001), 84% vs 22% for placebo (n=169; p<0.001), and 96% vs 94% for omeprazole (n=141). Duodenal ulcer healing rates for rabeprazole were 87% vs 45% for placebo (n=60; p<0.001), 88% vs 76% for ranitidine (n=359; p=0.005), and 99% vs 96% for omeprazole (n=201). Gastric ulcer healing rates for rabeprazole were 93% vs 55% for placebo (n=52; p=0.003), 89% vs 83% for ranitidine (n=335), and 93% vs 93% for omeprazole (n=223).
CONCLUSION: Rabeprazole is consistently effective for each indication based on integrated results of worldwide clinical trials.
Published in Gut 1999;44(suppl 1):A125.

61E. Heartburn: is step up/step down therapy out of step? Evidence from a large community-based trial. Colin W. Howden, M.D., FRCP, FACP, FACG, FCP, James M. Henning, M.S., *Janice S. Griffin, B.S.N.*, Nancy L. Lukasik, B.S.N., Bidan Huang, Ph.D.; Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; TAP Holdings Inc., Deerfield, IL; Abbott Laboratories, Abbott Park, IL.

PURPOSE: To compare lansoprazole (LAN) vs ranitidine (RAN) for symptomatic heartburn (HB) in a primary care setting.
METHODS: A total of 593 HB patients were randomized to one of 4 regimens: LAN 30 mg QD X 20 weeks (LAN/LAN), RAN 150 mg BID x 20 weeks (RAN/RAN), LAN 30 mg QD x 8 weeks, then RAN 150 mg BID x 12 weeks (LAN/RAN), or RAN 150 mg BID x 8 weeks, then LAN 30 mg QD x 12 weeks (RAN/LAN). The primary efficacy variable was HB assessment by patient diary.
RESULTS: ITT analyses compared second period HB diary data for step up (RAN/RAN vs RAN/LAN) or step down (LAN/LAN vs LAN/RAN). Patients stepped up to LAN experienced significantly less HB while patients stepped down to RAN experienced significantly more HB. Crossover patients (LAN/RAN and RAN/LAN) had less severe HB on LAN. LAN/LAN patients experienced significantly less HB than RAN/RAN patients throughout the entire 20 week study.
CONCLUSION: Neither step up nor step down strategies for heartburn in primary care appears optimal. Initiation and maintenance therapy with lansoprazole was superior to either a step up or step down approach.
Published in Gastroenterol, April 1999;116:A190.

62. Efficacy of omeprazole-based antibiotic regimens for eradication of *Helicobacter pylori* in patients with peptic ulcer disease. *Hyun Joo, Kang, M.S.*, Dong Hoon Kang, M.D., Ph.D., Jong Hyun Yoo, M.D., M.S., Sukhynag Lee, Pharm.D., M.S.; Sookmyung Women's University, Seoul , Korea.

PURPOSE: Peptic ulcer disease has been involved with *Helicobacter pylori* infection and antibiotic regimens are primary treatments. An optimal therapeutic regimen for eradication of *H. pylori* remains uncertain due to variable efficacy. The objectives of this study were to evaluate the efficacy of omeprazole-based antibiotic regimens in bacterial eradication, healing of peptic ulcer and to identify factors affecting the efficacy.
METHODS: Seventy-seven patients were enrolled in the prospective, open-trial from November 1997 to September 1998. *H. pylori* infection was identified with endoscopy, *H. pylori* stain and rapid urease test. The first group (OAC7) received omeprazole 20 mg twice daily for 4 weeks which were the same schedule for all, amoxicillin and clarithromycin 250 mg thrice daily for 1 week; the second group (OAC14), for 2 weeks on the same regimen as the first; and the last group (OACD) has taken bismuth in addition to the OAC7 regimen for 1 week. Eradication of *H. pylori* and healing of peptic ulcer were evaluated with endoscopy and tests for *H. pylori* before and after the end of treatments.
RESULTS: There were no significant differences in eradication rates; 61% in OAC7, 57% in OAC14, 65% in OACD (p=0.817) and healing rates; 64% in OAC7, 52% in OAC14, 77% in OACD(p=0.193). Compliance affected eradication rates significantly among regimens (p=0.049). Twenty three cases (29%) complained of the minor side effects.
CONCLUSIONS: OAC7 was better in convenience of dosing schedule and showed less side effects with shorter duration and lower cost although there was no significant difference in efficacy.

63. The effect of multiple doses of fluoxetine on the pharmacokinetics and cardiovascular safety of cisapride in healthy volunteers. *Qinying Zhao, Ph.D.*, Helen Pentikis, Ph.D., Ming Zheng, Ph.D., Mary Ann Wojcik, M.S., Peter Lee, Ph.D., Jean-Loup Parier, M.D., Ph.D., Luana Pesco-Koplowitz, M.D., Ph.D.; Janssen Research Foundation, Titusville, NJ; GloboMax LLC, Hanover, MD.

PURPOSE: To evaluate the effect of steady-state fluoxetine on the pharmacokinetics and cardiovascular safety of cisapride at steady state in healthy volunteers.
METHODS: Twelve male subjects were treated according to the following sequence: baseline (day 0); phase I (days 1-6), cisapride 10 mg QID; washout (days 7-13); phase II (days 14-44), fluoxetine 20 mg QD; and phase III, cisapride 10 mg QID (days 45-51) plus fluoxetine 20 mg QD (days 45-52). Blood samples for determining cisapride levels were collected at the end of phases I and III (days 6 and 51). Twelve-lead ECG recordings were obtained at baseline (day 0, baseline for phase I), washout (day 13, baseline for phases II and III), and the end of phases I and III (days 6 and 51).
RESULTS: Cisapride plasma levels reached steady state by day 5 during phases I and III. Geometric means of cisapride $AUC_{0\text{-}24h}$, C_{max}, and C_{min} for phase III were significantly lower than those for phase I. Fluoxetine had no effect on the T_{max} or terminal $t_{1/2}$ of cisapride. Changes from baseline in $QT_{c,\,avg}$, $QT_{c,\,max}$ and $QT_{lc,\,avg}$ were similar for the three treatments. No correlation was observed between changes from baseline in $QT_{c,\,avg}$ and $C_{avg,}$ or between changes from baseline in $QT_{c,\,max}$ and C_{max}. No clinically relevant interactions between cisapride and fluoxetine were observed with regard to ECG parameters and other safety results.
CONCLUSIONS: Fluoxetine does not inhibit cisapride metabolism. Cisapride 10 mg QID with fluoxetine 20 mg QID is well tolerated.

64. Pharmacokinetic/pharmacodynamic comparisons between lansoprazole and pantoprazole in healthy subjects. *Wei-Jian Pan, Ph.D.*, Yi-Lin Chiu, Ph.D., Roberta Keith, B.S.N., Betsy Pilmer, B.S.N.; Abbott Laboratories, Abbott Park, IL; TAP Holdings Inc., Deerfield, IL.

PURPOSE: To compare the pharmacokinetics/pharmacodynamics of 5-day lansoprazole 30 mg QD and pantoprazole 40 mg QD.
METHODS: Sixty-five healthy adult subjects received 5-day lansoprazole 30 mg QD or pantoprazole 40 mg QD in a randomized two-way crossover experiment. Plasma samples were analyzed for days 1 and 5 lansoprazole and pantoprazole pharmacokinetics. Twenty-four-hour gastric-pH evaluations were conducted at baseline and on days 1 and 5 of each period for pharmacodynamic evaluation.
RESULTS: Pharmacokinetic parameters, expressed as mean ± SD, and mean gastric pH were:

	Lansoprazole 30 mg QD		Pantoprazole 40 mg QD	
	Day 1	Day 5	Day 1	Day 5
C_{max} (ng/ml)	779.4 ± 290.1	759.4 ± 306.3	2138 ± 1012	2408 ± 1146
T_{max} (h)	1.4 ± 0.4	1.4 ± 0.3	2.4 ± 0.9	2.3 ± 1.0
$AUC_{0\text{-}24}$ (ng•h/ml)	1980 ± 1670	1948 ± 1753	4627 ± 5429	5488 ± 8192
$t_{1/2}$ (h)	1.05 ± 0.38	1.05 ± 0.36	1.00 ± 0.38	0.98 ± 0.34

Time Interval (h)	Mean Gastric pH on Day 1 and Day 5			
0-5	3.57	4.60	2.59†	4.10†
5-10	4.52	4.87	3.51†	4.64
10-15	4.50	4.49	3.76†	4.31
15-24	3.35	3.45	2.87†	3.44
0-24	3.88	4.21	3.13†	4.01

†significantly different from the lansoprazole 30 mg QD on days 1 or 5 (p<0.05)

CONCLUSIONS: Pantoprazole AUC_{0-24} increased on day 5 and showed higher inter-subject variability than did lansoprazole. Lansoprazole 30 mg QD was more effective in gastric-pH elevation than was pantoprazole on day 1 and was at least as effective as pantoprazole on day 5.

Geriatrics

65. Vitamin K usage in the elderly compared to the American College of Chest Physicians' recommendations. *Trang Y. Vo, Pharm.D.,* Mary Beth O'Connell, Pharm.D., BCPS; University of Minnesota; Institute for the Study of Geriatric Pharmacotherapy, Minneapolis, MN.

PURPOSE: To determine concordance between vitamin K use and the 1995 American College of Chest Physicians recommendations (ACCP) for hospitalized elderly patients.
METHODS: A secondary data analysis of a 23 center, retrospective chart review (n=1001) was conducted. Patients in the primary database were ≥ 65 years old who began and received at least 3 warfarin doses while hospitalized between 1/1–6/30, 1996. No warfarin guidelines or written pharmacist consults existed. 367 patients met the secondary inclusion criteria: had a high INR value but no bleed (n=261), had a bleed remotely related to warfarin (n=99) or had received vitamin K therapy without a high INR or bleed (n=7). Only ACCP steps 1, 2, 3 and 6 were evaluated since bleeding date was not recorded in primary database. Descriptive statistics (SPSS PC+ version 7.0) were used to determine concordance.
RESULTS: In the high INR group, 55% of the 687 high INRs were treated in concordance; 61% for step 1, 7% step 2, 6% for step 3 and 19% for step 6. In step 1, 2, and 3, 54%, 5%, and 10% patients, respectively, had 75-100% of their high INR treated in concordance. Only 11% and 26% of patients with a minor or major bleed received vitamin K, respectively. Seven patients who did not have a high INR or a bleed received vitamin K, however, need for rapid reversal could not be assessed.
CONCLUSIONS: Majority of over-anticoagulated elderly patients was not treated in concordance with ACCP recommendations. More education and recommendation dissemination are required.

66. Nephrotoxicity risk assessment of aminoglycoside dosing in a geriatric VA population. *Matthew T. Lane, Pharm.D.,* George A. Davis, Pharm.D.; Lexington VA Medical Center; University of Kentucky, Lexington, KY.

PURPOSE: Recent reports suggest that aminoglycoside nephrotoxicity in geriatrics is no greater than in younger populations. This study evaluated the overall incidence of nephrotoxicity occurring in geriatric patients receiving aminoglycosides in a VA medical center. The study also attempted to identify significant risk factors associated with aminoglycoside nephrotoxicity.
METHODS: All patients receiving gentamicin or tobramycin that were pharmacokinetically monitored during 1998 were identified. Those receiving aminoglycosides for less than 72 hours or baseline creatinine greater than 5 were excluded. Data collected included age, baseline serum creatinine (SrCr), maximum SrCr within 1 week after therapy, significant medical diagnosis (diabetes, gout, etc.), concomitant nephrotoxic medications and intravenous contrast were documented. Nephrotoxicity was defined as a SrCr elevation greater than 0.5 mg/dl of baseline.
RESULTS: Eighty-one patients were evaluated. Data (mean ± SD) included: age 74 ± 6 years, baseline SrCr 1.0± 0.3 mg/dl, duration of therapy 8.3 ± 3.0 days. Sixty-eight received gentamicin. Dosing regimens of < 3 mg/kg/dose, 3-5 mg/kg/dose and 7 mg/kg/dose were utilized in 20, 13, and 48 patients, respectively. Nephrotoxicity occurred in 20 cases (25%), all receiving 7 mg/kg/day. Nephrotoxic medications, intravenous contrast and concurrent medical diagnosis were not found to be statistically significant risk factors.
CONCLUSIONS: Nephrotoxicity occurred more frequently in this patient population compared to historical values demonstrating risks of 5-7%. Elderly patients are at a greater risk of nephrotoxicity compared to younger populations. Alternative antibiotics should be considered in this patient population whenever possible or more aggressive therapeutic drug monitoring may be warranted.

67E. Tolerability and efficacy of atypical antipsychotics in male geriatric inpatients. *Swapna K. Verma, M.D.,* Claudia A. Orengo, M.D., Mark E. Kunik, M.D., Victor Molinari, Ph.D., Danielle Halle, M.S.; Baylor, Houston, TX.

PURPOSE: The atypical antipsychotics are gradually becoming the mainstay of psychosis treatment in the elderly. The present study examines the efficacy of risperidone and olanzapine treatment in 34 matched male patients admitted to a geriatric inpatient unit.
METHODS: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia, the Cohen-Mansfield Agitation Inventory (CMAI), the Rating Scale for Side-Effects, the Extrapyramidal Rating Scale, and the Mini-Mental State Examination were administered at admission and discharge. Data were analyzed using t-tests to compare the differences between mean scores on these measures between risperidone and olanzapine groups.
RESULTS: Most of the patients on risperidone or olanzapine improved significantly with regard to less agitation, reduced positive symptoms, and higher global assessment of functioning. No significant differences were detected between the two groups with regard to length of hospitalization or reduction in scores on the PANSS or CMAI. Both medications were equally well tolerated.
CONCLUSIONS: Both risperidone and olanzapine appear to be well tolerated and equally efficacious in the treatment of late-life psychoses and behavioral disturbances in elderly patients with dementia.
Presented at the Annual Meeting of the American Psychiatric Association, Washington, DC, May 15-20, 1999.

Health Services Research

68E. Creation of a tool to assess quality of pharmaceutical care documentation. *Jay D. Currie, Pharm.D.,* Julie Kuhle, B.S., William R. Doucette, Ph.D., Jenelle L. Sobotka, Pharm.D., William A. Miller, M.S., Pharm.D., Randal P. McDonough, M.S., Angela L. Tice, Pharm.D.; University of Iowa, Iowa City, IA; The Iowa Pharmacy Association; Drake University, Des Moines, IA.

PURPOSE: This project was designed to develop guidelines as to the necessary data elements to be included in pharmacist documentation to allow the assessment of quality of pharmaceutical care delivered, and to develop a proposed process for assessing adherence to these guidelines.
METHODS: Consensus building took place in three steps. A review of the literature resulted in a list of 85 data elements to be considered in the documentation of care. A national practitioner panel reviewed element applicability. Additional questions identified current documentation methods and strategies. A Delphi technique was then used with an expert panel of pharmacists and other health care providers to determine essential elements. This process was completed with three mailings, with final changes leading to consensus made at a group meeting.
RESULTS: The expert panel reached consensus on a listing of 27 essential elements. These encompassed both individual patient encounter and longitudinal patient record elements. A description of each data element was created and a quality assurance tool and method were developed to evaluate patient care plans. Implementation and guideline use recommendations were delineated.
CONCLUSIONS: This project resulted in guidelines as to the necessary data elements to be documented to allow assessment of the quality of pharmaceutical care provided. These guidelines, validated through consensus, can serve as the cornerstone of a quality assessment process to assure quality pharmaceutical care documentation and allow for assessment of the care provided. The tool developed should provide guidance both to pharmacists providing care and to quality assessment organizations reviewing pharmacist-provided care.
Presented at the 1999 Annual Meeting of the American Pharmaceutical Association, San Antonio, Texas, March 5-9, 1999.

69. AAEP survey I: psychiatric emergency service structure and function. *Glenn W. Currier, M.D.,* Michael H. Allen, M.D., Randolph J. Hilliad, M.D., Douglas Hughes, M.D.; University of Southern California, Los Angeles, CA; Denver Health, Denver, CO; University of Cincinnati, Cincinnati, OH; Boston VA Medical Center, Boston, MA.

PURPOSE: Although psychiatric emergency services (PES) are widely acknowledged as central to the modern mental health "system", no consensus model for these services exists and there are few benchmarks, national standards or guidelines relevant to practice in this critical area. To address this problem, the American Association for Emergency Psychiatry (AAEP) conducted a comprehensive survey of PES characteristics during 1998.
METHODS: A 70-item questionnaire elicited data on a range of topics concerning the respondents' settings and practice patterns. Participants were selected on the basis of membership in AAEP, the emergency psychiatry subspecialty organization, and administrative responsibility for a PES. More than 90% were in academic settings and the average tenure in a leadership position was 6.8 years. The response rate was 91% and included urban and rural settings around the country.
RESULTS: In this report, we present the highlights of provider and site characteristics including data on numbers of beds, visits, hospital admissions, locked capacity, local regulations, physical restraint, length of observation stay, treatment available in the PES, aftercare arrangements, mobile outreach, crisis respite, payer sources, recidivism, formal protocols, consultation to emergency medicine and medical "clearance" procedures. Respondents reported an average of 400 visits per month, a mean of 9.2 beds, and a mean length of stay of 9.0 hours. Medications are initiated in 82% and 51% provide their own aftercare for a mean of 2.6 visits.
CONCLUSIONS: The data suggest psychiatric emergency services are increasingly complex and organizationally unique.

Hematology

70. Standard nomogram for initial stabilization of warfarin dosage in patients with cerebrovascular diseases. *Clarence Chant, Pharm.D.,* Mark J

Gorman, M.D.; St. Michael's Hospital; University of Toronto, Toronto, ON, Canada; Wayne State University, Detroit, MI.

PURPOSE: This study was designed to evaluate the effectiveness, efficiency, and safety of a modified, institution-specific nomogram for initial dosing of warfarin for patients with cerebrovascular diseases as compared to traditional empiric dosing by physicians.
METHODS: Patients in the prospective group received daily warfarin doses in accordance with the nomogram and the measured international normalized ratio (INR) values. A matched group of patients identified retrospectively who had their warfarin dosage empirically determined by house officers served as the control group. Endpoints of effectiveness, efficiency, and safety of the nomogram, defined as the proportion of patients with therapeutic INR upon discharge, time required to achieve therapeutic INR, and major and/or minor bleeding episodes, respectively, were statistically compared using Chi square test and survival analysis.
RESULTS: Sixty and 34 patients were enrolled into the prospective and control groups, with a mean age 63 ± 16 and 65 ± 15 years, respectively. Primary indications for warfarin were thrombotic/embolic strokes or transient ischemic attacks. Patients in the prospective group achieved a therapeutic INR significantly earlier (p=0.02), resulting in a trend towards shorter length of stay (7.8 ± 3.0 vs 9.0 ± 3.4 days, p=0.06) when compared to the control group. Both groups had a similar proportion of patients achieving a therapeutic INR prior to discharge. A similar number of supra-therapeutic INR values occurred in both groups, as was the number of episodes of major/minor bleeding.
CONCLUSION: A modified, institution-specific nomogram for initial stabilization of warfarin dosages in patients with cerebrovascular diseases was more efficient and equally safe and effective as empiric dosing by physicians.

71. A national survey of anticoagulation clinics on the use of brand versus generic warfarin. Rachel Bongiorno, Pharm.D., *Edith Nutescu, Pharm.D.*; University of Illinois at Chicago, Chicago, IL.

PURPOSE: The approval of a generic form of warfarin has generated debate over the appropriateness of therapeutic substitution with brand name warfarin. Minimal pharmacodynamic data is available to aid clinicians in this decision. The purpose of this project is to determine the current practice, views, and experience of anticoagulation clinics (ATCs) regarding generic warfarin substitution.
METHODS: A 39-item survey was designed consisting of check boxes, 5-point scales, and open ended questions. Surveys were sent to 570 ATCs in the United States registered with the Anticoagulation Forum. Survey questions examined product use, selection criteria, and factors influencing product preference.
RESULTS: The survey response rate was 177 (31%). Use of brand name warfarin was preferred by 118 (66.7%) clinics, generic warfarin by 8 (4.5%) clinics, and both brand and generic by 51 (28.8%) clinics. Many ATCs report concerns over potential differences in the response to or the safety of generic warfarin. Factors most often cited as important in the consideration of generic substitution include the possibility of life-threatening complications with nonoptimal dosing and the efficacy to toxicity ratio of warfarin. Approximately one-half of ATCs report complications when switching to generic warfarin. The majority (77.7%) of anticoagulation clinicians believe that current FDA bioequivalency guidelines are not adequate for warfarin. Approximately one-half of clinicians feel that third party payers mandate generic warfarin substitution.
CONCLUSION: Most ATCs prefer the brand preparation of warfarin over the generic due to lack of large, well-designed trials evaluating the pharmacodynamic response when alternating generic and brand warfarin.

72. Therapeutic range determination using the capillary and plasma activated partial thromboplastin time. *Christopher R. Zimmerman, Pharm.D.*, Mark A. Touchette, Pharm.D., Suzan N. Kucukarslan, Ph.D.; Henry Ford Hospital, Detroit, MI.

PURPOSE: The objectives of this study were to establish therapeutic ranges for the capillary and plasma activated partial thromboplastin time (aPTT) and compare agreement in clinical decision making between methods.
METHODS: General medicine patients with deep venous thrombosis (DVT) or pulmonary embolism (PE) receiving unfractionated heparin via a heparin nomogram were enrolled. Two consecutive paired blood samples were obtained. The CoaguChek Plus™ (CCP) coagulometer and central laboratory were used to measure the capillary and plasma aPTT, respectively. A chromogenic factor Xa inhibition assay (therapeutic range: 0.3 - 0.7 U/ml) was used to determine a heparin level for all plasma samples. Therapeutic ranges for the laboratory and CCP were determined by regression analysis (y = aPTT, x = anti-Xa heparin level).
RESULTS: Data from 104 samples (27 patients) were analyzed. Therapeutic ranges for the laboratory and CCP aPTT were similar at 62.7 - 105.5 seconds (r^2=0.493, p<0.05) and 69.8 - 106.5 seconds (r^2=0.417, p<0.05), respectively. Laboratory and CCP aPTT results agreed 51% of the time when compared against the heparin nomogram. When the laboratory and CCP derived aPTT values were interpreted using this nomogram (therapeutic aPTT = 55-85 seconds), a therapeutic heparin level was predicted in 8/23 and 10/23 samples, respectively. Sensitivity and specificity for the laboratory and CCP aPTT were 35 and 73% and 43 and 68%, respectively.
CONCLUSIONS: The laboratory and CCP methods produced disparate aPTT results; however, similar clinical decisions in heparin adjustment occurred in each group. Heparin nomograms should be tailored to the instrument being used based on calibration of the aPTT against the heparin level.

Herbal Medicine

73. Vitamin supplementation and natural or herbal product utilization among ambulatory clinic patients at a university medical center. *Melinda K. Lacy, Pharm.D.*, Shonee A. Metcalf, M.S., Patricia A. Howard, Pharm.D., Melissa J. Webb, Pharm.D., James M. Backes, Pharm.D., Phil J. Blaine, Pharm.D., MBA; University of Kansas Medical Center, Kansas City, KS; Legacy Good Samaritan Hospital and Medical Center, Portland, OR.

PURPOSE: The purpose of this study was to assess vitamin supplementation and natural or herbal product utilization among patients from various outpatient clinics at a university medical center.
METHODS: Data were collected prospectively over a six-month period. A front-and-back written survey was distributed to patients from several outpatient clinics (HIV, internal medicine, cardiology, lipid, warfarin, geriatric, and epilepsy) and the outpatient pharmacy. Surveys were completed either at home or at the clinic. Postage-paid envelopes were provided to facilitate response. Patients were asked to complete only one survey throughout the study period.
RESULTS: Of 634 surveys distributed to clinic patients, 315 were returned for a response rate of 50%. Forty-two more were completed at the outpatient pharmacy (no verified distribution count) for a final total of 357. Respondents were well matched for gender (52% female, 48% male), 46% were > 61 years old, and 58% indicated current use of a vitamin/mineral and/or natural/herbal product. Most products listed by patients were vitamin/mineral supplements (69%, 352/511). Regarding natural/herbal therapy, 24% (87/357) of patients indicated current use of 57 products with ginseng, ginkgo, and garlic most frequently noted. Most obtain information from physicians, magazines, or friends and the majority spend ≤$10/month. HIV patients account for the highest usage rate of natural/herbal products (50%, 13/26). Additionally, they spend > $75/month more frequently than any other group and are more likely to use the Internet for information.
CONCLUSION: These data show that the majority of ambulatory adults are currently taking a vitamin supplement and/or natural or herbal product.

74. Herb use in Anglo and Hispanic elders. *Carla A. Zeilmann, Pharm.D., BCPS*, Ernest J. Dole, Pharm.D., BCPS, Betty Skipper, Ph.D., Melvina McCabe, M.D., Tieraona Low Dog, M.D., Robert Rhyne, M.D.; St. Louis College of Pharmacy, St. Louis, MO; University of New Mexico, Albuquerque, NM.

PURPOSE: The purpose of this study was to determine the types and prevalence of use of herbal medicines by elderly Hispanic and Anglo patients. Secondary objectives were to compare herb use by ethnicity, gender, age, socioeconomic status, and educational level, and to determine beliefs about herbal medicine.
METHODS: The study design was a cross-sectional, individually administered survey of patients seeking care at an urban academic clinic. To be included, patients needed to be at least 65 years of age, Hispanic or Anglo, an established patient in the clinic, not demented, and living independently.
RESULTS: One hundred eighty-six patients completed the study, 34 Hispanic males, 50 Hispanic females, 47 Anglo males, and 55 Anglo females. Forty-nine percent (n=91) admitted to using herbs in the previous year, most (75%) without telling their physician. The most common herbs were mints, chamomile, aloe vera, garlic, osha, lavender, and ginger. Patients most commonly used herbs for health care maintenance or self perceived problems such as gastrointestinal symptoms, skin conditions, cold symptoms, insomnia, and arthritis. Hispanic patients were more likely to obtain herb information from family, and Anglo patients were more likely to get information from the media. Although half of patients purchased herbs where a pharmacist was working, none received herb information from a pharmacist.
CONCLUSIONS: Herb users tend to be in the 65-74 year age range, female, have the lowest or highest level of education, and are in the lower end of the income scale. In general, Hispanics use more herbs than Anglos.

75. Survey of herbal therapies usage and patients' beliefs. *Teresa B. Klepser, Pharm.D.*, William R. Doucette, Ph.D., Matthew R. Horton, Lucinda M. Buys, Pharm.D., Michael E. Ernst, Pharm.D., James D. Hoehns, Pharm.D., Holli A. Kautzman, Pharm.D., Craig D. Logemann, Pharm.D., John M. Swegle, Pharm.D., Michael Ritho, Michael E. Klepser, Pharm.D.; University of Iowa; Iowa City, IA.

PURPOSE: 1) Describe demographics of patients using herbal therapies in Iowa; 2) assess patient willingness to discuss herbal use with health care providers; 3) identify commonly used herbal therapies; and 4) assess patient

beliefs regarding safety and efficacy of herbs.
METHODS: A survey was distributed to two random samples: patients attending eight family care clinics and residents within the state (random mailing). Thirteen hundred surveys were distributed; 100 in each clinic and 500 mailings. Data were categorized according to respondent herb use and data from these groups were compared.
RESULTS: Seven hundred ninety-four surveys were completed (61%) with 42% of respondents reporting herbal use. Commonly used products were (descending order) aloe, garlic, ginseng, echinacea, and St. John's wort. Herb users were predominately white females. Seventy-five percent of users reported some college or vocational education. Herb use was lowest among those reporting a high school degree as their highest level of education ($p<0.05$). Use of prescription medication was higher among herb users ($p<0.05$). Overall, users rated the safety and efficacy of herbs higher than non-users and believed their providers shared this opinion. Both groups believed that health care providers should be aware of herbal use and would provide this information.
CONCLUSIONS: Regardless of prevailing medical beliefs regarding herbal therapies, health care practitioners need to identify patients using these products in order to insure safety. This study demonstrates high herbal use in the state of Iowa and identifies patient populations most likely to use these products.

HIV/AIDS

76. A pharmacokinetic/pharmacodynamic model to characterize the CD_4 response to recombinant interleukin-2 in HIV-infected patients. *Stephen Piscitelli, Pharm.D.*, Alan Forrest, Pharm.D., Susan Vogel, B.S.N., Julia Metcalf, B.A., Michael Baseler, Ph.D., Joseph A. Kovacs, M.D.; National Institutes of Health, Bethesda, MD; SIAC, Frederick, MD; State University of New York at Buffalo, Buffalo, NY.

IL-2 is an immunomodulator that has been shown to increase CD_4 counts in HIV-infected patients.
PURPOSE: To develop a pharmacokinetic/pharmacodynamic model which simultaneously characterizes concentrations of IL-2, soluble IL-2 receptors (sIL-2r) and CD_4 cells with IL-2 therapy.
METHODS: Seven HIV-infected patients received 6-12 MIU/d of recombinant IL-2 as a 5-day continuous intravenous infusion. Samples were collected daily for 10 days and at day 30 and analyzed for IL-2 and sIL-2r concentrations, and CD_4 cells. The data were fit with IT2S to a model that included 2 compartments and an effect compartment and for IL-2 with clearance dependent upon the sIL-2r concentration. SIL2-r was described by two compartments with formation driven by an indirect effect stimulatory model with a Hill-type function. CD_4 was described by tissue and peripheral compartments with a direct effect to describe early trafficking and a stimulatory indirect effect to characterize delayed proliferation.
RESULTS: IL-2 concentrations peaked at 24 hours and declined by 70% during the remainder of the infusion. SIL-2r concentrations increased over 10-fold from baseline and peaked at day 5, returning to baseline by day 30. The mean CD_4 count was 401 at baseline, initially decreased at 24 hours, then increased to a peak of 1740 cells/ml on day 6 before returning to a new baseline value of 497 at day 30. The model provided excellent fits of this complicated model with median r^2 values of 0.96, 0.93, 0.96 for IL-2, sIL-2r, and CD_4, respectively.
CONCLUSIONS: Increases in CD_4 cells following IL-2 therapy can be characterized with a PK/PD model that incorporates IL-2 and sIL-2r concentrations and both direct and indirect effects. Such models may be useful to describe responses to subsequent regimens and interventions to enhance safety and efficacy.

77. Assessing AIDS knowledge and attitude between rural and urban Botswana women. *Onalethata Johnson, Pharm.D.*, Craig A. Pedersen, Ph.D., Patty Fan-Harvard, Pharm.D.; Ohio State University, Columbus, OH.

Approximately 34% to 40% of all pregnant women are reported to be HIV-seropositive. The rising number of orphaned children is causing an enormous societal burden in a country where more than 50% of households are single mothers. Education is the mainstay of HIV/AIDS prevention. However, the effectiveness of these educational programs remains unknown.
PURPOSE: To assess and compare AIDS knowledge and attitude between rural and urban Botswana women using a published National Health Interview Survey AIDS questionnaire.
METHODS: Botswana women were surveyed in the city of Gaborone and from four villages, conveniently selected. The survey contained questions assessing general AIDS knowledge, HIV testing and self-perceived risk of becoming HIV infected.
RESULTS: A total of 321 (145 rural and 176 urban) Botswana women completed the survey. Higher annual income and levels of education were noted among urban than rural women ($p<0.05$). More rural women visited government facilities, traditional healers and religious healers while more urban women visited private doctors ($p<0.05$). A higher percentage of urban women demonstrated knowledge about AIDS as well as modes of HIV transmission. Only 35.7% of rural and 27.9% of urban women perceived the use of condoms as a very effective means of preventing the sexual transmission of HIV. Approximately 14% of rural and urban women self-assessed themselves at high risk of contracting HIV.
CONCLUSIONS: Mass media programs have been successful in educating the public about HIV/AIDS. However, there were a higher percentage of rural women who lacked understanding. More education is needed regarding condom use.

78. Comparison of adherence to Combivir® and abacavir in the H.E.A.R.T. (helping to enhance adherence to antiretroviral therapy) trial using MEMS® Trackcaps™. Melanie A. Thompson, M.D., *Mark S. Shaefer, Pharm.D.*, Karen H. Crawford, Diane Goodwin, Pharm.D., Vanessa C. Williams, Steve T. Ross; AIDS Research Consortium, Atlanta, GA; Glaxo Wellcome Inc., Research Triangle Park, NC.

PURPOSE: To evaluate whether two separate MEMS® (Medication Event Monitoring System) Trackcaps™ are necessary to evaluate adherence to each of two antiretroviral medications, Combivir® (COM; lamivudine 150 mg/zidovudine 300 mg) and abacavir(ABC), given on the same BID schedule, in subjects from under-represented populations (UP).
METHODS: Two hundred antiretroviral-naïve HIV positive adult subjects from UP (ethnic minorities, women, injection drug users) were enrolled in H.E.A.R.T. and randomized (1:1) to receive routine counseling or an educational adherence intervention (T.H.E. Course) plus routine counseling. Subjects were required to have HIV-1 RNA > 40 and < 100,000 c/ml and CD_4^+ lymphocytes ≥ 50 cells/mm^3. All subjects received COM 1 tablet BID plus ABC 300 mg BID and followed for responses in HIV-1 RNA and CD_4^+ cells. Both medications were dispensed with MEMS® Trackcaps™ microelectronic monitoring devices to record the date/time of each dose of study medication.
RESULTS: Preliminary MEMS® data are available for 73 subjects. Baseline demographics for these subjects are: median age 36, 74% male, 63% Black and 26% Hispanic. Overall 67% (49/73) and 64% (47/73) took 80-100% of COM and ABC doses, respectively. It was possible to match date/time of COM and ABC doses in 72 subjects. Considering all dose matches, the mean (SD) of the difference in time between doses was 1.6 (1.9) minutes. A range from 1 to 3 minutes was observed for differences in dosing times on a weekly basis.
CONCLUSION: Monitoring of either COM or ABC with MEMS® Trackcaps™ appears to provide a reliable estimate of adherence for both drugs.

79E. Single dose pharmacokinetics of dOTC (BCH-10652) in healthy, adult volunteers. *Patrick F. Smith, Pharm.D.*, Charles H. Ballow, Pharm.D., Alan Forrest, Pharm.D., Caroline Fortier, Ph.D., Louise Proulx, Ph.D.; State University of New York at Buffalo, Buffalo, NY; BioChem Pharma.

PURPOSE: To characterize PK of dOTC, a novel nucleoside analogue, in healthy adult male volunteers.
METHODS: Study 1 was a randomized, cross-over, single-blind study in 15 volunteers. Each received 2 of 5 oral doses (100, 200, 400, 800, 1600 mg) of dOTC and placebo in three periods separated by 1 week. Sixteen plasma samples over 24-48 hours were obtained, assayed (HPLC, CV < 8%), and fit by candidate PK models (ADAPT II). Model discrimination was by Aikake's information criterion. Statistical differences between arms were determined using non-parametric methods. Study 2 was a randomized, cross-over, open-label study in which 12 males received a single dose of dOTC (100 mg IV or 800 mg PO) while fed and fasted, separated by 1 week. Sixteen plasma samples over 72 hours were obtained, assayed (HPLC, CV < 8%), and PK parameters determined by S.H.A.M. methods. Statistical differences between arms were determined using non-parametric methods.
RESULTS: All doses were well tolerated. Study 1 demonstrated linear PK with low intersubject variability. Median (CV %) plasma $t_{1/2}$, CL/F, V_{ss}, and C_{max} ranged from 9.7-18.2 (26.5-41.4) hr, 16.1-22.7 (15.8-29.6) L/h/65 kg, 35.2-76.6 (21.6-57.0) L/65 kg, and 7.5-11.2 (19.2-39.4) mg/ml/800 mg, respectively. The goodness of fit was excellent, r^2 ranged from 0.995-1.0. Study 2 demonstrated an absolute bioavailability of approximately 80% when IV and PO doses were compared. There were no significant differences in PK parameters following administration of a meal.
CONCLUSIONS: Single oral doses up to 1600 mg were well tolerated. dOTC is well absorbed and has a long plasma half-life. The PK appears to be linear with low intersubject variability and is not influenced by food. The elimination half-lives suggest dose intervals of 12-24 hours are reasonable.
Presented at the 6th Conference on Retroviruses and Opportunistic Infections, Chicago, IL, February 1999.

80E. Use of rifabutin with protease inhibitors for HIV-infected tuberculosis patients. *Jerry J. Stambaugh, Pharm.D.*, Masa Narita, M.D., E. Ibraham, M.D., Jeanette Mollycheck, B.S.N., Elena S. Hollender, M.D., Arthur E. Pitchenik, M.D., David Ashkin, M.D.; A.G. Holley State Hospital, Lantana, FL; VA Medical Center; University of Miami, Miami, FL.

BACKGROUND: Treatment of HIV-positive tuberculosis (TB) patients is complicated by reported drug-interactions between rifamycins and protease inhibitors (PIs). Few studies examine the use of rifabutin (RBT) with PIs.

METHODS: The medical records of all HIV-positive TB patients admitted to A.G. Holley State Hospital who had serum drug levels measured 2 hours after dosing were reviewed.
RESULTS: Forty HIV-positive TB patients were admitted. Twenty-eight patients were treated with PI-containing highly active anti-retroviral therapy (HAART) and standard TB regimens with rifampin replaced with RBT. All 28 had TB-culture conversion within 2 months of starting TB therapy. CD_4 counts significantly increased after the initiation of HAART (mean ± SEM: 110.5 ± 25.1 [n=28]) vs 186.9 ± 29.5 [n=24]; p=0.013 using Mann-Whitney rank sum test). Viral load in log decreased significantly after HAART (4.86 ± 1.01 [n=28] vs 3.35 ± 0.23 [n=25]; p<0.001). Thirteen of 28 (46%) patients achieved viral loads < 400. Ten patients had RBT serum levels which significantly increased after HAART (0.12 ± 0.03 vs 0.22 ± 0.03 [n=10]; p=0.03 using paired t-test). There was no statistically significant difference in INH serum levels before and after HAART (11.9 ± 3.0 vs 9.6 ± 1.4 [n=6]; p=0.432). However, two patients had a 2-fold increase. PI levels measured while on RBT revealed nelfinavir 3.25 ± 1.17 (n=4); 1000 mg BID and indinavir 4.80 ± 0.97 (n=4); 1200 mg PO BID.
CONCLUSIONS: RBT and PIs can be given concomitantly with good clinical response. The role of therapeutic drug monitoring in order to optimize treatment needs further investigation.
Presented at the 99th General Meeting of the American Society for Microbiology, Chicago, IL, May 30-June 3, 1999.

Infectious Diseases

81. Susceptibility of clinical coagulase positive and coagulase negative staphylococcus isolates to vancomycin over an eight-year period using ETEST methodology. *Neil E. Klutman, Pharm.D.*, Michael Howard, B.A., Rebecca Horvat, Ph.D., Daniel R. Hinthorn, M.D.; University of Kansas Medical Center, Kansas City, KS.

PURPOSE: Of great concern is the increasing antibiotic resistance including vancomycin resistance in gram-positive bacteria. We evaluated the susceptibility of *Staphylococcus spp.* cultured from patients over an eight-year period in order to 1) determine if an increase in minimum inhibitory concentration (MIC) for different species occurred, and 2) determine if an increase in MICs for coagulase positive (CPS) or coagulase negative (CNS) could be detected.
METHODS: All gram-positive isolates (n=392) from patients with osteomyelitis from 1990 to 1997 were identified and speciated. The organisms were frozen at -70°C until testing. Susceptibility testing using ETEST methodology was performed. MICs of all *S. aureus* (methicillin sensitive or resistant), *S. epidermidis* (methicillin sensitive or resistant) and other coagulase negatives (*S. haemolyticus*, *S. hominis*, *S. saphrophyticus*, *S. warneri*) were determined. Average (and range) MIC for each group over the eight-year period was calculated.
RESULTS: The average MIC (range in ug/ml) of *S. aureus* (n=295) was 1.6 (0.75-4), MRSA (n=56) was 1.52 (0.75-3), *S. epidermidis* (n=62) was 2.23 ug/ml (1.5-4), MRSE (n=35) was 2.39 (1.5-4), all non-*S. epidermidis* CNS (n=35) was 2.4 ug/ml and all MRCNS (n=15) was 2.67 (1.8-4). Of concern was detection of 3 CPS isolates with a MIC of 4 ug/ml and 5 with a MIC of 3 ug/ml. In the CNS group, 26 isolates had a MIC of 3 ug/ml and 6 had a MIC of 4 ug/ml. Each group regardless of sensitivity to methicillin had at least one isolate with a MIC of 4 ug/ml. The first isolate with a MIC of 4 ug/ml was from 1994.
CONCLUSION: No trend toward increasing average MIC to vancomycin was observed. The average MIC for coagulase negative isolates was higher. Concern regarding individual isolates with vancomycin MICs of 4 ug/ml is warranted and indicates the need to continue monitoring.

82. Comparison of serum and intracellular pharmacokinetics of azithromycin in healthy and diabetic subjects. *Erika J. Ernst, Pharm.D.*, Michael E. Klepser, Pharm.D., Teresa B. Klepser, Pharm.D., Charles H. Nightingale, Ph.D., Lawrence G. Hunsicker, M.D.; University of Iowa, Iowa City, IA; Hartford Hospital, Hartford, CT.

PURPOSE: The intraleukocytic accumulation of the macrolide antibiotic azithromycin (AZTH) is an important characteristic for its effectiveness in treating intracellular pathogens. Other studies have shown that diabetic subjects display impaired leukocyte chemotaxis, phagocytosis and bacterial killing compared to non-diabetic individuals. Therefore, we compared the serum and intraleukocytic (PMN) concentration of AZTH in healthy and diabetic individuals.
METHODS: Twenty-four subjects were given 500 mg of AZTH on day one followed by 250 mg daily on days 2 and 3. Blood for serum measurement of AZTH was obtained just before the administration of the third dose and at 1, 1.5, 2, 2.5, 3, 6, 8, 12 and 24 hours following drug administration. Blood for measurement of the PMN concentration of AZTH was obtained before third dose and at 6, 12, 24, 48, 96 and 168 hours after administration.
RESULTS: Mean (± SD) pharmacokinetic parameters calculated using non-compartmental methods were determined.

	T_{max} (hr)	C_{max} (µg/ml)	AUC (µg•hr/ml)	$t_{1/2}$ (hr)
Healthy (PMN)	27.8 (48.2)	60.8 (16.6)	6660 (2546)	144 (55)
Diabetic (PMN)	22.8 (28.4)	69.6 (57.4)	6240 (4395)	204 (103)
Healthy (serum)	2.8 (0.34)	0.27 (0.09)	1.66 (0.48)	23 (13)
Diabetic (serum)	2.7 (1.19)	0.36 (0.16)	1.56 (0.52)	23 (13)

There were no differences between groups for T_{max}, C_{max}, AUC or $t_{1/2}$ in serum or PMNs. Significant differences in the PMN to plasma ratio were observed between groups at 12 (healthy, 936 ± 356; diabetic, 792 ± 387, p=0.05) and 24 (healthy 1210 ± 432; diabetic, 797 ± 332, p=0.03) hours.
CONCLUSION: These results indicate the fraction of drug penetrating the PMNs is lower in subjects with diabetes compared to healthy individuals.

83. Comparative fluoroquinolone pharmacodynamics against common pathogens. *Charles R. Bonapace, Pharm.D.*, Roger L. White, Pharm.D., Kurt R. Lorenz, Pharm.D., Long Diep, Pharm.D., John A. Bosso, Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: A pharmacodynamic parameter associated with efficacy of fluoroquinolones is the ratio of the 24-hour area under the serum concentration-time curve/MIC (AUC/MIC).
METHODS: Peer-reviewed studies (n=76) were assessed to obtain pharmacokinetic parameters and used to simulate unbound steady-state serum concentration-time profiles for a 70 kg adult for 8 drugs: IV and oral (PO) ciprofloxacin (CP), gatifloxacin (GA), ofloxacin (OF), levofloxacin (LV), moxifloxacin (MX) and trovafloxacin (TR), IV clinafloxacin (CL) and PO grepafloxacin (GR). Using all non-UTI regimens in the package inserts (or investigational trials), simulations were performed at a creatinine clearance of 100 ml/min and steady-state 24-hour AUCs were calculated. MIC_{90} values were obtained from a database of studies published from 1997-99 in North America (approximately 8000 isolates) for PCN-resistant *S. pneumoniae, E. coli, P. aeruginosa, K. pneumoniae, P. mirabilis, H. influenzae,* and *M. catarrhalis*. Then, the weighted (on number of isolates) geometric means were used to calculate AUC/MIC ratios for each drug against each organism. An AUC/MIC ≥ 100 was considered acceptable. A total of 119 dosing regimens were simulated.
RESULTS: Median AUC/MICs were unacceptable for all regimens against *P. aeruginosa* and *K. pneumoniae* and acceptable for all regimens against *H. influenzae* and *M. catarrhalis*. For each organism, the drugs with the lowest and highest median AUC/MICs were as follows*: S. pneumoniae* (CP PO 13, CL IV 177), *E. coli* (TR PO 30, CP IV 754), *P. aeruginosa* (MX IV/PO < 1, LV IV/PO 16), *K. pneumoniae* (TR PO 13, GA PO 99), *P. mirabilis* (MX PO 8, LV IV 630) *H. influenzae*,(TR PO 161, CL IV 1329), *M. catarrhalis* (MX PO 256, CL IV 1,176).
CONCLUSIONS: The pharmacodynamic profiles of fluoroquinolones vary among common pathogens; this should be considered in selecting agents for empiric therapy.

84. Effects of penicillin-resistance and pH variances on pneumococcal adherence to human lung fibroblasts and epithelial cells. *Melinda K. Lacy, Pharm.D.*, Rebecca T. Horvat, Ph.D., Laura Boyert, B.S., Mike Howard, B.A., Arla Mitchell, B.A., Daniel R. Hinthorn, M.D.; University of Kansas Medical Center, Kansas City, KS.

PURPOSE: The purpose of this study was to assess the effects of penicillin resistance and pH variances on pneumococcal adherence to human lung fibroblasts and epithelial cells.
METHODS: A validated in vitro bacterial cellular adherence model was used to study the binding of 36 clinical strains of *Streptococcus pneumoniae* to different human cell types. Penicillin-susceptible, -intermediate, and -resistant strains (12 each) were evaluated. A starting inoculum of $1x10^6$ CFU/ml was added to pH-adjusted (6.5, 7.0, and 7.4) growth media. Bacteria was then added to rinsed shell vials containing fresh human lung fibroblasts or epithelial cells and incubated for 2 hours at 37°C. After incubation the cell layers were washed extensively and stained for quantification of bound bacteria. Strains were categorized as follows (bound bacteria/100 cells): low (0-9), moderate (10-59), high (60-100), and very high (> 100). Studies were performed in triplicate for each isolate, pH, and cell type combination. A control strain was tested weekly for internal validation.
RESULTS: Pneumococcus preferentially bound to lung fibroblasts as compared to epithelial cells. Neither penicillin resistance or pH variances influenced binding. Binding of test strains to fibroblasts was classified as follows: low 20%, moderate 43%, high 20%, and very high 17%. Preliminary correlations of these results to clinical outcomes indicate a trend towards increased lengths of stay as bacterial binding increases.
CONCLUSIONS: Factors other than penicillin resistance and pH appear to influence pneumococcal adherence to lung fibroblasts and epithelial cells. Pneumococcus binds greater to lung fibroblasts as compared to epithelial cells. Further clinical correlations of this data are ongoing.

85. In vitro antibacterial activity of trovafloxacin versus methicillin resistant and susceptible clinical isolates of *Staphylococcus aureus*. *Michael A. Dietrich, Pharm.D.*, David W. Craft, Ph.D., John D. Butts, Pharm.D., BCPS; University of North Carolina Hospitals, Chapel Hill, NC.

PURPOSE: The new fluoronaphthyridone, trovafloxacin (IV/PO), has increased activity versus both methicillin sensitive and resistant *Staphylococcus aureus*. This agent may offer an alternative to intravenous vancomycin for the treatment of MRSA. This prompted us to evaluate the in vitro activity of trovafloxacin versus clinical blood isolates of both methicillin resistant and sensitive *S. aureus* (MRSA, MSSA).
METHODS: Thirty-two clinical blood isolates (21 MRSA, 11 MSSA), were evaluated between December 1998 and May 1999. Minimum inhibitory concentrations were determined by the E-test method. NCCLS procedures were followed and susceptibilities were determined using NCCLS MIC breakpoints.
RESULTS: The susceptibilities for 21 MRSA and 11 MSSA isolates to trovafloxacin were determined.

	S (≤ 2 mg/L)	I (4 mg/L)	R (≥ 8 mg/L)
MRSA (n=21)	14 (67%)	6 (28%)	1 (5%)
MSSA (n=11)	11 (100%)	0	0

MICs for the trovafloxacin susceptible MRSA strains averaged 2.0 mg/L (range 0.75-2 mg/L). This is at the NCCLS approved breakpoint for this organism and raises questions of trovafloxacin's utility in treating life-threatening bacteremias caused by *S. aureus*. The average MIC for the MSSA strains was 0.044 mg/L (range 0.006-0.094 mg/L), and it can be suggested that trovafloxacin will provide adequate coverage.
CONCLUSIONS: Because of the proximity of trovafloxacin activity to the established breakpoint and the recent information regarding safety, the utility of trovafloxacin for MRSA infections must be determined on a case by case basis. This must include the site of infection, pharmacodynamics of the agent, and the overall clinical course of the patient. The benefit must outweigh the potential risk.

86. Determination of in vitro antibacterial activity of eleven different antibiotics versus clinical strains of *Streptococcus pneumoniae* leading to a change in the hospital community acquired pneumonia pathway. *Michael A. Dietrich, Pharm.D.*, David W. Craft, Ph.D., John D. Butts, Pharm.D., BCPS; University of North Carolina, Chapel Hill, NC.

PURPOSE: Increasing *S. pneumoniae* resistance to penicillin has given rise to the expanded use of macrolides and fluoroquinolones (FQs) for treatment of community acquired pneumonia (CAP). The newer FQs have increased activity versus *S. pneumoniae*. Because of heightened awareness of national resistance patterns, the dire consequences of treatment failure, and the activity of the new FQs, we conducted a study to determine the in vitro activity of 11 antibiotics to clinical isolates of *S. pneumoniae*.
METHODS: Thirty-six clinical isolates were evaluated between December 1998 and May 1999. The microbiology lab first identified the isolates and minimum inhibitory concentrations were determined by the E-test method with quality controls performed weekly using an NCCLS approved isolate (ATCC 49619). The organisms were incubated in 5% CO_2 according to NCCLS procedures. Determined MICs were compared to NCCLS breakpoints for each agent when available; when not available, FDA approved breakpoints were used.
RESULTS: Susceptibilities of 36 clinical isolates were determined.

Agent	S	I	R
Vancomycin	36 (100%)	0	0
Penicillin	16 (44%)	15 (42%)	5 (14%)
Ceftriaxone	30 (83%)	4 (11%)	2 (6%)
Cefepime	26 (72%)	1 (3%)	9 (25%)
Ceftazidime	20 (56%)	2 (6%)	14 (39%)
Erythromycin	24 (67%)	0	12 (33%)
Azithromycin	24 (67%)	0	12 (33%)
Ciprofloxacin	23 (64%)	12 (33%)	1 (3%)
Levofloxacin	36 (100%)	0	0
Trovafloxacin	36 (100%)	0	0
Grepafloxacin	36 (100%)	0	0

CONCLUSIONS: The activity of the newer FQs was excellent, even for the penicillin-resistant isolates. There has been an 18% increase in macrolide-resistant isolates over the past year. This resistance further decreases the utility of azithromycin as monotherapy for CAP. There has also been a 31% increase in penicillin resistant strains (23% low-level, 8% high-level). This increase is also reflected in decreased susceptibility to ceftriaxone. These data lead to the reevaluation the standard of therapy for CAP at our institution increasing the role of the newer FQs.

87. Demonstration of partial energy dependent in vitro uptake and efflux of ^{14}C-grepafloxacin in stimulated and unstimulated human monocytes. *Michael A. Dietrich, Pharm.D.*, John D. Butts, Pharm.D., BCPS, Timothy J. Ives, Pharm.D., BCPS; University of North Carolina, Chapel Hill, NC.

PURPOSE: Differences between the newer quinolones are difficult to ascertain. A potential difference between the agents may be in the way the compound is acquired by, distributed within and cleared from human cells. We studied the pharmacokinetics and dynamics of ^{14}C-grepafloxacin to determine these characteristics within human monocytes.
METHODS: Uptake and efflux of ^{14}C-grepafloxacin into THP-1 human mononuclear cells was determined at 3 pHs and over 4 log antibiotic concentrations. Uptake studies were performed using cells stimulated with latex beads, lipopolysaccharide, zymogen A and in unstimulated cells. Energy dependence studies were conducted using verapamil and sodium azide. After 1 hour of monocyte loading with ^{14}C- grepafloxacin, and samples collected at eight time periods. Subcellular organelles were isolated by ultracentrifugation. The antibiotic was distributed throughout the cytosol, nuclei, lysosomes, mitochondria and ribosomes in stimulated cells with the highest concentration in the cytosol.
RESULTS: Efflux followed first order clearance and was essentially complete within 1 hour. Unstimulated monocytes sequestered ^{14}C-grepafloxacin through a potentially saturable process. The acquisition of ^{14}C-grepafloxacin was decreased when sodium azide was added, suggesting an energy dependent uptake process. Uptake was not completely blocked leaving the possibility of another uptake process, such as passive diffusion. The efflux of ^{14}C-grepafloxacin is partially blocked by the addition of verapamil, suggesting an energy dependent, calcium regulated process. Stimulated monocytes had an increased uptake of drug over time, with zymogen A providing the greatest increase in uptake over control.
CONCLUSION: Bacteria challenged monocytes may actively concentrate the antibiotic and studies are underway to evaluate this process.

88. Effect of food on a single oral dose of 400 mg moxifloxacin in healthy male volunteers. *John Lettieri, Ph.D.*, Ramon Vargas, M.D., Vipin Agarwal, Ph.D., Patrick Liu, Ph.D.; Bayer Corporation, West Haven, CT; Clinical Research Center, New Orleans, LA.

PURPOSE: To examine the effects of food on the pharmacokinetics of moxifloxacin following a single, oral 400 mg dose.
METHODS: This was a randomized, non-blinded crossover study conducted in young healthy males. Moxifloxacin was given under two conditions separated by a one-week washout period: fasting and fed (immediately after a standardized high fat breakfast). Moxifloxacin serum concentrations were determined by a validated HPLC procedure with fluorescence. The pharmacokinetic parameters C_{max}, T_{max}, AUC_{0-48}, $AUC_{0-\infty}$, and $t_{1/2}$ were estimated using non-compartmental methods. Natural logarithms of AUC and C_{max} were analyzed using ANOVA. Treatment effects were tested at the 5% significance level with two one-sided tests procedure and limits of 80% and 125% for AUC and 70% to 143% for C_{max}.
RESULTS: Eighteen subjects were enrolled in the study; 16 were considered evaluable. The mean serum concentration profiles were similar between the two treatments. The geometric mean $AUC_{0-\infty}$ values under fed and fasted conditions were almost identical, 37.7 vs 38.5 mg•h/L, respectively (90% CI of fed vs fasted was 95%-100%). Moxifloxacin absorption seems to be mildly delayed due to the effect of food with the median T_{max} of 1.0 and 2.5 hours for fasted and fed conditions, respectively. C_{max} values were 2.5 and 2.8 mg/L, for the fed and fasted doses, respectively (90% CI of fed vs fasted was 0.78-0.98).
CONCLUSIONS: A single oral dose of 400 mg moxifloxacin was well tolerated when taken with and without food and was not associated with any clinically significant changes in C_{max} or $AUC_{0-\infty}$ values.

89. Multidrug efflux pump inhibition can reduce quinolone antibiotic resistance in *Pseudomonas aeruginosa*. *Terri A. Hersey*, Jeffrey R. Aeschlimann, Pharm.D.; University of Connecticut, Storrs, CT; Saint Francis Hospital and Medical Center, Hartford, CT.

PURPOSE: Inhibition of multidrug efflux pumps in bacteria such *Staphylococcus aureus* reduces the emergence of quinolone-resistant mutants. Since multidrug efflux pumps expel quinolones from *P. aeruginosa*, we hypothesized that efflux pump inhibitors could also reduce the emergence of quinolone-resistance in this gram-negative bacterium.
METHODS: A well-characterized laboratory strain of *P. aeruginosa* (PAO1) was used in all experiments. Agar dilution MICs were determined for norfloxacin (NOR), nalidixic acid (NAL), and pipemidic acid (PIP). Then, 1 x 10^8 colony forming units (CFU) of PAO1 was grown on agar containing 2 x MIC of each quinolone ± 100 µg/ml of verapamil (a competitive inhibitor of the *Staphylococcus aureus* NorA multidrug efflux pump) or carbonylcyanide-m-chlorophenylhydrazone (CCCP, a non-specific efflux inhibitor via proton gradient disruption). Resistance frequencies were calculated by dividing the number of mutant CFU by the total number of CFU plated.
RESULTS: Resistance frequencies were 1.8 x 10^{-7} for NOR, 7.3 x 10^{-6} for NAL, and 7.9 x 10^{-6} for PIP. Addition of verapamil caused slightly higher resistance frequencies of 5.4 x 10^{-7} for NOR, 3.2 x 10^{-5} for NAL, and 1.0 x 10^{-5} for PIP. Addition of CCCP completely prevented growth of resistant mutants for all quinolones tested while having no effects on bacterial growth alone.
CONCLUSIONS: Verapamil did not reduce quinolone resistance for a standard strain of *P. aeruginosa*, suggesting that it does not have appreciable effects on its multidrug efflux pump system. CCCP completely prevented the isolation of quinolone-resistant *P. aeruginosa* mutants. Since CCCP is toxic for humans, other compounds that are safe for human administration that effectively disrupt the function of *P. aeruginosa* multidrug efflux pumps

would be important adjuncts during therapy of infections caused by this bacteria.

90E. In vitro and in vivo influence of adjunct clarithromycin on the treatment of *Pseudomonas aeruginosa*. *Khanh Q. Bui, Pharm.D.*, Mary A. Banevicius, B.S., Charles H. Nightingale, Ph.D., Richard Quintiliani, M.D., David P. Nicolau, Pharm.D.; Hartford Hospital, Hartford, CT.

PURPOSE: Recent evidence has substantiated the benefits of macrolides/azalides against *Pseudomonas aeruginosa* (PSA). As adjunctive therapy, they may alter the course of infection through inhibition of biofilm production or modulation of the host anti-inflammatory response. This study was undertaken to determine the adjunctive in vitro and in vivo effects of clarithromycin (CLR) with ceftazidime (CAZ) against a mucoid producing strain of PSA.
METHODS: A standard time-kill study was used for the in vitro experiment while a pneumonia model in neutropenic mice was used to observe the effects of different therapies in vivo. Mice were infected intranasally with 10^8 CFU of PSA and treated with oral CLR/subcutaneous CAZ monotherapy or with a combination of the two.
RESULTS: Following a 24-hour incubation with varying concentrations of CLR/CAZ monotherapy or in combination, synergy (≥ 2 $\log_{10}$ reduction) was noted with 0.5 x MIC CAZ combined with 0.5 or 2 x MIC CLR. In vivo, a statistical difference (p=0.04) resulted when mice were treated with CAZ x 2 plus CLR x 10 doses compared to mice receiving CAZ x 2 doses. No differences were noted when mice were treated with CAZ x 2 plus CLR x 6 doses as compared to CAZ x 2 doses (p=0.44) or with the combination containing a longer duration of CLR (p=0.19).
CONCLUSION: These data show that CLR has an adjunctive effect when administered with an antipseudomonal agent for the treatment of mucoid producing PSA in acute respiratory infection. The potential for use in humans will require additional studies.
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

91E. Pharmacokinetics and pharmacoeconomic evaluation of ticarcillin/clavulanate administered either as continuous or intermittent infusion with once-daily gentamicin. *Khanh Q. Bui, Pharm.D.*, Paul G. Ambrose, Pharm.D., Edward M. Grant, Pharm.D., Charles H. Nightingale, Ph.D., David P. Nicolau, Pharm.D., Richard Quintiliani, M.D.; Hartford Hospital, Hartford, CT.

PURPOSE: Ticarcillin/clavulanate (T-C) is traditionally administered intermittently (II), but there is no reason why it cannot be given by continuous infusion (CI). In severe infections involving *Pseudomonas aeruginosa, Enterococcus spp.* or unusual *Enterobacteriaceae*, this agent is often combined with a once-daily dose of gentamicin (7 mg/kg) for synergy. Case reports and static in vitro studies have documented the potential for the inactivation of these two antibiotics when given concomitantly.
METHODS: This study was undertaken to determine the extent of an in vivo inactivation of ticarcillin (dosed as T-C), either as II (3.1 grams IV q4h) or CI (500 mg/hr and 0.017 mg/hr of T-C, respectively), with and without gentamicin in healthy volunteers.
RESULTS: Eleven volunteers completed the II portion of the study with no statistically significant differences were noted in the AUC, C_{max}, or $t_{1/2}$ of three T-C doses given in the presence of gentamicin. In the nine volunteers dosed with a CI of T-C, a statistically significant ($p<0.008$) reduction in ticarcillin (70 vs 55 µg/ml) was observed following the administration of gentamicin. The AUC of gentamicin was unchanged whether the T-C was administered by CI or II.
CONCLUSION: Although the inactivation of ticarcillin resulted in lowered concentrations during CI, this reduction should be of minimal, if any, relevance clinically since the concentrations exceed the MIC for organisms encountered with this drug. Assuming no difference in clinical outcomes where T-C is given by CI or II, the CI method becomes an attractive option owing to the major economic gains obtained.
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

92. Serum enhances the in vitro activity of fluconazole against *Candida albicans*. *Erika J. Ernst, Pharm.D.*, Derek Adams, Michael E. Ernst, Pharm.D., Michael E. Klepser, Pharm.D.; University of Iowa, Iowa City, IA.

PURPOSE: The purpose of this study was to evaluate the effect of normal and heat-inactivated human serum on the minimum inhibitory concentration (MIC) of fluconazole against *Candida albicans*, and to compare the effect of serum from healthy patients versus diabetic patients' serum.
METHODS: MICs were conducted according to the NCCLS guidelines (M-27P), and with the addition of 10% human serum. RPMI with MOPS was used as culture medium. Six isolates of *C. albicans* were selected for study. These isolates have been studied previously, and MICs in the absence of serum range from 0.25 to > 128 µg/ml. Serum was collected from four healthy and 11 diabetic patients who had not received any agent with known antifungal activity within one month. MICs were conducted in duplicate.
RESULTS: The addition of 10% human serum, either normal or heat-inactivated, decreased the fluconazole MIC in 5 of 6 isolates tested. The MIC was similarly reduced by serum from healthy or diabetic subjects.

Isolate	MIC Without Serum	MIC With 10% Serum
90028 (S)	0.25	0.25
OY 31.5 (S)	0.25	0.12
1149579 (S)	1.0	0.25
1489828 (I)	32	0.12
2733A (R)	> 128	0.25
1426867 (R)	> 128	0.12

S = susceptible; I = intermediate susceptibility; R = resistant

CONCLUSIONS: Fluconazole activity against less susceptible and resistant isolates of *C. albicans* is increased with the addition of serum in vitro, as seen by the decrease in MIC. This effect was not altered by heat inactivation of serum, and was consistent in healthy and diabetic subjects.

93E. Comparative bactericidal activities of ciprofloxacin, clinafloxacin, grepafloxacin, levofloxacin, moxifloxacin, and trovafloxacin assessed in a dynamic in vitro model against *Streptococcus pneumoniae*. *Michael E. Klepser, Pharm.D.*, C. Rosemarie Petzold, B.S., Paul Rhomberg, B.S., Gary V. Doern, Ph.D.; University of Iowa; Iowa City, IA.

PURPOSE: The goal of this study was to compare the bactericidal dynamics of six quinolones against *S. pneumoniae*.
METHODS: Using a dynamic in vitro model, we constructed time-kill profiles for ciprofloxacin (CIP), clinafloxacin (CLIN), grepafloxacin (GREP), levofloxacin (LEVO), moxifloxacin (MOXI), and trovafloxacin (TROV) against three isolates of quinolone-susceptible *S. pneumoniae*. Three pharmacokinetic profiles were simulated for each of the study agents (1/10 x AUC, 1 x AUC, and 10 x AUC). Target 24-hour AUCs were based upon human pharmacokinetic data resulting from maximal daily doses of each agent. All experiments were conducted over 48 hours and performed in duplicate. The rates and extent of reduction in CFU/ml were compared and presence of regrowth, if any, was noted.
RESULTS: Against all three isolates CIP was the least active agent. At regimens simulating the human 24 hour AUC, CIP resulted in an initial, modest decline in CFU/ml; however, by 48 hours the CFU/ml returned to or exceeded the starting inocula. At the AUC, LEVO resulted in mixed bacteriostatic and bactericidal activity among the isolates. The remaining agents yielded bactericidal (99.9% reduction) activity by 48 hours at the AUC. At 1/10 x AUC CIP and LEVO produced no inhibitory effect, GREP exhibited bacteriostatic activity, TROV mixed static and cidal activity, and CLIN and MOXI resulted in significant reductions in CFU/ml by 48 hours. All six agents produced cidal activity at 10 x AUC.
CONCLUSIONS: In this dynamic in vitro model of infection, the quinolones demonstrated varying degrees of activity against *S. pneumoniae*. The rank order of activity is CIP (least active) << LEVO < GREP < TROV ≤ CLIN, MOXI (most active).
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

94E. In vivo tissue activity of high-dose liposomal amphotericin B in a neutropenic murine candidal thigh infection model. *Russell E. Lewis, Pharm.D.*, Michael E. Klepser, Pharm.D., Stephen C. Piscitelli, Pharm.D., Andreas Groll, M.D., Veronica C. DeLallo, Pharm.D., Richard Quintiliani, M.D., Erika J. Ernst, Pharm.D., Thomas J. Walsh, M.D., Michael A. Pfaller, M.D.; University of Iowa, Iowa City, IA; National Institutes of Health, Bethesda, MD; Hartford Hospital, Hartford, CT.

PURPOSE: To compare the in vivo fungicidal activity of amphotericin B deoxycholate (AmB-D) and high dose liposomal amphotericin B (L-AmB) using a neutropenic murine thigh infection model.
METHODS: Swiss-Webster mice (20-23 g) rendered neutropenic with cyclophosphamide pretreatment were injected with 100 mcl of a standardized *Candida albicans* (ATCC 90028) suspension to produce a localized thigh infection. Mice were then treated intravenously with six-fold escalating total daily dosages of either L-AmB (5 mg/kg-30 mg/kg/day) or AmB-D (0.5-2 mg/kg/day) dosed at q4, 8, 12, and 24 hour intervals. At predetermined timepoints following dosing (T = 0, 4, 8, 12, and 24 hours), mice were sacrificed, and thigh tissue was aseptically removed, homogenized, and plated on potato dextrose agar for colony count determination. Single dose pharmacokinetic studies of serum and thigh tissue concentrations were performed and analyzed by HPLC.
RESULTS: L-AmB dosed at 30 mg/kg q24h (tissue AUC_{0-24} of 60.16 µg/ml) was the most active of all regimens tested; achieving a 2-$\log_{10}$ decline in tissue fungal burden by 24 hours. AmB-D at 2 mg/kg/day reduced the fungal burden in the thigh by 0.5-1 $\log_{10}$. Thigh tissue AUC_{0-24} for L-AmB averaged < 10% of concurrent serum AUC_{0-24}. Good correlation was noted between tissue AUC_{0-24} and reduction of tissue fungal burden by a sigmoid E_{max} model (r^2=0.975).

CONCLUSIONS: High-dose L-AmB is better tolerated and improves early antifungal efficacy over AmB-D in the murine thigh model. Dosage escalation with L-AmB may be viable strategy for improving antifungal efficacy where AmB-D penetration is initially poor.
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

95E. Reduction in the incidence of nosocomial vancomycin resistant enterococcus infections by implementation of an antimicrobial formulary control process. *Vikas Gupta, Pharm.D., BCPS*; Owen Healthcare Inc., Lombard, IL.

BACKGROUND: Studies have also shown that decreasing inappropriate use of vancomycin, third generation cephalosporins and clindamycin can significantly reduce the fecal colonization rates of vancomycin resistant enterococcus (VRE; Clin Infect Dis 1996;23:1020-5). The occurrence of nosocomial VRE infection and percentage of VRE isolates at our institution had increased from 8 cases in 1994 and 13% in 1995 to 14 cases and 18% in 1996, prior to implementation of a comprehensive antimicrobial formulary control process.
PURPOSE: To present results of a comprehensive approach which evaluated antimicrobial usage, susceptibility trends and nosocomial and community acquired VRE infection rates at the hospital.
METHODS: The percentage of VRE, and the occurrence of nosocomial and community-acquired VRE infections were evaluated from 1994-1998. Antimicrobial usage was evaluated from 1996 to 1998 on a cost per adjusted patient day (APD) and g/1000 APD or g/100 patient days for third generation cephalosporins, vancomycin, and expanded spectrum agents (i.e., piperacillin/tazobactam, ampicillin/sulbactam, and ticarcillin/clavulanate [Z/U/T]).
RESULTS: The occurrence of nosocomial VRE infection and percentage of VRE isolates decreased from 14 cases and 18% in 1996 to 8 cases and 15% in 1998. The occurrence of community-acquired VRE infections increased from 12 cases in 1994 to 29 cases in 1998. Antibiotic costs decreased from $13.39/APD in 1996 to $7.84/APD in 1998. Use of third generation cephalosporins, vancomycin and Z/U/T decreased from 230 g/1000 APD, 100 g/1000 APD and 115 g/100 APD in 1996 to 80 g/1000 APD, 60 g/1000 APD and 62 g/100 APD, respectively.
CONCLUSIONS: Development of a comprehensive antimicrobial formulary control process can result in significant decrease in cost and the occurrence of nosocomial VRE infection.
Presented at the Annual Meeting of the American Society of Health-System Pharmacists, Reno, NV, June 6-9, 1999.

96. A longitudinal survey of prevalence and susceptibility of community-acquired bacteremic isolates. *Kimberly A. Boykin Couch, Pharm.D.*, Karen I. Plaisance, Pharm.D., Richard Schwalbe, Ph.D., Judith Lovchik, Ph.D., University of Maryland, Baltimore, MD.

PURPOSE: Changes in prevalence and susceptibility of community acquired bacteremic isolates were evaluated.
METHODS: Original microbiology records from the ER, clinics and birthing center for 6/91-12/98 were reviewed and the following data were abstracted: identifier; date, time, location of specimen; genus, species; antibiogram. Data for each unique isolate from 1992-1994 (early) and 1996-1998 (late) were analyzed; differences were assessed by Fisher's exact test.
RESULTS: Coagulase negative staphylococci (39%, 42.2%), *Staphylococcus aureus* (13.8%, 10.8%), *Enterobacteriaceae* (10.6%, 16.1%), *Streptococcus pneumoniae* (10.1%, 3.9%), and *Enterococcus spp.* (4.2%, 6.7%) were the most prevalent in the early and late time periods, respectively. There were significant differences in *S. epidermidis* susceptibility to ciprofloxacin, clindamycin, and oxacillin ($p<0.05$) but not to trimethoprim-sulfamethoxazole or erythromycin for the two time periods. There were no differences in susceptibility to oxacillin for *S. aureus* with 80.5% and 81.3% susceptible in the early and late periods, respectively. Although not significantly different, the percentage of oxacillin non-susceptible *S. aureus* (ORSA) isolates that were not susceptible to ciprofloxacin, clindamycin, erythromycin, and trimethoprim-sulfamethoxazole were 75.9%, 79.3%, 100%, and 65.5%, respectively (early) and 91.7%, 100%, 100%, and 66.7%, respectively (late). No changes in prevalence of *E. faecium* occurred however, more *E. faecium* were resistant to ampicillin and vancomycin in the later time period ($p<0.05$).
CONCLUSION: The predominant isolates have remained relatively constant during the time period evaluated. Reduced *S. aureus* susceptibility to oxacillin is reflected in other classes of antimicrobials. The high rate of ORSA in the community may warrant re-evaluation of empiric therapy in selected patients.

97E. Differential expression of a phosphatidylinositol 3-kinase homolog in fluconazole resistant isolates of *Candida albicans. P. David Rogers, Pharm.D., M.S.*, Donna C. Sullivan, Ph.D., Stanley W. Chapman, M.D., John D. Cleary, Pharm.D.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: *Candida albicans* has been shown to develop resistance to fluconazole during therapy in immunocompromised patients. The purpose of this study was to identify differentially expressed genes in fluconazole resistant isolates of *C. albicans* that contribute to fluconazole resistance.
METHODS: Differential display was used to compare mRNAs from isogenic matched sets of clinical isolates obtained from two patients who developed candidiasis caused by fluconazole resistant isolates of *C. albicans* while receiving therapy. Isolates were grown in brain heart infusion broth at 37°C in a shaking incubator until mid-log phase. The cell pellets were collected by centrifugation and RNA was isolated using the guanidinium isothiocyanate method. Reverse transcription of RNA from each isolate was performed using an 18 base arbitrary primer for first strand synthesis. Second strand synthesis and PCR amplification was completed using the same primer for a total of 40 cycles. PCR products were analyzed on a 6% acrylamide/urea gel and autoradiographed. Complementary DNA fragments corresponding to several apparently differentially expressed mRNAs were recovered and sequenced.
RESULTS: A complementary DNA fragment observed to be up-regulated in resistant isolates of both matched sets was highly homologous to the *Saccharomyces cerevisiae* gene for the phosphatidylinositol 3-kinase *TOR1* and the putative *C. albicans* gene *TOR1*.
CONCLUSION: The *TOR1* gene product has been shown to mediate protein synthesis, cell cycle progression, and cell-cycle–dependent organization of actin cytoskeleton in *S. cerevisiae*. These results suggest that the *C. albicans* homolog of *S. cerivasiae* TOR1 may be involved in fluconazole resistance in *C. albicans.*
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

98. Molecular mechanisms of the immunomodulatory activity of amphotericin B in human monocytic cells. *P. David Rogers, Pharm.D., M.S.*, Jonathan K. Stiles, Ph.D., Stanley W. Chapman, M.D., John D. Cleary, Pharm.D.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: Amphotericin B (AmB) has been shown to exhibit immunomodulatory properties including cytokine activation, enhancement of macrophage activity, and inhibition of chemotactic responsiveness and activity of neutrophils. The purpose of this study was to identify differentially expressed genes encoding immunomodulatory proteins in response to AmB in human monocytic cells.
METHODS: Human monocytic cells (THP-1) at 10^6 cells/ml were equilibrated for 24 hours at 37°C in 5% CO_2 in supplemented RPMI. Cells were then exposed to either AmB 5 µg/ml or media alone for 24 hours. The cell pellets were collected by centrifugation and total RNA was isolated using the guanidinium isothiocyanate method. Reverse transcription of RNA was performed using an oligo-dT primer. The resulting cDNAs were labeled with (α-^{32}P) dATP and used as probes. A complementary DNA gene array was used to compare mRNA populations from cells exposed to the two experimental conditions. The arrays were prehybridized for 30 minutes at 68°C and then hybridized with the probes at 68°C for 60 hours. The arrays were then washed and exposed to autoradiography. The two arrays were normalized for expression of housekeeping genes. Gene expression patterns were then compared for identification of differentially expressed genes.
RESULTS: Differential expression patterns were observed for several genes including those encoding intercellular adhesion molecule-1 (ICAM-1), cell adhesion molecule (CD44), monocyte chemotactic and activating factor (MCAF) and monocyte-derived neutrophil chemotactic factor (MDNCF).
CONCLUSION: AmB appears to activate human genes that encode for proteins that modulate immune function. This may explain the immunomodulatory properties observed with this agent.

99. Predisposing factors associated with colonization or infection with *Stenotrophomonas maltophilia* in an intensive care unit setting at a university hospital. *Julie R. Lowe, Pharm.D.*, P. David Rogers, Pharm.D., M.S., Rathel L. Nolan, M.D., John D. Cleary, Pharm.D.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: The purpose of this study was to identify risk factors for colonization or infection with *Stenotrophomonas maltophilia* in intensive care unit (ICU) patients at our institution.
METHODS: Charts of ICU patients from whom *S. maltophilia* was isolated were retrospectively reviewed. Two case control patients were identified for each case patient matched for ICU. Data collected included demographics, length of stay, underlying disease, prior and concurrent antibiotics and immunosuppressive therapy, site of infection, susceptibilities, medical devices, surgical procedures, respiratory treatments, nutrition and severity of illness.
RESULTS: Data for a total of seventy patients (thirty cases and forty controls) were collected over a 24-month period. Case patients included 15 female and 15 male patients, control patients included 15 female and 25 male patients. The mean age was 52 years and 44 years for case and control patients, respectively. Patients were distributed across all ICUs and medical services. Patients had a higher risk of colonization or infection if they had a central line, tracheostomy, Foley catheter, or mechanical ventilation; had received dialysis, parenteral nutrition, enteral nutrition, respiratory therapy, aminoglycosides or vancomycin prior to isolation; or had a surgical wound

infection (all p<0.05). The mean length of ICU stay was 25 days and 9 days for case and control patients, respectively (p<0.05). Sites of isolation included blood (3.4%), respiratory (75.9%), wound (6.9%), urine (3.4%), CNS (3.4%), and other (14.3%). Twenty-three isolations (66%) represented infection.
CONCLUSION: In the ICU setting at our institution, risk factors for colonization or infection with *S. maltophilia* are multifactorial.

100. Differential gene expression in isogenic isolates of fluconazole resistant *Candida albicans*. *P. David Rogers, Pharm.D., M.S.*, Donna C. Sullivan, Ph.D., Stanley W. Chapman, M.D., John D. Cleary, Pharm.D.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: The purpose of this study was to identify differentially expressed genes in fluconazole resistant isolates of *C. albicans* that might contribute to fluconazole resistance.
METHODS: Differential display was used to compare mRNAs from isogenic matched sets of clinical isolates obtained from two patients who developed candidiasis caused by fluconazole resistant strains of *C. albicans* while receiving therapy. Isolates were grown in brain heart infusion broth at 37°C in a shaking incubator until mid-log phase. The cell pellets were collected by centrifugation and RNA was isolated using the guanidinium isothiocyanate method. Reverse transcription of RNA from each isolate was performed using an 18 base arbitrary primer for first strand synthesis. Second strand synthesis and PCR amplification was completed using the same primer for a total of 40 cycles. The resulting products were analyzed on a 6% acrylamide/urea gel and autoradiographed. Complementary DNA fragments corresponding to several apparently differentially expressed mRNAs were recovered and sequenced.
RESULTS: Several complementary DNA fragments observed to be differentially regulated in resistant isolates shared sequence identity with putative open reading frames for the *CDR99, POR1, GCN1, STA1, RPA190,* verprolin and *CEX1* genes in *Candida albicans*.
CONCLUSION: The gene products of these genes are involved in a multitude of cellular functions including efflux of intracellular toxins, mitochondrial transport of NADH, translational control, and RNA polymerase activity. Our results suggest that these genes may be involved in fluconazole resistance in this pathogenic fungus and may serve as potential pharmacologic targets.

101E. Efficacy and safety of ciprofloxacin oral suspension versus TMP/SMX for treatment of community- and nursing home-residing elderly women with acute urinary tract infection. *I. Gomolin, M.D.*, P. Siami, M.D., D. Haverstock, M.S., A. Heyd, Ph.D.; Gurwin Jewish Geriatric Center, Commack, NY; Welborn Clinical Research, Evansville, IN; Bayer Corporation, West Haven, CT.

PURPOSE: To compare the efficacy and safety of ciprofloxacin oral suspension (CIP) compared to trimethoprim/sulfamethoxazole (TMP/SMX) oral suspension among elderly women with acute urinary tract infections (UTI).
METHODS: Prospective, open label multicenter study among elderly women (≥ 65 years) residing in the community or in a nursing home with a UTI. Patients were randomized to a 10-day oral suspension regimen of either CIP (250 mg [5 ml] BID) or TMP/SMX (160/800 mg [20 ml] BID). Clinical response at 4 to 10 days post-therapy (end of therapy) was the primary outcome measure.
RESULTS: Of 261 enrolled women, 86 patients in each treatment group had both a pretherapy bacterial isolate and also were valid for efficacy assessment. *Escherichia coli* was the predominant bacterium isolated in the pretreatment urine in both the community and nursing home populations. Resistance rates of all pretreatment bacteria were 4% to CIP and 13% to TMP/SMX. End-of-therapy clinical resolution was statistically superior following CIP (97%) vs TMP/SMX (85%; 95% $CI_{CIP\text{-}TMP/SMX}$ = 2.0%, 21.3%). Eradication of pretreatment bacterial isolates at the end of therapy was higher following CIP (95%) vs TMP/SMX (84%; 95% $CI_{CIP\text{-}TMP/SMX}$ = 2.7%, 21.3%). However, colonization was higher following CIP (31%) vs TMP/SMX (16%) therapy (p=0.02). For the intent-to-treat population, drug-related events were lower following CIP (17%) vs TMP/SMX (27%), including premature discontinuation due to adverse events (2% CIP, 11% TMP/SMX; p<0.01).
CONCLUSIONS: CIP suspension had superior clinical success rates and higher bacteriologic eradication rates of the initial isolate compared to TMP/SMX for both community- and nursing home-residing elderly women with acute UTIs. CIP suspension was associated with a 37% lower adverse event rate and 80% lower premature discontinuation rate compared to TMP/SMX suspension.
Presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Diego, CA, September 24-27, 1998.

102E. A pharmacokinetic comparison of ampicillin/sulbactam 1.5 g versus 3 g using a Monte Carlo simulation. *Michael T. Miller, Pharm.D.*, George L. Drusen, M.D., Ben Lomaestro, Pharm.D.; Albany Medical Center, Albany, NY.

PURPOSE: A Monte Carlo simulation of ampicillin/sulbactam was performed using ADAPT II to compare the pharmacokinetics of 1.5 g vs 3 g given every 6 hours. This was done due to a concern treatment failures could occur at the lower dose depending on which organisms are being treated.
METHODS: Kinetic parameters were entered into ADAPT and concentrations at 1.8 hours (30% of the dosing interval) and 3 hours (50% of the dosing interval) were compared. These time points were used because there is evidence to suggest time above MIC for 30% of the dosing interval will achieve a bacteriostatic effect and time above MIC for 50% of the dosing interval will achieve a bactericidal effect. The concentrations obtained at each time and dose were compared to the MICs of a number of organisms.
RESULTS: After performing the simulation, there was a significant difference in percentage of simulated subjects with concentrations at or above MICs of 4, 8, and 16 µg/ml at 1.8 hours (stasis). There was also a significant difference in percentage of subjects with concentrations at or above MICs of 1,2,4 and 8 µg/ml for 3 hours (cidal). When compared to the MICs of a number of organisms, pharmacodynamically, the 3 g dose appears to be superior.
CONCLUSION: While this does not take into account in vivo functions such as complement fixation or the cellular response to infection it appears the 3 g dose of ampicillin/sulbactam might be more successful in treating a number of common pathogens.
Presented at the Eastern States Residency Conference, Baltimore, MD, April 23, 1999.

103E. In vitro activity of ciprofloxacin, levofloxacin, sparfloxacin, and trovafloxacin alone or in combination with piperacillin, ceftazidime, and gentamicin against *Alcaligenes xylosoxidans* ssp. x*ylosoxidans*. *Cory G. Garvin, Pharm.D.*, Joan M. Duggan, M.D., Christopher R. McBurney, B.S., Eric G. Sahloff, B.S., Madhavi Manduru, Pharm.D., Steven J. Martin, Pharm.D.; University of Toledo; Medical College of Ohio, Toledo, OH.

PURPOSE: This study was designed to evaluate the in vitro activity of some of the newer fluoroquinolones alone and in combination with piperacillin, ceftazidime, and gentamicin against *Alcaligenes xylosoxidans* ssp. x*ylosoxidans* (AXX) following four cases of AXX pneumonia in our ICU. Optimal therapy for AXX infections has not been documented.
METHODS: Microbroth MICs (NCCLS) were determined for ciprofloxacin, levofloxacin, sparfloxacin, trovafloxacin, piperacillin, ceftazidime, and gentamicin against twelve clinical isolates and one ATCC strain of AXX. Time-kill studies were performed for the same agents alone and in multiple combinations to determine bactericidal activity as well as synergy.
RESULTS: MIC summary data for these isolates were:

	Cipro	Levo	Trova	Spar	Pip	Ceftaz	Gent
MIC_{90}	4	4	> 256	1	4	8	1024
Percent susceptible (NCCLS)	38	69	0	54	100	92	0

Time-kill summary data for 5 strains of AXX tested were:

	Ceftaz/Gent	Pip/Gent	Levo/Gent	Spar/Ceftaz	Spar/Pip
# of synergy	4/5	4/5	3/5	3/5	3/5
# of cidal activity	4/5	3/5	3/5	3/5	2/5

No single agent demonstrated bactericidal activity. Gentamicin combined with either piperacillin or ceftazidime demonstrated the best synergy activity. Combining either piperacillin or ceftazidime with levofloxacin or sparfloxacin, as well as levofloxacin with gentamicin demonstrated some activity.
CONCLUSIONS: The newer fluoroquinolones have variable activity against AXX alone. β-lactam/gentamicin combinations appear to be most active against the isolates tested. Piperacillin or ceftazidime combined with gentamicin were the most active combinations. Resistance was common with trovafloxacin and gentamicin. Clinical infections with AXX may be best treated with combination therapy including a β-lactam and gentamicin.
Presented at the 99th General Meeting of the American Society for Microbiology, Chicago, IL, May 30-June 3, 1999.

104E. Effect of antibiotics on human polymorphonuclear neutrophil apoptosis. *Paul A. Silverman, Pharm.D.*, Daniel P. Healy, Pharm.D., Alice N. Neely, Ph.D., Ian Alan Holder, Ph.D., George F. Babcock, Ph.D.; Shriners Hospitals for Children; University of Cincinnati, Cincinnati, OH.

PURPOSE: We and others have previously shown that antibiotics demonstrate differential effects on endotoxin release from gram negative bacteria with the subsequent production of inflammatory and antiinflammatory cytokines. We have also demonstrated antibiotic-mediated upregulation of CD_{14} and CD_{11b} as a result of bacterial killing. Since these and other factors have been linked to cellular apoptosis, the aim was to evaluate the direct and indirect effects of representative antibiotics, as a result of bacterial killing, on PMN apoptosis.
METHODS: EDTA-containing whole blood was collected from healthy subjects and incubated (37°C/4h) with and without *K. pneumoniae* (Kp 1.0 x 10^5 CFU/ml) plus (in µg/ml) ceftazidime (50; TAZ), gentamicin (5; GEN), ciprofloxacin (5; CIP), trovafloxacin (5, TRO), tetracycline (5; TET), doxycycline (5; DOX), erythromycin (5; ERY), azithromycin (5; AZI), Kp LPS (10) or PMA (0.04). After staining with FITC-labeled annexin V and 7-amino-actinomycin D, RBCs were lysed, cells were read by flow cytometry with gating on PMNs (n=10,000).
RESULTS: In the absence of Kp infection, antibiotics increased apoptosis 56% (range 25-94%) over untreated cells (p<0.002). AZI, ERY, TRO and TET

produced the largest increases(69-94%). In contrast, in the presence of Kp, all antibiotic treatments, even those with poor in vitro activity (TET, DOX, ERY) decreased apoptosis vs untreated cells (27%, 17-38%, $p<0.05$) and Kp-stimulated cells (37%, 28-46%, $p<0.05$).
CONCLUSION: All tested antibiotics in clinically relevant concentrations increased PMN apoptosis; however, this effect was reversed in the presence of Kp infection. These data are consistent with those involving AZI for *S. pneumoniae*. Further study involving the immunomodulatory properties of antibiotics is warranted.
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

105E. Efficacy and safety of moxifloxacin versus clarithromycin for the treatment of community-acquired pneumonia. *C. Fogarty, M.D.*, J. Williams, M.D., D. Haverstock, M.D., D. Church, M.D.; Spartanburg Pharmaceutical Research, Spartanburg, SC; the Community-Acquired Pneumonia Study Group; Bayer Corporation, West Haven, CT.

PURPOSE: To evaluate the efficacy and safety of moxifloxacin vs clarithromycin in the treatment of community-acquired pneumonia (CAP).
METHODS: In a prospective, double-blind, multi-center clinical trial, 474 adult patients were enrolled with signs and symptoms of CAP. Patients were treated for 10 days with either oral moxifloxacin 400 mg once daily or clarithromycin 500 mg twice daily. Clinical and bacteriologic responses were determined at the end-of-therapy (0-6 days post-therapy), follow-up (14-35 days post therapy), and overall (end-of-therapy plus follow-up).
RESULTS: Among 473 intent-to-treat patients, 382 (81%) patients were included in the efficacy analysis. Fifty-six percent of efficacy-valid patients had a pre-therapy causative organism identified (i.e., 277 organisms among 214 patients). The most common organisms identified included: *Chlamydia pneumoniae* (36%), *Mycoplasma pneumoniae* (16%), *Haemophilus influenzae* (14%) and *Streptococcus pneumoniae* (13%). The overall clinical resolution rates for the efficacy-valid population were 95% for both moxifloxacin and clarithromycin (95% CI = -3.7%, 5.3%). Bacteriologic success at follow-up, including end-of-therapy failures, was 96% for both treatment groups (95% CI = -5.8%, 6.2%). While drug-related events were equal in both moxifloxacin-treated patients (35%, 84/237) and clarithromycin-treated patients (34%, 81/236), only 6 (2%) moxifloxacin patients had study drug discontinuance because of an adverse event, as opposed to 12 (5%) clarithromycin patients. In both treatment groups, nausea and diarrhea were the most commonly reported adverse events (8%-9%).
CONCLUSIONS: Moxifloxacin 400 mg once daily was as effective and as safe as clarithromycin 500 mg twice daily in the treatment of adult outpatients with CAP.
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

106E. Determination of antibiotic effect in an in vitro model: comparison with an established animal model. *Charles R. Bonapace, Pharm.D.*, Lawrence V. Friedrich, Pharm.D., Roger L. White, Pharm.D., John A. Bosso, Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: Animal infection models have historically been used to study pharmacodynamic (PD) relationships. Similar results/conclusions could theoretically be produced using an in vitro PD model as an alternative.
METHODS: We compared the antibiotic effect of ticarcillin, administered in various doses/dosing regimens, against *Pseudomonas aeruginosa* ATCC 27853 under conditions analogous to that previously performed in a murine thigh infection model (Vogelman, et al. J Infect Dis 1988;158:831). Ticarcillin dosages of either 48, 96, 192, or 384 mg/day were administered at 1-, 2-, 4-, 8-, 12-, or 24-hour intervals into the central compartment of a 2-compartment model and murine concentration-time profiles were mimicked. An inoculum of $5x10^5$ CFU/ml was placed in the peripheral compartment of the in vitro model (PC). Drug concentrations and colony counts were determined over 24 hours. Linear regression was used to assess the relationship between % T > MIC in the central compartment and Δ log CFU/ml. Statistical analysis of the Δ log CFU/ml from 0 to 24 hours was performed for matched regimens in the in vitro and animal models based on % T > MIC.
RESULTS: % T > MIC was the PD parameter most associated with Δ log CFU/ml from 0 to 24 hours in the in vitro model. The % T > MIC vs Δ log CFU/ml regression equations in the murine and in vitro models were similar and the Δ log of the 0 to 24 hr colony counts at equivalent % T > MIC were not statistically different ($p=0.722$).
CONCLUSIONS: This study comparing PD principles between a murine and in vitro model detected a very similar relationship between % T > MIC and effect. Further comparative studies of these models utilizing a variety of antimicrobials and organisms are warranted.
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

107E. Comparative activity of trovafloxacin and tobramycin, in combination with piperacillin and cefepime against clinical isolates of *Acinetobacter baumannii* assessed by three different methods. *Charles R. Bonapace, Pharm.D.*, Roger L. White, Pharm.D., Lawrence V. Friedrich, Pharm.D., Linda B. Mihm, Pharm.D., John A. Bosso, Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: *Acinetobacter baumannii* (AB) has become a problematic pathogen in many institutions due to development of multiple drug resistance; combination therapy may therefore be attractive or necessary.
METHODS: We performed synergy testing using time-kill (TK), checkerboard (CB), and epsilometer test (ET) on 10 clinical isolates of AB with trovafloxacin (TV) and tobramycin (TM) in combination with cefepime (CF) and piperacillin (PI). Results from TK were based on duplicate 0- and 24-hour observations while microtiter plates for CB were read after 18 hours of incubation at 35°C. Concentrations of each agent in the TK combinations included 2 x MIC, $^1/_4$ x MIC, and 2 x MIC plus $^1/_4$ x MIC. Standard definitions were used to define synergy (S), additivity/indifference (A/I), and antagonism (A) for all methods. Ranges of MICs (µg/ml) of TV, TM, CF and PI were 0.03-> 32, 0.25-32, 1-96 and 8-3072, respectively. Five isolates had MICs to TV that exceeded its solubility in broth and were tested against combinations using only TM by TK and CB. ET testing was performed in duplicate by crossing the strips at a 90° angle to one another at the MIC of each drug.
RESULTS: Overall, A/I accounted for 75% of the possible combinations for all 10 isolates using the TK method. Agreement among ET and TK occurred in 90 of 120 cases (75%). Agreement among CB and TK occurred in 62 of 120 instances (52%). Although S occurred infrequently, such combinations may be useful in the treatment of AB infections. Although we were unable to assess the interaction of TV and PI by ET when MICs exceeded those represented on the strips, agreement of results with TK testing was still higher for ET than CB.
CONCLUSIONS: These data provide further evidence that using ET for simple synergy testing is feasible.
Presented at the 98th General Meeting of the American Society for Microbiology, Atlanta, GA, May 1998.

108E. Worldwide trends in fluoroquinolone susceptibility patterns, 1983-1999. *Charles R. Bonapace, Pharm.D.*, Roger L. White, Pharm.D., Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D.; Medical University of South Carolina, Charleston, SC.

PURPOSE: Susceptibility (S) of bacteria decreases over time, although rate and extent of change are largely unknown.
METHODS: We assessed S trends for 8 fluoroquinolones (FQs: ciprofloxacin [CIP], clinafloxacin, gatifloxacin, grepafloxacin [GRP], levofloxacin [LEV], moxifloxacin, ofloxacin [OFL], trovafloxacin [TRO]) using a database of studies published from 1983-99. Using ≥ 3 years of data, linear regression of $\log_{10}$ MIC_{50} and MIC_{90} was performed for each organism/drug combination.
RESULTS: 330 drug/organism combinations (120,933 isolates) were evaluated (181, 75 and 74 from North America [NA], Asia [A] and Europe [E], respectively). Median increases over time in MIC_{50} and MIC_{90} were 4- and 8-fold, respectively. Positive (+) slopes, indicating decreasing S over time, were detected in 51%, 71%, and 68% of possible instances for NA, A, and E. In a subset of data reflecting the steepest + slopes, 11, 58, and 32% occurred in NA, A, and E, respectively. With FQ, approximately 60% of relationships resulted in + slopes with the exceptions of GRP (33%), LEV (38%), and TRO (17%). CIP, OFL, and TRO accounted for most of the subset of steepest slopes (75% of total). 13 Gram-positive and 34 Gram-negative bacterial species were evaluated, with increases in MIC_{90} more frequently associated with the former. The largest increases in MIC_{90} occurred with staphylococci (42% of total) and enterococci (16%). With Gram-negative organisms, the greatest increases in MIC_{90} were with *P. aeruginosa* (11%).
CONCLUSIONS: We detected increases in MIC_{50} and MIC_{90} of FQ over time against numerous pathogens. Increases were highest for drugs that have been used for the longest periods of time; increases were also noted for FQs yet to be marketed. This type of quantitative analysis of MIC_{90} trends may detect changes in S prior to methods using categorical breakpoint data.
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

Managed Care

109. Clinical analysis of drug formularies for managed care organizations participating in TennCare. *Peter A. Chyka, Pharm.D.*, J. Douglas Wurtzbacher, Pharm.D., Teresa D. Holimon, Pharm.D., James E. Bailey, M.D., M.P.H.; University of Tennessee, Memphis, TN.

PURPOSE: To compare the drug formularies of 11 managed care organizations (MCO) for compliance with minimum guidelines based on specific AHFS categories and overall clinical utility.
METHODS: Every MCO participating in TennCare submitted an electronic version of their 1997 drug formulary upon the request of the state's TennCare Bureau. An integrated computerized database was created which included generic drug name, route of administration, prior authorization status, and

AHFS category by MCO. Descriptive comparisons among formularies were performed on a computerized spreadsheet and served as indicators for the clinical utility of each formulary.
RESULTS: The formularies complied to the guidelines with levels that ranged from 91 to 99%. The average percentage of the number of drugs available per AHFS category for all MCOs was 59% (range = 49 to 93%). Of the 971 agents in the TennCare-specified AHFS categories, 190 (20%) were included by all MCOs and 379 (39%) were included in the majority of the programs. The average percentage of drug categories requiring prior authorization for all MCOs ranged from 1% to 23% (average = 10%). Of the 349 agents available in the TennCare-specified AHFS categories by prior authorization, 153 (44%) required prior authorization by all MCOs.
CONCLUSIONS: The minimum formulary guidelines provided a framework for rational formulary development. All of the formularies can be generally deemed to be therapeutically sound; however, some inadequacies were noted. This type of integrated analysis of drug formularies for several MCOs provides a baseline to improve patient care through ongoing comprehensive formulary review.

Nephrology

110. Cisapride use in endstage renal disease: should it be contraindicated? *Melissa J. Hentges, Pharm.D.*, Brent Gunderson, Pharm.D. candidate, Matthew J. Lewis, Pharm.D., BCPS.; Hennepin County Medical Center; University of Minnesota, Minneapolis, MN.

PURPOSE: This study involves a retrospective inpatient chart review of endstage renal disease (ESRD) patients receiving hemodialysis to observe if cisapride significantly increases heart rate (HR), QT, and corrected QT (QTc) intervals on 12-lead EKG.
METHODS: Medical records for 61 patients were obtained and reviewed. HR, QT, and QTc on all 12-lead EKGs, reason for admission, past medical history, and concomitant medications were documented. Twenty-three patients met the inclusion criteria of active hemodialysis and ≥ 2 EKGs while on cisapride and ≥ 2 EKGs while off cisapride. Statistical analysis was done using the Student's t-test.
RESULTS: A total of 528 EKGs (278 on cisapride/250 off) were included. The results, on versus off cisapride, respectively, were average HR: 88 vs 84 beats/minute (p=0.18), QT: 373 vs 382 msec (p=0.24), and QTc: 443 vs 441 msec (p=0.39). Overall, on cisapride, 7/23 patients had a significantly faster average HR; 4/23 patients had a significantly longer average QT and average QTc. No significant difference was found in the number of admissions/month while on or off cisapride. One patient did expire from ventricular arrhythmias shortly after discontinuing cisapride. The patient's QTc was significantly longer on versus off cisapride (487 vs 462 msec, p=0.0066); however, the patient had experienced syncopal episodes, atrial arrhythmias and ventricular conduction problems prior to cisapride use.
CONCLUSION: This study found no significant overall difference in HR, QT, and QTc interval or admissions/month on versus off cisapride. These results re-emphasize the question: should cisapride be contraindicated in ESRD patients?

111E. In vitro model for tobramycin disposition during hemodialysis with low- and high-flux biocompatible membranes. *G.R. Matzke, Pharm.D.*, T.D. Nolin, M.S., R.F. Frye, Pharm.D., Ph.D., D.A. Baritot, B.S.N., P. Palevsky, M.D.; University of Pittsburgh; VA Pittsburgh HCS, Pittsburgh, PA.

PURPOSE: Conventional HD only effectively removes small molecules (MW < 500D), which are minimally protein bound. The introduction of high-flux biocompatible membranes has dramatically increased the clearance of mid-MW drugs such as vancomycin. The clearance of many commonly utilized small MW drugs, however, have not been evaluated under these dialytic conditions. This in vitro study was designed to quantify the disposition of tobramycin (MW 468D) during HD with a low flux and high flux biocompatible polymethylmethacrylate (PMMA) dialyzer.
METHOD: In vitro dialysis was performed for 3 h using 6.0 L of phosphate buffered saline. The aqueous buffer was pumped through the dialyzer at 100 to 300 ml/min to approximate a blood flow of 150 to 450 ml/min based on Hct of 34%. Dialysate flow was ~ 500 ml/min. Low-flux (Toray B3-2.0A) and high-flux (Toray BK-2.1 U) PMMA dialyzers were evaluated. The clearance (Cl_D) of urea, creatinine and tobramycin was determined as the mean amount of solute recovered during two discrete dialysis collections divided by the area under the buffer concentration time curve of the intervals.
RESULTS: The sieving coefficients of urea, creatinine and tobramycin were similar between the two filters: 0.99 ± 0.03 vs 0.98 ± 0.06, 0.99 ± 0.03 vs 0.99 ± 0.05 and 0.98 ± 0.02 vs 0.96 ± 0.14 (mean ± SD). The Cl_D (ml/min) of urea, creatinine and tobramycin between the two dialyzers was not significantly different (p>0.05) at all three flow rates.

Flow rate	Urea		Creatinine		Tobramycin	
(ml/min)	200	300	200	300	200	300
Low-flux	204 ± 10	265 ± 25	202 ± 10	230 ± 11	173 ± 39	199 ± 13
High-flux	217 ± 14	297 ± 31	207 ± 7	246 ± 15	143 ± 37	179 ± 39

CONCLUSIONS: The Cl_D of tobramycin by both PMMA dialyzers significantly exceeded previously reported values of 31.4 to 51.2 ml/min for cuprophane and cellulose acetate dialyzers (Int J Clin Pharm Ther Tox 1987;25:50-5 and Antimicrob Agents Chemother 1984;25:128-30). The projected fraction of tobramycin removed by three hours of HD (blood flow rate = 300 ml/min) ranged from 75.5% to 81.3% for PMMA vs 26.6% to 41.4% for the conventional dialyzers. These findings indicate that the post-HD supplemental dose of tobramycin must be increased to 75 to 80% of the normal dose to maintain adequate therapeutic plasma concentrations when PMMA dialyzers are utilized.
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112E. A randomized controlled trial of clinical pharmacists' interventions versus standard care for anemia management in hemodialysis patients. *G.R. Matzke, Pharm.D.*, T.J. Comstock, Pharm.D., S.J. Coons, Pharm.D., The Hospital Pharmacy Cooperative Study Group; University of Pittsburgh, Pittsburgh, PA; Virginia Commonwealth University, Richmond, VA; University of Arizona, Tucson, AZ.

PURPOSE/METHODS: In this 52-week randomized controlled trial of 605 hemodialysis patients, the effect of clinical pharmacists' (CP) interventions on HCT, the utilization of EPO and iron, iron stores, clinical events and patient-reported quality of life were evaluated. CPs evaluated the HCT, EPO and iron usage of treatment (TRT) and control (CTL) patients weekly. They made EPO and iron dosage recommendations at 4-6 week intervals on the basis of computerized pharmacodynamic modeling and iron needs assessment for TRT patients only. Age, gender, race, cause of ESRD, HCT, ferritin, TSAT, and EPO dosage were similar at baseline in the two groups. All statistical evaluations were adjusted for multiple comparisons.
RESULTS: The proportion of TRT and CTL patients achieving target HCT (73.4% and 67.9%, respectively) within the first 26 weeks and the average time to achievement (10.6 ± 6.7 weeks vs 9.4 ± 6.8 weeks, respectively) were not statistically significantly different. TRT patients who achieved the target range, however, were 1.33 times more likely than CTL patients to have a HCT ≥ 33%, p<0.001. A significant downward trend in EPO dosage (U/kg/week) was evident after 24 weeks of study participation in the TRT group compared to the CTL group: slope of the dose vs time relationship was -3.02 for TRT patients vs + 1.07 for CTL patients (p=0.0332). The fraction of TRT patients who received IV iron and had TSATs ≥ 20% increased 3 and 1.33 fold, respectively. The total dose of IV iron administered during the study was 2369.5 ± 1899.0 mg in the TRT patients vs 2042.3 ± 1547.5 mg in the CTL patients (p=0.0517). This may have contributed to the higher proportion of TRT vs CTL patients with TSATs ≥ 20 in quarters 2 and 4: p=0.002 and p=0.048. Quality of life measurements and the incidence of bleeding, hospitalizations, hypertension, and thrombosis in the TRT and CTL group were similar. The incidence of infections was the same (33.6%) during the first six months. However, it was lower in the TRT patients during the second six-months of the study, 45.3% vs 33.6%, p=0.013. This may have contributed to the difference in EPO dosage.
CONCLUSIONS: The study demonstrated clinical pharmacists' interventions can improve anemia management for hemodialysis patients.
Published in J Am Soc Nephrol 1999;10:Abstract A1372.

113E. Vancomycin removal by low- and high-flux hemodialysis with polymethylmethacrylate dialyzers. *G.R. Matzke,Pharm.D.*, R.F. Frye, Pharm.D., Ph.D., T.D. Nolin, M.S., D.A. Baritot, B.S.N., P. Palevsky, M.D.; University of Pittsburgh; VA Pittsburgh HCS, Pittsburgh, PA.

PURPOSE: Drug disposition during hemodialysis (HD) is affected by several physiochemical properties, including molecular size, protein binding, lipophilicity, and ionization. Conventional HD effectively removes only small molecules which are minimally protein bound. High-flux dialysis increases the clearance of vancomycin, a prototypical middle molecule (MW = 1400D), by up to 8-10 fold relative to conventional HD. The purpose of this study was to ascertain if the enhanced dialytic clearance of vancomycin was associated with the ultrafiltration coefficient of the dialyzer (i.e., low vs high flux) or a property of the dialyzer membrane.
METHODS: In vitro dialysis was performed for 3 h using 6.0 L of phosphate buffered saline. The aqueous solution was pumped through the dialyzer at 100 to 300 ml/min to approximate a blood flow of 150 to 450 ml/min based on Hct of 34%. Dialysate flow was ~ 500 ml/min. Four low-flux (Toray B3-2.0A; LFD) and high-flux (Toray BK-2.1U; HFD) PMMA dialyzers were evaluated. The sieving coefficient (SC) and clearance (Cl_D) was determined via standard methods from the pre-dialyzer, post dialyzer and ultrafiltrate concentrations determined every 5-10 min during dialysis.
RESULTS: The SC of urea and creatinine with the two dialyzers were similar: 0.99 ± 0.03 vs 0.98 ± 0.06 and 0.99 ± 0.03 vs 0.99 ± 0.05, respectively (mean ± SD). However, the SC of vancomycin with the HFD significantly exceeded the LFD value, 0.91 ± 0.14 vs 0.81 ± 0.20. The Cl_D [ml/min] of urea, creatinine and vancomycin increased as the flow rate increased. However, there was no significant difference with a given solute between the HFD and LFD at the same flow rate.

	High-Flux		Low-Flux	
Flow Rate (ml/min)	200	300	200	300
Vancomycin	92 ± 42	132 ± 40	95 ± 43	108 ± 31
Urea	217 ± 14	297 ± 31	204 ±10	265 ± 25
Creatinine	207 ± 7	246 ± 15	202 ± 10	230 ± 11

CONCLUSIONS: The Cl_D of vancomycin by these PMMA dialyzers in the absence of protein binding appears to be predominantly dependent on the characteristics of the membrane (i.e., pore radius rather then the ultrafiltration coefficient). Although the molecular size of vancomycin greatly exceeds that of urea and creatinine, since these endogenous solutes are efficiently cleared with HFD and LFD, their clearance or markers thereof (KT/V) may be utilized to individualize vancomycin therapy for HD patients.
Published in J Am Soc Nephrol 1999;10:Abstract A1374.

114E. Cefazolin and ceftazidime clearance during hemodialysis with low- and high-flux polymethylmethacrylate dialyzers. *G.R. Matzke, Pharm.D.*, R.F. Frye, Pharm.D., Ph.D., T.D. Nolin, M.S., D.A. Baritot, B.S.N., P. Palevsky, M.D.; University of Pittsburgh; VA Pittsburgh HCS, Pittsburgh, PA.

PURPOSE: The introduction of high-flux and biocompatible membranes has dramatically increased the clearance of vancomycin (MW ~ 1400D). The clearance of cefazolin and ceftazidime, which are frequently utilized for the management of access and systemic infections in HD patients, however, have not been evaluated under these new dialytic conditions. This in vitro study was designed to quantify the disposition of cefazolin (MW ~ 455D) and ceftazidime (MW ~ 547D) during HD with low and high flux biocompatible dialyzers.
METHODS: In vitro dialysis was performed for 3 h using 6.0 L of phosphate buffered saline. The aqueous buffer was pumped through the dialyzer at 100 to 300 ml/min to approximate a blood flow of 150 to 450 ml/min based on Hct of 34%. Dialysate flow was ~ 500 ml/min. Two different PMMA dialyzers were evaluated: low-flux (Toray B3-2.0A) and high-flux (Toray BK-2.1U). The clearance (Cl_D) of urea, creatinine, cefazolin and ceftazidime was determined as the mean amount of solute recovered during two discrete dialysate collections divided by the area under the buffer concentration time curve of the intervals.
RESULTS: The sieving coefficients (SC) of all four solutes determined during isolated ultrafiltration with the high-flux dialyzer were > 0.99. The Cl_D (ml/min) of urea, creatinine, cefazolin and ceftazidime by both dialyzers was flow rate dependent.

	Low-Flux		High-Flux	
Flow Rate (ml/min)	200	300	200	300
Cefazolin	124 ± 21 #	142 ± 20 #	163 ± 9 #	193 ± 22 #*
Ceftazidime	99 ± 23	114 ± 17	147 ± 8 *	169 ± 19 *

*p<0.05 high vs low, # p<0.05 cefazolin vs ceftazidime

CONCLUSIONS: Since the MW of cefazolin and ceftazidime are similar and the degree of protein binding is not a confounding variable in this aqueous media, the reason why the Cl_D of cefazolin in both dialyzers significantly exceeded the ceftazidime values is unclear. The observed ceftazidime Cl_D exceeded a previously reported value of 60 ml/min for ciprophane by 1.5 to 3 fold and was similar to the value for a polysulfone dialyzer. These findings indicate that the maintenance dose of cefazolin and ceftazidime for HD patients may need to be increased to maintain adequate therapeutic plasma concentrations when PMMA dialyzers are utilized.
Published in J Am Soc Nephrol 1999; 10:Abstract A1373.

115E. Role of caspase-1, -3, and -6 in apoptosis induced by cisplatin nephrotoxic injury. *Alan H. Lau, Pharm.D.*, Cheng Jin Li, M.S., Anna Santos, B.S., Rong Yu, Ph.D., Tony Kong, Ph.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: Cisplatin use is often limited by nephrotoxicity. High doses can cause renal cell necrosis while apoptosis was seen after lower doses. Many intracellular cysteine proteases, caspases, are activated and responsible for dismantling cell structures during apoptosis. We evaluated the role of caspases in cisplatin-induced renal (LLC-PK1) cell apoptosis.
METHODS: Cell viability was determined by CellTiter 96 Cell Proliferation Assay‘. Apoptosis was detected by condensed or fragmented nuclei visualized under fluorescence microscopy after DAPI staining. DNA fragmentation was confirmed by a typical ladder pattern during gel electrophoresis. Caspase activity was determined by a fluorogenic assay.
RESULTS: A dose-dependent relationship was observed between the percentage cell viability and cisplatin dose (30-300 mcM) as well as time of exposure (4-48 hours). The percentage of cells with fragmented nuclei increased from 11% to 42% as exposure to 100 mcM cisplatin increased from 8 to 24 hours. DNA laddering began to appear after 12 hours. While there was no significant change in caspase-1 and caspase-6 activities after cisplatin exposure, caspase-3 activity was increased 2-fold after 6 hours and became 41-fold after 24 hours. The induced caspase-3 activities were dose-dependent between 15-100 mcM of cisplatin and declined from 100-300 mcM. The ICE (interleukin 1β-converting enzyme) inhibitor, z-VAD-fmk, reduced caspase-3-like activities and apoptosis in a dose-dependent manner.
CONCLUSIONS: Caspase-3 may play an important role in cisplatin-induced renal cell apoptosis. Novel strategies to prevent injury or enhance recovery can be devised based on this new understanding of the molecular mechanisms.
Presented in the XV International Congress of Nephrology, Buenos Aires, Argentina, May 4, 1999.

116. Effect of cisapride discontinuation on QT interval in patients with endstage renal disease. Mia A. Kim, Pharm.D., Kevin M. Sowinski, Pharm.D., Michael A. Kraus, M.D., Ruchir Sehra, M.D., Gregory T. Alterose, M.D., Bruce A. Mueller, Pharm.D., *Meri K. Scott, Ph.D.*; Purdue University, Indianapolis, IN; Indiana University, Indianapolis, IN.

PURPOSE: Endstage renal disease (ESRD) patients taking cisapride with medications that inhibit its metabolism have been found to have QT interval prolongation. Cisapride's labeling includes renal failure as a contraindication due to potential cardiac arrhythmias in these patients. However, no published data exists evaluating this risk in patients with ESRD. This study evaluated the impact of cisapride discontinuation on QTc interval and QTc dispersion in ESRD patients.
METHODS: Nine subjects from the Indiana University Outpatient Hemodialysis Center (5 men/4 women) receiving cisapride underwent 12-lead electrocardiography before and again 2-4 weeks after discontinuation of cisapride. Subjects were not taking any antiarrhythmic drugs or medications known to interact with cisapride. Twelve-lead electrocardiograms were evaluated by two blinded investigators. The QT interval was corrected for heart rate to determine QTc interval. The QTc dispersion was calculated as the difference between the maximum and minimum QTc interval in any of the 12 electrocardiogram leads. Paired t-test was used to compare data before and after discontinuing cisapride. Data are presented as mean ± SD (range).
RESULTS: The QTc interval before and after discontinuing cisapride was 474 ± 32 (424-539) msec and 460 ± 26 (419-505) msec, respectively ($p<0.05$). The degree of QTc dispersion was 48 ± 11 (23-64) msec on cisapride and 39 ± 12 (24-57) msec after discontinuation ($p<0.05$).
CONCLUSION: Our data support the recent contraindication for patients with renal failure, as cisapride prolongs the QTc interval in patients with ESRD. Additionally, these patients have abnormal QTc intervals even off cisapride, suggesting a possible substrate for arrhythmogenesis.

117. Chronic hemodialysis patients' blood pressures do not vary as a function of weekly dialysis session number. *James D. Coyle, Pharm.D.*, Maria C. Pruchnicki, Pharm.D., William H. Bay, M.D.; The Ohio State University, Columbus, OH.

PURPOSE: To test the hypothesis that chronic hemodialysis patient blood pressures (BPs) are higher at the first weekly dialysis session compared to subsequent sessions due to eccentric intervals in thrice weekly dialysis.
METHODS: Demographic information and four consecutive weeks of pre- and post-dialysis systolic (SBP) and diastolic (DBP) BPs were analyzed for all patients served by a university outpatient hemodialysis center.
RESULTS: The patient population (n=42), median age 51.5 years (range 25-84) and dialysis duration of 26 months (range 1-167), was 54.8% male, 69.0% African-American, and 28.6% Caucasian. BP data were not normally distributed and not normalized by usual transformations (Kolmogorov-Smirnov test, $p<0.0001$); medians and nonparametric statistical tests were therefore employed. Each patient's pre-dialysis SBP, pre-dialysis DBP, post-dialysis SBP, and post-dialysis DBP were estimated for each weekly dialysis session as the median of all corresponding observations over the study period. Median (range) BPs in mm Hg for the first, second, and third weekly dialyses were:

	Pre-dialysis SBP	Pre-dialysis DBP	Post-dialysis SBP	Post-dialysis DBP
First	146	79	133	71
	(72-198)	(38-100)	(66-191)	(36-98)
Second	139	78	134	73
	(70-198)	(40-100)	(61-166)	(39-96)
Third	146	80	131	72
	(72-190)	(39-98)	(58-182)	(36-90)

BP differences among the dialysis sessions were not significant (Friedman tests, $p>0.05$).
CONCLUSIONS: The results do not support our hypothesis, suggesting that weekly dialysis session number need not be considered when evaluating BPs in chronic hemodialysis patients. The results also suggest that medians and nonparametric tests should be used to accurately summarize and analyze BP data in these patients.

Neurology

118. Reduction in the amount of deterioration in Alzheimer's disease patients with rivastigmine, a new cholinesterase inhibitor. John Messina, Pharm.D., Richard Hartman, Ph.D., *Lisa Malaty, Pharm.D.*; Novartis Pharmaceuticals, East Hanover, NJ; Rutgers College of Pharmacy, Piscataway, NJ.

PURPOSE: The assessment of benefit from cholinesterase inhibitors (CHE-

Is) in the symptomatic treatment of Alzheimer's disease (AD) has been focused on their ability to improve cognition, global functioning, and activities of daily living. Since AD is a progressive, neurodegenerative disease, maintaining the current level of function or reducing worsening should be considered beneficial when assessing a treatment. The objectives of the current analysis were to determine the effects of rivastigmine on reducing the amount of worsening on: 1) cognition as measured by the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), 2) global functioning as measured by the Clinician's Interview Based Impression of Change with Caregiver Input (CIBIC-Plus) and 3) activities of daily living as measured by the Progressive Deterioration Scale (PDS).
METHODS: Analyses were conducted on 625 mild to moderately severe AD patients in one of the phase 3 controlled rivastigmine studies. Analyses were performed to compare the incidence of different levels of worsening of the observed cases population between the 6-12 mg/day rivastigmine group and the placebo group, and the 1-4 mg/day rivastigmine group and the placebo group at week 26 on the ADAS-Cog (0-, 4-, and 7-point decline), CIBIC-Plus (stabilized or worsened), and PDS (any worsening).
RESULTS: A greater percentage of patients receiving placebo worsened on the ADAS-Cog, CIBIC-Plus, and PDS compared to high dose (6-12 mg/day) and low dose rivastigmine (1-4 mg/day). The difference between the placebo and the 6-12 mg/day rivastigmine group was statistically significant for the 0-, 4-, and 7-point decline on the ADAS-Cog, stabilized or worsened on the CIBIC-Plus, and for any worsening on the PDS ($p<0.05$).
CONCLUSION: Improvement from baseline with rivastigmine on cognition, global functioning, and activities of daily living has been demonstrated in two double-blind, placebo-controlled studies. These data also shows that AD patients treated with rivastigmine do not worsen on cognition, global function, and activities of daily living as much as patients treated with placebo.

119. Effect of cholesterol level on cognitive function in Alzheimer's disease patients treated with rivastigmine, a new cholinesterase inhibitor. *John Messina, Pharm.D.*, Richard Hartman, Ph.D., Lisa Malaty, Pharm.D., Juliana Hornstein, Pharm.D.; Novartis Pharmaceuticals, East Hanover, NJ; Rutgers College of Pharmacy, Piscataway, NJ.

PURPOSE: It has been hypothesized that elevated cholesterol may be a risk factor for dementia. A corollary to this would be that elevated cholesterol is associated with greater cognitive deficits. This study was a retrospective analysis of serum cholesterol levels and its effect on cognition in patients with mild to moderately severe Alzheimer's disease (AD) in clinical trials with the acetylcholinesterase inhibitor, rivastigmine. The objectives were to determine if higher baseline cholesterol levels: 1) correlate with greater cognitive impairment, 2) influence cognitive decline, and 3) predict response to rivastigmine.
METHODS: Analyses were conducted on 1848 AD patients enrolled in three 26-week, double-blind, placebo-controlled rivastigmine clinical studies. Patients in each randomized treatment group were categorized by their baseline mean total cholesterol, and comparisons of cognitive changes were based on the difference between baseline and week 26 assessments on the cognitive subscale of the Alzheimer's Disease and Assessment Scale (ADAS-Cog).
RESULTS: ADAS-Cog scores at baseline were similar in both cholesterol groups. There was a slight difference in the mean change in ADAS-Cog scores in the placebo groups from baseline for total cholesterol (TC) $\geq$ 200 mg/dl or < 200 mg/dl (2.38 point vs 3.26 point worsening, respectively). There was no clinically significant or statistically significant difference seen in the mean change on the ADAS-Cog scores between the placebo patients in either cholesterol category. The mean TC was comparable for both responders and nonresponders.
CONCLUSION: TC levels neither predicted severity of cognitive deficits nor the rate of decline in cognition over time in AD patients. Total cholesterol levels did not alter the patient's response to rivastigmine treatment. Increased total cholesterol does not appear to be a risk factor for worsening cognition and is not predictive of AD severity.

120. Readability of printed sources of information for epileptic patients: implications for patient education. *David R. Foster, Pharm.D.*, Denise H. Rhoney, Pharm.D.; Wayne State University; Detroit Receiving Hospital and University Health Center, Detroit, MI.

PURPOSE: Written information can be a valuable tool in patient education. Studies evaluating written information for various disease states have frequently demonstrated that the majority of written literature is written at a readability level that exceeds that of the average patient, and it has been recommended that written communications with patients should be at a fifth grade level or lower. The purpose of this study was to assess the readability of written patient information available to epileptic patients.
METHODS: One hundred one samples of written patient information were obtained from various sources, including state and national epilepsy organizations, government organizations, pharmaceutical manufacturers, the Internet, universities, pharmacy resources (Micromedex, USPDI), the lay press, and medical centers (hospitals and clinics). The information was classified based on content and intended audience, and readability was assessed using the Flesch-Kincaid grade level (FKGL) as calculated by Grammatik™.
RESULTS: The mean FKGL for all samples was 9.4. When analyzed according to content, mean FKGLs were: general disease information, 9.7; general treatment information, 11.9; drug specific information, 9.0; surgical options, 8.5; information for families, 10.6; childhood seizures, 7.2; first aid, 8.5; diet, 9.1; nonpharmacological therapy, 10.8. Mean FKGL for different sources of information were: state epilepsy organizations 10.3 (printed), 7.2 (Internet); national epilepsy organizations 8.7 (printed), 12.0 (Internet); pharmaceutical manufacturers, 9.1; government organizations, 12.0; Internet (university based), 11.1; Internet (non-university/non-state or organization based), 11.03; Micromedex/USPDI, 7.8; lay press, 9.3; hospitals/clinics, 8.8. Mean FKGLs for information intended for adults, adolescents and children were 9.4, 6.5 and 4.1, respectively.
CONCLUSIONS: The majority of written information tested was written at a level that exceeds the reading ability of many patients. Information intended for adults may be ineffective, as it contains information written at higher grade levels, while information intended for children and adolescents may be written at levels appropriate for adults. This study emphasizes the importance of direct patient education, and the limitations of written patient information. Efforts should be taken to develop written teaching tools that target low-level readers, and we are currently working to develop better written epilepsy teaching tools at our institution.

121E. Effect of nimodipine dosage adjustments for patients experiencing hypotension after aneurysmal subarachnoid hemorrhage. *Denise H. Rhoney, Pharm.D.*, Alison Tran, Pharm.D., Kellie R. Murry, Pharm.D., William M. Coplin, M.D.; Wayne State University; Detroit Receiving Hospital, Detroit, MI.

PURPOSE: To evaluate the incidence of nimodipine induced hypotension in patients with aneurysmal subarachnoid hemorrhage (SAH). Secondary objectives were to: evaluate whether adjusting the dosing regimen alleviates hypotension; identify risk factors that potentiate hypotension; and evaluate the relationship between nimodipine associated hypotension and outcome.
METHODS: We reviewed random charts of patients admitted between 1996 and 1997 with SAH who received nimodipine. Study endpoints included hypotension, vasospasm, ischemic stroke, and specific outcomes. Hypotension was defined as a fall in mean arterial pressure (MAP) of $\geq$ 5 mm Hg. A p-value < 0.05 was considered statistically significant.
RESULTS: We included 62 patients, 73% female, mean age 50 $\pm$ 15 years. Median admission Hunt & Hess, Fisher, and Glasgow Coma Scale scores were 2(1-5), 3(1-4), and 14(3-15), respectively. Hypotension attributed to nimodipine developed in 12% (n=7) of patients; six of these seven underwent dosage adjustment to 30 mg q2h. Mean MAP changed with nimodipine 60 mg q4h from 96 $\pm$ 13 to 93 $\pm$ 15 mm Hg; however, mean MAP with the 30 mg q2h dose changed from 97 $\pm$ 20 to 85 $\pm$ 13. The only significant risk factor for development of hypotension was pre-existing cardiovascular disease ($p=0.02$). The mean time to onset of hypotension was 7 $\pm$ 5 days. The development of hypotension did not influence patient outcome.
CONCLUSIONS: The incidence of hypotension associated with nimodipine after SAH in our institution is 12%. The incidence and effects of hypotension may have been masked by hypertensive, hypervolemic therapy. The only risk factor found was the presence of preexisting cardiovascular disease. Dosage reduction did not alleviate nimodipine induced hypotension and had very little impact on the patient's overall outcome.
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Oncology

122. Societal costs of high-dose chemotherapy in women with breast cancer. *Jeffrey W. Hui, Pharm.D.*, Gary C. Yee, Pharm.D., FCCP, Raafat A. Seifeldin, M.S., Pharm.D., Ph.D., Renee Boyette, B.S.N., James C. Lynch, Ph.D., John R. Wingard, M.D.; University of Nebraska Medical Center, Omaha, NE; University of Florida; Shands Hospital, Gainesville, FL; G.D. Searle, Chicago, IL.

PURPOSE: The purpose of the study was to determine the economic burden of high-dose chemotherapy (HDC) followed by hematopoietic stem cell transplantation in 100 women with breast cancer.
METHODS: Clinical and resource utilization data were collected prospectively from the pre-transplant work-up and continuing for 30 days following discharge in patients treated at six U.S. transplant centers. Resource units were converted to costs based on Shands databases and Medicare fee schedules. Caregiver time and out-of-pocket costs were collected from interviews pre- and post-transplant.
RESULTS: Results from 66 women (median age: 50 years) with stage II (n=17), III (n=22), or IV (n=27) disease have been analyzed. Eleven patients had post-transplant complications; one patient died on day + 11 post-transplant from renal and respiratory failure and sepsis. Median times to neutrophil and platelet recovery were 11 and 17 days, respectively. Mean

length of stay was 21 days (range: 7-57). The average direct medical cost per hospital day was $2402. Mean total direct medical cost was $69,293 (range: $37K-217K); the largest cost categories were hospital (37%), drugs (28%), and procedures (25%). Multivariate analysis showed that patients who had post-transplant complications (OR = 23.03) or delayed platelet engraftment (OR = 24.1) were significantly associated with a total direct medical cost > $100,000. Caregivers spent an average of 321 hours (range: 0-1410) assisting each patient and $1417 (range: $0-6652) in out-of-pocket costs.
CONCLUSIONS: These results show that the cost of HDC is considerable with higher costs related to complications. Furthermore, caregivers contribute significant resources in supporting the patient.

123. Assay development and interim pharmacokinetic analysis of karenitecin: a novel highly lipophilic camptothecin derivative. *Judith A. Smith, Pharm.D.*, Fred Hausheer, Robert Newman, Ph.D., Timothy L. Madden, Pharm.D.; University of Texas M.D. Anderson Cancer Center, Houston, TX; BioNumerik Pharmaceuticals, Inc., San Antonio, TX.

PURPOSE: Determine the clinical pharmacokinetics of IV karenitecin, a novel supercomputer engineered highly lipophilic camptothecin derivative.
METHODS: Blood and urine samples were obtained from phase I patients with solid tumors receiving escalating doses of karenitecin, administered daily x 5 consecutive days as a 60 minute infusion every 21 days. The starting dose level was 0.15 mg/m^2/d with escalation to 0.3, 0.6, 1.2 and 2.4 mg/m^2/d by accelerated dose titration until dose limiting toxicity (DLT) was observed. Samples were obtained on days 1-5 at numerous timepoints. The samples were analyzed for karenitecin by HPLC. Compartmental models were fit to the plasma and urine concentration time data using ADAPT II.
RESULTS: Six patients enrolled in the study have had pharmacokinetic (PK) data analyzed to date. First course DLT (myelosuppression - expected) was reached at 2.4 mg/m^2. A 2-compartment model best describes the plasma karenitecin data. Mean lactone PK parameters: V_C = 32.9 L/m^2 (8.5-48.5 L/m^2), Cl_t = 7.5 L/hr/m^2 (4.4-10.4 L/hr/m^2), and $t_{1/2\beta}$ = 21.7 hours (8.5-48.6 hr). Comparison of lactone to total drug concentration indicate that, unlike other camptothecins, 85 to 100% of circulating karenitecin is unchanged lactone. The lactone AUC ranged from 29-510 ng/L/hr. No other metabolites are observed.
CONCLUSION: Karenitecin persists in human plasma almost exclusively as active lactone, and has a significantly longer half-life than what has been previously reported for camptothecin derivatives; these observations confirm the preclinical design goals for the drug. These characteristics suggest the clinical pharmacokinetics of karenitecin may be more uniform than other camptothecins.

124. NQOR reduces 4-hydroxy flutamide, 4-hydroxy tamoxifen, cocetaxel, and 5-FU. *Jill M. Kolesar, Pharm.D.*, Judith A. Miller, B.S., Peter G. Allen, M.S.; University of Wisconsin, Madison, WI.

PURPOSE: NQOR (NAD[P]H:quinone oxidoreductase) is a two electron reductase that reduces quinones and other compounds such as benzene. Up to 5% of Caucasians have an allelic form of the gene NQO1, which produces inactive NQOR enzyme. Since NQOR activates the quinone containing anticancer agent mitomycin C (MMC), individuals with this genotype may be unable to activate MMC. Candidate antineoplastics were screened to identify additional substrates for NQOR.
METHODS: NQO1 was purified from overexpressing CHO-812 cells by affinity chromatography. Antineoplastics were analyzed for reduction by NQOR with MTT as the colorimetric indicator. Each MTT assay was performed with and without dicoumarol, an inhibitor of NQO1, and analyzed spectrophotometrically at 610 nm. The difference in absorbance between the uninhibited and inhibited reactions was considered the reduction attributable to NQOR.
RESULTS: Menadione, the positive control, was reduced at a rate of 128.06 nmol/min/mg. Four screened agents, 4-hydroxy flutamide (4-OHF), 4-hydroxy tamoxifen (4-OHT), docetaxel and 5-fluorouracil (5-FU), were identified as substrates for NQO1, with reduction rates 41.64, 22.79, 14.22, and 0.905 nmol/min/mg, respectively. Tamoxifen, flutamide and paclitaxel were not substrates for NQO1 when measured by the MTT assay.
CONCLUSIONS: 4-OHT, 4-OHF, docetaxel, and 5-FU were identified as substrates for NQOR. Whether these compounds are activated or deactivated by two electron reduction is unknown and an important avenue for further investigation. If activated by NQOR, individuals without active NQOR (5% of Caucasians) may be unable to activate and respond to these compounds. If inactivated by NQOR, individuals without active NQOR may be unable to deactivate these compounds and experience greater toxicity.

125. A minority of patients with acute myeloid leukemia have neutralizing antibodies against DT_{388}-GMCSF, a novel fusion toxin consisting of a truncated diphtheria toxin linked to human granulocyte macrophage colony stimulating factor. *Philip D. Hall, Pharm.D., BCPS*, Arthur E. Frankel, M.D.; Hollings Cancer Center; Medical University of South Carolina, Charleston, SC; Wake Forest University, Winston-Salem, NC.

PURPOSE: We are developing a fusion toxin (DT_{388}-GMCSF) consisting of the catalytic and translocation subunits of diphtheria toxin (DT_{388}) linked to human granulocyte-macrophage colony stimulating factor (GMCSF) for the treatment of acute myeloid leukemia (AML). In our preclinical studies, we found that healthy individuals immunized against diphtheria produced antibodies that cross-reacted with DT_{388}-GMCSF. We therefore proceeded to determine if AML patients had adequate concentrations of pre-existing anti-diphtheria antibodies to inhibit DT_{388}-GMCSF.
METHODS: Serum from 46 patients with either AML (n=44) or chronic myeloid leukemia in blast crisis (n=2) was tested by an in vitro bioassay, utilizing MTT, to inhibit DT_{388}-GMCSF. Three patients were sampled both before and after therapy, and all others were sampled before therapy for a total of 49 samples. For the AML patients, new diagnosis, relapse, and remission represented 19, 24, and 4 samples, respectively. Serum samples were diluted by two-fold four times in media containing DT_{388}-GMCSF and incubated for 20 minutes at 37°C, 5% CO_2. The samples were then added to media containing 5x10^4 HL60 cells for 48 hours. Samples with titers ≥ 1:8 were considered positive if the serum sample inhibited DT_{388}-GMCSF by ≥ 50%.
RESULTS: Five patients (10.9%) had titers that inhibited DT_{388}-GMCSF. These 5 patients demonstrated complete neutralization at the 1:8 titer. At the 1:16 titer, the activity of DT_{388}-GMCSF was inhibited by ≥ 50% in 4 of the 5 patients, but all 5 demonstrated no inhibition at the 1:32 titer. Four of the five patients with neutralizing antibodies had relapsed AML at the time of sampling.
CONCLUSIONS: The minority of patients with AML have neutralizing antibodies against DT_{388}-GMCSF. Future work will correlate an ELISA assay with our bioassay results. We have initiated a phase I trial of DT_{388}-GMCSF in relapsed AML patients and will determine if neutralization of DT_{388}-GMCSF in this assay correlates with response or altered pharmacokinetics.

126. The comparison of lenograstim and filgrastim on autologous peripheral blood stem cell transplantation patients with high-dose chemotherapy. *In Hyang Kim, M.S. candidate*, Jung Mi Oh, Pharm.D., Sung Kyu Park, M.D.; Sookmyung Women's University; Soonchunhyang University Hospital, Seoul, Korea.

PURPOSE: High-dose chemotherapy following by autologous bone marrow transplantation is a therapeutic option for patients with chemotherapy-sensitive malignancies who have relapses. Hematopoietic growth factors are accepted as accelerating hematopoietic recovery after bone marrow grafting. The comparison of two different recombinant granulocyte colony-stimulating factors (G-CSF), lenograstim (glycosylated) and filgrastim (nonglycosylated) was performed.
METHODS: The comparison of two different recombinant granulocyte colony-stimulating factors (G-CSF), lenograstim (glycosylated) and filgrastim (nonglycosylated) was performed in 85 patients after peripheral blood stem cell transplantation (PBSCT) following high-dose chemotherapy (HDCT) to compare the effects of the different forms of G-CSF. One day after stem cell infusion, 49 patients received lenograstim 250 μg per day, and 36 patients received filgrastim (non-glycosylated) 300 μg per day.
RESULTS: ANC recovery to above 500/mm^3 for three consecutive days was earlier in filgrastim-treated group than lenograstim group (19.0 ± 10.0 vs 13.2 ± 8.0, p=0.004). Time to WBC recovery above 4000/mm^3 was earlier in filgrastim-treated patients than lenograstim group (29.9 ± 16.6 vs 16.9 ± 9.7, p=0.001). The difference of platelet recovery was significant in filgrastim-treated patients (27.2 ± 3.8 vs 19.5 ± 11.6, p=0.006). Furthermore, filgrastim-treated patients received fewer days of antibiotic administration and spent less days in hospital. However, days of neutropenic fever, kinds of antibiotics and transfusion times were similar in both groups. There was no significant drug-related toxicity ascribed to both groups.
CONCLUSION: In patients undergoing autologous PBSCT following HDCT for neoplastic disease, filgrastim significantly reduced duration of neutropenia and led to earlier hospital discharge than lenograstim in this study.

127. Empiric antibiotic prescribing practice in febrile neutropenia: compliance to the IDSA guidelines. *Jennifer Newman, B.Sc.Phm.*, Cheryl Thompson, B.Sc.Phm., Zafar Hussain, M.D., FRCPC, Anne Marie Bombassaro, Pharm.D.; London Health Sciences Centre, London, ON, Canada.

PURPOSE: To assess compliance of empiric antibiotic therapy to the 1997 Infectious Diseases Society of America (IDSA) guidelines for febrile neutropenia (FN). Selected outcomes for compliant and non-compliant therapy were evaluated.
METHODS: A concurrent, non-interventional chart review of 50 consecutive episodes of FN between January and May 1999 at a university-affiliated, tertiary referral oncology centre was conducted. Empiric antibiotic therapy was assessed for compliance relative to the IDSA guidelines. Definitions of infection and response to therapy were assessed using previously published criteria.
RESULTS: An empiric regimen compliant to the guidelines was prescribed in 28/50 episodes (56%). Hematological malignancy constituted a greater percentage of the compliant than noncompliant group (75% vs 50%, p<0.001). There was no significant difference between compliant and

noncompliant episodes with respect to the following: number of microbiologically-defined infections, defervescence at 72 hours, number of antibiotic modifications, response to therapy, duration of the empiric regimen, number of adverse reactions necessitating a regimen modification, admission to the intensive care unit and mortality. The mean duration of antibiotic therapy, time to discharge from the onset of FN and the number of infectious disease consults were greater for compliant versus non-compliant episodes (p=0.02, p=0.04, p=0.005, respectively).
CONCLUSION: Compliance to IDSA guidelines for empiric antibiotic therapy of FN was 56%. Episodes of FN associated with hematological malignancy were most often prescribed compliant empiric antibiotic therapy. Results do not suggest the need for a widespread prescriptive policy enforcing compliance to the guidelines for all episodes of FN at our oncology centre.

128. Estimation of creatinine clearance in patients with ovarian cancer. *Megan J. Montgomery, Pharm.D.*, Paul M. Beringer, Pharm.D., BCPS, Stan G. Louie, Pharm.D., Ph.D., Mark A. Gill, Pharm.D.; University of Southern California, Los Angeles, CA.

PURPOSE: This study evaluated the predictive performance of four methods for estimating creatinine clearance (CrCl) in patients with ovarian cancer: Cockcroft and Gault, Jelliffe, and two equations derived in cancer patients, Robinson, et al. and Tsubaki, et al.
METHODS: Estimated CrCl values obtained by each method using actual weight (ABW), ideal weight (IBW) and lower of ABW and IBW were compared with measured values determined by 24-hour urine collection for 14 patients. Linear regression and correlation analysis was performed to assess the relationship between predicted and measured CrCl. The mean prediction errors (ME) and mean absolute errors (MAE) were calculated to evaluate the bias and precision, respectively, of each method.
RESULTS: The relationship between predicted and measured CrCl is fair (r=0.39 to 0.55). Cockcroft and Gault using ABW (p=0.21), Robinson using ABW (p=0.44), and Jelliffe (p=0.17) were equally unbiased predictors of measured CrCl. All other methods significantly underestimated measured CrCl. All methods appeared to be equally imprecise (p<0.05). The results, using ABW, are:

Method	ME ± SD	p	MAE ± SD	p
Cockcroft and Gault using ABW	-8.1 ± 23.1	0.2128	20.0 ± 13.2	<0.0001
Jelliffe	-6.4 ± 16.6	0.1711	13.1 ± 11.6	0.001
Robinson using ABW	-3.7 ± 17.6	0.4445	14.6 ± 9.8	<0.0001
Tsubaki using ABW	-27.5 ± 18.7	0.0001	27.5 ± 18.7	0.0001

p<0.05 indicates a significant difference from measurement obtained by 24-hour urine collection
CONCLUSION: The use of standard equations for estimating CrCl in patients with ovarian cancer is predictive of the measured 24-hour value. The use of oncology specific equations did not improve on the accuracy or precision of these estimates.

Pediatrics

129. Clinical experience with tissue plasminogen activator in infants: a retrospective review. *Jennifer H. Justice, Pharm.D.*, Philip E. Empey, Pharm.D., Margaret K. Winkler, M.D., Robert J. Kuhn, Pharm.D.; University of Kentucky Medical Center, Lexington, KY.

PURPOSE: While tissue plasminogen activator (t-PA) has been widely studied in adults, there is little data to support its use in pediatric patients. This retrospective chart review is to assess the usage pattern of t-PA at a children's hospital and develop guidelines for the administration of this agent to pediatric patients at our institution.
METHODS: We report the management of thromboembolic events in nine infants; all were admitted to the children's hospital from July 1998 through February 1999. Demographic data, indication for use, dates of therapy, dosing regimen, concurrent therapies, venous access sites, pertinent laboratory values and radiologic studies were recorded to assess the average dose and regimen, outcomes of therapy and frequency of adverse drug reactions.
RESULTS: Nine patients were treated with t-PA at our institution over an 8-month period. The average age was 3 months (range 6 days-19 months) with a weight of 3.4 kg (range 815 g-10.4 kg). Indications for the use of t-PA included arterial and venous thrombosis, B-T shunt and catheter-related clots, SVC syndrome, and pulmonary veno-occlusive disease. Sixteen courses of therapy with an average dose of 0.3 mg/kg/hr for 6.25 hours were administered. Clot improvement/resolution was observed in 89% of patients. Concurrent therapy consisted of enoxaparin (4/9), heparin (1/9), and fresh frozen plasma (5/9), with no serious adverse events reported.
CONCLUSION: t-PA aids in clot resolution with a low incidence of adverse effects. Based on our experience, we are currently recommending 0.3 mg/kg/hr for 6 hours until more definitive data is available.

130. The study on efficacy and safety of deflazacort in Korean children with nephrotic syndrome. *Mijeong Kim, M.S.*, Dong Kyu Jin, M.D., Ph.D., Sukhynag Lee, Pharm.D., M.S.; Sookmyung Women's University; Samsung Medical Center; Sungkyunkwan University, Seoul, Korea.

PURPOSE: To study efficacy and safety of deflazacort in children with nephrotic syndrome. Deflazacort, an oxazoline derivative of prednisolone, has been claimed to have anti-inflammatory effects with few side effect profiles compared to prednisone.
METHODS: Patients were eligible when the children with nephrotic syndrome were treated with deflazacort at Samsung Medical Center, Seoul, Korea, from October 1994 to April 1999. The nephrotic syndrome was defined as less than 2.5 mg/dl of albumin level and more than 40 mg/m^2 BSA/hr of protein excretion in 24-hour urine. The exclusion criteria were the secondary nephrotic syndrome due to systemic lupus erythema, chronic renal failure, multiple myeloma and etc. The primary parameters evaluating efficacy of deflazacort to treat nephrotic syndrome were response rate, frequency of relapse and time to respond. The safety profiles assessed were the impact on children's growth, calcium sparing effect, glucose metabolism and lipid profile by comparing between pre- and post-treatment. Adverse drug reactions associated with deflazacort were evaluated.
RESULTS: The median time to respond was 12 days (7-110 days) and frequency of relapse was 1 (0-6). The change of plasma calcium was from pre-treatment level of 7.55 ± 3.86 mg/dl to post-treatment level of 9.98 ± 3.77 mg/dl (p<0.0001), but phosphate level was not significantly changed (5.02 ± 0.67 mg/dl vs 5.04 ± 0.75 mg/dl, p>0.05). Weight/height ratio was increased from 22.05 ± 3.47 kg/m to 23.20 ± 3.44 kg/m (p<0.001). The fasting blood glucose level was not significantly changed (91.92 ± 3.53 vs 98.19 ± 4.78 mg/dl, p=0.072) while the change of total cholesterol was significant (362.3 ± 12.0 vs 251.4 ± 11.5 mg/dl, p<0.0001).
CONCLUSIONS: Deflazacort had similar efficacy compared to prednisone with less impact on growth inhibition and metabolic side effects of hyperglycemia and hyperlipidemia in treatment of children with nephrotic syndrome.

131. The use of methadone to prevent fentanyl withdrawal in the pediatric intensive care unit. *Ralph A. Lugo, Pharm.D.*, Robert MacLaren, Pharm.D., Jared Cash, B.S.; University of Utah; Primary Children's Medical Center, Salt Lake City, UT.

PURPOSE: Prolonged administration of fentanyl often results in opioid dependence in critically ill children and rapid discontinuation may precipitate opioid abstinence syndrome (OAS). Transitioning to low-dose enterally administered methadone in advance of fentanyl discontinuation may reduce the risk of OAS. In addition, methadone's long half-life may simplify the taper schedule. The objective of this retrospective study was to evaluate and describe the use of methadone to expedite fentanyl discontinuation and prevent signs/symptoms of withdrawal in children in the PICU.
METHODS: PICU clinical guidelines for initiating enteral methadone (via nasojejunal tube) and rapidly discontinuing fentanyl in children at risk for OAS were implemented 3 years prior to data collection. All PICU patients during the 3-year period who were at high risk for OAS (≥ 9 days of continuous fentanyl infusion) were included in the study. Medical records were evaluated for fentanyl/methadone utilization and documented signs/symptoms of withdrawal. OAS was defined as ≥ 3 predetermined signs/symptoms of withdrawal occurring within 72 hours of fentanyl/methadone dose reductions.
RESULTS: Twenty-two patients were included in the analysis (mean age 6.1 ± 5.4 years). Duration of continuous fentanyl administration = 17.8 ± 8.4 days; peak infusion rate = 5.9 ± 3.8 µg/kg/hr; median infusion rate 24 hours before rapid fentanyl discontinuation = 4.8 µg/kg/hr. Methadone (0.50 ± 0.22 mg/kg/day) was initiated 1.0 day (median) prior to rapid fentanyl discontinuation. Fentanyl was discontinued in 2.6 days (median) and 21/22 patients had no documented OAS. The single patient with OAS required increased doses of fentanyl/methadone. Methadone was tapered in 18.2 ± 11.9 days with no OAS (n=22).
CONCLUSIONS: The use of enteral methadone facilitates rapid discontinuation of fentanyl and may prevent OAS in children at high risk for fentanyl withdrawal.

132. Pharmacokinetics/pharmacodynamics of omeprazole suspension in critically ill pediatric liver/intestinal transplant patients. *Kimberly L. Bergman, Pharm.D.*, Stuart Kaufman, M.D., Dean Collier, Pharm.D., Jill A. Rebuck, Pharm.D., Keith M. Olsen, Pharm.D., FCCP; University of Nebraska Medical Center, Omaha, NE.

PURPOSE: This study characterized the pharmacokinetics and pharmacodynamics of omeprazole suspension in critically ill pediatric liver/intestinal transplant patients.
METHODS: Eleven pediatric liver and/or intestinal transplant patients were administered omeprazole suspension 0.5 mg/kg every 12 hours via nasogastric tube within twelve hours of transplantation. Gastric pH was monitored continuously for 48 hours via a single channel pH probe, and sequential initial and multiple dose blood samples were obtained for determination of plasma omeprazole concentrations via HPLC. Data are expressed as means ± SD.

RESULTS: Eleven subjects (age 3.6 ± 4.0 years; range 18 weeks to 14 years) were studied. Baseline pH was 1.0 ± 0.8, and onset of omeprazole action (time to pH > 4.0) was 62 ± 84 minutes (range 2 to 226 minutes). Percentage of the dosage interval for which pH > 4.0 was 78.8 ± 18.9% and 97.8 ± 5.4% upon first and multiple doses, respectively. Pharmacokinetic parameters were measured

Parameter	First	Multiple
C_{max} (ng/ml)*	812.0 ± 409.1	1258.7 ± 286.2
T_{max} (h)	1.2 ± 0.8	1.3 ± 0.5
AUC_{0-12} (ng•h/ml)*	3818.1 ± 2274.5	6000.6 ± 2361.1
AUC_{0-4} (ng•h/ml)*	4956.3 ± 3305.4	7622.9 ± 2738.0
$t_{1/2}$ (h)	4.9 ± 3.5	5.1 ± 2.4

*p<0.05

CONCLUSIONS: Although onset of action of omeprazole suspension was highly variable in this study population, omeprazole adequately maintained baseline and mean gastric pH greater than 4.0 throughout the dosage interval upon multiple doses in a pediatric liver/intestinal transplant population.

133. Case control study of corrected QT intervals in premature infants treated with cisapride. *Corey S. Cuthrell, Pharm.D.*, Christopher M. Rubino, Pharm.D., J. Laurence Ransom, M.D., McCrae Smith, M.D., Rita Carlos, M.D., Andrew Davey, M.D., Annavic Dimagulia, M.D., James Pascale, M.D., Peter Gal, Pharm.D.; Greensboro Area Health Education Center, Moses Cone Health System, Greensboro, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC.

PURPOSE: Secondary to the recent warning that cisapride may cause corrected QT interval (QTc) prolongation in neonates, results of electrocardiograms (ECG) were compared between patients receiving cisapride and those who were not.
METHODS: Our computerized neonatal patient database was used to identify all patients born between April 1997 and May 1999 who received cisapride (CIS) for gastroesophageal reflux with an ECG during therapy. Each CIS patient was matched to two controls (CON) who had received an ECG some time during hospitalization. Cisapride dosing history was collected for the CIS patients and QTc intervals and dates of the ECGs were collected for both groups. Presence of electrolyte abnormalities and concurrent medications known to alter QTc were recorded for both groups.
RESULTS: Forty-five patients were evaluated: 15 CIS vs 30 CON. There was no statistically significant difference in the median QTc in CIS versus CON patients (410 vs 416, respectively; p=0.38). Nine of the 45 patients had a prolonged QTc ≥ 450 msec (2/15 CIS vs 7/30 CON). Univariate analysis showed no correlation between the dose or duration of cisapride prior to the ECG and the maximum QTc. For 6/7 CON, potential causes of prolongation were identified (electrolyte abnormalities, dexamethasone use, and diuretic use) and no causes other than cisapride were found in the two CIS patients with increased QTc. In the CON group, there were no differences in gestational age, birth weight, or postnatal age for those with prolonged QTc intervals although CON patients with hypocalcemia were more likely to have prolonged QTc intervals than those with normal calcium levels (43% vs 17%, respectively).
CONCLUSIONS: Cisapride is an acceptable etiology for prolonged QTc intervals in premature infants. In the absence of concurrent interacting drugs; however, cisapride does not seem to place infants at higher risk for proarrhythmias than their control counterparts.

134. Granulocyte colony-stimulating factor serum and urine concentration in neutropenic neonates before and following the intravenous administration of recombinant G-CSF. Darlene A. Calhoun, D.O., *Mark W. Veerman, Pharm.D.*, Alan D. Hutson, Ph.D., Robert D. Christensen, M.D.; University of Florida; Shands Hospital, Gainesville, FL; Amgen Corporation.

PURPOSE: Recombinant granulocyte colony-stimulating factor (rG-CSF) has been suggested as a treatment for certain varieties of neonatal neutropenia, but little is known about the pharmacologic disposition of rG-CSF in this population. The purpose of this study to evaluate serum and urine concentrations of G-CSF in neonates after administration of rG-CSF.
METHODS: Ten neutropenic neonates were treated with rG-CSF 10 µg/kg intravenously once-daily for three to five days. Serum and urine samples were obtained prior to rG-CSF dosing and at intervals thereafter for G-CSF quantification by ELISA.
RESULTS: Five neutropenic neonates (group 1) were not infected, but likely had hyporegenerative neutropenia. Five others (group 2) had neutropenia accompanying bacterial sepsis and shock. Prior to receiving the first dose of rG-CSF, endogenous G-CSF serum and urine concentrations were low in group 1, averaging 130 pg/ml in serum and 53 pg/ml in urine. Serum concentrations immediately before the final dose were higher (range, 81-24,835 pg/ml, p<0.0001), while urine concentrations were unchanged (range, < 7 pg/ml to 126 pg/ml). In group 2 patients, prior to receiving the first-dose of rG-CSF, endogenous concentrations were very high, averaging 59,575 pg/ml in serum and 3189 pg/ml in urine (both p<0.001 vs group 1, pre-first dose). Pre-dose serum concentrations before the final dose (range 427-14,460 pg/ml) were lower than before the first dose (p<0.0001). The AUC following the first dose of rG-CSF administration in group 1, was significantly lower than after the first dose in group 2 (p<0.0002), but no difference in AUC was observed between groups 1 and 2 after the last dose of rG-CSF (p=0.57)
CONCLUSIONS: The principle means of clearing G-CSF from the serum is by saturable binding to specific G-CSF receptors. Therefore, the very high G-CSF serum and urine concentrations of group 2 patients prior to the first rG-CSF dose suggests G-CSF receptors were saturated before the dose was given. We speculate if G-CSF receptors are saturated with endogenous G-CSF, treatment with rG-CSF will add little or nothing to the granulocytopoietic effort. Neonates with septic shock and neutropenia are unlikely to benefit from rG-CSF administration.

135E. Efficacy and safety of oral ondansetron in the control of acute chemotherapy induced nausea and vomiting in chemotherapy-naive pediatric patients. Vinita B. Pai, Pharm.D., *Milap C. Nahata, Pharm.D.*, Amanda M. Rauck, M.D., Frederick B. Ruymann, M.D., John Koepke, Pharm.D., Diane Davis, B.S.N.; Ohio State University; Columbus Children's Hospital, Columbus, OH.

PURPOSE: The objective of this study was to evaluate efficacy and safety of oral ondansetron (0.15 mg/kg or 0.3 mg/kg) with oral dexamethasone (0.15 mg/kg or 0.3 mg/kg) administered as single doses before bolus chemotherapy or every twelve hours with continuous infusion chemotherapy.
METHODS: Forty-six chemotherapy naive patients, between 4 months and 17 years of age have been enrolled in an ongoing open label trial. Dosing guidelines for ondansetron and dexamethasone are based on a 5-level chemotherapy emetogenic potential (J Clin Oncol 1997;15:103-9). Emesis, retching, severity of nausea, food intake, rescue antiemetics, delay in chemotherapy completion and nausea/vomiting related rehospitalizations were evaluated each day of chemotherapy and up to 24 hours after the last dose.
RESULTS: Forty of 46 (87%) patients experienced 0-2 emetic episodes, 3/46 (6.5%) had 3-5 episodes and 3/46 (6.5%) experienced > 5 emetic episodes after their first cycle of chemotherapy. Patients experiencing > 5 emetic episodes primarily received cisplatin (≥ 60 mg/m^2). Of the 46 patients, 20 reported no nausea, 10 mild, 5 moderate and 4 severe nausea. Forty-two of 46 patients had solid or liquid oral food intake. Adverse effects were diarrhea (3 patients), headache (1), and abdominal pain (2); none could definitely be related to ondansetron. Chemotherapy was completed on time in all patients; none were rehospitalized solely for nausea/vomiting.
CONCLUSION: Based on these results, oral ondansetron along with oral dexamethasone can be recommended as first-line antiemetic to prevent acute chemotherapy induced nausea and vomiting due to moderate, moderately high and highly emetogenic chemotherapy with the exception of cisplatin.
Presented at 1999 Joint Annual Meeting of the International Society of Pediatric Oncology and the American Society of Pediatric Hematology/ Oncology, Montreal, PQ, Canada, September 15, 1999.

136. A multicenter evaluation of gentamicin therapy in the neonatal intensive care unit. *Christopher L. Shaffer, Pharm.D., BCPS*, Mark L. Glover, Pharm.D., Christopher M. Rubino, Pharm.D., BCPS, Corey Cuthrell, Pharm.D., Shellie Schoening, Erika Cole, M.D., David Potter, Peter Gal, Pharm.D., BCPS, FCCP, FSHP; Children's Hospital; Creighton University, Omaha, NE; Nova Southeastern University, Ft. Lauderdale, FL; Miami Children's Hospital, Miami, FL; Women's Hospital of Greensboro; Greensboro AHEC, Greensboro, NC; University of North Carolina, Chapel Hill, NC.

PURPOSE: To evaluate individualized pharmacokinetic (IPD) versus nomogram dosing (ND) of gentamicin among neonatal intensive care unit (NICU) patients.
METHODS: A multicenter, retrospective chart review of all patients admitted to the NICU from November 1, 1997 to November 1, 1998 was performed. Patients receiving gentamicin within the first 10 days of life were included and received either ND of 2.5 mg/kg/dose with dosing intervals based on gestational and postnatal age or IPD based on a 5 mg/kg load with subsequent doses and intervals based upon individualized pharmacokinetic analysis of serum concentrations obtained with the loading dose. Information collected for all patients included gestational age, birth weight, 1 and 5 minute APGAR scores, perinatal and concurrent disease states, concurrent medications, renal function, and gentamicin dosing history including concentrations.
RESULTS: Two hundred fifty patients were evaluated: 65 IPD (Greensboro) vs 185 ND (Omaha/Miami). Demographic characteristics were comparable between the two groups. Sixty-five percent of patients receiving IPD had initial peak gentamicin concentrations > 8 mg/L compared to 17% of patients on ND (p<0.001). In addition, trough concentrations exceeding 2 mg/L were reported in 38% of patients receiving ND compared to none in IPD group (p<0.001). Forty percent of ND patients required dosage adjustments versus 10% of IPD (p<0.01). The average number of concentrations obtained per patient for ND was 2.5 versus 2.2 for IPD.
CONCLUSIONS: Compared to ND, IPD of gentamicin in patients admitted to the NICU allows for rapid achievement of desired gentamicin serum concentrations, potential for less toxicity, and a decreased number of dosing changes.

137. Angiotensin converting enzyme inhibitor use in pediatric patients with dilated cardiomyopathy. Linda K. Ohri, Pharm.D., *Christopher L. Shaffer, Pharm.D., BCPS*, Jon K. Izumi, Leland T. Nogawa; Creighton University; Children's Hospital, Omaha, NE.

PURPOSE: This retrospective study documented use of angiotensin converting enzyme inhibitors (ACEIs) in pediatric patients with dilated cardiomyopathy (DC).
METHODS: Review of pediatric cardiology clinic charts identified 19 patients (group A) treated with captopril or enalapril between January 1987 and May 1999. Charts for 11 age/gender/DC matched no ACEI patients (group B) were compared to a subgroup (A_1) of 11 ACEI patients. Demographic, medical history, ACEI regimen, concurrent therapy, test result, and outcome data were documented.
RESULTS: Age at initiation of ACEI therapy ranged from 8 days to 17 years. Seventeen patients received captopril. The mean initial/maintenance doses of captopril were 1.1/1.0 mg/kg/d (range: 0.2/0.1 to 2.9/2.7 mg/kg/d) BID or TID. The mean duration of therapy was 31 (3 to 113) months. Two enalapril recipients were maintained on 0.5 and 0.1 mg/kg/d (BID) for 6 and 24 months, respectively. Group A_1 patients had more severe DC at initiation of therapy compared to group B patients (19% vs 32% mean shortening fraction, respectively). Shortening fractions (SFs) increased in 61% of 18 evaluable ACEI patients. Subgroup analysis showed a SF increase in 50% (5/10) of group A_1 compared to 12.5% (1/8) of group B patients. Overall status improved in 47% of 19 group A, 36% of 11 group A_1, and 0% of 11 group B patients. Three ACEI patients eventually received heart transplants; one additional treated infant died awaiting transplant. ACEIs were well tolerated.
CONCLUSIONS: ACEI therapy was initiated in patients with relatively severe dilated cardiomyopathy, and was associated with improvement or stabilization of the SF for all treated patients.

138E. Ranitidine pharmacokinetics and concentration-related control of gastric pH in critically ill children. *Ralph A. Lugo, Pharm.D.*, A. Marc Harrison, M.D., John Sweeley, B.S., Jared Cash, B.S., Donald D. Vernon, M.D.; University of Utah; Primary Children's Medical Center, Salt Lake City, UT.

PURPOSE: Maintaining gastric pH ≥4 reduces the risk of stress ulceration in critically ill patients. We analyzed ranitidine pharmacokinetics in critically ill children in the PICU and determined the plasma concentrations associated with a gastric pH ≥4 for greater than 75% of a 24-hour period.
METHODS: Children ≥ 10 kg who required IV ranitidine for stress ulcer prophylaxis were prospectively studied. Blood samples were collected at 0, 0.5, 1, 2, 4, 6, and 8 hours after 2 mg/kg IV ranitidine. Following the final blood sample, patients received 0.5 mg/kg IV ranitidine followed by 0.1 mg/kg/hr infusion. Gastric pH was measured hourly via NG pH probe. For low gastric pH (pH < 4 on 6 hourly occasions in previous 24 h), 0.5 mg/kg IV ranitidine was administered and the infusion was increased by 0.05 mg/kg/hour. This sequence was repeated until gastric pH was ≥ 4 for > 75% of a 24-hour period. Steady-state plasma concentrations were measured. Plasma concentrations were measured by HPLC and pharmacokinetics were determined by noncompartmental methods.
RESULTS: Nineteen ventilated children (median 8.7 years and 30 kg) were enrolled. PK parameters were $t_{1/2}$=3.1 ± 1.5 hours; Cl = 8.93 ± 3.72 ml/kg/min; Vd_{ss} = 2.4 ± 1.8 L/kg. Nine patients achieved gastric pH control (6.0 ± 0.5) with ranitidine 0.17 ± 0.07 mg/kg/hr and a steady-state plasma concentration of 291.2 ± 123.2 ng/ml. Mean plasma concentration associated with low gastric pH (2.7 ± 0.9) was 206.9 ± 100.0 ng/ml.
CONCLUSION: We conclude that ranitidine pharmacokinetics are variable in critically ill children. Gastric pH ≥ 4 is associated with a mean steady state concentration of 291 ng/ml. This concentration may be achieved with IV ranitidine 0.7 mg/kg followed by 0.15 mg/kg/hr continuous infusion or intermittent intravenous administration of 1.5 mg/kg every 6 hours.
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139. Risperidone versus placebo for conduct disorder in mentally retarded children. *Michael G. Aman, Ph.D.*, Robert Findling, M.D., Martin Brecher, M.D.; Nisonger Center, Columbus, OH; University Hospital Psychiatry, Cleveland, OH; Janssen Pharmaceutica Research Foundation, Titusville, NJ

PURPOSE: This randomized, double-blind study compared risperidone and placebo in the outpatient treatment of conduct disorder in children with mild to borderline mental retardation.
METHODS: After a 1-week placebo run-in, 118 children aged 5 to 12 years with an IQ of 35 to 84 were treated with placebo or risperidone each morning for 6 weeks. Doses could be adjusted within a range of 0.02 to 0.06 mg/kg/day. The primary efficacy instrument was the conduct disorder subscale of the Nisonger Child Behavior Rating Form (N-CBRF), from which changes from baseline were compared. Secondary efficacy variables included other subscales of the N-CBRF, the Behavior Problems Inventory, and the Clinical Global Impression. Safety assessments were based on reported adverse events.
RESULTS: Statistically significant differences favoring risperidone over placebo were observed from week 1 through week 6 and at endpoint for the primary efficacy variable. Significant differences favoring risperidone were also observed for the secondary variables. Adverse events were reported in 54 of the 55 risperidone patients and in 44 of the 63 placebo patients. No serious adverse events were reported. In the risperidone group they included somnolence in 51%, headache in 29%, vomiting in 20%, dyspepsia and weight increase each in 15%, hyperprolactinemia in 13%, and increased appetite and rhinitis each in 11%. Treatment was discontinued in 2 patients in the risperidone group (somnolence and somnolence plus dyspepsia in 1 each).
CONCLUSION: Risperidone effectively and safely improves conduct disorder in mentally retarded children.

Pharmacoeconomics

140. Clinical pharmacy services, pharmacist staffing, and drug costs in U.S. hospitals. *C.A. Bond, Pharm.D., FASHP, FCCP*, Cynthia L. Raehl, Pharm.D., FASHP, Todd Franke, Ph.D.; Texas Tech University-Health Sciences Center, Amarillo, TX; University of California at Los Angeles, Los Angeles, CA.

PURPOSE: This study evaluated the associations between clinical pharmacy services, pharmacist staffing, and drug costs in U.S. hospitals.
METHODS: A database was constructed from the American Hospital Association's Abridged Guide to the Health Care Field and the National Clinical Pharmacy Services Database. A multiple regression analysis, controlling for severity of illness, was employed to determine the associations.
RESULTS: Study population = 934 hospitals. Four clinical pharmacy services were associated with lower drug costs: in-service education ($p<0.016$), drug information ($p=0.015$), drug protocol management ($p=0.049$), and medication admission histories ($p=0.011$). Additionally, as staffing increased for hospital pharmacy administrators ($p<0.0001$), dispensing pharmacists ($p<0.0001$), and pharmacy technicians ($p<0.0001$), drug costs increased. As staffing increased for clinical pharmacists, drug costs decreased ($p=0.018$). Drug costs per hospital per year were lower when these 4 clinical pharmacy services were present: in-service education $77,879.19 (a total of $48,518,735 for the 623 hospitals offering this service), drug information $430,579.84 (a total of $90,852,356 for the 211 hospitals offering this service), drug protocol management $137,333.67 (a total of $45,045,443 for the 328 hospitals offering this service), and medication admission histories $213,388.21 (a total of $5,548,093 for the 26 hospitals offering this service).
CONCLUSION: The results of this study suggest that increased staffing levels of clinical pharmacists and some clinical pharmacy services may reduce hospital drug costs.

141. Pharmacist management of diabetes and hyperlipidemia: comparison to other primary care providers in a community family practice office. *Gordon A. Ireland, Pharm.D.*, Talonna M. Iser, Pharm.D.; Shore Health System; University of Maryland, Easton, MD.

PURPOSE: To study the documented outcomes data of patients treated for diabetes and/or hyperlipidemia in a community family practice office in order to 1) determine the clinical effectiveness of pharmacist disease management interventions, 2) determine the cost-effectiveness of pharmacist interventions, and 3) evaluate effect of pharmacist disease management on physician time.
METHODS: The medical records of 217 patients, matched for age and evenly divided between 2 physicians, a nurse practitioner, and a pharmacist, were reviewed. The HgA_{1c}, total cholesterol, LDL, triglycerides, HDL values, and number of office visits were collected for the period of January 1 to December 31, 1998. These numbers were compared between the 4 practitioners.
RESULTS: Patients managed by the pharmacist had more severe disease ($p<0.05$) but reached outcome goals, $HgA_{1c} < 7$, total cholesterol < 200, LDL < 160, LDL < 130, LDL < 100, HDL > 35, and triglyceride < 200, similar to or better than the other practitioners. Mean change in HgA_{1c} and LDL was significant ($p<0.05$) when compared to the other practitioners. Physicians/nurse practitioner saw patients less frequently when seen by the pharmacist ($p<0.05$). Pharmacist intervention saved an average of $600 per patient per year.
CONCLUSION: Given the harder-to-manage and noncompliant patients, the pharmacist achieved outcomes equal to 1 practitioner and better than 2 practitioners. Significant diversity was noted between practitioners. The pharmacists interventions saved practitioner time and were clinically cost effective.

142. Patient valuation of a pharmacist provided asthma management program using the contingent valuation method. Kelly Whitaker, Pharm.D., *Karen Blumenschein, Pharm.D.*, Magnus Johannesson, Ph.D., Beth Miller, M.D.; University of Kentucky, Lexington, KY; Stockholm School of Economics.

PURPOSE: This study utilized the contingent valuation approach to benefit-cost analysis to assess the patient perceived value of a pharmacist provided asthma management service.
METHODS: Patients with asthma were recruited from an asthma specialty clinic. The patients were provided with an in-depth description of a

pharmacist provided asthma management service. Then they were surveyed to obtain their perceived value of the pharmacist provided asthma management service. The survey was conducted utilizing a dichotomous choice contingent valuation question followed with a bidding game to obtain the maximum willingness to pay for the program. The survey also assessed the patient's self-perceived severity of disease.
RESULTS: Forty-four patients with a documented history of asthma symptoms completed the survey. 43.2% of the respondents rated their asthma symptoms as mild, 43.2% as moderate and 13.6% as severe. Utilizing the bidding game approach, the mean willingness to pay for the pharmacist provided asthma management program was $30.20 per month. Correlations between disease severity and willingness to pay will be presented.
CONCLUSION: Overall, 86.4% of those surveyed were willing to pay some amount for a pharmacist provided asthma management program. In this study, the mean willingness to pay for the pharmacist provided asthma management program represented approximately 1% of the respondent's income. Further research on the relationship between asthma severity and patient valuation of pharmacist provided asthma management services is warranted and should include objective assessment of asthma severity.

143. Influence of patient adherence on number-needed-to-treat calculations for cholesterol-lowering therapy. *Rex W. Force, Pharm.D., BCPS*, Paul S. Cady, Ph.D., Vaughn L. Culbertson, Pharm.D., Wendy S. Force, B.S.; Idaho State University, Pocatello, ID.

PURPOSE: Patient adherence to pharmacotherapy in clinical trials may differ from actual clinical practice, influencing the generalizability of trial data. Number-needed-to-treat (NNT) calculations for cardiovascular endpoints are available for primary prevention (WOSCOPS, NEJM 1995;333:1301) with pravastatin (P) and secondary prevention (4S, Lancet 1994;344:1383) with simvastatin (S). We recalculated NNT values to reflect actual patient adherence using Medicaid claims.
METHODS: Continuously enrolled Medicaid recipients who initiated P or S during the study period (May 1992 to January 1999) were included in the study. We defined adherence as mean patient-months (MP-M) on P or S and drug discontinuation as no prescriptions filled for ≥ 90 days. MP-M were 58.8 and 64.8 for WOSCOPS and 4S, respectively. Medicaid data were utilized to calculate new NNTs:

$$MP\text{-}M_{(literature)}/MP\text{-}M_{(Medicaid)} \times NNT_{(literature)} = NNT_{(Medicaid)}.$$

Mean doses of P and S were calculated for the Medicaid population.
RESULTS: During the study period, 458 and 362 patients received P and S, respectively. Patients received a mean of 23.3 mg of P and 17.5 mg of S. MP-M on therapy was 14.4 (± 16.2) and 17.1 (± 16.5) for P and S, respectively. Therefore, NNTs for myocardial infarctions were adjusted to 163 for WOSCOPS (from 40) and to 61 for 4S (from 16). Total mortality NNTs were adjusted to 453 for WOSCOPS (from 111) and 114 for 4S (from 30).
CONCLUSIONS: Medicaid patients do not appear to receive adequate doses or duration of P and S. Generalizing NNT data from clinical trials to this population may overestimate expected treatment benefits because of the observed decrease in patient adherence.

144. Costs and benefits of bupropion in a smoking cessation program. *Michael T. Halpern, M.D. Ph.D.*, Zeba M. Khan, Ph.D., Carmelina Battista, Pharm.D., Terri L. Young, Ph.D.; Bethesda, MD.

PURPOSE: While cessation programs are generally cost-effective, the short term costs and benefits of covering prescription smoking cessation aids from the perspective of an employer or health plan are often unknown. In order to quantify the economic and health care outcomes from smoking cessation programs incorporating bupropion, we developed a user-friendly computer model called Return On Smoking Cessation Opportunity (ROSCO).
METHODS: ROSCO evaluates the costs and outcomes of covering versus not covering prescription smoking cessation aids by an employer or health plan. Users specify the population size, geographic location, and category of their worksite/health plan; defaults for all other parameters are present. The model follows a population of employees or health plan members from the start of the model through either retirement/age 65 or death/age 85. Outcomes are compared for coverage versus no coverage of smoking cessation prescription aids.
RESULTS: Outputs from ROSCO include the health care costs and indirect costs (from productivity and absenteeism) for the employees/health plan members with and without smoking cessation coverage; change in the number of smokers and cases of smoking-related illness; per member per month or per employee per year costs of cessation activities; cost-benefit ratio for coverage of smoking cessation activities; and the return on investment of covering cessation activities. The impact of different levels of cessation counseling and of promotion of cessation activities can also be evaluated.
CONCLUSION: ROSCO permits users to assess the specific costs and benefits of covering smoking cessation prescription aids within their worksites or health plans.

145. Cost-effectiveness of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. *Kjel A. Johnson, Pharm.D.*, Tracy A. Mascari, Pharm.D.; UPMC Health Plan, Pittsburgh, PA.

PURPOSE: To determine the cost effectiveness of glycoprotein (GP) IIb/IIIa inhibitors in acute coronary syndromes (ACS).
METHODS: GP IIb/IIIa inhibitors are now frequently used in ACS, but the cost-effectiveness of this is not known. Therefore, we combined the published literature of GP IIb/IIIa inhibitor use in ACS with cost data from a large managed care organization to determine cost-effectiveness. Non Q-wave myocardial infarction (NQMI) and adverse events from the PRISM-PLUS and PURSUIT trials were evaluated. All event costs were paid amounts determined from ICD-9 codes in a large managed care organization. The number of events reduced by GP IIb/IIIa inhibitor treatment was multiplied by paid costs to determine amount saved. Mean duration of infusion and dose was taken from the two published trials of interest. The cost of major bleeds, reported as patients with TIMI scale major bleeds, were combined with the medication average wholesale costs to determine the net expense. The economic analysis was based upon 30-day results from both studies, and evaluated paid costs only.
RESULTS: Modeled costs were $7789 for NQMI, and $457 for a bleed. The PRISM-PLUS net expense was $658,200 ($850/patient), $32,900 cost per infarction saved (CIS). The PURSUIT net expense was $6,103,000 ($1300/patient), $145,300 CIS.
CONCLUSIONS: GP IIb/IIIa inhibitors are cost-effective in reducing infarction compared to other medical interventions, but do not lead to actual cost savings.

146. Comprehensive sickle cell pain management program impact on the length of stay and readmission of patients with sickle cell crisis. *Ru-Ming Fan, Pharm.D., M.P.H.*, Mark Levin, M.D., Song Ja Shin, M.S.; Brookdale University Hospital and Medical Center, New York, NY.

PURPOSE: The purpose of the study is to evaluate the effectiveness of the program/clinical guidelines for pain management for patients with sickle cell crisis. The outcome of effectiveness is defined as decreasing the length of stay (LOS) and number of times of re-admission.
METHODS: A retrospective cohort study was conducted by review of the medical records of sickle cell crisis patients at the Brookdale University Hospital and Medical Center. Due to seasonal variation with respect to the manifestation of pain in sickle cell disease patients, cases (n=56) were selected from November 1, 1997 to October 31, 1998 and controls(n=56) were selected from November 1, 1996 to October 31, 1997. The comprehensive program/clinical guidelines for pain management were implemented on November 1, 1997. Cases and controls were matched by month of admission, sex, age, race, and the severity of the pain when the patients were admitted to the hospital. Multivariate logistic regression model was used to demonstrate the significance of some factors such as infections, co-morbid illness, analgesic regimens, and the specialty of physicians for the prolongation of length of stay.
RESULTS: Cases were selected after implementation of the program with average LOS of 4.6 days and 1.3 times re-admission per patient. Controls were selected prior to implementation of the program/clinical guidelines with average LOS of 7.8 days and 2.6 times re-admission per patient. The results from multivariate logistic regression model demonstrated that the patients diagnosed with infections such as pneumonia or UTI (RR = 7.9, χ^2 = 25.3, 95% CI: 7.5 -22.7, $p<0.05$), patients with co-morbid illness (RR = 4.5, χ^2 = 8.8, 95% CI: 6.3-22.3, $p<0.05$), patients received narcotics other than meperidine during hospitalization (RR = 1.5, χ^2 = 4.1, 95% CI: 1.7 -16.5, $p<0.05$), and the pain management specialist consultation (RR = 2.3, χ^2 = 4.9, 95% CI: 1.9-17.7, $p<0.05$), all had statistical significance with prolongation of the length of stay.
CONCLUSIONS: Due to the hospital's geographical location, many sickle cell disease patients were admitted to the hospital. Implementation of the comprehensive pain management program/clinical guidelines to decrease the LOS and number of times re-admission per patient and the results demonstrated that the program is successful to reduce hospital use by adult patients with sickle cell crisis.

147. Inpatient costs for major medical and surgical cardiovascular events. *Paul W. Radensky, M.D., J.D.*, Jennifer Archer, M.P.P., Susan Dournaux, B.S.N., J.D., Elise Berliner, Ph.D.; McDermott, Will & Emery, Miami, FL.

PURPOSE: A challenge in evaluating the cost of treating cardiovascular disease in a clinical trial setting is that a method for determining the actual cost of items and services incurred in the trial is not readily available. We describe a methodology to assign inpatient costs to major cardiovascular events using a uniform approach based on publicly available data sources.
METHODS: For hospital costs, the 1997 Medicare Provider Analysis Review average allowed charges for cardiac diagnostic related groups were converted to costs using the national median cost-to-charge ratio and updated to 1999 using the Medicare Payment Advisory Commission's hospital operating payment update framework. The 1999 Medicare physician fee schedule global surgery plus anesthesia fees were used to estimate physician costs for surgical admissions; an allowance for attending visits was used for medical admissions. For "unlisted" physician services (no RBRVS payment available), the allowed charge from the Medicare Part B Extraction and Surveillance System for 1998 was updated to 1999 using the Medicare economic index.

RESULTS: Total costs for medical admissions ranged from $3388 for angina (no complications) to $8997 for acute myocardial infarction (complications). Costs for surgical admissions ranged from $6089 (cardiac catheterization, no complications) to $44,587 (CABG plus PTCA).
CONCLUSIONS: This study demonstrates a reproducible method for assigning inpatient hospital costs for cardiovascular events using publicly available sources that may be easily updated from year to year. This approach may be used by those conducting economic analyses of cardiovascular disease and would allow for comparison of costs with other studies using a similar approach.

148E. Use of atypical antipsychotics in a Veterans Administration Medical Center. *Matthew A. Fuller, Pharm.D.*, Jonathan Laich, B.S.; Louis Stokes Cleveland Department of VA Affairs Medical Center, Cleveland, OH.

PURPOSE: Records of all patients treated with clozapine, risperidone, olanzapine, or quetiapine during 1998 in the Cleveland VA Medical Center were reviewed to assess concurrent medication use, length of stay, hospital admissions, and costs of treatment.
RESULTS: Clozapine was received by 145 patients, risperidone by 636, olanzapine by 395, and quetiapine by 40. The patients' mean ages ranged from 49 to 54 years; > 90% were men. Their diagnoses included schizophrenia, schizoaffective disorder, bipolar disorder, and posttraumatic stress disorder. Concurrent antipsychotic medications were received by 39% of the clozapine patients, 24% of the risperidone patients, 47% of the olanzapine patients, and 73% of the quetiapine patients (the difference between risperidone and the other three groups was significant; $p<0.05$). Psychiatric admissions were significantly more frequent in the clozapine group (1.1 admissions/patient/year) and the quetiapine group (1.5) than the risperidone or olanzapine group (0.8 in both; $p<0.05$). Length of hospital stay after psychiatric admissions was shorter in the risperidone group (17.8 days), than the clozapine (40.5 days), olanzapine (20.1 days), or quetiapine groups (31.2 days).
CONCLUSION: Total costs of treatment (antipsychotic drug + concurrent psychotropics + psychiatric admission and visit costs/patient/year) were lower for risperidone ($13,012) than clozapine ($30,665), olanzapine ($14,502), or quetiapine ($21,988).
Presented at the International Congress on Schizophrenia Research Biennial Meeting, Santa Fe, NM, April 17-21, 1999.

149E. Atypical antipsychotics: differences in length of stay, length of remission and total daily cost. *Stephen R. Saklad, Pharm.D.*, Larry Ereshefsky, Pharm.D., Dennis J. Pabbis, Pharm.D., Daniel J. Still, Pharm.D., Julia E. Vertrees, Pharm.D.; University of Texas, Austin, TX; State Hospital of San Antonio, San Antonio, TX.

PURPOSE: Outcomes and effectiveness of atypical antipsychotics were analyzed using data combining a pharmacy distribution system and an administrative database.
METHODS: Data (1994-1998) from the San Antonio State Hospital (SASH) pharmacy and the Texas Department of Mental Health and Mental Retardation were analyzed. Inclusion criteria: a single atypical antipsychotic prescribed on discharge from SASH and the patient was subsequently readmitted.
RESULTS: Of the 377 patients (546 admissions) 59% were male; 48% were Hispanic, 40% Caucasian, 11% African American, and 1% other. Age at discharge was 35 ± 12 years. Primary DSM diagnoses were schizophrenia (59%) and bipolar disorder (32%). Mean period between discharge and readmission was 226 days on risperidone (n=303); 205 days on clozapine (n=59); 136 days on olanzapine (n=178); and 36 days on quetiapine (n=7). Olanzapine vs risperidone was significant with $p=0.001$. Mean length of stay was 442 days on clozapine; 110 days on risperidone; 101 days on olanzapine; and 71 days on quetiapine (clozapine vs olanzapine $p<0.0001$; clozapine vs risperidone $p<0.0001$). Mean total daily cost of drug therapy was $11.88 for clozapine; $9.94 for olanzapine; $7.87 for quetiapine; and $6.08 for risperidone (clozapine vs risperidone $p<0.0001$; olanzapine vs risperidone $p<0.0001$).
CONCLUSIONS: Length of stay was greater for patients discharged on clozapine than either olanzapine or risperidone. Length of remission was greater for patients discharged on risperidone than olanzapine. Total daily cost of pharmacotherapy was less for patients discharged on risperidone than clozapine or olanzapine.
Presented at the New Clinical Drug Evaluation Unit Annual Meeting, Boca Raton, FL, June 1-4, 1999.

150. An economic evaluation of in-hospital use of piperacillin/tazobactam versus imipenem/cilastatin in the treatment of intra-abdominal infection. C. Stark, *R. Mallick*, K. Clark, M.W. Wible, E.T. Zito, B. Wester, R.M. Guttman, G.P. Sillup; Wyeth-Ayerst Research, Radnor, PA.

PURPOSE: Inpatient treatment of intra-abdominal infections (IAI) has important cost components including length of stay (LOS), costs of IV drugs, cost of administration, and post discharge outcomes.
METHODS: Hospital time-to-discharge (H-TTD) was assessed for 258 IAI patients who received piperacillin/tazobactam (pip/tazo 4 g/500 mg) or imipenem/cilastatin (imip/cil 1 g/1 g) q8h in a randomized, double-blind, efficacy/safety study in 422 patients. Severity was evaluated by using the Acute Physiology And Chronic Health Evaluation (APACHE II). After adjusting for APACHE II scores and accounting for censored hospital days due to in-patient death, a Cox proportional hazards analysis was used to estimate H-TTD.
RESULTS: Unadjusted baseline APACHE II scores were higher in the pip/tazo group than in the imip/cil group, especially among the intent-to-treat population (ANOVA, $p=0.02$). The pip/tazo group had a 23% lower instantaneous rate of hospital discharge (IRHD), and a proportionally greater estimated median H-TTD, compared with the imip/cil group ($p=0.04$). After adjusting for severity by using APACHE II scores, treatment-related differences in IRHD were not statistically significant ($p=0.13$) and post discharge outcomes (e.g., need for oral antibacterials) were similar. Treatment of the primary infection required an average of 7.6 days for pip/tazo vs 7.1 days for imip/cil. Imputing costs for study drugs (imip/cil $169.89 vs pip/tazo $64.26) translated into a saving of $718 per course of therapy.
CONCLUSIONS: Treatment with pip/tazo is equivalent to that of imip/cil in duration and efficacy and is expected to save costs.

151. Cost-effectiveness model for reducing LDL-cholesterol in chronic renal failure patients with hyperphosphatemia. *Donald F. Brophy, Pharm.D.*, Joel F. Wallace, Pharm.D., David A. Holdford, Ph.D., Daniel T. Kennedy, Pharm.D.; Virginia Commonwealth University, Richmond, VA; University of California Los Angeles, Los Angeles, CA.

PURPOSE: To compare the cost-effectiveness of sevelamer hydrochloride to calcium carbonate + atorvastatin for reducing LDL-cholesterol (LDL-C) to NCEP goal in chronic renal failure (CRF) patients with hyperphosphatemia.
METHODS: A cost-effectiveness model was developed from the perspective of the consumer. We compared the total yearly costs of sevelamer 2 capsules TID AC to calcium carbonate 1 g TID AC + atorvastatin 10 mg QD for reduction of LDL-C. The decision tree used data obtained from published and site-specific sources regarding percentage estimates of safety and efficacy (goal 30% LDL-C reduction) and costs and prices associated with both regimens. The target population included CRF patients without CHD but with 2 CHD risk factors and LDL-C between 160-190 mg/dl and stable phosphorus concentrations < 7.5 mg/dl. Sevelamer and calcium carbonate were assumed to be equivalent in their phosphorus-lowering ability. Outcome measures included total cost, and cost per goal LDL-C achieved.
RESULTS: The combination of calcium carbonate 1 g TID AC + atorvastatin 10 mg QD was more cost-effective than sevelamer 2 capsules TID AC. Total yearly costs were $1468 and $1852 for calcium carbonate + atorvastatin and sevelamer, respectively, per patient treated. The cost-effectiveness ratio (cost/patient achieving goal LDL-C) was $1736 and $3679 for calcium + atorvastatin and sevelamer, respectively. One way sensitivity analysis validated our cost-effectiveness model.
CONCLUSIONS: This analysis suggests calcium carbonate 1 g TID AC + atorvastatin 10 mg QD is more cost-effective than sevelamer 2 capsules TID AC for the treatment of hyperlipidemia in CRF patients with hyperphosphatemia.

152. Cost-minimization analysis of phenytoin and fosphenytoin in the emergency department. Daniel R. Touchette, Pharm.D., *Denise H. Rhoney, Pharm.D.*; Wayne State University; Detroit Receiving Hospital, Detroit, MI.

PURPOSE: To determine the value of fosphenytoin compared with phenytoin in the treatment of post-seizure patients in the emergency department (ED).
METHODS: We developed a simple decision analytic model representing the variable costs of treating post-seizure patients in the ED. A cost-minimization analysis comparing phenytoin and fosphenytoin was performed from a hospital perspective. Adverse event rates and resource utilization for events were estimated from a comparative clinical trial involving 256 patients in our institution (base case). Charts were abstracted to identify delayed complications such as purple glove syndrome (PGS). Sensitivity analyses and a scenario analysis were performed to determine the robustness of the model.
RESULTS: In our base case, phenytoin was the preferred option, with an expected total treatment cost of $5.39 compared with $110.14 for fosphenytoin. Although delayed complications were not observed in any of our patients, sensitivity analyses demonstrated that the incidence and cost of treating PGS could univariately affect the decision. A two-way sensitivity analysis indicates that at an incidence of 1%, the average cost of treating PGS must be greater than $10,000 to make fosphenytoin a preferred option. A Monte Carlo simulation showed phenytoin was the preferred option 97.3% of the time. The scenario analysis also favored phenytoin ($32.38) to fosphenytoin ($110.86).
CONCLUSIONS: When the variable costs of care are used to calculate the value of phenytoin compared with fosphenytoin in the ED, phenytoin is the preferred option. The decision to use phenytoin was very robust and changed only when both the incidence and cost of PGS was high.

153E. Comparison of erythromycin, clarithromycin, amoxicillin/clavulanate, and cefuroxime axetil for treatment of outpatient community-acquired

pneumonia: a cost analysis. *Patrick P. Gleason, Pharm.D., BCPS*, David R. Guay, Pharm.D., Michael J. Fine, M.D., M.S.; University of Minnesota, Minneapolis, MN; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: Guidelines for outpatient (OP) community-acquired pneumonia (CAP) treatment recommend macrolides as first-line agents and beta-lactams for specific populations. Using data from the Pneumonia Patient Outcomes Research Team (PORT) multicenter cohort study, CAP treatment with erythromycin (E) resulted in similar mortality and hospitalization rates, symptomatic response, and quality of life (JAMA 1997;278:32-9) compared to treatment with other agents. However, complete resource utilization was not considered.
METHODS: The objective of this study was to compare the economic consequences of monotherapy with E (n=430), clarithromycin (C; n=85), amoxicillin/clavulanate (A/C; n=34), and cefuroxime axetil (CA; n=27) using PORT data. Decision analysis was done using all available resource utilization data during a 30-day follow-up period including confirmed pneumonia-related hospitalizations, emergency department and physician visits, and all antimicrobial use. Medicare reimbursable costs were assigned in 1993 dollars (mid-point PORT). All findings were adjusted for baseline differences in severity of illness risk class between study groups.
RESULTS: Sensitivity analysis using 10,000 Monte Carlo simulations demonstrated the following mean (SD) and median (95% CI, respectively, costs per treatment: E $254 ($1056), $80 ($8-$203); C $315 ($1013), $105 ($37-$322); A/C $215 ($706), $40 ($40-$174); and CA $250 ($795), $101 ($49-$197). A multivariate sensitivity analysis varying 11 parameter estimates (e.g., hospital costs) did not change the results. However, other outcomes were not measured (e.g., symptom resolution).
CONCLUSIONS: Due to the high cost of hospitalization and low probability of this event, large differences were seen between mean and median treatment costs for each antimicrobial. There do not appear to be substantive differences in treatment cost for the four antimicrobials, suggesting that antimicrobial selection should be based on physician preferences.
Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy of the American Society for Microbiology, San Francisco, CA, September 26-29, 1999.

Pharmacoepidemiology

154. Using survival analysis to evaluate adherence to cholesterol lowering therapies. Paul S. Cady, Ph.D., *Rex W. Force, Pharm.D., BCPS*, Vaughn L. Culbertson, Pharm.D., Wendy S. Force, B.S.; Idaho State University, Pocatello, ID.

PURPOSE: An understanding of adherence rates between different medications used to treat the same condition is important for product selection. This project evaluated the adherence to therapy for cholesterol lowering medications (CLM).
METHODS: Medicaid claims data, for patients who received CLM between May 1, 1992 and January 1, 1999, were used in the project. To be included, patients were required to be enrolled in Medicaid for ≥ 90 days prior to receiving a CLM. Discontinuation of therapy was defined as ≥ 90 days without a prescription claim for a CLM. Patients receiving more than one of the study drugs were excluded. Survival analysis was used to examine the data. For the purposes of this project, drug discontinuation was analogous to death in the survival analysis.
RESULTS: Six medications, atorvastatin, simvastatin, fluvastatin, lovastatin, gemfibrozil, and pravastatin, were used by 98.1% of the patients. 280 (10%) of the patients were lost to follow up while 1156 (42%) remained on medication at the end of the study period. The mean duration of therapy for all medications was 13.5 months. Analysis revealed significant differences in the survival curves ($p<0.05$). Adherence with atorvastatin was significantly longer than all other medications except simvastatin. Adherence to therapy was significantly shorter with gemfibrozil than all but fluvastatin. Significant differences were also found between the medications at 12, 24 and 36 months ($p<0.05$).
CONCLUSION: Statistically significant differences in adherence were apparent between the CLM studied. Survival analysis proved a useful technique for evaluating adherence to therapy between different medications.

Pharmacokinetics/Drug Metabolism

155. An open label study evaluating the pharmacokinetics of 99m technetium P280 in patients at risk for venous thrombosis. *William B. Webster, Pharm.D.*, Tina Vo, Pharm.D., Andrew F. Nasseri, B.S., Steven J. Harwood, M.D., Ph.D., Sam Hakki, M.D., Robert G. Carroll, M.D., Michele Morrissey, B.S., John Camblin, M.D., Tatjana Webster, M.D.; Bay Pines VA Medical Center, Bay Pines, FL; University of Florida, Gainesville, FL; Nova Southeastern University, Ft. Lauderdale, FL; Mercer University, Atlanta, GA; University of South Florida.

PURPOSE: This is a phase I study to determine the plasma pharmacokinetics of a diagnostic radiolabeled peptide, Tc-99m P280 in patients with suspected or at risk for venous thrombosis development. The peptide, P280, binds with high affinity to the activated platelet glycoprotein IIb/IIIa receptor.
METHODS: Thirteen patients with clinical evidence or at high risk for venous thrombosis, were administered ~20mCi Tc-99mP280 (~100 µg P280 peptide) and serial blood/plasma samples were taken at three minutes and at increasing intervals to 24 hours. Resultant plasma/urine radioactivity as counts per minute (CPM)/ml was corrected for radioactive decay to the time of administration. These data were fit to a biexponential equation, $CPM/ml_{(corrected)} = A_1 \bullet e^{-\lambda_1 \bullet t} + A_2 \bullet e^{-\lambda_2 \bullet t}$ using WinNonlin 1.1 (Scientific Consulting, Inc) with a weight of 1/y and the resultant parameters analyzed as described in Webster, et al. J Nucl Med 1992:33:498-504. Urine clearance was determined as the total radioactivity excreted in the urine, calculated by a sigmoid E_{max} model, divided by the total plasma AUC. Data are reported as the mean ± SEM.
RESULTS and CONCLUSIONS: Data from the plasma tracer radioactivity as CPM/ml is assumed to represent 99mTc-P280. The mean plasma terminal elimination or β half life for the 99mTc-P280 was 2.98 ± 0.42 hours - 88.4 ± 2.09% of the total plasma AUC was in the β elimination phase. The distribution or α half life was 13.2 ± 3.6 minutes. The corresponding effective half-lives (corrected for both radioactive decay and elimination) were 1.91 ± 0.16 hours and 12.6 ± 3 minutes. The apparent volume of the central compartment was 10.4 ± 1.2 liters. The equilibrium or steady state volume of distribution is 25 ± 3.2 liters. The volume of the tissue compartment is 14.6 ± 2.1 liters. The probability of an injected 99mTc-P280 molecule leaving the central pharmacokinetic space was 75 ± 3%. Those molecules eliminated from the body had a mean residence time of 3.76 ± 0.5 hours. Those molecules reaching the peripheral pharmacokinetic space had a mean residence time of 2.96 ± 0.5 hours. At any time, the ratio of molecules in the peripheral kinetic space was 20 ± 4% of the total body activity. Renal clearance of 99mTc-P280 was 90 ± 13.1 ml/minute (74.2 ± 5.7% of total body clearance). Compared to the calculated creatinine clearance of 70.9 ± 6.7 ml/minute, the renal elimination exceeds the filtration rate and therefore a portion of the renal elimination is by active secretion or metabolism.

156. Comorbidities, medication dosing, and adherence to calcium channel blocker therapy in older adults: a comparison of amlodipine and felodipine. *Joseph Menzin, Ph.D.*, Kathleen Lang, Ph.D., William J. Elliott, M.D., Ph.D., Luke Boulanger, M.A., Mark Friedman, M.D.; Boston Health Economics, Inc., Billerica, MA; Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL.

PURPOSE: This study evaluated comorbidities, medication dosing, and treatment adherence in clinical practice among older adults prescribed either of two once-daily dihydropyridine calcium antagonists.
METHODS: Medical and pharmacy claims were reviewed retrospectively for a 10% sample of California Medicaid recipients aged 50+ years who were newly started on amlodipine (n=3296) or felodipine (n=239) between February 1995 and April 1996. Cardiovascular comorbidities were documented based on relevant diagnosis codes. Medication dosing and adherence to treatment were evaluated over one year. Multivariate methods were used to adjust for differences between groups in potential confounding factors.
RESULTS: Although study patients were of similar age and gender, those prescribed amlodipine were more likely to have angina or other ischemic heart disease, more likely to be receiving multiple medications, and less likely to be newly starting any antihypertensive therapy. After adjusting for these differences, patients prescribed amlodipine were significantly less likely ($p<0.01$) to discontinue treatment (odds ratio 0.65; 95% CI: 0.50 to 0.85), and had more covered days of medication over one year (63% versus 55% for felodipine; $p<0.01$). More patients in the amlodipine group (77% versus 66% for felodipine) were started at a lower dose (2.5 or 5.0 mg daily). The final adjusted daily dose (mean ± SD) also was lower ($p<0.05$) for amlodipine (6.6 ± 3.7 mg) than for felodipine (7.9 ± 4.1 mg).
CONCLUSIONS: In routine clinical practice, comorbidities, medication dosing, and treatment adherence may differ among patients who are prescribed drugs that are viewed as being pharmacologically similar. These factors may be important for therapeutic decision making.

157. Assessment of the possible influence of patient demographics on the pharmacokinetics of a new antibody-chemotherapeutic agent for relapsed acute myelogenous leukemia. *Joan M. Korth-Bradley, Pharm.D., Ph.D.*, James A. Dowell, Ph.D., Mark S. Berger, M.D., Hank Liu, Ph.D., S. Peter King, Ph.D.; Wyeth-Ayerst Research, Radnor, PA.

PURPOSE: To assess the possible influence of gender, age, and weight on the pharmacokinetics of CMA-676.
METHODS: CMA-676 is a novel chemotherapeutic agent that consists of a human engineered anti-CD33 antibody (hP67.6) linked to a cytotoxic agent, N-acetyl-gamma calicheamicin DMH, with a bifunctional AcBut linker. The pharmacokinetic parameters from 58 CD33 positive patients with relapsed acute myelogenous leukemia (AML) who received 9 mg/m^2 by intravenous infusion have been determined. Plasma samples were assayed for hP67.6 and calicheamicin derivatives (total and unconjugated) by enzyme-linked

immunosorbent assays and pharmacokinetic parameters were determined by noncompartmental methods. Comparisons between groups were made by analysis of variance.
RESULTS: The mean (± SD) hP67.6 pharmacokinetic parameters for the first dose period are:

		C_{max} (mg/L)	$t_{1/2}$ (h)	AUC (mg•h/L)	Cl (L/h)	V_{ss} (L)
Males	(n=29)	2.99 ± 1.63	66.8 ± 39.4	137 ± 124	0.254 ± 0.229	20.0 ± 20.8
Females	(n=29)	2.72 ± 0.98	77.9 ± 44.5	110 ± 82	0.277 ± 0.232	21.9 ± 22.6
< 60 years	(n=34)	3.03 ± 1.36	74.1 ± 47.7	129 ± 91	0.239 ± 0.207	19.2 ± 19.0
≥ 60 years	(n=24)	2.61 ± 1.31	69.8 ± 33.1	115 ± 125	0.304 ± 0.258	23.4 ± 24.9
All patients	(n=58)	2.86 ± 1.35	72.4 ± 42.0	123 ± 105	0.265 ± 0.229	20.9 ± 21.5

There was no difference observed when comparing men to women, nor when comparing patients greater than or equal to 60 years of age to those less than 60 years of age ($p<0.05$). The concentration-time profiles of calicheamicin were similar to hP67.6, with no relationship observed between pharmacokinetics and demographics.
CONCLUSION: No influence due to gender, age, or weight was observed in the CMA-676 pharmacokinetic parameters of 58 patients with relapsed AML.

158. Evaluation of vancomycin dosing and monitoring strategies in hematology/oncology patients. *Sheila A. Salamunovich, Pharm.D.*, Paul M. Beringer, Pharm.D., Alfred Chin, Pharm.D.; University of Southern California, Los Angeles, CA.

PURPOSE: 1) Determine the accuracy and precision of a published pharmacokinetic model in predicting serum vancomycin concentrations (SVC), and 2) evaluate the applicability of a recently published vancomycin dosing nomogram in hematology/oncology patients.
METHODS: Forty-eight patients who met the inclusion criteria were identified by a retrospective analysis of concurrently gathered vancomycin data. First, a priori predictions of all SVC were performed using a published two-compartment pharmacokinetic model. Second, Bayesian analysis was used to predict future SVC based on a) the first set of measured peak and trough concentrations, and b) the first measured trough concentrations. Third, future SVC were predicted using a published vancomycin nomogram.
RESULTS: A significant correlation (0.81) was observed between predicted and measured SVC. There was no significant difference in predicted future SVC among the various monitoring strategies. Target trough concentrations were achieved in 68% of the patients utilizing the nomogram.

	A Priori	A Posteriori Peak/Trough	A Posteriori Trough
Percentage ME (95% CI)	-6 (-12 to -1)	-14 (-21 to 8)	-8 (-14 to -2)
Percentage MAE (95% CI)	32 (29 to 36)	31 (27 to 35)	29 (24 to 33)

CONCLUSIONS: The a priori model was a good predictor of SVC in hematology/oncology patients. SVC monitoring (peak/trough versus trough only) did not improve upon the a priori model. The nomogram may be a useful alternative for dosing of vancomycin in hematology/oncology patients.

159. Once-daily aminoglycoside monitoring: sampling considerations for an extended distribution phase. *Heath R. Jennings, Pharm.D.*, Elizabeth A. Coyle, Pharm.D., Paul Kearney, M.D., George A. Davis, Pharm.D.; University of Kentucky Medical Center, Lexington, KY.

PURPOSE: A recent study in healthy volunteers demonstrated a prolonged distribution phase following the administration of once-daily aminoglycosides (ODA). This has led to questioning the accuracy of conventional ODA sampling strategies that assume complete drug distribution in 60 minutes. The purpose of this study is to evaluate a conventional two-concentration sampling strategy by determining the difference in pharmacokinetic parameters when considering prolonged distribution.
METHODS: In this prospective study of 20 surgery patients, gentamicin or tobramycin (7 mg/kg) was infused over 30 minutes. Peak (C_{pk}) and two random concentrations ($C_{3.5h}$ and $C_{9.5h}$) were obtained 0.5, 3.5, and 9.5 hours post-infusion, respectively. Pharmacokinetic parameters (PK) and an estimated 24-hour trough (C_{24h}) were calculated using two-concentration strategies: a conventional strategy using C_{pk} and $C_{9.5h}$ and a study strategy using $C_{3.5h}$ and $C_{9.5h}$. An estimated peak (C_{est}) was calculated using the study strategy.
RESULTS: Dose = 7.0 ± 0.6 mg/kg; PK parameters (conventional and study, respectively): C_{pk} = 22.5 ± 6.1 mg/L and C_{est} = 14.3 ± 3.2 mg/L ($p<0.001$); C_{24h} = 0.24 ± 0.46 mg/L and C_{24h} = 0.47 ± 0.92 mg/L ($p<0.05$); V_d = 0.27 ± 0.08 L/kg and V_d = 0.44 ± 0.11 L/kg ($p<0.001$); k_e = 0.26 ± 0.09 h^{-1} and k_e = 0.20 ± 0.08 h^{-1} ($p<0.001$).
CONCLUSION: PK parameters based upon conventional ODA sampling strategies may not be optimal since C_{pk} appears to be drawn during the distribution phase. Clinical significance includes an overestimation of C_{pk}/MIC, and an underestimation of C_{24h}. Specifically, 14 patients (70%) would have received incorrect or unnecessary dosing adjustments and 3 patients (15%) would have been inappropriately re-dosed with a C_{24h} > 1 mg/L if conventional sampling strategies were utilized. Considering these results, a revised two-concentration sampling strategy may be warranted to account for prolonged distribution.

160. Morphine pharmacokinetics in African-American males with and without sickle cell anemia. *Aaron H. Burstein, Pharm.D.*, Jason A. Gross, Pharm.D., Griffin Rodgers, M.D., Richard Gracely, Ph.D., Wendy Smith, Ph.D., Linda Williams, B.S.N., M.A., Mitchell Max, M.D., Cynthia Chicca, B.S.N., Patricia Griffith, B.S.N., Mark Hoffman, M.D., Frank Pucino, Pharm.D.; National Institutes of Health, Bethesda, MD; Zenith Goldline Pharmaceuticals, Ft. Lauderdale, FL; Long Island Jewish Medical Center, New Hyde Park, NY.

PURPOSE: To evaluate single dose morphine pharmacokinetics (PK) following intravenous (IV) administration in sickle cell anemia patients (SCA) not in vaso-occlusive crisis and race-matched normal volunteers (N).
METHODS: Morphine (10 mg) was administered as an IV injection over 2 minutes. Blood samples for determination of morphine plasma concentrations were collected at baseline and 0.125, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 7, and 8 hours following initiation of dosing. Samples were analyzed by HPLC (LLQ 3 ng/ml). Data were fit (WinNonlin v1.5) by a linear, open, 2-compartment model. Noncompartmental analysis was performed to determine area under the curve to infinity ($AUC_{0-\infty}$). Maximal concentration (C_{max}), and half-life ($t_{1/2}$) were determined by visual inspection of data. Comparison of PK between SCA and N was by Wilcoxon signed rank test.
RESULTS: Ten subjects (5 SCA, 5 N) were studied. SCA and N subjects had a mean (SD) age of 34.4 (9.9) and 28 (6.6) years, respectively. Median (interquartile range) morphine PK parameter estimates for SCA and N are as follows: V 102.6 (69.9, 156.6) vs 150.29 (56.4, 165.3) L; k_{12} 4.4 (1, 2.3) vs 3.8 (2.9, 6.1) h^{-1}; k_{21} 1.5 (0.8, 2.3) vs 1.2 (0.9, 1.7) h^{-1} ; k_{10} 1.7 (1, 2.3) vs 1.4 (0.8, 1.6) h^{-1}; C_{max} 86 (79.8, 143.5) vs 70.1 (58.1, 179.4) ng/ml; $AUC_{0-\infty}$ 64.3 (60.3, 88.8) vs 83.9 (59.2, 92.8) ng•h/ml; $t_{1/2}$ 1.7 (1.4, 3.6) vs 2.4 (1.5, 2.5) h. No statistically significant differences were found in PK parameter values between SCA and N.
CONCLUSIONS: Morphine PK in adult African-Americans with and without SCA has not been previously reported. The results suggest no difference in IV morphine PK between stable SCA and N.

161E. St. John's wort: evaluation of effect on CYP3A4 and CYP2D6 activity. *Carol A. Roby, Pharm.D., M.S.*, Gail D. Anderson, Ph.D., Eric Kantor, B.A., Donna A. Dryer, M.D., Aaron H. Burstein, Pharm.D.; University of Maryland, Baltimore, MD; University of Washington, Seattle, WA.

PURPOSE: To evaluate the effect of reagent grade St. Johns wort on CYP3A4 and CYP2D6 activity.
METHODS: Normal healthy volunteers, 18-45 years old, medication free for at least 2 weeks, ingested a 300 mg tablet of 0.3% hypericin standardized reagent grade St. Johns wort three times a day for 14 days. Baseline (day 0) and post-treatment (day 14) CYP3A4 and CYP2D6 activities were evaluated using urine 6-β-hydroxycortisol/cortisol and dextromethorphan/ dextrorphan (DM/DX) ratios, respectively. At baseline and post-treatment 30 mg of dextromethorphan was ingested followed by urine collection for 24 hours. Urine specimens were analyzed by HPLC. Baseline and day 14 ratios were compared using the paired Student's t-test with statistical significance declared at $p<0.05$.
RESULTS: Thirteen subjects (4 males, 9 females) with a mean (SD) age of 30 (7.5) years completed the study. The mean (SD) urine 6-β-hydroxy-cortisol/cortisol ratio significantly increased from a baseline value of 7.1 (4.5) to 13 (4.9) after treatment ($p=0.003$), with a mean (SD) increase of 114% (95%). The mean (SD) urine DM/DX ratios at baseline and post treatment were 0.0063 (0.0066) and 0.0070 (0.0090), with a mean (SD) increase of 17% (45%; $p=0.675$).
CONCLUSIONS: Treatment with reagent grade St. John's wort for 14 days resulted in a 114% increase in urine 6-β-hydroxycortisol/cortisol ratios implicating St. John's wort as an inducer of CYP3A4. No significant effect was seen on the CYP2D6 surrogate marker dextromethorphan. The potential for drug:drug interactions involving the CYP3A4 metabolic pathway should be considered for individuals taking St. Johns Wort.
Presented at the 39th Annual Meeting of the National Institutes of Mental Health, New Clinical Drug Evaluation Unit Program, Boca Raton, FL, June 1-4, 1999.

162. Steady-state drug-drug interaction assessment between celecoxib and methylphenidate. *Todd P. Semla, M.S., Pharm.D., FCCP*, Antoni A. Piergies, M.D., Dawn Bradford, B.S., C-B. Wallemark, M.S., Aziz Karim, Ph.D.; Evanston Hospital, Evanston, IL; G.D. Searle & Co., Skokie, IL.

PURPOSE: To assess the effects of methylphenidate (M) and celecoxib (C) on the other's steady-state pharmacokinetics in healthy adults.
METHODS: Open label, randomized, multiple dose, crossover design. Volunteers received either C 200 mg BID alone or with M 5 mg BID on days 1-7, and the alternative regimen on days 8-14, or M 5 mg BID alone or with C 200 mg BID on days 1-7, and the alternative regimen on days 8-14. Blood and urine specimens were collected over 24 hours on days 7 and 14. Genotyping for the 2D6 isozyme is pending.
RESULTS: Twenty-six men and 6 women (17 Caucasians, 10 African-Americans, 4 Hispanics and 1 other) with a mean age 35.5 years completed

the study. M had no effect on the bioavailability of C: AUC_{0-12h} (ng•hr/ml), C 9387.97 vs C + M 9324.82; AUC_{0-24} (ng•hr/ml), C 18095.38 vs C + M 17881.99; C_{max} (ng/ml), C 1529.5 vs C + M 1570.88 and T_{max} (hr) C 2.44 vs C + M 2.63. A significant sequence effect was found: AUCs for C were 50% greater in C + M, then C-alone group compared to the C-alone, then C + M group. Methylphenidate had no effect on the urinary excretion of C or its metabolite. Neither M's, nor ritalinic acid's (RA) AUC_{0-12}, AUC_{0-24}, and C_{max} differed significantly comparing M-alone to M + C. The ratio of M + C:M for both the amount and rate of urinary excretion of M in 24 hours were 1.32 (95% CI: 102.2, 171.0). These ratios did not differ significantly for RA.
CONCLUSION: Neither C nor M are affected the others steady-state pharmacokinetics.

163. Effects of a high fat meal on the absorption of M100907 in healthy subjects. *Dan C. Dimmitt, B.S.*, John Shelton, Ph.D., Doris Robbins-Weilert, Ph.D., Mark Eller, Ph.D.; Quintiles, Inc., Kansas City, MO.

PURPOSE: The effect of a high-fat breakfast on the absorption of M100907, a novel antipsychotic agent, was assessed following administration of prototype tablets, commercial tablets, and a commercial oral liquid formulation.
METHODS: In three studies, 20 mg single doses of M100907 prototype tablets (15 subjects) and a commercial tablet (28 subjects) and oral liquid (28 subjects) were administered in a crossover design. Drug administrations were given following both high-fat breakfast and fasted treatments. Blood samples were collected to 60 hours post dose and quantitated for plasma M100907. Bioavailability comparisons within each formulation were made between the fed and fasted treatments to assess the food effect.
RESULTS: With all formulations, the high-fat breakfast increased the bioavailability of plasma M100907 compared to the fasted treatment. Increases in mean $AUC_{0-\infty}$ ranged from 39% for the prototype tablet to 25% for the oral liquid. Increases in mean C_{max} were 33% and 42% for the commercial tablet and prototype tablet, respectively, with the oral liquid showing no increase in C_{max} with the fed treatment. Terminal $t_{1/2}$ did not change in all comparisons and the T_{max} was unchanged in both tablet formulations. With the oral liquid, the T_{max} increased about 1.2 hours with fed treatment compared to fasted treatment.
CONCLUSIONS: While increases in bioavailability of up to 39% were observed with M100907 formulations when given with a meal, these changes would not alter the therapeutic or safety profile of the drug because of the tolerability seen in healthy volunteers.

Pharmacy Practice

164. Assessment of asthma outcomes in a pharmacotherapy clinic. *Bryan F. Yeager, Pharm.D., BCPS*; University of Kentucky, Lexington, KY.

PURPOSE: To evaluate the clinical outcomes of a pharmacist-managed clinic compared to traditional care for asthmatic patients seen in a university-based family medical center.
METHODS: Sixty-five patients with a diagnosis of asthma were screened by medical record review and phone interview to determine eligibility. Patients were determined to be high-risk for asthma complications if they had: 1) history of medication nonadherence, 2) average peak expiratory flow rate < 80% of personal best, 3) asthma-related emergency room visit in the last 6 months, or 4) short-acting beta-agonist use > 2 times per week. High-risk asthma patients were enrolled into a pharmacotherapy clinic (PTC) for collaborative drug therapy management and patient education. Individuals were seen in clinic every 2 to 4 weeks. Clinical outcomes, medication adherence and emergency room visits were measured 3 months before and after PTC enrollment.
RESULTS: Mean peak expiratory flow rates were higher after PTC enrollment compared to traditional care (93% vs 72% of personal best, $p<0.001$). There was a favorable trend towards decreased beta-agonist use per week (25 vs 2, $p=0.08$), long-term control medication adherence (54.4% vs 37.5%, $p=0.10$) and emergency room visits (3 vs 1, $p>0.05$) for patients before and after PTC enrollment.
CONCLUSION: Asthma control is improved for high-risk patients referred to and seen routinely in a pharmacist-managed clinic. This improved control may be due to better adherence with long-term control medications, adjustment or initiation of long-term control medication, more frequent home monitoring and educational efforts.

165. Evaluating the impact of providing smoking cessation services to an indigent population. *Michael B. Doherty, Pharm.D.*, Ruth E. Emptage, Pharm.D., Martin R. Giannamore, Pharm.D., Craig A. Pedersen, Ph.D.; The Ohio State University, Columbus, OH.

PURPOSE: Smoking cessation programs provided to the general population report cessation rates of 25.5%. This study evaluated smoking cessation rates and abstinence barriers of indigent patients enrolled in a pharmacist-managed smoking cessation program at a primary care setting. Patients' perceived change in health status and overall satisfaction with the program were also evaluated.
METHODS: Patients that attempted to quit smoking as part of a smoking cessation program were evaluated. Data collection occurred in three phases for each patient: retrospective baseline chart review, and chart review and phone call survey 6 months after enrolling in the program.
RESULTS: Thirty-three patients enrolled in the program qualified for evaluation. Six month cessation rates were 27.3% (9/33). Twenty-four of 33 (72.7%) patients completed the phone survey, eight of which quit smoking (33.3%). Unsuccessful patients identified stress as the main reason for relapse (7/16, 43.8%). Patients viewed personal visits with pharmacists as the greatest strength of the program (11/24, 45.8%), while difficulty obtaining medications was identified as the greatest weakness (6/24, 25.0%). Patients who quit smoking viewed their health as better ($p=0.02$) and were more satisfied with the program ($p=0.02$) than those who did not quit smoking. Regardless of smoking status, patients were satisfied with the program: 8/8 (100%) quitters and 14/16 (87.5%) non-quitters.
CONCLUSIONS: Comparable cessation rates between an indigent and general population demonstrate the value of providing services to an under-served population. Improving stress management strategies and medication accessibility may further enhance cessation rates and the quality of the program.

166E. Effect of pharmacist initiated home blood pressure monitoring on hypertension. *Brenda M. Mehos, Pharm.D.*, Joseph J. Saseen, Pharm.D., Eric J. MacLaughlin, Pharm.D.; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: This study evaluated the impact of pharmacist initiated home blood pressure (BP) monitoring on BP control, medication compliance, and quality-of-life (QOL).
METHODS: Thirty-six subjects met inclusion criteria in this six-month prospective, randomized, controlled study. All patients received initial counseling on drug therapy and lifestyle modification. Intervention subjects (n=18) received home BP monitors, a diary, and instructions to measure BP twice daily. Clinical pharmacists in a family medicine clinic evaluated subjects' home measurements. Primary care physicians were contacted with recommendations if mean BP values were ≥ 140/90 mm Hg. Control patients did not receive home monitors or pharmacist intervention. Office BP measurements and QOL surveys (SF-36) were obtained at baseline and after 6-months.
RESULTS: Systolic BP (SBP) and diastolic BP (DBP) were significantly reduced from baseline in intervention subjects (mean absolute SBP/DBP reductions 17.0/10.5; both $p<0.0001$) but not in control subjects (mean absolute SBP/DBP reductions 7.0/3.8; $p=0.12$/$p=0.09$). Mean percent decreases in SBP/DBP from baseline were greater in intervention versus control subjects (10.4/11.0% versus 4.3/3.6%; $p=0.06$/$p=0.02$). More intervention subjects (8 of 18) had controlled BP (< 140/90) at 6 months compared to controls (4 of 18). During the 6-month study period, 83.3% (15 of 18) of intervention subjects had medication changes versus only 33% (6 of 18) in the controls ($p<0.01$). Medication compliance and QOL were not significantly affected.
CONCLUSIONS: Our data suggests that the combination of pharmacy intervention with home monitoring can improve BP control in uncontrolled hypertensive patients. This may be related to increased modifications of drug regimens.
Presented at the 100th Annual Meeting of the American Association of Colleges of Pharmacy, Boston, MA, July 3-7, 1999.

167. Interventions performed by clinical pharmacists in high-risk ambulatory veterans: the IMPROVE trial. *Samuel L. Ellis, Pharm.D.*, Daniel C. Malone, Ph.D., Barry L. Carter, Pharm.D.; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: This randomized, prospective study evaluated patient care interventions provided by ambulatory care clinical pharmacists during the Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers (IMPROVE) study.
METHODS: A total of 523 patients were randomized into the intervention arm of this multi-centered study in nine Veteran Affairs medical centers. Patients were selected for this study if they were considered to be at high risk for medication-related problems. Pharmacists were asked to document, on a standard form, length of visit, method of contact, medical problems addressed and drug-related problems addressed and resolved during each intervention.
RESULTS: Seventy-eight ambulatory care clinical pharmacists documented a total of 1855 interventions, an average of 3.54 ± 2.31 per patient, over a 12-month period. The length of visits was ≥ 15 minutes for 73% of interventions. In-person interventions accounted for 1421 visits (76.6%) with the remainder being telephone contacts. During each intervention the average number of drug-related problems addressed and resolved were 1.60 ± 1.14 and 1.11 ± 0.97, respectively. More drug-related problems were addressed and resolved when visits were ≥ 15 minutes ($p=0.001$) and when the method of pharmacist-patient contact was in person ($p<0.001$).
CONCLUSION: Ambulatory care clinical pharmacists addressed and resolved more problems when seeing patients in person as compared to using the telephone. This may provide valuable information to clinical pharmacists

developing pharmacy-managed clinics for patients at high risk for medication-related problems.

Psychiatry

168. Anxiolytic efficacy and safety of triazolam and chloral hydrate in developmentally disabled adults as premedication for medical procedures. *Brian J. Fitzgerald, Pharm.D.*, Anthony J. Okos, M.D.; Fircrest Residential Habilitation Center; University of Washington, Seattle, WA.

PURPOSE: Most developmentally disabled residents in long-term care facilities require sedative premedications for their medical procedures. The anxiolytic efficacy and safety of triazolam and chloral hydrate were evaluated in the developmentally disabled individuals at our facility.
METHODS: The pharmacy sent out a presedate report form with all presedate medication orders from January 1, 1998 to December 31, 1998. This form required nurses to document anxiolytic efficacy as a yes or no response and to document adverse reactions occurring within 24 hours after dose administration. Complete forms were collected by the pharmacy. Triazolam was used for most procedures except for EEG recordings which were premedicated with chloral hydrate. Dose was determined by cautious optimization over several years of clinical practice. Data regarding adverse reactions were analyzed by t-test in relation to dose, patient age and concurrent CNS medication.
RESULTS: The study data were comprised of 484 completed forms. Triazolam was effective in 351 of 418 (84%) procedures. Chloral hydrate was effective in 49 of 66 (74%) procedures. The mean average doses of triazolam and chloral hydrate were 0.6 and 2000 mg, respectively. The dose ranges of triazolam and chloral hydrate were 0.25-1.5 and 1000-3500 mg, respectively. Excess drowsiness was reported in ten triazolam and two chloral hydrate cases. Hypotension and hypothermia were reported in one of these triazolam cases. In this study the adverse reactions to triazolam and chloral hydrate were significantly ($p<0.008$) associated with above-average age. Adverse reactions to either of the two medications resolved quickly without permanent sequelae.
CONCLUSION: Triazolam and chloral hydrate proved to be highly effective and safe for medical procedures in this population of developmentally disabled adults. In our study adverse reactions were significantly associated with above-average age.

169. Consumer use of St. John's wort: a survey on effectiveness, safety, and tolerability. Stephanie E. Beckman, Pharm.D., *Roger W. Sommi, Pharm.D., BCPP*, Joy Switzer, B.S.N., CRC; University of Missouri-Kansas City; Western Missouri Mental Health Center, Kansas City, MO.

PURPOSE: This study surveyed consumer experiences with St. John's wort (SJW) in order to gain insight into reason for use, effectiveness and tolerability, and evaluate discontinuation effects and drug interactions.
METHODS: Forty-three subjects ≥ 18 years of age who had taken SJW participated in a telephone survey designed to assess demographics, psychiatric/medical conditions, dose, duration of use, reason for use, source of information, side effects, concomitant medications, consultation with a medical professional, effectiveness, reoccurrence of depressive symptoms and withdrawal effects.
RESULTS: Sixty-three percent reported using SJW for mild depression and 7% for severe depression. Mean dose was 475.6 ± 360 mg/d (range 300-1200 mg/d). Mean duration of use was 7.3 ± 10.1 weeks (range 1 day - 5 years). Among 84% (n=36) reporting improvement, 50% (n=18) had a psychiatric diagnosis. Forty-seven percent (n=20) reported side effects with 12% (n=5) resulting in discontinuation and 1 ER visit. Among 5 reporting concomitant use with serotonergic drugs, 40% (n=2) experienced symptoms of serotonin syndrome. Among 39 coingesting tyramine-rich foods or sympathomimetic OTCs, 8% (n=3) experienced a food/drug reaction. Among 28 reporting noncompliance with SJW, 46% (n=13) experienced withdrawal symptoms. Two consumers switched from their antidepressant to SJW and both experienced depressive relapse. Seventy-four percent did not seek medical advice before or during use.
CONCLUSION: Our study found an alarming incidence of risky behaviors and adverse events. These data suggest the need for greater consumer health awareness of the potential risks of SJW in the self-care of depression and related syndromes.

170. Safety and kinetics of a novel risperidone depot formulation. *Merete Rasmussen, M.D.*, An Vermeulen, Marielle Eerdekens, Richard Lowenthal, Archiel Van Peer; Janssen Research Foundation, Beerse, Belgium; Janssen Research Foundation, Titusville, NJ.

PURPOSE: Presentation of an international, open trial comparing steady-state plasma levels of risperidone tablets (2, 4, or 6 mg, QD) with depot (25, 50, or 75 mg, q2 weeks).
METHODS: Subjects, first stabilized on 2, 4, or 6 mg daily oral risperidone for at least 4 weeks, continued oral therapy the first 3 weeks on full dose, the next 2 on half the dose. From week 2, subjects on oral risperidone 2, 4, or 6 mg received five 23, 50, or 75 mg risperidone depot IM, respectively. Use of antipsychotics other than risperidone was allowed. Risperidone and the active moiety plasma concentrations were assessed; safety, tolerability, and efficacy were documented.
RESULTS: The 90% percent confidence intervals for the mean steady-state active moiety AUC (risperidone depot vs oral) were all within the bioequivalence range of 80-120%. During depot treatment a significant reduction ($p<0.05$) in C_{max} was observed: average C_{max} 70-77% of oral. The average steady-state C_{min} was not different ($p>0.05$) between depot and oral (average C_{min} 96-108% of oral). Risperidone depot caused less plasma level fluctuations. Complete safety results will be presented.

171. Olanzapine plasma concentrations and clinical response: acute phase results of the North American olanzapine trial. *Brian C. Lund, Pharm.D.*, Paul J. Perry, Ph.D., Todd Sanger, Ph.D., Charles Beasley, M.D.; University of Iowa, Iowa City, IA; Eli Lilly and Co., Indianapolis, IN.

PURPOSE: Olanzapine plasma concentrations ≥ 9.3 ng/ml (24 hours post-dose) have been identified as a predictor of clinical response in acutely ill schizophrenic patients. We report a receiver operator characteristic (ROC) curve analysis of 12-hour olanzapine concentrations and therapeutic response from the North American Double-Blind Olanzapine Trial.
METHODS: Patients meeting DSM-III-R criteria for schizophrenia were randomized to receive olanzapine, haloperidol or placebo. After a 4-7 day placebo lead-in, patients randomized to olanzapine received daily doses ranging from 2.5 to 17.5 mg/day for up to six weeks. Olanzapine samples were obtained between 10 and 16 hours (11.7 ± 1.7 hr) post-dose. Therapeutic response data and olanzapine concentrations used for analysis were obtained from the endpoint visit for each patient if the patient had been on a fixed olanzapine dose for at least the last two weeks of the study. Plasma concentrations from previous visits were used if endpoint concentrations were invalid. Response was defined as ≥ 20% reduction in Brief Psychiatric Rating Scale (BPRS) and a clinical global impression severity score of ≤ 3 or a final BPRS of ≤ 35.
RESULTS: The final ROC analysis included data from 84 patients. Fifty-two percent of patients with 12-hour olanzapine concentrations ≥ 23.2 ng/ml responded, whereas only 25% of patients < 23.2 ng/ml responded. Furthermore, this threshold was a predictor of response in the Scale for the Assessment of Negative Symptoms.
CONCLUSIONS: A 12-hour olanzapine plasma concentration of ≥ 23.2 ng/ml was a predictor of therapeutic response in acutely ill schizophrenic patients.

172. Prolactin elevations in patients treated with olanzapine. *Daniel R. Wilson, M.D.*, Leo D'Souza, M.D., Henry Nasarallah, M.D., Mark Newman, M.D.; The Lewis Center, Cincinnati, OH; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: With the advent of novel antipsychotic compounds relatively free of extrapyramidal symptoms, increased interest is now directed to other side effects and their clinical relevance. Systematic studies of such side effects are limited.
METHODS: In a 6-week open-label study, the authors evaluated the prolactin response in patients receiving a fixed titration schedule of olanzapine. All patients were enrolled in an academically affiliated state hospital adult inpatient unit and all met DSM-IV criteria for schizophrenia. The dose of 30 mg/day of olanzapine was achieved in 2 weeks. Serial serum assays were obtained from fasting samples drawn consistently to control for diurnal fluctuations and possible postprandial effects.
RESULTS: Results of preliminary data analysis in the first 10 patients revealed acute and marked prolactin elevations associated with olanzapine in 4 patients, including dramatic elevation in 1 neuroleptic-naïve patient studied. The study is being extended to determine whether these findings are replicated in a larger study population and sustained beyond 6 weeks.

173. Correlation between total cholesterol and response in clozapine-treated patients. *Charles F. Caley, Pharm.D.*, Robert L. Dufresne, Ph.D.; University of Connecticut, Storrs, CT; Institute of Living, Hartford, CT; University of Rhode Island, Kingston, RI; VA Medical Center, Providence, RI.

PURPOSE: This study was performed to evaluate the association between total cholesterol and brief psychiatric rating scale (BPRS) score changes in patients with refractory schizophrenia/schizoaffective disorder who were treated with clozapine.
METHODS: Medical records of 25 clozapine-treated patients (16M/9F) diagnosed with refractory schizophrenia (n=20) and schizoaffective disorder (n=4) were reviewed retrospectively. Patient demographics, diagnosis, previous antipsychotic treatment, concurrent psychotropic treatment, tardive dyskinesia severity, weight, total cholesterol, serum triglyceride and BPRS scores were documented.
RESULTS: Regression analysis indicated that baseline total cholesterol was a significant predictor of changes in total BPRS scores (Pearson r=0.601, r^2=0.361, F=11.307, p=0.003), thinking disturbance (Pearson r=0.489, r^2=0.239, F=6.273, p=0.021) and paranoid disturbance (Pearson r=0.558, r^2=0.311, F=9.048, p=0.007) sub-scale scores; mean scores were reduced by

approximately 30%. No association was found between baseline total cholesterol and changes in the anxious depression or withdrawal retardation sub-scale scores. Changes in total cholesterol were also not associated with any BPRS score changes. There was no association found between changes in BPRS scores and any of the remaining variables including age, gender, concurrent psychotropic use or weight.
CONCLUSION: Higher total cholesterol at treatment onset with clozapine predicted reductions in BPRS total and positive symptom sub-scale scores. Our results suggest that total cholesterol predicts positive symptom response to clozapine in subjects with refractory schizophrenia/schizoaffective disorder.

174E. Association between cytochrome P4502D6 genotype, neuroleptic exposure, and abnormal involuntary movement scale score. *Vicki L. Ellingrod, Pharm.D., BCPP*, Susan K. Schultz, M.D., Stephan Arndt, Ph.D., Paul J. Perry, Ph.D., BCPP, Nancy C. Andreasen, M.D., Ph.D., Tim L. Holman, M.A., Frank Fleming, B.S.N.; University of Iowa, Iowa City, IA.

The metabolism of many antipsychotics cosegregates with the metabolic activity of the polymorphic cytochrome P4502D6 (CYP2D6). Approximately 5-10% of Caucasians show impaired metabolism due to lack of this enzyme. By phenotyping patients for 2D6, we are unable to determine those homozygous for 2D6 (Wt/Wt) and those with a mutation (Wt/m). The number of Wt alleles is associated with the metabolic activity of CYP2D6. Genotyping allows us to determine this.
PURPOSE: To determine if an association between CYP2D6 genotype, neuroleptic exposure, and AIMS score exists.
METHODS: Patients with schizophrenia (DSM-III-R) were genotyped for CYP2D6*1, *3, and *4 alleles by using nested polymerase chain reaction. Full psychiatric and medication history and evaluations were recorded. Neuroleptic exposure was converted into dose years (chlorpromazine equivalents x years used). A linear model was run with AIMS scores as the dependent variable. Genotype, gender, neuroleptic exposure, and interactions were independent variables.
RESULTS: A total of 31 patients were included. Twenty were Wt/Wt and 11 were Wt/m. No poor metabolizers were found. Mean neuroleptic dose years between the two groups were different (Wt/Wt 142.86 ± 74.7 vs Wt/m 72.79 ± 60.27; $p<0.0125$). The interaction of neuroleptic*genotype was the only significant variable ($p<0.0055$).
CONCLUSION: This association showed that those with the Wt/m genotype had a greater association with higher AIMS scores (slope = 0.044) than those Wt/Wt (slope = 0.001). These results suggest that patients with a mutated CYP2D6 allele are at a higher risk for developing abnormal movements due to neuroleptic use.
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175. Differences in titration rates between patients starting pharmacotherapy on olanzapine and risperidone. *David S. Hutchins, MBA, M.H.S.A.*, Bryan M. Johnstone, Ph.D., P. Joseph Gibson, Ph.D., William F. Signa, B.S., Devora Mitrany, B.A.; PCS Health Systems Inc., Scottsdale, AZ; Eli Lilly and Company, Indianapolis, IN.

PURPOSE: This retrospective study compares titration rates for patients starting a course of therapy on either olanzapine or risperidone to assess prescribing differences.
METHODS: Patients who were dispensed olanzapine (n=3544) or risperidone (n=23,302) as their first antipsychotic between October 1 and December 31, 1996 were selected from a large U.S. claims database. All antipsychotic prescriptions for one year preceding and following each patient's first antipsychotic prescription were used to identify initiators (patients with no prior antipsychotic use: olanzapine, n=283; risperidone, n=1386) and to calculate titration rates and the time to the first titration. Rates were calculated for all patients and for those aged 18 to 64 with and without accounting for duration of therapy.
RESULTS: Regardless of age and whether duration was taken into account, fewer olanzapine (36.0%, all ages; 37.2% aged 18 to 64) than risperidone (42.6%; 39.1%) initiators were titrated. Differences were significant for all ages ($p\leq0.05$). Similar differences were generally observed for comparisons accounting for duration of pharmacotherapy. The number of days from the first titration occurred later in the course of treatment for olanzapine (86.7; 89.7 days from date of first prescription) than for risperidone (82.2; 83.2 days).
CONCLUSIONS: Patients initiating a treatment episode on olanzapine were less likely to be titrated and were titrated later in the course of therapy than those on risperidone. These results may indicate tolerability, effectiveness, and/or physician practice differences, which should be explored for potential treatment implications.

176E. Lack of pharmacokinetic interaction between desipramine and α_2-adrenergic agonists in children and adolescents. *Louise Glassner Cohen, Pharm.D.*, Joseph Biederman, M.D., Sophie Lanjuin, Pharm.D., Sabrina Whitt, Pharm.D., Timothy E. Wilens, M.D., Erick Mick, Sc.D., Thomas Spencer, M.D., Carolyn M. Hahn, Pharm.D., David Polisner, B.A.; Massachusetts General Hospital; Harvard Medical School, Boston, MA.

Combined pharmacotherapy is used increasingly to address treatment resistance, comorbidity and attenuate the adverse effects of medications. Tricyclic antidepressants (TCAs), desipramine (DMI) and others are combined with clonidine or guanfacine to treat complex cases of ADHD with comorbid tic, behavioral or anxiety disorders not responsive to TCAs alone, or to alleviate symptoms of ADHD-associated sleep disturbances in children on TCAs. However, drug-drug interactions may occur between DMI and other medications resulting in decreased DMI clearance and increased DMI toxicity. Thus, it is important to examine the influence of α_2-adrenergic agonists on the pharmacokinetics of DMI in children and adolescents to assure the safety of combined pharmacotherapy.
PURPOSE: To examine the influence of clonidine and guanfacine on the pharmacokinetics of DMI using routinely monitored DMI serum concentrations in children and adolescents receiving DMI alone or in combination with α_2-adrenergic agonists clonidine or guanfacine.
METHODS: DMI pharmacokinetic parameters were calculated for a total of 157 youth (between 6 and 17 years, 133 males, 24 females) from 441 weight and dose-normalized serum concentrations. Subjects received either DMI (368 serum concentrations, 131 subjects) or DMI + α_2-agonist (73 serum concentrations, 26 subjects).
RESULTS: DMI pharmacokinetic parameters, mean weight corrected dose (DMI, DMI + α_2-agonists) (3.77 ± 1.51 mg/kg, 3.41 ± 1.61 mg/kg, p=0.24), weight and dose normalized DMI serum concentrations (46.36 ± 38.66 [(μg/L)/(mg/kg)], 50.43 ± 34.89 [(μg/L)/(mg/kg)], p=0.550) and DMI clearance (0.690 ± 0.879 (L/kg)/hr, 0.517 ± 0.472 (L/kg)/hr, p=0.147) were similar for both populations. When stratified by age and gender, there was no difference detected ($p>0.05$) in the DMI group. When the DMI + α_2-agonist group was stratified by age, the mean DMI dose was lower in adolescents than in children (3.6 ± 1.75 mg/kg, 2.67 ± .787 mg/kg, p=0.013). However there the DMI weight and dose normalized DMI serum concentrations and clearance were similar indicating the absence of a drug-drug interaction. When the DMI + α_2-agonist group was stratified by gender (22 males, 4 females), a difference in DMI clearance was detected between males and females respectively (0.688 ± 0.908 (L/kg)/hr, 0.682 ± 0.583 (L/kg)/hr, p=0.032). Although not clinically significant, this difference may result from the small number of females in the sample.
CONCLUSION: Our findings suggest the absence of a clinically significant interaction between DMI and α_2-adrenergic agonists regardless of age. However, the influence of gender on the drug-drug interaction should be examined further in a larger population.
Presented at the 39th Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, FL, June 1-4, 1999.

176EA. Pharmacotherapy of attention deficit hyperactivity disorder in psychiatrically referred girls. *Louise Glassner Cohen, Pharm.D.*, Joseph Biederman, M.D., Susan Gilson, Pharm.D., Sabrina Whitt, Pharm.D., Jean Frazier, M.D., Janet Wozniak, M.D., Timothy E. Wilens, M.D., Thomas Spencer, M.D., Erick Mick, Sc.D.; Massachusetts General Hospital; Harvard Medical School, Boston, MA.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is the most widely diagnosed and researched neuropsychiatric disorder in children and adolescents. Despite the large number of published trials describing pharmacologic, psychosocial and educational interventions in children with ADHD, there are no data to describe the treatment of ADHD in girls. Recent research suggest that gender-related differences in the neuropsychological function in children with ADHD exist. These differences in function, coupled with developmental and gender-related differences in the pharmacokinetics of medications, may significantly influence the pharmacodynamics of medications in girls with ADHD and ultimately influence patient outcome.
PURPOSE: To describe the pharmacotherapy of ADHD in psychiatrically referred girls.
METHODS: Data from a total of 41 girls (33 children and 8 adolescents) referred to the Pediatric Psychopharmacology Unit between 1992 and 1996 for treatment by a board-certified child psychiatrist were retrospectively collected. All diagnostic assessments were based on DSM-III-R structured clinical interview and Kiddie-SADS-E, 4th version. Subjects had a history of lifetime and current ADHD and were treated in the clinic for more than one month.
RESULTS: The subjects were referred to the pediatric psychopharmacology unit for treatment of ADHD and comorbid disorders at a mean age of (mean ± SD) 9.7 ± 3.2 years. In addition to ADHD, 14 had major depressive disorder (34%), 17 had ODD (41%), 5 had bipolar II disorder (12%), 21 had one or more anxiety disorders (60%). Of these, 28 (65%) had received previous drug therapy; 20 (48%) had received therapy for ADHD, and of these, 13 (31%) had received stimulants. The average length of treatment captured was 646 ± 503.62 days, 21 (70%) are still treated in the clinic. Combined pharmacotherapy for the treatment of ADHD and comorbid disorders was common. Of the courses of treatment prescribed during the study, 18 (46%) subjects received therapy with only one medication, 27 (65%) received two medications, 18 (43%) received three medications and 6 (15%) received 4 medications at one time. Stimulants were the most frequently used medication (31 subjects; 75%), but were prescribed as monotherapy in only

13 (30%) subjects. Methylphenidate was prescribed in 31 subjects (75%) up to the maximal dose of 1.18 mg/kg (MPH). Clonidine, SSRIs, anxiolytics and mood stabilizers were combined with stimulants to address treatment resistance, to treat comorbid disorders or to treat adverse effects of medications.
CONCLUSIONS: In a sample of psychiatrically referred girls with ADHD, combined pharmacotherapy with stimulants and other medications is required to address treatment resistance, to treat comorbid disorders or to treat adverse effects of medications during long-term therapy.
Presented at the 39th Annual New Clinical Drug Evaluation Unit Meeting, Boca Raton, FL, June 1-4, 1999.

177. Characteristics of psychotropic medication use in South Australian extended care facilities. *Christopher P. Alderman, B.Pharm., FSHP, BCPP*, Maria Crotty, B.Med., FAFM, Craig Whithead, B.Med., FRACP; General Hospital, Daw Park, South Australia.

PURPOSE: To analyze characteristics of psychotropic drug usage in South Australian extended care facilities. This baseline data will be used to measure the effect of an academic detailing intervention directed at reducing falls in these facilities.
METHODS: Patterns of psychotropic drug prescribing and administration were examined for a cohort of 924 residents of randomly selected South Australian hostels and nursing homes. Data were collected by retrospective review of medication charts over a 14-day period.
RESULTS: The most commonly encountered psychotropic drugs were the benzodiazepines, prescribed for 408 (44%) of patients. Temazepam was the most prescribed psychotropic agent (n=269, 29%), with other commonly prescribed benzodiazepines being diazepam (n=68, 7.3%) and oxazepam (n=69, 7.4%). The option to administer benzodiazepines on a "when required" basis was specified in less than 50% of cases. Antipsychotic medication was prescribed for 222 subjects (23.9%), with pericyazine the most commonly used agent from this class (n=110, 11.8%). Prophylactic anticholinergic medication was available to less than 1% of subjects. Antidepressants were prescribed for 264 subjects (28.4%), with the most commonly used classes being tricyclic antidepressants (n=76) and serotonin reuptake inhibitors (n=106). In over 50% of cases, tricyclic antidepressants were prescribed at a dose of less than 50 mg. The most commonly prescribed antidepressant agent was sertraline (n=57).
CONCLUSION: Psychotropic drug use was prevalent in this cohort. Several characteristics of usage patterns may contribute to the likelihood of falls, and will be targeted in the intervention phase of the study.

177A. Outpatient SSRI dosing in the VA system. *John C. Voris, Pharm.D.*; University of South Carolina; Columbia, SC.

PURPOSE: The study was designed to answer the questions: What are the average outpatient doses of fluoxetine, paroxetine, and sertraline? What affects the changes in average daily cost, and is there dose escalation?
METHODS: Data were collected on more than 111,000 outpatient SSRI prescriptions from eight VA hospitals in three adjoining states. Data (average daily dose, cost and number of prescriptions for each drug) were divided into three six-month groups, covering a total of 2.5 years.
RESULTS: The average daily dose for fluoxetine decreased 18% throughout the study (30.9 mg/day to 25.3 mg/day). The cost of the drug only increased approximately 1%. The proportion of the 10 mg capsule used increased from 2.8% of the total fluoxetine prescriptions to 6.1%. Sertraline's average dose/day increased 8.4% from 87.8 mg/day to 95.2 mg/day. Drug cost increased 9.3%. The 100 mg tablet was used 75.6% initially, increasing to 80.1%. Paroxetine's daily dose of 24.2 mg/day increased to 25.1 mg/day (3.7% increase). Daily drug cost remained stable while the use of the 20 mg dose decreased from 96% of all paroxetine prescriptions to 82.1%.
CONCLUSION: Fluoxetine's dose decreased significantly, sertraline's increased. Fluoxetine's cost increase was due to greater use of the 10 mg capsule. Paroxetine's level cost is due to greater use of higher (level priced) strengths. Sertraline's cost increased due to higher dose and acquisition cost. Sertraline is the most prescribed SSRI.

178E. Risperidone versus haloperidol for prevention of relapse in schizophrenia and schizoaffective disorders: a long-term double-blind comparison. *John Csernansky, M.D.*, Akiko Okamoto, Sc.D., Martin Brecher, M.D., D.M.Sc.; Washington University, St. Louis, MO; Janssen Research Foundation, Titusville, NJ.

PURPOSE: A multicenter, randomized, double-blind comparison of risperidone (RIS) and haloperidol (HAL) in stable outpatient schizophrenics and patients with schizoaffective disorder was conducted to compare the time to relapse.
METHODS: Patients continued double-blind treatment until the last patient had completed 1 year. Assessments were made weekly for the first 4 weeks and at 4-week intervals thereafter. Scales used to assess efficacy included the total score on PANSS and all PANSS subscale scores. Safety evaluations included ESRS and clinical laboratory tests, including weight gain.
RESULTS: Of 365 treated patients in the trial, 41 (23.2%) in the RIS and 65 (34.6%) in the HAL groups relapsed by the end of the first year (p=0.009). During the entire trial, 45 (25.4%) patients on RIS and 75 (39.9%) patients on HAL relapsed (p=0.002). Patients in the RIS group experienced only a modest degree of weight gain (5.0 pounds at endpoint), a low rate of TD (0.6%), and a low rate of EPS.
CONCLUSIONS: This study provides evidence for the long-term effectiveness of RIS and corroborates earlier pivotal trials in which RIS was found to be significantly superior to HAL against both positive and negative symptoms of schizophrenia. Previous short-term trials have shown RIS to be statistically superior to HAL in the control of positive and negative symptoms. This trial confirms the superior efficacy of RIS over HAL in long-term treatment. Patients treated with RIS also experienced a desirable safety profile in long-term treatment.
Presented at 54th Annual Scientific Convention of the Society of Biological Psychiatry, Washington, DC, May 13, 1999.

Pulmonary

179. The role of nebulized magnesium sulfate in addition to standardized therapy with albuterol in the treatment of acute asthma exacerbations in adults. *Olga Bessmertny, Pharm.D.*, Henry Cohen, M.S., Pharm.D., Ellen Becker, Ph.D., Thomas Johnson, M.S., Darrell Looney, M.D., Jonathan Golden, M.D., Lewis Kohl, D.O., Robert V. DiGregorio, Pharm.D.; Shands Hospital at the University of Florida, Gainesville, FL; Long Island University; Brookdale University Hospital and Medical Center, Brooklyn, NY.

PURPOSE: To compare the efficacy and safety of alternating treatments of nebulized magnesium sulfate ($MgSO_4$) and albuterol to that of albuterol and normal saline in adult patients with mild-to-moderate acute asthma exacerbations.
METHODS: Patients were randomized to receive nebulized $MgSO_4$ (384 mg in 6 ml) or an equal volume of placebo (normal saline) in a double-blind fashion after each dose of nebulized albuterol (2.5 mg/3 ml) every 20 minutes for the first hour of the study. Spirometry was performed at baseline and every 20 minutes for two hours. Monitoring for safety included vital signs, pulse oximetry, and serum magnesium levels. Improvement in percent-predicted forced expiratory volume in first second (FEV_1) was chosen as a primary efficacy endpoint. Secondary efficacy endpoints included improvement in percent-predicted peak expiratory flow rate (PEFR) and rate of hospital discharge.
RESULTS: Seventy-four patients were equally randomized to each of the study groups. There were no statistically significant differences in baseline patient characteristics with exception of age, height, and weight. There were no statistically or clinically significant differences between two study groups in primary or secondary efficacy endpoints. There were no significant differences in vital signs, pulse oximetry or serum magnesium levels at any point during the study. The most common reported adverse events were dizziness, headache, somnolence, bitter taste of the study drug, and burning sensation in the throat.
CONCLUSIONS: The combination of nebulized $MgSO_4$ and albuterol provides no additional benefit over the standardized therapy with albuterol and normal saline in adult patients with mild-to-moderate asthma exacerbations.

Substance Abuse/Toxicology

180. Influence of smoking cessation on dehydroepiandrosterone and DHEA-sulfate concentrations. *Eric A. Wright, Pharm.D.*, Sherrie L. Aspinall, Pharm.D., Melissa McNeil, M.D., M. Maggie Folan, B.S.N., Roslyn A. Stone, Ph.D., Patricia D. Kroboth, Ph.D.; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: Acute cigarette smoking increases concentrations of adrenocorticotropic hormone (ACTH), which stimulates adrenal secretion of not only cortisol, but also dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S). Epidemiological studies have shown that DHEA-S, the most abundant hormone in the systemic circulation, is higher in habitual smokers than in nonsmokers. There have been no longitudinal studies to date describing DHEA and DHEA-S concentrations during the acute smoking cessation period. This study was designed to determine the effects of smoking cessation on serum concentrations of DHEA and DHEA-S in subjects enrolled in a smoking cessation clinic.
METHODS: We conducted a prospective, longitudinal, naturalistic study at the smoking cessation clinic of the VA Pittsburgh Healthcare System. Venous samples were obtained at weekly visits to determine DHEA and DHEA-S concentrations by radioimmunoassay.
RESULTS: Thirty-one subjects signed informed consent; 18 subjects quit smoking by self-report. Age-adjusted DHEA levels in quitters dropped an average of 0.6 ng/ml (CI = -1.3 ng/ml to 0.1 ng/ml; p=0.095) from baseline. Mean decreases from baseline in DHEA-S on weeks 1, 2, and 3 after quitting were 7%, 13%, and 16%, respectively.
CONCLUSIONS: These data from a small number of smokers are consistent with the hypothesis that smoking cessation is associated with a decrease in DHEA and DHEA-S shortly after smoking withdrawal. The decline in these

concentrations suggests that the management of the rate of decline in DHEA and DHEA-S concentrations may have a role in decreasing withdrawal symptoms and rates of relapses during smoking cessation. Larger investigational trials should be conducted to verify these hypotheses.

181. A pilot study on the impact of guideline implementation on the use of benzodiazepines in patients with a discharge diagnosis of alcohol withdrawal or delirium tremens. *Barbara S. Chong, Pharm.D.*, Sarah K. Warren, M.D., Charles R. Bonapace, Pharm.D., Kit Simpson, Dr.P.H.; Medical University of South Carolina, Charleston, SC.

PURPOSE: To determine whether treating patients with benzodiazepines (BZDs) based on symptoms will optimize outcome.
METHODS: A chart review was performed on all patients with a discharge diagnosis of alcohol withdrawal or delirium tremens prior to (July 1998 to February 1999, n=18) and following (March to June 1999, n=9) implementation of a treatment protocol based on Clinical Institute Withdrawal Assessment-Alcohol revised scores. The protocol was not applied during intensive care unit (ICU) stays. Data collected included demographics, daily lorazepam equivalents, days receiving benzodiazepines, length of stay (LOS), and outcome (e.g., seizure, hallucination). Data collection post-protocol is ongoing.
RESULTS: Pre-protocol versus post-protocol, patients were well matched by age and gender with LOS of 5 versus 8 days. The median lorazepam equivalents on days BZDs were administered were 4.2 and 9.9 mg/day pre-protocol and post-protocol, respectively. Although the median number of days receiving BZDs increased from 5 to 7 days post-protocol, the BZD days/LOS (%) decreased from 100% to 88%. Pre-protocol, 11% (2/18) of patients were admitted to the ICU versus 56% (5/9) post-protocol. For patients never treated in the ICU, the median lorazepam equivalents on days BZDs were given increased post-protocol from 4.2 to 5.3 mg/day (n=15 versus n=4), whereas the median BZD days/LOS (%) decreased from 100% to 50%. Seizure rates pre-protocol and post-protocol were 27% and 25%, respectively, while rates of delirium tremens declined post-protocol (40% versus 25%). Generally, restraint use, hallucinations and over-sedation increased post-protocol independent of whether patients were treated in the ICU.
CONCLUSIONS: Patients post-protocol had increased rates of admission to the ICU probably representing a sicker population. Trends were seen toward both improved and worsened outcomes post-protocol and additional post-protocol data is needed.

182E. Detection of the novel metabolite ethylphenidate after methylphenidate overdose with ethanol coingestion. John S. Markowitz, Pharm.D., Barry K. Logan, Ph.D., Fran Diamond, B.S., *Kennerly S. Patrick, Ph.D., FCP*; Medical University of South Carolina, Charleston, SC.

PURPOSE: To determine whether the transesterification pathway known to convert cocaine (benzoylecgonine methyl ester) and ethanol to the toxic metabolite cocaethylene (benzoylecgonine ethyl ester) in humans will similarly convert structurally related methylphenidate (ritalinic acid methyl ester) to ethylphenidate (ritalinic acid ethyl ester) when dosed with ethanol.
METHOD: Postmortem blood samples from two methylphenidate/ethanol overdoses were analyzed by a method developed for this study. After solid phase extraction, samples were analyzed by liquid chromatography-mass spectrometry using a deuterated internal standard and selected monitoring of analyte molecular ions.
RESULTS: This method provided a < 0.5 ng/ml limit of quantitation for ethylphenidate and a calibration plot linearity of r=0.9998. The chromatograms were free of significant interferences. In case 1, ethylphenidate and methylphenidate blood concentrations were 8 and 310 ng/ml, respectively. In case 2, the corresponding values were 1 and 1600 ng/ml.
CONCLUSIONS: The new metabolite ethylphenidate was detected after fatal methylphenidate overdoses with ethanol coingestion. Ethylphenidate is an active catecholamine transporter inhibitor whose metabolic formation would be expected to contribute to central nervous stimulation, as well as to sympathomimetic side effects. The doses of methylphenidate and ethanol are unknown in the above two fatalities. The extent of ethylphenidate formation under controlled conditions is presently being investigated in human volunteers in order to establish whether this biotransformation pathway represents the basis of a potentially significant drug-drug interaction.
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183. Effect of intensive pharmacist counseling in a university-based smoking cessation program. *John M. Conry, Pharm.D.*, Tina J. Kanmaz, Pharm.D., Sheila Botts, Pharm.D.; Wilkes University, Wilkes-Barre, PA; St. John's University, Jamaica, NY.

PURPOSE: Evaluate the effect of intensive pharmacist counseling on smoking abstinence rates and depression in a university-based population.
METHODS: This was an 8-week randomized, pilot study with 6-month follow-up. Subjects were assigned to receive intensive smoking cessation counseling by a trained pharmacist or no counseling. Subjects were smokers and ≥ 18 years old. Baseline measurements included Beck Depression Inventory (BDI) and exhaled carbon monoxide (CO). All subjects received daily nicotine transdermal patches and attended weekly sessions to assess smoking status, CO, and BDI. In addition, counseled subjects attended weekly, 30-minute sessions, focusing on skills training and relapse prevention. The primary outcome was abstinence at end of treatment (EOT) and 6 months.
RESULTS: Twenty-three subjects were included (11 counseled, 12 non-counseled). Mean age 34 ± 13 years, 10 (44%) females, 15 (65%) Caucasian. Mean cigarettes/day: 20 ± 9; mean years smoked: 16 ± 12. Approximately 70% of subjects had 1-4 previous quit attempts. A total of 9 (39%) and 14 (61%) subjects had dropped out at EOT and 6 months, respectively. At EOT, 5 (46%) counseled and 4 (33%) non-counseled subjects were abstinent (p=0.680). At 6 months, 2 (18.2%) counseled and none of the non-counseled subjects were abstinent (p=0.217). BDI scores for each treatment group were comparable and within normal limits.
CONCLUSION: Intensive smoking cessation counseling by a pharmacist non-significantly increased abstinence rates compared to non-counseled subjects. The small sample size limited our ability to detect a significant difference. Larger studies are needed to evaluate the impact of pharmacist counseling on abstinence rates.

184. Safety of bupropion in patients with co-existing medical and/or psychiatric conditions. *Mary T. Roth, Pharm.D.*, Eric C. Westman, M.D., M.H.S.; University of North Carolina-Chapel Hill, Chapel Hill, NC; Durham VAMC; Duke University Medical Center, Durham, NC.

PURPOSE: Bupropion (Zyban®) has been shown to be an effective agent for smoking cessation. However, prior studies have primarily involved generally healthy smokers. The purpose of this study was to describe our experience with bupropion in smokers who have co-existing medical and psychiatric disorders.
METHODS: Subjects were referred by their physician for treatment with bupropion 150 mg twice daily for 8 weeks. Subjects had to be smoking at least 10 cigarettes/day and motivated to quit smoking. Exclusion criteria included a presence or history of seizures, anorexia, bulimia, and current use of a bupropion hydrochloride, a MAO inhibitor, or nicotine replacement therapy. Telephone follow up was performed by a pharmacist on or around the quit date and periodically thereafter for eight weeks. Subjects returned to clinic for an 8-week and a 6-month follow up.
RESULTS: Seventy subjects met both inclusion and exclusion criteria and were treated with bupropion Ninety-six percent were men with a mean age of 54.0 years (SD = 10.1) who smoked a mean of 20.8 cigarettes per day (SD = 13.0). Sixty-four percent had co-existing medical conditions, including hypertension, coronary artery disease, and chronic obstructive pulmonary disease. Thirty-seven percent were receiving treatment for psychiatric diagnoses, including depression, post traumatic stress disorder, and bipolar disorder. Mild adverse effects (dry mouth, insomnia, bad taste) were noted in approximately 14% of subjects. One subject with bipolar disorder experienced precipitation of his mania on 150 mg twice daily of bupropion which resolved after reducing his dose to 150 mg daily.
CONCLUSIONS: Bupropion appears safe for smoking cessation in patients with co-existing medical and psychiatric conditions; however, careful monitoring may be prudent in those with underlying agitation, irritability, and mania.

Transplantation/Immunology

185. Effect of pharmaceutical care services on the blood pressure of renal transplant patients. *Marie A. Chisholm, Pharm.D.*, Leslie J. Vollenweider, Pharm.D., Bess O. Reinhardt, Pharm.D., Bradley C. Martin, Ph.D., Holly E. Rogers, Pharm.D. candidate, J. Russell May, Pharm.D., Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: To determine the influence of pharmaceutical care services on renal transplant patients' systolic and diastolic blood pressures.
METHODS: Renal transplant patients at the Medical College of Georgia Renal Transplant Clinic were prospectively randomized into an intervention group or a control group. Patients in the intervention group received pharmaceutical care services which included ongoing medication reviews, with emphasis on preventing or resolving medication-related problems and providing pharmacotherapy recommendations. Patients in the intervention group interacted with the renal transplant clinical pharmacist at least monthly. Patients in the control group received routine clinic services but had no clinical pharmacist interaction. At each clinic visit, patients in both arms of the study underwent a physical exam which included blood pressure measurements. Analysis to detect differences in baseline and quarterly systolic and diastolic blood pressures between the intervention and control groups was performed for all patients who were enrolled in the trial for at least 15 months.
RESULTS: Thirty-three patients were included in the analysis, 18 in the intervention group and 15 in the control group. The groups were similar in sex, age, race, kidney donor type, the number of hypertensive patients, and baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP). Patients in the intervention group had a mean SBP/DBP change of -8 mm Hg/-

2 mm Hg, -12 mm Hg/-7 mm Hg, -11 mm Hg/-9 mm Hg, and -7 mm Hg/-4 mm Hg for the first, second, third and fourth quarters of the study, respectively. Patients in the control group had a mean SBP/DBP change of -6 mm Hg/-1 mm Hg, +8 mm Hg/+3 mm Hg, +8 mm Hg/+2 mm Hg, and +10 mm Hg/+5 mm Hg for the first, second, third and fourth quarters of the study, respectively. No significant differences in change scores from baseline for SBP and DBP were observed at the first quarter. Significant differences in change scores from baseline for SBP and DBP between the intervention and control groups were observed at the second, third, and fourth quarters of the study ($p<0.05$).
CONCLUSION: Renal transplant clinic patients who received pharmaceutical care services in addition to routine clinic services had greater reductions in blood pressure than patients who did not receive pharmaceutical care services. Pharmaceutical care services in a renal transplant clinic have a positive impact on patients' blood pressure control.

186. Absence of nephrotoxicity with the concomitant use of amphotericin B lipid complex and cyclosporine. *Steven P. Gelone, Pharm.D.,* the CLEAR Steering Committee; Temple University, Philadelphia, PA.

PURPOSE: Transplant patients who receive the immunosuppressive agent cyclosporine are at risk for fungal infections that may require treatment with amphotericin. Since both drugs are nephrotoxic, the impact of the concurrent use of cyclosporine and amphotericin B lipid complex (ABLC) was assessed.
METHODS: The CLEAR™ database, representing data from patients treated with ABLC since commercial release, was queried to identify patients who concomitantly received cyclosporine. Creatinine values were assessed prior to and at the completion of therapy to assess the nephrotoxicity potential of combination therapy.
RESULTS: Data were available from 2285 patients treated with ABLC since January 1996. Of these, 427 (19%) also received concomitant cyclosporine. Of the 427 patients, 238 (56%) underwent recent allogeneic stem cell transplantation, while 116 (27%) had a solid transplant. ABLC was given empirically to 44% (189/427), while 66% received drug for a specified fungal diagnosis most often aspergillosis (103/427, 24%) or candidiasis (110/427, 26%). The median dose of ABLC was 4.8 mg/kg/day (range 0.7-11.2 mg/kg/day) for a median duration of 17 days (range 4-201 days). For all patients who received concomitant cyclosporine, the median baseline serum creatinine was 1.5 mg/dl (range 0.1-7.1 mg/dl) and the median end-of-therapy creatinine was 1.7 mg/dl (range 0.1–6.7 mg/dl). For allogeneic stem cell transplant recipients who received both drugs, despite receiving an average duration of ABLC treatment of 19 days, the median change in creatinine was only + 0.3 mg/dl.
CONCLUSIONS: Concomitant ABLC and cyclosporine administration in the treatment of fungal infections is tolerated without significant increases in serum creatinine.

187. Comparison of the pharmacokinetics of rapamycin liquid and tablet formulations in renal transplant recipients. *Patrick A. Kelly, Pharm.D.,* Reginald Frye, Pharm.D., Ph.D., Kimberly L. Napoli, Ph.D., Lisa Kalloch, B.S.N., Barry D. Kahan, Ph.D., M.D.; University of Houston; University of Texas-Houston, Houston, TX; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: Clinical trials investigating the new immunosuppressant rapamycin (Rapamune®) have thus far utilized an oil-base liquid formulation (L-RAPA). Recently, a new tablet formulation of rapamycin (T-RAPA) has begun clinical trials. In this study, we compared the steady-state pharmacokinetics of L-RAPA to that of T-RAPA administered de novo to renal transplant recipients.
METHODS: Subjects were randomized to receive either L-RAPA (n=13) or T-RAPA (n=11) as part of a multicenter clinical trial comparing the efficacy of the two formulations. At our center, 24-hour pharmacokinetic profiles were conducted after two weeks de novo rapamycin dosing (2 mg q24h). Whole-blood samples were drawn immediately prior to and at 1, 2, 3, 5, 8, 12, and 24 hours post-dosing. Rapamycin concentrations were determined by HPLC. Comparisons between L-RAPA and T-RAPA were by Student's t-test.
RESULTS: The RAPA $AUC_{0\text{-}24}$ of L-RAPA was similar to that of T-RAPA (145.5 ± 103.5 vs 152.1 ± 51.9 ng•hr/ml, respectively) suggesting similar relative bioavailability. Additionally, there were no differences between the two formulations for C_0, C_{24}, C_{max}, or C_{ave} values. There was, however, a significant difference in the percent fluctuation between the observed C_{max} and C_0 values for the two formulations. L-RAPA fluctuation was higher at 223 ± 127.2% compared to 121.2 ± 63.2% for T-RAPA ($p = 0.02$).
CONCLUSIONS: Steady-state pharmacokinetic parameters for L-RAPA were not different when compared to those of T-RAPA. However, the lower percent fluctuation of T-RAPA may provide more consistent immuno-suppressive exposure over the dosing interval and over the long term.

188. Efficacy of daclizumab versus muromonab CD3 in preventing acute rejection in kidney and kidney/pancreas transplant recipients at high risk of allograft dysfunction. *Jeong M. Park, Pharm.D., M.S.,* David I. Min, Pharm.D., M.S., Muralikrish S. Golconda, M.D., Stephen C. Rayhill, M.D., You-Min Wu, M.D.; University of Iowa, Iowa City, IA.

PURPOSE: To compare the efficacy of daclizumab (DCZ) and muromonab CD3 (OKT3) in preventing acute rejection (AR) when used as an induction agent in kidney and kidney/pancreas transplant recipients, thought to be at risk of delayed allograft function or AR.
METHODS: We retrospectively reviewed 199 cadaveric kidney and kidney/pancreas transplant cases (age ≥ 18 years) in University of Iowa Hospitals and Clinics from January 1996 to February 1999. Patients who received investigational immunosuppressants were excluded. By our protocol for high-risk group, either OKT3 (5 mg/day for 7-10 days) or DCZ (2 mg/kg body weight immediately prior to transplant, followed by 1 mg/kg body weight on post-operative day 5) was initiated and cyclosporine or tacrolimus was deferred until allograft function was improved. Main outcomes measured were incidence of AR and infection during the first 3 months after transplantation.
RESULTS: A total of 64 patients (32 in DCZ, 32 in OKT3) met the selection criteria. The two groups were comparable with regard to gender, number of patients receiving multiple transplantation, and immunosuppressive regimen. Mean ages of patients in the two groups were different (45.9 ± 13.6 years [DCZ] vs 38.2 ± 8.0 years [OKT3], $p<0.05$).

	DCZ	OKT3	p value
Cumulative dose per patient (Mean ± SD)	3.0 ± 0.9 mg/kg	38.3 ± 10.8 mg	-
AR within 3 months	6/32 (18.8%)	12/32 (37.5%)	0.09
Infection within 3 months	17/32 (53.1%)	14/32 (43.8%)	0.45

Although there was a trend toward lower incidence of AR in DCZ, it did not reach statistical significance ($p<0.05$). One patient in DCZ lost a kidney due to ischemic damages from severe hypotension on post-operative day 15, compared to none in OKT3. There were no patient deaths in either group during the first 3 months.
CONCLUSIONS: In kidney or kidney/pancreas transplant recipients at high risk of allograft dysfunction, induction therapy with DCZ was as efficacious as that with OKT3 in prevention of AR without increasing incidence of infection during the first 3 months. A further study on cost effectiveness of DCZ versus OKT3 is ongoing.

189. The comparison of mycophenolate mofetil to azathioprine for the prevention of acute graft rejection in pancreas transplant patients. *Jung Mi Oh, Pharm.D.,* Paul J Weidle, Pharm.D., Anne M. Wiland, Dave Klassen, M.D., University of Maryland Medical System.

PURPOSE: The study was performed to compare the efficacy of mycophenolate mofetil (MMF) and azathioprine (AZA) within a standard immunosuppressive regimen for the prevention of acute allograft rejection during the first 6 months after simultaneous pancreas kidney (SPK), pancreas after kidney (PAK) or pancreas transplant alone (PTA) pancreas transplantation.
METHODS: In this case-controlled study, MMF is compared to historical controls of AZA in the prevention of acute pancreas rejection in two different but comparable periods for patients receiving pancreas transplants. The primary endpoint was treatment failure, defined as the occurrence of biopsy proven graft rejection, graft loss, patient death, or discontinuation of the study drugs. Adverse drug events or infection during the first 6 months after transplant were also compared.
RESULTS: A total of 101 pancreas transplant patients were evaluated. In addition to AZA (n=57) or MMF (n=54), patients received calcineurin inhibitors (CsA or tacrolimus), corticosteroid, and antilymphocyte therapy (OKT3 or ATGAM) as part of quadruple induction protocol. Comparison for the primary efficacy endpoint showed that significantly fewer ($p<0.05$) proportion of patients had biopsy proven rejection episodes during the first 6 months after transplantation with MMF (46%) than with AZA (69%). Time to first biopsy proven rejection episode or treatment failure was longer for MMF versus AZA. Patients in the AZA group received a greater number of full courses of antirejection treatment as compared with the MMF. At 6 months after transplant, graft and patient survival were similar between the groups. Overall, the frequency of adverse events and discontinuation from the study drugs were similar between the groups, although MMF group experienced higher incidence of gastrointestinal adverse events and CMV disease.
CONCLUSION: MMF significantly reduced the rate of biopsy proven rejection during the first 6 months after pancreas transplantation and was well tolerated.

190. Evaluation of the efficacy and cost of cytomegalovirus immune globulin after lung transplantation. *Deb S. Sherman, Pharm.D.,* Douglas N. Fish, Pharm.D., Tony N. Hodges, M.D., Marty R. Zamora, M.D.; University of Colorado Health Sciences Center; University Hospital, Denver, CO.

PURPOSE: Cytomegalovirus (CMV) is a major cause of morbidity following lung transplant (LTX) with an incidence of 60-85%. The purpose of this study was to determine the cost-effectiveness of CMVIG in preventing CMV infection after LTX.
METHODS: A retrospective case-controlled analysis of all LTX between 1992 and 1998 was performed. Patients expiring less than 30 days after or prior to discharge from the LTX admission, or at low risk for CMV infection (CMV-negative donor and recipient) were excluded. All patients received CMV

prophylaxis with CMVIG 150 mg/kg on post-LTX day 1 and 100 mg/kg on days 15 and 30, plus IV ganciclovir for 28 days; donor+/recipient- patients received CMVIG for 7 doses and ganciclovir for 100 days. CMV infection included either syndrome/viremia or disease. Cost analysis included actual costs (LTX admission excluded) for the first year post-transplant.
RESULTS: Efficacy of CMVIG was evaluated in 102 patients. The first year incidence of CMV infection was 25%. Based on our institution's historical incidence of CMV prior to CMVIG (75%), 77 cases would have been expected rather than the 25 observed. Cost data was available for 34 patients. Mean ± SD costs in patients with and without CMV infection were $85,174 ± 67,819 versus $49,526 ± 59,976 per patient, respectively (p=0.18). Based on an excess of $35,648 per patient with CMV infection, the savings in 52 prevented cases was $1,853,696.
CONCLUSIONS: CMV infection is associated with substantially increased costs in the first year post-transplant. Combination therapy of CMVIG and ganciclovir provides cost-effective prophylaxis for CMV following LTX.

190A. Conversion from Sandimmune® to SangCya™ and Neoral® oral solution: results of a double-blind, randomized, crossover study of cyclosporine pharmacokinetics in stable cardiac allograft recipients. *Jeffrey A. Haroldson, Pharm.D.*, Kathleen D. Lake, Pharm.D., Maria-Teresa Olivari, M.D., Marc R. Pritzker, M.D., Robert W. Emery, M.D.; University of Michigan Medical Center, Ann Arbor, MI; Abbott Northwestern Hospital/Minneapolis Heart Institute, Minneapolis, MN.

PURPOSE: SangCya™ is an FDA-approved modified cyclosporine (CyA) formulation rated AB to Neoral® oral solution. SangCya™ and Neoral® have been shown to be bioequivalent in healthy volunteers and in renal and hepatic transplants, but both have higher bioavailability than Sandimmune®. We assessed CyA pharmacokinetics (PK) in transplant patients when they were receiving Sandimmune® and after conversion to SangCya™ and Neoral®.
METHODS: Stable cardiac transplant patients on Sandimmune® were assigned to receive SangCya™ and Neoral® in a double-blind, randomized, single-center, crossover study. Steady-state CyA PK were evaluated after administration of Sandimmune®, SangCya™ and Neoral®. PK parameters were derived from CyA levels (measured by TDx assay) collected over 12 hours.
RESULTS: Seven (7) stable cardiac transplant recipients (4M/3F; mean ± SD age 60 ± 5 years) were studied. All patients were receiving stable CyA (Sandimmune®) dosages prior to enrollment. There were no significant differences in PK parameters (p>0.05, Wilcoxon sign rank test) or serum creatinine levels (1.4 ± 0.3 vs 1.4 ± 0.4) between SangCya™ and Neoral®, respectively. Both SangCya™ and Neoral® demonstrated significantly faster absorption than Sandimmune® (T_{max} p<0.02). No allograft rejections or patient deaths were observed.

PK Parameters	SangCya™	Neoral®	Sandimmune®	p value*
AUC_{0-12} (ng•h/ml)	4096 ± 594	4103 ± 587	3840 ± 997	0.81
C_{max} (ng/ml)	683 ± 166	670 ± 202	673 ± 221	0.94
T_{max} (h)	1.4 ± 0.5	1.6 ± 0.5	4.6 ± 2.2	0.38

*SangCya™ vs Neoral®

CONCLUSIONS: SangCya™ and Neoral® oral solutions demonstrate similar PK parameters, and both have different blood concentration-time profiles to Sandimmune® in stable cardiac allograft recipients. There is no difference in safety between SangCya™ and Neoral®, based on laboratory and clinical evaluations.

191E. Bioequivalence between two modified cyclosporine oral solutions (SangCya™ and Neoral®) regardless of assay methodology or ingestion of a high fat meal. *Gary L. Chan, Pharm.D.*, William Irish, Ph.D., Daniel M. Canafax, Pharm.D.; SangStat Medical Corporation, Menlo Park, CA.

PURPOSE: We undertook this study to determine what, if any, effect assay methodology had on determination of bioequivalence between two modified cyclosporine (CyA) oral solutions (SangCya™ and Neoral®).
METHODS: A randomized, 3-period crossover study was conducted in 19 healthy volunteers. In each crossover period, each subject received a single 500 mg dose of CyA oral solution: SangCya™ after a high-fat meal, Neoral® after a high-fat meal, or SangCya™ under fasting conditions. Serial blood samples were collected, and whole blood CyA concentrations were determined using TDx, EMIT, and HPLC/MS/MS.
RESULTS: Mean ± SD CyA pharmacokinetic parameters, as measured by 3 different assays, for the 3 treatments were:

	Parameter	TDx	EMIT	HPLC/MS/MS
C_{max}	SangCya™, fed(A)	1670 ± 332	1560 ± 416	1326 ± 272
(ng/ml)	Neoral®, fed (B)	1710 ± 364	1590 ± 417	1413 ± 351
	SangCya™, fasted(C)	1680 ± 294	1510 ± 243	1344 ± 260
	90% CI (A/B)	91-104	87-105	87-101
	90% CI (A/C)	93-106	93-112	92-105
$AUC_{0-\infty}$	SangCya™, fed(A)	15600 ± 2870	13000 ± 2730	10720 ± 2334
(ng•hr/ml)	Neoral®, fed (B)	15300 ± 2870	12600 ± 2500	10760 ± 2520
	SangCya™, fasted(C)	14600 ± 2810	11800 ± 2670	9945 ± 2311
	0% CI (A/B)	96-105	96-107	95-103
	0% CI (A/C)	103-111	104-116	104-113

90% CI = 90% confidence interval, based on log-transformed data

Irrespective of the assay used, bioequivalence was demonstrated between SangCya™ and Neoral® under fed conditions , and between SangCya™ under fasted and fed conditions. TDx and EMIT yielded blood CyA concentrations that were 50% and 15%, respectively, higher than HPLC/MS/MS.
CONCLUSIONS: SangCya™ and Neoral® oral solution are bioequivalent in healthy volunteers, regardless of the CyA assay method used. Moreover, high-fat meal ingestion does not significantly affect CyA absorption after oral administration of SangCya™.
Presented at the Minneapolis Transplant Congress, Minneapolis, MN, October 20-23, 1999.

192E. Cyclosporine metabolite pharmacokinetics and tolerability in stable hepatic allograft recipients comparing SangCya™ and Neoral® oral solutions. *Shi-Hui Pan, Pharm.D.*, Victor Sunga, M.D., Linda Sher, M.D., Allen Hoffman, M.D., Sergio Rojter, M.D., Richard Lopez, M.D.; Comprehensive Liver Disease Center, Los Angeles, CA.

PURPOSE: We evaluated the pharmacokinetics (PK) of cyclosporine (CyA) and its metabolites and assessed the clinical tolerability after long-term administration of SangCya™ and Neoral® in stable liver transplant (LT) recipients. Bioequivalence has been demonstrated between SangCya™ and Neoral® in this patient population.
METHODS: SangCya™ and Neoral® were administered in a randomized, double-blind, 2-period crossover study. Each period consisted of 7 days of SangCya™ or Neoral® at the same dosage. PK of CyA and its metabolites were measured using an HPLC assay. After day 15, the second assigned formulation was administered for 12 months in a blinded fashion for evaluation of long-term tolerability.
RESULTS: Twenty-six patients were enrolled and 21 have completed 12-month follow up. At enrollment, age (mean ± SD) was 53 ± 10 years, and the mean time posttransplant was 4.5 years. Mean PK parameters of CyA, AM1 and AM9 are shown below. There were no significant differences (p>0.05, Anova) between SangCya™ and Neoral®.

	CyA (n=22)		AM1 (n=22)		AM9 (n=22)	
	SangCya™	Neoral®	SangCya™	Neoral®	SangCya™	Neoral®
C_{max} (ng/ml)	460 ± 141	521 ± 223	229 ± 133	240 ± 99	126 ± 47	147 ± 67
C_{min} (ng/ml)	217 ± 117	191 ± 62				
T_{max} (h)	3.2 ± 1.0	2.9 ± 1.1	3.8 ± 1.4	3.8 ± 1.6	4.1 ± 1.9	3.5 ± 1.2
AUC_{0-12} (ng•h/ml)	2988 ± 1084	3188 ± 1189	1997 ± 1131	2051 ± 925	819 ± 413	920 ± 442

There have been no graft losses or allograft rejections during the 12-months following enrollment (part II). Mean ± SD CyA daily dose (mg/day), serum creatinine levels (mg/dl), ALT (u/L), and bilirubin (mg/dl) were similar (p>0.05) between patients receiving SangCya™ and Neoral® at 12 months.

	CyA dose	Creatinine	ALT	Total Bilirubin
SangCya™ (n=10)	217 ± 117	1.5 ± 0.7	35 ± 35	0.8 ± 0.6
Neoral® (n=11)	191 ± 62	1.4 ± 0.4	62 ± 52	0.9 ± 0.5

CONCLUSIONS: SangCya™ and Neoral® demonstrate comparable PK of CyA and its metabolites, as well as similar clinical tolerability in stable LT recipients. The results suggest that these two CyA formulations are interchangeable.
Presented at the 18th Annual Meeting the American Society of Transplantation, Chicago, IL, May 15-19, 1999.

Women's Health

193. Peak expiratory flow rates and premenstrual symptoms in healthy non-asthmatic females. *Elaine Chong, B.S.*, Mary H.H. Ensom, Pharm.D., FASHP, FCCP; University of British Columbia; Children's and Women's Health Centre of British Columbia, Vancouver, BC, Canada.

PURPOSE: To characterize intra- and inter-subject and diurnal variability in peak expiratory flow rates (PEFR) of healthy non-asthmatic females over at least one complete uninterrupted menstrual cycle; to determine whether a relationship exists between PEFR and premenstrual symptoms in healthy non-asthmatic females; to provide a unique opportunity to educate female pharmacy students via interactive study participation.
METHODS: Forty healthy non-asthmatic female pharmacy students were enrolled and 31 (age 22.1 ± 1.5 years, mean length of menstrual cycle 29.0 ± 2.3 days) completed the study. During the longitudinal, investigator-blinded 9-week study, the subjects were followed for two menstrual cycles with at least one uninterrupted cycle. Throughout the study period, each woman recorded premenstrual symptom questionnaire scores (15 mood and physical symptoms, graded 0-3 severity) daily. The subjects also measured and recorded PEFR (three consecutive attempts) every morning and every evening.
RESULTS: Over half of the subjects (58.1%) showed classic patterns of premenstrual symptoms, whereas PEFR fluctuated randomly over the course of the cycle. The average coefficients of variation (CV) for intra-subject variability were 4.17 ± 2.09% for morning PEFR, 3.97 ± 2.25% for evening PEFR, and 3.72 ± 2.55% for mean daily PEFR. The CV for inter-subject variability was 14% for morning, evening, and mean daily PEFR. The average absolute diurnal variation was 17.13 ± 12.46 L/min and the relative diurnal variation was 3.98 ± 2.52%. Only 14 of 124 (11.3%) correlations between

PEFR and premenstrual symptoms were significant ($p<0.05$).
CONCLUSIONS: Intra- and inter-subject variability in PEFR is minimal in non-asthmatic females; similarly, diurnal variation in PEFR also is low. The menstrual cycle appears to have little effect on pulmonary function in healthy non-asthmatic females. Pharmacy students who take part in serial PEFR monitoring gain a new appreciation for asthma and asthmatic patients.

Clinical Pharmacy Forum

These abstracts describe the delivery, development, justification, or documentation of innovative clinical pharmacy services; they may be descriptive only and need not contain an evaluative component.

194. A retrospective analysis of cisapride use in an adult ambulatory population: implications for formulary removal. *Martin R. Giannamore, Pharm.D.*, Bella Mehta, Pharm.D., Ruth E. Emptage, Pharm.D.; The Ohio State University, Columbus, OH.

PURPOSE: This drug use evaluation (DUE) was conducted to monitor physicians' adherence to the manufacturer's warnings, precautions, and contraindications regarding cisapride use in our health center network.
METHODS: Medical records of 23 patients receiving cisapride were retrospectively evaluated for the following parameters: presence of interacting drugs (as listed in the prescribing information); presence of disease states or conditions for which cisapride is contraindicated or likely to increase the risk of cardiac dysrhythmias; and, documented trial of alternative GI medications (e.g., metoclopramide, H_2-antagonists, proton pump inhibitors).
RESULTS: Drug interaction data was classified as follows: two patients (9%) were receiving concomitant agents which could have produced major (life-threatening) interactions; three patients (13%) were receiving agents which could have produced moderate (increasing morbidity) interactions; and, thirteen patients (57%) were receiving agents which could have produced minor interactions. Four patients (17%) had drug-disease interactions which increase the risk of cardiac dysrhythmias. Cisapride was utilized as a first-line agent for the treatment of gastroesophageal reflux disease (GERD) in 13 (57%) of patients evaluated.
CONCLUSION: The use of cisapride in our population placed a substantial number of patients at risk for drug-drug and drug-disease interactions. This data was presented to the Pharmacy and Therapeutics Committee and resulted in removal of cisapride from the formulary. In addition, this DUE provides opportunities for medical staff education regarding drug interactions and the pharmacotherapy of GERD.

195. Utilization of glycoprotein IIb/IIIa receptor antagonists, its relationship to patient characteristics and outcomes. *Judy W.M. Cheng, Pharm.D., BCPS*, Karin A. Greenberg, Pharm.D., Bernard Mehl, DPS; Mount Sinai Medical Center, New York, NY; Long Island University, Brooklyn, NY.

PURPOSE: To describe the utilization of glycoprotein IIB/IIIA inhibitors (GP2b3a) in a tertiary care center; to evaluate whether patient characteristics, cardiovascular risk factors, and coronary interventions affect physicians' selection of GP2b3a. To justify the necessity for maintaining three GP2b3a on formulary.
METHODS: Medical records of 100 patients admitted with acute ischemic coronary syndrome (AICS) were reviewed. Patient demographics, past medical history, coronary intervention and outcomes were recorded. These parameters were compared among groups using chi squared or ANOVA.
RESULTS: Important demographics, coronary intervention and outcomes are summarized below. Patients who received 2 GP2b3a were in a research study. Data reviewed that our institution is a high volume intervention center. Most GP2b3a were used for procedures. If abciximab and either eptifibatide or tirofiban were kept on formulary, a cost of $1500 per 100 patients will be saved with abciximab and eptifibatide based on our population.

	Abciximab (n=29)	Eptifibatide (n=7)	Tirofiban (n=48)	Abciximab + Tirofiban (n=16)	p value
Age (years)	67 ± 12	63 ± 13	66 ± 13	60 ± 11	NS
Framingham risk score for developing ischemic heart disease	12 ± 3	11 ± 5	10 ± 4	9 ± 4	NS
Indications					NS
Intervention	29	7	42	16 (abciximab)	
AICS	0	0	6	16 (tirofiban)	
Angioplasty, stent, atherectomy, bypass	26, 26, 4,0	6, 7, 1, 0	35, 36, 8, 6	13, 11, 2, 2	NS
Arrhythmia, major bleeding, death, thrombocytopenia	1, 0, 0, 0	1, 0, 0, 0	2, 2, 1, 4	0, 0, 1, 2	NS

CONCLUSIONS: Patient characteristics, risk factors and interventions did not determine selection of GP2b3a. Since we are a primary intervention institution, maintaining all three agents on formulary may not be justified.

196. An innovative pharmacy program improves management of cholesterol in patients with coronary artery disease. Lisanne DiTusa, Pharm.D., Aileen Bown Luzier, Pharm.D., Marc Reinhardt, Gary Brady, B.S., Brian D. Snyder, M.D.; State University of New York at Buffalo; Health Care Plan, Buffalo, NY.

PURPOSE: To assess the impact of a pharmacy-based cholesterol management program in a health maintenance organization.
METHODS: We developed a program to evaluate and manage cholesterol in patients with documented coronary artery disease (CAD). During routine visits to the pharmacy for medication refills, patients designated as CAD were enrolled in the program. After patient interview and review of medical records, a physician report was completed by the pharmacist which detailed an assessment of available fasting lipid profiles (FLP) and therapy recommendations. Medication recommendations were sensitive to the cost effectiveness of the various agents. After physician approval, the pharmacist implemented therapy changes and monitoring. At subsequent visits, all patients received medication counseling and dietary reinforcement, and were informed about their FLP. Regardless of cholesterol status, all patients enrolled in the program were followed to ensure quality of care.
RESULTS: Initial assessment of the first 300 patients enrolled in the program showed only 50% of patients had appropriate FLP monitoring by their physician, 60% of patients were receiving cholesterol medication and 33% of patients had achieved target cholesterol. Four months after program implementation, FLPs were available for > 96% of patients, 72% of patients were on medication and 71% were at target cholesterol, with mean (SD) LDL of 98 (± 18). This was associated with a mean increase in drug costs of $3 per patient per month.
CONCLUSION: Capitalizing on the pharmacist-patient interaction in this setting provides improved cholesterol management in a large number of CAD patients with a minimal increase in drug cost.

197. Impact of pharmacist home visits on medication appropriateness in geriatrics. *Michele A. Schrecengost-Kibbey, B.S.*, Richard J. Ptachcinski, Pharm.D., FCCP, Amy L. Tuttle MBA; University of Pittsburgh Medical Center, Pittsburgh, PA.

High medication use in the elderly increases their risk of receiving inappropriate drugs or experiencing drug-related problems (DRPs). The Living-at-Home Program (LAHP) is a case management program for individuals ≥ 70 years old living in the Pittsburgh area that has existed for eleven years and has recently added a pharmacist to the staff.
PURPOSE: Evaluate the impact of a pharmacist making home visits on medication appropriateness.
METHODS: The pharmacist visits individuals enrolled in the LAHP and evaluates medication appropriateness index (MAI), DRPs and barriers to compliance at baseline and on follow up visits.
RESULTS: In the first five months of the program, 116 visits have been completed. The mean MAI score at baseline was 13.0 ± 3.1, which improved to 10.5 ± 0.8, representing a 19.2% change. The most common DRPs were untreated problems (1.7%), improper drug selection (1.7%), failure to receive drug (22.4%), overdose (0.86%), adverse drug reactions (1.7%) and drug use without indication (0.86%). Barriers to compliance included lack of education about medications (36%), disorganization of medications (33%), physical/mental problems (33%), fear of adverse reaction to medication (13%) and pharmacy inconvenience (27%).
CONCLUSION: In home visits by a pharmacist help to improve medication appropriateness, and identify DRPs barriers to compliance for geriatrics in the home setting.

198. Evaluation of pharmaceutical care on hypertension and diabetes control in an urban outpatient medicine clinic. Sara L. Schroeder, Pharm.D., *Kai Ian Cheang, Pharm.D.*, Thomas P. Lonergan, Pharm.D., BCPS, Yoon Kang, M.D.; Barnes-Jewish Hospital, St. Louis, MO; Washington University, St. Louis, MO.

PURPOSE: To determine the potential impact of pharmaceutical care on hypertension and diabetes control in an urban medicine clinic.
METHODS: The inclusion criteria of this pilot study were blood pressure ≥ 150/95 mm Hg (≥ 140/90 mm Hg in diabetic patients) and/or HgA_{1c} ≥ 8% or a blood glucose ≥140 mg/dl measured in the clinic. Patients were randomized to intervention or control. Pharmacists made pharmacotherapy recommendations to physicians and educated intervention patients on their disease and drug therapy. The control group received usual care provided by physicians. The primary outcome was percentage of patients meeting blood pressure (≤ 140/90 mm Hg or ≤ 130/85 mm Hg if diabetic) and HgA_{1c} (≤ 8%) goals; secondary outcomes were mean changes in above values.
RESULTS: Baseline characteristics were similar between groups with 49 and 40 patients in the intervention and control arms respectively. Patients were predominantly African-American with a mean age of 60 years. Intervention patients were seen an average of 2.5 times by a pharmacist, with an average follow-up of 128 days. At the end of the study, the percentage of hypertensive patients at blood pressure goal was 33% in the intervention arm and 21% in the control arm. The mean blood pressure reduction was 17/3 mm Hg vs 9/8 mm Hg in the intervention and control arms respectively. A minimal decrease

in HgA_{1c} was observed in both groups.
CONCLUSION: Over a brief period of time, pharmacist interventions appear to result in a greater blood pressure reduction than usual care, but little effect on HgA_{1c}. A larger trial is warranted.

199. Appropriateness of medication use in treatment of congestive heart failure by internal medicine physicians. *Pat S. Rafferty, Pharm.D.*, Robert L. Talbert, Pharm.D., BCPS; South Texas Veterans Health Care System; University of Texas Health Science Center at San Antonio, San Antonio, TX; University of Texas at Austin, Austin, TX.

PURPOSE: To evaluate physician prescribing patterns in the care of patients with congestive heart failure (CHF).
METHODS: Patients assigned an ICD-9 code for CHF from May 1998 to May 1999 were assessed for frequency of use and dose prescribed of angiotensin-converting enzyme inhibitors (ACEI). Patients had to be on ACEI for at least one year and already undergone dose titration. In addition, use of aspirin, lipid-lowering therapies, and other cardiovascular medications were evaluated. Ventricular ejection fractions (EF) were obtained via echocardiogram, MUGA or angiogram.
RESULTS: One hundred male patients (69.7 ± 9.8 years) were identified; 77% with ischemic cardiomyopathy, 23% with idiopathic cardiomyopathy, and 72% with systolic dysfunction. Of patients with ischemic disease, 66% were on aspirin, and 60% met an LDL goal of < 100. The median daily doses of ACEI in systolic dysfunction were: captopril 150 mg, fosinopril 40 mg, lisinopril 40 mg. Of patients with systolic dysfunction not on warfarin, 40% had severe dysfunction (EF < 25). The percent of patients, stratified by type of ventricular dysfunction, treated with each agent were:

Type (%)	ACEI	Diuretic	Digoxin	Vasodilator	Beta-blocker	Warfarin	CCB
Systolic (72)	90%	89%	72%	32%	29%	26%	21%
Diastolic (9)	55%	100%	11%	67%	33%	11%	44%
Normal (19)	68%	100%	26%	37%	42%	21%	37%

CONCLUSION: ACEI therapy is well-utilized in the treatment of systolic dysfunction at our institution. However, concerns regarding appropriateness of digoxin and CCB prescribing indicate the need for educational efforts to ensure optimal management of patients with CHF. Educational initiatives will be presented.

200. Utilization of perioperative beta-blockade in elective non-cardiac surgery patients in a community hospital. *Mary A. Miller, Pharm.D. candidate*, Angela S. Stewart, Pharm.D.; Washington State University, Yakima, WA.

PURPOSE: This study evaluated utilization of perioperative beta-blockade in patients undergoing elective non-cardiac surgery.
METHODS: A chart review of patients admitted to a community hospital for elective non-cardiac surgical procedures was undertaken. Patient charts were reviewed to identify those meeting criteria for perioperative beta-blockade. Criteria included known coronary artery disease or the presence of two or more coronary disease risk factors. Coronary disease included a history of myocardial infarction or angina and risk factors included age (> 65 years), hypertension, hypercholesterolemia (> 240 mg/dl), diabetes, or current smoking. Pre-hospital and in hospital beta-blocker use was recorded as well as beta-blocker contraindications. Patient charts were also reviewed for documentation of post-operative myocardial ischemia.
RESULTS: Charts from 116 consecutive patients admitted to a community hospital for elective non-cardiac surgery were reviewed. Thirty-one patients met the criteria for use of perioperative beta-blocker therapy. Seven patients had documented coronary artery disease and 24 had two or more risk factors for coronary disease. No patients received beta-blocker therapy post-operatively. Four patients received pre-operative labetolol for blood pressure control. Two of those patients met the criteria for perioperative beta-blockade and two did not. Beta-blocker therapy was contraindicated in one patient with coronary disease risk factors.
CONCLUSIONS: Beta-blocker therapy to prevent perioperative myocardial ischemia in patients with coronary disease or risk factors is underutilized. Efforts to improve beta-blocker utilization in this setting are warranted.

201E. The efficiency and impact of atypical antipsychotics in county-wide outpatient managed care services. *Douglas Del Paggio, Pharm.D., M.P.A.*; Alameda County Behavioral Health Care Services, Oakland, CA.

PURPOSE: This prospective, naturalistic study, initiated November 1, 1996, used the mirror image design to contrast costs and efficacy associated with the initiation of the atypical antipsychotics risperidone and olanzapine.
METHODS: Two 6-month periods, prior and post antipsychotic initiation, were analyzed regarding costs and services utilized. The main questions posed were: would these newer agents 1) improve symptoms, 2) reduce utilization of high cost services, and 3) reduce overall expenditures, although the agents cost more than older, cheaper medications? To assess the impact on client symptoms, each psychiatrist quarterly scored the PANSS and AIMS.
RESULTS: Although the average olanzapine prescription costs more than $300/Rx, olanzapine (n=46) reduced overall high costing service utilization, offsetting medication expenses. This resulted in a cost savings of $333/month per client. Clients demonstrated a dramatic drop in both high costing inpatient (74%) and crisis service utilization, and increased utilization of outpatient (10%), vocational and med visits (13%). With risperidone (n=27) initiation, the average cost per client of medication and services increased by $275/month per client. This was due to the average prescription cost ($163/Rx) and increased inpatient utilization by 61%. But risperidone clients had a significant increase in outpatient (46%), day treatment, vocational and med visits (300%). As measured by the PANSS, the overall and negative subscale scores decreased by an average of 20% for both agents. This documented clinical improvement in the symptoms of schizophrenia. Furthermore, both agents demonstrated a decrease in the AIMS score.
CONCLUSIONS: This study supports the use of higher costing newer antipsychotics due to their impact on treatment resistant symptoms, client services and overall costs. The reduction of costly services, and trend towards more outpatient care offsets the higher prices of these medications.
Presented at the Annual Meeting of the American Psychiatric Association, Washington, DC, May 15-20, 1999.

202. Doctoral clerkship students and pharmaceutical care: a five-year analysis. *Marie A. Chisholm, Pharm.D.*, David W. Hawkins, Pharm.D., Holly E. Rogers, Pharm.D. candidate, A. Thomas Taylor, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: This study evaluated 5 years of pharmaceutical care provided by Doctor of Pharmacy (Pharm.D.) students on acute care clerkships at the Medical College of Georgia. Objectives of the study included: 1) teaching pharmacy students how to identify, document, solve, and prevent medication-related problems; 2) documenting the number and types of recommendations made by Pharm.D. students to medical teams; 3) determining the acceptance rate of these suggestions; and 4) determining the potential impact of students' recommendations on patient care.
METHODS: Seventy-seven Pharm.D. students enrolled at the University of Georgia College of Pharmacy assigned to a general medicine or family medicine service at Medical College of Georgia Hospital during September 1994 through March 1999 were included in the study. Under the supervision of a faculty preceptor, the students were responsible for preventing and resolving patient medication-related problems and providing appropriate pharmacotherapy recommendations.
RESULTS: Of the 608 recommendations that were made, approximately 88.5% (n=537) were accepted by the medical teams. Improper medication selection (24%), untreated indication (23%), and overdosage (19%) accounted for approximately 66% of the medication-related problems. The most commonly accepted recommendations involved anti-infective (36%) and cardiovascular (17%) medications. Two pharmacists evaluated each accepted recommendation by using Hatoum's criteria for assessing potential impact on patient care. This evaluation indicated that 77% of the accepted recommendations would have a significant (56%), very significant (20%) or extremely significant (1%) potential impact on patient care outcomes.
CONCLUSION: During the 5-year study period, pharmacy students performed pharmaceutical care activities that had a positive impact on patient care.

203. The development and implementation of an antibiotic surveillance program. *Chelsea O. Church, Pharm.D.*, Debbie C. Byrd, Pharm.D., BCPS, Charles T. Taylor, Pharm.D., BCPS, Leslie M. Stewart, Pharm.D.; DCH Regional Medical Center, Tuscaloosa, AL; Auburn University, Auburn, AL.

PURPOSE: Develop an antibiotic surveillance program (ASP) to educate pharmacy students in antimicrobial therapy, evaluate appropriateness of selected antibiotics, evaluate students' antimicrobial therapy knowledge, and evaluate potential cost avoidance of interventions.
METHODS: Criteria were developed and approved for six target antibiotics. An examination was developed to evaluate students' baseline antimicrobial knowledge. Students completed a training session to ensure accuracy and consistency of policies, procedures, and outcomes. Once training was complete, patients on the target antibiotics were assessed and recommendations were made for physician review. Interventions were documented in the medical center's computerized database. A post-surveillance antimicrobial examination was administered to students upon completion of rotations at the medical center and scores were compared to baseline.
RESULTS: Mean baseline antimicrobial examination scores for Pharm.D. (n=8) and B.S. (n=2) students were 50% and 21%, respectively. Post-surveillance examination scores showed a 25% and a 69% improvement over baseline for Pharm.D. and B.S. students, respectively. Over the 8-week study period, there were 270 assessments. Inappropriate regimens for monitored antibiotics included: ciprofloxacin (n=3) 6%, imipenem/cilastatin (n=9) 11%, ticarcillin/clavulanate (n=127) 9%, tobramycin (n=14) 7%, trovafloxacin (n=45) 44%, and vancomycin (n=26) 8%. Overall, inappropriate regimens (n=38) included 58% not switched to PO, 13% inappropriate doses, 24% inappropriate schedules, 2.5% inappropriate indications, and 2.5% lacked serum levels. An estimated total cost avoidance of $5204 was documented.
CONCLUSIONS: ASP was successful in improving students' antimicrobial knowledge scores, potentially improved appropriateness of antibiotic therapy, and made a positive financial impact on the medical center.

204. An innovative method for educating pharmacy students about alcohol pharmacokinetics and substance-related disorders. *Bethany A. DiPaula, Pharm.D., BCPP*, Anthony C. Tommasello, M.S.; University of Maryland, Baltimore, MD.

PURPOSE: Approximately 90% of adults have had some experience with alcohol, and a substantial number (60% of males, 30% of females) have had one or more alcohol-related adverse events. The lifetime prevalence of substance-related disorders varies by agent and may range between 11.36% (females) and 25.54% (males). Pharmacists are exposed to substance-related disorders in patients, peers, family members, and potentially self. However, many pharmacists are poorly informed and therefore may feel uneasy. This laboratory provides a comfortable forum for discussion to educate pharmacy students about the absorption and elimination pharmacokinetics of alcohol. Information on diagnosis and management of substance-related disorders is conveyed through case presentations.
METHODS: Two students consent to drink 1-2 beers. Classmates obtain blood alcohol levels (BAL) at 15 minute intervals using Intoximeters-. Each BAL data point is graphed and drinkers share corresponding subjective feelings. When not gathering data, the class discusses relevant case vignettes. Students complete anonymous pre and post-tests to assess educational value and attitudes.
RESULTS: Thirty-three of 34 (97%) students surveyed had never used a breath analyzer to monitor BAL. Sixteen of 34 (47%) students reported that this laboratory would affect their personal drinking behaviors. Twenty-nine of 34 (85%) students commented that this exercise would affect their interaction with patients. The average didactic test scores increased from 52% to 75%.
CONCLUSIONS: Providing an interactive forum for discussion of substance-related disorders can teach new skills, change student attitudes towards alcohol consumption, and increase the comfort and educational level of future pharmacists.

205. A case-based, interactive computer program improves pharmacists' knowledge in antimicrobial pharmacotherapy. Jamie Kilar-Gasaway, Pharm.D., *Andrew D. Luber, Pharm.D.*, Robin L. Corelli, Pharm.D., B. Joseph Guglielmo, Pharm.D., Mary Anne Koda-Kimble, Pharm.D.; University of California San Francisco, San Francisco, CA.

PURPOSE: University of California San Francisco (UCSF) has utilized an antimicrobial order sheet (AOS) review system since 1990. Pharmacists screen all antimicrobial orders using P&T approved guidelines. We developed a case-based, interactive antimicrobial computer program to educate dispensing pharmacists in proper antimicrobial review. The program uses clinical situations routinely encountered by pharmacists at UCSF. Our purpose was to assess the impact of the program on pharmacists' knowledge of antimicrobial pharmacotherapy.
METHODS: Participants included all inpatient staff pharmacists and residents. Seven competencies based upon P&T approved criteria were developed by the anti-infective pharmacy team: allergy screening, dosing (aminoglycosides, vancomycin, ceftriaxone) and indication for use (intravenous fluconazole, liposomal amphotericin B, oral vancomycin). An interactive case-based computer program stressing these competencies was administered (pre-test, interactive tutorial and post-test). Pre-test scores < 85% required completion of an interactive tutorial prior to post-test administration. Upon successful completion (score > 85% in either the pre or post-test) participants completed a self-assessment evaluation.
RESULTS: Forty-four participants were evaluated. Twenty-seven pharmacists (61%) scored > 85% on the pre-test. Among pharmacists with pre-test scores <85% (n=17; 39%), successful completion of the program resulted in increased post-test scores in all 7 competencies. The program increased pharmacists' perceived "comfort levels" with antimicrobial pharmacotherapy from 3.3 ± 1.2 to 4.0 ± 0.8 (1 = not comfortable; 5 = very comfortable) and was comparable to baseline "comfort levels" among participants with pre-test scores > 85% (4.1 ± 0.8). Each section of the program took between 30 and 60 minutes to complete. Most participants rated the computer program as "fairly clear" or "very easy" to use and highly representative of situations encountered in their day to day activities.
CONCLUSIONS: A case-based, interactive staff development computer program is easy to use, representative of day to day activities and improves pharmacists' knowledge in antimicrobial pharmacotherapy. Similar programs targeting different health care professionals and disease states can be developed using this project as a prototype.

206. A multidisciplinary approach to physician credentialling: the thalidomide experience. *Beth M. McLendon, Pharm.D.*, Angela W. Smith, Pharm.D., Brandee L. Hayhurst, Alvin Wells, M.D., Ph.D., Kathleen G. Hundley, M.Ed., Joseph S. Green, Ph.D.; Duke University Medical Center; Duke University, Durham, NC.

The Pharmacy and Therapeutics (P&T) Committee approved thalidomide for formulary addition contingent upon the development of a credentialling program for prescribers. The program would educate prescribers regarding the manufacturer's prescribing requirements and present additional policies mandated by the P&T Committee. A committee composed of pharmacists, educators, and a physician designed and implemented this process. The committee conducted two grand rounds seminars. These seminars encompassed the necessary information for credentialling and provided category 1 continuing medical education credit. During the seminars, the audience received a pretest utilizing an audience response system, a review of thalidomide's history, an explanation of the S.T.E.P.S. system, our institution's policies for in-patient use, and insights into thalidomide's place in therapy for various disease states. Both pharmacists and physicians served as presenters at these grand rounds. Upon the presentation's completion, participating prescribers could complete a post-test. They were also offered the opportunity to complete the test at a later date via the Internet. To provide credentialling to new prescribers and to update others, the pharmacy department developed an Intranet website dedicated to thalidomide.

207E. An online Doctor of Pharmacy program for pharmacy practitioners: development and evaluation of six courses. *Christine K. O'Neil, Pharm.D.*, Therese I. Poirier, Pharm.D.; Duquesne University, Pittsburgh, PA.

PURPOSE: The goals of this project were to: 1) develop an online Pharm.D. program that prepares practitioners with background and skills to provide pharmaceutical care; and 2) evaluate the impact of the program on the knowledge of participants, their preparedness to provide pharmaceutical care, and frequency of pharmaceutical care activities.
METHODS: Curriculum for six credits in a 38-credit program was developed. Content areas focused on clinical skills and pharmacotherapy of cardiovascular, endocrine, gastrointestinal, rheumatoid and respiratory patients. Instructional strategies consisted of self-study with PowerPoint™ presentations and readings, synchronous chat sessions using First Class Intranet Client™, and case-based assignments. The impact of the project was evaluated in two ways. Upon entry into the program, participants completed a 70-item pretest of knowledge that reflected the content areas covered in the first six courses. Participants also completed a survey of their current pharmaceutical care activities, attitudes, and preparedness to provided specialty pharmaceutical care activities. Program effectiveness was evaluated comparing baseline scores of knowledge and survey results to scores upon completion of developed curricular content.
RESULTS: By the end of Spring 1999, 28 students completed courses in the program. There was significant improvement in test scores (p=0.0001) and participants' preparedness to provide specialty pharmaceutical care services (p=0.01).
CONCLUSIONS: The first six courses in the online program were successful in increasing the knowledge and preparedness to provide pharmaceutical care. The success of this project provided the stimulus for development of the entire Pharm.D. program.
Presented at the 100th Annual Meeting of the American Association of Colleges of Pharmacy, Boston, MA, July 3-7, 1999.

208. Development of a transplant pharmacist certificate program. *Kristine S. Schonder, Pharm.D.*, Kevin J. Lynch, Pharm.D., BCPS, Thomas L. Rihn, Pharm.D., Gordon J. Vanscoy, Pharm.D., MBA; Stadtlander Drug Co.; University of Pittsburgh, Pittsburgh, PA.

Because transplantation is a highly specialized field that deals with a unique population of patients with remarkably individualized needs, it is most effectively managed by clinicians with specialty training in transplant. However, pharmacists in the community setting may be the primary health care contact with these patients as they dispense refills for medications. Providing quality pharmaceutical care to transplant patients may be a challenge to community pharmacists with regard to the complexity both of the literature and concepts of immunology, as well as the availability of specialty information in the core medical journals (i.e., N Engl J Med, JAMA). To ensure the delivery of specialty pharmaceutical care to transplant patients, a university-based transplant pharmacist certificate program was developed to strengthen expertise and competency in transplantation. Instructors for the program were selected based on their expertise in transplant and included distinguished physicians, university faculty and clinical specialists. Seven hours of didactic and experiential education were delivered to participants in the program, centering on the basics of immunology, drug interactions with immunosuppressants, complications of transplantation, adherence, psychosocial and financial issues relating to the transplant patient. The certificate process culminated with a comprehensive written examination. 122 pharmacists nationwide (85% practiced in specialty pharmacies) completed the educational components of the program for continuing education credits. Of these, 86 pharmacists completed the examination process to be certificated, 88% of which passed the examination overall.

209. Clinical decision making and economic outcomes in the implementation of an outpatient infliximab infusion program for patients with Crohn's disease. *Philip K. Yeung, Pharm.D., BCPS*; Owen Healthcare Inc., Chicago, IL.

The incidence of Crohn's disease is estimated at 5/100,000 or, 380,000 to 480,000 people. The cost of illness was over $1.7 billion or $9197 per patient annually. New medication, infliximab, was approved by the FDA for the

treatment of moderate to severely active Crohn's disease in patients with or without fistulas. However, the cost of infliximab therapy is very expensive, $2340 per treatment vs $941 for the standard therapy. Since the case mix of our institution is about 70% Medicare, the projected reduction in DRG reimbursement ranged from 25.5% to 47.3%.
PURPOSE: In order to provide the latest therapy and prevent hospitalization, we sorted inputs from GI clinic, patient billing service, quality assurance and the manufacturer (Centocor). Our decision is to implement an outpatient infliximab infusion program since there was minimal overheads incurred in the GI clinic and the manufacturer would provide support in billing, reimbursement and patient assistant program.
METHODS: Pharmacy and GI service established the appropriate use criteria, standing orders, monitoring form for infliximab infusion. A process chart was mapped out to ensure prior authorization, facilitating ordering and applying for patient assistant program. From November 1998 to May 1999, 11 infusions were administered to 6 eligible patients.
RESULTS: No adverse drug reactions were observed in all the patients. One patient has complete closure of fistulas, diarrhea was halted in 2 patients. No need to follow up within 6 month. Since the program is ongoing, we will follow up the rest of the patients for their progress. In term of reimbursement, 10 treatments were approved and reimbursed; over 70% of the charge were covered. One claim was rejected due to inadequate documentation. (We have re-submitted the claim and await reimbursement). Outpatient account receivable was 1.5 month and collected $31,420.78. The return on investment was 71%.
CONCLUSION: In order to demonstrate the value of clinical pharmacy services, we need to participate in the business process to optimize cares and to ensure reimbursement for the institution. Overall, we think the infusion program is successful. And we will learn from this experience to foster other outpatient programs and grow the business.

210. The application of a pharmacoeconomic model to determine cost-effectiveness of academic detailing clinical pharmacy services in improving angiotensin converting enzyme inhibitor utilization in type-2 diabetics with albuminuria. *Joseph J. Medicis, Pharm.D., BCPS*, Elizabeth Jones, Pharm.D., BCNSP, Cathy Sinnott, B.S.N., Ruth Weinstock, M.D., Ph.D, Roy Guharoy, Pharm.D., Dave Lehmann, M.D., Pharm.D.; University Hospital; State University of New York; Health Science Center at Syracuse, Syracuse, NY.

PURPOSE: Angiotensin converting enzyme inhibitors (ACEI) remain underutilized despite their well-documented efficacy in slowing the progression to endstage renal disease in diabetics with albuminuria. We developed a pharmacoeconomic Markov model which evaluated the impact of enhancing the utilization of ACEI in this population through clinical pharmacy services.
METHODS: In our clinic 232 patients had type-2 diabetes of which 47 had clinically significant levels of urinary albumin with a 48.9% utilization rate of ACEIs. ACEI utilization was assumed to improve to 80% with clinical pharmacy services. Transition probabilities between the Markov health states and utilities were derived from literature values. Sensitivity analysis varied ACEI utilization rates and success rates. Academic detailing clinical pharmacy services were considered cost-effective at a level of $50,000/QALY (quality adjusted life year).
RESULTS: Cost of care per year was $23,688 without clinical pharmacy services and $21, 930 with such services. An addition of 0.2 quality adjusted life years was gained by the addition of ACEI. Our analysis revealed a potential savings of $7,972 per QALY ranging from $3,295 to $12,171.
CONCLUSIONS: Academic detailing clinical pharmacy services could be cost-saving in the ambulatory care of type-2 diabetics in a primary care setting even with modest improvements in the utilization of ACEI. Validation of pharmacist success rates of ensuring ACEI therapy constitutes our next phase of study.

211. Improving the utilization and effectiveness of HMG-CoA reductase inhibitors in patients with coronary artery disease. Kathleen Wooley, Catherine Ashby, Joyce Mashni, Michelle Faulkner, Pharm.D., *Daniel E. Hilleman, Pharm.D.*; Creighton University, Omaha, NE.

PURPOSE: Despite overwhelming evidence that the HMG-CoA reductase inhibitors (statins) reduce the risk of cardiovascular morbidity and mortality, utilization of this class of drugs in high-risk coronary artery disease (CAD) patients is erratic. We evaluate the ability of a post-hospital discharge intervention aimed at prompting physicians to improve the utilization and effectiveness of statins in CAD patients.
METHODS: The baseline (control) population included 303 consecutive CAD patients admitted to the coronary care unit (CCU) of our teaching hospital from 10/01/98 through 12/31/98. The intervention group included 309 consecutive CAD patients admitted to the CCU from 01/04/99 through 03/31/99. Intervention patients had follow-up letters sent to their physicians with patient specific recommendations concerning lipid therapy at 2, 8 and 12 weeks after hospital discharge.
RESULTS Utilization and outcome of lipid-lowering therapy in the two groups is summarized below.

	Number of Patients	Lipid Status Known	Patients Treated	Achieved LDL-C Goal	Initial Dose	Titrated Dose
Control group	303	142 (47%)	122 (40%)	54 (18%)	97 (80%)	25 (20%)
Intervention group	309	239 (77%)	173 (56%)	162 (52%)	104 (70%)	69 (30%)

CONCLUSION: The use of a relatively simple physician prompting intervention significantly improved: 1) the assessment of lipid status, 2) the frequency of use of statins, 3) the achievement of LDL-C treatment goals, and 4) the titration of lipid drugs. This intervention tool should be applied more broadly across patient populations.

212E. Training future faculty members: the addition of a teaching/learning component to a residency program. *Nancy M. Waite, Pharm.D.*, Eric H. Hobson, Ph.D.; Albany College of Pharmacy, Albany, NY.

PURPOSE: Although residency/fellowship programs provide practice and research training, practitioners and pharmacy practice faculty start their teaching careers with little-to-no teaching/learning training. Yet they are expected to teach in classrooms and practice settings, often without additional teaching support. To remedy this situation an existing ambulatory care residency program was modified to include pedagogical training in adult learning and application of these principles in both the didactic and clinical teaching settings.
METHODS: The addition of a teaching/learning specialist to the ACP faculty provided an opportunity to incorporate training in adult teaching/learning into a rural ambulatory care residency program. The teaching/learning components include: information processing and acquisition; child-adult learning differences; teaching/learning adaptation for specific goals and contexts; and formative and summative assessment techniques. Application opportunities include developing patient education materials and programs, implementing case-based, small group pharmacotherapeutics classes, participating in ongoing teaching research, and teaching/assessing learning in other coursework.
RESULTS: Recruitment for the 1999 residency cycle yielded qualified and motivated candidates. Deans and division directors from other colleges of pharmacy who have followed this program's development wish to recruit the program's graduates. External requests for financial support have met with interest.
CONCLUSIONS: As demands on practitioners and faculty increase and recruitment becomes more difficult, advanced training in teaching/learning via a combined residency program is ideal for the graduate, health-care institutions and colleges of pharmacy.
Presented at the 100th Annual Meeting of the American Association of Colleges of Pharmacy, Boston, MA, July 3-7, 1999.

213. Evaluation of heparin-induced thrombocytopenia practice guidelines. *Nicole T. Ansani, Pharm.D.*, Simone E. Taylor, Pharm.D., Mary M. Hess, Pharm.D., Amy L. Seybert, Pharm.D.; University of Pittsburgh Medical Center Health System, Pittsburgh, PA.

PURPOSE: This outcome assessment of lepirudin and danaparoid for the management of heparin-induced thrombocytopenia (HIT) evaluated the time to platelet recovery and the incidence of new thromboembolic and bleeding complications.
METHODS: Evidence-based practice guidelines for the treatment of HIT were developed by the departments of pharmacy and hematology. Once implemented, all patients who received treatment for suspected HIT were evaluated. Bleeding complications were evaluated using TIMI criteria for major and minor bleeding.
RESULTS: During a 6-month period, a total of 14 patients received danaparoid (n=4) and/or lepirudin (n=12). Of the 10 newly diagnosed HIT patients, the mean platelet nadir was 41.8 x 10^9/L, the mean duration of heparin therapy was 6.7 days, the majority of patients were on a cardiology service and most experienced a > 30% fall in baseline platelet count. Mean time to platelet recovery was 10.7 and 6.6 days with danaparoid and lepirudin, respectively. Two lepirudin patients experienced major bleeding, while a new thromboembolic complication occurred in one patient on danaparoid. Two patients failed danaparoid but responded to lepirudin.
CONCLUSIONS: Based upon preliminary data, lepirudin appears to result in a more rapid platelet recovery with fewer thromboembolic complications. Adverse drug events were more frequent with lepirudin, possibly due to the full anticoagulant dose provided, in contrast to the prophylaxis dosing of danaparoid. As the database expands, a pharmacoeconomic analysis will be performed.

214. Use of weight-based heparin dosing nomograms in a community teaching hospital. *Anne M. Stoysich, Pharm.D.*, Fred Massoomi, Pharm.D., Paula L. Danekas, Pharm.D.; Nebraska Methodist Hospital, Omaha, NE.

PURPOSE: To minimize the risk of thromboembolism and bleeding by promptly achieving and maintaining the target therapeutic APTT range using weight and diagnosis based heparin dosing nomograms.
METHODS: A medication utilization evaluation (MUE) was conducted in a community hospital prior to and following initiation of weight based heparin nomograms. A low dose nomogram for treatment of AF, CP, CVA, and AMI

recommended a bolus of 60 units/kg and an infusion of 14 units/kg/hour. A high dose nomogram for treatment of DVT and PE recommended a bolus of 80 units/kg and an infusion of 18 units/kg/hr. APTTs were drawn every 6 hours until two consecutive therapeutic APTTs, then daily. Dosage adjustments were made based on the weight based nomograms. The MUEs compared weight based nomograms (WBN) and standard care protocols (SCP) at baseline and follow up.
RESULTS:

Dosing	Percent Attained Therapy Threshold x at 24 Hours	Percent Subtherapy at 24 Hours	PTTs/Day-Length of Therapy	ADR (min/maj)
SCP (baseline)	26/45 (57%)	12/45 (27%)	2.0-4.8	6/0 (13.3%)
WBN (follow up)	44/52 (85%)	3/52 (4%)	1.8-4.1	3/0 (5.1%)
SCP (follow up)	40/53 (75%)	17/53 (32%)	2.1-4.2	4/0 (7.1%)

CONCLUSION: Correlation between the prompt achievement and maintenance of a target APTT range and the reduced risk of bleeding should promote the use of weight based nomograms for initial heparin bolus determination and subsequent dosage adjustments. Weight based heparin nomograms are widely generalizable and have been shown to be more effective, safe and superior to SCP.

215. Pharmaceutical care for HIV-infected patients in transition between health care delivery settings. *Kimberly K. Summers, Pharm.D.*, Thomas C. Hardin, Pharm.D.; South Texas Veterans Health Care System; University of Texas Health Science Center at San Antonio, San Antonio, TX; University of Texas at Austin, Austin, TX.

PURPOSE: To describe a pharmaceutical care program for providing continuity of care to patients infected with HIV who are in transition between in-patient and out-patient health care settings.
METHODS: A clinical pharmacist prospectively reviewed the records for all HIV-infected patients admitted to the hospital for the months of January through April of 1997. When necessary and appropriate, a pharmacist-initiated intervention was made to resolve any therapeutic-related problems. Outcome data for the active study period were compared to a matched historical control group. A cost-avoidance was calculated for interventions resulting in a change in dosing or discontinuation of an unnecessary medication.
RESULTS: Fifty-one interventions were made during the 4-month study period. Forty-nine percent of the interventions were related to a critical drug omission or use of an unnecessary medication. The number of errors (medication omissions, unnecessary medications, duplicative therapy, incorrect drug or dose for an indication) per transition was significantly lower in the active study period compared to the historical data group (13 vs 43, $p<0.001$). There was no statistical difference in the number of drug-related events (drug-therapy related admissions, adverse drug reactions, or significant drug interactions) between the two groups. A 0.25 FTE clinical pharmacist was required for the study period. A total cost avoidance of $4676 was documented as a result of pharmaceutical care interventions over the 4-month study period. The average cost-avoidance per intervention was $246.
CONCLUSIONS: We were able to document that a clinical pharmacist dedicated to the continuity of care for HIV-infected patients as they transition between health care settings can have a dramatic impact on the quality and cost of care delivered.

216. A clinical pharmacist-based expanded access medication program for patients with HIV infection. *Kimberly K. Summers, Pharm.D.*, Thomas C. Hardin, Pharm.D., Philippe Chiliade, M.D.; South Texas Veterans Health Care System; University of Texas Health Science Center at San Antonio, San Antonio, TX; University of Texas at Austin, Austin, TX.

Drug therapy represents a significant component of the care for HIV-infected patients. Many HIV-infected patients with advanced disease are highly antiretroviral experienced with limited treatment options. Early access to HIV medications prior to final FDA approval significantly broadens therapeutic options, as well as, provides drug therapy at no cost to the patient or the institution.
PURPOSE: To document the financial impact of a clinical pharmacist-based expanded access medication program for HIV infected patients.
METHODS: The clinical pharmacist is responsible for completion of all case report forms and initial screening for program eligibility. The clinical pharmacist works directly with the primary care physician to provide monthly patient monitoring, assessment, and education. In addition, the clinical pharmacist is responsible for inventory control of the investigational agents and coordination with the out patient pharmacy for commercially available agents. Monthly summaries of the expanded access drug program activities and associated cost avoidance were computed between the months of July 1998 to April 1999.
RESULTS: Twenty-four, 38, and 26 patients participated in the adefovir dipivoxil, abacavir, and efavirenz programs, respectively. The total equivalent cost avoidance observed for the eleven-month period was $94,463. A clinical pharmacist had an average of 65 patient contacts per month, representing approximately 30-40% of the patients scheduled for the clinic.
CONCLUSIONS: The clinical pharmacist based expanded access drug program provides enhanced drug therapy options with a significant cost avoidance to the health care institution. The impact of these services on treatment outcomes is being assessed.

217. Evaluating clinical outcomes among patients receiving lipid-lowering interventions in a managed care plan. *Gene D. Felber, Ph.D., M.S.P.H.*, Bruce Fallik, M.S., H. Ed Perez, Pharm.D.; Total Therapeutic Management, Inc., Kennesaw, GA; Blue Cross Blue Shield of Colorado, Denver, CO.

PURPOSE: To evaluate outcomes in a hyperlipidemic population receiving statin therapy at a managed care organization with regard to 1) National Cholesterol Education Panel (NCEP) Adult Treatment Panel II goal attainment, and 2) percentage reduction in low-density lipoprotein cholesterol (LDL-C).
METHODS: Charts were reviewed to collect demographic, clinical, and medication utilization data in 1998-1999 from a random sample of patients in a southwestern U.S. managed care plan. Univariate and stratified categorical analyses were conducted to assess factors related to LDL-C reduction and NCEP goal attainment.
RESULTS: Data were analyzed from 270 men and women whose mean age at baseline was 58.8 years (range 28-84 years). The majority (64%) had ≥ 2 coronary heart disease (CHD) risk factors. Drug utilization was 31.5%, 26.7%, 13%, 8.9%, and 5.2%, respectively, for atorvastatin, pravastatin, simvastatin, fluvastatin, and lovastatin; 14.1% were treated with other agents. Follow-up LDL-C readings were available for 228 patients (84%) indicating that 76%, 68%, 65%, 62%, and 62% of patients, respectively, receiving atorvastatin, simvastatin, fluvastatin, lovastatin, and pravastatin, met their treatment goals. Overall goal attainment was 67%. Goal attainment among patients with CHD was 32%. Percentage LDL-C reduction was -33.43%, -30.95%, -24.12%, -23.10%, and -21.50%, respectively, for atorvastatin, simvastatin, fluvastatin, lovastatin, and pravastatin.
CONCLUSION: While NCEP goal attainment was superior to national averages, among CHD patients it is an area of potential quality improvement, along with improved LDL-C follow-up documentation and cost-effective formulary management.

218. Implementation of a multidisciplinary-developed intranet site for the management of nutritional support at Scott & White Memorial Hospital. *Annie Herrington, Pharm.D., BCPS*, Kim Culp, M.D., Donald Rawls, M.D., Tim Pfanner, M.D., Glen Willie, M.D., Eileen Dietscher, M.S., R.D., C.N.S., Jim Mendenhall, B.S.N., C.N.S.N., Catherine Arnold, M.S., R.D.; Scott & White Memorial Hospital, Temple, TX.

The development of an intranet site to standardize the care of patients receiving nutritional support was identified as a quality improvement initiative within the institution. A comprehensive intranet site was developed by a multidisciplinary group consisting of pharmacists, gastroenterologists, dietitians, nephrologists, and nutritional support nurses. The intranet site consists of the statement and purpose of the nutritional support team followed by a departmentally developed algorithm for providing enteral and parenteral nutrition. Sections are subdivided into nutritional risk, patient assessment, nutritional plan development, nutrition monitoring, and specific disease states. An in-depth review and recommendations of nutritional support in patients with pulmonary disease, liver disease, pancreatic disease, malabsorptive disease, renal disease, and refeeding syndrome is described. Surgical and medical attending staff and residents will be educated on the use of the intranet site. Following implementation, a retrospective review of 200 patients, 100 patients before and after development of the intranet site, will be evaluated. Patients will be reviewed for selection and appropriateness of enteral and parenteral nutrition. Efficacy, length of stay, length of nutritional therapy, complications, and total hospital and nutrition costs will be collected. It is hypothesized that education through the use of an available intranet site located on each unit will improve the selection and appropriateness of nutritional support with decreased costs.

219. Development and implementation of a medication management program in a pediatric attention deficit hyperactivity disorder clinic. *Tracy M. Hagemann, Pharm.D.*, Stacy Schrader, Pharm.D., Mary Beth Logue, Ph.D.; University of Oklahoma, Oklahoma City, OK.

PURPOSE: To describe the development and implementation of a medication management program in an attention deficit hyperactivity disorder (ADHD) clinic in a pediatric setting.
METHODS: A psychologist and pediatric medical resident-run ADHD clinic was begun at a university teaching hospital in July 1997. The clinic meets twice weekly and is being developed in two phases. Phase I included initial set-up and education of providers in diagnostic skills. Phase II is the development of treatment and monitoring guidelines. Clinical pharmacy services was contacted to help draft medication documentation and practice guidelines for phase II in order to educate providers on medications used, decrease polypharmacy and diminish medication adverse effects in this population. Treatment algorithms were developed to include initial choice of

medication, dose and regimen adjustments. Wall charts were created for identifying and minimizing medication adverse effects. A patient medication profile was also generated for inclusion in the patient's clinic chart. A pre-implementation survey was administered to residents to determine knowledge of ADHD medications, adverse drug events and interactions.
RESULTS: Residents have been educated as to how the algorithms work and how to utilize them effectively. A clinical pharmacist attends the clinic weekly. Patient charts will be reviewed for medication use. The survey will be re-administered to assess the acquisition of information essential for appropriate management of ADHD in pediatric primary care settings.
CONCLUSION: This pediatric ADHD medication program promotes medication management and is a method of educating health care providers on appropriate evaluation, dosage adjustment, follow up and provision of medication education to their patients.

220. Establishment of a pharmaceutical care network between a teaching hospital and community pharmacies in Taiwan. Shing-Mei Hsu-Lee, B.S., Tzu-Chang Chou, M.S., Li-Hua Huang, M.S., You-Mei Lin, M.S., Tzu-Han Wu, M.S.,*Hsiang-Yin Chen, M.S., Pharm.D.*; Taipei Municipal Wang Fang Hospital; Taipei Medical College, Taipei, Taiwan.

BACKGROUND: A law related to separation of pharmacy practice from medicine profession was implemented at 1997 in Taiwan; however, the general public has been accustomed to being diagnosed as well as having prescriptions filled at the hospital. Only very few prescriptions were filled in community pharmacies. It consequently causes difficulty to perform pharmaceutical care. The present study built-up a network to improve current pharmacy practice in Taiwan.
METHOD: Pharmacists from 24 community pharmacies near Taipei Municipal Wang-Fang Hospital (TMWFH) were trained twice a week with courses provided by TMWFH staff. Patients were asked for written informed consent at outpatient service in TMWFH. Chronic diseases patients who were willing to enroll were therefore closely followed-up by both hospital and community pharmacists.
RESULTS: One hundred fifty patients with chronic diseases were enrolled into the network service from April 1998 to May 1998 and went to TMWFH-affiliated community pharmacies from April 1998 to June 1998. The total number of counseling service was 990 times (2106 questions), including 777 (36.9%) questions related to administrative methods, 673 (32.0%) related to medication actions, 358 (17.0%) related to side effects, 180 (8.5%) related to cautions and contraindications, and 102 (4.8%) related to dosage. Average numbers of counseling and questions per patient in three months were 6.6 and 14.4, respectively. The total number of referrals from these community pharmacies back to TMWFH was 209 during three-month period.
CONCLUSION: A large number of counseling and questions asked by patients implicated that pharmacist is a really helpful professional. The present study demonstrated that convenient and personal communication is a key to success of pharmaceutical care in Taiwan.

221. Renal transplant clinic patients' satisfaction with health care quality: effect of pharmaceutical care services. *Marie A. Chisholm, Pharm.D.*, Bess O'Kelley Reinhardt, Pharm.D., Leslie Vollenweider, Pharm.D., Laura Mulloy, D.O., Muralidharan Jagadeesan, M.D., Holly E. Rogers, Pharm.D. candidate, J. Russell May, Pharm.D., James J. Wynn, M.D., Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: This is a prospective trial to determine the influence of pharmaceutical care services on renal transplant patients' satisfaction with the quality of health care received from a renal transplant clinic. This interim data analysis is part of a larger study to assess the impact of pharmaceutical care on health outcomes.
METHODS: Renal transplant patients at the Medical College of Georgia Renal Transplant Clinic were randomized into an intervention group and a control group. The intervention group received pharmaceutical care services which included ongoing medication reviews for each patient for one year post study enrollment, with emphasis on preventing or resolving medication-related problems and providing appropriate pharmacotherapy recommendations. The control group received no pharmacist intervention in addition to the routine services received by all patients in the clinic. At the end of one year, all patients were given the Health Care Attitude Questionnaire (HCAQ) to measure satisfaction with health care quality based on whether or not they received pharmaceutical care services. Differences in HCAQ scores for “overall quality of health care provided by the clinic” and “pharmacy-related” health care were tested.
RESULTS: Thirty-eight patients completed the HCAQ. Patients who received pharmaceutical care services (n=21) had mean HCAQ scores of 89.9 and 90.7 (highest achievable satisfaction score on each scale is 100) on the “overall quality of health care provided by the clinic” and “pharmacy-related” health care, respectively. Patients who did not receive pharmaceutical care services (n=17) had significantly lower mean HCAQ scores of 82.8 and 84, for the same measures, respectively ($p<0.05$).
CONCLUSION: Renal transplant clinic patients who received pharmaceutical care services from the renal transplant pharmacist were more satisfied with the quality of health care than patients who did not receive pharmaceutical care services in the clinic. Pharmaceutical care services may be justified based on improvements in patient satisfaction with the overall perceived quality of health care.

222. Analysis of pharmaceutical care provided by a clinical pharmacist in a renal transplant clinic over an 18-month time period. *Marie A. Chisholm, Pharm.D.*, Bess O'Kelley Reinhardt, Pharm.D., Leslie J. Vollenweider, Pharm.D., Holly E. Rogers, Pharm.D., candidate, J. Russell May, Pharm.D., Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: This is a prospective trial to determine the influence of clinical pharmacist involvement on health care outcomes in renal transplant patients. Pharmaceutical care objectives included: (1) identifying, documenting, solving, and preventing medication-related problems; (2) documenting the number and types of recommendations made by the clinical pharmacist to the clinic's physicians; (3) determining the physician acceptance rate of these suggestions; and (4) determining the potential impact of the clinical pharmacist's recommendations on patient health care outcomes.
METHODS: The renal transplant pharmacist performed medication reviews and was responsible for preventing or resolving patients' medication-related problems and providing appropriate pharmacotherapy recommendations for renal transplant patients seen in the Medical College of Georgia Renal Transplant Clinic. All recommendations and interventions that were made by the renal transplant clinical pharmacist from October 1997 to May 1999 were classified according to medication-related problem and class of medication. Two pharmacists (other than the renal transplant clinic pharmacist) independently evaluated each accepted recommendation by using Hatoum's criteria for assessing potential impact on patient care.
RESULTS: Eight-hundred and forty-four recommendations were made during the 18-month study period, and approximately 96% (n=811) of the recommendations were accepted by the clinic's physicians. Untreated indication (28%), overdosage (27%), and subtherapeutic dosage (18%) accounted for greater than 70% of the medication-related problems. The most commonly accepted recommendations involved immunosuppressant (33%) and cardiovascular (28%) medications. Greater than 95% percent of the recommendations were judged to have a significant (76%) or a very significant (22%) potential impact on patient health care outcomes.
CONCLUSION: During the first 18 months of renal transplant clinical pharmacy services, the pharmacist performed pharmaceutical care activities that were well received by the clinic's physicians and had a positive potential impact on patient health care outcomes.

223. Development, implementation, and evaluation of a compliance management service. *Lorinda Rasor Babb, Pharm.D.*, Ruth E. Emptage, Pharm.D.; The Ohio State University, Columbus, OH.

PURPOSE: The purpose of this study is to develop and implement a pharmacist-based compliance management service and evaluate its effectiveness through documented changes in refill histories, measurable treatment outcomes, and frequency of health care utilization.
METHODS: Physicians, nurses, and pharmacists at two outpatient clinic systems refer patients for potential enrollment. The pharmacist administers a detailed questionnaire that assesses potential barriers to compliance. For each compliance issue identified, the pharmacist makes patient-specific interventions. The patient returns at least monthly until compliance goals are achieved. At each visit, compliance is evaluated through refill histories and measurable treatment outcomes. Information on the frequency of physician visits, emergency room visits, and hospitalizations is also collected.
RESULTS: To date, ten patients are enrolled in the service. Data for six patients after at least 3 months of compliance counseling demonstrate a change in the prescription refill rate from 67.5% to 69.1%. The following average changes in treatment outcomes were observed: systolic blood pressure +1 mm Hg (6 patients); diastolic blood pressure + 6 mm Hg (6 patients); pulse -5.8 beats per minute (four patients); fasting blood glucose -103 mg/dl (two patients). From 3 months prior to 3 months after counseling, physician visits per patient decreased from 1.8 to 1.7.
CONCLUSIONS: Preliminary results suggest that individualized medication compliance counseling improves compliance, improves treatment outcomes, and decreases physician visits. Collection of outcome data will continue as more patients are enrolled in the service. Future applications include utilizing the data to establish justification for reimbursement.

224. Cost justification of a scheduled refill service for patients in a university-based pharmaceutical care center. *Nancy L. Shapiro, Pharm.D., BCPS*, Sara Samuel, Pharm.D. candidate, Mark Kliethermes, MBA; University of Illinois at Chicago, Chicago, IL.

PURPOSE: The purpose of this study is to measure the financial performance of a scheduled refill service (Refill-10) for patients that receive ten or more chronic prescriptions per month from the Pharmaceutical Care Center. Patients are seen monthly by an assigned pharmacotherapist by appointment to help coordinate care, organize prescription refills, encourage compliance, provide patient education, minimize pharmacy visits, and to maximize patient outcomes.

METHODS: Currently, five half-days of a pharmacotherapist's time are devoted to providing care to Refill-10 patients. All prescriptions are processed on the evening shift 1-2 days before the scheduled appointment. One-month prescription data for 105 patients from September 1998 was analyzed to retrieve actual reimbursements, acquisition cost of drugs, and net profit. Annual projections were made using the September data. Actual one-year reimbursements, costs, and profits will be presented. Continued enrollment has been occurring, with 130 current patients.
RESULTS: Preliminary results indicate the 105 enrolled patients in September filled 1314 prescriptions, with an average of 12.5 prescriptions per patient. Total monthly revenues were $64,798, with total monthly profits of $11,896, averaging $617 revenue/patient, and $113 profit/patient. Annual projections using the 105 patients indicated total revenues of $777,575, and profits of $145,254, averaging $1,383/patient. These profits more than offset the FTEs required to provide the service.
CONCLUSIONS: The Refill-10 Service is a profit-generating program. Annual projected profits are sufficient to justify the pharmacist's time. Increasing the number of patients in the program will likely increase profits to the pharmacy.

225. A retrospective, qualitative review of antihyperlipidemic drug use in psychiatric patients. *Michael T. Jones, Pharm.D.*, Steven C. Stoner, Pharm.D., BCPP, Leonard Ramlatchman, B.S., BCPP; Northwest Missouri Psychiatric Rehabilitation Center, St. Joseph, MO.

PURPOSE: The central focus in treating psychiatric patients is on the management of psychiatric symptoms, often with less attention given to physical disease. Many psychotropic drugs contribute to sedation, serum lipid changes, and weight gain. These factors present barriers to adopting a healthy lifestyle. This drug use evaluation prompted the development of a dyslipidemia clinic and evaluated current dyslipidemia management at Northwest Missouri Psychiatric Rehabilitation Center. Findings were compared to Adult Treatment Panel II (ATP-II) guidelines to assess level and quality of dyslipidemia care.
METHODS: Thirty-one patients were identified from February 1, 1998 to February 1, 1999 who had lipid levels above the goal levels described in ATP-II guidelines. Data was collected by retrospective chart review and included demographics, concurrent medications, labs, and dietary status.
RESULTS: Seven patients (22.6%) were identified as having no coronary heart disease (CHD) and < 2 risk factors. Six of those (85.7%) had appropriate treatment with four (80%) reaching desired lipid goals. Twenty-one patients (67.7%) had no CHD and ≥ 2 risk factors. Seventeen of those (81%) received appropriate treatment. Of nineteen patients treated a minimum of 6 months with medications, diet, or a combination of both, seven (36.8%) reached their desired lipid levels. Three patients (9.7%) had CHD and all received appropriate therapy, with only one reaching goal.
CONCLUSION: The average percentage of patients reaching their desired lipid goals was higher (44.4%) as compared to the general population (25%). Given these findings, this psychiatric population showed a more favorable response to dyslipidemia management and monitoring than the general population.

226. A survey of atypical antipsychotic prescribing trends. *Jackie Y. Raskind, Pharm.D.*, Sheila R Botts, Pharm.D., BCPP; Hillside Hospital, Glen Oaks, NY; St. John's University, Jamaica, NY.

PURPOSE: This survey assessed atypical antipsychotic prescribing trends in order to 1) document extent of atypical utilization and agent selection in specific patient populations; 2) evaluate factors influencing antipsychotic selection; 3) describe utilized sources drug information; 4) evaluate knowledge base of cost and side effect profile; 5) describe dosing strategies, adequate medication response time, off-labeled use and polypharmacy regimens.
METHODS: A 34 item anonymous questionnaire was distributed to all psychiatrists (n=253) employed at a private, university-affiliated, non-profit psychiatric institution. Surveys were distributed at an administrative meeting and via inter-office mail
RESULTS: Approximately 50% (126/253) of psychiatrists responded. Risperidone and olanzapine were the most common antipsychotic agents selected in first episode, chronic schizophrenia with positive or negative symptomatology, geriatric and pediatric populations. History of treatment response (85%), side effect profile (79%), personal experience with the agent (75%) were considered very important factors in antipsychotic selection. The majority of respondents (77%) indicated that journal articles were their most utilized and influential sources of new drug information followed by hospital sponsored continuing education (38%), and peer discussion (25%). Only 22-36% of psychiatrists correctly identified the atypical antipsychotic cost, most often underestimating. Thirty-five percent of psychiatrists indicated they titrated olanzapine every three days. Sixty-four percent of respondents combine typical and atypical antipsychotics.
CONCLUSIONS: Atypical antipsychotics are used first line in all schizophrenia patient populations. Physician education is needed in the area of antipsychotic dosing, response time, and costs. Additionally efforts are needed to increase the utilization of pharmacists as a source of drug information.

227. Antidote preparedness of Illinois hospitals. Kevin S. Webster, M.D., Anthony M. Burda, B.S., Todd Sigg, Pharm.D., Linnea O'Neill, M.Ph., *Frank P. Paloucek, Pharm.D.*, Cheryl A. Kapustka, Pharm.D.; Illinois Poison Center; Resurrection Medical Center; University of Illinois at Chicago; Metropolitan Chicago Healthcare Council, Chicago, IL.

PURPOSE: We wish to determine antidote preparedness of Illinois hospitals for nine crucial antidotes.
METHODS: In July 1998, the Illinois Poison Center (IPC) surveyed 201 Illinois hospitals with emergency departments. Quantities of the following antidotes were requested: crotalidae antivenin, cyanide kit, deferoxamine, digoxin immune-Fab, ethanol 10%, fomepizole, glucagon, pralidoxime, and IV pyridoxine. Amounts were compared to suggested minimum stock quantities as published in the 1997 IPC Antidote Chart. We tabulated the range, median, number of hospitals with no stock, and number meeting minimum suggestions.
RESULTS: Data were obtained from the 147 responding hospitals.

	Crotalidae	Cyanide kit	Deferoxamine	Digoxin-Fab	IV EtOH 10%
Range	0 to 20 vials	0 to 4 kits	0 to 168 vials	0 to 35 vials	0 to 30 liters
Median	0	1	4	6	0
None (hospitals)	80	22	53	24	74
Minimum (hospitals)	4	15	44	9	36
IPC chart	10 vials	3 kits	12 vials	20 vials	8 liters

	Fomepizole	Glucagon	Pralidoxime	IV Pyridoxine
Range	0 to 4 kits	0 to 140 vials	0 to 18 grams	0 to 82 grams
Median	0	10	3	3
None	119	2	39	34
Minimum	28	4	79	5
IPC chart	1 kit	50 vials	3 grams	25 grams

CONCLUSION: Our data demonstrate inadequate antidote stocking in many Illinois hospitals. Treatment with these nine antidotes can be life-saving, and time does not permit transferring patients or borrowing drugs from alternate sources when critically poisoned patients need treatment. We urge hospital pharmacy managers nationwide to evaluate current inventories of these crucial antidotes.

227A. Transplant pharmacists' interventions in solid organ transplant recipients. *Essy Mozaffari, Pharm.D., M.P.H.*, Julie A. Suko, Pharm.D., Monica L. White, Pharm.D., Gail G. Bridges, Pharm.D., Karen M. Whalen, Pharm.D., Joan S. Kramer, Pharm.D., Randy J. Correia, Pharm.D.; The Transplant Pharmacy, Menlo Park, CA.

PURPOSE: To describe the types of clinical and economic interventions performed by transplant pharmacists in solid organ transplant recipients.
METHODS: An interim analysis of a multicenter, prospective study of transplant pharmacists' interventions was conducted to describe the types of interventions led by the pharmacists. The study population consisted of solid organ transplant recipients enrolled in a pharmacy service specific to transplant disease management. A pre-tested pharmacist intervention documentation (PID) form was used to record the types of interventions encountered in organ transplant recipients. The transplant pharmacists documented the type of intervention, recommendations, actions taken, and anticipated outcomes. More than one type of intervention may have been discovered at a particular consultation. All PID forms completed between October 1998 and May 1999 were considered for this analysis. Descriptive statistics were used to summarize the results.
RESULTS: PID forms were completed by transplant pharmacists among four geographically dispersed transplant centers. A total of 513 (26%) of the pharmacy consultations were for interventions that were related to medication regimens (21.1%), appropriate therapeutic selection (33.7%), compliance (11.3%), cost (20.1%), and adverse effect (10.3%). Of the recommendations made by the pharmacists, 97.3% were accepted. The interventions were in transplant recipients who had been transplanted for kidney (81.5%), kidney/pancreas (9.5%), liver (7.3%), or heart (1.8%) organs. Sixty-five percent of the interventions were conducted within one year and 43% within six months post-transplantation.
CONCLUSIONS: Pharmaceutical care in organ transplant recipients resulted in interventions that had both clinical and economic implications. This study emphasizes the importance of transplant disease management post solid organ transplantation.

Research Institute

The following papers, based on Fellowships and Research Awards provided by the ACCP Research Institute, will be presented. Full titles and authors are listed, although a complete abstract may not be available for all papers at the time of this printing.

228. Bayer Critical Care Fellowship: Oxandrolone use in trauma patients. *Jane M. Gervasio, Pharm.D.*, Roland N. Dickerson, Pharm.D., Jessica Swearingen, Pharm.D., Mary E. Yates, Pharm.D., Timothy C. Fabian, M.D., Martin A. Croce, M.D., Rex O. Brown, Pharm.D.; University of Tennessee; Memphis and Regional Medical Center at Memphis, Memphis, TN.

PURPOSE: The erosion of body cell mass in patients following multiple trauma has been reported. The effect of oxandrolone (Ox) administration on nutritional and clinical outcome following multiple trauma was studied.
METHODS: Patients who were injured and required enteral nutrition (EN) were randomized to receive either Ox 10 mg BID or placebo (P) for a maximum of 28 days. Total urinary nitrogen (TUN), nitrogen balance, and body cell mass were measured on day 1 of EN, and then at day 7, day 10, and study exit. Patients were assessed daily for infectious complications. Body cell mass was measured by BIA and TUN was measured by chemiluminescence.
RESULTS: Sixty multiple trauma patients were entered into the study; 30 in each group. The two groups were similar for patient demographics and dose of EN. Measurement of TUN at study entry demonstrated both groups to be highly catabolic (Ox = 17.2 ± 4.8 versus P = 19.1 ± 10.8 g/d; NS). On days 7 and 10, TUN increased in both groups; however, there was no significant difference between groups. Nitrogen balance was negative at study days 1, 7, and 10 in each group. The body cell mass decreased slightly in both groups over the first 10 days. Prealbumin serum concentrations increased significantly in both groups at days 10 and study exit when compared to study entry. There was no significant difference between groups for length of hospital stay, length of ICU stay, and incidence of pneumonia or sepsis.
CONCLUSION: Oxandrolone does not demonstrate obvious benefit in nutritional and clinical outcome during the first month following multiple trauma.

229. Merck and Company Cardiovascular Fellowship: Effect of fluoxetine on carvedilol pharmacokinetics and autonomic balance in heart failure patients. *Donald W. Graff, Pharm.D.*, Kristin M. Williamson, Pharm.D., John A. Pieper, Pharm.D., FCCP, Stanley W. Carson, Pharm.D., FCCP, Kirkwood F. Adams, Jr., M.D., Wayne E. Cascio, M.D., J. Herbert Patterson, Pharm.D., FCCP; University of North Carolina, Chapel Hill, NC.

PURPOSE: Carvedilol (C), the only beta-blocker approved for treatment of heart failure (HF), is administered as a racemic mixture, with each enatiomer possessing different pharmacological effects. While both enantiomers possess $alpha_1$-blocking activity, only S(-)C has beta-blocking activity. Fluoxetine (F) and its major metabolite, norfluoxetine, are potent inhibitors of CYP2D6. Because C is extensively metabolized by CYP2D6, concomitant administration with F may increase plasma concentrations of C, potentially resulting in enhanced pharmacodynamic effects.
METHODS: Ten (6 males, 8 African American) extensive metabolizers of CYP2D6 with NYHA class I-III HF were administered 20 mg F or placebo QD for 28 days in addition to C (25-50 mg BID) in a randomized, double-blind, cross-over study. Plasma was collected over the 12-hour C dosing interval and analyzed by HPLC for R(+)C and S(-)C concentrations. Pharmacokinetic parameters (AUC_{0-12}, oral clearance [CL_O], $t_{1/2}$) and pharmacodynamic assessments [heart rate variability (HRV) time- and frequency-domain measures, blood pressure (BP), heart rate (HR)] were examined during both study phases.
RESULTS: Compared to placebo, F increased R(+)C AUC_{0-12} by 77% (p=0.01) although S(-)C AUC_{0-12} increased by only 35% (p=0.17). Cl_O of both R(+)C and S(-)C decreased significantly (56%, p=0.004, and 34%, p=0.03, respectively). R(+)C $t_{1/2}$ also increased (p=0.04), although S(-)C $t_{1/2}$ did not. There were no significant changes in HRV, BP, or HR between study phases.
CONCLUSION: F coadministration resulted in a stereoselective inhibition of C metabolism, affecting R(+)C to a greater extent than S(-)C. However, this interaction did not result in significant pharmacodynamic changes in our patients.

230. Merck and Company Cardiovascular Fellowship: Effect of intravenous haloperidol on ventricular monophasic action potential duration and effective refractory period. *James A. Tisdale, Pharm.D.*, Neeta B. Amin, Pharm.D., Saeed Rasty, Pharm.D., Takayuki Mishima, M.D., Steven Borzak, M.D., Hani Sabbah, Ph.D.; Wayne State University; Henry Ford Hospital, Detroit, MI.

231. Merck and Company Cardiovascular Fellowship: Regional L-type calcium channel inhibition does not alter defibrillation energy requirements. *J. Jason Sims, Pharm.D.*, Allison W. Miller, Pharm.D., Michael R. Ujhelyi, Pharm.D.; University of Georgia; Medical College of Georgia; Augusta VA Medical Center, Augusta, GA.

PURPOSE: Implantable defibrillators decrease sudden cardiac death mortality, but are limited by the energy required to defibrillate (i.e., high DER values). Regional myocardial ischemia, such as occurs during myocardial infarction, increases DER values and impairs defibrillation. However, the mechanism of this disease-device interaction is unknown. Data indicate that regional myocardial ischemia may increase DER values by impairing regional calcium handling via L-type calcium channel conductance. Therefore, the purpose of this study was to determine the effects of regional L-type calcium inhibition on DER values.
METHODS: Sixteen swine were instrumented with a coronary artery (LAD) perfusion catheter and pacing/recording electrodes at five myocardial sites (three epicardial, two endocardial). Swine were randomized to receive either low-dose regional verapamil 0.025 mg/kg/hr or regional placebo (normal saline) infusion. DER and electrophysiologic values were determined at baseline and during a regional infusion phase.
RESULTS: DER values are reported for both groups. Regional verapamil infusion did not alter DER values from baseline. Regional verapamil did not alter refractoriness or action potential duration at any myocardial site. Placebo infusion did not alter any parameter.

	Baseline	Phase 1
Verapamil (n=9)	12 ± 2 J	14 ± 2 J
Placebo (n=7)	12 ± 1 J	13 ± 2 J

CONCLUSIONS: Decreasing regional L-type calcium channel conductance does not alter DER values. Therefore, ischemia may not alter DER values by altering L-type calcium conductance. Although, other mechanisms than L-type calcium conductance must alter DER values, this does not rule out impaired calcium handling as a potential cause for ischemia's effects on DER values. Thus, other methods of calcium handling need to be assessed.

232. Ortho-McNeil Infectious Diseases Fellowship: Adherence as a determinant of virologic response to potent protease inhibitor therapy. *Lori D. Esch, Pharm.D.*, Mark J. Shelton, Pharm.D., Ross G. Hewitt, M.D., Gene D. Morse, Pharm.D.; State University of New York at Buffalo, Buffalo, NY.

233. Rhône-Poulenc Rorer Oncology Fellowship: Topotecan disposition is not altered in combination with vincristine in a murine model. *Margaret K. Ma, Pharm.D.*, Peter J. Houghton, Ph.D., Suzan K. Hanna, M.S., Clinton F. Stewart, Pharm.D.; St. Jude Children's Research Hospital, Memphis, TN.

PURPOSE: The combination of topotecan (TPT) and vincristine (VCR) has shown enhanced antitumor activity against pediatric solid tumors in mice bearing neuroblastoma (NB), rhabdomyosarcoma, and brain tumor xenograft lines. Thus, we evaluated TPT and VCR disposition in non-tumor bearing for a potential drug interaction.
METHODS: Serial plasma samples (three mice/time point) were obtained for TPT and VCR concentrations in non-tumor bearing mice receiving IV TPT (1.25 mg/kg) or IV VCR (1 mg/kg), or TPT and VCR in combination. TPT lactone concentrations were measured by HPLC with fluorescence detection, and VCR concentrations were measured by HPLC with ultraviolet and electrochemical detection. A 2-compartment model was fit to TPT or VCR plasma concentration-time data by maximum likelihood estimation (ADAPT II).
RESULTS: TPT plasma clearance (CL) and half-life was similar in mice receiving TPT and TPT + VCR. Likewise, the TPT area under the concentration-time curve (AUC) was similar between the two groups. VCR systemic clearance was comparable in the presence or absence of TPT.

	TPT PK Parameters		VCR PK Parameters	
Treatment	TPT Alone	VCR + TPT	VCR Alone	VCR + TPT
$t_{1/2\beta}$ (hr)	1.6	2.2	39.5	29.9
Cl (L/hr/m^2)	20.8	24.5	4.3	3.5
$AUC_{0-\infty}$ (ng•hr/ml)	160	145.6	298	231

CONCLUSIONS: We were unable to identify a drug interaction between TPT and VCR in non-tumor bearing mice. This observation does not preclude an interaction in tumor bearing animals. Thus, we are currently evaluating the potential for a drug interaction between TPT and VCR occurs in tumor bearing animals. Moreover, we are investigating the effect of VCR on TPT tumor extracellular fluid exposure in mice bearing NB xenografts as a possible mechanism of this greater than additive antitumor activity.

234. Amgen Biotechnology Research Award: Hepatitis A vaccine: cytokine and antibody levels. *Mary S. Hayney, Pharm.D., BCPS*; University of Wisconsin, Madison, WI.

PURPOSE: To examine the cytokine response as an immune mechanism driving the antibody response to hepatitis A immunization. The cytokine response may be a useful measure of cellular immune activation. The value of using plasma for measuring cytokine levels is that it is an easy biological fluid to obtain facilitating epidemiological studies.
METHODS: Hepatitis A seronegative subjects (n=24) were immunized with inactivated hepatitis A vaccine and cytokine levels were followed by serial blood draws on days 2, 5, 7, and 10. Hepatitis A antibody levels were measured using ELISA on day 28. Interferon-γ (IFN-γ), interleukin-2 (IL-2), interleukin-4 (IL-4), and tumor necrosis factor α (TNF-α) levels were measured in plasma using ELISA (Pharmingen OptEIA kits).
RESULTS: Twenty of the 24 subjects responded to the hepatitis A vaccine with a measurable antibody response (GMT = 2.62). Only four subjects had measurable IL-2 levels in plasma and three had measurable levels of IL-4. IFN-γ was detected in all plasma samples, but no peak and trough pattern indicative a response to an antigen was identified. In general, there was little change from baseline. TNF-α was not detected in the plasma of any subjects.
CONCLUSIONS: Cytokine levels in plasma are not useful as a measure of cellular immunity following hepatitis A immunization and may not reflect local immune activation. Studies of cytokine production by peripheral blood mononuclear cells may be better markers of cellular immune response following hepatitis A immunization. These studies are in progress.

235. Bayer Community Infectious Diseases Research Award: Characterizing cytochrome P450 activity in HIV-1 infected women. *Angela D.M. Kashuba, Pharm.D.*, S. Karl Gotzkowsky, Pharm.D., Jodi M. Weidler, Pharm.D., Ralph H. Raasch, Pharm.D., Charles M. van der Horst, M.D.; University of North Carolina, Chapel Hill, NC.

236. Glaxo-Wellcome Pharmacotherapy Research Award: Effect of grapefruit juice on the systemic availability of itraconazole oral solution in healthy adults. *Paul M. Gubbins, Pharm.D.*, Scott A. McConnell, Pharm.D., Bill J. Gurley, Ph.D., Amy M. Franks, Pharm.D. candidate, Scott R. Penzak, Pharm.D., Michael Saccente, M.D.; University of Arkansas, Little Rock, AR.

237. Rhône-Poulenc Rorer Cardiovascular Research Award: Humoral and hemodynamic responses to sleep apnea. *Bradley G. Phillips, Pharm.D.*, Masahiko Kato, M.D., Ph.D., Virend K. Somers, M.D., Ph.D.; University of Iowa, Iowa City, IA.

238. Rhône-Poulenc Rorer Oncology Research Award: Evaluation of NQO1 gene expression in NSCLC tumors and matched normal lung tissue by RT-PCR CE-LIF. *Jill M. Kolesar, Pharm.D.*, Eric W. Olson, B.S., Lisa A. Hillman, B.S., Judith A. Miller, B.S., Howard L. McLeod, Pharm.D.; University of Wisconsin, Madison, WI; University of Aberdeen, Aberdeen, Scotland.

PURPOSE: NQOR (NAD(P)H:quinone oxidoreductase) is a flavoprotein that catalyzes the two-electron reduction of quinones and their derivatives. Since quinones are known constituents of cigarette smoke and implicated in the pathogenesis of lung cancer, our hypothesis is that NQO1 activity is increased in NSCLC. The purpose of this study is to evaluate NQO1 activity by gene expression and mutation status in NSCLC and matched normal tissue.
METHODS: Matched biopsy samples (tumor and normal margins) were obtained from 50 patients undergoing resection of their primary tumor. RNA was by standard techniques and quantitated spectrophotometrically. Gene expression is quantitated by RT-PCR (reverse transcription-polymerase chain reaction) with a competitive, reaction specific internal standard and analysis by capillary electrophoresis with laser induced fluorescence (CE-LIF). Mutation at bp609 is evaluated by restriction fragment polymorphism (RFLP) with analysis by CE-LIF.
RESULTS: All 50 subjects have been recruited to the protocol. Gene quantitation is currently available for 18 subjects. The mean gene expression in the normal lung tissue is $7.4x\ 10^{-15}$ ng/ml ± 0.7 and the mean gene expression in the NSCLC 8.2×10^{-13} ± 163 ng/ml (p=0.08). NQO1 gene expression in normal lung tissue ranged from $0\text{-}1.88 \times 10^{-14}$ ng/ml and from $0\text{-}5.13 \times 10^{-12}$ ng/ml in the tumor tissue. One subject did not express NQO1 in either the tumor or the normal tissue.
CONCLUSION: NQO1 gene expression is similar in normal lung tissue. NQO1 was overexpressed and highly variable in tumor samples. Results are trending towards a significant difference between NQO1 gene expression in normal tissue and matched lung samples. This may represent an important avenue for exploration in the pathogenesis of lung cancer and drug selectivity as quinones such as MMC are activated by NQO1 and may be preferentially activated where NQO1 is overexpressed.

239. Rhône-Poulenc Rorer Pulmonary Research Award: Validation of a pediatric ventilated lung model. *Sandra S. Garner, Pharm.D.*, Donald B. Wiest, Pharm.D., David M. Habib, M.D.; Medical University of South Carolina, Charleston, SC.

240. Wyeth-Ayerst Women's Healthcare Research Award: Gender differences in β_2-adrenoceptor responsiveness in endstage renal disease. *Kevin M. Sowinski, Pharm.D.*, Meri K. Scott, Ph.D., Bruce A. Mueller, Pharm.D., Michael A. Kraus, M.D.; Purdue University, Indianapolis, IN; Indiana University.

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